Universidad del País Vasco | Euskal Herriko Unibertsitatea

NAZIOARTEKO BIKAINTASUN CAMPUSA
CAMPUS DE EXCELENCIA INTERNACIONAL

Synthesis and C-H functionalization of 1*H*-1,2,3-triazole N-oxides

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Doctoral Thesis

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Department of Organic Chemistry I

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List of publications

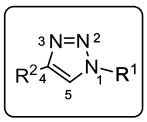
1. *Discovery of a novel family of FKBP12 "reshapers" and their use as calcium modulators in skeletal muscle under nitro-oxidative stress.* Aizpurua, J. M.; Miranda, J. I.; Irastorza, A.; Torres, E.; Eceiza, M.; Sagartzazu-Aizpurua, M.; Ferrón, P.; Aldanondo, G.; Lasa-Fernández, H.; Marco-Moreno, P.; Dadie, N.; Lopez de Muniain, A.; Vallejo-Illarramendi, A. *Eur. J. Med. Chem.* **2021**, *213*, 113160.

2. *RGD-Functionalized Fe_3O_4 nanoparticles for magnetic hyperthermia.* Arriortua, O. K.; Insausti, M.; Lezama, L.; Gil de Muro, I.; Garaio, E.; de la Fuente, J. M.; Fratila, R. M.; Morales, M. P.; Costa, R.; Eceiza, M.; Sagartzazu-Aizpurua, M.; Aizpurua, J. M. *Colloids Surf. B: Biointerfaces* **2018**, *165*, 315.

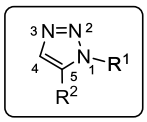
3. *Covalent immobilisation of magnetic nanoparticles on surfaces via strain-promoted azide-alkyne click chemistry.* Fratila, R. M.; Navascuez, M.; Idiago-López, J.; Eceiza, M.; Miranda, J. I.; Aizpurua, J. M.; de la Fuente, J. M. *New. J. Chem.* **2017**, *41*, 10835.

Laburpena

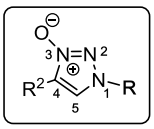
1*H*-1,2,3-triazolak azken 15 urteetan garrantzi handia hartu duten konposatu heterozikliko ak dira. Alde batetik, konposatu heterozikliko hauek kimika farmazeutikoan, materialen zientzian etab. eduki ditzaketen aplikazioengatik. Bestetik, konposatu hauek sintetizatzeko erraztasunagatik, Cu(I) edo Ru(II) bidez katalizaturiko azida eta alkino arteko “click” zikloadizio bitartez ala konposatu karboniliko eta aziden bitarteko organokatalisi bidez lor baitaitezke. Gainera, triazol horien N-oxidazioa burutzen bada, triazol mota desberdinak osa daitezke aplikazio desberdinak eduki ditzaketenak, nahiz eta euren kimika ez den oso aztertua izan.



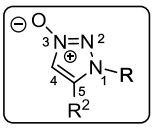
1*H*-1,2,3-triazola
(1,4-diordezkatua)



1*H*-1,2,3-triazola
(1,5-diordezkatua)



1*H*-1,2,3-triazol N-oxidoa
(1,4-diordezkatua)



1*H*-1,2,3-triazol N-oxidoa
(1,5-diordezkatua)

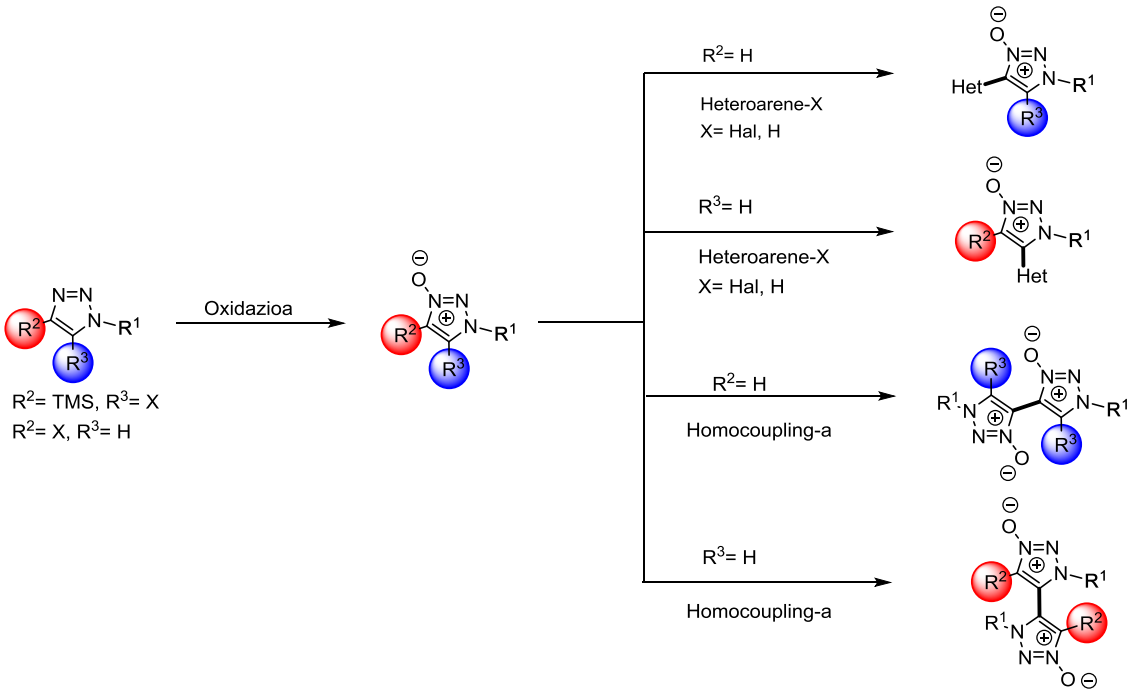
Doktoretza tesi honen helburu nagusia 1*H*-1,2,3-triazol N-oxidoen sintesiaren eta erreaktibitatearen ikerketa egitea izango da, izan ere, N-oxidoak sor dezakeen aktibazioa baliatu nahi da egitura berriak sortzeko. Horregatik, hainbat helburu zehaztu dira:

1. 1*H*-1,2,3-triazol N-oxido desberdinen diseinu eta sintesia burutzea. Are gehiago, erreakzioaren mugak eta talde funtzional desberdinekiko sentikortasuna ere ikertuko da.

2. C-H aktibazioa dela medio, 1,4,5-triordezkatutako triazolen sintesia burutzea kobre eta paladio bidez katalizaturiko erreakzio bideak erabiliz. Horretarako erreakzio aktibazio desberdinak erabiliko dira, hala nola, zuzeneko C-H arilazioak edo C-H aktibazio bikoitzekoak.

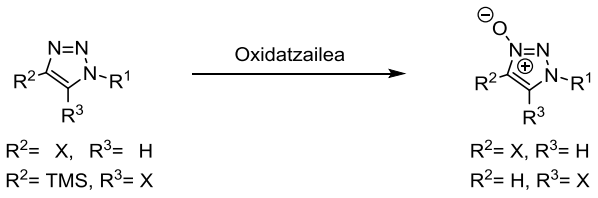
3. C-H aktibazioa erabiliz, bistriazol desberdinen sintesia burutzea.

Helburu nagusiak jasotzen dituen erreakzio eskema bat aurkezten da jarraian.



1 1*H*-1,2,3-triazol N-oxidoen zuzeneko sintesia 1*H*-1,2,3-triazoletatik abiatuta.

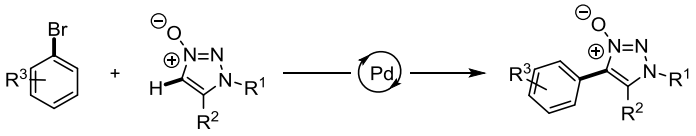
Lehen helburua aurrera eraman ahal izateko, 1*H*-1,2,3-triazol familia sorta bat sintetizatu ziren eta oxidatzaile desberdinak erabiliz euren oxidazio erreakzioen optimizazioa aurrera eraman zen. Bibliografia begiratuz, 1987an argitaraturiko artikulu bat aurkitu zen, non triazolen oxidazio erreakzioak denbora luzekoak (4-7 egun bitartekoak) ziren eta etekin kaskarrekoak. Ordutik 2019 arte ez da artikulu gehiagorik argitaratu baina urte horretan bertan, Cuevas-Yañez-en taldeak denbora laburreko eta etekin bikaineko prozedurak argitaratu zituzten. Hala ere, emaitza horiek ez ziren erreproduzigarriak izan. Horregatik, 1*H*-1,2,3-triazol N-oxidoen sintesi protokolo eraginkor bat sortzea erabaki zen.



Optimizaturiko prozedura, 1,4- eta 1,5-triazol diordezkatuekiko konpatiblea zen, etekin globalak 40-82 % tartekoak zirelarik. 1,5-triazol diordezkatuek oro har, 1,4-triazol diordezkatuek baina etekin hobeak eman zituzten.

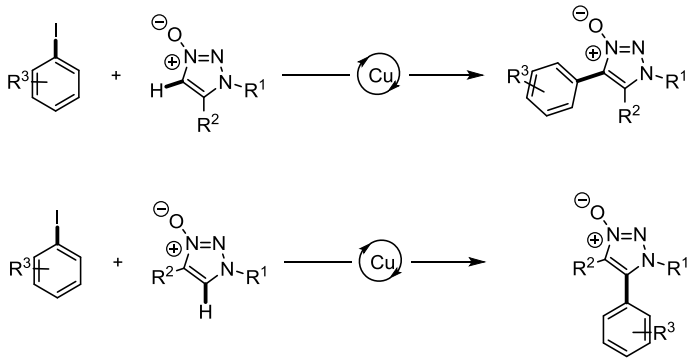
2 Paladio eta kobre bidez katalizaturiko 1*H*-1,2,3-triazol N-oxidoen zuzeneko arilazio erreakzioak.

Beharrezko 1*H*-1,2,3-triazol N-oxidoak sintetizatu ostean, N-oxido horrek eragin zezakeen aktibazioa ikertzeari ekin zitzaion. Jakina zen beste heteroziklo N-oxido batzuk zirela medio, N-oxidoak Brønsted-en azidotasuna handitzen zuela heterozikloaren α C-H loturan. Datu hauek kontutan harturik, lehenik 1*H*-1,2,3-triazol N-oxidoek paladio bidez katalizaturiko zuzeneko arilazio erreakzioak ikertu ziren.



Aril bromuro desberdinak erabiliz, 1,4,5-triordezkaturiko triazol desberdinak sintetizatu ziren, zeinak, "click" erreakzio sinple batetik sor ezin daitezkeen. Oro har, erreakzio etekinak 50-94 % tartekoak ziren. Azpimarratzekoa da erreakzioa oxidatu gabeko 1*H*-1,2,3-triazolekin burutzen zenean 25 % konbertsioa soilik lortzen zela, eta beraz, N-oxidoaren presentzia beharrezkoa zela frogatu zen.

Gerora, kobre katalisi bidezko zuzeneko arilazio erreakzioak ikertzea erabaki zen, kasu honetan, aril ioduro desberdinak erabiliz. Paladio katalisian ez bezala, kasu honetan erreakzioa 1,4-triazol diordezkatuekin burutzea posiblea zen bai eta aril ioduro desberdin askorekin ere.

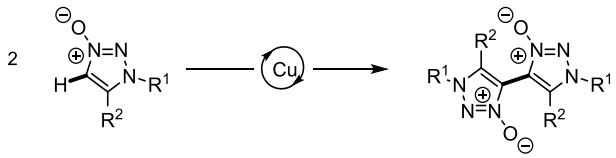


Are gehiago, frogatu zen adibide hauek ikusirik, N-oxidoaren eragina batez ere α CH loturan zela eta horregatik 1,5-diordezkatutako triazolen kasuan lortu ziren etekin handienak, 50-98 % tartekoak hain zuzen ere. 1,4-Diordezkatutako triazol N-oxidoen kasuan aldiz, 14-73 % arteko etekinak lortu ziren.

3 Kobre katalisi bidezko 1*H*-1,2,3-triazol N-oxidoen akoplamendu erreakzioak.

Tesiko hurrengo atalean, eta aurrekoen ildo beretik jarraituz, hots, 1,2,3-triazol N-oxidoen erreaktibitatearen ikerketan, kasu honetan, 4,4'- eta 5,5'- bistriazol N-oxidoak sintetizatzeko metodologia berri bat garatu zen.

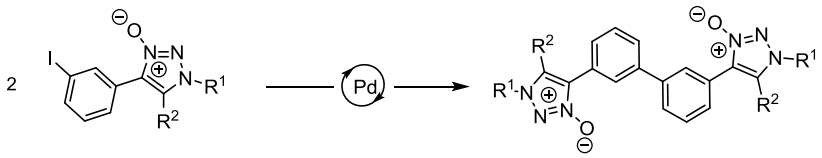
Alde batetik, 1,5-triazol diordezkatuen akoplamendu erreakzioa ikertu zen, zeinak 4,4'-bistriazol N-dioxido produktuak ematen zituen.



Erreakzio etekinak 56-80 % tartekoak ziren. Erreakzioa R^1 talde aromatiko ala alifatiko ez azidikoetara mugatua zegoen, izan ere, base sendo baten presentzia beharrezkoa zen errekazioa aurrera joan zedin. R^2 taldeak eragozpen desberdinetako taldeak izan zitezkeen, fenilo ala *tert*-butilo kasu. Hala ere, kalkulu konputazional batzuek erakutsi zutenaren arabera, erabilitako R^2 taldeetako bat berak ere ez luke eragozpen nahikoa edukiko barrera errotazionala gainditzeko.

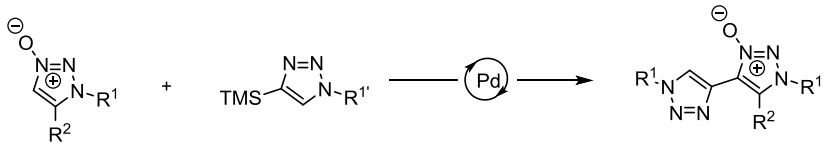
Bestetik, 1,4-triazol diordezkatuen akoplamendu erreakzioa ikertu eta optimizatu zen, zeinak 5,5'-bistriazol N-dioxidoak ematen dituen produktutzat. Erreakzio bide honek ere mugak zituen, izan ere, C4 karbonoan metalarekin koordina zitekeen heteroatomo bat egon behar zuen, piridina kasu.

Azkenik, aurreko atalean sintetizaturiko konposatu batzuei aplikazioa emanez, biaril bistriazol familia bat sintetizatu zen, paladio bidez katalizaturiko aril ioduroen arteko akoplamenduan oinarriturik eta erreakzio etekinak 63-90 % artekoak zirelarik. Produktu sorta honek ere, ligando gisa jokatzeko balioko luke.

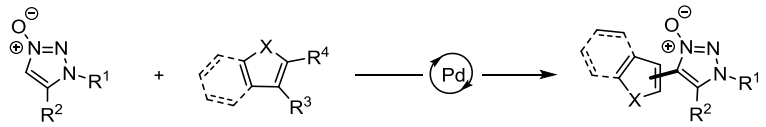


4 C-Si aktibazio eta CH/CH aktibazio bikoitzeko paladio bidezko katalisia 1,5-triazol N-oxidoak substratutzat erabiliz.

Tesiko azken kapituluan eta aurreko atalen ildo beretik, hau da, triazol N-oxidoen erreaktibitatearekin jarriatuz, bi aktibazio mota desberdin ikertu dira. Alde batetik, 4-trimetilsilil-1,2,3-triazol desberdinak erabili dira C-Si loturaren aktibazioaz baliatu eta C-C lotura berriak osatzeko. Modu honetan, 4,4'-bistriazol N-oxido ez simetrikoen produktu sorta bat sortu da 50-60 % etekinekin. Azpimarratzekoa da erreakzioak aktibatu gabeko trimetilsililo taldearekin burutzen direla eta horrek eragina duela erreakzioaren konbertsioan.



Beste alde batetik, eta tesiari amaiera emanez, paladio bidez katalizaturiko CH aktibazio bikoitza ikertu zen, zeinetan diordezkatutako 1,5-triazol N-oxido eta elektroietan aberatsak diren heteroaromatiko talde ezberdinak erabili ziren. Hala, 1,4,5-triordezkatutako triazol N-oxidoak lortuko lirateke 66-83 % etekinean.



List of abbreviations, Acronyms, and Symbols

ACE	Heavy wall pressure vessels
Aq.	Aqueous
BuLi	Butyllithium
cat.	Catalyst
CDC	Cross-Dehydrogenative Coupling
CMD	Concerted Metalation Deprotonation
CuAAC	Copper-catalyzed Azide Alkyne Cycloaddition
d	Doublet (NMR)
DCM	Dichloromethane
dd	Doublet of doublets (NMR)
ddd	Doublet of doublets of doublets (NMR)
DFT	Density Functional Theory
DG	Directing Group
DIPEA	N,N-Diisopropylethylamine
DMDO	Dimethyldioxirane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets (NMR)
dq	Doublet of quartets (NMR)
δ	Chemical shift (NMR)
EDG	Electron-Donating Group
ESI	Electrospray ionization (Mass spectrometry)

Eq	Equivalents
EWG	Electron-Withdrawing Group
FMO	Frontier Molecular Orbital
h	Hours
HIV	Human Immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation Spectroscopy
HOMO	Highest Ocuppied Molecular Orbital
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant (NMR)
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
m	Multiplet (NMR)
M	Metal
*m*CPBA	3-Chloroperbenzoic acid
MHz	Megahertz
mp	Melting point
MS	Mass Spectrometry
MW	Microwave
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect

Pyr	Pyridine
PPO	Phthaloyl peroxide
q	Quartet (NMR)
r.t.	Room temperature
RLM	Rat Liver Microsomes
RuAAC	Ruthenium-catalyzed Azide Alkyne Cycloaddition
s	Singlet (NMR)
S_EAr	Electrophilic aromatic substitution
t	Triplet (NMR)
T	Temperature
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBTA	Tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine
td	Triplet of doublets (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	N,N,N',N'-Tetramethylenediamine
TMS	Trimethylsilyl group
Trz	Triazole
UV	Ultraviolet

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1

Introduction and general objectives

1. Introduction and general objectives.

1.1 Introduction

1.1.1 Pyridine-related heteroarene N-oxides

During recent decades, N-oxides of aromatic heterocycles have emerged as compounds with considerable potential to display anticancer, antibacterial, antihypertensive, antiparasitic, anti-HIV, anti-inflammatory or herbicidal properties.[1] Indeed, the N-oxide motif has been successfully employed in a number of recent drug development projects, demonstrating that the introduction of such small structural moiety confers improved pharmacokinetic properties, selective bioactivity and cleaner metabolism to some drugs. Several examples of therapeutic drugs comprising the N-oxide group are depicted in the following figure.

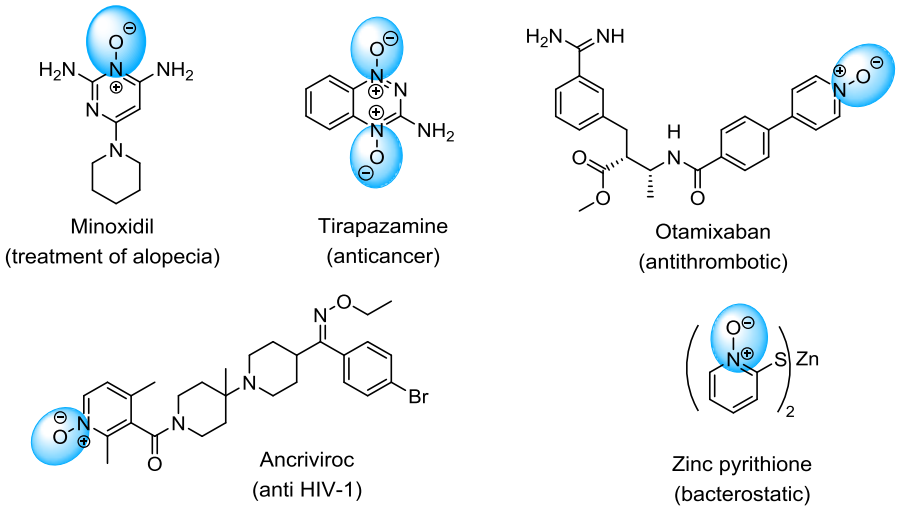


Figure 1.1. Illustrative examples of heterocyclic N-oxides with therapeutic applications.

Besides their use in medicinal chemistry, heteroarene N-oxides have been employed as agrochemicals[2] or ligands for metal or metal-free catalysis.[3] Owing to such applications,

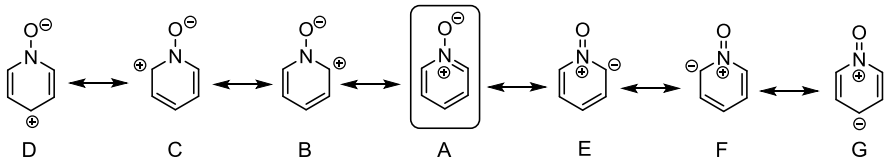
[1] For some selected examples, see: a) Chung, P.-Y.; Blan, Z.-X.; Pun, H.-Y.; Chang, D.; Chan, A. S.-C.; Chui, C.-H.; Tang, J. C.-O.; Lam, K.-H. *Future Med. Chem.* **2015**, *7*, 947. b) Mfuh, A. M.; Larionov, O. V. *Curr. Med. Chem.* **2015**, *22*, 2819. c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.

[2] Cerecetto, H.; Dias, E.; Di Maio, R.; González, M.; Pacce, S.; Saenz, P.; Seoane, G. *J. Agric. Food Chem.* **2000**, *48*, 2995.

[3] a) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, 29. b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373.

the chemistry of N-oxide compounds has also experienced an increasing activity in recent years.

Pyridine N-oxide can be considered as the prototypical example of heteroarene N-oxide. It contains a 1,2-dipolar nitrogen-oxygen bond with the charges delocalized within the aromatic ring[4] as depicted in Scheme 1.1.



Scheme 1.1. Canonical resonance Lewis structures of pyridine N-oxide.

As pointed out in the scheme, the positive nitrogen charge of structure A is delocalized to the *ortho* and *para* carbon atoms (structures B-D), conferring to them a mild electrophilic nature. Alternatively, the negative charge on the oxygen atom can delocalize into the pyridine ring (structures E-G). In general, the N-oxidation of pyridine enhances the acidity of the protons adjacent to the N-oxide function and stabilizes the intermediate species participating, for example, in cross-coupling reactions involving *ortho* C-H functionalization[5]. Additionally, the oxygen atom can act as a Lewis base in pyridine-like N-oxides, directing or facilitating remote reactions that include arylation, alkenylation, alkynylation, acyloxylation, amination, amidation or sulfonylation[6] (Scheme 1.2 A). Alternatively, the heteroarene N-oxide moiety can act as a 1,3-dipole to give cycloaddition reactions (Scheme 1.2 B).[7] Finally, taking advantage of the combined weakness of the N-O bond and the nucleophilicity of the oxygen atom, some heteroarene

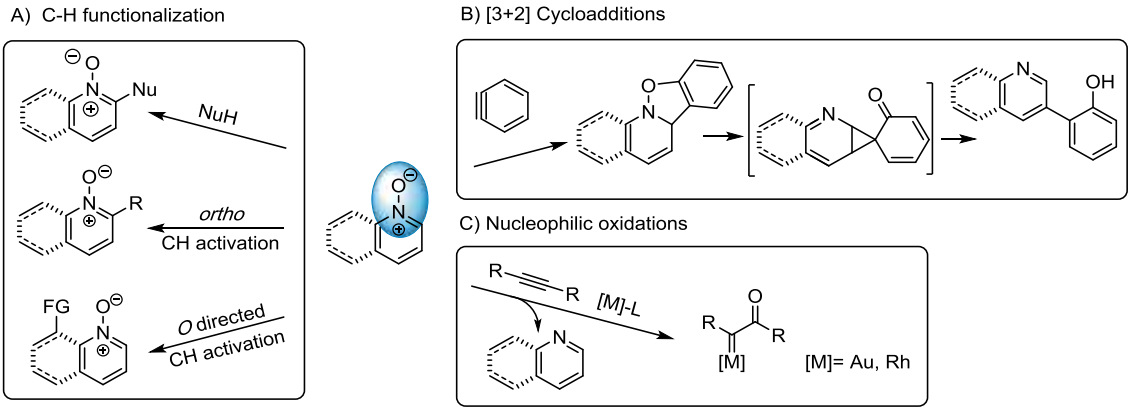
[4] For a selected review, see: Wang, Y.; Zhang, L. *Synthesis* **2015**, *47*, 289.

[5] Stephens, D. E.; Larionov, O. V. *Top Heterocycl. Chem.* **2017**, *53*, 59.

[6] For a selected review, see: a) Yan, G.; Borah, A. J.; Yang, M. *Adv. Synth. Catal.* **2014**, *356*, 2375.

[7] For a selected review, see: a) Loska, R. *Top Heterocycl. Chem.* **2017**, *53*, 85. For some selected examples, see: b) Loska, R.; Mąkosza, M. *Chem. Eur. J.* **2008**, *14*, 2577. c) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689. d) Jeschke, P.; Harder, A.; Etzel, W.; Gau, W.; Göhrt, A.; Benet-Buchholz, J.; Thielking, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2375. e) Lindner, H. J.; Krebs, A.; Förster, J.-H.; Sinnwell, V. *Heterocycles* **1997**, *45*, 811. f) Hisano, T.; Harano, K.; Matsuoka, T.; Suzuki, T.; Murayama, Y. *Chem. Pharm. Bull.* **1990**, *38*, 605.

N-oxides have been used to conduct the smooth oxidation of alkynes and allenes catalyzed by gold[8] and rhodium[9] complexes. (Scheme 1.2 C).



Scheme 1.2. General reactivity of pyridine-derived heteroarene N-oxides.

Despite their use as synthetic building blocks or reactants, pyridine-derived heteroarene N-oxides have also been used as ligands for metal-free catalysis[10] and asymmetric catalysis[11], mostly related to organosilicon chemistry, due to the affinity of the silicon atom for oxygen. For instance, chiral ligands including bipyridyl based N-dioxides, trioxides or binaphthyl based N-oxides, among others (Scheme 1.3) have been used to catalyze reactions such as the asymmetric allylation of aldehydes,[12] the enantioselective

[8] For some selected examples, see: a) Wang, L.; Xie, X.; Liu, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 13302. b) Hashmi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. *J. Org. Chem.* **2012**, *77*, 7761. c) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2011**, *50*, 6911. d) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. e) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. f) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070.

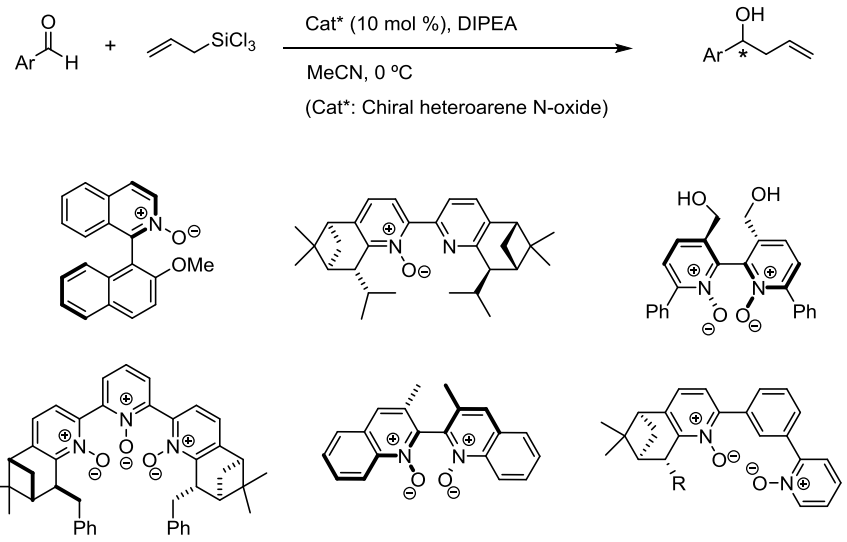
[9] Liu, R.; Winston-McPherson, G. N.; Yang, Z.-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 8201.

[10] Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. *Top Heterocycl. Chem.* **2017**, *53*, 29.

[11] For a selected review, see: Wrzeszcz, Z.; Siedlecka, R. *Molecules* **2020**, *25*, 330.

[12] a) Fulton, J. R.; Glover, J. E.; Kamara, L.; Rowlands, G. J. *Chem. Commun.* **2011**, *47*, 433. b) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron*. **2008**, *64*, 7574. c) Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality*. **2005**, *17*, 396. d) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem*. **2003**, *68*, 6329. e) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kocovský, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674. f) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett*. **2002**, *4*, 2799. g) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett*. **2002**, *4*, 1047. h) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc*. **1998**, *120*, 6419.

ring opening of meso-epoxides[13] or the cyanosilylation of ketones[14] and imine derivatives.[15]



Scheme 1.3. Pyridine N-oxide moiety-containing chiral organocatalysts used in the asymmetric allylation of benzaldehydes.

The general rational of the reaction activation and asymmetric induction observed in the former reactions is based on the formation of chiral hypervalent silicate intermediates from the highly oxophilic organosilicon reagents and the N-oxide chelating ligands.

Chiral heteroarene N-oxides can also be employed as ligands in transition metal-catalyzed reactions, such as the cyanosilylation of ketones[16] or the Michael additions[17] among others[18]. In such transformations, heteroarene N-oxides form sigma complexes through

[13] a) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett*. **2002**, *43*, 8827.

[14] a) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett*. **2003**, *5*, 949. b) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* **2003**, *59*, 5667. c) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Synlett* **2003**, 558. d) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 793.

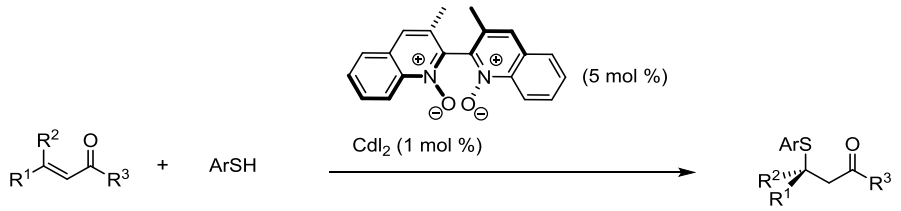
[15] a) Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem*. **2003**, *19*, 3818. b) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. *Synlett* **2001**, 1551.

[16] a) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2004**, 129. b) Shen, Y.; Feng, X.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 1353.

[17] a) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307. b) Nakajima, M.; Yamaguchi, Y.; Hashimoto, S. *Chem. Commun*. **2001**, 1596.

[18] Wong, W.-L.; Lee, W.-S.; Kwong, H.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 1485.

the oxygen atom with various metal cations. For example, Nakajima[19] developed an asymmetric catalytic procedure for the enantioselective conjugate addition of thiophenols to α,β-unsaturated carbonyl compounds catalyzed with a complex of CdI_2 and the N-oxide ligand shown in Scheme 1.4.



Scheme 1.4. Asymmetric enantioselective conjugate addition of thiophenols to α,β-unsaturated carbonyl compounds catalyzed by Cd(II) and chiral heteroarene N-oxides.

The synthesis of heteroarene N-oxides is usually conducted from the parent heteroarenes by utilizing strong oxidants such as, *m*-chloroperbenzoic acid (*m*CPBA),[20] magnesium monoperphthalate,[21] dimethyldioxirane[22] (DMDO) or peroxycarboxylic acids generated *in situ* from inorganic peroxide salts. Although the redox potential of hydrogen peroxide is relatively high, N-oxidation of azaarene substrates with H_2O_2 is slow and activation of the O-O bond is generally required. This can be achieved with Bronsted acids via

[19] a) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun*. **2000**, 1851. b) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589.

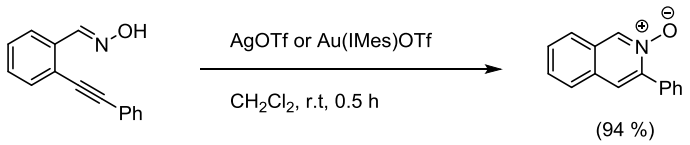
[20] For some selected examples, see: a) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgare, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792. b) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842.

[21] Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.

[22] Murray, R. W.; Jeyaraman, R. *J. Org. Chem*. **1985**, *50*, 2847.

protonation, employing transition metal catalysts such as Fe,[23] Mo[24] and Re[25] among others,[26] or using hydrogen peroxide complexes of urea[27] or sodium perborate.[28]

Finally, azaarene N-oxides are also accessible, via ring closing reactions, from substrates that already incorporate a nitrogen-oxygen bond. As an example, isoquinoline N-oxides can be synthesized from *ortho*-alkynylbenzaldoximes using a cationic gold (I) catalyst or silver triflate,[29] as shown in Scheme 1.5.



Scheme 1.5. Direct formation of an isoquinoline N-oxide from an *ortho*-alkynylbenzaldoxime.

1.1.2 1,2,3-Triazole N-oxides

Five-membered azole N-oxides and, more particularly 1,2,3-triazoles, constitute a family of aromatic nitrogenated compounds formally derived from 1-hydroxy-1,2,3-triazole

[23] Sullivan, S. Z.; Ghosh, A.; Biris, A. S.; Pulla, S.; Brezden, A. M.; Collom, S. I.; Woods, R. M.; Munshi, P.; Schnackenberg, L.; Pierce, B. S.; Kannarpady, G. K. *Chem. Phys. Lett.* **2010**, *498*, 359.

[24] a) Gonçalves, D. A. F.; Alvim, R. P. R.; Bicalho, H. A.; Peres, A. M.; Binatti, I.; Batista, P. F. R.; Teixeira, L. S.; Resende, R. R.; Lorençon, E. *New. J. Chem.* **2018**, *42*, 5720. b) Yang, C.; Zhao, W.; Cheng, Z.; Luo, B.; Bi, D. *RSC Adv.* **2015**, *5*, 36809. c) Larionov, O. V.; Stephens, D.; Mfuh, A. M.; Arman, H. D.; Naumova, A. S.; Chavez, G.; Skenderi, B. *Org. Biomol. Chem.* **2014**, *12*, 3026.

[25] a) Campeau, L. C.; Stuart, D. R.; Leclerc, J.–P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.–Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc*. **2009**, *131*, 3291. b) Copéret, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740. c) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *Tetrahedron Lett.* **1996**, *37*, 805.

[26] For other selected examples, see: a) Zhao, W.; Wang, X.; Yang, C. *Synth. Commun*. **2014**, *44*, 150. b) Ding, Y.; Zhao, W.; Song, W.; Zhang, Z.; Ma, B. *Green Chem.* **2011**, *13*, 1486. c) Bamoharram, F. F.; Heravi, M. M.; Roshani, M.; Abrishami, F. *J. Mol. Catal. A: Chem*. **2007**, *267*, 241. d) Thellend, A.; Battioni, P.; Sanderson, W. Mansuy, D. *Synthesis* **1997**, 1387.

[27] a) Rong, D.; Phillips, V. A.; Rubio, R. S.; Ángeles Castro, M.; Wheelhouse, R. T. *Tetrahedron Lett.* **2008**, *49*, 6933. b) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189.

[28] McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145.

[29] Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, *6*, 924. For some examples utilizing AgOTf, see: a) Wang, T.; Li, R.; Yu, D.; Gu, C.; Xiong, F.; Chen, Z. *Synthesis* **2014**, *46*, 3213. b) Li, Y.; Gao, L.; Zhu, H.; Li, G.; Chen, Z. *Org. Biomol. Chem.* **2014**, *12*, 6982. c) Zhao, X.; Fan, W.; Miao, Z.; Chen, R. *Synth. Commun.* **2013**, *43*, 1714.

(Figure 1.2). This N-hydroxylic triazole possesses two stable N-oxide tautomers that are the parent compounds of two families of substituted 1,2,3-triazole N-oxides. The nomenclature of these compounds is obvious in the case of substituted 2*H*-1,2,3-triazole N-oxides; however, it deserves some comment in the case of 1*H*-1,2,3-triazole N-oxides since, according to the IUPAC nomenclature, the N-H position in the parent tautomer takes numbering preference over the N-O position.[30]

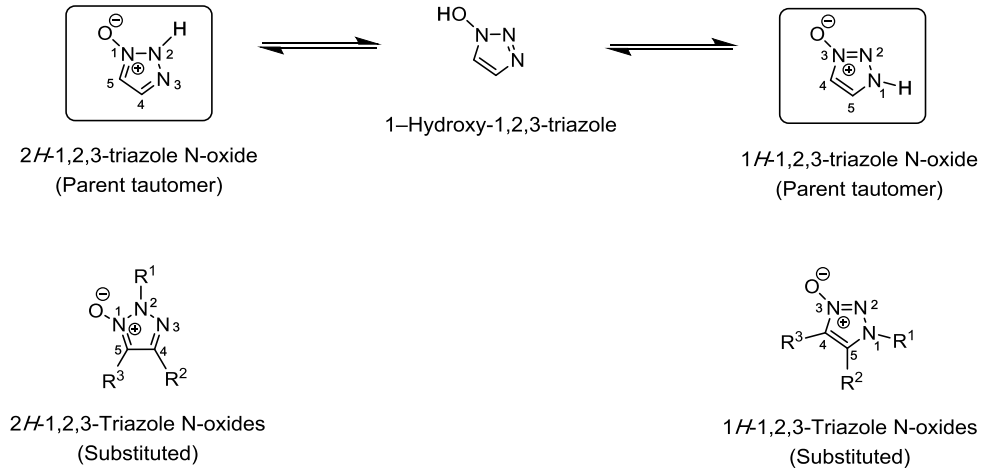


Figure 1.2. General framework of substituted 1,2,3-triazole N-oxides, including their IUPAC ring numbering based on the parent tautomer hydrogen position.

Synthetic developments in the realm of 1,2,3-triazole N-oxides have received comparatively less attention than, for example, the chemistry of pyridine-based heteroarene N-oxides. This fact is not surprising and can be explained, in part, by the difficulty to obtain both 1*H*-1,2,3-triazole N-oxides and 2*H*-1,2,3-triazole N-oxides bearing a wide variety of substituents by the direct N-oxidation of the corresponding preformed heteroarenes. In the case of 2*H*-1,2,3-triazole N-oxides this drawback has been partially solved by conducting the synthesis from non-triazolic materials (see next Section), but in the case of 1*H*-1,2,3-triazole N-oxides, this alterative remains currently inviable or extremely limited at a preparative scale.

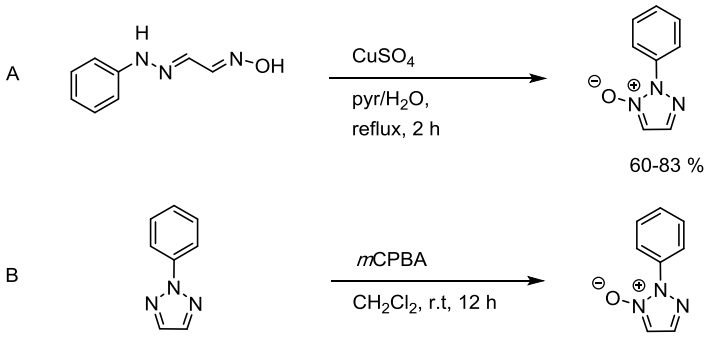
Paradoxically, polysubstituted 1*H*-1,2,3-triazoles have become much more popular compounds than the 2*H*-tautomer counterparts, pushed by the development of the "click" chemistry during the last two decades. Actually, 1*H*-1,2,3-triazoles have been widely

[30] Begtrup, M. *Adv. Heterocycl. Chem*. **2012**, 106, 1.

used as synthetic building blocks, organic materials[31] or therapeutic drugs[32] and the access to their N-oxides would pave the way towards new molecules with improved properties and/or novel applications.

1.1.2.1 Synthesis and general reactivity of 2*H*-1,2,3-triazole N-oxides

2*H*-1,2,3-Triazoles are typically prepared following two different methods (Scheme 1.6). On the one hand, by cyclization of glyoxylic hydrazine oximes,[33] a method limited to the synthesis of 2-aromatic-4,5-unsubstituted N-oxides (Scheme 1.6A) and, on the other hand, by direct oxidation of preformed 2*H*-1,2,3-triazoles utilizing *m*CPBA or related oxidants[34] (Scheme 1.6 B). In this case, the method is also limited to N(2)-monosubstituted 2-aryl-2*H*-1,2,3-triazoles, since the N-oxidation of 2,4-disubstituted-2*H*-1,2,3-triazoles gives rise to mixtures of regioisomeric N-oxides.



Scheme 1.6. Synthesis of 2*H*-1,2,3-triazole N-oxides.

Studies on the reactivity of 2*H*-1,2,3-triazole N-oxides have focused mostly on the formation of C-C bonds adjacent to the N-O moiety (Scheme 1.7). Since the N-oxide

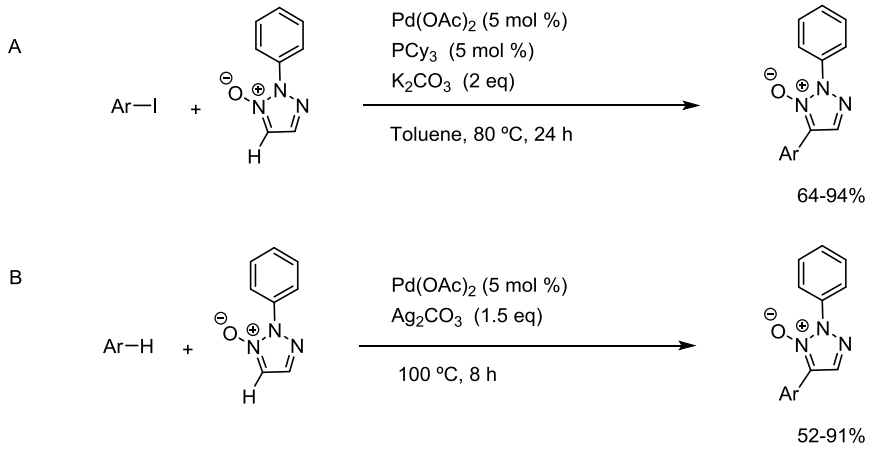
[31] a) Brunel, D.; Dumur, F. *New. J. Chem.* **2020**, *44*, 3546. b) Xiaosong, C.; Yi, S.; Haifeng, G. *Synlett* **2017**, *28*, 391. c) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689. d) Flood, A. H. *Beilstein J. Org. Chem.* **2016**, *12*, 611. e) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2010**, *39*, 2522.

[32] a) Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Yar, M. S. *Eur. J. Med. Chem.* **2017**, *125*, 143. b) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086. c) Ustyugov, A. A.; Aliev, G. M. *Russ. Chem. Bull.* **2016**, *65*, 1151. d) Alfonso, M.; Tárraga, A.; Molina, P. *Tetrahedron Lett.* **2016**, *57*, 3053. e) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* **2010**, *39*, 1388.

[33] Mikael, B.; John, H. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 503.

[34] Jha, A. K.; Jain, N. *Eur. J. Org. Chem.* **2017**, *32*, 4765.

group enhances the Brønsted acidity[35] of the proximal C-H bond, 2*H*-1,2,3-triazole N-oxides are excellent candidates to participate in Pd-catalyzed direct arylation reactions. Kuang[36] first demonstrated in 2013 the coupling of 2*H*-1,2,3-triazole N-oxides with iodoarenes *via* C-I/C-H activations (Scheme 1.7 A), and the direct coupling with arenes, *via* CH/CH dual activation (Scheme 1.7 B).



Scheme 1.7. Synthesis of disubstituted 2*H*-1,2,3-triazole N-oxides *via* palladium-catalyzed cross-coupling reactions.

These reactions will be disclosed in full detail in the introductions of chapters 3 and 5 of this thesis, at section 3.1.2.3.1 and 5.1.2.2.1, respectively.

1.1.2.2 Synthesis and general reactivity of 1*H*-1,2,3-triazole N-oxides

1*H*-1,2,3-triazole N-oxides can be prepared from the corresponding preformed azaarenes by N-oxidation of 1*H*-1,2,3-triazoles (Scheme 1.8 A) or by N-alkylation of 1-hydroxy-1,2,3-triazoles[37] (Scheme 1.8 B). Alternatively, some particular 5-amino-substituted 1,2,3-triazole N-oxides can be synthesized by cyclization of triazene N-oxides[38] formed *in situ* from α-hydroxylamino-nitriles and arenediazonium salts (Scheme 1.8 C). The last

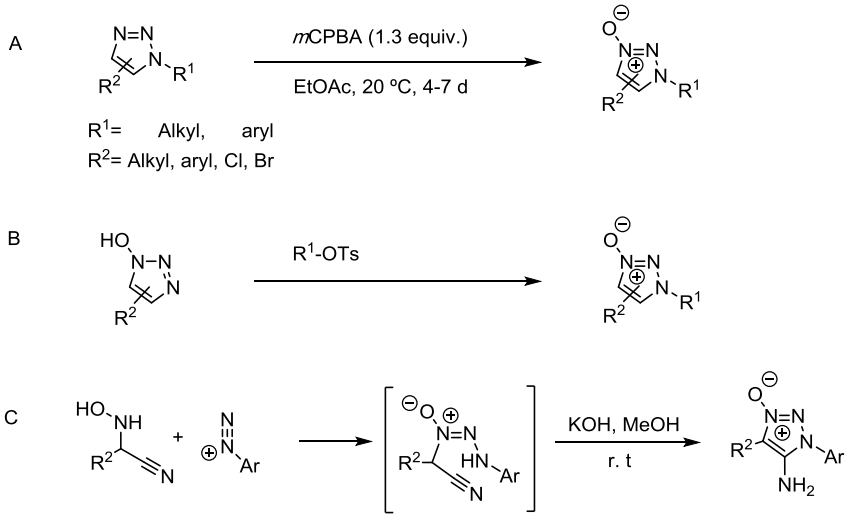
[35] a) Kreuger, S. A.; Paudler, W. W. *J. Org. Chem.* **1972**, *37*, 4188. b) Paudler, W. W.; Humphrey, S. A. *J. Org. Chem.* **1970**, *35*, 3467.

[36] a) Liu, W.; Li, Y.; Wang, Y.; Kuang, C. *Eur. J. Org. Chem.* **2013**, 5272. b) Liu, W.; Li, Y.; Xu, B.; Kuang, C. *Org. Lett.* **2013**, *15*, 2342.

[37] a) Begtrup, M.; Vedsø, P. *Acta Chem. Scand.* **1996**, *50*, 549. For other related examples, see: b) Eskildsen, J.; Vedsø, P.; Begtrup, M. *Synthesis* **2001**, 1053. c) Paulson, A. S.; Eskildsen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2002**, *67*, 3904.

[38] Zlotin, S. G.; Prokshits, O. V.; Strelenko, A. Yu.; Luk´yanov, O. A. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1992**, *10*, 1895.

two methods are subjected to important scope limitations and, from a practical viewpoint, only the direct N-oxidation of 1*H*-1,2,3-triazoles can be considered as synthetically acceptable.



Scheme 1.8. Main synthetic routes to 1*H*-1,2,3-triazole N-oxides

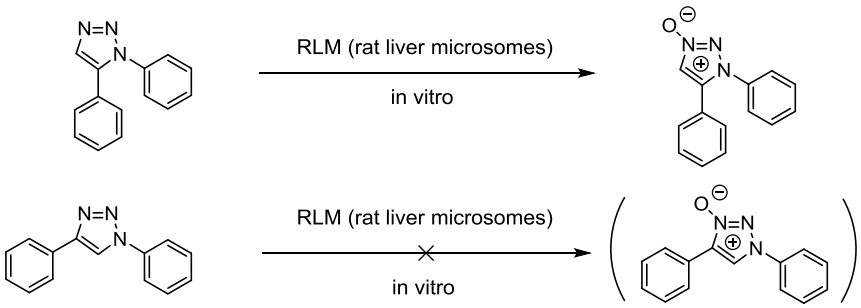
The synthesis of the first substituted 1*H*-1,2,3-triazole N-oxide was reported in 1987 by Begtrup[39], who also pioneered the chemistry of such compounds[40]. He described the direct oxidation of a few 1*H*-1,2,3-triazoles using *m*CPBA in ethyl acetate at room temperature for extensive reaction times (4 to 7 days). The reaction scope comprised a few 1-monosubstituted and 1,4-disubstituted or 1,5-disubstituted 1*H*-1,2,3-triazoles bearing groups such as phenyl, benzyl, methoxy or halogens. Reaction conversions were often low and, as expected, the reaction yields dropped drastically for triazoles substituted with electron withdrawing groups. In 2019, Cuevas-Yáñez et al[41] described a variation of the N-oxidation method claiming a wide scope and high-yielding oxidation of 1,4-disubtituted 1,2,3-triazoles using a mixture of H_2O_2 and TFA. Unfortunately, repeated attempts in our laboratory to reproduce these results, failed systematically to provide the expected triazole N-oxides (see section 2.1.2 for discussion).

[39] Begtrup, M.; Jonsson, G. *Acta Chem. Scand.* **1987**, *41*, 724.

[40] For a review, see: Begtrup, M. *Bull. Soc. Chim. Belg.* **1988**, *97*, 573.

[41] Gonzalez-Mojica, N.; Almazán-Sánchez, L.; García-Torres, J. G.; Santana-Martinez, I.; Martínez-Otero, D.; Sánchez-Carmona, M. A.; Cuevas-Yañez, E. *Synth. Commun.* **2019**, 679.

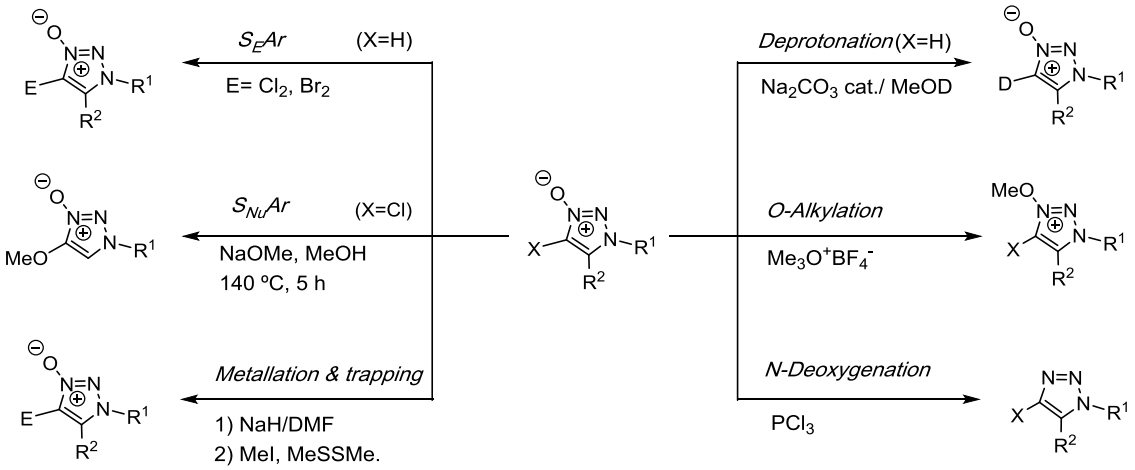
In an interesting paper exploring the pharmacokinetic properties of 1*H*-1,2,3-triazoles as potential pharmacophores for drug design, Massarotti[42] revealed the surprisingly different behavior of 1,4-diphenyl- and 1,5-diphenyl-1,2,3-triazoles when submitted to the standard rat deliver microsome metabolic test (RLM). Indeed, only the 1,5-diphenyl triazole was metabolized *in vitro* to the corresponding N-oxide, whereas the 1,4-disubstituted isomer remained unchanged under the same conditions (Scheme 1.9).



Scheme 1.9. Different outcome of 1,5-diphenyl-1*H*-1,2,3-triazole and 1,4-diphenyl-1*H*-1,2,3-triazole isomers in the *in vitro* rat liver microsome *in vitro* metabolic test.

As outlined above, Begtrup also studied the reactivity[39] of 1*H*-1,2,3-triazole N-oxides and reported electrophilic and nucleophilic aromatic substitution reactions at the carbon atom adjacent to the N-O bond when such position is unsubstituted or halogenated. Moreover, he demonstrated that 1*H*-1,2,3-triazole N-oxides can be deprotonated with NaH to form carbanions that can be trapped *in situ* with sulfur- or carbon electrophiles. Finally, the N-oxide function can be O-alkylated or N-deoxygenated, as shown in Scheme 1.10.

[42] Massarotti, A.; Aprile, S.; Mercalli, V.; Del Grosso, E.; Grosa, G.; Sorba, G.; Tron, G. C. *ChemMedChem* **2014**, *9*, 2497.



Scheme 1.10. Examples of reactions reported for 1*H*-1,2,3-triazole N-oxides.

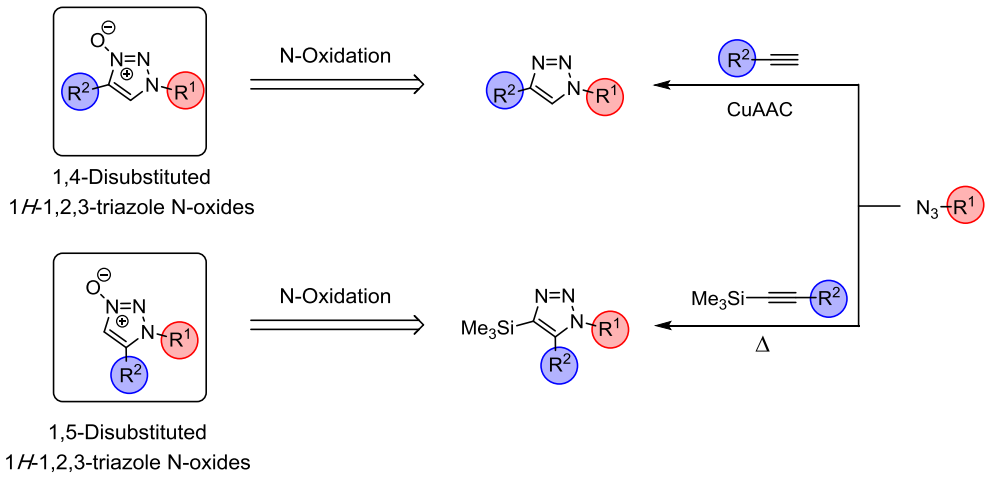
As far as we are aware, the coupling reactions of 1*H*-1,2,3-triazole N-oxides remain unreported. Therefore, at the beginning of our work, we concluded that new reliable methods to obtain diversely substituted 1*H*-1,2,3-triazole N-oxides would be highly desirable to pave the way to the study of such compounds and to develop new synthetic methods to prepare structurally complex multisubstituted and polyheterocyclic 1*H*-1,2,3-triazole N-oxides via $C(sp^2)$-$C(sp^2)$ bond formation.

1.2 General objectives

In agreement with the preceding considerations, the main subjects of this thesis will focus on the following topics:

1.2.1 Synthesis of 1*H*-1,2,3-triazole N-oxides (Chapter 2)

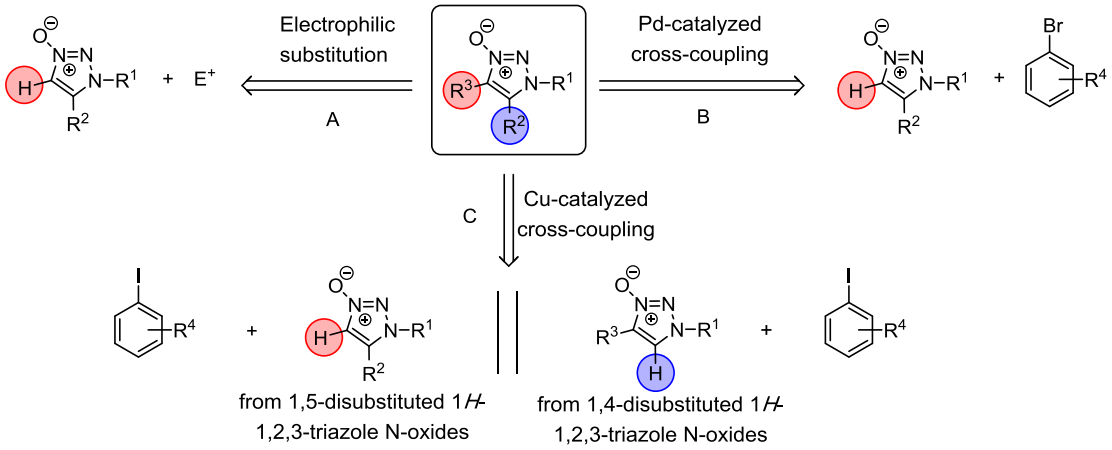
Our first goal consisted in the development of a reliable, practical and general synthetic method for the preparation of regioisomerically pure 1,4-disubstituted and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides. Different oxidizing reagents were explored to achieve the N-oxidation of the parent 1,4-disubstituted 1*H*-1,2,3-triazoles and 4-trimethylsilyl-1,5-disubstituted 1*H*-1,2,3-triazoles under mild conditions and seeking for maximized reaction conversions.



Scheme 1.11. Regiocontrolled synthesis of disubstituted 1*H*-1,2,3-triazole N-oxides.

1.2.2 Palladium- and copper-catalyzed C-H bond direct arylation reactions of 1*H*-1,2,3-triazole N-oxides (Chapter 3)

This chapter comprises three complementary approaches intended to the preparation of 1,4,5-trisubstituted 1*H*-1,2,3-triazole N-oxides. The first one (Scheme 1.12 A) involves the deprotonation/electrophilic capture at the position adjacent to the N-oxide moiety and is expected to be particularly suitable to form $C(sp^3)$-$C(sp^2)$ bonds. The second one (Scheme 1.12 B) covers the first study of the palladium-catalyzed direct arylation reaction of 1*H*-1,2,3-triazole N-oxides with haloarenes. Finally, in the third access (Scheme 1.12 C) is described the use of Cu(I)-catalyzed reactions to form $C(sp^2)$-$C(sp^2)$ bonds, either from 1,5-disubstituted- or 1,4-disubstituted 1*H*-1,2,3-triazole N-oxides. The chemical behavior observed in these reactions (activation, regiochemistry, etc…) is compared to the nonoxidized triazole analogs.

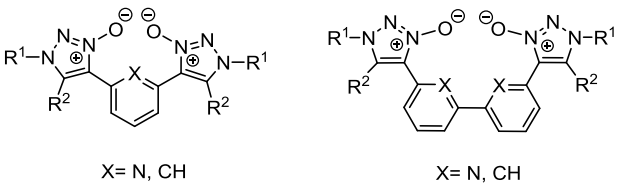


Scheme 1.12. Three different pathways (A-C) proposed for the synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides.

1.2.3 Copper-catalyzed homocoupling reactions of 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides (Chapter 4)

This chapter focuses on the synthesis of different bistriazole N-oxides. The development of symmetric 4,4'-bistriazole N-dioxides will be developed together with 5,5'-bistriazole N-dioxides.

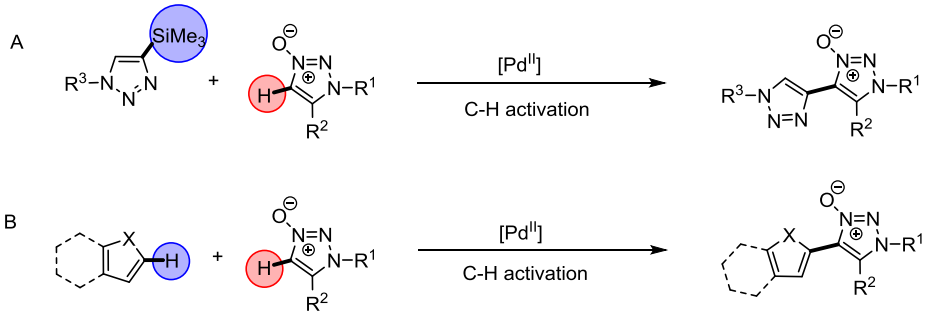
Furthermore, this chapter would also developed the synthesis of different biaryl bistriazole type N-dioxides. It would be a new family of ligands that could be used in organocatalysis or transition metal catalysis as depicted in Scheme 1.13.



Scheme 1.13. Triazole N-oxide based different ligands.

1.2.4 Palladium-catalyzed coupling reactions of 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides *via* C-Si activation and C-H/C-H dual activation (Chapter 5)

In the last chapter, the coupling between triazole N-oxide and 4-trimethylsilyl-1,2,3-triazoles would lead to a new family of 4,4'-unsymmetric polysubstituted bistriazole N-oxides (Scheme 1.14 A). Furthermore, a double CH activation would allow the synthesis of 1,4,5-trisubstituted triazole N-oxides, and complex triazoles that cannot be prepared from standard cycloaddition reactions (Scheme 1.14 B).



Scheme 1.14. CH activation of 1,5-disubstituted triazole 1*H*-1,2,3-triazole N-oxides.

2

N-Oxidation of 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazoles

2. N-Oxidation of 1,4- and 1,5-disubstituted 1*H*-1,2,3- triazoles.

2.1 Introduction

2.1.1 Disubstituted 1*H*-1,2,3-triazoles

Although the 1*H*-1,2,3-triazole structural motif does not occur in Nature, in the last decades many compounds containing such heterocyclic moiety have attracted much interest and have been utilized in different research areas such as medicinal chemistry,[43,32] material science[31] and optoelectronics[44] among others. For example, the remarkable chemical stability of 1*H*-1,2,3-triazoles and their easy synthetic accessibility[45] are routinely exploited in drug discovery programs aimed to treat diseases and conditions such as, cancer,[32a] malaria[46] or microbial[47] infections (Figure 2.1).

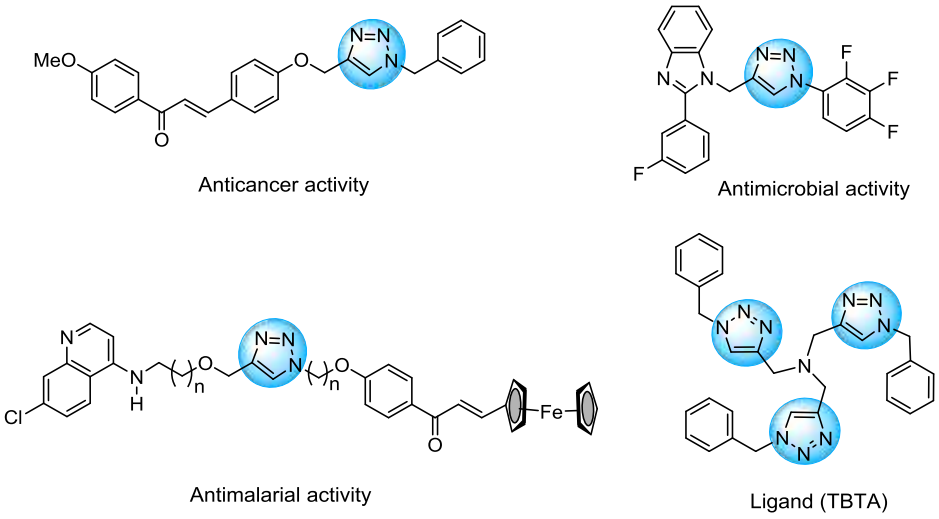


Figure 2.1. Illustrative examples of 1,4-disubstituted 1*H*-1,2,3-triazoles and their applications.

[43] For a selected review, see: a) Kumar, S.; Sharma, B.; Mehra, V.; Kumar, V. *Eur. J. Med. Chem.* **2021**, *212*, 113069. b) Bonandi, E.; Christodoulou, M. S.; Fumagalli, G.; Perdicchia, G.; Rastelli, G.; Passarella, D. *Drug Discovery Today* **2017**, *22*, 1572.

[44] a) Marrocchi, A.; Facchetti, A.; Lanari, D.; Santoro, S.; Vaccaro, L. *Chem. Sci.* **2016**, *7*, 6298. b) Dou, L.; Liu, Y.; Hong, Z.; Li, G.; Yang, Y. *Chem. Rev.* **2015**, *115*, 12633.

[45] Tomé, A. C. *Science of Synthesis;* Thieme: Stuttgart, **2015**, *13*, 415.

[46] a) Singh, A.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2017**, *125*, 269. b) Santos, J.; Pereira, G. R.; Brandão, G. C.; Borgati, T. F.; Arantes, L. M.; de Paula, R. C.; Soares, L. F.; do Nascimento, M. F. A.; Ferreira, M. R. C.; Taranto, A. G.; Varotti, F. P.; de Oliveira, A. B. *J. Braz. Chem. Soc.* **2016**, *27*, 551.

[47] Abdel-Wahab, B. F.; Khidre, R. E.; Awad, G. E. A. *J. Heterocyclic. Chem.* **2017**, *54*, 489.

On the other hand, 1*H*-1,2,3-triazoles are highly promising components for supramolecular assembling[48] and also for metal catalysis upon coordination to the metal centers as nitrogen ligands or mesoionic carbenes.[49]

2.1.1.1 Synthesis of 1*H*-1,2,3-triazoles

The first triazole was prepared by Michael[50] in 1893, but such compounds only attracted the interest of chemists several decades later, when Huisgen[51] described the thermal cycloaddition reaction of organic azides[52] and terminal alkynes. From a synthetic point of view, however, this [3+2] 1,3-dipolar cycloaddition suffers from a serious drawback, because the reaction leads to mixtures of 1,4- and 1,5- regioisomers (Scheme 2.1 A). As a solution to this problem, Meldal[53] and Sharpless[54] independently implemented in 2002 the use of *in situ* generated Cu(I) species as efficient catalysts to get 1,4-disubstituted 1*H*-1,2,3-triazoles in a fully regioselective manner (Scheme 2.1 B). This Cu-catalyzed cycloaddition reaction represents one of the early examples of a "click" process.[55]

[48] a) Lim, J. Y. C.; Marques, I.; Thompson, A. L.; Christensen, K. E.; Félix, V.; Beer, P. D. *J. Am. Chem. Soc.* **2017**, *139*, 3122. b) Lehn, J. M. *Science* **1993**, *260*, 1762.

[49] a) Gazvoda, M.; Virant, M.; Pevec, A.; Urankar, D.; Bolje, A.; Kočevar, M.; Košmrlj, J. *Chem. Commun.* **2016**, *52*, 1571. b) Hollering, M.; Albrecht, M.; Kühn, F. E. *Organometallics* **2016**, *35*, 2980. c) Qureshi, Z.; Kim, J. Y.; Bruun, T.; Lam, H.; Lautens, M. *ACS Catal.* **2016**, *6*, 4946. d) Huang, D.; Zhao, P.; Astruc, D. *Coord. Chem. Rev.* **2014**, *272*, 145.

[50] Michael, A. *J. Prakt. Chem.* **1893**, *48*, 94.

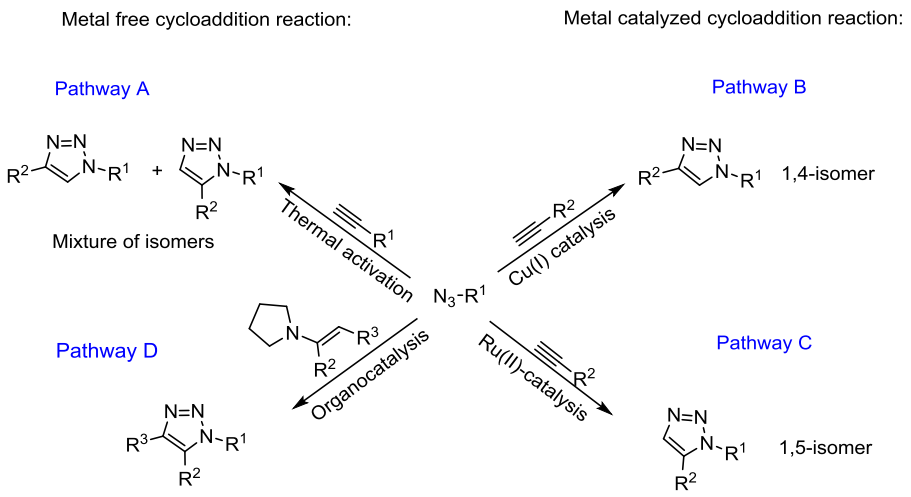
[51] Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565.

[52] Huanga, D.; Yan, G. *Adv. Synth. Catal.* **2017**, *359*, 1600.

[53] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

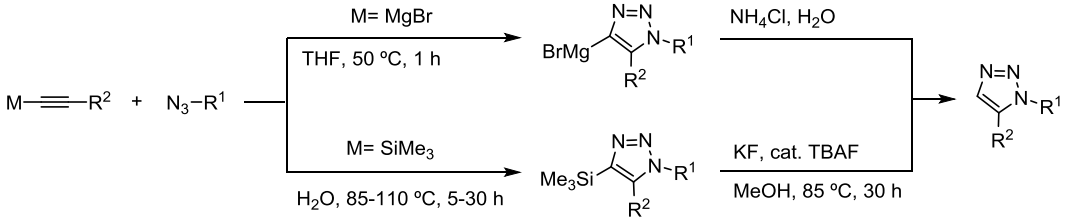
[54] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

[55] The "click" concept was introduced by the group of K. B. Sharpless to describe reactions easy to perform, modular, wide in scope and high-yielding. The experimental features required to met such conditions involve: simple reaction conditions, available starting materials and reagents, easily removable solvents, usually exothermic reactions, most of them including the formation of carbon-heteroatom bonds, and tolerance to the presence of oxygen and water. For a selected review, see: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.



Scheme 2.1. Different synthetic routes to 1*H*-1,2,3-triazoles.

Alternatively, the regiocontrolled catalytic synthesis of 1,5-disubstituted 1*H*-1,2,3-triazoles was developed by Fokin using a ruthenium-catalyzed 1,3-dipolar cycloaddition reaction[56] (Scheme 2.1 C). Previously, several other methods were reported to prepare such compounds utilizing alkynes with strong electron-donating groups (EDG), such as magnesium acetylides[57] or silylacetylenes[58] (Scheme 2.2).



Scheme 2.2. Regiocontrolled synthesis of 1,5-disubstituted-1*H*-1,2,3-triazoles from alkynes bearing electron-donating groups.

Finally, some metal-free methods[59] have been developed to prepare polysubstituted 1*H*-1,2,3-triazoles, including the Bertozzi's[60] cycloaddition reaction of strained alkynes with

[56] Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

[57] Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237.

[58] Kloss, F.; Köhn, U.; Jahn, B. O.; Hager, M. D.; Görls, H.; Schubert, U. S. *Chem. Asian J.* **2011**, *6*, 2816.

[59] For a selected review, see: Opsomer, T.; Dehaen, W. *Chem. Commun.* **2021**, *57*, 1568.

[60] a) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793. b) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046.

azides and several organocatalyzed reactions[61] of azides with enamines,[62] via enolates[63] or via iminium intermediates[64] (Scheme 2.1 D).

2.1.1.2 Thermally activated azide–alkyne 1,3-dipolar cycloaddition

The [3+2] Huisgen cycloaddition reaction is a high activation energy reaction (24-26 kcal/mol) and heating is often needed for the process to occur. Alkyl azides possess a 1,3-dipole electronic configuration characterized by the presence of a nucleophilic nitrogen atom attached to the alkyl chain and an electrophilic nitrogen atom at the terminal position, as shown in Figure 2.2.

In the next sections of this chapter we will disclose the salient mechanistic features of the azide-alkyne cycloaddition reactions described in Scheme 2.1 pathways A-C.

[61] For some selected reviews, see: a) Jalani, H. B.; Karagöz, A. Ç.; Tsogoeva, S. B. *Synthesis* **2017**, *49*, 29. b) John, J.; Thomas, J.; Dehaen, W. *Chem. Commun.* **2015**, *51*, 10797. c) Lima, C. G. S.; Ali, A.; van Berkel, S. S.; Westermann, B.; Paixão, M. W. *Chem. Commun.* **2015**, *51*, 10784.

[62] For some selected examples, see: a) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. *Chem. Commun.* **2016**, *52*, 2885. b) Wan, J.-P.; Cao, S.; Liu, Y. *J. Org. Chem.* **2015**, *80*, 9028. c) Li, W.; Du, Z.; Huang, J.; Jia, Q.; Zhang, K.; Wang, J. *Green Chem.* **2014**, *16*, 3003. d) Ramachary, D. B.; Shashank, A. B. *Chem. Eur. J.* **2013**, *19*, 13175. e) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun.* **2013**, *49*, 10187. f) Yeung, D. K. J.; Gao, T.; Huang, J.; Sun, S.; Guo, H.; Wang, J. *Green Chem.* **2013**, *15*, 2384. g) Belkheira, M.; Abed, D. E.; Pons, J.-M.; Bressy, C. *Chem. Eur. J.* **2011**, *17*, 12917. h) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. *Chem. Eur. J.* **2008**, *14*, 9143.

[63] For some representative examples, see: a) Ramachary, D. B.; Krishna, P. M.; Gujral, J.; Reddy, G. S. *Chem. Eur. J.* **2015**, *21*, 16775. b) Ramachary, D. B.; Shashank, A. B.; Karthik, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 10420. c) Ali, A.; Corrêa, A. G.; Alves, D.; Zukerman-Schpector, J.; Westermann, B.; Ferreira, M. A. B.; Paixão, W. P. *Chem. Commun.* **2014**, *50*, 11926. d) Li, W.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 14186. e) Shashank, A. B.; Karthik, S.; Madhavachary, R.; Ramachary, D. B. *Chem. Eur. J.* **2014**, *20*, 16877. f) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 13265. g) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210.

[64] Li, W.; Du, Z.; Zhang, K.; Wang, J. *Green Chem.* **2015**, *17*, 781.

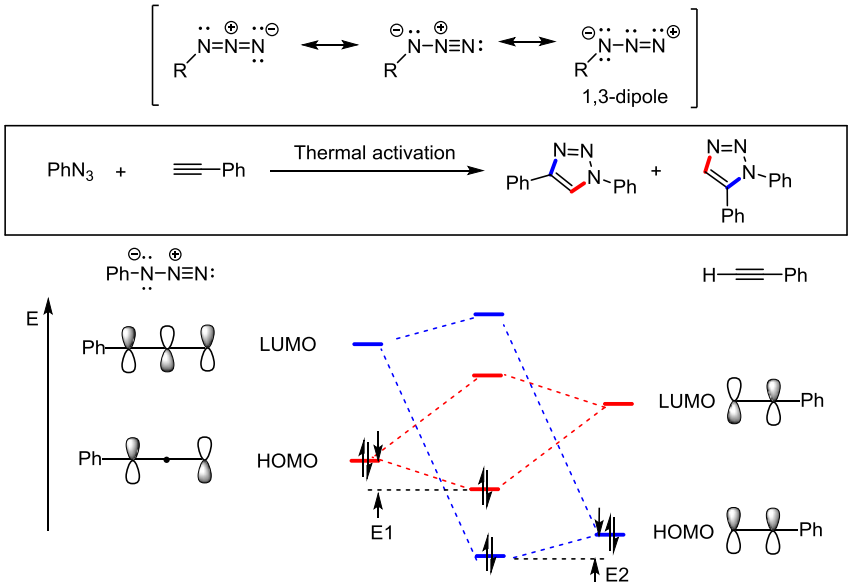


Figure 2.2. Resonance structures of organic azides and FMO interaction diagram for the azide-alkyne 1,3-cycloaddition reaction.

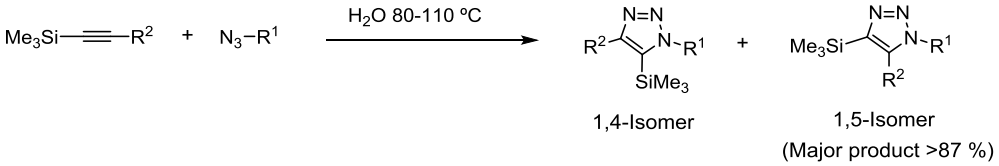
Sustmann[65] and Houk[66] applied the frontier molecular orbital (FMO) model to account for the experimentally observed 1,2,3-triazole regioisomer ratios (Figure 2.2). When the azide dipole has a high-lying HOMO which overlaps with the LUMO of the alkyne, it is referred to as *HOMO-controlled dipole* or nucleophilic dipole. In this case, the azide HOMO-raising electron-donating groups (EDG) as well as alkyne LUMO-lowering electron-withdrawing groups (EWG) increase the reaction rate and favor the 1,4-isomer. Conversely, an inverse demand FMO-interaction is possible when the azide dipole has a low-lying LUMO (*LUMO-controlled dipole* or electrophilic dipole). If the difference in energy of ΔE_1 and ΔE_2 is large, the cycloaddition is defined as asynchronous and, under such conditions, strongly electron-donating substituents (e.g. $SiMe_3$) in the alkyne component favor the formation of the 1,5-dialkyl(aryl)substituted isomer.[57,58]

Indeed, in 2011, Schubert[58] and co-workers utilized trimethylsilyl acetylenes as dipolarophiles to conduct the thermal cycloadditions shown in Scheme 2.3. The trimethylsilyl group acts as a "dummy proton" leading to 4-trimethylsilyl-1,2,3-triazoles in high selectivity. Although the regiocontrolling parameters of the trimethylsilyl group

[65] a) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569. b) Sustmann, R.; Trill, H. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 838. c) Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717.

[66] a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. c) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287.

have not been completely unraveled yet, it is considered that a combination of steric and electronic effects leads to an increase of the electrophilicity of the alkyne carbon β- to the silicon atom.[67]



Scheme 2.3. Trimethylsilyl group-directed regioselective synthesis of 1,5-disubstituted 1*H*-1,2,3-triazoles by thermal cycloaddition of silylacetylenes and alkyl azides.

2.1.1.3 Copper-catalyzed azide-alkyne cycloaddition (CuAAC)

When compared to the thermal process, the copper-catalyzed azide alkyne cycloaddition (CuAAC)[68] increases the reaction rate by a factor of 10^7 and allows the completely regiocontrolled synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles.

The first mechanistic proposal developed by Fokin and Sharpless showed that mononuclear Cu-intermediates were the key species of the process. However, further kinetic experiments[69] and computational modeling[70] revealed that the intermediacy of dinuclear species would be more likely. The mechanism[71] is shown in Scheme 2.4, in which some intermediates like **B** and **E** have been fully characterized.

The reaction starts with the coordination of Cu(I) species with the corresponding alkyne to form the intermediate **A**, enhancing the CH acidity of the terminal alkyne and thus, assisting the subsequent formation of σ, π-di copper acetylide **B**.[72] This intermediate

[67] Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett*. **2005**, *7*, 1469. b) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem*. **1994**, *59*, 6184.

[68] For selected reviews see: a) Singh, M. S.; Chowdhury, S.; Koley, C. *Tetrahedron* **2016**, *72*, 5257. b) Haldon, E.; Nicasio, M. C.; Pérez, P. J. *Org. Biomol. Chem.* **2015**, *13*, 9528. c) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev*. **2010**, *39*, 1302.

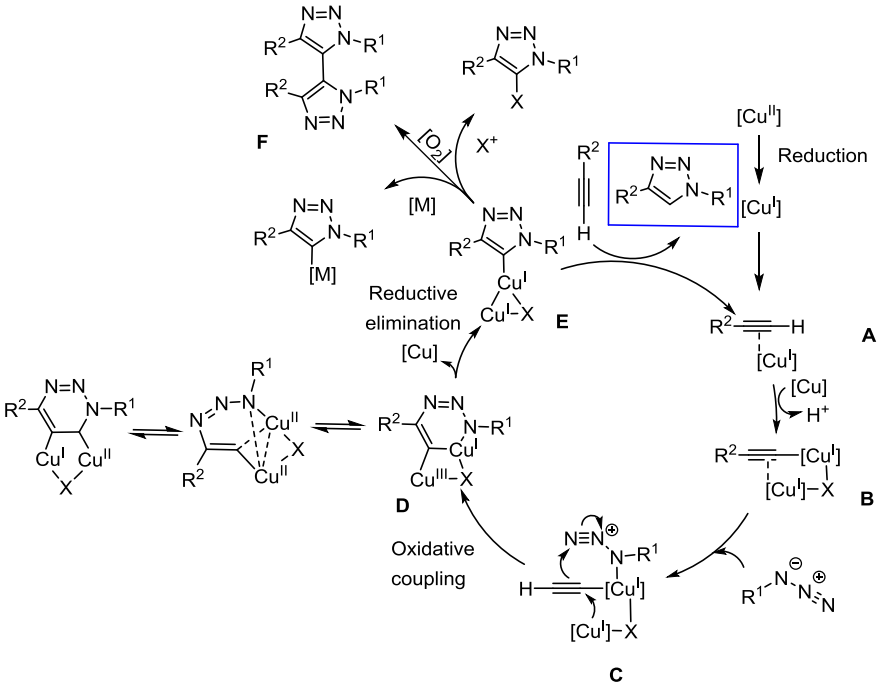
[69] a) Presolski, S. I.; Hong, V.; Cho, S.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2010**, *132*, 14570. b) Rodionov, V. O.; Presolski, S. I.; Díaz, D. D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705. c) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 2210.

[70] a) Ahlquist, M.; Fokin, V. V. *Organometallics* **2007**, *26*, 4389. b) Straub, B. F. *Chem. Commun.* **2007**, 3868.

[71] Zhu, L.; Brassard, C. J.; Zhang, X.; Guha, P. M.; Clark, R. J. *Chem. Rec.* **2016**, *16*, 1501.

[72] Jin, L.; Tolentino, D. R.; Melaimi, M.; Bertrand, G. *Sci. Adv.* **2015**, *1*, e1500304.

reacts with the azide to form the complex **C**,[73] which experiences an oxidative coupling to the metallacycle **D**, bearing one Cu(I) atom and an oxidized Cu(III) center stabilized by a chelating coordination. This six membered metallacycle undergoes a reductive elimination to the Cu(I)-bound triazolide **E**, which is protonated by the starting alkyne to the triazole product. If Cu(II) species are formed in the medium by oxidation or disprotonation of Cu(I) species, the 5,5'-bistriazoles **F** byproducts can be formed,[74] although this pathway is efficiently suppressed by adding reducing agents, such as sodium ascorbate. Finally, the intermediate copper triazolide **E** can be trapped with metal complexes or electrophilic halogen sources to give transmetallation reactions[75] or ring halogenations.[76]



Scheme 2.4. Mechanistic outcome of the CuAAC reaction.

[73] a) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457. b) Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 2101.

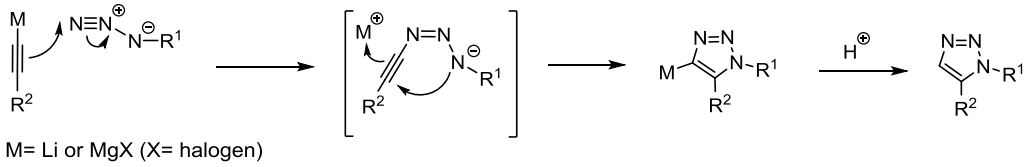
[74] a) González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corona, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011**, *52*, 3514. b) Angell, Y.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.

[75] Liu, S.; Müller, P.; Takase, M. K.; Swager, T. M. *Inorg. Chem.* **2011**, *50*, 7598.

[76] Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503.

2.1.1.4 Ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC)

Early reports to synthesize 1,5-disubstituted 1*H*-1,2,3-triazoles involved the use of several metal acetylides,[77] like Sn, Ge, Si and Na. Subsequent studies by Akimova[78] in the 1960s extended the process to the use of highly reactive lithium and magnesium acetylides. The reaction occurs via nucleophilic attack of the metal acetylide to the electrophilic terminal nitrogen atom of the azide, followed by ring closure to form the corresponding 4-metallo-1,2,3-triazole, which is subsequently protonated during the acidic work-up to afford 1,5-disubstituted 1*H*-1,2,3-triazoles as shown in the following scheme.



Scheme 2.5. Proposed mechanism for the synthesis of 1,5-disubstituted 1*H*-1,2,3-triazoles via cycloaddition of alkyl azides with lithium or magnesium acetylides.

The main disadvantages of this reaction are the incompatibility of the strongly basic conditions used with many organic functional groups and the need to employ stoichiometric amounts of metal to form the acetylides. To overcome these drawbacks, in 2005 Fokin developed a catalytic azide-alkyne cycloaddition reaction promoted by ruthenium (RuAAC).[56]

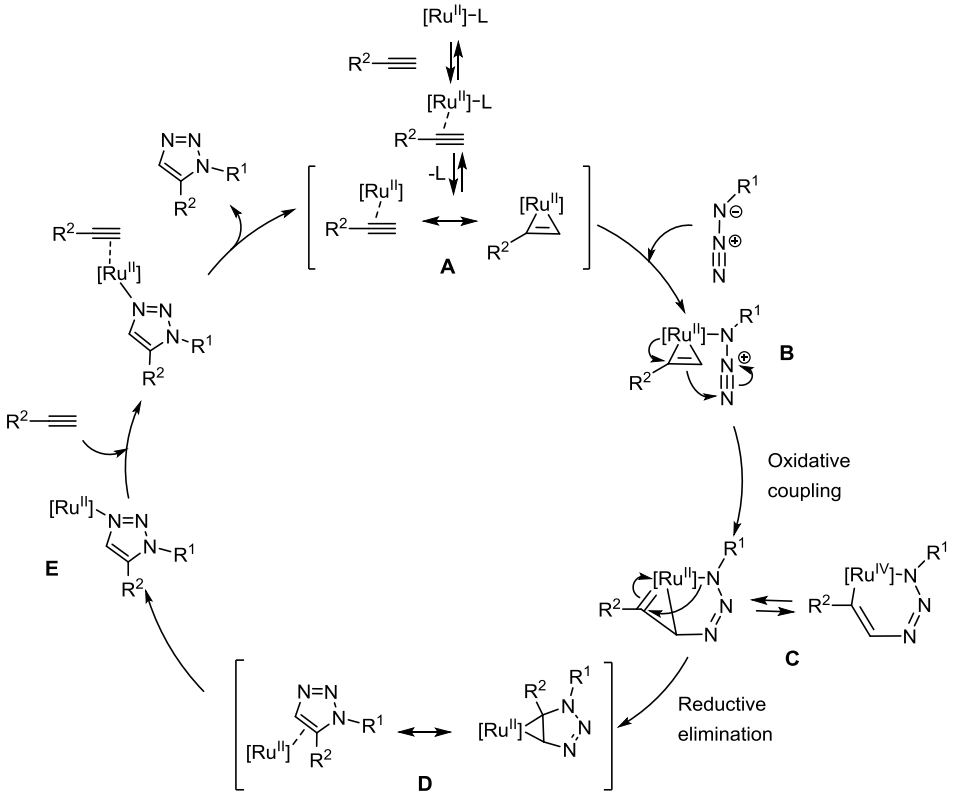
Typical RuAAC reactions are catalyzed by the complexes having the general formula Cp*Ru(L)X and are conducted in nonprotic solvents.[79] Although heating is often required to shorten the reaction times, RuAAC reactions conducted at room temperature have also been reported using more reactive ruthenium catalysts. It should be mentioned that RuAAC reactions are conducted under harsher operative conditions than CuAAC

[77] a) Himbert, G.; Frank, D.; Regit, M. *Chem. Ber.* **1976**, *109*, 370. b) Boyer, N.; Mack, C.; Goebel, N.; Morgan, L. *J. Org. Chem.* **1958**, *23*, 1051.

[78] a) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1968**, *4*, 389. b) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1967**, *3*, 968. c) Akimova, G.; Chistokletov, V.; Petrov, A. *Zh. Obshch. Khim.* **1967**, *3*, 2241.

[79] a) Johansson, J. R.; Beke-Somfai, T.; Stålsmeden, A. S.; Kann, N. *Chem. Rev.* **2016**, *116*, 14726. b) Wang, C. L.; Ikhlef, D.; Kahlal, S.; Saillard, J. Y.; Astruc, D. *Coord. Chem. Rev.* **2016**, *316*, 1.

cycloadditions. Nevertheless, RuAAC reactions are compatible with terminal and internal alkynes, which allows the direct access to 1,4,5-trisubstituted 1*H*-1,2,3-triazoles in one synthetic operation. In the following scheme is depicted a consistent mechanism[80] for the RuAAC reaction catalyzed by [Cp*RuCl] complex which is assumed to proceed via ruthenacyclopentadiene intermediates.[81]



Scheme 2.6. Mechanistic outcome of the ruthenium-catalyzed RuAAC reaction.

The reaction starts with the formation of a 16-electron Ru complex upon ligand dissociation of the precatalyst in the presence of the alkyne leading to the π-coordinated complex **A**. Then, ligation with the internal nitrogen atom of the azide generates the intermediate **B** which, upon subsequent nucleophilic attack, provides a six membered metallacycle **C**. Then, a reductive elimination occurs to furnish the triazole-complex **D**,

[80] a) Boz, E.; Tüzün, N. Ş. *J. Organomet. Chem.* **2013**, *724*, 167. b) Lamberti, M.; Fortman, G. C.; Poater, A.; Broggi, J.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *Organometallics* **2012**, *31*, 756. c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

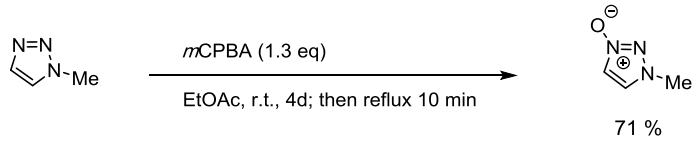
[81] Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721.

which further isomerizes to intermediate **E**. Finally, substitution with the alkyne delivers the target triazole derivative and closes the catalytic cycle.

It should be noted that the oxidative coupling controls the regioselectivity of the overall process, which is taking place between the more electronegative and less sterically-demanding carbon atom of the alkyne and the terminal nitrogen atom of the azide.

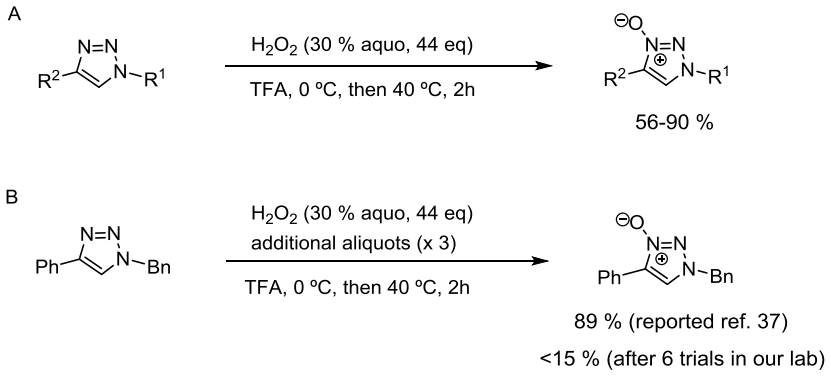
2.1.2 Methods for the synthesis of 1*H*-1,2,3-triazole N-oxides

As mentioned in the general introduction of this thesis (Section 1.1.2.2) very few reports have been published describing the oxidation of 1*H*-1,2,3-triazoles into their corresponding N-oxides. The original method for the preparation of triazole N-oxides, reported by Begtrup,[39] was totally unsuitable for synthetic purposes, because it required extremely long reaction times (4-7 days) to achieve only low to moderate yields and partial conversions (typically, 20-50 %). Just a few triazoles as, for example the N-monosubstituted 1-methyl-1*H*-1,2,3-triazole, were oxidized in an efficient way (Scheme 2.7).



Scheme 2.7. Oxidation of 1*H*-1,2,3-triazoles according to ref 37.

Accessibility to 1*H*-1,2,3-triazole N-oxides seemed finally unlocked after the recent communication by Cuevas-Yañez[41] reporting the "extremely efficient and wide scope" oxidation of 1,4-disubstituted triazoles utilizing H_2O_2-TFA as depicted in Scheme 2.8 A.

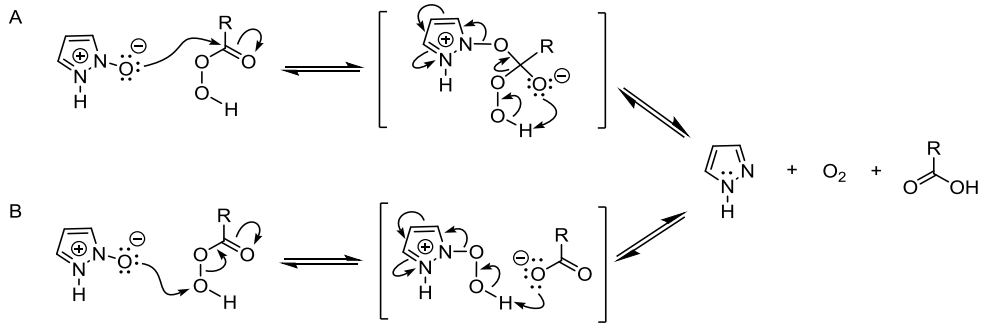


Scheme 2.8. Oxidation of 1,4-disubstituted 1*H*-1,2,3-triazoles according to ref 39.

Because of its operative simplicity, high yields and short reaction times, the method immediately attracted our attention. However, after extensive trials trying to reproduce the rather simple procedure, only very low conversions to the expected N-oxide were detected in the ^{1}H-NMR spectra of the reaction crudes. For example, as shown in Scheme 2.8 B, the prototypical 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide was systematically obtained in a maximum 15 % conversion, mixed with the unchanged starting triazole (>80 %). Following the indication of Cuevas-Yañez "*..if necessary, add 30 % H_2O_2 solution (17 eq.) every hour (maximum 5 h) to total disappearance of the starting material monitored by TLC..*" also failed to increase the conversion of the triazole N-oxide.

A detailed revision of the literature revealed that Begtrup[82] had previously screened in detail the N-oxidation of different N-substituted azoles, including 1,2,3-triazoles, with many oxidizing systems, comprising *m*CPBA, 30 %-H_2O_2/HCO_2H, 60 %-H_2O_2/HCO_2H, 60 %-H_2O_2/H_3CCO_2H, 60 %-H_2O_2/F_3CCO_2H, urea-H_2O_2/F_3CCO_2H and $NaBO_3$/*t*-$BuCO_2H$. He concluded that the most effective oxidants for 1,2,3-triazoles were *m*CPBA and 60 %-H_2O_2/HCO_2H. Both reagents provided N-hydroxy-1,2,3-triazole in 39 % yield after reaction times of 7 and 2.5 days at 20 ºC, respectively. He also confirmed the unsuitability of the hydrogen peroxide/trifluoroacetic acid system hailed by Cuevas-Yañez as "efficient". Importantly, Begtrup also realized that N-deoxygenation of the azole N-oxide products could occur when the oxidations were conducted at moderate-to-high temperatures. Under such conditions, oxygen gas was liberated when *in situ* generated peracids were used as oxidants, giving back the starting NH-azole. Furthermore, this process was enhanced by strong acids upon protonation of the azole nucleus, as illustrated for the pyrazole N-oxide by two alternative mechanisms (Scheme 2.9).

[82] Begtrup, M.; Vedsø, P. *J. Chem. Soc., Perkin Trans. 1,* **1995**, 243.

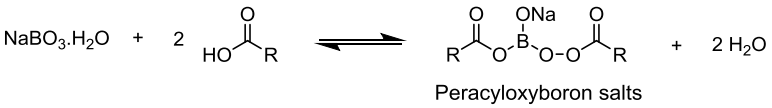


Scheme 2.9. Possible mechanisms of the deoxygenation reaction of N-oxide pyrazoles with peracids (ref 44).

2.2 Hypothesis and objectives

On the basis of the previous discussion, we regarded the development of an efficient preparative method for the obtention of 1*H*-1,2,3-triazole N-oxides with the concomitant control of the 1,4- and 1,5-disubstitution at the heterocycle nucleus as a standing synthetic challenge. Our approach to solve this problem was based on a double hypothesis.

First, we considered that nonacidic or slightly acidic peracyloxyboron salts[28], formed *in situ* from perborate salts and carboxylic acids, could oxidize 1,2,3-triazoles, while preventing or minimizing at the same time the deoxygenation reactions described by Begtrup.



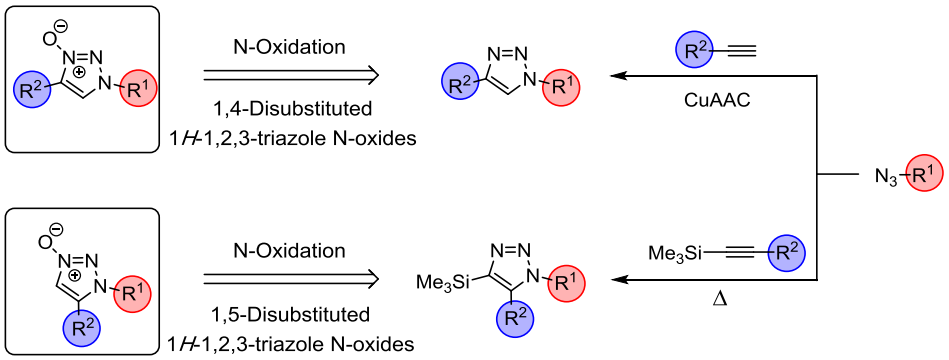
Scheme 2.10. Peracyloxyboron salts from sodium perborate and carboxylic acids.

Second, we surmised that not only 1,4-disubstituted 1*H*-1,2,3-triazoles, but also 4-trimethylsilyl-1,5-disubstituted 1*H*-1,2,3-triazoles could be suitable substrates to conduct the N-oxidation reaction to obtain directly the corresponding triazole N-oxides, since the C-desilylation of silylheteroarenes is known to be promoted by oxygen nucleophiles.[83]

Thus, we selected the following objectives for the first part of this doctoral thesis work:

[83] For some selected examples, see: a) Yao, W.; Li, R.; Jiang, H.; Han, D. *J. Org. Chem.* **2018**, *83*, 2250. b) Itami, K.; Terakawa, K.; Yoshida, J.-i.; Kajimoto, O. *J. Am. Chem. Soc*. **2003**, *125*, 6058. c) Nakanishi, H.; Sumi, N.; Aso, Y.; Otsubo, T. *J. Org. Chem.* **1998**, *63*, 8632. d) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809.

1. Design and synthesis of two sets of 1,4-disubstituted 1*H*-1,2,3-triazoles and 4-trimethylsilyl-1,5-disubstituted 1*H*-1,2,3-triazoles.
2. Study of the N-oxidation of 1*H*-1,2,3-triazoles and 4-trimethylsilyl-1*H*-1,2,3-triazoles using different oxidizing systems, including peracyloxyboron salts.



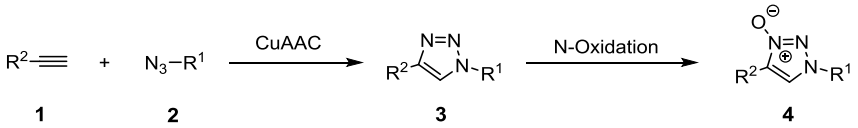
Scheme 2.11. Proposed synthesis routes to 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides.

2.3 Results and discussion

To accomplish the general goal of our schedule, we stablished a working plan consisting of two separate studies of the synthesis and oxidation of 1,4-disubstituted 1*H*-1,2,3-triazoles (section 2.3.1) and 4-trimethylsilyl-1,5-disubstituted 1*H*-1,2,3-triazoles (section 2.3.2).

2.3.1 Synthesis of 1,4-disubstituted 1*H*-1,2,3-triazole N-oxides

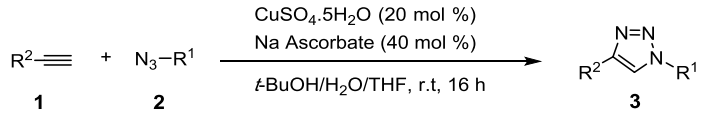
A set of representative 1,4-disubstituted triazoles **3** was first prepared following the azide-alkyne CuAAC approach and then, several oxidizing systems were tested to transform them into the corresponding N-oxides **4** (Scheme 2.12).

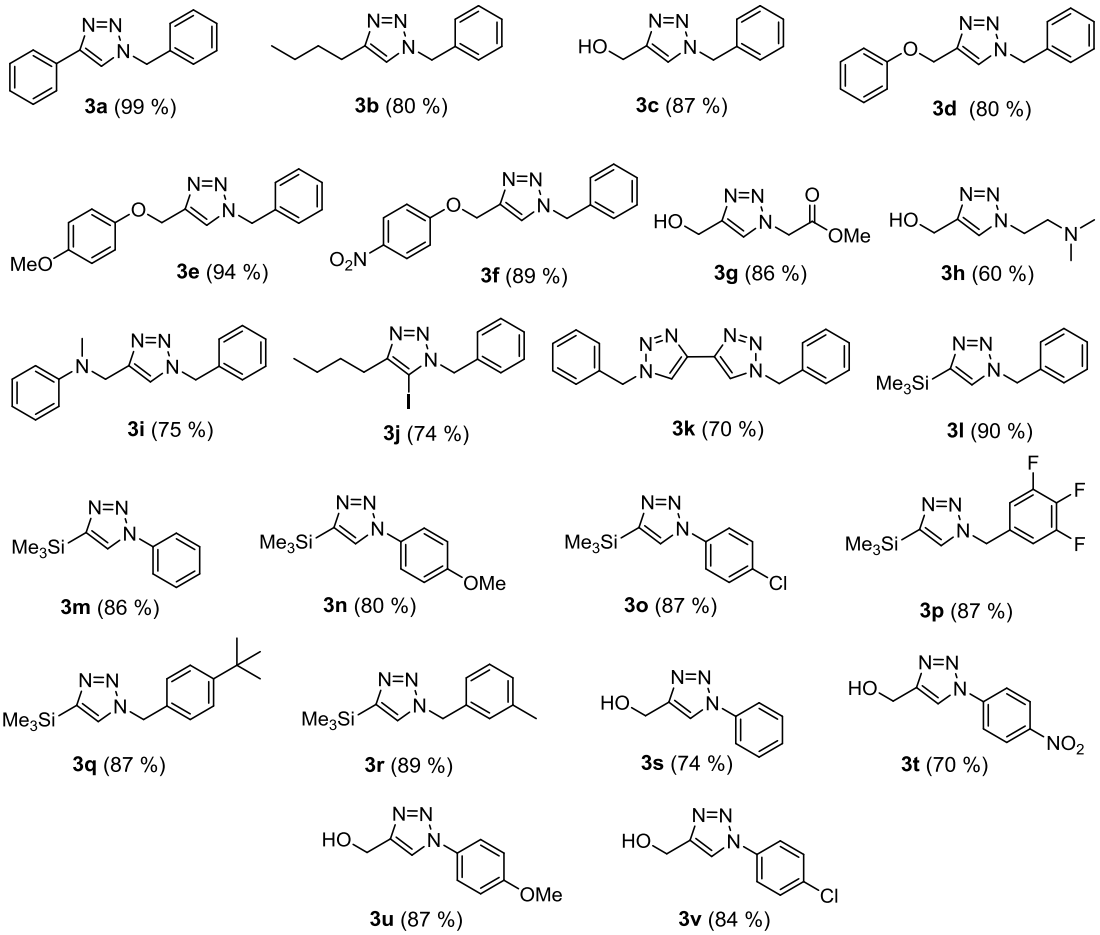


Scheme 2.12. Synthesis of 1,4-disubstituted 1*H*-1,2,3-triazole N-oxides.

As shown in Table 2.1, twenty two model triazoles **3a-v** were synthesized in good to excellent yields (60-99 %) from a variety of terminal alkynes bearing aryl, alkyl, aryloxymethyl, arylaminomethyl or silyl groups, and azides with aryl, alkyl or functionalized substituents. The reactions were carried out in gram scale under standard "click" conditions in the presence of catalytic amounts of $CuSO_4.5H_2O$ and sodium ascorbate. 5-Iodotriazole **3j** was prepared similarly, but performing the reaction under anhydrous conditions in the presence of stoichiometric amounts of a mixture of CuI and N-bromosuccinimide, which can be considered a source of electrophilic iodine.

Table 2.1. Synthesis of model 1,4-disubstituted 1*H*-1,2,3-triazoles[a]





[a]Yields of isolated pure products.

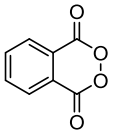
With the model triazoles in hand, we selected compounds **3a** and **3b** to study their N-oxidation reaction using several reagents and reaction conditions (Table 2.2). First, some peracid-promoted oxidations were tested (entries 1-3). Using *m*CPBA, peracetic acid or trifluoroperacetic acid generated *in situ* from 35 % hydrogen peroxide at temperatures ranging from 20 ºC to 40 ºC, led to trace conversions of **3a** to the expected triazole N-oxide **4a** in all instances. In particular, the method of Cuevas-Yañez (entry 3) provided only a 15 % conversion, albeit in a short reaction time (1h). The conversion could not be increased by prolonging the reaction time or by adding up to 5 more aliquots of the oxidant to the mixture. Attempts to carry out the oxidation with hydrogen peroxide under

the catalysis of phosphomolibdic acid[24c] (entry 4) in an ACE sealed tube at 50 ºC also met with failure.

Table 2.2. N-oxidation of 1,4-disubstituted 1*H*-1,2,3-triazoles **1a-b** under different reaction conditions[a].

3a (R^2= Ph)
3b (R^2= *n*-Bu)

4a (R^2= Ph)
4b (R^2= *n*-Bu)

Entry	Triazole	Reagent	Solvent	T (ºC)	Time (h)	Conv[a]/Yield[b] (%)
1	**3a**	*m*CPBA	EtOAc	20	24	<10 (--[c])
2	**3a**	35%-H_2O_2	Ac_2O	40	16	<5 (--[c])
3[d]	**3a**	35%-H_2O_2	F_3CCO_2H	40[e]	1[d]	15 (--[c])
4[e]	**3a**	35%-H_2O_2 (PMA 3 mol %)	MeCN	50 (ACE)[f]	24	<5 (--[c])
5	**3a**	Oxone[g]	F_3CCO_2H	20	2	<2 (--[c])
6	**3a**	Oxone	F_3CCO_2H	60	16	<5 (--[c])
7[h]	**3a**		$(CH_2Cl)_2$	80 (ACE)	24	0 (--[c])
8	**3b**	Urea-H_2O_2	AcOH	85 (ACE)	4[i]	45 (--[c])
9	**3a**	$NaBO_3.H_2O$	AcOH	90 (ACE)	24[j]	55 (45)
10	**3b**	$NaBO_3.H_2O$	AcOH	90 (ACE)	24	70 (65)
11	**3a**	$NaBO_3.H_2O$	AcOH	90	24	40 (--[c])

[a] Conversion determined by ^{1}H-NMR integration of the C$\underline{H_2}$Ph signals in the reaction crude. [b] Yields of isolated pure products; mean values of tripled experiments. [c] Not determined. [d] (ref 39) 5 additional aliquots of 35%-H_2O_2 added. [e] (ref 47) PMA: phosphomolybdic acid: $(HO)_2Mo(=O)_2$-$P(=O)(OH)_2$. [f] Reaction conducted in ACE sealed tube. [g] Oxone: $KHSO_5.KHSO_4.1/2K_2SO_4$. [h] (ref. 48). [i] Extended 24 h reaction time gave the same conversion. [j] Shorter reaction times (e. g. 8 h) led to lower conversions.

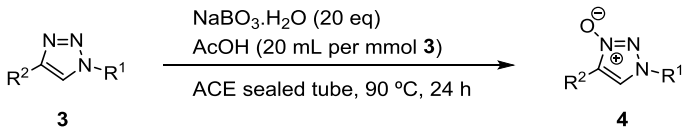
Since heating concentrated hydrogen peroxide constitutes a potentially dangerous operation for multigram scale organic reactions, we turned out our attention to more stable alternative sources of inorganic or complexed oxidizing reagent (entries 5-8). Thus, oxone (a stabilized hydrogen persulfate salt), phthaloyl peroxide PPO[84] (a source of phthaloyloxy free radical species), the urea-hydrogen peroxide complex, or sodium perborate were investigated as alternative oxidizing agents using reaction conditions involving heating at 60-90 ºC in trifluoroacetic acid, dichloroethane or acetic acid solvents. Most of these experiments resulted in the recovery of essentially unchanged materials (entries 5-7), but the combination of urea-hydrogen peroxide complex and acetic acid solvent, led, after 4 h, to a promising conversion of 45 % for the triazole **3b** (entry 8). In order to improve such conversion, the reaction time was extended to 24 h, but no amelioration was observed.

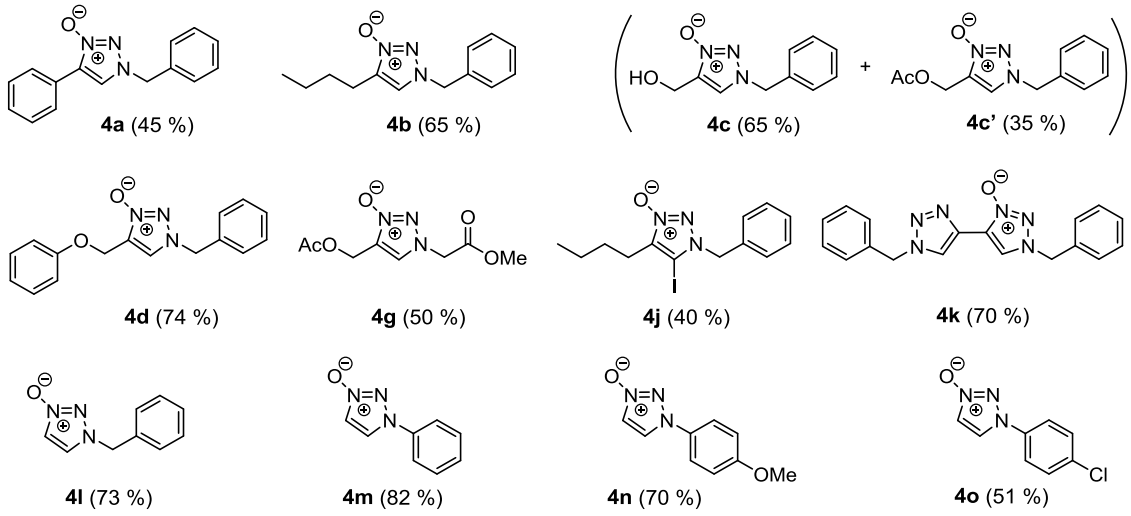
Finally, we found that sodium perborate in acetic acid was the oxidizing system of choice to get the expected triazole N-oxides **4a-b** when the reaction was conducted at 80 ºC for 24 h (entries 9-11). Lower temperatures or shorter reaction times were detrimental for the conversion and the change of a sealed ACE tube for an open flask to carry out the reaction also resulted in a slightly lower conversion (entry 11).

Next, we applied the optimized reaction conditions to perform the N-oxidation of some of the model 1,4-disubstituted 1*H*-1,2,3-triazoles, and the results are collected in Table 2.3.

[84] a) Gan, S.; Yin, J.; Yao, Y.; Liu, Y.; Chang, D.; Zhu, D.; Shi, L. *Org. Biomol. Chem*. **2017**, *15*, 2647. b) Yuan, C.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. *Tetrahedron Lett.* **2011**, *52*, 2540.

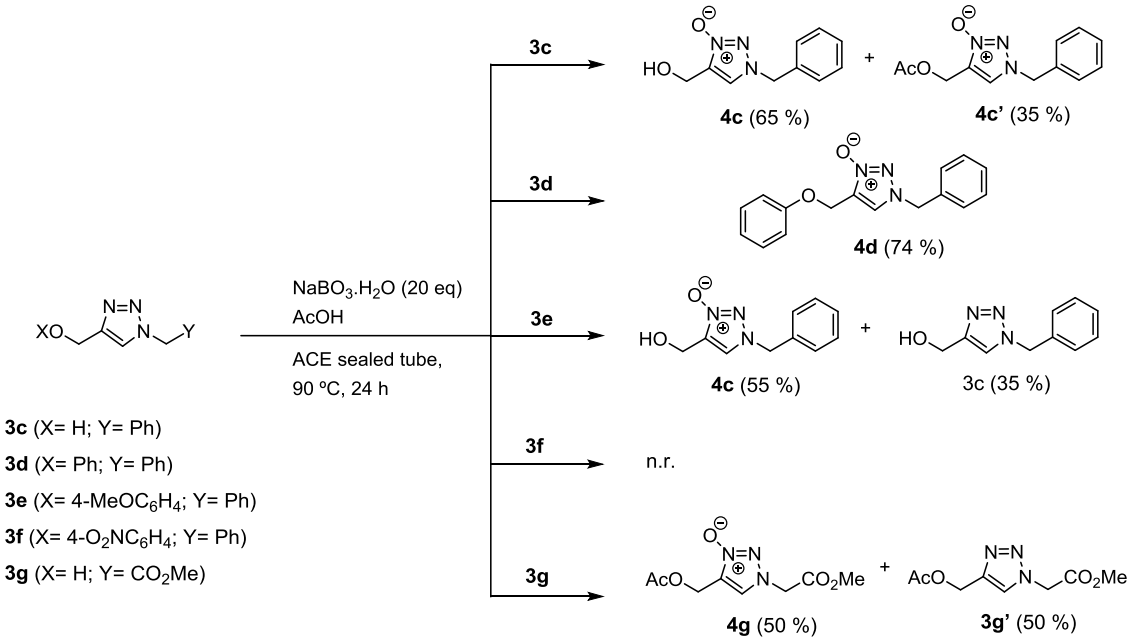
Table 2.3. Reaction scope of the synthesis of 1,4-disubstituted 1*H*-1,2,3-triazole N-oxides.





[a]Yields of isolated pure products.

The method worked fair with nonfunctionalized aryl- or alkyl-substituted triazoles (e.g. **3a-b**). However, the compatibility with hydroxylic or aryl ether functional groups was whimsical (Scheme 2.13). For example, when free hydroxylic groups were present in the substrate (e. g. **3c** or **3g**), partial or total acetylation was often observed in the N-oxide products. On the other hand, the chemical behavior of triazoles bearing aryloxy groups (e.g. **3d-f**) was strongly dependent of the presence of electron donating or electron attracting groups in the aromatic ring. Thus, while **3d** gave a clean reaction to the N-oxide **4d** in good yield, the 4-nitrophenyl analogue **3f** gave no oxidation. In contrast, the 4-methoxyphenyl analogue **3e** was degraded to a mixture of the alcohols **4c** and **3c**, suggesting that cleavage of the methoxyaryl moiety occurred before the N-oxidation of the triazole ring. This result is in full agreement with a similar report describing the oxidative O-dearylation of 4-methylphenoxy- and 4-isopropylphenoxy- ethers with peroxytrifluoroacetic acid.[41]



Scheme 2.13. Reaction scope of oxygen functionalized triazoles **3c-g**.

The NMR spectra of the starting ether **3e** and the dearylated products **4c** and **3c** are compared in Figure 2.3 and show the complete vanishment of the aromatic doublet system of the starting aryloxy group at around 6.9ppm.

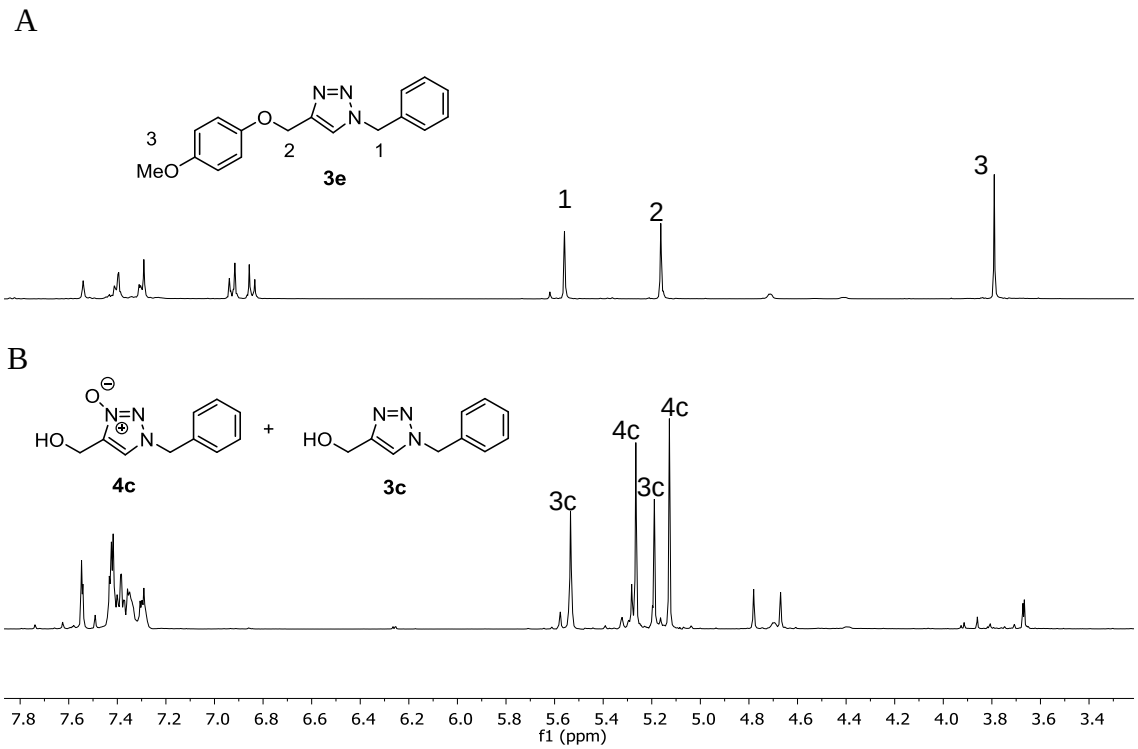
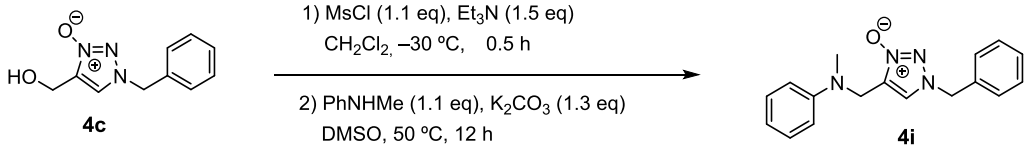


Figure 2.3. ^{1}H NMR spectra of (A) 4-(aryloxymethyl)triazole **3e**; (B) reaction crude product obtained after the oxidation of **3e**.

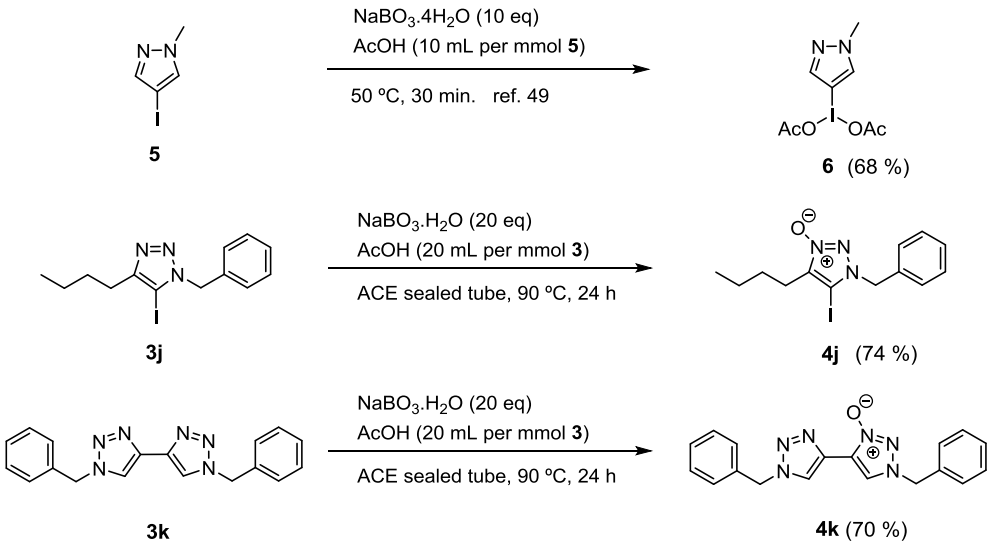
Not surprisingly, triazoles comprising tertiary amine-substituted groups (e.g. **3h**, **3i**, Table 2.1) completely decomposed under the reaction conditions, likely because of Cope-type elimination reactions undergone by the unstable tertiary amine N-oxides formed during the transformations. Nonetheless, to partially overcome this limitation, an indirect non-oxidative route to aminoalkyl triazole N-oxides (e.g. **4i**) was demonstrated by activating the hydroxyl function of **4c** as a mesylate, followed by a nucleophilic substitution with secondary amines (e.g. N-methylaniline) (Scheme 2.14).



Scheme 2.14. Non-oxidative synthesis of 1*H*-1,2,3-triazole N-oxide **4c** bearing an aminoalkyl group.

Another instance of the unexpected chemoselective behavior of functionalized 1*H*-1,2,3-triazoles was found when the 5-iodotriazole **3j** was subjected to the general oxidation conditions described above (Scheme 2.15). Literature is well documented with examples of the formation of hypervalent iodane compounds from iodoarenes and iodoheteroarenes when they are oxidized with the sodium perborate/acetic acid system.[85] Accordingly, 4-iodo-1-methyl-1*H*-pyrazole **5** has been reported to give the λ^3-iodane diacetate **6** in 68 % yield with no trace of N-oxidation byproducts.[85a] In sharp contrast with this result, iodotriazole **3j** failed to give any trace of λ^3-iodane and, instead, it formed exclusively the N-oxide **4j** in moderate yield. Other chemoselective oxidation reactions were also found when bistriazoles (e.g. **3k**) were used as substrates. Only one of the N(3) nitrogen atoms was transformed into the corresponding N-oxide, deactivating the whole conjugated system and preventing a double N-oxidation.

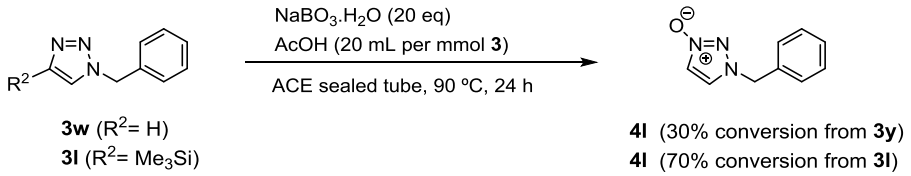
[85] a) Wu, Y.; Izquierdo, S.; Vidossich, P.; Lledós, A.; Shafir, A. *Angew. Chem. Int. Ed*. **2016**, *55*, 7152. b) McKillop, A. Kemp, D. *Tetrahedron* **1989**, *45*, 3299.



Scheme 2.15. Chemoselective oxidation reactions of 1*H*-1,2,3-triazoles.

Finally, we explored the oxidation of a few 4-trimethylsilyl substituted triazoles (e.g. **3l-o**, see Table 2.1) and found that they were transformed in a particularly clean and efficient way, although this process occurred with the concomitant loss of the trimethylsilyl group, leading to the monosubstituted 1*H*-1,2,3-triazole N-oxides **4l-o** in good to excellent yields (see Table 2.3). This fact was not totally surprising, because the oxophilic cleavage of C–Si bonds is a well-documented process.[83]

In order to briefly investigate the role played by the trimethylsilyl group in the apparent activation of the reaction, we compared in a test experiment the oxidation of 1-benzyl-triazole **3w** and its 4-trimethylsilyl-analog **3l** with sodium perborate/acetic acid to produce the N-benzyl-triazole N-oxide **4l** (Scheme 2.16)



Scheme 2.16. Activating effect of the trimethylsilyl group in the N-oxidation of 4-trimethylsilyl-1*H*-1,2,3-triazoles.

Figure 2.4 shows the ^{1}H-NMR spectra A-C corresponding, respectively, to the starting materials **3w**, **3l** and the product **4l**. It also shows the spectra of the reaction crude products obtained *via* oxidation of the 1-benzyl triazole **3w** (D) and from the desilylative oxidation of triazole **3l** (E). In the former case, the formation of the N-oxide **4l** proceeded in 30 %

conversion, while the 4-trimethylsilyl triazole **3l** gave a far superior 70 % conversion. Importantly, no trace of the 4-trimethylsilyl-triazole N-oxide was detected in the spectra, suggesting that the desilylation step of the triazole **3l** should occur either simultaneously to the N-oxidation of very fast after the N-oxidation step.

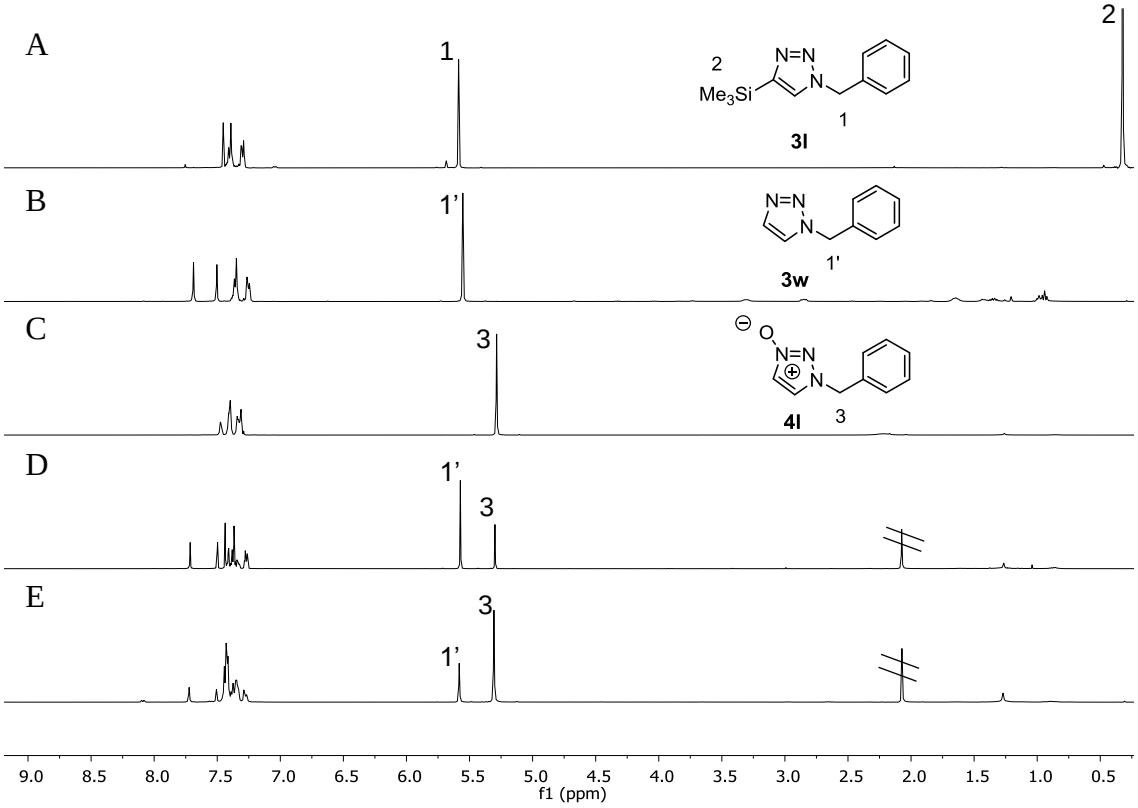


Figure 2.4. Comparison of the ^{1}H-NMR spectra of the pure substrates (A-B); triazole N-oxide product (C) and the reaction crude products obtained from the oxidation of 1*H*-1,2,3-triazole **3w** (D) and from the desilylative oxidation of 4-trimethylsilyl-1*H*-1,2,3-triazole **3l** (E).

In view of the remarkable results obtained, we decided to extend the desilylative oxidation reaction to 1,5-disubstituted triazoles and the results are described in the next section.

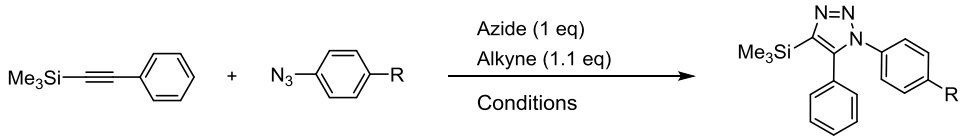
2.3.2 Synthesis of 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides

2.3.2.1 Synthesis of 1,5-disubstituted 4-trimethylsilyl-1*H*-1,2,3-triazoles

To conduct the desilylative N-oxidation experiments, we first synthesized a set of representative 1,5-disubstituted 4-trimethylsilyl-1*H*-1,2,3-triazoles **8** by reacting several azides **2** and trimethylsilylacetylenes **7** under thermal conditions. As previously mentioned in section 2.1.1.1 (Schemes 2.2 and 2.3), such reactions occur with virtually complete regioselectivity.[58] Besides, microwave activation has been proposed to

accelerate similar [2+3] cycloaddition.[86] Therefore, in order to select the optimum conditions to conduct the transformation with our substrates, we briefly studied the reaction of a couple of model arylazides with 2-phenylethynyl-trimethylsilane **7** applying several combinations of solvents, temperature and microwave activation times, as shown in Table 2.4.

Table 2.4. Screening of reaction conditions for the thermal cycloaddition of 2-phenylethynyl-trimethylsilane **7** and model arylazides **2a-b**.



7 **2a** (R=H) **2b** (R=OMe) **8a** (R=H) **8b** (R=OMe)

Entry	Substrate	Solvent	Conditions	Yield (%)[a]
1	**2b**	H_2O	85 ºC[b]	30
2	**2a**	H_2O	110 ºC[b]	45
3	**2a**	H_2O	110 ºC[b]	60
4	**2a**	H_2O	MW[c]	50
5	**2a**	Toluene	MW[c]	60

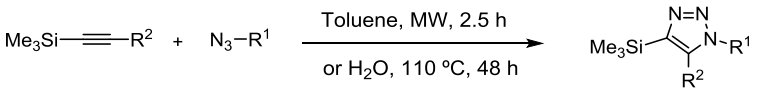
[a]Yields of isolated pure products; mean values of tripled experiments. [b]Reaction conducted in ACE sealed tube. [c]Microwave conditions.

Good conversions typically required 48 h reaction times at 110 ºC in a sealed ACE tube using water as solvent (entry 3) and final silyltriazoles were isolated as pure products in yields around 60 %. Using microwave activation significantly reduced the reaction time and rendered the transformation compatible with apolar aprotic solvents, like toluene (entry 5). Therefore, the reaction was optimized using toluene as the solvent under microwave activation conditions, albeit occasionally it was also performed using water in ACE sealed tubes when large amounts of silyltriazoles **8** were needed.

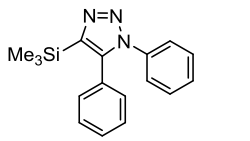
The extension of the former reaction conditions to an array of representative silylacetylenes **7** and organic azides **2** is collected in Table 2.5.

[86] Rodríguez-Rodríguez, M.; Gras, E.; Pericàs, M. A.; Gómez, M. *Chem. Eur. J.* **2015**, *21*, 18706.

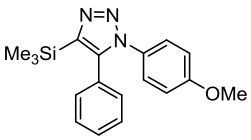
Table 2.5. Synthesis of 1,5-disubstituted-4-trimethylsilyl-1*H*-1,2,3-triazoles.



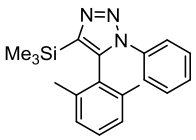
7 **2** **8**



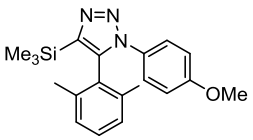
8a (60 %)



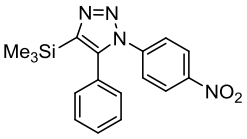
8b (60 %)



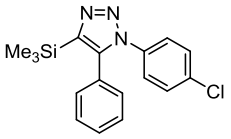
8c (60 %)



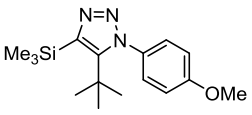
8d (60 %)



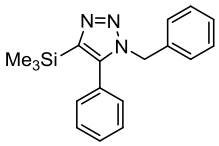
8e (70 %)



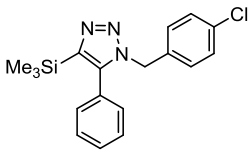
8f (70 %)



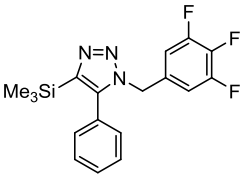
8g (40 %)



8h (90 %)



8i (90 %)



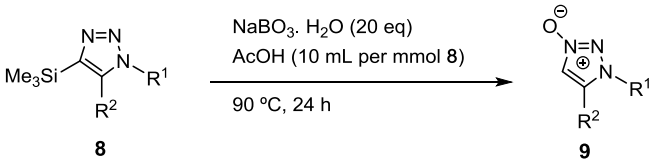
8j (50 %)

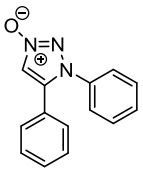
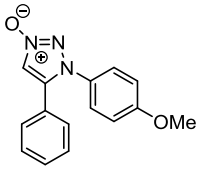
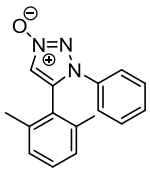
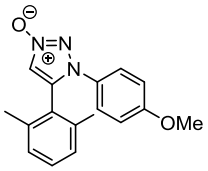
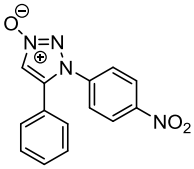
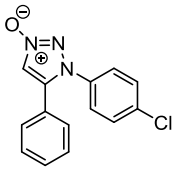
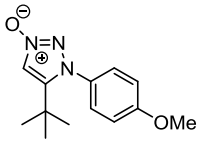
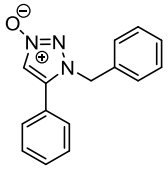
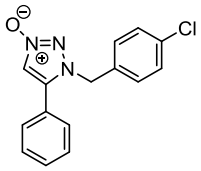
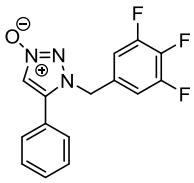
In general, the desired 1,5-disubstituted 4-trimethylsilyl-1,2,3-triazoles **8a-j** were obtained in good to excellent isolated yields as single regioisomers. As expected, the more reactive aliphatic azides provided comparatively higher yields (e.g. **8h**, **8i**), excepting for triazole **8j** bearing strongly electron-withdrawing fluorine groups.

2.3.2.2 Desilylative oxidation of 1,5-disubstituted 4-trimethylsilyl-triazoles

With a set of trimethylsilyl-triazoles **8** in hand, we undertook their desilylative oxidation to the N-oxides **9** using the sodium perborate-acetic acid reagent under the reaction conditions previously optimized for nonsilylated 1*H*-1,2,3-triazoles **4**. The results collected in Table 2.6 clearly confirmed our hypothesis that trimethylsilyl group acts as a strong activator of the reaction, as judged for the good yields and clean transformations observed in all the instances studied.

Table 2.6. Oxidation of 1,5-disubstituted-4-trimethylsilyl-1*H*-1,2,3-triazoles.[a]



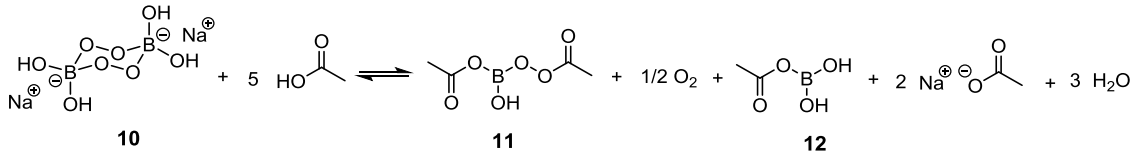
 **9a** (70 %)	 **9b** (50 %)	 **9c** (65 %)	 **9d** (70 %)
 **9e** (70 %)	 **9f** (63 %)	 **9g** (70 %)	 **9h** (70 %)
 **9i** (70 %)	 **9j** (50 %)		

[a]Yields of isolated pure products.

After a full spectroscopic characterization of the novel 1*H*-1,2,3-triazole N-oxides **9a-j** prepared, they were stored to be used as starting components in different coupling reactions through their activated C-H bond adjacent to the N-oxide moiety (see Chapter 3-5).

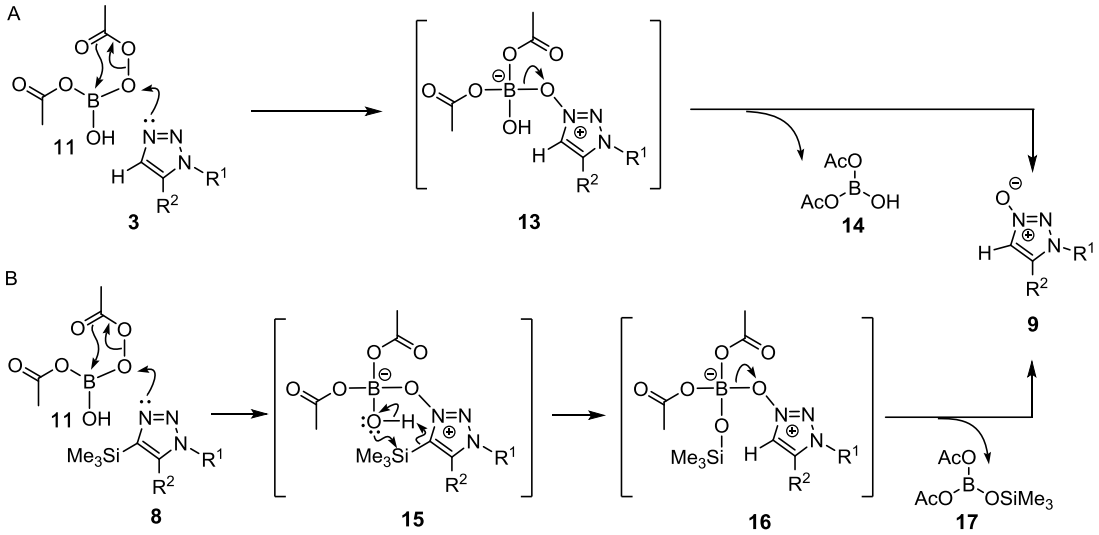
2.3.3 Mechanistic proposal of the N-oxidation reaction of 1*H*-1,2,3-triazoles

Although the detailed composition of the oxidant species generated from sodium perborate **10** in the presence of acetic acid is no totally clear, there is good evidence suggesting the formation of stabilized peracetoxyboric acid **11** and acetoxyboric acid **12** as the main equilibrium boron products, together with the release of molecular oxygen (Scheme 2.17).[28]



Scheme 2.17. *In situ* formation of peracetoxyboric acid **11** from sodium perborate.

Peracetoxyboric acid **11** can account either for the oxidation of 1*H*-1,2,3-triazoles **3** or 4-trimethylsilyl-1*H*-1,2,3-triazoles **8** to the corresponding N-oxides **9** (Scheme 2.18). In the former case (Scheme 2.18 A), the triazole N(3) atom would cleave the O-O bond in **11**, leading to the triazolium borate ester **13** which, releasing diacetoxyboric acid **14**, gives rise to the triazole N-oxide **9**.



Scheme 2.18. Comparative mechanistic proposals accounting for the peracetoxyboric acid oxidation of 1*H*-1,2,3-triazoles **4** (A), and 4-trimethylsilyl 1*H*-1,2,3-triazoles **8** (B).

In the second case (Scheme 2.18 B), a similar **11**/**8** initial interaction would lead to the C-silylated intermediate **15**, and a thermodynamically favored silatropy from the triazole

C(4) atom to the borate O atom should provide the driving force to form the intermediate **16**, which, upon elimination of the silyl borate **17**, could afford the N-oxide **9**.

2.4 Conclusions

We have demonstrated that 1,4-disubstituted 1*H*-1,2,3-triazoles can be reliably transformed into the corresponding N-oxides in fair to good yields using the sodium perborate acetic acid oxidizing system by conducting the reaction at 90 ºC over 16-24h. The scope of the reaction, as expected, excludes oxidation-sensitive groups such as amines and some aroyl ethers and is strongly dependent on the electron-donating nature of the triazole substituents. On the other hand, we have found that readily accessible 4-trimethylsilyl-1*H*-1,2,3-triazoles are particularly suitable substrates to prepare 1-substituted- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides. It has been proven that this unprecedented transformation is strongly favored by the trimethylsilyl group when compared to the protonated triazole substrates. A possible mechanistic rational of the reaction, involving the participation of peracetoxyboron species has been proposed.

3

Palladium- and copper-catalyzed C-H bond direct arylation reactions of 1*H*-1,2,3-triazole N-oxides *via* C-H bond activation

3. Palladium- and copper-catalyzed C-H bond direct arylation reactions of 1*H*-1,2,3-triazole N-oxides *via* C-H bond activation

To address the second general objective of the thesis, consisting in the transformation of 1,5- and 1,4-disubstituted triazole N-oxides into trisubstituted triazoles, we selected to explore two synthetic routes involving the activation of C-H bonds. On one hand, the base-promoted formation of metalated triazole N-oxides, followed by trapping with electrophiles, and, on the other hand, the direct C-H bond arylation reaction of triazole N-oxides with haloarenes promoted by palladium and copper catalysts.

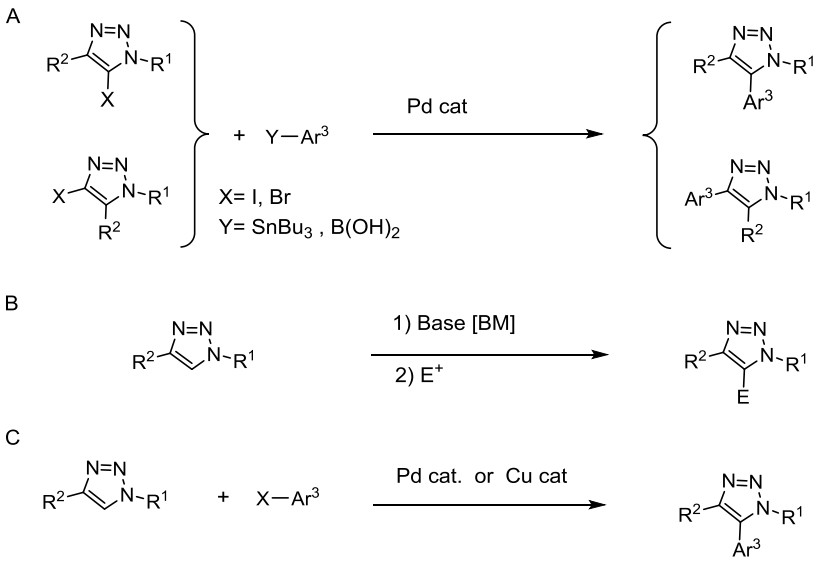
3.1 Introduction

Trisubstituted 1*H*-1,2,3-triazoles are a particularly interesting class of heteroarenes because their fully substituted framework provides wider chemical diversity when compared to the 1,4-disubstituted counterparts and, therefore, additional application opportunities.[87] For that reason, in the upcoming sections of this introduction we will briefly review the main contributions accounting for their preparative synthesis.

As outlined above in section 2.1.1.1 (Scheme 2.1 D), trisubstituted 1*H*-1,2,3-triazoles can be obtained directly from organic azides using organocatalyzed cycloaddition reactions with internal alkynes,[88] methylene ketones or 1,2-disubstituted alkenes. Unfortunately, such approach usually leads to regioisomer mixtures of trisubstituted triazoles. To overcome this limitation, it is often preferable to prepare first the 1,4-disubstituted triazoles or, in a lesser extent, the 1,5-disubstituted triazoles and transform them afterwards into the 1,4,5-trisubstituted compounds. Scheme 3.1 represents the three main synthetic approaches used to carry out such transformations.

[87] For some selected examples of biologically active 1,4,5-trisubstituted 1*H*-1,2,3-triazoles: a) Alam, M. S.; Huang, J.; Ozoe, F.; Matsumura, F.; Ozoe, Y. *Bioorg. Med. Chem.* **2007**, *15*, 5090. b) Tullis, J. S.; VanRens, J. C.; Natchus, M. G.; Clark, M. P.; De, B.; Hsieh, L. C.; Janusz, M. J. *Bioorg. Med. Chem, Lett*. **2003**, *13*, 1665.

[88] a) Wang, Z.-X.; Qin, H.-L. *Chem. Commun*. **2003**, 2450. b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *Tetrahedron Lett*. **2002**, *43*, 9707.



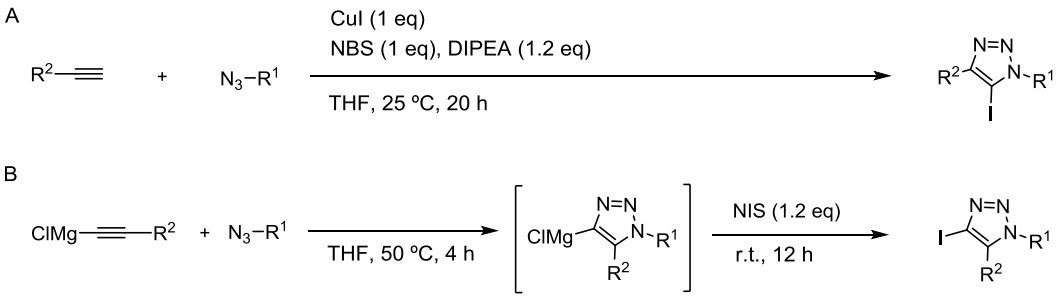
Scheme 3.1. Synthetic approaches to trisubstituted 1*H*-1,2,3-triazoles by chemical modification of disubstituted triazole precursors. (A) Palladium-catalyzed cross-coupling of halo-triazoles *via* C-X bond activation. (B) Trapping of 4-metalated 1,2,3-triazoles with electrophiles *via* C-H bond deprotonation. (C) Palladium or copper-catalyzed cross-coupling with haloarenes *via* C-H bond activation.

The first approach involves the activation of halo-triazoles with palladium catalysts through the C-X bond and the cross-coupling of the resulting palladated triazoles with aryl or vinyl trialkylstannanes or boronic acids (Scheme 3.1 A). The second approach requires the base-promoted deprotonation of the triazole ring, followed by the trapping of the resulting metalated triazole intermediate with suitable electrophiles (Scheme 3.1 B). Finally, the direct modification of 1,4-disubstituted 1,2,3-triazoles through coupling reactions, catalyzed by Pd or Cu *via* C-H bond activation, has also been used to prepare trisubstituted triazoles (Scheme 3.1 C). Taking into account their considerable operational simplicity and biger atom-economy, the last two approaches are generally preferred over the first one when efficacious preparative methods are required.

In the next sections of this introduction the salient features of each of these approaches will be disclosed and, finally, their implementation to triazole N-oxides will be also commented.

3.1.1 Palladium-catalyzed cross-coupling reactions of halo-1,2,3-triazoles

An essential requisite to use halo-1,2,3-triazoles as components for cross-coupling reactions is their availability in a regiocontrolled manner.[89] Thankfully, a few procedures have been developed to cover such need (Scheme 3.2)



Scheme 3.2. Regiocontrolled preparation of iodo-1*H*-1,2,3-triazoles.

Conducting the CuAAC reactions of azides with terminal alkynes in the presence of stoichiometric amounts of copper(I) salts and halonium sources, such as NBS[90] or ICl[91] allows an effective one-pot synthesis of 1,4-disubstituted 5-halo-1*H*-1,2,3-triazoles (Scheme 3.2 A).[92] Moreover, the reaction could also be performed directly from iodoalkynes.[93] Conversely, the reaction of organic azides with metalated alkynes,

[89] For some selected reviews, see: a) Arenas, J. L.; Crousse, B. *Eur. J. Org. Chem.* **2021**, 2665. b) Danilkina, N. A.; Govdi, A. I.; Balova, I. A. *Synthesis* **2020**, *52*, 1874.

[90] a) Gribanov, P. S.; Topchiy, M. A.; Karsakova, I. V.; Chesnokov, G. A.; Smirnov, A. Y.; Minaeva, L. I.; Asachenko, A. F.; Nechaev, M. S. *Eur. J. Org. Chem.* **2017**, 5225. b) Morris, J. C.; Chiche, J.; Grellier, C.; Lopez, M..; Bornaghi, L. F.; Maresca, A.; Supuran, C. T.; Pouysségur, J.; Poulsen, S.-A. *J. Med. Chem.* **2011**, *54*, 6905. c) Malnuit, V.; Duca, M.; Manout, A.; Bougrin, K.; Benhida, R. *Synlett* **2009**, 2123.

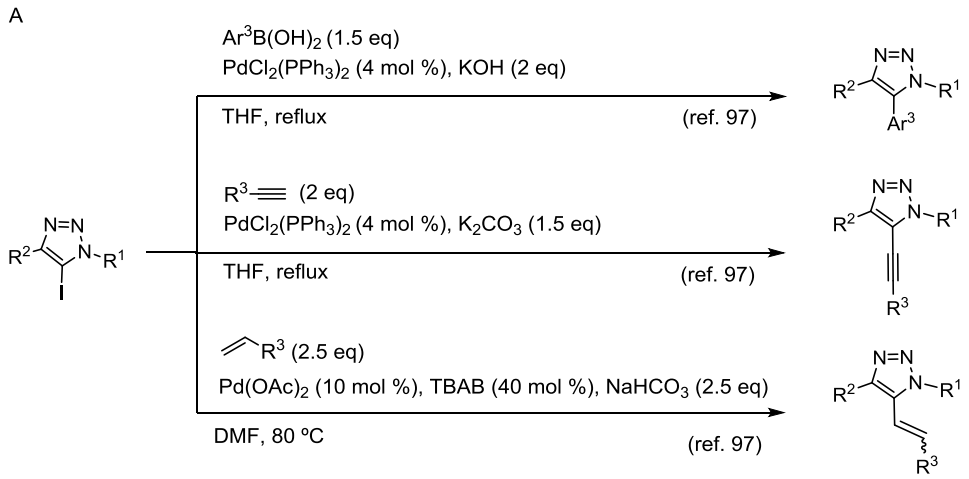
[91] Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314.

[92] a) Irastorza, A.; Aizpurua, J. M.; Correa, A. *Org. Lett.* **2016**, *18*, 1080. For other selected examples, see: b) Mayooufi, A.; Romdhani-Younes, M.; Carcenac, Y.; Thibonnet, J. *Synth. Commun.* **2019**, *49*, 2168. c) Lim, J. Y. C.; Bunchuay, T.; Beer, P. D. *Chem. Eur. J.* **2017**, *23*, 4700. d) Huang, Y.; Zhang, Y.; Yuan, Y.; Cao, W. *Tetrahedron* **2015**, *71*, 2124. e) Li, L.; Hao, G.; Zhu, A.; Liu, S.; Zhang, G. *Tetrahedron Lett*. **2013**, *54*, 6057. f) Li, L.; Zhang, G.; Zhu, A. *J. Org. Chem.* **2008**, *73*, 3630.

[93] For some selected examples, see: a) Wang, C.; Zhu, R.-Y.; Liao, K.; Zhou, F.; Zhou, J. *Org. Lett.* **2020**, *22*, 1270. b) Chung, R.; Vo, A.; Fokin, V. V.; Hein, J. E. *ACS Catal*. **2018**, *8*, 7889. c) Pérez, J. M.; Crosbie, P.; Lal, S.; Díez-González, S. *ChemCatChem* **2016**, *8*, 2222. d) Lal, S.; Rzepa, H. S.; Díez-González, S. *ACS Catal*. **2014**, *4*, 2274. e) Bédard, A.-C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 5286. f) Wang, D.; Chen, S.; Chen, B. *Tetrahedron Lett.* **2014**, *55*, 7026. g) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2009**, *48*, 8018.

followed by trapping with halonium sources, affords 1,5-disubstituted 4-halo-1*H*-1,2,3-triazoles. [94] For example, various research groups have used magnesium acetylides[95] to prepare 4-iodo-triazoles regioselectively by trapping the 4-halomagnesium triazole intermediates with N-iodosuccinimide or equivalent reagents (Scheme 3.2 B).[96]

Owing to the accessibility of the disubstituted halogenated triazoles demonstrated above, their conversion into trisubstituted triazoles using palladium-catalyzed cross-coupling reactions has been exploited since the first report by Wu (Scheme 3.3)[97]

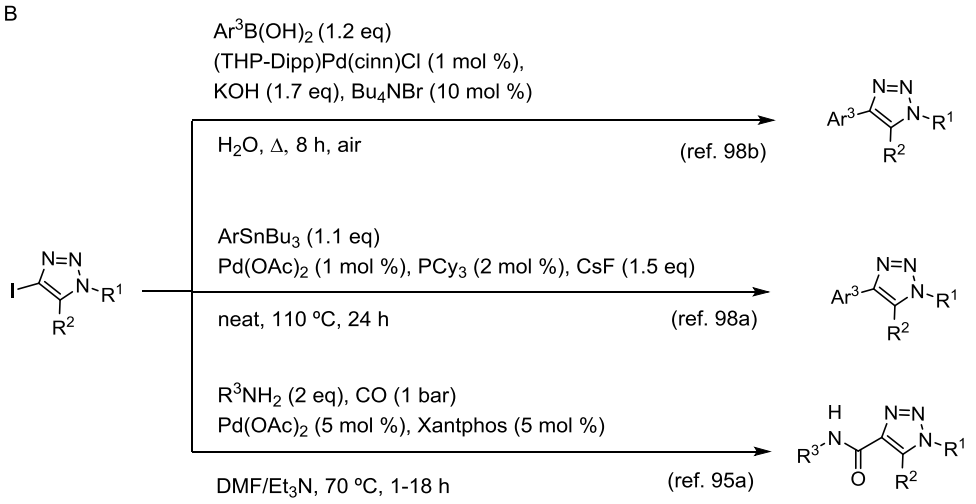


[94] For some selected examples, see: a) Zhang, J.; Chen, W.; Wang, B.; Zhao, Z.; Wang, X.; Hu, Y. *RSC. Adv.* **2015**, *5*, 14561. b) Wang, B.; Liu, N.; Chen, W.; Huang, D.; Wang, X.; Hu, Y. *Adv. Synth. Catal.* **2015**, *357*, 401. c) Worrell, B. T.; Ellery, S. P.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2013**, *52*, 13037. d) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2607; *Angew. Chem.* **2010**, *122*, 2661.

[95] For some other examples, see: a) Szuroczki, P.; Molnár, L.; Dörnyei, Á.; Kollár, L. *ChemistrySelect* **2020**, *5*, 448. b) Karsakova, I. V.; Smirnov, A. Y.; Baranov, M. S. *Chem. Heterocycl. Compd.* **2018**, *54*, 755. c) Papudippu, M.; Shu, H.; Izenwasser, S.; Wade, D.; Gulasey, G.; Fournet, S.; Stevens, E. D.; Lomenzo, S. A.; Trudell, M. L. *Med. Chem. Res.* **2012**, *21*, 4473.

[96] Karsakova, I. V.; Smirnov, A. Y.; Baranov, M. S. *Chem. Heterocycl. Compd.* **2018**, *54*, 755.

[97] Deng, J.; Wu, Y.-M.; Chen, Q.-Y. *Synthesis* **2005**, 2730.



Scheme 3.3. Examples of palladium-catalyzed cross-coupling reactions of iodo-1*H*-1,2,3-triazoles.

As illustrated in the scheme, diversely trisubstituted 1*H*-1,2,3-triazoles have been obtained after being coupled with aryl and alkenyl-substituted boronic acids (Suzuki-Miyaura reaction), alkynes (Sonogashira reaction), acrylates (Heck reaction) or organostannanes (Stille reaction).[97,98]

3.1.2 Deprotonation of disubstituted triazoles followed by trapping with electrophiles

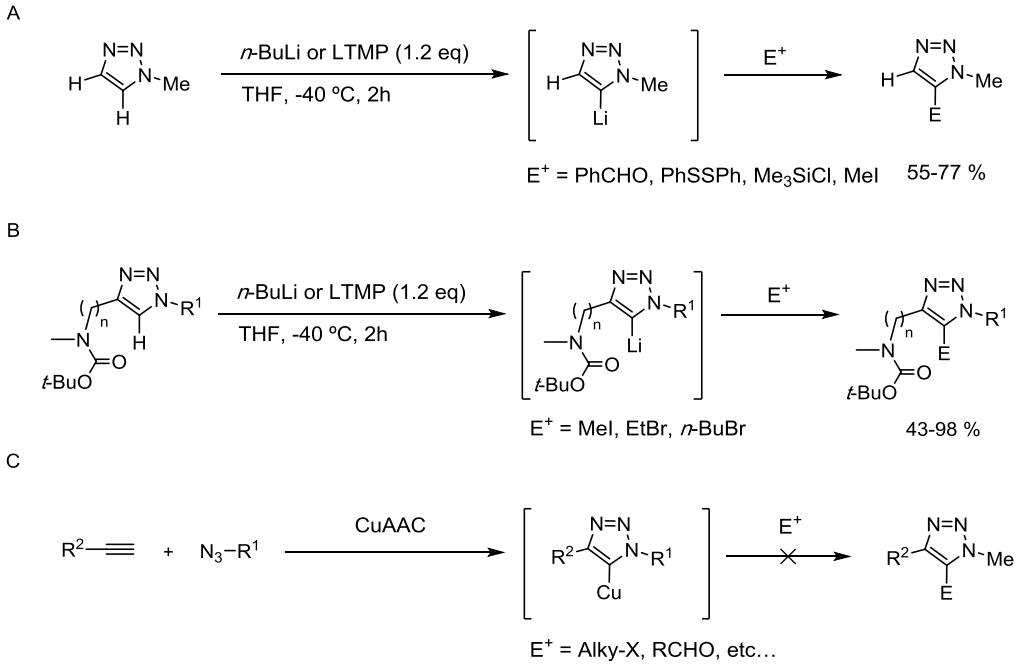
Complete deprotonation of simple triazoles is difficult and can be accomplished only with strong bases, such as, *n*-BuLi, LDA or LiTMP. Since the first lithiation reaction of 1-phenyl-1*H*-1,2,3-triazoles reported by Raap[99] in 1971, several authors have documented the selective C(5)H deprotonation[100] of N-monosubstituted triazoles and the subsequent trapping with different electrophiles (Scheme 3.4 A). Unfortunately, the deprotonation of 1,4-disubstituted 1*H*-1,2,3-triazoles only occurs successfully when non-acidic groups or

[98] For some selected examples, see: a) Gribanov, P. S.; Chesnokov, G. A.; Dzhevakov, P. B.; Kirilenko, N. Y.; Rzhevskiy, S. A.; Ageshina, A. A.; Topchiy, M. A.; Bermeshev, M. V.; Asachenko, A. F.; Nechaev, M. S. *Mendeleev Commun.* **2019**, *29*, 147. b) Gribanov, P. S.; Chesnokov, G. A.; Topchiy, M. A.; Asachenko, A. F.; Nechaev, M. S. *Org. Biomol. Chem.* **2017**, *15*, 9575.

[99] Raap, R. *Can. J. Chem.* **1971**, *49*, 1792.

[100] a) Ellis, M. J.; Stevens, M. F. G. *J. Chem. Res. (S)* **2003**, 75. b) Ohta, S.; Kawasaki, I.; Uemura, T.; Yamashita, M.; Yoshioka, T.; Yamaguchi, S. *Chem. Pharm. Bull.* **1997**, *45*, 1140. c) Uhlmann, P.; Felding, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1997**, *62*, 9177. d) Holzer, W.; Ruso, K. *J. Heterocycl. Chem.* **1992**, *29*, 1203.

when lithiation-assisting groups (e.g Boc) are placed close to the triazole ring (Scheme 3.4 B).[101] Similarly, attempts to intercept 5-cuprated-1,2,3-triazole intermediates formed during CuAAC reactions with carbon electrophiles have proven unsuccessful and they provide exclusively the C(5)-protonated products instead (Scheme 3.4 C).



Scheme 3.4. Functionalization of 1*H*-1,2,3-triazoles. (A) *via* base-promoted metalation, followed by trapping with electrophiles, (B) attempted interception of CuAAC intermediates with carbon electrophiles.

In view of the important synthetic limitations of the former procedures, more sustainable strategies based on the transition metal catalyzed direct C-H activation under mild reaction conditions have been developed during the last decade to prepare trisubstituted 1,2,3-triazoles.

[101] a) Ferroni, C.; Pepe, A.; Kim, Y. S.; Lee, S.; Guerrini, A.; Parenti, M. D.; Tesei, A.; Zamagni, A.; Cortesi, M.; Zaffaroni, N.; De Cesare, M.; Beretta, G. L.; Trepel, J. B.; Malhotra, S. V.; Varchi, G. *J. Med. Chem.* **2017**, *60*, 3082. b) Di Prieto, O.; Alencar, N.; Esteban, G.; Viayna, E.; Szalaj, N.; Vázquez, J.; Juárez-Jiménez, J.; Sola, I.; Pérez, B.; Solé, M.; Unzeta, M.; Muñoz-Torrero, D.; Luque, F. J. *Bioorg. Med. Chem.* **2016**, *24*, 4835. c) Tepper, R.; Schulze, B.; Görls, H.; Bellstedt, P.; Jäger, M.; Schubert, U. S. *Org. Lett.* **2015**, *17*, 5740. d) Lim, J. Y. C.; Cunningham, M. J.; Davis, J. J.; Beer, P. D. *Chem. Commun.* **2015**, *51*, 14640.

3.1.3 Transition metal-catalyzed direct arylation of 1,2,3-triazole C-H bonds

Transition metal-catalyzed cross-coupling techniques are powerful tools in modern organic chemistry. The major drawbacks of these reactions are the several steps that are needed to synthesize the required substrates and the production of a substantial amount of by-product waste that often accompanies them. In recent years, a new dimension has been opened as an alternative to typical cross-coupling reaction with the activation of C-H bonds utilizing transition metal catalysts.[102] The direct catalytic cleavage and transformation of C-H bonds, which are ubiquitous in organic molecules, avoids the need of preparing preactivated cross-coupling precursors (typically the organometallic species) and is replaced by an unfunctionalized (hetero)arene. Thus, fewer steps are needed for the assembly of the desired products, offering a virtually unlimited library of simple starting materials.

Direct C-H bond functionalization reactions are limited by two fundamental challenges. Firstly, the inert nature of most carbon−hydrogen bonds. As a solution to this challenge, the introduction of transition metals has been developed, which can react with C-H bonds to form new C-M bonds in a process known as "C-H activation".[103] The resulting C-M bonds are more reactive than their counterparts and they can be further converted into new functional groups. Secondly, the requirement to control site-selectivity in molecules that contain various C−H motifs.

In this way, the introduction of transition metals in the field of C-H activation was described in the literature as early as the 1960s[104]. Some years later, Trofimenko[105] introduced the term "cyclometalation" to describe the activation reaction between the

[102] For selected reviews, see: a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333. b) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Catal. A: Chem.* **2017**, *426*, 275. c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. d) Santoro, S.; Kozhushkov, S. I.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2016**, *18*, 3471. e) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2. f) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. g) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. h) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362. i) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. j) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

[103] a) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* **2017**, *117*, 8622. b) Hartwig, J. F. *Nature* **2008**, *455*, 314.

[104] Halpern, J. *Discuss. Faraday Soc*. **1968**, *46*, 7.

[105] Trofimenko, S. *Inorg. Chem.* **1973**, *12*, 1215.

metal and the C-H bond in an intramolecular fashion. These reactions are known to proceed by different mechanisms depending on the metal species, kind of substrate, and their reaction conditions, including oxidative addition, electrophilic activation, concerted metalation/deprotonation, and σ-bond metathesis. A vast array of transition metals has been used in C-H activations, such as, Pd,[106] Pt,[107] Ru,[108] Rh.[109]

However, palladium is the most widely used and investigated metal due to its own characteristics, including the three-oxidation states that facilitate the understanding of the reaction mechanism in comparison to other metals, and the easy isolations of palladium complex intermediates. Besides, Pd^{II} catalysts are of especial interest in the field of C-H activation, because they are compatible with many oxidants and functional groups.

In the upcoming sections, palladium-catalyzed and copper-catalyzed direct arylation reactions of 1,2,3-triazoles will be disclosed.

3.1.3.1 Palladium-catalyzed direct arylation reaction of 1,2,3-triazoles *via* C-H activation

Since the seminal work by Ohta,[110] the palladium-catalyzed direct arylations of heteroarenes with aryl halides has been quickly implemented to the arylation and alkenylation[111] of 1,2,3-triazoles (Scheme 3.5).

[106] a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754. b) Jiang, H.; Zhang, Y.; Chen, D.; Zhou, B.; Zhang, Y. *Org. Lett.* **2016**, *18*, 2032. c) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272.

[107] a) Kumar, M. K.; Ramaprabhu, S. J. *Phys. Chem. B* **2006**, *110*, 11291. b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859.

[108] a) Ruiz, S.; Sayago, F. J.; Cativiela, C.; Urriolabeitia, E. P. *J. Mol. Catal. A: Chem.* **2017**, *426*, 407. b) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. *Org. Lett.* **2016**, *18*, 4954.

[109] a) Chidipudi, S. R.; Burns, D. J.; Khan, I.; Lam, H. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975.

[110] a) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257. b) Akita, Y.; Inoue, A.; Yamamoto, K.; Ohta, A.; Kurihara, T.; Shimizu, M. *Heterocycles* **1985**, *23*, 2327.

[111] Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem.* **2010**, 1227.

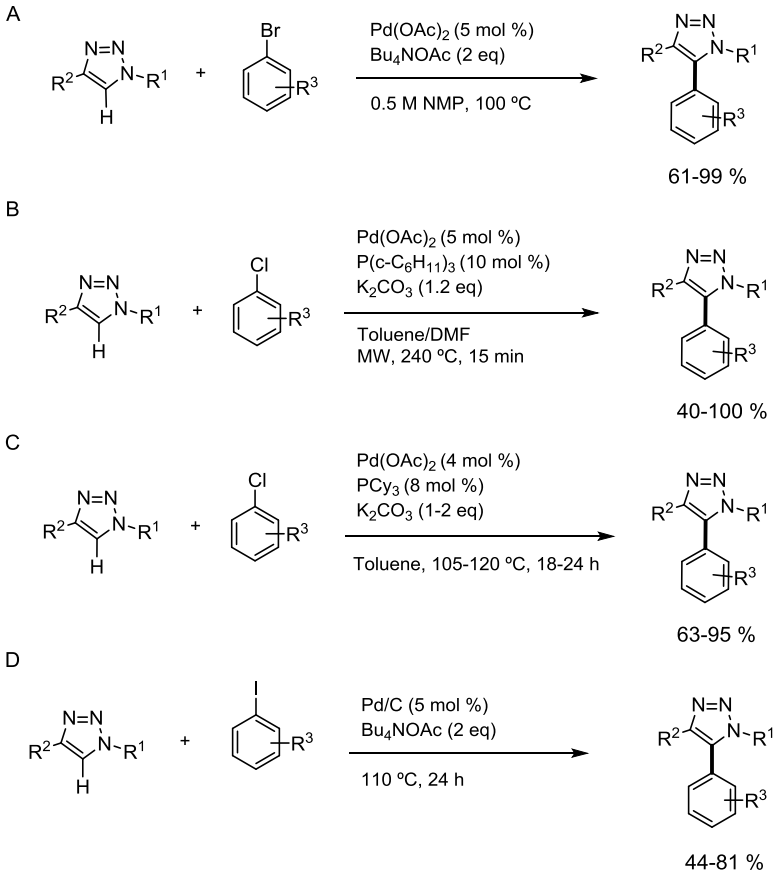
Gevorgyan[112] reported the first arylation of 1,2,3-triazoles with bromoarenes, catalyzed by palladium acetate and tetrabutylammonium acetate in NMP at 100 ºC (Scheme 3.5 A). Interestingly, when N-monosubstituted triazoles (R^2 = H) were submitted to such conditions, the corresponding 1,5-disubstituted triazoles were selectively obtained. In parallel, Oshima[113] reported the direct coupling between 1,4-disubtituted triazoles and weakly reactive chloroarenes. The combined use of tricyclohexylphosphine ligand and microwave heating at 250 ºC was necessary to complete the reactions within only 15 min (Scheme 3.5 B). However, Ackermann[114] and co-workers demonstrated that a similar transformation could be achieved under milder conditions using conventional heating at 105-120 ºC, albeit for within longer reaction periods (Scheme 3.5 C).[115]

[112] a) Chuprakov, S.; Chernyak, N, Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. For intramolecular Heck-type vinylation of 1,2,3-triazole, see: b) Chen, W.-L.; Su, C.-L.; Huang, X. *Synlett* **2006**, 1446.

[113] Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian. J.* **2007**, *2*, 1430.

[114] Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741.

[115] For some other examples of direct arylation of 1,2,3-triazoles examples, see: a) Nguyen, Q.-H.; Guo, S.-M.; Royal, T.; Baudoin, O.; Cramer, N. *J. Am. Chem. Soc.* **2020**, *142*, 2161. b) Markandeya, S. V.; Renuka, Ch.; Lakshmi, P. K.; Rajesh, A.; Sridhar, C.; Babu, K. R. *Synth. Commun*. **2018**, *48*, 135. c) Hu, L.-Q.; Deng, R.-L.; Li, Y.-F.; Zeng, C.-J.; Shen, D.-S.; Liu, F.-S. *Organometallics* **2018**, *37*, 214. d) Ahmed, J.; Chandra Sau, S.; P, S.; Kumar Hota, P.; Vardhanapu, P. K.; Vijaykumar, G.; Mandal, S. K. *Eur. J. Org. Chem.* **2017**, 1004. e) Zhang, C.; You, L.; Chen, C. *Molecules* **2016**, *21*, 1268. f) Yamajala, K. D. B.; Patil, M.; Banerjee, S. *J. Org. Chem*. **2015**, *80*, 3003. g) Wei, F.; Li, H.; Song, C.; Ma, Y.; Zhou, L.; Tung, C.-H.; Xu, Z. *Org. Lett*. **2015**, *17*, 2860. h) Luo, B.-T.; Liu, H.; Lin, Z.-J.; Jiang, J.; Shen, D.-S.; Liu, R.-Z.; Ke, Z.; Liu, F.-S. *Organometallics* **2015**, *34*, 4881. i) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novák, P.; Büttner, L. *Org. Lett*. **2010**, *12*, 2056.



Scheme 3.5. Palladium-catalyzed direct arylation reactions of 1,4-disubstituted 1*H*-1,2,3-triazoles with haloarenes.

Finally, seeking for environmentally more benign requirements to carry out these transformations,[116] Farinola[117] reported the direct arylation of 1,4-disubstituted 1,2,3-triazoles under solvent-free conditions using the Pd/C catalyst (Scheme 3.5 D).

3.1.3.2 Copper-catalyzed direct arylation reactions of 1,2,3-triazoles v*ia* C-H activation

In the last decades, the economically advantageous use of copper over other precious metals has led to a remarkable progress in the development of copper-catalyzed coupling reactions. In a pioneering work, Miura demonstrated that copper salts could change the

[116] For some selected examples, see: a) Ferlin, F.; Luciani, L.; Santoro, S.; Marrocchi, A.; Lanari, D.; Bechtoldt, A.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2018**, *20*, 2888. b) Tian, X.; Yang, F.; Rasina, D.; Bauer, M.; Warratz, S.; Ferlin, F.; Vaccaro, L.; Ackermann, L. *Chem. Commun.* **2016**, *52*, 9777. c) Ackermann. L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922.

[117] Punzi, A.; Zappimbulso, N.; Farinola, G. M. *Eur. J. Org. Chem.* **2020**, 3229.

regioselectivity of palladium-catalyzed arylations of electron-rich heteroarenes[118] and, later on, Do and Daugulis reported the Cu(I)-catalyzed C-arylation of various azole derivatives, with iodoarenes or bromoarenes in the presence of copper iodide catalyst and employing *t*-BuOLi or *t*-BuOK bases.[119]

In the realm of 1,2,3-triazoles, Ackermann[120] discovered that a single copper catalyst (CuI) could promote two sequential transformations: a) the CuAAC reaction of alkynes with *in situ* generated aryl azides and, b) the C(5)-H bond functionalization of the intermediate 1,2,3-triazoles with a second iodoarene to afford 1,4,5-trisubstituted triazoles in a chemo- and regioselective way- (Scheme 3.6 A). Similar reaction conditions were reported by Fukuzawa, using CuCl as the catalyst.[121]

In another contribution, Ackermann also described the synthesis of fully substituted 1,2,3-triazoles through an intramolecular C-H bond arylation[122] (Scheme 3.6 B).

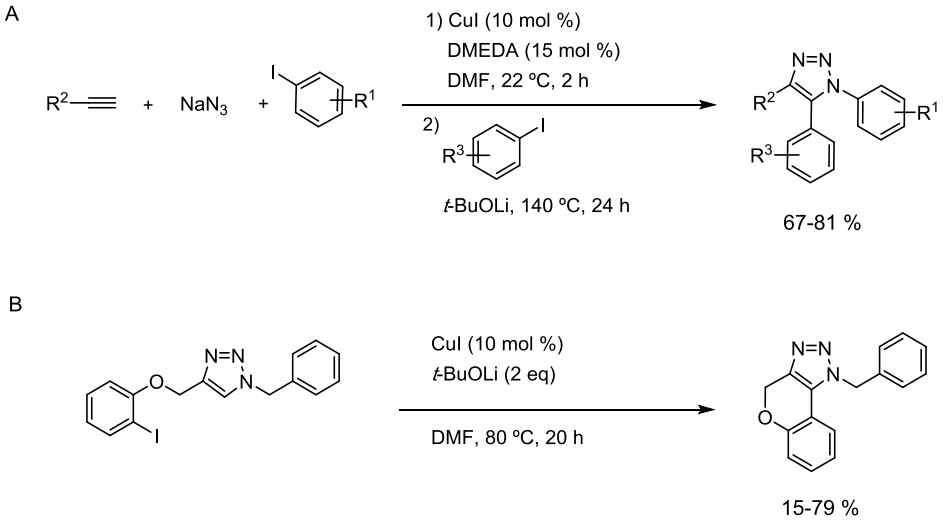
[118] Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem.* Soc. Jpn. **1998**, *71*, 467.

[119] a) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc*. **2008**, *130*, 15185. b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc*. **2007**, *129*, 12404. For other selected examples, see: c) Pandey, D. K.; Shabade, A. B.; Punji, B. *Adv. Synth. Catal.* **2020**, *362*, 2534. d) Khambhati, D. P.; Sachinthani, K. A. N.; Rheingold, A. L.; Nelson, T. L. *Chem. Commun.* **2017**, *53*, 5107. e) Jia, N.-N.; Tian, X.-C.; Qu, X.-X.; Chen, X.-X.; Cao, Y.-N.; Yao, Y.-X.; Gao, F.; Zhou, X.-L. *Sci. Rep.* **2017**, *7*, 43758. f) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3296.

[120] Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081.

[121] Fukuzawa, S.-I.; Shimizu, E.; Ogata, K. *Heterocycles* **2009**, *78*, 645.

[122] Jeyachandran, R.; Potukuchi, H. K.; Ackermann, L. *Beilstein J. Org. Chem.* **2012**, *8*, 1771.



Scheme 3.6. Copper-catalyzed direct arylations to synthesize trisubstituted 1*H*-1,2,3-triazoles. (A) Intermolecular tandem transformation. (B) Intramolecular reaction.

3.1.4 Direct arylation reactions of heteroarene N-oxides

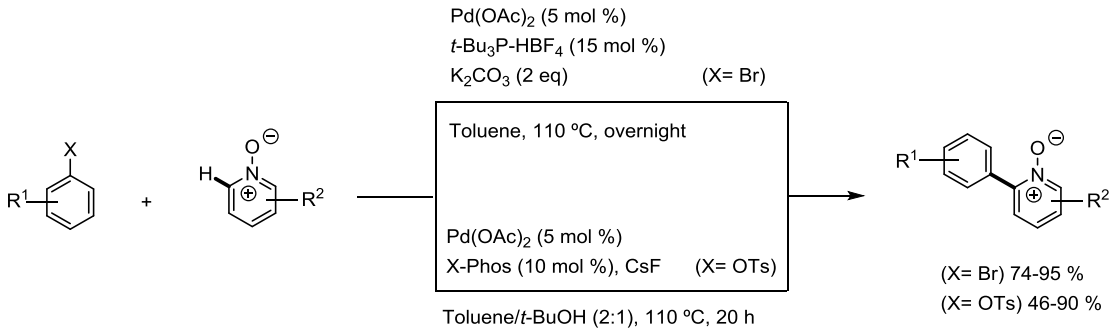
Only a few types of heteroarene N-oxides have been arylated *via* C-H bond activation employing palladium or copper catalysts. As expected, pyridine N-oxides were among the first molecules selected as models to study the cross-coupling reactions of heteroarene N-oxides with haloarenes. Interestingly, 2*H*-1,2,3-triazoles have also been used to achieve that goal.

3.1.4.1 Palladium-catalyzed direct arylations of pyridine N-oxides *via* C-H activation

In a seminal work, Fagnou demonstrated that 2-arylpyridine N-oxides are effectively synthesized from the parent pyridine N-oxides and aryl bromides[123] when the reaction is catalyzed by palladium(II) acetate in the presence of a phosphine ligand and potassium carbonate base (Scheme 3.7). An advantageous variation of the reaction was introduced by Ackermann using moisture-stable and inexpensive aryl tosylates.[124]

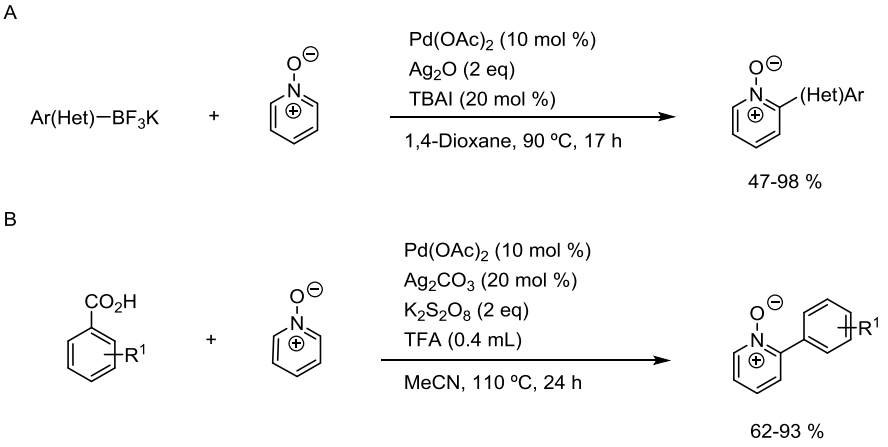
[123] Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

[124] Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430.



Scheme 3.7. Palladium-catalyzed regioselective direct arylation of pyridine N-oxides with aryl bromides and aryl tosylates.

Further progress was made in this area when other coupling partners with a broader substrate scope were utilized (Scheme 3.8). As an example, Wei and Li[125] employed heteroaryltrifluoroborate salts (Scheme 3.8 A) as coupling components. Recently, Dabiri[126] reported the palladium-catalyzed decarboxylative C-H bond arylation of pyridine N-oxides promoted by potassium persulfate and silver carbonate (Scheme 3.8 B).



Scheme 3.8. Direct arylations of pyridine N-oxide. (A) Palladium-catalyzed coupling with aryltrifluoroborates. (B) Palladium-catalyzed decarboxylative C-H arylation.

[125] Li, M.; Li, X.; Chang, H.; Gao, W.; Wei, W. *Org. Biomol. Chem*. **2016**, *14*, 2421.

[126] Dabiri, M.; Alavioon, S. I.; Movahed, S. K. *Eur. J. Org. Chem.* **2019**, 1479.

In recent years this research field has deserved considerable interest and several publications supporting the reactivity-enhancing effect of heteroarene N-oxides have been reported,[25a,127]

Finally, some examples of direct alkylation reaction of heteroarene N-oxides through the formation of an alkyl radical intermediates have also been described.[128]

3.1.4.2 Palladium-catalyzed direct arylations of 2*H*-1,2,3-triazole N-oxides *via* C-H activation

Arylation of non-oxidized regular 2*H*-1,2,3-triazoles with aryl halides *via* coupling reactions remains essentially undocumented. In contrast, their N-oxides have been demonstrated to be excellent substrates for such reactions, owing to the presence of the activated C-H close to the N-oxide function.

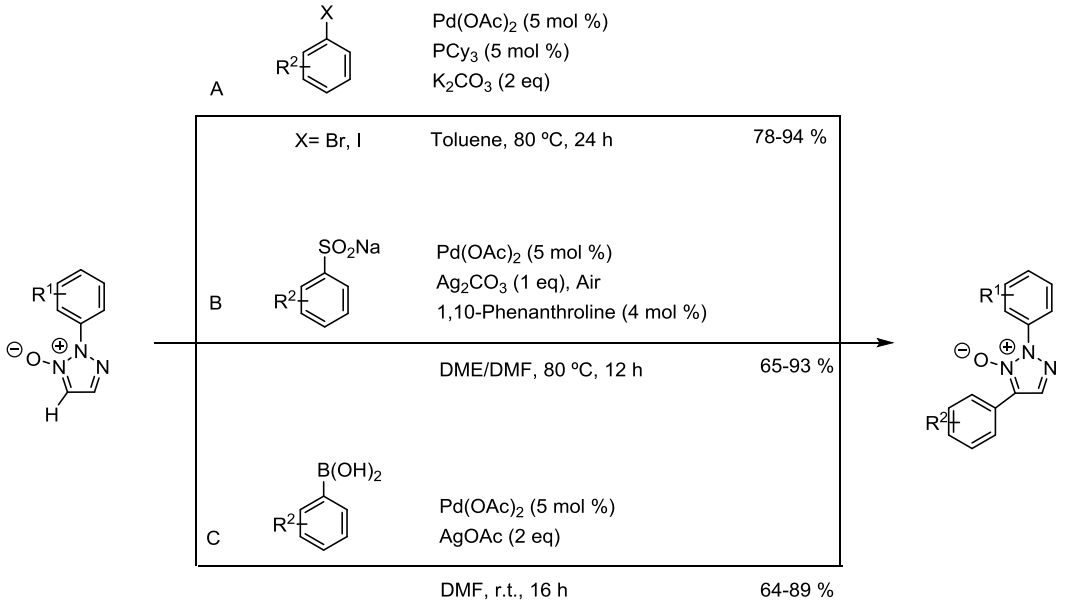
Different arene components have been investigated to carry out this transformation (Scheme 3.9). For example, aryl halides have been coupled to 2*H*-1,2,3-triazole N-oxides under reductive conditions through the usual Pd(II)/Pd(0) catalytic pathway. As mentioned in section 1.1.2.1, Kuang[36a] proved that iodoarenes and bromoarenes undergo a smooth and high-yielding reaction with 2-aryl-2*H*-1,2,3-triazole N-oxides catalyzed by palladium (II) acetate in the presence of tris(cyclohexyl)phosphine (Scheme 3.9 A).

The arylation of the active C-H bond of 2-aryl-2*H*-1,2,3-triazole N-oxides has also been carried out under oxidative conditions, by adding a stoichiometric amount of silver(I) oxidant (Scheme 3.9 B-C). In this regard, Liu has described recently the use of

[127] For some selected examples, see: a) Li, D.; Liang, C.; Jiang, Z.; Zhang, J.; Zhuo, W.-T.; Zou, F.-Y.; Wang, W.-P.; Gao, G.-L.; Song, J. *J. Org. Chem.* **2020**, *85*, 2733. b) Yuan, J.-W.; Qu, L.-B. *Chin. Chem. Lett.* **2017**, *28*, 981. c) Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 9690. d) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, 562. e) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. f) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. g) Leclerc, J. P.; Fagnou, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7781.

[128] For some selected examples, see: a) Gao, Y.; Li, L.; Liu, J.; Wang, L.; Wang, M. *Synthesis* **2021**, *53*, 1636. b) Zhang, W.-M.; Dai, J.-J.; Xu, J.; Xu, H.-J. *J. Org. Chem.* **2017**, *82*, 2059. c) Jha, A. K.; Jain, N. *Chem. Commun.* **2016**, *52*, 1831. d) Sun, W.; Xie, Z.; Liu, J.; Wang, L. *Org. Biomol. Chem*. **2015**, *13*, 4596. e) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem. - Eur. J.* **2009**, *15*, 333.

arylsulfinates[129] and arylboronic acids[130] as coupling components for such reaction and, remarkably, in the second instance, the reaction was conducted at room temperature (Scheme 3.9 C)



Scheme 3.9. Direct arylation of 2*H*-1,2,3-triazole N-oxides catalyzed by palladium(II) acetate (A) Conventional transformation with haloarenes. (B-C) Transformations conducted in the presence of silver(I) oxidants.

3.2 Hypothesis and objectives

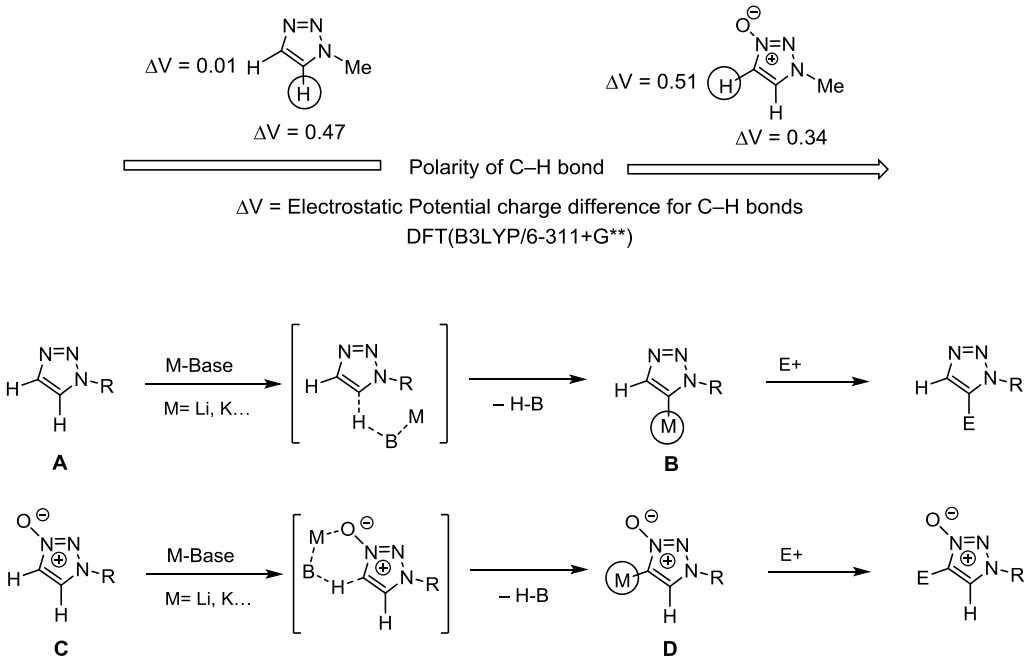
In view of the precedent discussion, we expected that 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides could be particularly convenient substrates to test various C-C bond-forming reactions that would allow the synthesis of unprecedented trisubstituted 1,2,3-triazole N-oxide derivatives.

Our hypothesis was supported by the different polarities of the C-H bonds of 1*H*-1,2,3-triazoles **A** and the corresponding N-oxides **C** (Scheme 3.10). Indeed, an *ab initio* DFT calculation, computed at B3LYP(6-311+G**) level, anticipated an electrostatic potential difference of ΔV= 0.51 between the carbon and hydrogen atoms of the C-H bond α- to the N-oxide moiety, while the equivalent bond of the triazole ring is essentially nonpolar

[129] Zhu, J.; Chen, Y.; Lin, F.; Wang, B.; Huang, Q.; Liu, L. *Synlett* **2015**, *26*, 1124.

[130] Liu, W.; Yu, Y.; Fan, B.; Kuang, C. *Tetrahedron Lett.* **2017**, *58*, 2969.

(ΔV= 0.01). These C-H bond polarization differences account simultaneously for the enhancemet of the Brønsted acidity of triazoles when transformed into their N-oxides and the metalation regioselectivities observed experimentally both for 1*H*-1,2,3-triazoles **B** and their N-oxides **D**.

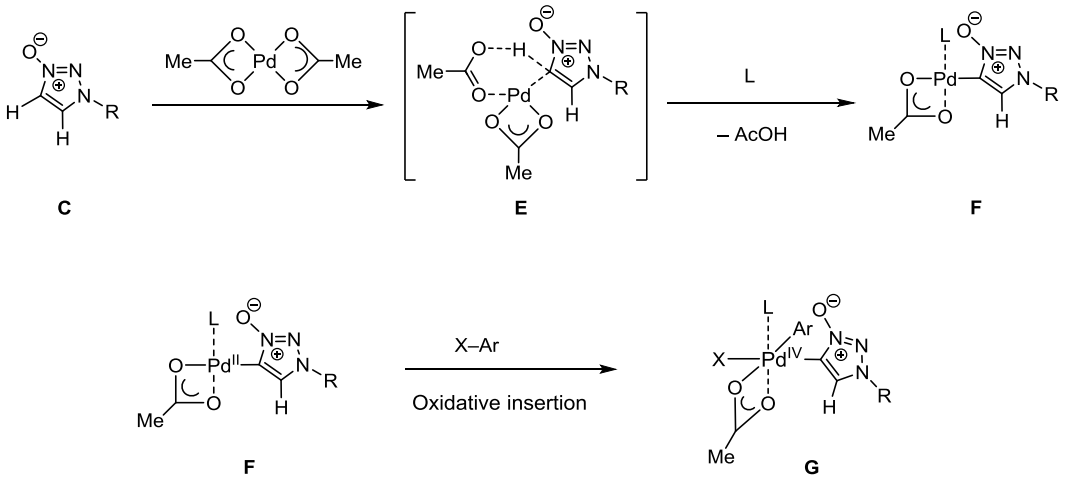


Scheme 3.10. Regular regiochemistry of the deprotonation followed by electrophile trapping of 1,2,3-triazoles and their N-oxides.

As detailed in section 3.1.3.1 (Scheme 3.5), 1,2,3-triazoles have been successfully used as coupling components for palladium-catalyzed direct arylation reactions to get trisubstituted triazoles. However, all reports rely on 1-substituted or 1,4-disubstituted triazoles, which exhibit their larger polarization at the C(5)-H bond. Thus, we hypothesized that 1,5-disubstituted triazole N-oxides could be better substrates for direct arylation reactions with haloarenes at the C(4)-H bond under palladium-catalyzed conditions. Our assumption was based on the concerted metalation-deprotonation (CMD) mechanism proposed by Fagnou[131] for the direct deprotonative palladation of pyridine N-oxides using Pd(II) diacetate (Scheme 3.11). Additionally, we also anticipated that palladium(II)-triazole N-oxide complexes **F** would experience the oxidative addition of

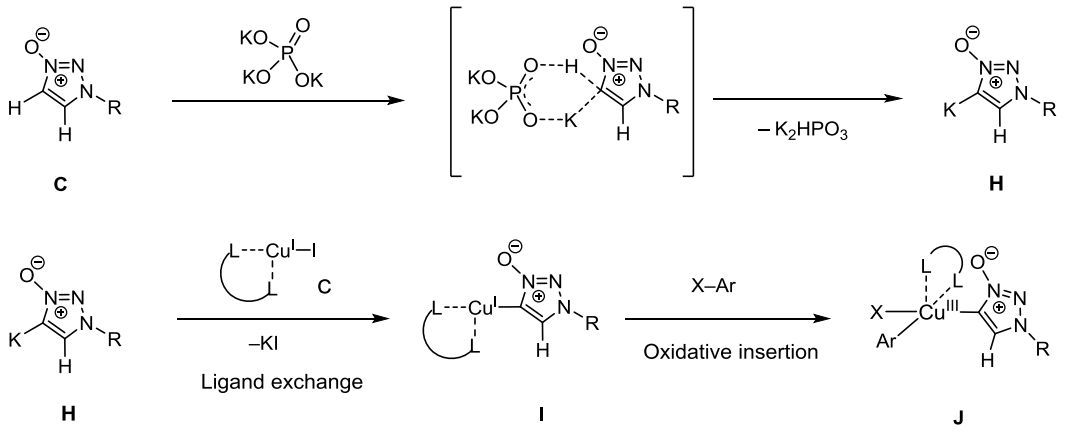
[131] Sun, H. Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L. C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180.

haloarenes to form Pd(IV) intermediates **G** before the reductive coupling leading to the 4-aryl-triazole N-oxide final products.



Scheme 3.11. Concerted metalation-deprotonation (CMD) model for 1*H*-1,2,3-triazole N-oxides promoted by palladium(II) acetate. Oxidative addition of haloarenes into palladium(II) complexes to form palladium(IV) intermediates.

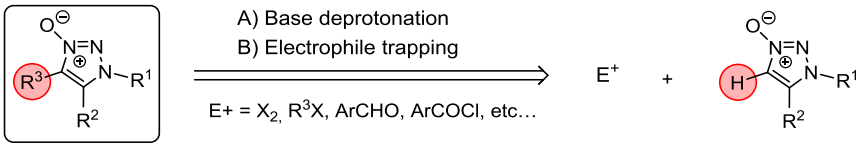
Finally, as previously noted in section 3.1.3.2 (Scheme 3.6), the formation of 1,4,5-trisubstituted triazole *via* copper-catalyzed coupling reactions with haloarenes, makes necessary the use of strong bases, such as, lithium *tert*-butoxide. We hypothesized that metalated triazole N-oxides **H** could be formed using milder bases, such as potassium phosphate, and incorporated *via* ligand exchange into copper(I) intermediates **I** in the presence of chelating ligand additives. Ultimately, these complexes could undergo an oxidative addition with haloarenes to form copper(III) intermediates **J** before delivering the coupling products.



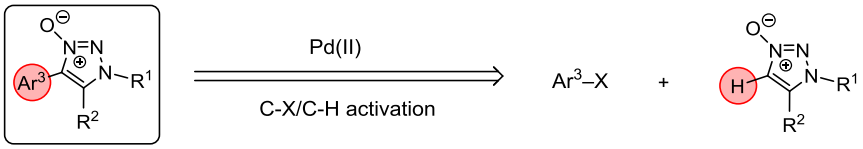
Scheme 3.12. Copper-catalyzed Ulmann-type direct arylation reactions of 1*H*-1,2,3-triazole N-oxides with haloarenes.

In order to test experimentally the hypotheses disclosed above, we addressed our working activity to reach the following activities.

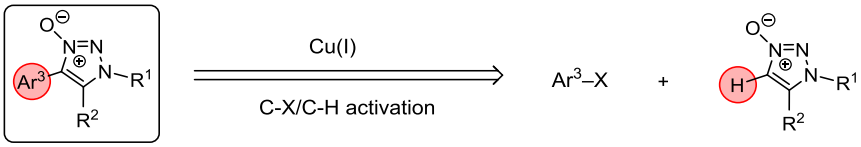
1- Synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides using a two-step one-pot protocol consisting of a base-promoted deprotonation of 1,5-disubstituted 1,2,3-triazole N-oxides, followed by trapping with electrophiles.



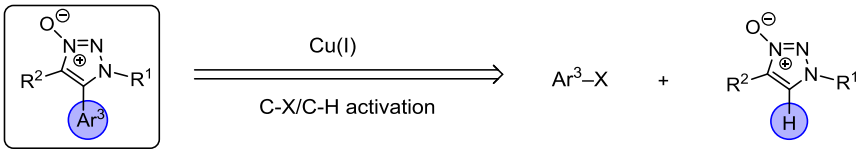
2 Synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides using a palladium-catalyzed direct arylation of 1,5-disubstituted triazole N-oxides with haloarenes.



3 Synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides using a copper(I)-catalyzed direct arylation of 1,5-disubstituted triazole N-oxides with haloarenes.



4 Extension of the former methodology to the synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides from 1,4-disubstituted triazole N-oxides with haloarenes.



3.3 Results and discussion

3.3.1 Synthesis of 1,4,5.trisubstituted 1*H*-1,2,3-triazole N-oxides *via* C-H deprotonative metalation and trapping with electrophiles

In order to test the feasibility of our first proposal, we selected a set of model triazole N-oxides (**9a**, **9c** and **9h**) and electrophiles (I_2 and MeI) and submitted them to the action of several bases in THF solvent under different deprotonation and electrophile trapping conditions. A summary of the main results obtained is collected in Table 3.1.

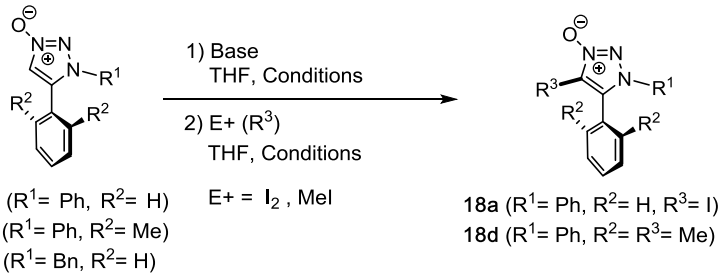
We started our screening process by using *n*-butyllithium at -78 ºC and iodine as the electrophile to trap the intermediate carbanion at room temperature (entry 1). Under these conditions, the starting N-oxide **9a** totally vanished and the trisubstituted triazole N-oxide **18a** was obtained in 60 % yield, although accompanied with considerable amounts of decomposition unidentified products. Changing the base to the more hindered-lithium hexamethyldisilazane and carrying out the deprotonation at -60 ºC led to a very low reaction conversion (<10 %) when iodine was utilized as the electrophile (entry 2). Altering the temperatures of the deprotonation or trapping steps did not improved the reaction outcome. However, we found that using potassium *tert*-butoxide as the base and conducting the deprotonation step at 0 ºC afforded the expected iodotriazole **18a** in 90 % yield (entry 3). Disappointingly, when the reaction was repeated utilizing iodomethane as electrophile and prolonging the trapping time overnight, no trace of the alkylated product was detected and the starting material was recovered unchanged (entry 4). In contrast with these results, the combination of lithium hexamethyldisilazane and methyl iodide provided the methylated product **18d** in 70 % yield (entry 5).

Finally, we wanted to check the reaction with triazole N-oxides like **9h**, bearing a benzyl group, which could suffer deprotonation at the methylene position with strong bases. When the reaction was tried using potassium *tert*-butoxide, only decomposition products were formed, but no trace of the expected iodotriazole (entry 6). Trying to overcome this limitation, we repeated the reaction using potassium phosphate as a base, following related methods reported in the literature (entries 7-8).[132] Unfortunately, we observed that the reaction did not proceed and the starting N-oxide **9h** was recovered unchanged. Many

[132] Popov, I.; Do, H-Q.; Daugulis, O. *J. Org. Chem*. **2009**, *74*, 8309.

trials were run at different temperatures and utilizing different bases but they all deliverded no trace of the expected products.

Table 3.1. Reaction conditions screening for the deprotonative modification of 1*H*-1,2,3-triazole N-oxides with electrophiles.



9a (R^1= Ph, R^2= H)
9c (R^1= Ph, R^2= Me)
9h (R^1= Bn, R^2= H)

18a (R^1= Ph, R^2= H, R^3= I)
18d (R^1= Ph, R^2= R^3= Me)

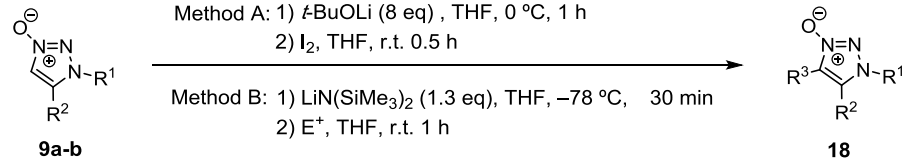
Entry[a]	Substrate	Base (eq)	E+ (eq)	Conditions[b] T (ºC)/ t(h)	Product	Yield[c] (%)
1	**9a**	*n*-BuLi (1.2)	I_2 (3.0)	1) –78 / 1 2) 20 / 1	**18a**	60[d]
2	**9a**	$LiN(SiMe_3)_2$ (2.0)	I_2 (3.0)	1) –60 / 0.5 2) 20 / 0.5	**18a**	<10
3	**9a**	*t*-BuOK (8.0)	I_2 (3.0)	1) 0 / 0.5 2) 20 / 0.5	**18a**	90
4	**9a**	*t*-BuOK (8.0)	MeI (3.0)	1) 0 / 0.5 2) 20 / 0.5	---	0
5	**9c**	$LiN(SiMe_3)_2$ (2.0)	MeI (3.0)	1) –60 / 0.5 2) 20 / 1	**18d**	70
6	**9h**	*t*-BuOK (8.0)	I_2 (3.0)	1) 0 / 0.5 2) 20 / 0.5	---[d]	0
7	**9h**	K_3PO_4 (5.0)	I_2 (3.0)	60 / 24	---[e]	0
8	**9h**	K_3PO_4 (5.0)	MeI (3.0)	60 / 24	---[e]	0

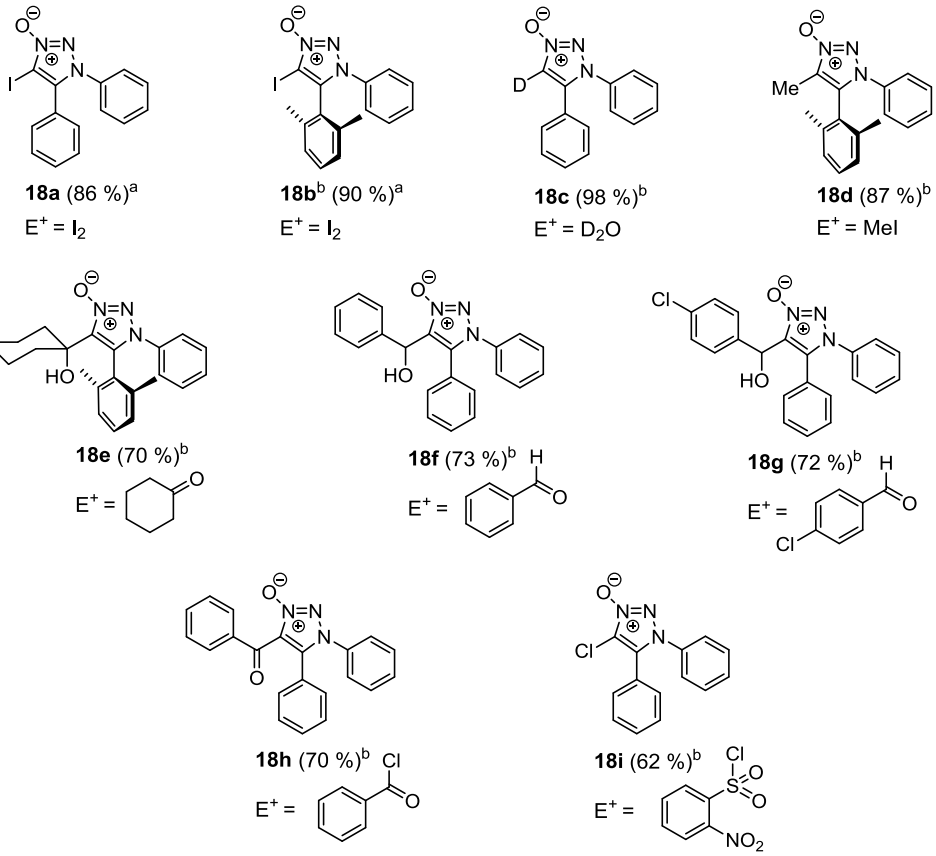
[a]Substrate concentration: 1 mmol 9 in 20 mL THF. [b]Reaction conditions of step 1) and step 2) [c]Yield of isolated pure products. [d] Non identified byproducts. [e] Starting N-oxide 9h recovered. [f] One-pot reaction conducted in DMF solvent.

In summary, the deprotonative electrophilic functionalization of 1*H*-1,2,3-triazole N-oxides is limited by the acidic nature of the substituent groups and the optimum bases for the triazole ring deprotonation strongly depend on the nature of the electrophile used. While potassium *tert*-butoxide was selected for non-carbon electrophiles, lithium hexamethyldisilazane was found to be more efficient for carbon electrophiles.

With the former requirements in mind, we extended both methods to the preparation of a set of trisubstituted triazole N-oxides, which are collected in Table 3.2.

Table 3.2. Synthesis of 1,4,5-trisubstituted 1*H*-1,2,3-triazole N-oxides *via* deprotonation/trapping with several electrophiles.





[a] Method A: Triazole N-oxide (0.12 mmol), electrophile (0.16 mmol), base (0.16 mmol) in THF (2.4 mL) at -60 ºC for 30 min. [b] Method B: Base:electrophile (0.36 mmol), tBuOK (0.96 mmol) at 0 ºC for 30 min.

As shown in the table, with the exception of the iodination reaction assisted by potassium *tert*-butoxide (method A), all the functionalizations were better promoted by lithium hexamethyldisilazane (method B). Accordingly, good yields of the trisubstituted triazole N-oxides **18d**-**18h** were obtained by trapping the intermediate C(4)-lithiated triazole N-

oxides with cyclohexanone, benzaldehydes or benzoyl chloride. Remarkably, when 2-nitrobenzenesulfonyl chloride was used as the electrophile, 4-chloro triazole N-oxide **18i** was obtained instead of the expected 4-(2-nitrobenzenesulfonyl)-triazole N-oxide.

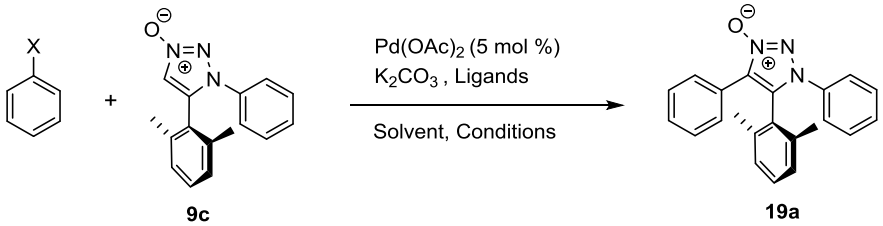
From these results, it is possible to confirm that 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides are convenient substrates for accessing trisubstituted triazole N-oxides *via* C-H bond deprotonation, followed by electrophile trapping, although the presence of competitive acidic protons (e.g benzylic groups) can limit the substitution pattern of the triazoles available for such transformations. Obviously, this approach is also impracticable for the incorporation of aryl groups at the C(4) position of the triazole ring.

In the next sections of this chapter some direct arylation reactions will be developed to access trisubstituted 1*H*-1,2,3-triazole N-oxides, compatible with benzylic substituents and bearing C(4) aromatic groups, activated by palladium and copper catalysts.

3.3.2 Synthesis of 1,4,5-trisubstituted 1,2,3-triazole N-oxides *via* palladium catalyzed direct arylation reactions

To undertake the second objective of our working plan and check the feasibility of the palladium-catalyzed approach to prepare trisubstituted 1*H*-1,2,3-triazole N-oxides, we selected the model triazole N-oxide **9c** and halobenzenes as coupling components. After a survey of the literature demonstrating that triazole N-oxides were slowly deuterated at the α-position in the presence of alkali metal carbonates[39] and their efficiency to promote concerted metalation-deprotonation in pyridine N-oxides,[131] we decided to select potassium carbonate as the base for the reaction (Table 3.3). We also explored the effect of a few ligands and solvents on the reaction outcome.

Table 3.3. Screening of reaction conditions for the palladium-catalyzed arylation of the model 1*H*-1,2,3-triazole N-oxide **9c** with halobenzenes.



9c **19a**

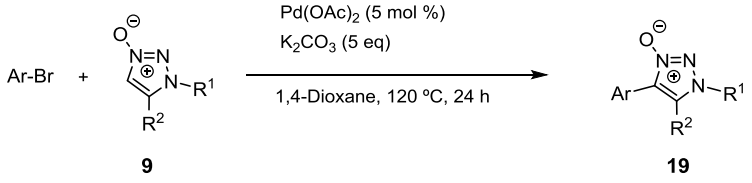
Entry	X	K_2CO_3 (eq)	Ligand (mol %)	Solvent	Conditions[a] T (ºC)/ t(h)	Conversion[b] (%)
1	Br	2.0	P(*t*-Bu)$_3$ (6)	Toluene	120 / 24	>95
2	Br	2.0	PPh_3 (15)	Toluene	120 / 24	>95
3	Br	5.0	----	Toluene	120 / 18	70
4	Br	5.0	----	1,4-Dioxane	120 / 24	>95
5	Br	5.0	----	1,4-Dioxane	80 / 24	30
6	I	5.0	----	1,4-Dioxane	120 / 24	>95
7	Cl	5.0	----	1,4-Dioxane	120 / 24	0

[a] Molar ratio **9c**/halobenzene: 1.0/1.3. [b] Determined by NMR CH_3 signals.

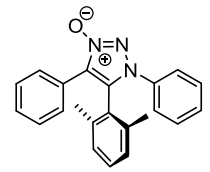
We first tested the reactivity of **9c** with bromobenzene in the presence of phosphine ligands in toluene at 120 ºC for 24 hours (entries 1-2). Although, 1,2,3-triazole N-oxide arylation took place in almost total conversion in both cases, the purification of the reaction crude resulted particularly troublesome, due to the extremely difficult separation of the product from phosphine oxides formed during the reaction. So, to prevent this unexpected operational inconvenience and get a simpler and more robust procedure, we repeated the reaction in the absence of ligands by adding 5 equivalents of potassium carbonate (entry 3). Under these conditions, a 70 % conversion was attained after 18h. Lower amount of base or longer reaction times did not improved the reaction conversion. Then, we analyzed the influence of the solvent and replaced the apolar and noncoordinating toluene by 1,4-dioxane. Indeed, we were able to afford the product in almost total conversion (entry 4). We next evaluated the influence of the temperature and repeated the reaction at lower temperatures (entry 5). A dramatic drop of the conversion

to 30 % was observed when the reaction was performed at 80 ºC. At 100 ºC the conversion was raised again to 90 % (not shown in the table), but to ensure a total conversion of >95 %, we ultimately selected the 120 ºC as the optimum reaction temperature. Finally, we checked the reaction using other aryl halides (entries 6-7). Not surprisingly, when iodobenzene was used, the reaction occurred in almost total conversion, while chlorobenzene gave no conversion and only the starting material was recovered unchanged. After these experiments, we selected the reaction conditions of entry 4 as the optimal and explored the scope of the reaction to evaluate the behavior of differently substituted triazole N-oxides and aryl bromides (Table 3.4).

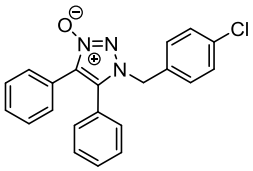
Table 3.4. Palladium-catalyzed direct arylation of 1*H*-1,2,3-triazole N-oxides **9** with aryl bromides.[a]



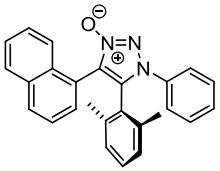
9 **19**



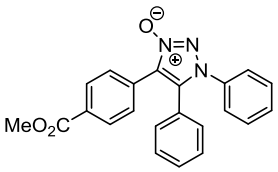
19a (80 %)



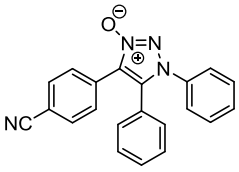
19b (83 %)



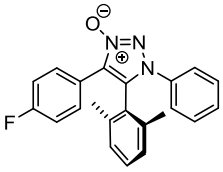
19c (70 %)



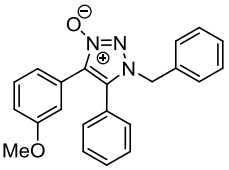
19d (90 %)



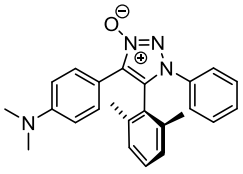
19e (94 %)



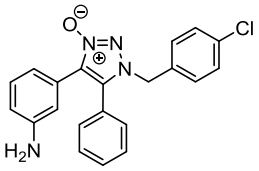
19f (65 %)



19g (84 %)



19h (89 %)

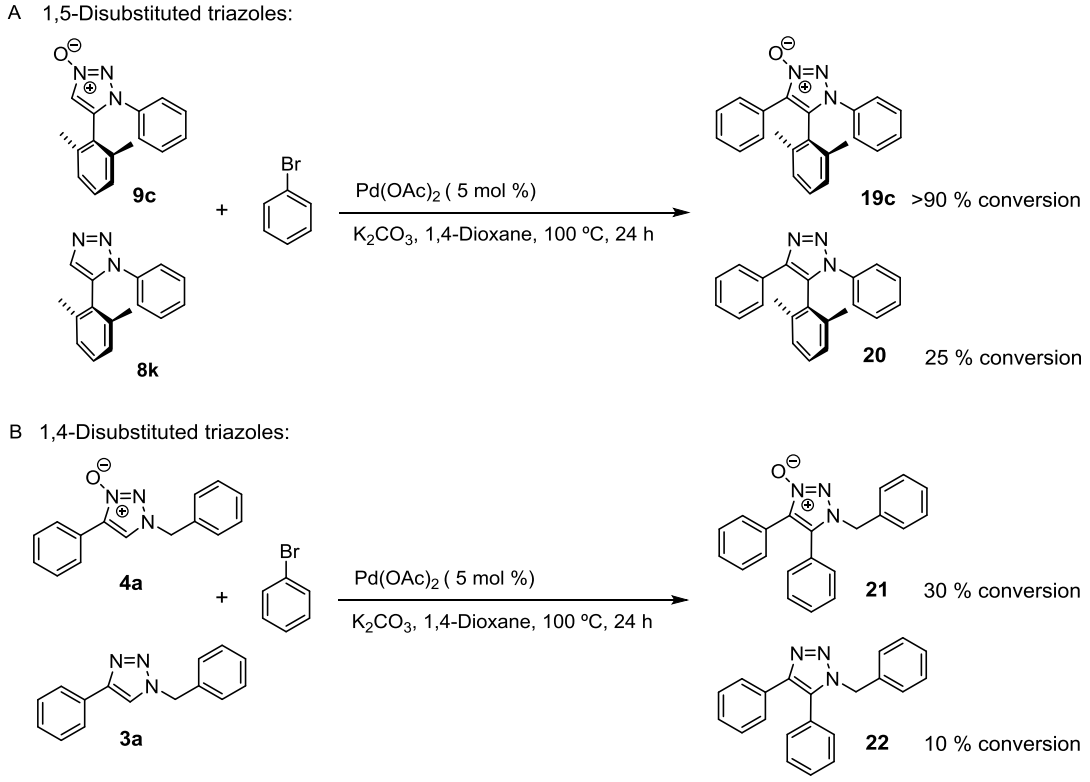


19i (50 %)

[a]Triazole N-oxide **9**/aryl bromide molar ratio = 1.0:1.3; Substrate concentration: 0.2 M.

As collected in the table, diverse triazole N-oxides were cleanly arylated at the C(4) position to provide the trisubstituted triazole N-oxides **19a-i** in moderate to excellent yields. Interestingly, owing to the mild basic conditions employed, a variety of triazoles bearing benzylic substituents were prepared properly, thus solving the limitations found with the deprotonative method described in section 3.3.1. Besides, various groups such as chlorinated aromatic rings, amines, esters or nitriles were compatible with the method, and the arylation reaction performed equally well with bromoarenes bearing electron-donating or electron-withdrawing groups.

In order to get further empirical evidence regarding the C(4)-H bond activating effect of the triazole N-oxide moiety on the coupling reactions studied, we performed several control experiments to compare the reactivity of the model 1,5-disubstituted 1,2,3-triazole N-oxide **9c** with its non-oxidized counterpart **8k** (Scheme 3.13). In parallel, to explore the eventual extension of such activation to the C(5)-H bond, we also compared the arylation of the 1,4-disubstituted triazole N-oxide **4a** with its precursor **3a**. To better observe the electronic effects, all the reactions were conducted at 100 ºC for a period of 24 h.



Scheme 3.13. Comparison of the reactivities of disubstituted 1*H*-1,2,3-triazoles and N-oxides towards the palladium-catalyzed arylation with bromobenzene.

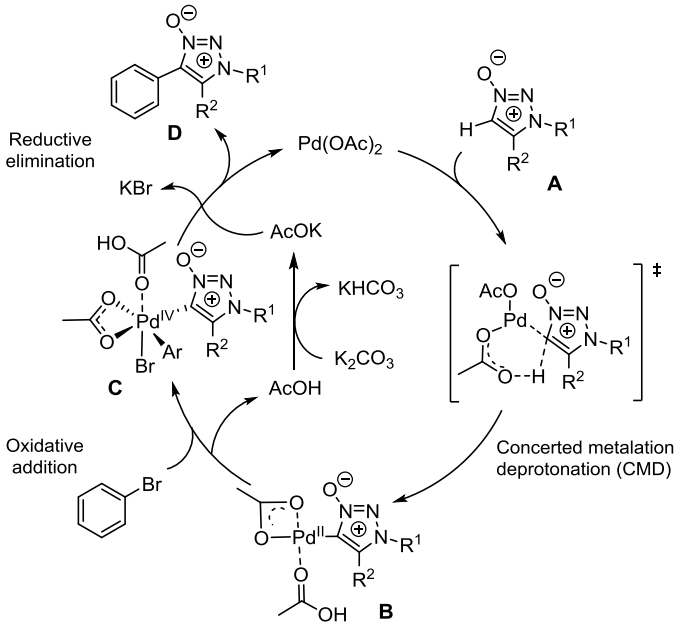
As shown in the scheme, the reaction activation generated by the N-oxide moiety could be clearly perceived in both C(5)-H and C(4)-H positions, although much more in the former one. Actually, 1,5-disubstituted triazole N-oxide **9c** gave almost total conversion under the arylation conditions used, whereas the equivalent triazole was arylated in only 25 %. As expected, the conversion differences between 1,4-disubstituted triazoles **3a** and **4a** were much shorter (10 % vs 30 %, respectively), but clearly appreciable.

3.3.2.1 Reaction mechanism proposal

Palladium-catalyzed direct arylation reactions leading to aryl-(hetero)aryl bond formation from haloarenes and involving a C-H palladation step, can follow two different pathways including Pd(II)/Pd(0) or Pd(II)/Pd(IV)[133] complex-systems. The prevalence of each pathway strongly depends on the acidity of the C-H bonds of the starting material, the catalyst precursors, the incorporation of ligands or oxidant additives and the reaction conditions. A reaction mechanism for the arylation of triazole N-oxides with haloarenes in the absence of ligands or other additives should exclude the Pd(II)/Pd(0) system and, therefore, we selected the Pd(II)/Pd(IV) catalytic system as the more plausible (Scheme 3.14).

In the first step, the triazole N-oxide **A** would experience a concerted metalation deprotonation process[131] leading to the Pd(II)-intermediate **B**. Then, the oxidative addition of the aryl halide to **B** would generate the Pd(IV) intermediate **C**. Finally, the reductive elimination of the later could take place to afford the 4-aryl-1,2,3-triazole N-oxide **D**. In this mechanism, potassium carbonate should neutralize the acetic acid formed in the medium and recover the acetate to regenerate the active palladium (II) acetate catalyst.

[133] For some selected reviews, see: a) Gandeepan, P.; Cheng, C.-H. Arylation Using a Palldium(II)/Palladium(IV) Catalyst System in Science of Synthesis: Catalytic Transformations via C-H Activation, **2016**, 1, 69. Georg Thieme Verlag, Sttutgart, 1st edn. b) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.



Scheme 3.14. Reaction mechanism proposal for the palladium-catalyzed direct arylation of 1*H*-1,2,3-triazole N-oxides with haloarenes.

A critical point of the former proposal was the likely dual action exerted by the acetate anion as a weak palladium ligand and a Brønsted base during the CMD palladation step, according to the Fagnou's model.[131] To shed light on this point, a collaboration with Dr José Ignacio Miranda (SGIker, EHU-UPV) was established to conduct a computational study of the palladium acetate-promoted concerted metalation-deprotonation (CMD) of 1-methyl-1*H*-1,2,3-triazole and its N-oxide analog. Density functional theory calculations were conducted utilizing Gamess 30 DEC 2019 (R9) from Iowa State University suite of programs.[134] Full geometry optimizations and harmonic analyses were carried out by use of the B3LYP hybrid functional [39] and the def2-SVP basis set.[135] An ECP (efective core potencial) was used for Pd.[136]

To confirm the experimentally observed extra activation promoted by the N-oxide moiety, we computed the CMD process at the C(4)-H and C(5)-H bonds of 1-methyl-triazole N-oxide and compared it with the triazole counterpart to calculate the activation

[134] Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus T. L.; Together with Dupuis, M.; Montgomery J. A. *J. Comput.Chem.* **1993**, *14*, 1347.

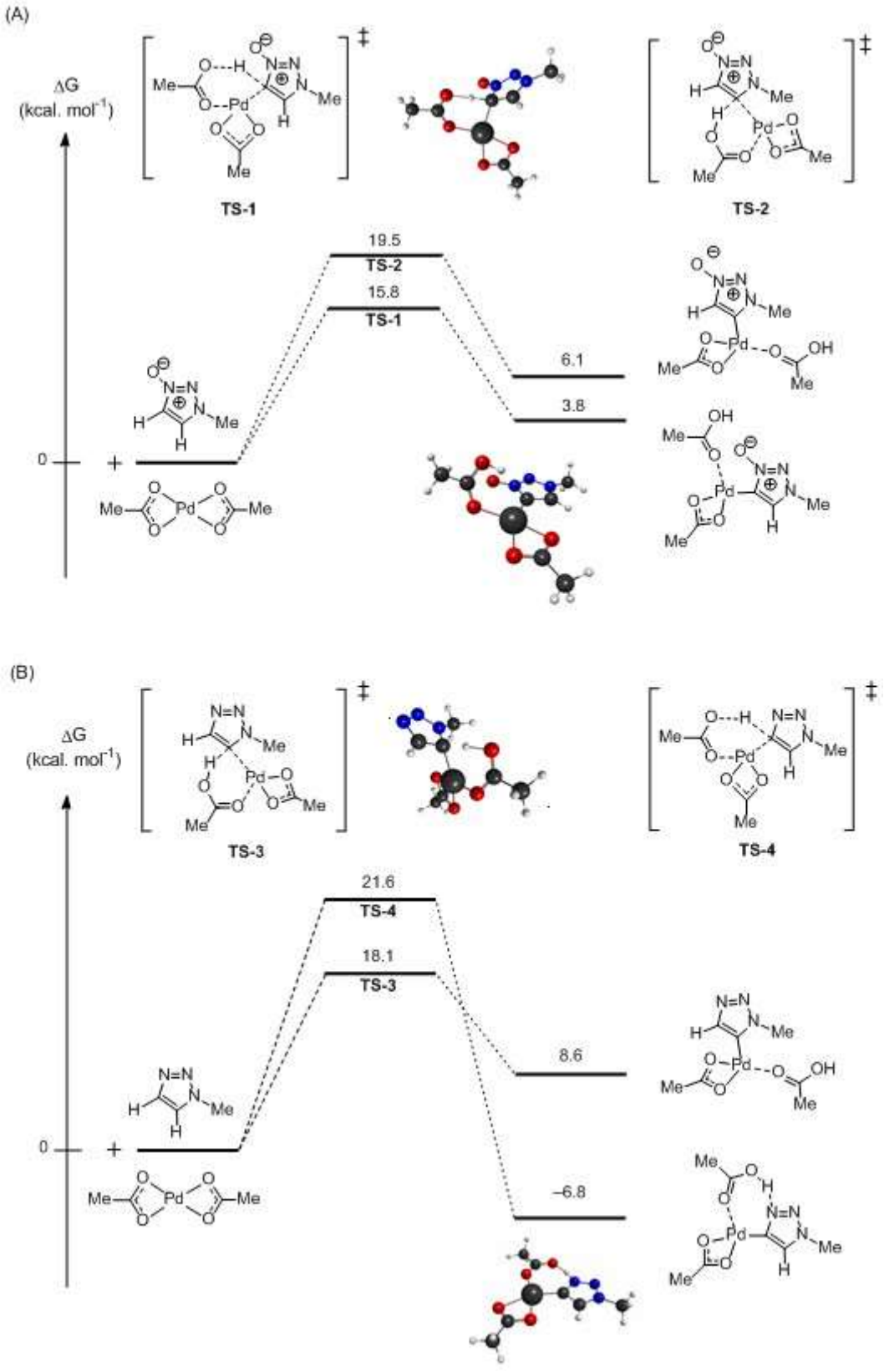
[135] Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

[136] Andrae, D.; Häußermann, U.; Dolg, M.; Stoll, H.; Preuß, H. *Theor. Chim. Acta* **1990**, *77*, 123.

barriers ($\Delta G^{\ddagger}$) leading to the corresponding palladated triazole intermediates. The free energy profiles are represented in Scheme 3.15.

As expected, the more favorable CMD process was found at the C(4)-H bond of the triazole N-oxide, reaching computationally characterizable transition states 15.8 kcal/mol and the product 3.8 kcal/mol. In contrast, the equivalent pathway of the unoxidized triazole involved a transition state with comparatively higher activation barrier of 21.6 kcal/mol.

It should be mentioned that the reason of having a low free energy of the palladated triazole product TS-4 was the hydrogen bond was formed between the ligand and the nitrogen of the triazole. However, the transition state of it was the highest one comparing with other transition states.



Scheme 3.15. *Ab initio* DFT(B3LYP-321-G**) transition states and reaction intermediates computed for the concerted cyclometallation deprotonation reaction. (A) CMD process for 1-methyl-1,2,3-triazole N-oxides. (B) CMD process for 1-methyl-1,2,3-triazole.

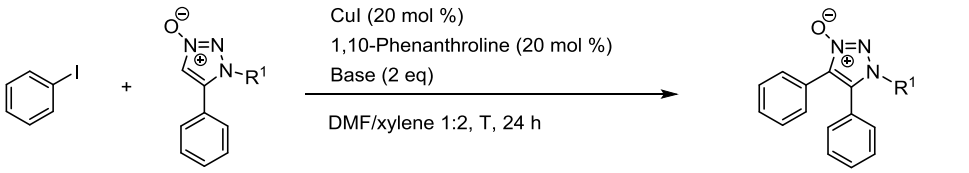
3.3.3 Synthesis of 1,4,5-trisubstituted 1,2,3-triazole N-oxides *via* copper-catalyzed direct arylation reactions

3.3.3.1 Cross-coupling reactions from 1,5-disubstituted triazole N-oxides

As outlined in the introduction of this chapter (section 3.1.3.2) the synthesis of trisubstituted triazoles can be accomplished using the Ullmann-type direct arylation of 1,4-disubstituted 1,2,3-triazoles with iodoarenes. However, the assistance of strong bases, such as, *t*-BuOK is necessary to deprotonate the C(5)-H bond and form the triazole anion intermediates required to participate in the copper-catalyzed coupling reaction.

In view of the dramatic activation of the CMD process observed during the palladium-catalyzed arylation reaction of triazole N-oxides, we decided to investigate a similar methodology for copper-catalyzed arylations carried out in the presence of softer bases, such as potassium carbonate or potassium phosphate (Table 3.5). All reactions were conducted using iodobenzene and CuI catalyst in the presence of 1,10-phenanthroline, which is known to chelate and stabilize various types of copper complexes. We selected the triazole N-oxide models **9a** and **9h**, bearing respectively phenyl and benzyl N-substituents, to check their chemical stability under the reaction conditions tested.

Table 3.5. Screening of bases and reaction conditions for the copper-catalyzed direct arylation of 1,5-disubstituted triazole N-oxides.



9a (R^1= Ph)
9h (R^1= Bn)

23a (R^1= Ph)
23b (R^1= Bn)

Entry	N-oxide	Base	Temperature (ºC)	Time (h)	Conversion (%)
1	**9d**	K_2CO_3	120	24	<30
2	**9d**	K_2CO_3	140	24	>90
3	**9e**	K_2CO_3	140	24	<20
4	**9d**	K_3PO_4	140	24	85
5	**9e**	K_3PO_4	140	30	80

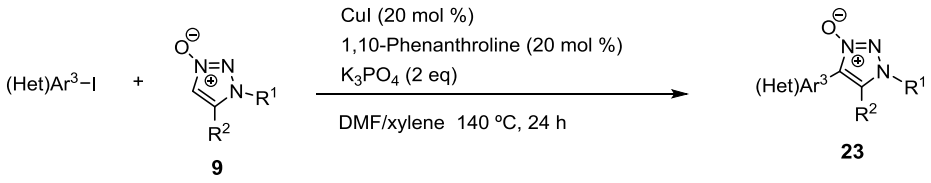
[a]Molar ratio: triazole N-oxide **9**/iodobenzene=1:1.4

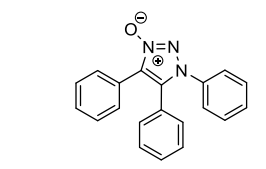
In a first trial, triazole N-oxide **9a** was reacted with iodobenzene in the presence of 2-equivalents of potassium carbonate at 120 ºC (entry 1). This temperature was selected because it was demonstrated to be enough to promote the CMD process in the palladium-catalyzed direct arylation described in the previous section 3.3.2. Unfortunately, in the instance tested in entry 1, only a poor conversion to the product **23a** was observed. Consequently, we repeated the experiment raising the reaction temperature to 140 ºC (entry 2), and were delighted to observe almost total conversion. Next, we changed the triazole N-oxide to the benzylic compound **9h** and repeated the experiment (entry 3), but a poor conversion accompanied with degradation products was obtained. Finally, changing the base to potassium phosphate and conducting the reaction at 140 ºC resulted in a clean transformation to the desired N-oxides **23a** and **23b** in good yield (entries 4 and 5).

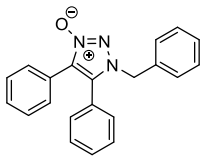
We next studied the scope of the reaction using triazole N-oxides bearing either aromatic ot benzylic substituents, and aromatic or heteroaromatic iodides, as is depicted in Table 3.6.

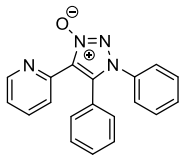
In general, when N-arylated triazole N-oxides were used, better yields were attained comparing to the N-benzylic ones, which were obtained from moderate to good yields. The reaction also worked well with iodoarenes derived from pyridine or thiophene. A double coupling of two equivalents of N-oxide with diiodoarenes provided a direct route to potentially interesting multidentate ligands for binding metal, such as compounds **23aa**, **23ab**. Finally, the reaction was compatible with halogen groups, such as fluorine or bromine, and a few functional groups. Compounds such as **23m**, were obtained in moderate yields, probably due to the steric hindrance of the aryl iodide.

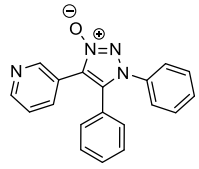
Table 3.6. Reaction scope of the copper-catalyzed direct arylation of 1,5-disubstituted triazole N-oxides with iodo(hetero)arenes.[a]

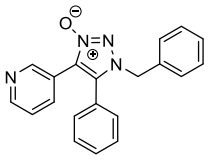


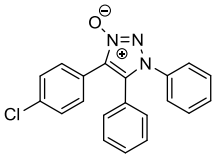

23a (80 %)

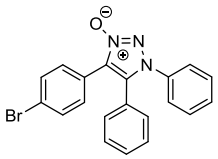

23a (75 %)

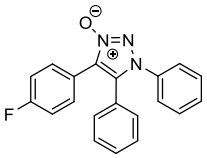

23c (98 %)

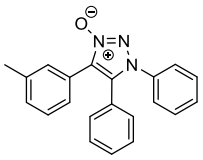

23d (84 %)

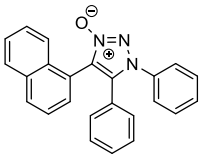

23e (60 %)

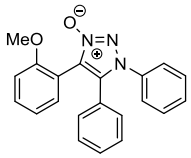

23f (60 %)

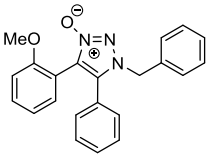

23g (60 %)

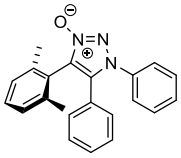

23h (56 %)

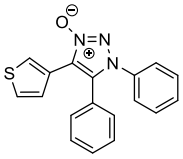

23i (42 %)

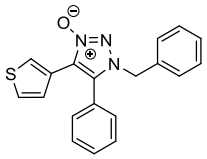

23j (84 %)

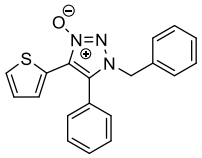

23k (72 %)

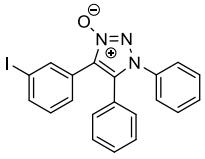

23l (72 %)

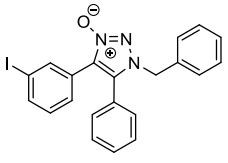

23m (50 %)

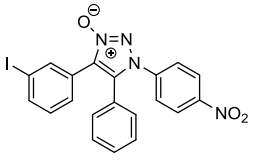

23n (60 %)

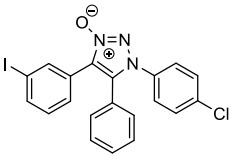

23o (50 %)

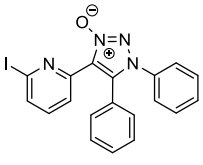

23p (50 %)

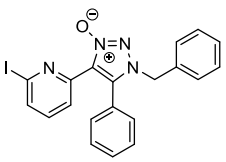

23q (54 %)

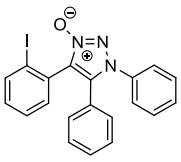

23r (50 %)

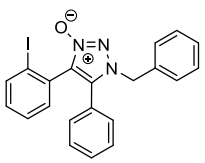

23s (65 %)

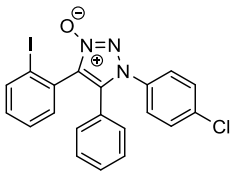

23t (73 %)


23u (70 %)

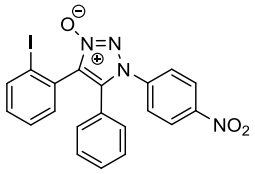

23v (63 %)


23w (50 %)

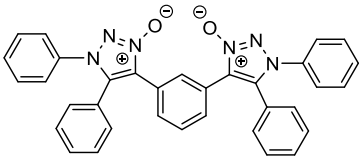

23x (50 %)



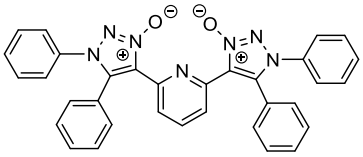
23y (59 %)



23z (72 %)



23aa (76 %)



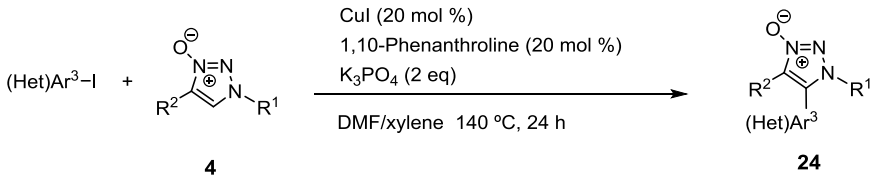
23ab (65 %)

[a]Molar ratio: triazole N-oxide **9**/iodo(hetero)arene = 1:2. Yields of isolated pure products.

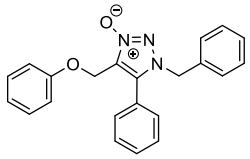
3.3.3.2 Cross-coupling reactions from 1,4-disubstituted triazole N-oxides

In view of the good results obtained with the CuI/K_3PO_4/1,10-phenanthroline system for the arylation reaction of 1,5-disubstituted triazole N-oxides with iodo(hetero)arenes, we decided to extend the same synthetic method to the 1,4-disubstituted triazole N-oxides. Although we ran some experiments to explore modifications of the method, such as using stronger bases (*t*-BuOLi) and varying the equivalents of base or iodoarene employed, we could not observed significant improvements and, finally, we decided to maintain the general procedure substantially unchanged (see Table 3.7). Nevertheless, during these experiments, we found that controlling of the initial concentration of the substrate was important for the successful outcome of the reaction. Actually, we observed that conducting the reaction with the N-oxides **4** bearing a pyridil R^2 group at 0.5M concentration, as used previously for 1,5-disubstituted triazole N-oxides, led to the desired trisubstituted product **24**, accompanied by a 30 molar % of the 5-5'-bistriazole dimerization product (see section 4.4.3.2 for details). Fortunately, we found that diluting the initial concentration of N-oxides **4** to 0.1M minimized the dimerization reaction and, therefore, we conducted all the reactions under such conditions.

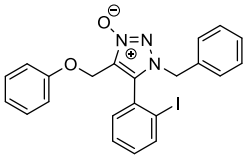
Table 3.7. Reaction scope of the copper-catalyzed direct arylation of 1,4-disubstituted N-oxides with iodo(hetero)arenes.[a]



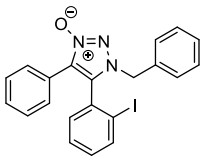
4 **24**



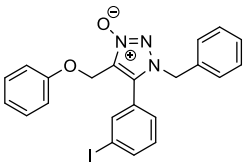
24a (73 %)



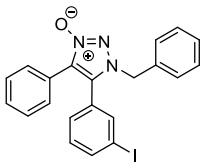
24b (52 %)



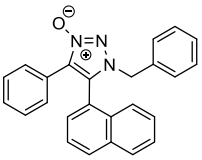
24c (60 %)



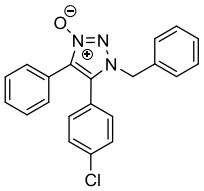
24d (53 %)



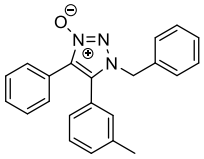
24e (40 %)



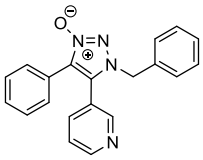
24f (70 %)



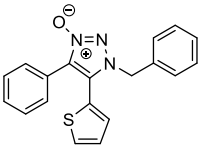
24g (14 %)



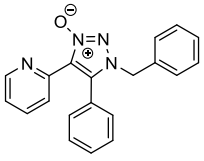
24h (77 %)



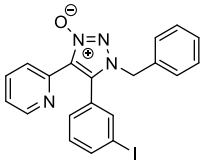
24i (40 %)



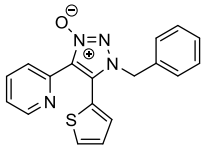
24j (64 %)



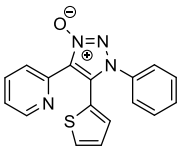
24k[b] (73 %)



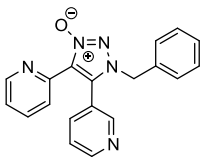
24l[b](55 %)



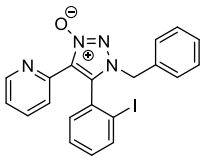
24m[b] (52 %)



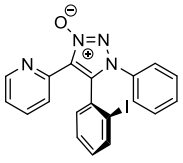
24n[b] (67 %)



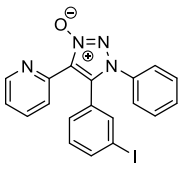
24o[b] (66 %)



24p[b] (52 %)



24q[b] (60 %)



24r[b] (57 %)

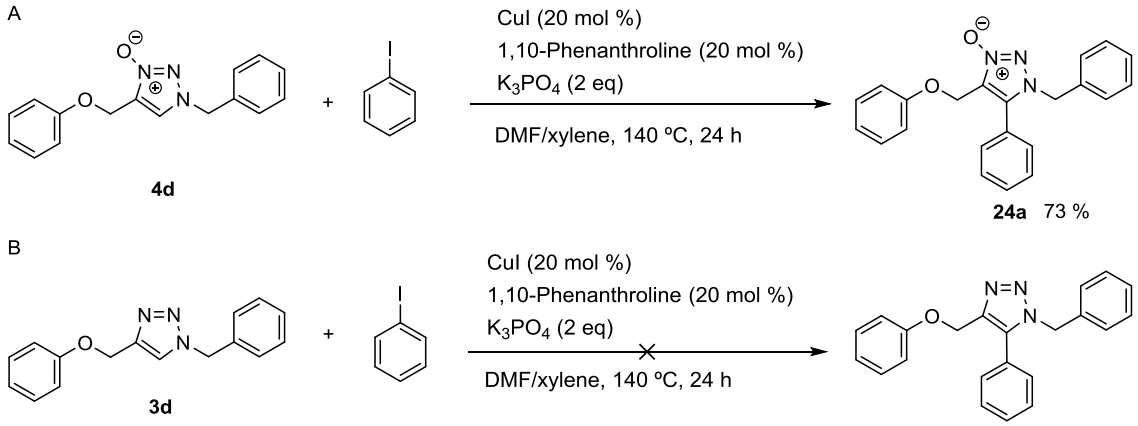
[a] Molar ratio: triazole N-oxide **4**/iodo(hetero)arene = 1:2. [b] Initial concentration of substrate 4 0.1M. Yields of isolated pure products.

As shown in the table, all the trisubstituted N-oxides **24** were obtained in yields ranging from moderate to good, but in general, yields were slightly lower when compared to 1,5-disubstituted triazole N-oxides **23** (Table 3.6). Again, the reaction was compatible with N-benzylic substrates and diiodoarenes. Interestingly, in case of pyridyl-substituted

triazoles **24m-o**, different combinations of two heteroaryl groups at the C(4) and C(5) positions of the triazole N-oxide were available.

3.3.3.3 Mechanism and control experiments of copper-catalyzed cross-coupling reactions with triazole N-oxides

In order to study the influence of the N-oxide moiety on the activation of the reaction, we compared the direct arylation reaction of the 1-benzyl-4-(phenoxymethyl)-1,2,3-triazole N-oxide (**4d**) (Scheme 3.16 A) and its counterpart triazole (**3d**) (Scheme 3.16 B) under the same reaction conditions.

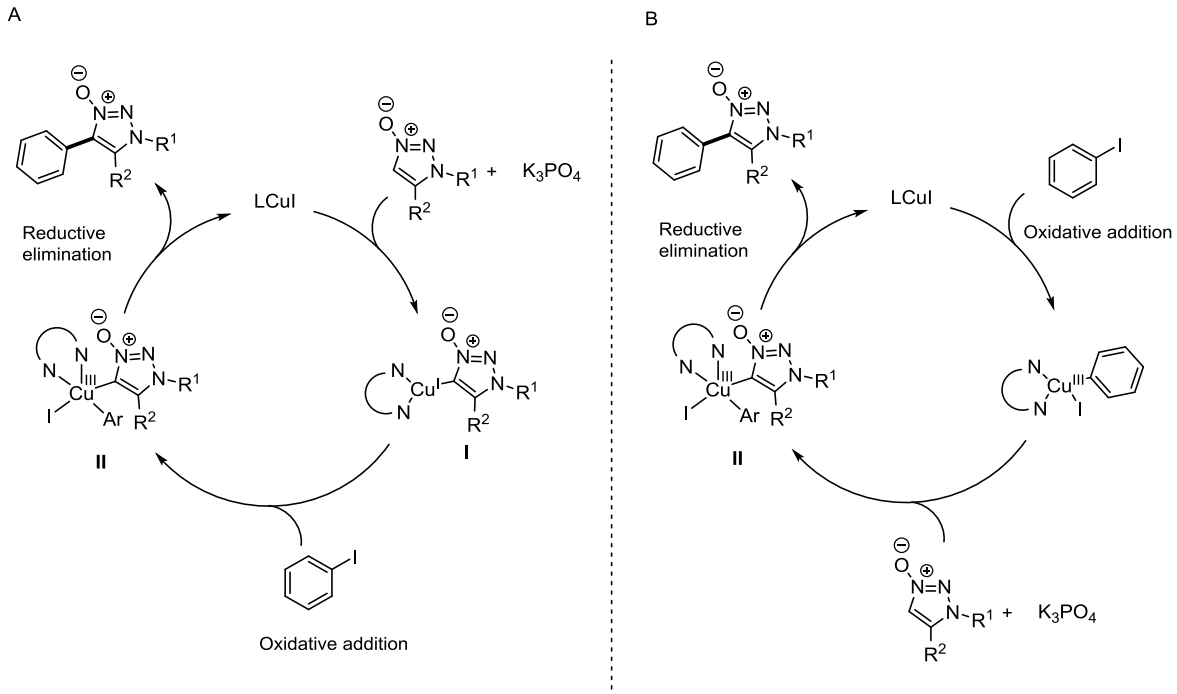


Scheme 3.16. Compared reactivity of the triazole N-oxide **4d** and its triazole counterpart **3d** in copper-catalyzed arylation reaction with iodobenzene.

When the reaction was performed with triazole **3d**, no traces of the expected product were detected in the reaction crude and the starting material was recovered unchanged. In contrast, the N-oxide **4d** gave a clean arylation to the product **24a**, meaning that the N-oxide moiety effectively activates the reaction, even at the remote C(5)-H bond position and not only at the α-proton adjacent to it.

A pair of mechanism proposal for the copper-catalyzed direct arylation of triazole N-oxides with iodobenzene is shown in Scheme below 3.17. The mechanism is explained with 1,5-disubstituted triazoles but the same procedure is supposed to happen with 1,4-disubstituted ones. Unlike the Pd(0) coupling reaction, in which the oxidative addition is considered to happen first, in copper-catalyzed reaction the relative order of this step is uncertain. However, some reports and some experimental data based on the reactivity of isolated LCu^{I} nucleophile complexes support the mechanism in which the coordination

of copper-nuchleophile occurs first (mechanism A).[137] Thus, herein we propose a plausible mechanism where the deprotonated triazole N-oxide nucleophile attacks the copper center to form intermediate I first step of the catalytic cycle. Then, oxidative addition is happening to form a copper (III) intermediate[138] with a final reductive elimination to from the product.



Scheme 3.17. Plausible mechanisms of the copper-catalyzed direct arylation reaction of 1*H*-1,2,3-triazole N-oxides with iodobenzene.

3.4 Conclusions

Considering the increasing practical importance of 1,2,3- triazoles in synthetic chemistry, along with the sustainable nature of C–H bond functionalization, we have developed different methods for the regiocontrolled preparation of 1,4,5-trisubstituted 1*H*-1,2,3-triazole N-oxides, an unprecedented family of heterocyclic compounds.

[137] a) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301. b) Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338.

[138] For selected examples see: a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. b) Xifra, R.; Ribas, X.; Llobet, A.; Poater, A.; Duran, M.; Solà, M.; Stack, T. D. P.; Benet-Buchholz, J.; Donnadieu, B.; Mahía, J.; Parella, T. *Chem.–Eur. J.*, **2005**, *11*, 5146. c) Cohen, T.; Wood, J.; Dietz, A. G. *Tetrahedron Lett.* **1974**, *15*, 3555.

It is a new way for affording the activation of triazoles, and products were obtained under mild conditions, compared to nonoxidized triazole counterparts. Firstly, an electrophilic substitution was developed, and the products were obtained in good yields, although, the method was limited to aromatic triazole N-oxides.

An efficient palladium-catalyzed direct arylation reaction was developed for 1,5-disubstituted triazole N-oxides. We were able to avoid the use of expensive phosphines as ligands, and thus, simplify the reaction conditions that was not possible in the case of triazoles. We have demonstrated that N-oxide moiety is activating the reaction because these conditions are not efficient for 1,5-triazoles.

Furthermore,few methods were published about copper-catalyzed triazole coupling reactions which were limited to the use of strong bases, such as, lithium *tert*-butoxide. Herein, a highly efficient copper-catalyzed protocol using milder bases like potassium phosphate, was developed which was compatible with 1,5-disubstituted and 1,4-disubstituted triazole N-oxides.

In general, reactions proceeded in higher yields when 1,5-disubstituted triazole N-oxides were used, which justifies that the most activate C-H bond is the one adjacent to the N-oxide moiety.

4

Copper-catalyzed homocoupling reactions of 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides.

4. Copper-catalyzed homocoupling reactions of 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides.

The forth chapter will be focused on three main sections: the synthesis of C-4 ligand directed disubstituted triazole N-oxides, the synthesis of different 4,4'- and 5,5'-bistriazole N-dioxides and the synthesis of biaryl bistriazole N-dioxides.

4.1 Introduction

4.1.1 Directing groups in C-H functionalization

Given the large number and diversity of C-H bonds generally present in a molecule, it is important to control the regioselectivity. The use of a directing group or functional group can largely overcome the issue of regiocontrol by coordinating or binding with the catalyst to come into a non-functionalized position proximal to the directing group, which in most of the cases is the *ortho* position of the directing group. The key factor for the facilitation of the activation of unreactive CH bonds is the stabilization formed between the π system of the arene or alkene and the transition metal center. Generally, the reaction proceeds by the formation of a thermodynamically favorable five or six membered metallacycle intermediate.[139] This process is considered one of the most promising approaches as a new carbon–carbon or carbon–heteroatom bond.[140] In this manner, previously mentioned classical catalytic cross-coupling reactions involving the coupling of organohalides with organometallic species R−M (M = Li, MgX, ZnX, BR_2, SnR_3, SiR_3, etc.) can be replaced in certain cases by more atom-economical and sustainable C−H functionalization processes.

Furthermore, one of the main inconvenient is that additional synthetic steps are often required to both install the DG into the starting material and to manipulate it after C-H functionalization. Nevertheless, some of the directing groups can play an important role in further applications, especially those derived from carboxylic acids and carboxylic

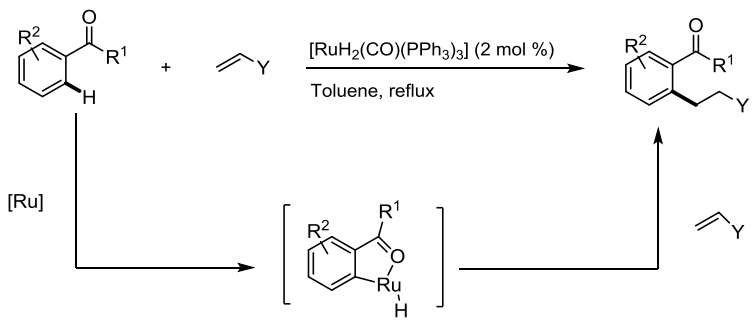
[139] For selected reviews, see: a) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236. c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

[140] For some selected reviews, see: a) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev*. **2009**, *38*, 2447. b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. c) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949. d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev*. **2007**, *36*, 1173. e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731.

acids themselves[141]. In addition, significant attention has been focused on the development of easily modifiable or removable directing groups.[142]

Historically, the first example reported of transition metal catalyzed, regioselective functionalization of a C-H bond was in 1955 by Murahashi, in which insertion of CO took place catalyzed by cobalt at high temperatures.[143] But it was not until 1963, when Kleiman and Dubeck defined the reaction mechanism and characterized the cyclometalated complex.[144] Several improvements were made over the years, but the main problem was that in all of them stoichiometric amounts of metal were used.

Although some advances were made respect with this main problem, it was not until 1993 when Murai[145] and co-workers reported a highly efficient and selective ortho-alkylation reaction of aromatic ketones with olefins catalyzed by ruthenium salts (Scheme 4.1).



Scheme 4.1. Ruthenium catalyzed *ortho* alkylation of aromatic ketones.

Since this pioneering work, a wide variety of functional groups have been used as directing groups. Recent research in this area has revealed that nitrogen-containing functional groups such as pyridines and derivatives,[146] imines, oximes (and ethers),

[141] Drapeauand, M. P.; Gooßen, L. J. *Chem. Eur. J.* **2016**, *22*, 18654.

[142] a) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Asian J. Org. Chem.* **2015**, *4*, 846. b) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145. c) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

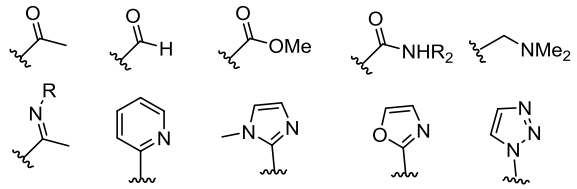
[143] a) Murahashi, S. *J. Am. Chem. Soc*. **1955**, *77*, 6403.

[144] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc*. **1963**, *85*, 1544.

[145] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

[146] For representative examples, see: a) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2011**, *133*, 4455. b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2009**, *131*, 9651. c) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc*. **2009**, *131*, 3466. d) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc*. **2008**, *130*, 14926. e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 11904. f) Zaitsev, V. G.; Shabashov, D.; Daugulis,

oxazolines and amidines as well as oxygen-containing functional groups such as amides, esters, ketones, carboxylic acids and phenols effectively act as directing groups for regioselective C–H functionalization[147] (Scheme 4.2). It should be highlight that triazoles could also act as ligand directing groups.[148]



Scheme 4.2. Some examples of directing groups.

In the last decades, in order to extend the concept of directed C-H functionalization, a wide variety of different directing groups have been developed. Indeed, in 2005, Daugulis[146f] reported the first bidentate ligand, 8-aminoquinoline. Since then, different bidentate directing groups were developed.[149]

4.1.1.1 Directing groups in copper-catalyzed C-H functionalization

In the last decades, copper has been explored as an alternative catalyst for the functionalization of C-H bonds.[150] Indeed, in 2006 Yu[151] reported chelated directed

O. *J. Am. Chem. Soc*. **2005**, *127*, 13154. g) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **2001**, *123*, 10935. h) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem*. **1997**, *62*, 2604.

[147] Some representative examples of ligand directed groups: a) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem*. **2012**, *124*, 2290; *Angew. Chem. Int. Ed*. **2012**, *51*, 2247. b) Li, Z.; Ma, L.; Xu, J.; Kong, L.; Wu, X.; Yao, H. *Chem. Commun*. **2012**, *48*, 3763. c) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Chem. Asian J*. **2012**, *7*, 1208. d) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc*. **2011**, *133*, 13864. e) Thirunavukkarasu, V. S.; Cheng, C.-H. *Chem. Eur. J*. **2011**, *17*, 14723. f) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci*. **2010**, *1*, 331.

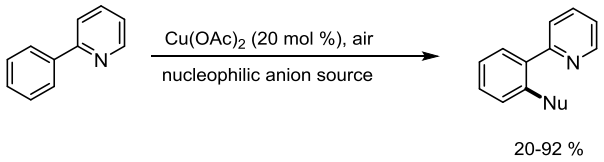
[148] Cera, G.; Haven, T.; Ackermann, L. *Chem. Eur. J*. **2017**, *23*, 3577. c) Zhang, G.; Xie, X.; Zhu, J.; Li, S.; Ding, C.; Ding, P. *Org. Biomol. Chem*. **2015**, *13*, 5444. d) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed*. **2014**, *53*, 3868; *Angew. Chem*. **2014**, *126*, 3949. e) Ye, X.; Shi, X. *Org. Lett*. **2014**, *16*, 4448.

[149] For a selected review, see: a) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev*. **2020**, *120*, 1788.

[150] For a selected review, see: Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem*. **2011**, *123*, 11256; *Angew. Chem. Int. Ed*. **2011**, *50*, 11062.

[151] Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc*. **2006**, *128*, 6790.

oxidative C-H functionalization reactions utilizing a pyridil group as a directing group as it is shown in the following Scheme 4.3.



Scheme 4.3. Cu(II)-mediated C-H functionalization.

It was demonstrated that a variety of 2-arylpyridines could be reacted under different nucleophiles. Cheng subsequently expanded the reaction to acyloxylation of 2-arylpyridines using different aryl and alkyl anhydrides, providing a different set of mono- or diacetoxylated 2-arylpyridines in moderate to good yields. [152]

Besides, Miura and Hirano developed a copper-mediated intermolecular direct biaryl coupling of arylazines and azoles[153] (Scheme 4.4 A), utilizing pyridil groups as ligand directed groups. Moreover, they reported the coupling between indoles and 1,3-azoles by the introduction of the 2-pyrimidil directing group in the indole.[154] (Scheme 4.4 B). Several other reports were published using different directing groups which were catalyzed by copper (II) salts.[155]

A major breakthrough came when bidentate directing groups were utilized for C-H functionalization under copper-catalyzed reactions.[156] As an example, Miura and co-workers highlighted the potential of bidentate directing groups for use in direct biaryl coupling through a doble C-H activation in copper catalyzed reactions[157] (Scheme 4.4 C).

[152] Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415.

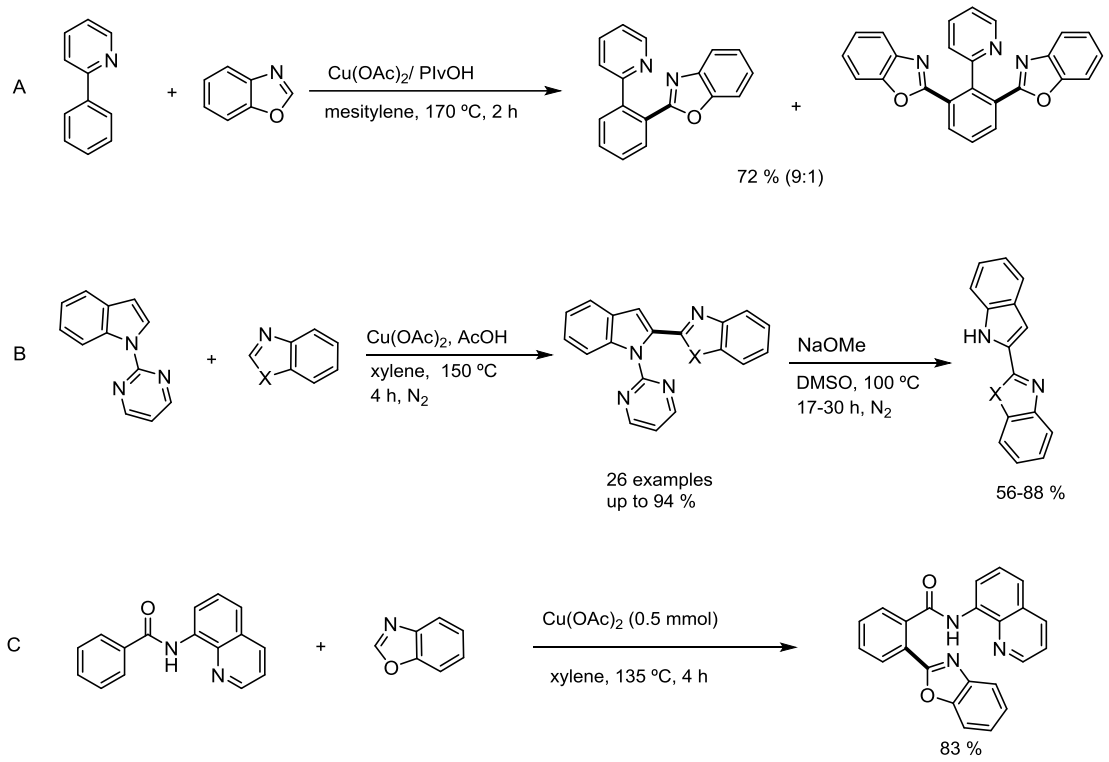
[153] Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc*. **2011**, *133*, 2160.

[154] Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed*. **2012**, *51*, 6993.

[155] For some selected examples, see: a) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 10784. b) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 11590. c) Shang, M.; Sun, S. Z.; Dai, H. X.; Yu, J. Q. *Org. Lett*. **2014**, *16*, 5666.

[156] For some selected examples, see: a) Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed*. **2017**, *56*, 5353. b) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043. c) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842.

[157] Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem*. **2013**, *125*, 4553; *Angew. Chem. Int. Ed*. **2013**, *52*, 4457.



Scheme 4.4. C-H functionalization of azoles by Miura, Hirano and co-workers.

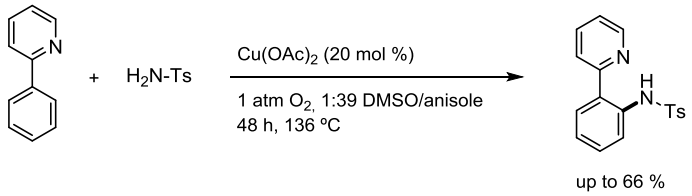
Apart from C-C bond formation, ligand directed copper-catalyzed C-H activation was also applicable to C-heteroatom bond. In this way and taking into consideration the original study of Yu,[151] Chatani reported chelate-directed amination of 2-phenylpyridine derivatives with aniline under stoichiometric $Cu(OAc)_2$.[158]

Further improvements led to the use of catalytic amount of copper (II) salts.[159] As an example, Nicholas[160] published the amidation of 2-phenylpyridine utilizing 20 mol % of copper acetate as depicted in Scheme 4.5.

[158] For other examples of stoichiometric use of Cu(II) salt, see: a) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J. *Q. J. Am. Chem. Soc*. **2014**, *136*, 3354. b) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. c) Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun*. **2009**, 3413. d) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett*. **2006**, *35*, 842.

[159] For some selected examples, see: a) Martínez, A. M.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun*. **2014**, *50*, 2801. b) Li, Q.; Zhang, S.–Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett*. **2014**, *16*, 1764. c) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett*. **2014**, *16*, 2892. d) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal*. **2010**, *352*, 632.

[160] John, A.; Nicholas, K. M. *J. Org. Chem*. **2011**, *76*, 4158.



Scheme 4.5. Amidation reaction under catalytic copper (II) acetate.

Other carbon heteroatom bond formation are also possible under copper-catalyzed reactions, such as, sulfenylations,[158b] methylthiolations,[161] arylthiolations[162] and azidations.[163]

4.1.2 Synthesis of bistriazoles via CuAAc reactions

Bis(1,2,3-triazoles) have gained significant attention due to their potential application in supramolecular, pharmaceutical, biological and organometallic chemistry.[164]

4.1.2.1 Synthesis of 4,4'-bistriazoles

In recent years, few methods for the synthesis of 4,4' bistriazoles have been reported, based on the one-pot double CuAAC reaction of 1,3-butadiyne with azides or the two successive CuAAC reactions with different or same azides that require the deprotection of the second reactive site to liberate another alkyne moiety. In this manner, Fiandanese[165] utilized a trimethylsilylgroup as protecting group for the selective cycloaddition reaction (Scheme 4.6 A).[166]

[161] a) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, *80*, 4116. b) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett*. **2010**, *12*, 1644.

[162] a) Sharma, P.; Jain, N. *J. Org. Chem.* **2019**, *84*, 13045. b) Zhu, L.; Cao, X.; Qiu, R.; Iwasaki, T.; Reddy, V. P.; Xu, X.; Yin, S.-F.; Kambe, N. *RSC Adv.* **2015**, *5*, 39358.

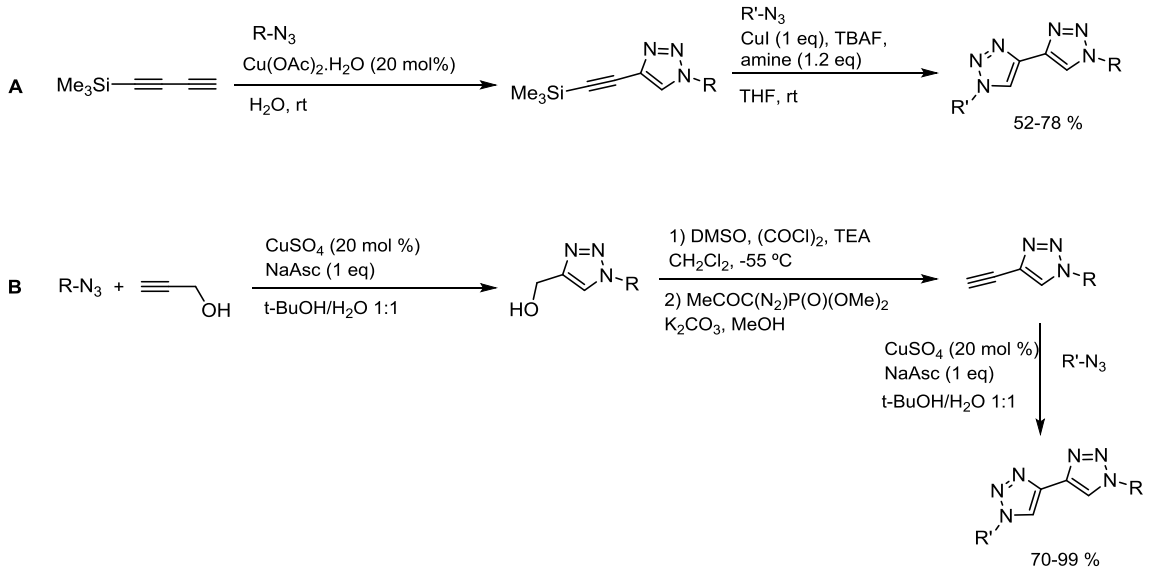
[163] Azad, C. S.; Narula, A. K. *RSC Adv.* **2015**, *5*, 100223.

[164] Zheng, Z.-J.; Wang, D.; Xu, Z.; Xu, L.-W. *Beilstein J. Org. Chem.* **2015**, *11*, 2557.

[165] a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573. b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett*. **2003**, *44*, 9087.

[166] For other examples, see: a) Boratyński, P. J.; Kowalczyk, R. *J. Org. Chem.* **2016**, *81*, 8029. b) Doak, B. C.; Scanlon, M. J.; Simpson, J. S. *Org. Lett.* **2011**, *13*, 537.

Alternatively, our group[167] have developed a similar method which starts with the CuAAC reaction of propargyl alcohol and azides followed by Swern oxidation and Bestmann-Ohira homologation reaction, and finally, another CuAAC reaction to provide unsymmetrical bistriazoles (Scheme 4.6 B).



Scheme 4.6. Synthesis of 4,4'-unsymmetric bistriazoles.

In this way, both symmetric and asymmetric bistriazoles could be obtained.

4.1.2.2 Synthesis of 5,5'-bistriazoles

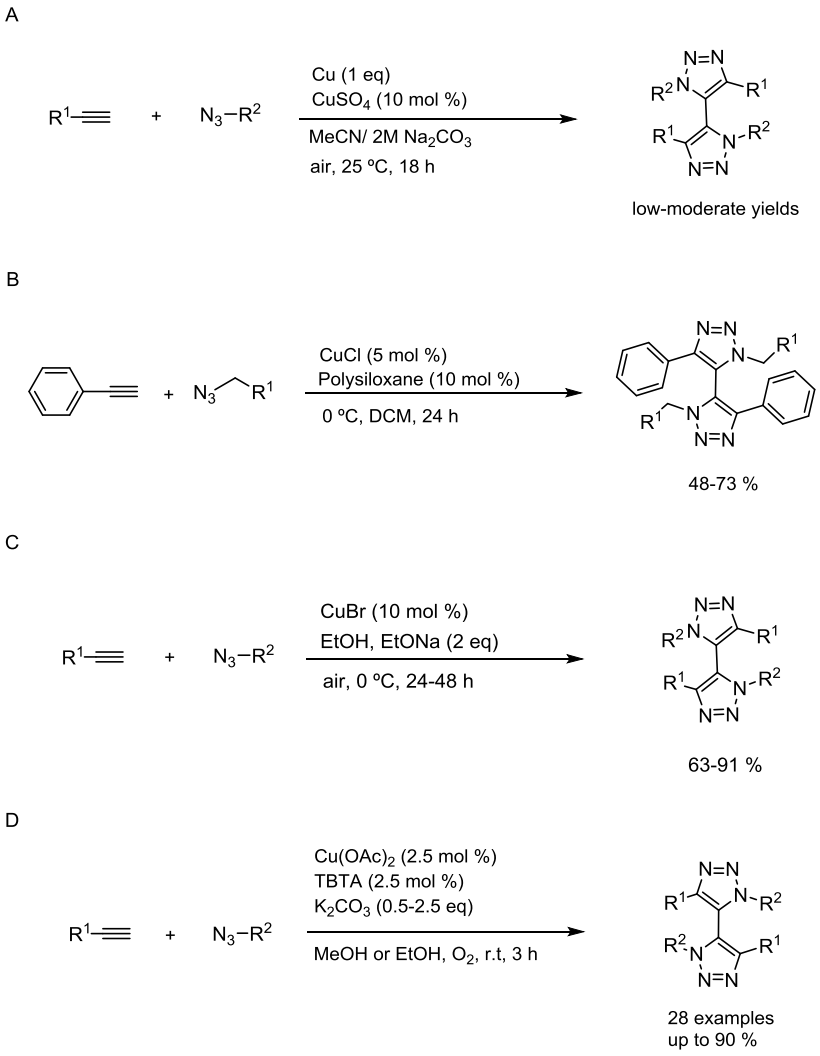
The synthesis of optically active 5,5'-bistriazoles is expected to be of the most interesting for the synthesis of new chiral ligands and auxiliaries. The possible impediment of the free rotation about the axis, which is called atropisomerism, made the bistriazole chiral.[168]

Originally, Sharpless[54] observed that CuAAC reactions provided a minor impurity, although, it was not until 2007, when Burgess[74b] observed that the minor impurity formed in CuAAC was attributed to the oxidative dimer, which depending on the reaction conditions could be afforded as major product. Hence, they successfully developed an oxidative coupling method starting from azides and terminal alkynes to obtain with

[167] Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010**, *12*, 1584.

[168] a) Burgess, K.; Angell, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.

moderate to high yields by using stoichiometric amount of Cu powder, catalytic amounts of $CuSO_4$ (10 mol %) and utilizing 1:1 mixture of MeCN/ 2M Na_2CO_3 (Scheme 4.7 A).



Scheme 4.7. Synthesis of 5,5'-bistriazoles.

Jeon also reported the formation of bistriazoles in low to moderate yields and selectivities in the presence of CuI or CuBr and two equivalents of diisopropylethylamine (DIPEA).[169] However, it was observed that only alkynes containing propargylic ethers and acetylenic amides could specifically result in moderate to good yields. The oxidative coupling-click dimerization did not work well when the alkynes or azides were linked directly with

[169] a) Kwon, M.; Jang, Y.; Yoon, S.; Yang, D.; Jeon, H. B. *Tetrahedron Lett.* **2012**, *53*, 1606. For other example using CuI/DIPEA or Et_3N system, see: b) Oladeinde, O. A.; Hong, S. Y.; Holland, R. J.; Maciag, A. E.; Keefer, L. K.; Saavedra, J. E.; Nandurdikar, R. S. *Org. Lett.* **2010**, *12*, 4256. c) Del Hoyo, A.; Latorre, A.; Diaz, R.; Urbano, A.; Carreño, M. C. *Adv. Synth. Catal.* **2015**, *357*, 1154.

hindered group or aromatic moiety. As a solution, Xu[170] modified the stability and the catalytic activity of active Cu^{I} species with amine-functional polysiloxanes.[171] The reaction was carried out at 0 ºC and was catalyzed by CuCl and the polysiloxanes in 10 mol %, affording bistriazoles in moderate to good yields (Scheme 4.7 B).

Cuevas-Yañez[74a] and Zhang[172] independently realized that some of the key factors for the control of bistriazole/5-prototriazole ratio were the temperature or the base (Scheme 4.7 C). Concerning all the advances made,[164] Zhu[173] made a breakthrough and provided a method that achieved high conversion and good selectivity towards 5,5'-bistriazole, which was compatible with aromatic azides (Scheme 4.7 D). This method consist on the use of potassium carbonate as an additive, methanol or ethanol as solvent and an atmosphere of oxygen.

Finally, Pericàs[174] studied the synthesis and configurational stability of 5,5'-bistriazoles and proved that this type of bistriazoles have big potential. Indeed, the authors find a catalytic application for their $Sc(OTf)_3$ complexes.

Alternatively, our group published a different synthetic method to afford 5,5'-bistriazoles.[175] *In situ* generated butadiyne was submitted to the CuAAC reaction with 2 equivalents of pivaloyloxymethylazide to give, respectively, 4,4'- bistriazole, followed by a double methylation of the 4,4'-bistriazole with methyl triflate and a *in-situ* N-dealkylation with potassium carbonate to get the target product 5,5'-bistriazole in 61 % yield (Scheme 4.8). However, this method was restricted to some alkyl triflates.

[170] Zheng, Z. J.; Ye, F.; Zheng, L. S.; Yang, K. F.; Lai, G. Q.; Xu, L. W. *Chem. Eur. J.* **2012**, *18*, 14094.

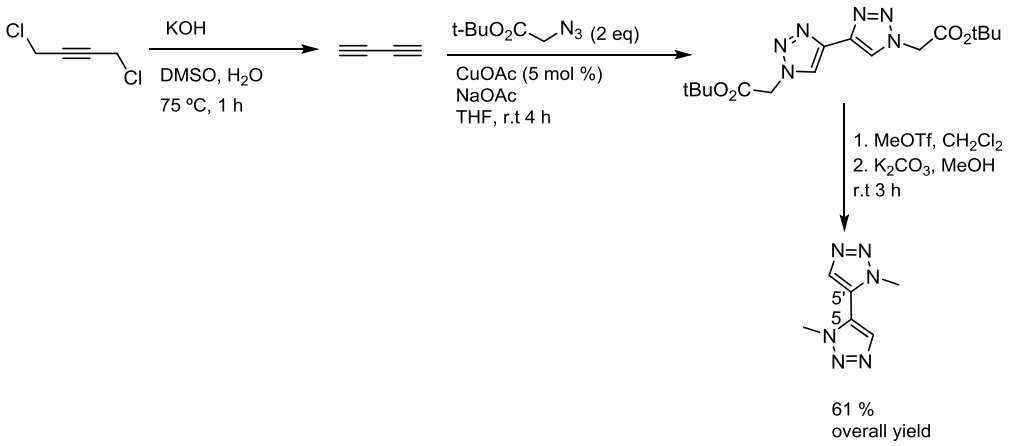
[171] Wang, C. Y.; Zou, J. F.; Zheng, Z. J.; Huang, W. S.; Li, L.; Xu, L. W. *RSC Adv.* **2014**, *4*, 54256.

[172] a) Li, L.; Fan, X.; Zhang, Y.; Zhu, A.; Zhang, G. *Tetrahedron* **2013**, 9939.

[173] Brassard, C. J.; Zhang, X.; Brewer, C. R.; Liu, P.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2016**, *81*, 12091.

[174] Etayo, P.; Escudero-Adán, E. C.; Pericàs, M. A. *Catal. Sci. Technol.* **2017**, *7*, 4830.

[175] Monasterio, Z.; Irastorza, A.; Miranda, J. I.; Aizpurua, J. M. *Org. Lett.* **2016**, *18*, 2511.



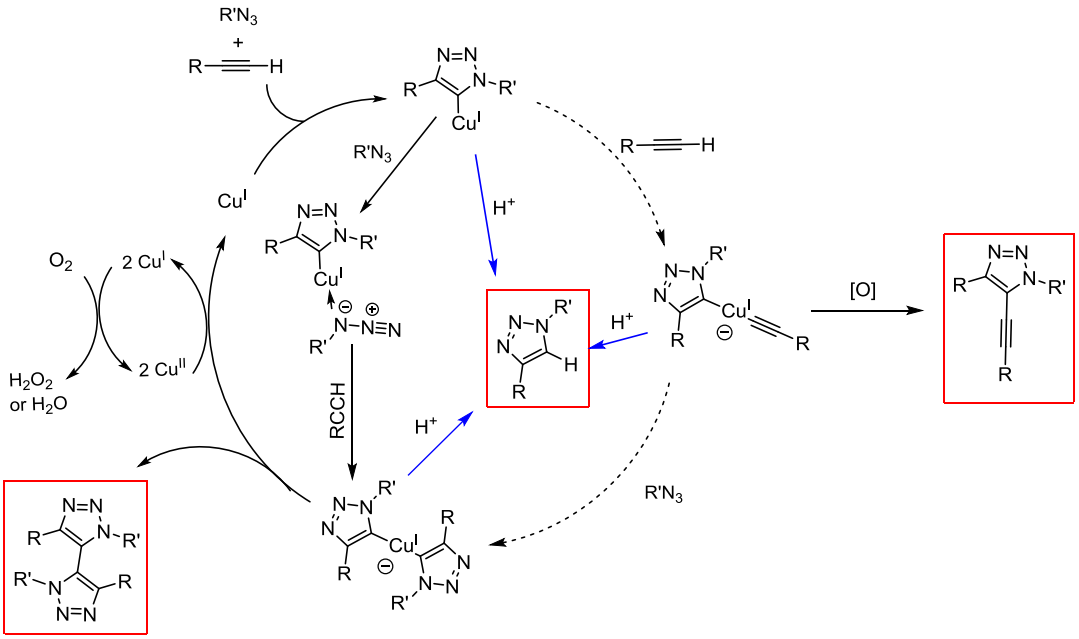
Scheme 4.8. Alternative method for the synthesis of 5,5'-bistriazoles.

4.1.2.2.1 Mechanistic studies of synthesis of 5,5'-bistriazoles

Experimentally, it was demonstrated that 5-prototriazoles and 5-alkynyl-1,2,3-triazoles were not intermediates of the reaction. Thus, the synthesis of 5,5'-bistriazoles was a result of the oxidation of copper triazole intermediates. This hypothesis finds precedence in the "aromatic Glaser-Hay"[176] reaction, in which the conjugate base of an aromatic heterocycle is oxidized by copper (II) salts to the homocoupled dimmer under aerobic conditions.

Although similar pausible mechanisms have been published[172] a review published by Zhu[173] showed that the mechanism started with the formation of triazolyl copper complex, which recruits either an alkyne or azide to initiate the second triazole formation. In case copper triazolyl complex reacts with alkyne, it goes through π-complexation followed by formation of an σ-complex to further react with the azide and form bistriazlyl copper intermediate. The oxidation of copper (I) bistriazolide by copper (II) salts gives bistriazole as product, while the resulting copper (I) is recycled back to give copper (II) via aerobic oxidation. As it is marked by blue arrows, protonation of different intermediates could occur and thus, 1,4-disubstituted triazoles are formed. This particular side product could be dismissed by the presence of a base.

[176] Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052.



Scheme 4.9. Pausible mechanism for the formation of 5,5'-bistriazoles.

Although mononuclear species were drawn, in reality, the species formed are bi or multinuclear copper centers.[177]

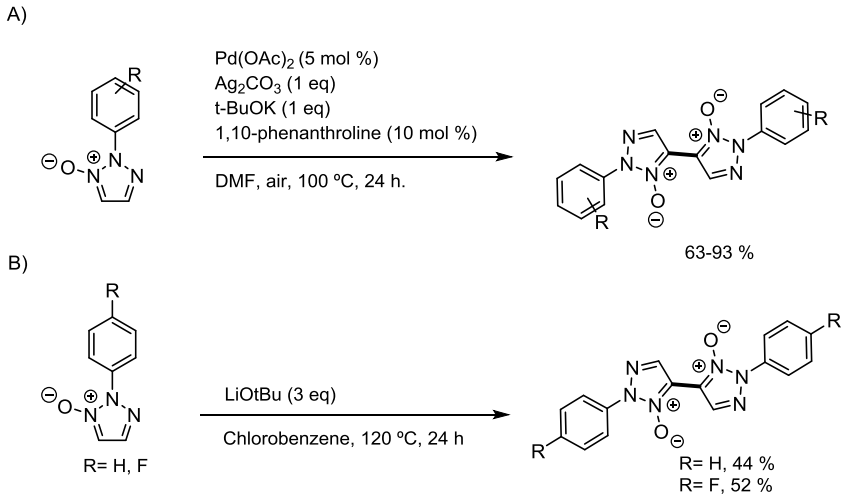
4.1.2.3 Synthesis of bistriazoles by CH activation of 2*H*-1,2,3-triazole N-oxides

Originally, 2*H*-1,2,3-bistriazoles N-oxides were detected as side products of different cross-coupling reactions.[129,178] Therefore, Liu, Zhu and co-workers[179] developed a convenient protocol for the homocoupling of 2*H*-1,2,3-triazole N-oxides (Scheme 4.10 A). The reaction provided a new way for developing C-C bonds under mild conditions with several advantages, such as, operational simplicity, highly regioselective and absence of inert atmosphere.

[177] a) Qi, X.; Bai, R.; Zhu, L.; Jin, R.; Lei, A.; Lan, Y. *J. Org. Chem.* **2016**, *81*, 1654. b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068. c) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2006**, *25*, 4097.

[178] a) Zhu, J.; Kong, Y.; Lin, F.; Wang, B.; Chen, Z.; Liu, L. *Eur. J. Org. Chem.* **2015**, 1507. b) Liu, W.; Li, Y.; Wang, Y.; Kuang, C. *Org. Lett.* **2013**, *15*, 4682.

[179] Peng, X.; Huang, P.; Jiang, L.; Zhu, J.; Liu, L. *Tetrahedron Lett.* **2016**, *57*, 5223.



Scheme 4.10. Homocoupling of 2*H*-1,2,3-triazole N-oxides.

Recently, Jain[34] published an example of the oxidative coupling of 2*H*-1,2,3-triazole N-oxides using lithium *tert*-butoxide as base in chlorobenzene at 120 ºC for 24 hours, providing the product in moderate yields (Scheme 4.10 B).

In view of this precedents, we hypothesized that 1*H*-1,2,3-triazole N-oxides could also be good substrates for oxidative couplings and therefore, achieve fully substituted bistriazole N-dioxides.

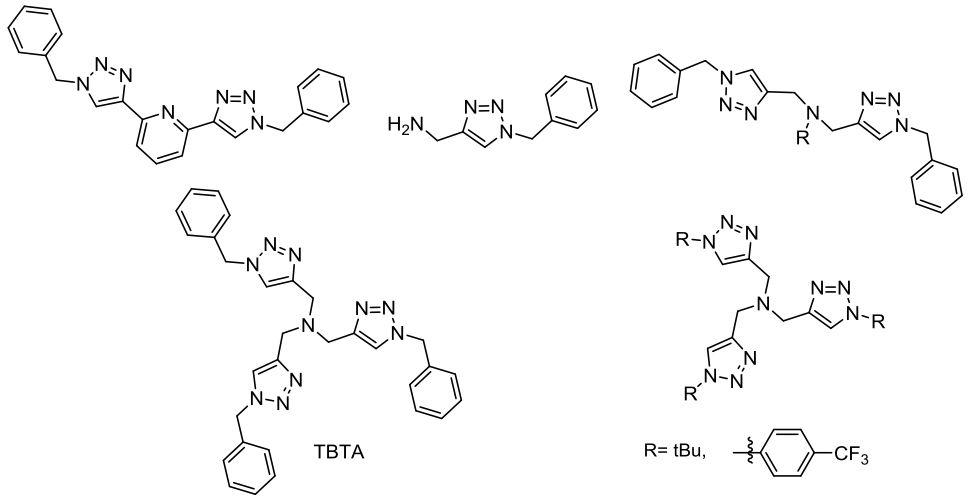
4.1.3 Triazoles motifs as ligands in transition metal catalysis

The success of metal complexes as catalysts for organic transformation has been largely attributed to the variety of different ligands capable of coordinating and tuning the reactivity of the metal center. The design of ligand systems and chelators to provide metal complexes with optimal properties is fundamental in this respect. One challenge is to find novel strategies, which gives access to large sets of potent metal chelators, while at the same time reducing the synthetic complexity of ligand preparation. In that way, 1,2,3-triazoles are good examples for coordination[180], because they are bearing several donor sites, which are key for metal coordination.[181] Moreover, triazoles are astonishingly stable, easy to synthesize and essentially inert to hydrolysis or reduction. It should be

[180] Aromi, G.; Barrios, L. A.; Rubeau, O.; Gamez, P. *Coord. Chem. Rev.* **2011**, *255*, 485.
[181] Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675.

mentioned, that apart from metal catalysis, triazole motifs have also been used as organocatalysts.[182]

There are mainly three modes in which the triazole is combining with the metal, such as, N3, N2 or C5 coordination with deprotonated triazoliums to form N-heterocyclic carbenes.[49d] In the majority of reports of triazole containing chelators, N3 of the triazole is assumed to be coordinated to the metal center. In view of the coordination capability, Fokin[183] synthesized a family of polytriazole containing compounds as stabilizing agents for Cu(I) and investigated their effect on the yield of the Cu(I) catalyzed cycloaddition, in which, tris-(benzyltriazolylmethyl)amine (TBTA) was identified as being particularly efficient (Scheme 4.11). This particular ligand is effective because the amine provides additional electron density to the metal center while the triazole facilitates the formation of Cu(I) acetylide/ligand complex.[181]



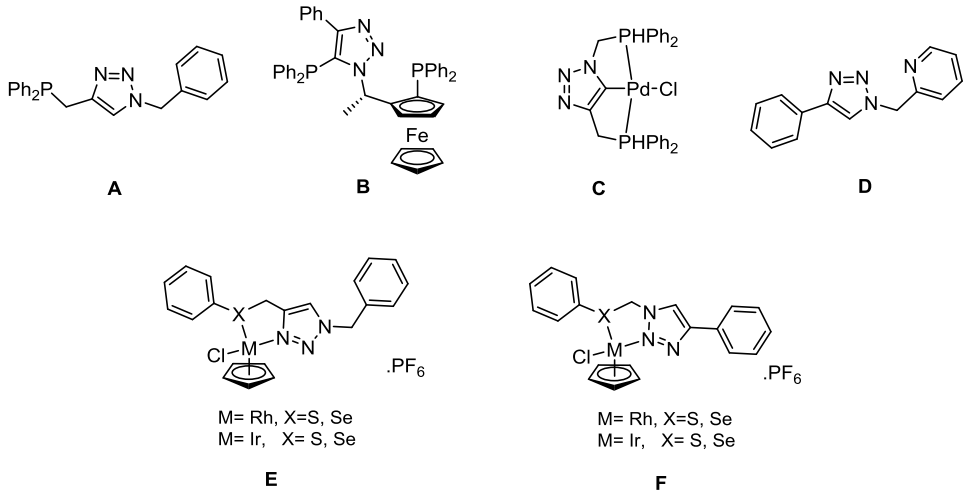
Scheme 4.11. Some examples of Fokin's politriazoles.

Furthermore, a wide variety of triazoles could act as ligands for potential applications in palladium and other transition metal catalyzed reactions, such as, triazole-containing

[182] a) Zhu, Y. W.; Yi, W. B.; Cai, C. *Fluorine Chem.* **2011**, *132*, 71. b) Zhao, Y.-B.; Zhang, L.-W.; Wu, L.-Y.; Zhong, X.; Li, R.; Ma, J.-T. *Tetrahedron: Asymmetry* **2008**, *19*, 1352. c) Chandrasekhar, B.; Tiwari, B.; Parida, B. B.; Reddy, C. R. *Tetrahedron: Asymmetry* **2008**, *19*, 495.

[183] Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett*. **2004**, *6*, 2853.

analogues of phosphine ligands,[184] bidentate P,N-chelates[185] (Scheme 4.12 A), ferrocenyl complexes[186] (Scheme 4.12 B), pincer ligands[187] (Scheme 4.12 C), which are tridentate ligands with three coplanar donor groups, pyridil ligands[188] (Scheme 4.12 D) and abnormal carbenes for late transition metals.[189] As an example, Zhang synthesized a series of monophosphine-triazole compounds that were effective ligands for palladium complexes used in the cross-coupling reactions of aryl chlorides.[190]



Scheme 4.12. Potentially active triazole ligands.

Remarkably, apart from these ligands, several other functional groups were also potentially active as ligands.[191] As an example, in 2014, Singh and co-workers reported

[184] Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett*. **2005**, *7*, 4907.

[185] a) Dolhem, F.; Johansson, M. J.; Antonsson, T.; Kann, N. *J. Comb. Chem*. **2007**, *9*, 477. b) Detz, R. J.; Heras, S. A.; de Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227.

[186] a) Badèche, S.; Daran, J.-C.; Ruiz, J.; Astruc, D. *Inorg. Chem*. **2008**, *47*, 4903. b) Fukuzawa, S.-i.; Oki, H.; Hosaka, M.; Sugasawa, J.; Kikuchi, S. *Org. Lett*. **2007**, *9*, 5557.

[187] Schuster, E. M.; Botoshansky, M.; Gandelman, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 4555.

[188] a) Amadio, E.; Scrivanti, A.; Chessa, G.; Matteoli, U.; Beghetto, V.; Bertoldini, M.; Rancan, M.; Dolmella, A.; Venzo, A.; Bertani, R. *J. Organomet. Chem.* **2012**, *716*, 193. b) Amadio, E.; Bertoldini, M.; Scrivanti, A.; Chessa, G.; Beghetto, V.; Matteoli, U.; Bertani, R.; Dolmella, A. *Inorg. Chim. Acta*. **2011**, *370*, 388.

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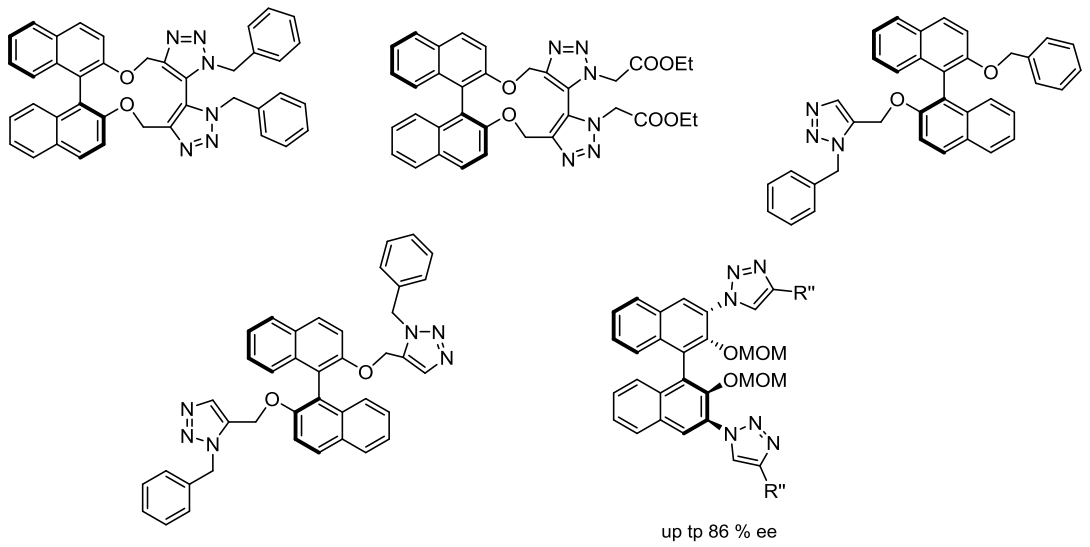
[190] a) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem*. **2006**, *71*, 3928.

[191] For some selected examples, see: a) Vuong, K. Q.; Timerbulatova, M. G.; Peterson, M. B.; Bhadhade, M.; Messerle, B. A. *Dalton Trans*. **2013**, *42*, 14298. b) Zamora, M. T.; Furguson, M. J.; McDonald, R.; Cowie. M. *Organometallics* **2012**, *31*, 5463.

the first Rh(III)/ Ir(III) complexes of 1,2,3-triazole-based organochalcogen ligands[192] (Scheme 4.12 E, F).

Considering the important advances that have been developed to date in a large variety of triazole based ligands, chiral ligands can be considered a reliable strategy for obtaining stereoselective reactions. In this regard, different BINOL derivatives have been synthesized (Scheme 4.13).[193]



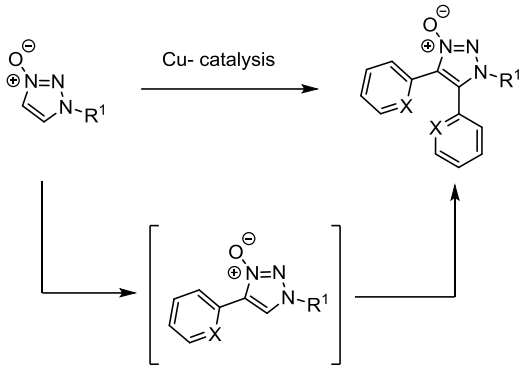
Scheme 4.13. Some BINOL based triazole derivatives.

4.2 Hypothesis and objectives

In view of the precedent discussion, we expected that (hetero)arene halides could be particularly convenient coupling partners to test their function as directing groups in 1*H*-1,2,3-triazole N-oxides.

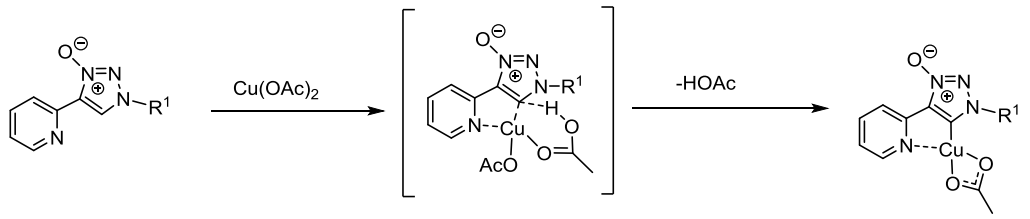
[192] Saleem, F.; Kumar Rao, G.; Kumar, A.; Mukherjee, G.; Singh, A. K. *Organometallics* **2014**, *33*, 2341.

[193] For some selected examples, see: a) Handa, S.; Jin, B.; Bora, P.P.; Wang, Y.; Zhang, X.; Gallou, F.; Reilly, J.; Lipshutz, B. H. *ACS Catal*. **2019**, *9*, 2423. b) Milo, A.; Neel, A. J.; Toste, F. D.; Sigman, M. S. *Science* **2015**, *347*, 737. c) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc*. **2013**, *135*, 14044. d) Beckendorf, S.; Garcia Mancheño, O. *Synthesis* **2012**, *44*, 2162. e) Recsei, C.; McErlean, C. S. P. *Tetrahedron* **2012**, *68*, 464. f) Liu , X.; Yang, X.; Fu, Y.; Zhu, C.; Cheng, Y. *Tetrahedron* **2011**, *67*, 3181. g) Recsei, C.; McErlean, C. S. P. *Tetrahedron: Asymmetry* **2010**, *21*, 149. h) Rajakumar, P.; P.; Raja, R. *Tetrahedron Lett.* **2010**, *51*, 4365.



Scheme 4.14. One-pot synthesis of 1,4,5-trisubstituted triazole N-oxides

As detailed in section 4.1.3, 1*H*-1,2,3-triazoles have been successfully used as ligands for transition-metal catalysis. Thus, we also considered the convenience of exploring the synthesis of diverse bistriazole N-dioxides through the coupling of 1,5-disubstituted triazole N-oxides or 1,4-disusbtituted triazole N-oxides to afford 4,4'-bistriazole N-oxides and 5,5'-bistriazole N-oxides, respectively. As explained in section 4.1.2.2, the formation of 5,5'-bistriazoles could be achieved by oxidative addition of alkyne and azides, but never from the homocoupling of 1,4-disubstituted triazoles. Therefore, we anticipated that the N-oxide moiety together with a ligand directing group in C(4) could coordinate with copper catalyst and facilitate the oxidative coupling to form 5-5'-bistriazole N-dioxides.

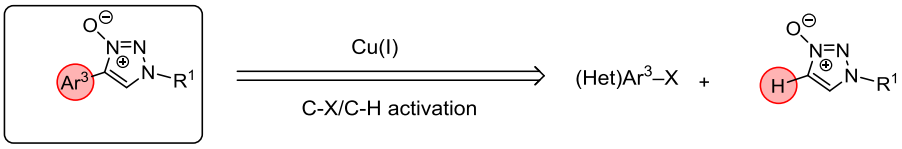


Scheme 4.15. Copper-catalyzed concerted metalation deprotonation (CMD) process of 4-pyridil-1,2,3-triazole N-oxides.

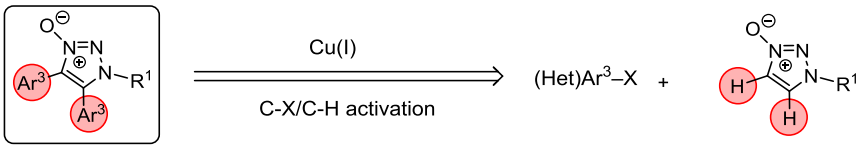
Finally, as previously noted in section 4.1.3, the mayority of triazoles coordinate to the metal through N3. In this way, Fokin[183] synthesized a family of polytriazoles that were effective for coordination with metal. Thus, we hypothesized that previously synthesized iodoaryl triazole N-oxides (**3o-t**) could be good substrates for cross-coupling reactions and therefore build up a wide family of ligands for transition metal catalysis.

In order to test experimentally the hypotheses disclosed above,we addressed our working activity to reach the following activities.

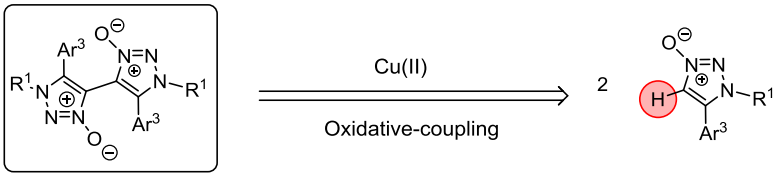
1- Synthesis of 1,4-disubstituted triazole N-oxides using a copper-catalyzed direct arylation of 1-substituted 1*H*-1,2,3-triazole N-oxides with iodo(hetero)arenes.

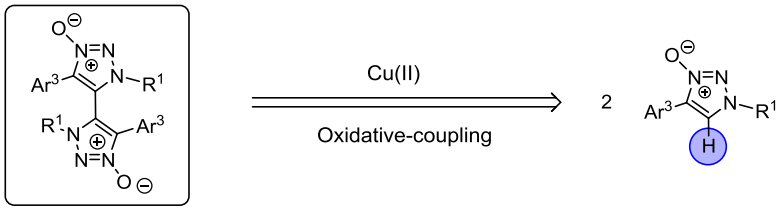


2- Extension of the former methodology to the synthesis of trisubstituted 1*H*-1,2,3-triazole N-oxides from 1-substituted 1*H*-1,2,3-triazole N-oxides with iodo (hetero)arenes.

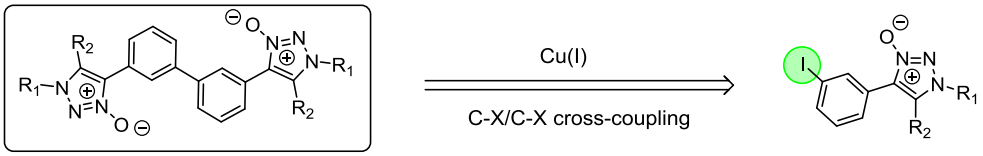


3- Synthesis of a representative series of 4,4'-bistriazole N-oxides and 5,5'-bistriazole N-oxides starting from their counterparts 1,5-disubstituted triazole N-oxides and 1,4-disubstituted triazole N-oxides, respectively, by following an oxidative addition reaction utilizing copper catalysts.





4- Synthesis of biaryl-bistriazole N-oxides through Ullmann type cross-coupling reaction.



4.3 Results and discussion

To address the proposed objectives, we divided our working plan into three tasks. First, the preparation of 1,4-disubstituted and 1,4,5-trisubstituted triazole N-oxides from 1-substituted triazole N-oxides. Second, the synthesis of different 4,4'- and 5,5' bistriazole N-dioxides starting from their counterpart 1,5- and 1,4'- disubstituted triazole N-oxides. Finally, to perform simple cross-coupling arylations to synthesize biphenyl bistriazole N-dioxides.

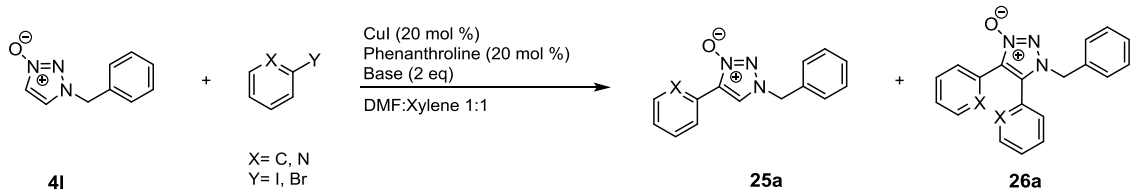
4.3.1 Synthesis of ligand directed 1,4-disubstituted triazole N-oxides

As stablished in the first objective of our working plan, we aimed to developed a methodology to synthesize 1,4-disubstituted triazole N-oxides starting from 1-substituted triazole N-oxides, those which can not be synthesized from the oxidation reaction of 1,4-disubstituted triazoles.

With a substantial amount of 1-benzyl 1,2,3-triazole N-oxide (**4l**), we set out an evaluation of the experimental viables. We started our screening process by using the same reaction conditions as with 1,5- or 1,4-disubstituted triazole N-oxides (chapter 3) as, K_3PO_4 (2 eq) and 2-iodopyridine at DMF/Xylene. However, decomposition of the product took place, probably due to the instability of 1-substituted triazole N-oxides at high temperatures. In this respect, as it is shown in entry 2, we attempt the same reaction conditions but decreasing the temperature to 120 ºC. Unexpectedly, 1,4,5-trisubstituted triazole N-oxides was afforded in total conversion and no traces of 1,4-disubstituted triazole N-oxide was detected.

In parallel, we also performed the reaction utilizing 2-bromopyridine as coupling partner (Table 4.1, entry 3) in order to test if a different ratio of products could be obtained but the same result was afforded.

Table 4.1. Screening of the synthesis of 1,4-disubstituted triazoles.



Entry	Aryl Halide (eq)	Base (eq)	T (ºC)	Time (h)	Conversion	Ratio **25a**/**26a**
1	2-iodopyridine (2)	K_3PO_4 (2)	140	24	---	---
2	2-iodopyridine (2)	K_3PO_4 (2)	120	24	>90	0/100
3	2-bromopyridine (2)	K_3PO_4 (2)	120	24	>90	0/100
4	2-iodopyridine (2)	K_3PO_4 (2)	120	5	>80	30/70
5	2-iodopyridine (1.5)	K_3PO_4 (2)	120	5	80	50/50
6	2-iodopyridine (1)	K_3PO_4 (1)	100	24	80	>85/ <15
7	2-iodoanisole (2)	K_3PO_4 (2)	120	24	>90	100/0

[a] Reaction conditions: 1-substituted triazole N-oxide (1 mmol), aryl iodide (1.1 mmol), CuI (20 mol %), 1,10-phenanthroline (20 mol %), K_3PO_4 (1 eq), DMF:Xylene 1:2 at 100 ºC for 24 hours.

Encouraged by these results, we further analyze if shorter reaction times could avoid the second arylation reaction. Indeed, we were able to detect partial conversion of 1,4-substituted triazole N-oxides (entry 4). At this stage, we decided to use 1.5 equivalents of 2-iodopyridine and notice that we were able to detect 1:1 molar ratio of products (entry 5). Finally, decreasing the temperature to 100 ºC, and using equimolar amounts of base and coupling partners, we afford good conversion and ratio of 1,4-disubstituted triazole

N-oxide (entry 6). To confirm the influence of iodopyridine, we decided to set up the reaction utilizing 2 equivalents of 2-iodoanisole as coupling partner and 2 equivalents of K_3PO_4 at 120 ºC for 24 hours, providing 1,4-disubstituted product as sole product.

In view of this results, it was clear that pyridine was acting as a directing group, which was able to coordinate or bind with copper, and thus deliver the catalyst to a proximal C-H bond, favouring a second coupling reaction. The stabilization interaction formed between the triazole N-oxide and the transition metal center is presumably a key factor for facilitating the activation of the otherwise unreactive C-H bonds.

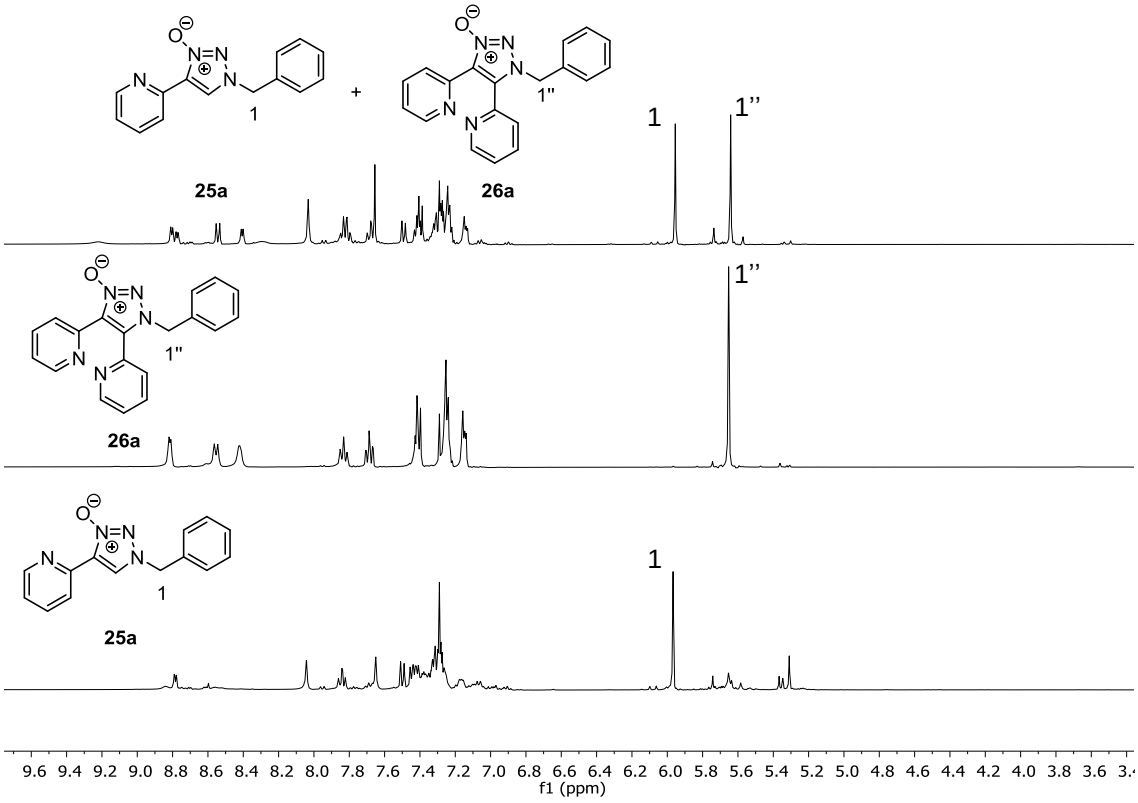
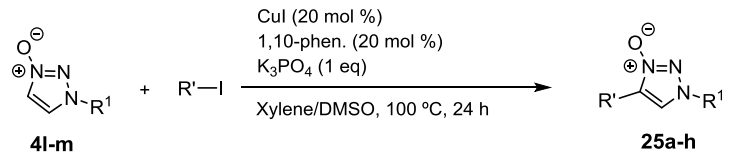
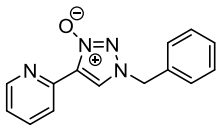


Figure 4.1. 1,4-Disubstituted and 1,4,5-trisubsituted triazole N-oxides.

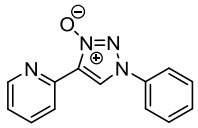
With the optimal conditions in hand, we next explore the scope of the reaction evaluating the influence of different heterocyclic iodides as depicted in table 4.2.

Table 4.2. Scope of 1,4-disubstituted triazole N-oxides.

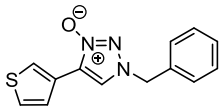




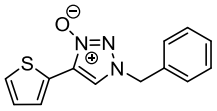
25a (60 %)



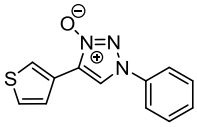
25b (50 %)



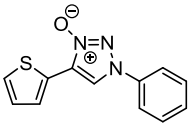
25c (65 %)



25d (63 %)



25e (59 %)



25f (55 %)

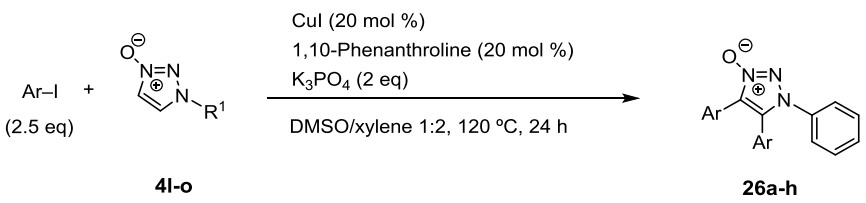
[a] Reaction conditions: 1-substituted triazole N-oxide (15 mg, 0.09 mmol), aryl iodide (0.1 mmol), CuI (20 mol %), 1,10-phenanthroline (20 mol %), K_3PO_4 (1 eq), DMSO:Xylene 1:2 at 100 ºC for 24 hours.

Different heterocycles were inserted from moderate to good yields. Apart from those reported in the table, the reaction could also be performed with other aryl iodides, those which do not act as directing groups.

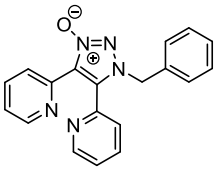
As mentioned in table 4.1, when the reaction was performed with two equivalents of 2-iodopyridine and at 120 ºC total conversion of 1,4,5-trisubstituted triazole N-oxide was afforded. In view of those conditions, we decided to do the scope of the reaction as depicted in table 4.3.

The optimized procedure was general in scope and trisubstituted triazole N-oxides were afforded from moderate to good yields. Moreover, the reaction was compatible with 3-iodo heteroarenes, such as, 3-iodopyridine or 3-thiophenes and it was tolerant with aromatic and aliphatic triazole N-oxides.

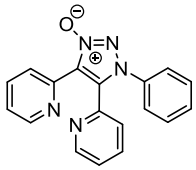
Table 4.3. Scope of 1,4,5-trisusbtituted triazole N-oxides.



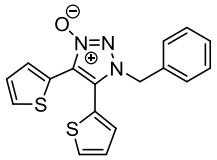
4l-o **26a-h**



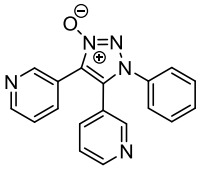
26a (67 %)



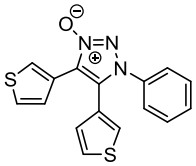
26b (80 %)



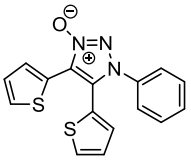
26c (50 %)



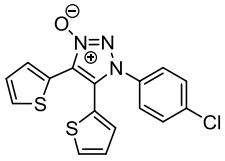
26d (50 %)



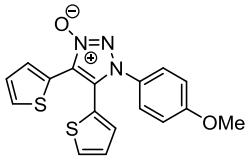
26e (85 %)



26f (60 %)



26g (61 %)



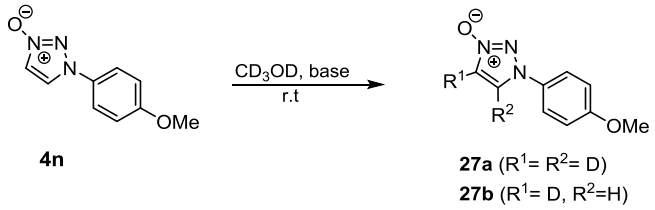
26h (57 %)

[a] Reaction conditions: 1-substituted triazole N-oxide (0.09 mmol), aryl iodide (2.5 eq), CuI (20 mol %), 1,10-phenan. (20 mol %), K_3PO_4 (2 eq), DMSO/Xylene 1:2 at 120 ºC for 24 hours.

4.3.1.1 Control experiments and reaction mechanism

Accordingly, we made some deuteration experiments utilizing strong and weak bases, in order to check the acidity of different protons and demonstrate that the most activated one is the adjacent to the N-oxide moiety (Table 4.4).

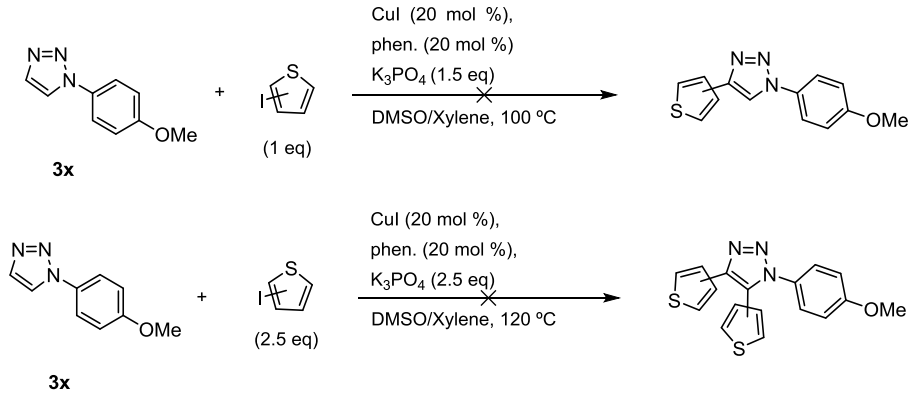
Table 4.4. Deuteration reaction under different base conditions.



Entry	Base	T (ºC)	Time (h)	Product
1	*t*-BuOK	r.t	0.05	**27a**
2	K_3PO_4	r.t	24	**27b**

We first selected a strong base such as, potassium *tert*-butoxide and after 5 minutes C(4) and C(5) positions were deuterated, providing **27a** without selectivity. Instead, when a weak base was used as it is seen in entry 2, we afforded product **27b** with total selectivity and as a unique product.

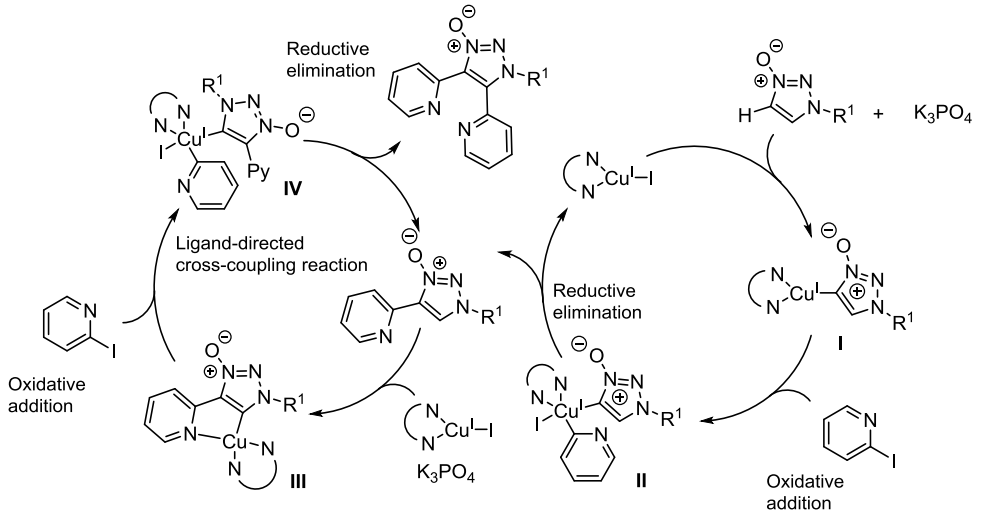
Moreover, we wanted to compare if the reaction optimization of triazole N-oxides was applicable to 1-substituted triazoles as shown in the following scheme 4.16.



Scheme 4.16. Copper catalyzed direct arylation coupling employin 1-(4-Methoxyphenyl)-1,2,3-triazole as substrate.

As expected, the presence of the N-oxide moiety was crucial for the reaction to take place, because when triazoles were submitted under the same conditions the reaction did not take place and starting material was recovered. Even at 120 ºC, the reaction did not worked and starting material was recovered.

Considering these control experiments, a plausible mechanism is depicted in Scheme 4.17.



Scheme 4.17. Plausible mechanism of 1,4- and 1,4,5-trisubstituted triazole N-oxides.

As it was explained in chapter 3, the plausible mechanism starts with the formation of intermediate **I** followed by oxidative addition in this case of 2-iodopyridine to form intermediate **II** and with a final reductive elimination to afford 1,4-disubstituted triazole N-oxide. Remarkably, if we possess a ligand assisted at C(4) a second catalytic pathway could be possible if we add two equivalents of coupling partner. In this way, pyridine could coordinate with copper and facilitate the formation of triazolyl intermediate **III**. Then, another oxidative addition could take place with a final reductive elimination to afford 1,4,5-trisubstituted triazole N-oxide.

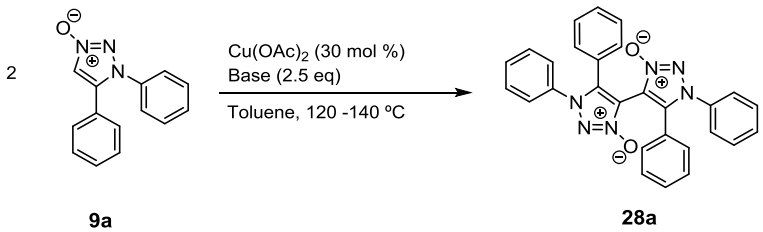
4.3.2 Synthesis of homocoupled-bistriazole N-dioxides

In this section, we aimed to develop a methodology to synthesize novel 4,4'- and 5,5'-bistriazole N-oxides from the corresponding 1,5- and 1,4-disubstituted triazole N-oxides. Both 4,4'- and 5,5'- bistriazole N-oxides could have potential applications as ligands for metal catalysis or organocatalysis.

4.3.2.1 Synthesis of 4,4'-bistriazole N-dioxides

In order to synthesize 4,4'-bistriazole N-oxides, we chose 1,5-diphenyl triazole N-oxide (**9a**) as model substrate, potassium phosphate as base and copper acetate as catalyst at 120 ºC and 140 ºC (Table 4.5, entry 1-2). However, we did not detect traces of product and starting material was recovered.

Table 4.5. Homocoupling reaction of 1,5-triazole N-oxides.



9a **28a**

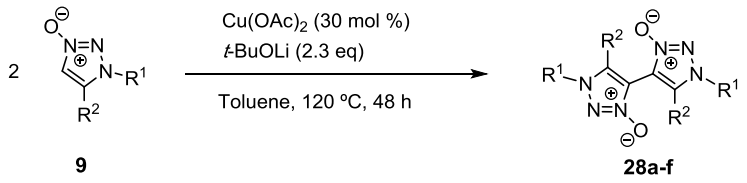
Entry	Catalyst (%)	Base	Oxidant	Conditions	Yield (%)
1	30	K_3PO_4	O_2	120 ºC, 48 h	--
2	30	K_3PO_4	O_2	140 ºC, 24 h	--
3	20	*t*-BuOLi	O_2	120 ºC, 48 h	60
4	30	*t*-BuOLi	O_2	120 ºC, 48 h	70

We next found that the use of a strong base, such as, *t*-BuOLi, provided the product in 60 % yield (entry 3). With the aim to improve the reaction conversion, we increased the catalyst amount to 30 mol %, providing 70 % yield (entry 4). Higher amounts of copper catalyst or higher temperatures did not improve the yield.

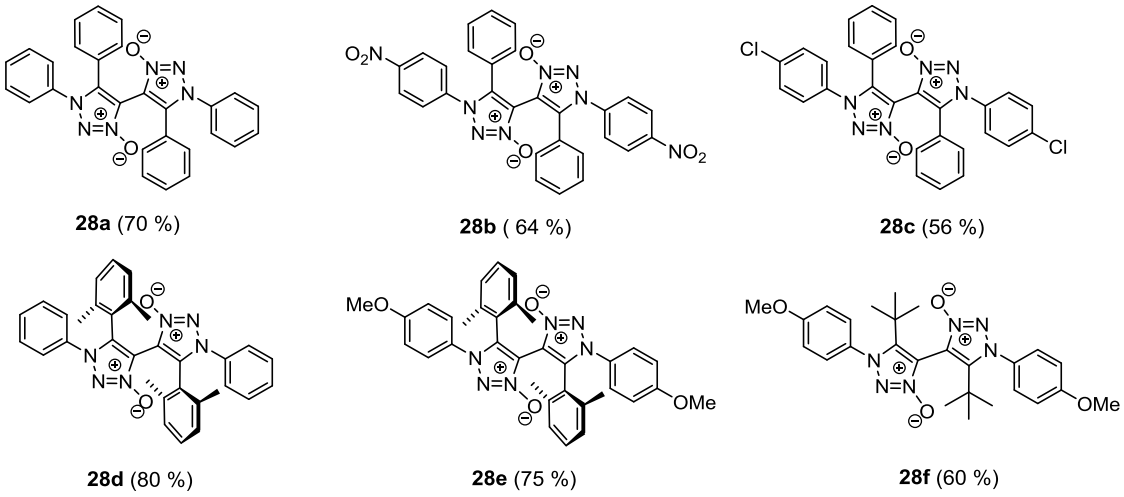
Thus, we optimized the reaction conditions utilizing 2.5 equivalents of *t*-BuOLi, $Cu(OAc)_2$ (30 mol %) and oxygen as oxidant at 120 ºC for 48 hours.

After setting the optimal conditions, we next explore the scope of the reaction, evaluating the influence of C(5) group (Table 4.6).

Table 4.6. Scope of homocoupling reaction of 1,5-triazole N-oxides.



9 **28a-f**



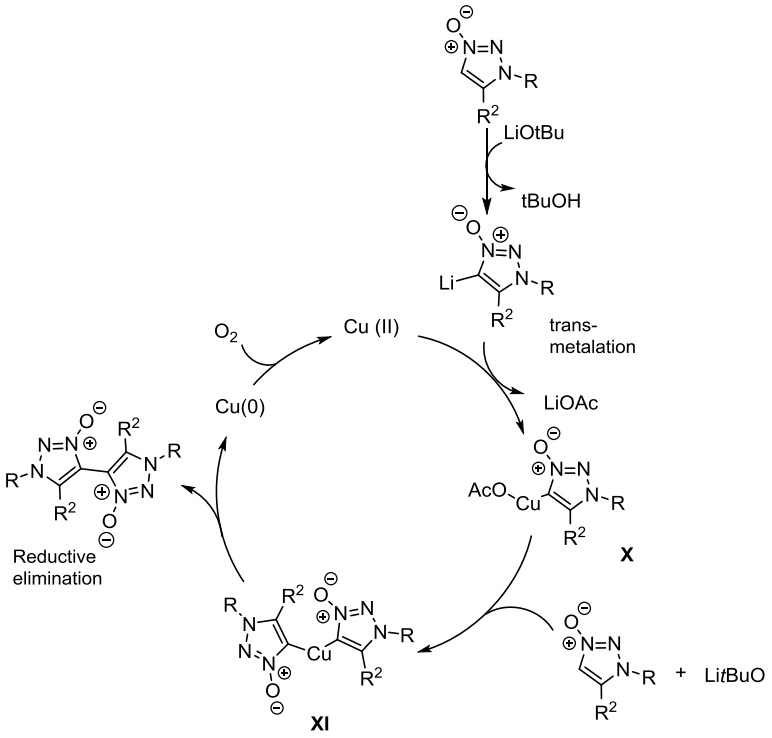
28a (70 %) **28b** (64 %) **28c** (56 %)

28d (80 %) **28e** (75 %) **28f** (60 %)

[a]Reaction conditions: Triazole (1 mmol), $Cu(OAc)_2$ (0.15 mmol), tBuOLi (2.5 eq) in toluene at 120 ºC for 48 h.

As depicted in Table 4.6, a variety of 1,5-disubstituted N-oxides with different steric hindrance in C(5) were found to be effective to afford 4,4'-bistriazole N-dioxides in good yields. Remarkably, 2,6-dimethylphenyl or *tert*-butyl groups were perfectly accommodated. However, the reaction scope was limited to aromatic triazoles, because when benzylic groups were used, decomposition of it was afforded due to the presence of strong bases.

The plausible mechanism of the homocoupling reaction could be the following one.



Scheme 4.18. Pausible pathway to afford homocoupling product catalyzed by copper (II) salt.

First, the copper (II) catalyst reacts with the deprotonated 1*H*-1,2,3-triazole N-oxide to form the intermediate X, which is subsequently displaced by another deprotonated 1,2,3-triazole N-oxide to form intermediate XI. Finally, reductive elimination affords the product and Cu(0) is reoxidized to Cu(II) by O_2.

Finally, we perform an x-ray of compound **28e**. In general, bistriazole rings core are positioned in opposite sites. However, in this case, the x-ray showed that both triazole core were in the same side performing a 77º angle and the two phenyl groups formed a π-stacking. Although the structure was not chiral, it would be an interesting ligand to coordinate with metals.

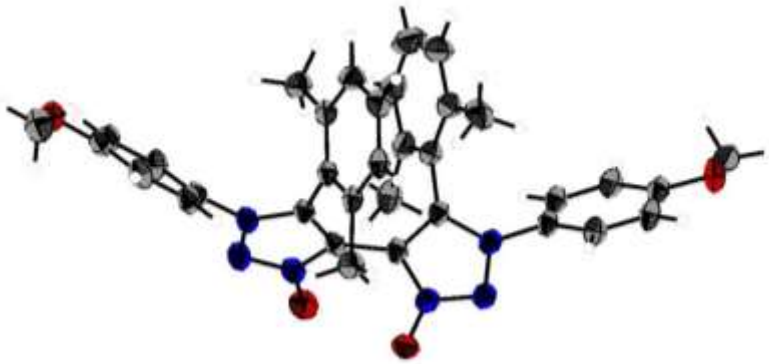
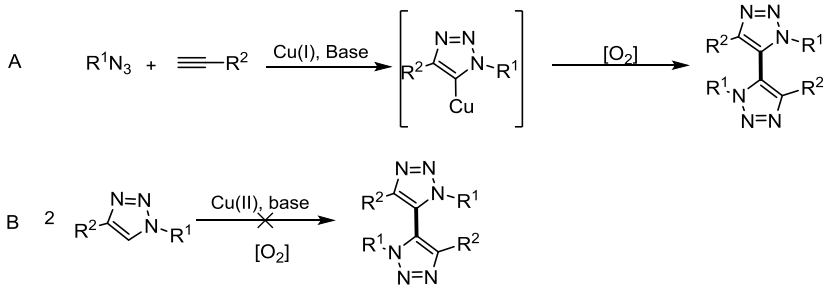


Figure 4.2. X-ray of 4,4'-bistriazole N-dioxide **28e**.

4.3.3 Synthesis of 5,5'-bistriazole N-dioxides

4.3.3.1 Antecedents

As it was explained in the introduction, copper (II) acetate under aerobic conditions catalyzes the formation of 5,5'-bistriazoles from organic azides and terminal alkynes by the oxidative homocoupling of copper (I) triazolide intermediate as shown in Scheme 4.19 A. However, when 5-prototriazoles were treated in the presence of strong bases under catalytic or stoichiometric amount of copper (II) salts the reaction did not proceed[168,172] (Scheme 4.19 B).



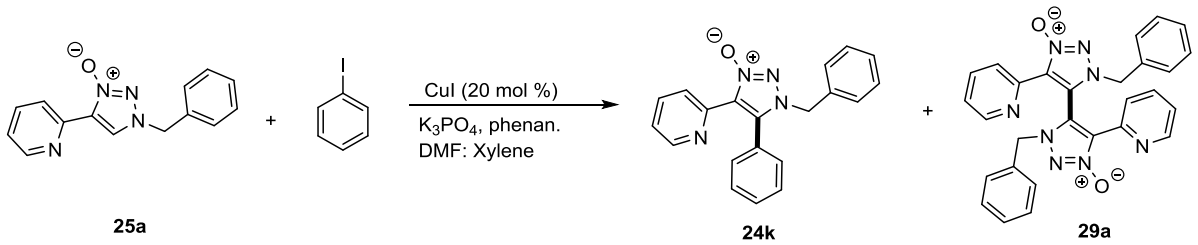
Scheme 4.19. Homodimerization reaction of 1,4-disusbtituted triazoles.

Thus, in this section we wanted to further study if disubstituted N-oxides under oxidative conditions could afford 5,5'-bistriazoles N-dioxides. Although we already know that this approach was more challenging than the homocoupling of 1,5-disubstituted triazole N-oxides mentioned above.

4.3.3.2 Results and discussion

In the third chapter (Section 3.3.3.2) we studied the direct arylation of 1,4-disubstituted triazole N-oxides and we observed that when 1-benzyl-4-pyridil-1,2,3-triazole N-oxide was used as a substrate in 0.4 M concentration (table 4.7, entry 1) bistriazole **29a** was afforded as a side product. However, the formation of the bistriazole **29a** was minimized when the reaction was diluted to 0.1 M concentration.

Table 4.7. Ligand directed direct arylation reaction.

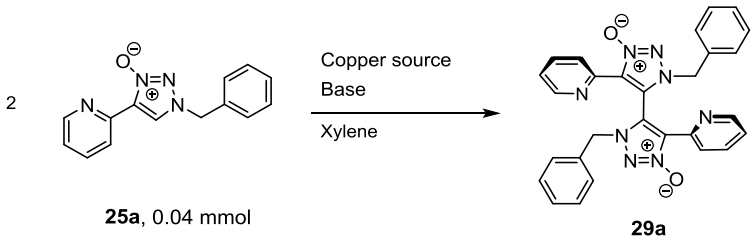


25a **24k** **29a**

Entry	Aryl halide	Solvent	Conditions	Conversion 24k/29a
1	4.0 eq	DMF: Xylene (0.4 M)	140 ºC, 24h	70/30
2	4.0 eq	DMF: Xylene (0.1 M)	140 ºC, 24h	90/10

Encouraged by these results, we decided to optimize the reaction conditions to afford 5,5'-bistriazole N-dioxides. We first selected 1-benzyl-4-pyridil-1,2,3-triazole N-oxide (**25a**) as model substrate and copper (I) iodide as catalyst as shown in table 4.8 entry 1 and 90 % conversion was afforded.

Table 4.8. Screening of homocoupling reaction.



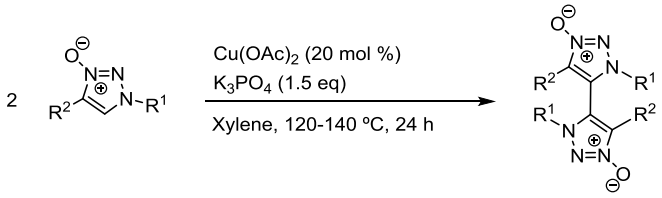
Entry	Copper cat.	Base	Conditions	Solvent (ml)	Oxidant	Conversion
1	CuI (0.2 eq)	K_3PO_4	120 ºC, 24h	DMF: Xylene (0.15 mL)	--	>90
2	$Cu(OAc)_2$ (1 eq)	--	120 ºC, 24h	Xylene (0.2 mL)	O_2	>90
3	$Cu(OAc)_2$ (0.2 eq)	--	120 ºC, 24h	Xylene (0.2 mL)	O_2	>90

[a] Reaction conditions: Triazole N-oxide (1 mmol), $Cu(OAc)_2$ (20 mol %), xylene (3.3 mL) at 120 ºC for 24 hours.

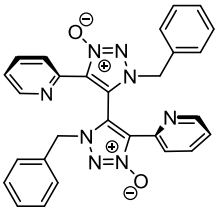
We repeat the reaction but decreasing the temperature to 120 ºC as shown in entry 2 and excellent conversions were obtained. In parallel, we tried utilizing copper (II) acetate in stoichiometric and catalytic amounts, entry 3 and 4 respectively, utilizing oxygen as oxidant and as in previous entries excellent conversions were achieved.

Once we had optimized the reaction conditions, we made the scope of the reaction as shown in the following table 4.9.

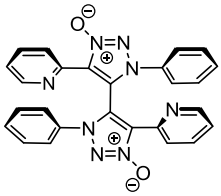
Table 4.9. Scope of the synthesis of 5,5'-bistriazole N-dioxides.



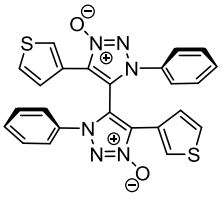
4d-25 **29a-e**



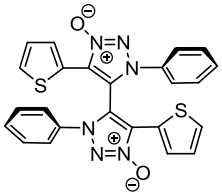
29a[a] (65 %)



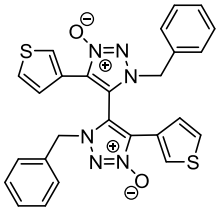
29b[a] (80 %)



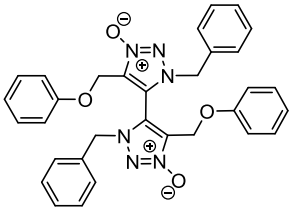
29c[b] (72 %)



29d[b] (83 %)



29e[b] (72 %)

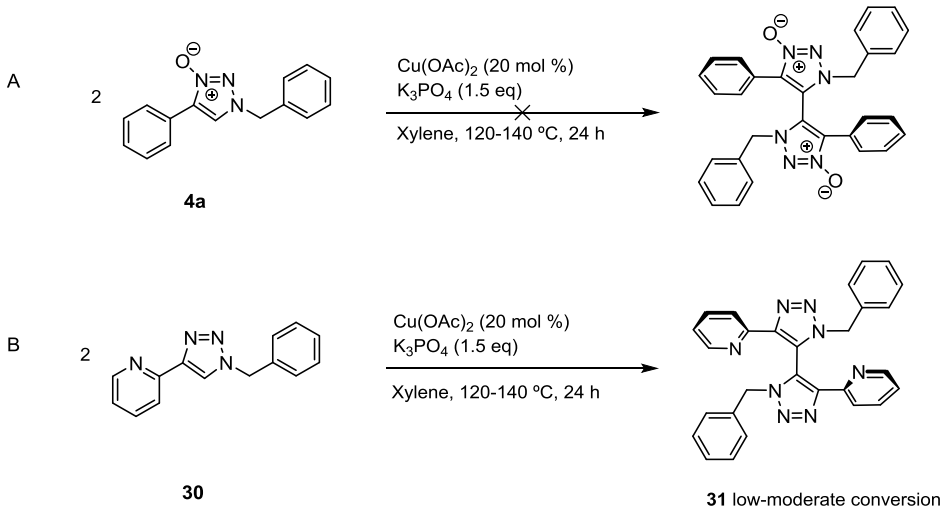


29f[b] (traces)

[a] Reaction conditions: Triazole N-oxide (0.06 mmol), $Cu(OAc)_2$ (20 mol %), xylene (0.2 mL) at 120 ºC for 24 hours. [b]Reaction at 140 ºC in Xylene (0.1 mL)for 24 hours.

The products were afforded in good yields when ligand directed groups, such as, pyridine or thiophene were used. However, when iodothiophenes were used higher temperatures and more concentrated solutions were needed to afford almost total conversion. Furthermore, when triazole **4d** was submitted into oxidative conditions, only traces of product **29f** was obtained.

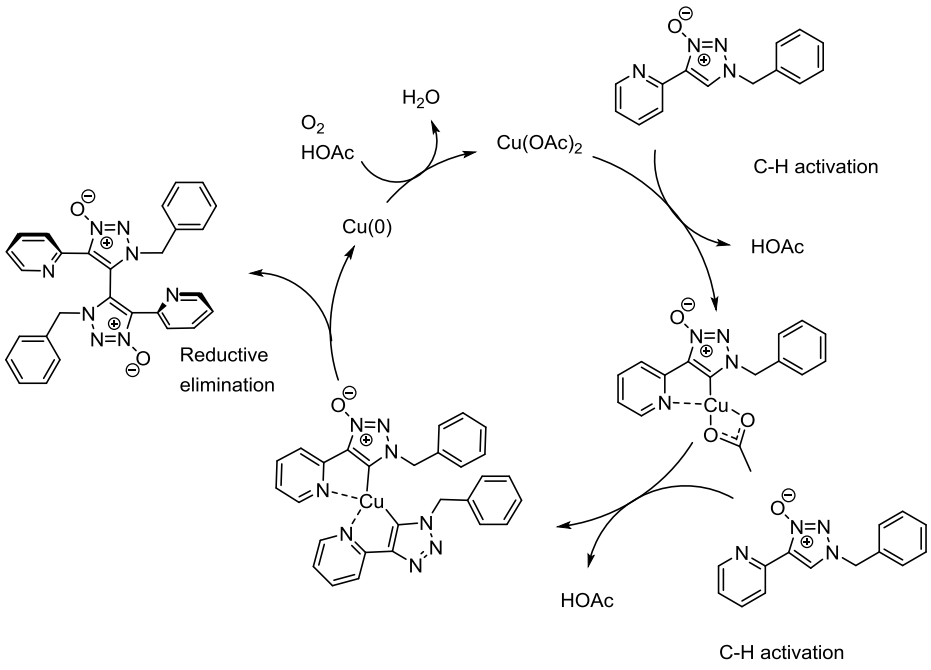
Further studies indicate that the presence of a directing group was essential for the oxidative coupling (Scheme 4.20 A). Additionally, in the absence of the N-oxide moiety, the reaction proceed in a low-moderate conversion (Scheme 4.20 B)



Scheme 4.20. Synthetic scope limitations of the formation of 5,5'-bistriazoles. (A) When the presence of a ligand directed group was suppressed. (B) When the reaction was performed in the absence of the N-oxide moiety.

4.4.3.2.1. Reaction mechanism

In view of these results, a plausible mechanism is proposed, which, follows an oxidative cross-dehydrogenative coupling (CDC) pathway (Scheme 4.21).



Scheme 4.21. Pausible mechanism of the formation of 5,5'-bistriazole N-dioxides.

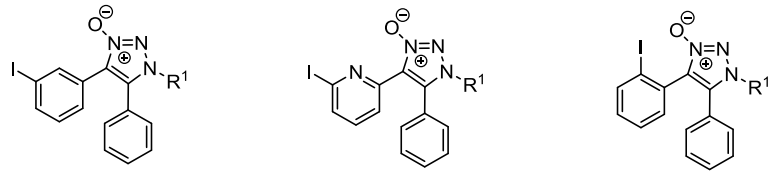
The reaction starts with the C-H activation of triazole N-oxide with copper acetate to form intermediate **I**, followed by a second activation of the triazole to give the intermediate **II**.

Finally, the reductive elimination takes place providing the product and copper (0) is oxidized by oxygen to regenerate copper (II) active catalyst, releasing water.

4.3.4 Synthesis of biaryl-bistriazoles that could act as ligands for transition-metal catalysis.

Biaryl compounds play important roles in organic chemistry due to a variety of physical and chemical properties. Ulmann developed the homocoupling of aryl halides in the presence of stoichiometric amounts of copper salts.[194] However, since then, many procedures including palladium-catalyzed protocols have been developed utilizing arylboronic acids,[195] arylstannanes,[196] or arylzinc reagents.[197] The inconvenience of utilizing these reagents are the requirements of stoichiometric amounts of organometallic reagents generally prepared from aryl halides. Thus, the direct method was the direct coupling of aryl halides. Indeed, various nickel[198] and palladium[199] catalyst precursors have been reported to promote cross-coupling reactions under relative mild conditions.

Taking advantage of previously synthesized iodoaryltriazoles (**23q-z**), we wanted to develop the first biphenyl bistriazole N-oxides.



Scheme 4.22. Key intermediates for cross-coupling reactions.

[194] Ullmann, F. *Ber*. **1903**, *36*, 2389.

[195] Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457.

[196] Farina, V. *Pure Appl. Chem*. **1996**, *68*, 73.

[197] Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

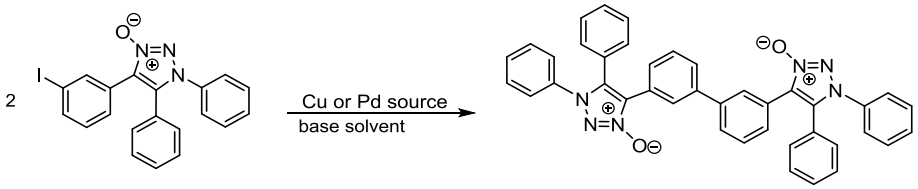
[198] For some selected examples, see: a) Massicot, F.; Schneider, R.; Fort, Y.; Illy-Cherrey, S.; Tillement, O. *Tetrahedron* **2001**, *57*, 531. b) Lin, G.-Q.; Hong, R. *J. Org. Chem*. **2001**, *66*, 2877. c) Massicot, F.; Schneider, R.; Fort, Y. *J. Chem. Res*. **1999**, 664.

[199] For some selected examples, see: a) Wang, L.; Lu, W. *Org. Lett.* **2009**, *11*, 1079. b) Boger, D. L.; Goldberg, J.; Andersson, C.-M. *J. Org. Chem*. **1999**, *64*, 2422. c) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett*. **1999**, *1*, 1205. d) Venkatraman, S.; Li, C.-J. *Org. Lett*. **1999**, *1*, 1133. e) Luo, F.-T.; Jeevanandam, A.; Basu, M. K. *Tetrahedron Lett*. **1998**, *39*, 7939. f) Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793.

4.3.4.1 Results and discussion

In order to test the feasibility of our approach, we first selected as model substrate 1,5-diphenyl-4-(3-iodophenyl) 1,2,3-triazole N-oxide (**23q**) and optimize the reaction condition as shown in Table 4.10.

Table 4.10. Screening of cross-coupling reaction.



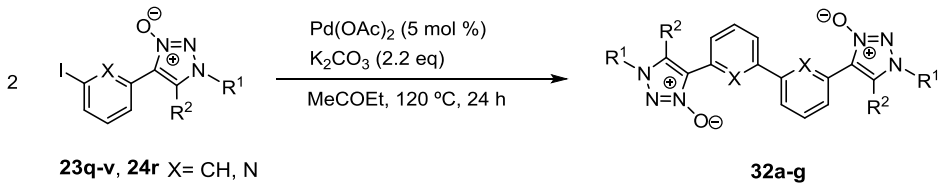
23q **32a**

Entry	Catalyst	Base	Solvent	Conditions	Conversion
1	CuI (20 mol %)	--	DMF	120 ºC, 24h	--
2	CuI (20 mol %)	K_3PO_4	DMF	140 ºC, 24h	--
3	$Pd(OAc)_2$ (5 mol %)	K_2CO_3	MeCOEt	120 ºC, 5h	<30
4	$Pd(OAc)_2$ (5 mol %)	K_2CO_3	MeCOEt	120 ºC, 24h	100

[a] Reaction conditions: Triazole N-oxide (1 mmol), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (2.5 eq), MeCOEt (3 mL) at 120 ºC for 24 hours.

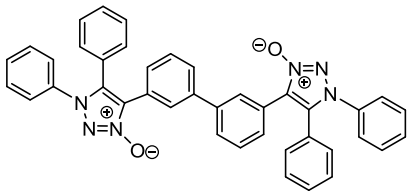
We first tried utilizing copper iodide as catalyst (entries 1-2). However, the reaction did not proceed and starting material was recovered. At that stage, we decided to change the catalyst to palladium acetate and follow a reported procedure published by Lu[199a] (entry 3) affording the product in partial conversion. Longer reaction times provided the product in total conversion (entry 4). With the optimized conditions in hand, we worked on the scope of the reaction as it is depicted in the following table 4.11.

Table 4.11. Scope of biaryl coupling.

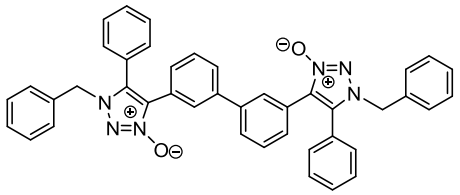


23q-v, **24r** X= CH, N

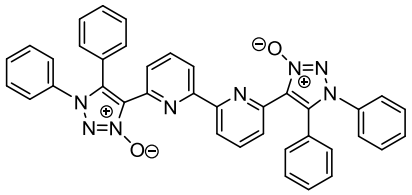
32a-g



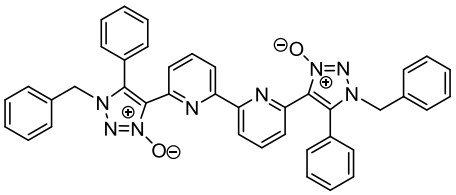
32a (80 %)



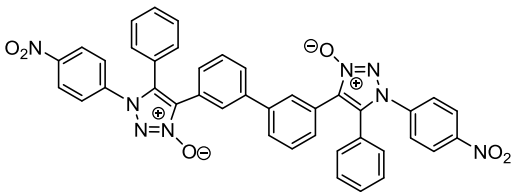
32b (90 %)



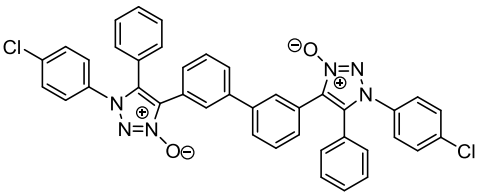
32c (76 %)



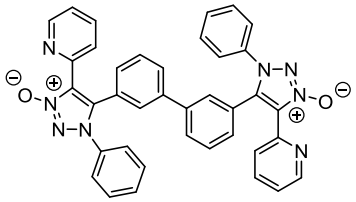
32d (77 %)



32e (80 %)



32f (82 %)



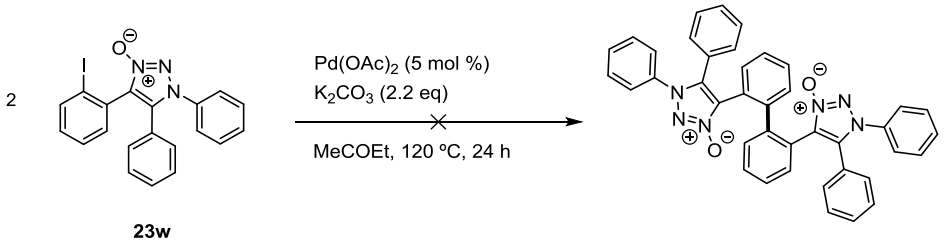
32g (63 %)

[a] Reaction conditions: Triazole N-oxide (0.035 mmol, 15 mg), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (0.084 mmol), MeCOEt (0.1 mL) at 120 ºC for 24 hours.

The products were obtained from moderate to good yields. Products derived from 1,5-disubstituted triazole N-oxides were more interesting comparing with 1,4-disubstituted ones, due to the special orientation and the capability for coordinating. Although we have not done a wide variety of examples, this method could be able to synthesize a wide variety of ligands.

Compound **32c** and **32d** could be particularly interesting for trapping a metal due to the four coordinating places.

Encouraged by these results, we further analyzed the cross-coupling reaction utilizing 1,5-disubstituted-4-(2-iodoaryl)-1,2,3-triazole N-oxides as substrates. However, decomposition of the substrate took place, probably due to the unstable palladacycle intermediate. Several other attemps[200] were made, utilizing different conditions, without having success.



Scheme 4.23. 1,5-Diphenyl-4-(2-iodoaryl)-1,2,3-triazole N-oxide cross-coupling reaction.

4.3.5 Deoxygenation reaction of triazole N-oxides

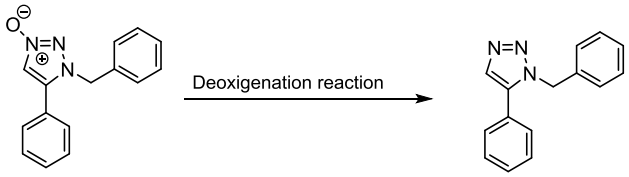
All over this chapter, we had synthesized a wide variety of different triazole N-oxides that could be desoxygenated and thus, we could make a new family of different trisubstituted triazoles, bistriazoles or biaryl bistriazoles.

Therefore, first we selected a simple triazole N-oxide to undergo deoxygenation reaction and find optimized conditions. Several methods exit in the bibliography for the deoxygenation of the N-oxide moiety[25a,36b,201] and some of them are summarized in the following table 4.12.

[200] Chang, Y. M.; Lee, S. H.; Cho, M. Y.; Yoo, B. W.; Rhee, H. J.; Lee, S. H.; Yoon, C. M. *Synth. Commun.* **2005**, *35*, 1851.

[201] a) Balicki, R. *Synthesis* **1989**, *8*, 645. For an eco-friendly methodology method, see: b) Rubio-Presa, R.; Fernández-Rodríguez, M. A.; Pedrosa, M. R.; Arnáiz, F. J.; Sanz, R. *Adv. Synth. Catal.* **2017**, *359*, 1752.

Table 4.12. Optimization of the deoxygenation reaction.



9h **33a**

Entry	Conditions	Conversion
1	PCl_3, CH_2Cl_2, 50 ºC, 4h	--
2	Zn (5 eq), NH_4Cl, THF, 70 ºC, 2h	partial
3	Zn (5 eq), NH_4Cl, THF, 70 ºC, overnight	70
4	Zn (10 eq), NH_4Cl, THF, 70 ºC, 24 h	total

[a] Reaction conditions: Triazole N-oxide (0.04 mmol), Zn (0.4 mmol) in NH_4Cl:THF (1:1, 0.6 mL) at 70 ºC for 24 hours.

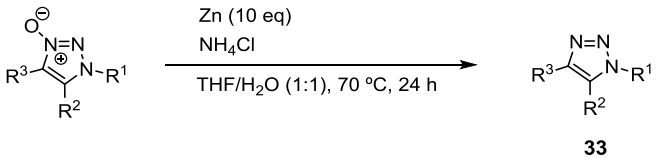
As shown in table 4.12, we first tried with the typical conditions reported[178b,202] to some heterocycle N-oxides as shown in entry 1, but in our case the reaction did not take place and starting material was recovered. Thus, we changed the reducing agent to others reported as zinc[178b,203] as shown in entry 2 and partial conversion was afforded. We performed several changes on the reported procedure, and we end up optimizing the reaction conditions as shown in entry 4, by utilizing 10 equivalents of zinc at 70 ºC for 12 hours.

Once optimized the reaction, we performed the reaction with biaryl bistriazoles as shown in the following table 4.13.

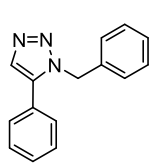
[202] For some selected examples, see: a) Zhao, H.; Wang, R.; Chen, P.; Gregg, B. T.; Hsia, M. M.; Zhang, W. *Org. Lett.* **2012**, *14*, 1872. b) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310. c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254.

[203] a) Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, *8*, 891.

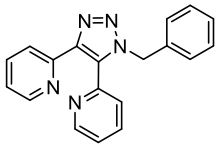
Table 4.13. Scope of deoxygenation reaction.



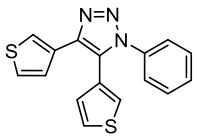
33



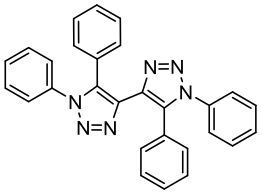
33a (90 %)



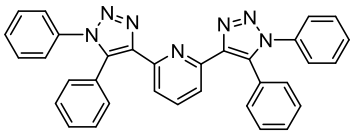
33b (79 %)



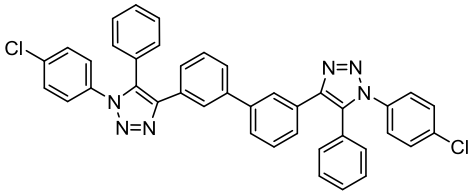
33c (92 %)



33d (86 %)



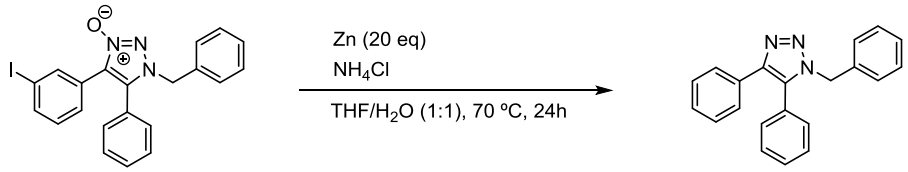
33e (85 %)



33f (87 %)

[a] Reaction conditions: Triazole N-oxide (0.04 mmol), Zn (0.4 mmol) in NH_4Cl:THF (1:1, 0.6 mL) at 70 ºC for 24 hours.

As summarized in the scope shown above, the deoxygenation reaction was afforded from good to excellent yields, both with mono deoxygenation or bi- deoxygenation. However, this procedure has some synthetic limitations as, the deoxygenation of 1-benzyl-4-(3-iodophenyl)-5-phenyl-1,2,3-triazole N-oxide in which appart from the deoxygenation reaction, carbon-iodine cleavage took place affording 1-benzyl-4,5-diphenyl-1,2,3-triazole as depicted in the following scheme 4.24.



Scheme 4.24. Deoxygenation and desiodation of triazole N-oxide.

4.4 Conclusion

In conclusion, we have demonstrated that there is another way to synthesize 1,4-disubstituted triazole N-oxides from the coupling of 1-substituted triazole N-oxides and aryl halides, and thus, insert functional groups that would not be compatible with oxidation reaction. Furthermore, the synthesis of ligand directed functional group at C4 of the triazoles opens a new way for the synthesis of 5,5'-bistriazole N-oxides, or the direct synthesis of 1,4,5-trisubstituted triazoles starting from simple 1-substituted triazole N-oxides. In addition, 1,5-disusbtituted triazole N-oxides are also good structures for the formation of 4,4'-bistriazole N-dioxides.

Finally, the development of previously reported iodine derivatives 1,4,5-trisubstituted triazole N-oxides derivatives are good substrates for the synthesis of biaryl *metha* bistriazole ligands, which could act as hindered ligands or for trapping metals due to the different coordination sites.

5

Palladium-catalyzed coupling reactions of 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides *via* C-Si activation and C-H/C-H dual activation

5. Palladium-catalyzed coupling reactions of 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides *via* C-Si activation and C-H/C-H dual activation

To address the last general objective of this thesis, consisting in the development of novel synthetic methods to prepare 1,4,5-trisubstituted 1*H*-1,2,3-triazole N-oxides bearing heterocyclic substituents, we selected two approaches. First, silver oxide-mediated activation of C-Si bonds in 4-trimethylsilyl-substituted triazoles and, second, the oxidative heterocoupling of 1,5-disubstituted triazole N-oxides with heteroarenes *via* C-H/C-H dual activation.

5.1 Introduction

5.1.1 Palladium-catalyzed cross-coupling reactions *via* C-Si bond activation

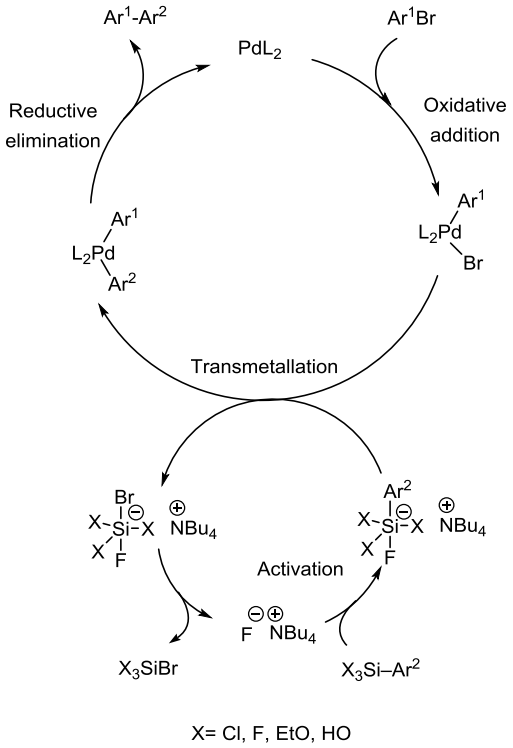
Palladium-catalyzed Stille[204] and Suzuki[195] reactions are acknowledged as very popular methods to synthesize biaryl compounds, although they suffer from some drawbacks regarding the toxicity of tin halides and the accessibility and stability of the boronic acids required to implement such reactions. As an alternative, silicon-based[205] aryl and vinyl donors have been developed to provide for a simultaneous substrate easy access and low environmental impact.

Organosilicon compounds are weak nucleophiles compared to other organometallic compounds because of the limited polarization of the carbon-silicon bond. This feature is synthetically advantageous to achieve a wider tolerance and compatibility towards a variety of functional groups, provided appropriate methods to activate either organosilicon compounds or electrophilic substrates are available. Hiyama[205a,206] developed the first method for the efficient activation of arylsilanes and vinylsilanes using strong silicon nucleophile additives (e.g. fluoride ion) to turn them into more polarized pentacoordinate silicates, which are suitable to transmetallate Pd(II) complex intermediates during cross-coupling reactions (Scheme 5.1)

[204] a) Stille, J. K. *Angew. Chem. Int. Ed. Engl*. **1986**, *25*, 508. b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1978**, *100*, 3636.

[205] a) Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011**, *40*, 4893. b) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth*. **2004**, *1*, 211. c) Denmark, S. E.; Sweiss, R. F. *Acc. Chem. Res*. **2002**, *35*, 835.

[206] Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett*. **1988**, *29*, 97.



Scheme 5.1. Proposed mechanism for the Hiyama cross-coupling reaction of arylsilanes with aryl bromides.

The efficiency of silicon activation and the following cross-coupling reaction are strongly dependent on the silicon substitution[205a,207]. Actually, silicon moieties such as halosilanes,[208] silanols,[209] siloxanes,[210] or silacyclobutanes[211] are required as coupling partners to achieve efficient cross-couplings reactions. Although this limitation has hampered the use of the Hiyama coupling in the field of heterocyclic chemistry,[212] some examples of arylsilane-mediated syntheses of pyridyl biarenes were reported by

[207] Foubelo, F.; Nájera, C.; Yus, M. *Chem. Rec.* **2016**, *16*, 2521.

[208] a) Homsi, F.; Hosoi, K.; Nozaki, K.; Hiyama, T. *J. Organomet. Chem*. **2001**, *624*, 208. b) Goda, K.-I.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett*. **1997**, *38*, 439.

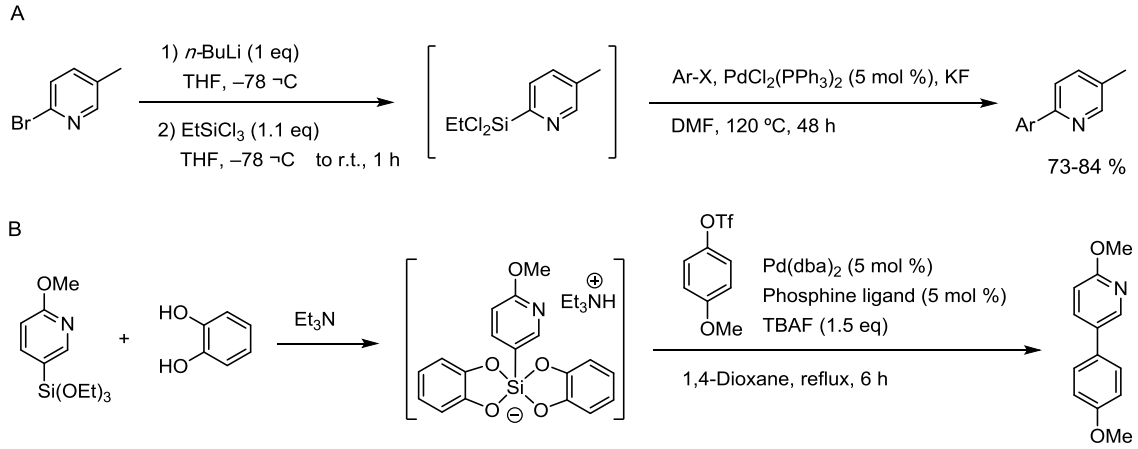
[209] a) Beaulieu, L.-P. B.; Delvos, L. B.; Charette, A. B. *Org. Lett*. **2010**, *12*, 1348. b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem*. **2000**, *65*, 5342. c) Denmark, S. E.; Neuville, L. *Org. Lett*. **2000**, *2*, 3221.

[210] a) Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett*. **2008**, *49*, 3939. b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. c) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc*. **2003**, *125*, 5616. d) McElroy, W. T.; DeShong, P. *Org. Lett*. **2003**, *5*, 4779.

[211] a) Denmark, S. E.; Choi, J.-Y. *J. Am. Chem. Soc*. **1999**, *121*, 5821. b) Denmark, S. E.; Wu, Z. *Org. Lett*. **1999**, *1*, 1495.

[212] For direct arylation utilizing silyl substituted thiophenes: Chen, L.; Roger, J.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *Chem. Commun.* **2011**, *47*, 1872.

Hiyama[213] and DeShong[214]. Hiyama used the unstable 2-dichloroethylsilyl-picoline generated in situ, while DeShong reported the coupling between aryltriflates and pyridyl-biscatechol silicates as exemplified in the following scheme.



Scheme 5.2. Synthesis of arylpyridines using the reactions of Hiyama (A) and DeShong (B) reactions mediated by pyridyldichlorosilanes and pyridylbiscatechol silicates, respectively.

A major improvement of these cross-coupling reactions came when halosilanes and alkoxysilanes were replaced by simple and stable trimethylsilylated coupling partners. In 2005, Gros succeeded to activate the reaction of a 2-trimethylsilylpyridine using CuI and an excess of TBAF as additives (Scheme 5.3 A).[215] The main drawback of this reaction was the use of an excess of TBAF, which caused purification difficulties and functional group tolerance issues. In order to avoid these problems, Yoshida reported the cross-coupling of aryl iodides with 2-allyl(dimethyl)silyl-pyridines promoted by a stoichiometric amount of silver oxide[216]. Later on, the cross-coupling of 2-trimethylsilylpyridines and aryl halides was reported by Whittaker[217] and Gros[218] utilizing silver (I) oxide in the presence with a catalytic amount of TBAF additive (Scheme 5.3 B). According to these authors, 2-silver-pyridyl intermediates would be the actual heteroaryl

[213] Hiyama, T. *J. Organomet. Chem*. **2002**, *653*, 58.

[214] Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137.

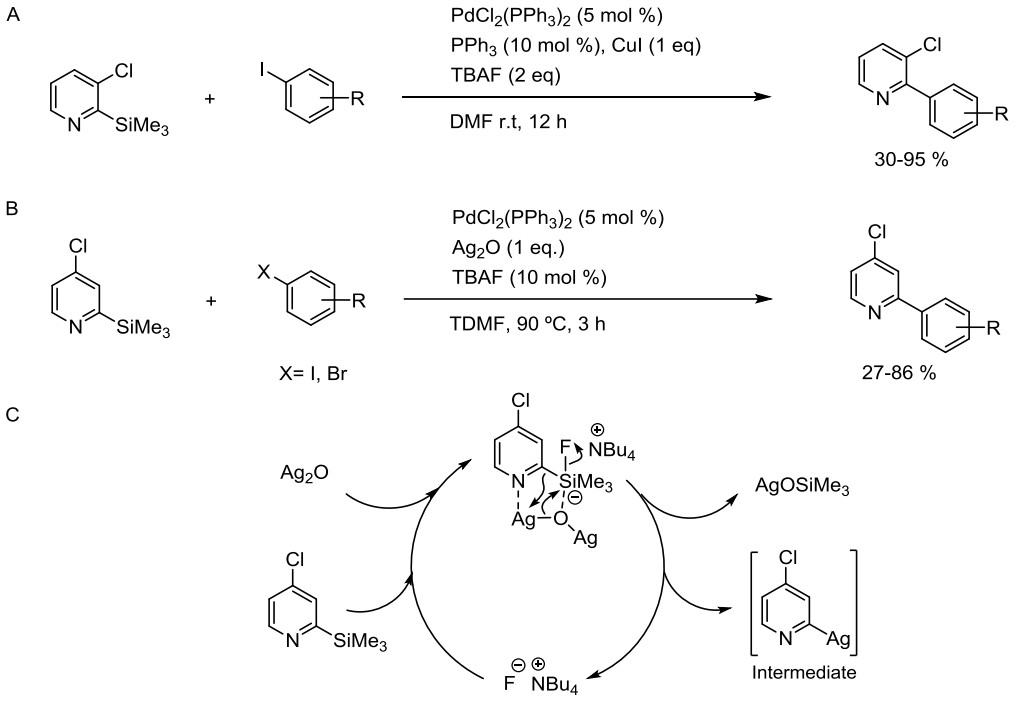
[215] Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697.

[216] Nokami, T.; Tomida, Y.; Kamei, T.; Itami, K.; Yoshida, J.-i. *Org. Lett.* **2006**, *8*, 729.

[217] Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett*. **2008**, *49*, 6314.

[218] Louërat, F.; Tye, H.; Napier, S.; Garrigou, M.; Whittaker, M.; Gros, P. C. *Org. Biomol. Chem.* **2011**, *9*, 1768.

donor sources to the palladium diaryl complexes in the transmetallation step of the coupling catalytic cycle (Scheme 5.3 C).



Scheme 5.3. (A) Palladium-catalyzed cross-coupling reaction utilizing trimethylsilylpyridines. (B) Reactions promoted by silver (I) oxide in the presence of TBAF. (C) Proposed mechanism for the formation of 2-silver-pyridine intermediates from 2-trimethylsilylpyridines.

As an alternative to the use of silver oxide, Marples[219] has developed a palladium-catalyzed arylation of 2-trimethylsilyl-pyridine using copper(I) iodide and potassium fluoride to activate the silyl group, but the reaction requires the use of up to 20 mol % of the expensive di(1-adamantyl)*n*-butylphosphine (CataCXium A) to proceed properly. Finally, the cross-coupling of silylpyridines has also been catalyzed using rhodium complexes.[220]

Despite the large majority of palladium-catalyzed cross-coupling reactions using organosilyl-components have been studied for arylation reactions, other transformations including alkylation reactions,[221] homocoupling reactions[222] or alkenylation reactions have also been described. For instance, in 1988, Hiyama and Hatanaka reported that

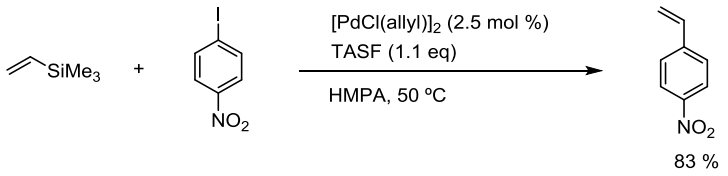
[219] Blakemore, D. C.; Marples, L. A. *Tetrahedron Lett.* **2011**, *52*, 4192.

[220] Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal*. **2011**, *353*, 1285.

[221] Schweizer, S. A.; Bach, T. *Synlett* **2010**, 81.

[222] Shibata, M.; Ito, H.; Itami, K. *Chem. Lett.* **2017**, *46*, 1701.

vinyltrimethylsilane undergoes the palladium-catalyzed cross-coupling reaction with aryl and alkenyl halides in the presence of the very active fluoride ion source tris(dimethylamino)sulfonium difluorotrimethylsilicate TASF.[223] The reaction has been extended to substituted vinylsilanes bearing alkylsilyl groups[224] or alkoxysilyl groups.[225]



Scheme 5.4. Hiyama and Hatanaka palladium-catalyzed cross-coupling reaction of vinyltrimethylsilane.

No examples of the "Hiyama-type" cross-coupling reactions using silylated 1,2,3-triazoles were reported in the literature. So, we decided to explore the potential of the readily available 4-trimethylsilyl-1*H*-1,2,3-triazoles (see, Table 2.1) as heteroaryl components in palladium catalyzed cross-coupling reactions. More particularly, we became interested in the reaction of such heteroaromatic silanes with some of the 1,5-disubstituted 1,2,3-triazole N-oxides previously prepared in this thesis. The details of our working hypothesis and the results obtained will be disclosed in detail below (sections 5.2 and 5.4.1).

5.1.2 Palladium-catalyzed coupling reactions *via* C-H/C-H dual activation

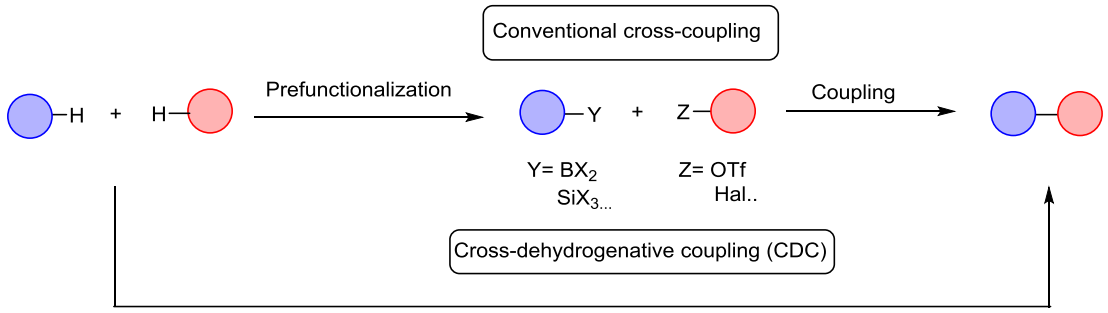
Preactivation of heteroarene carbon fragments to participate in $C(sp^2)$-$C(sp^2)$ bond-forming cross-coupling reactions usually involves several previous synthetic steps to prepare the required (hetero)aryl precursors (e.g. halides, trialkyltin compounds,

[223] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

[224] For some selected examples, see: a) Omote, M.; Tanaka, M.; Tanaka, M.; Ikeda, A.; Tarui, A.; Sato, K.; Ando, A. *J. Org. Chem.* **2013**, *78*, 6196. b) Omote, M.; Tanaka, M.; Ikeda, A.; Nomura, S.; Tarui, A.; Sato, K.; Ando, A. *Org. Lett.* **2012**, *14*, 2286. c) Junker, C. S.; Welker, M. E.; Day, C. S. *J. Org. Chem.* **2010**, *75*, 8155.

[225] a) Cornelissen, L.; Cirriez, V.; Vercruysse, S.; Riant, O. *Chem. Commun.* **2014**, *50*, 8018. b) Gordillo, A.; Ortuño, M. A.; López-Mardomingo, C.; Lledós, A.; Ujaque, G.; de Jesús, E. *J. Am. Chem. Soc.* **2013**, *135*, 13749. c) Frye, E. C.; O'Connor, C. J.; Twigg, D. G.; Elbert, B.; Laraia, L.; Hulcoop, D. G.; Venkitaraman, A. R.; Spring, D. R. *Chem. Eur. J.* **2012**, *18*, 8774. d) Marciniec, B.; Majchrzak, M.; Prukala, W.; Kubicki, M.; Chadyniak, D. *J. Org. Chem.* **2005**, *70*, 8550.

arylboronic acids, trialyl(alkoxy)silanes, etc...).[226] As a consequence, these synthetic approaches usually display poor atom economy. To mitigate this problem, the catalytic oxidative C-H/C-H dual cross-coupling approach is often the strategy of choice. In the literature, such process is also referred to as cross-dehydrogenative coupling (CDC)[227] (Scheme 5.5). It involves the bonding of two nucleophilic centers with the concomitant formal release of H_2 and the participation of an oxidant to become thermodynamically favorable. Various oxidants have been used to this purpose, including peroxides, copper salts, silver salts and molecular oxygen, among others.



Scheme 5.5. Cross-coupling versus Oxidative coupling.

Although different transition metals have been used in a vast array of C-H activations, the most widely used metal is, by far, palladium. Accordingly, in the last two decades, some pioneering reports have paved the way to the Pd(II)-catalyzed C-H/C-H dual cross-coupling between arenes and (hetero)arenes containing a directing group,[228] between two

[226] de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions;* Wiley-VCH: Weinheim, **2004**.

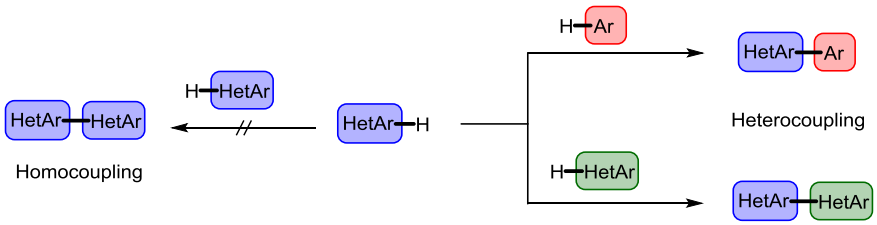
[227] For some selected reviews, see: a) Huang, C.-Y.; Kang, H.; Li, J.; Li, C.-J. *J. Org. Chem.* **2019**, *84*, 12705. b) Funes-Ardoiz, I.; Maseras, F. *ACS Catal.* **2018**, *8*, 1161. c) Gini, A.; Brandhofer, T.; García Mancheño, O. *Org. Biomol. Chem.* **2017**, *15*, 1294. d) Varun, B. V.; Dhineshkumar, J.; Bettadapur, K. R.; Siddaraju, Y.; Alagiri, K.; Prabhu, K. R. *Tetrahedron Lett*. **2017**, *58*, 803. e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. f) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. g) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

[228] For some selected examples, see: a) Lou, S.-J.; Mao, Y.-J.; Xu, D.-Q.; He, J.-Q.; Chen, Q.; Xu, Z.-Y. *ACS Catal* **2016**, *6*, 3890. b) Jiao, L.-Y.; Smirnov, P.; Oestreich, M. *Org. Lett.* **2014**, *16*, 6020. c) Jiao, L.-Y.; Oestreich, M. *Chem. Eur. J.* **2013**, *19*, 10845. d) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem.* **2008**, *120*, 1131; *Angew. Chem. Int. Ed.* **2008**, *47*, 1115. f) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

arenes[229] between a heteroarene and an arene[153,230] or between two heteroarenes. This last approach will be disclosed in more detail in the following sections.

5.1.2.1 Palladium-catalyzed coupling of heteroarenes *via* C-H/C-H dual activation

An obvious difficulty to overcome when dealing with coupling reactions of heteroarenes driven *via* C-H dual activation is the need to prevent the formation of homocoupling products[231] (Scheme 5.6). This side reaction is specially favored by Pd(II) catalysts in electron-rich five-membered heteroarenes, such as furans or thiophenes. Luckily, playing with the C-H acidity differences of the two reaction partners often provides the option to minimize the undesired homocoupling side reactions.



Scheme 5.6. Palladium-catalyzed coupling patterns of heteroarenes *via* CH/CH dual activation.

In a seminal paper, Fagnou stated a significant breakthrough in the Pd(II)-catalyzed oxidative C-H/C-H dual activation of heteroarenes and simple nonactivated arenes[232]

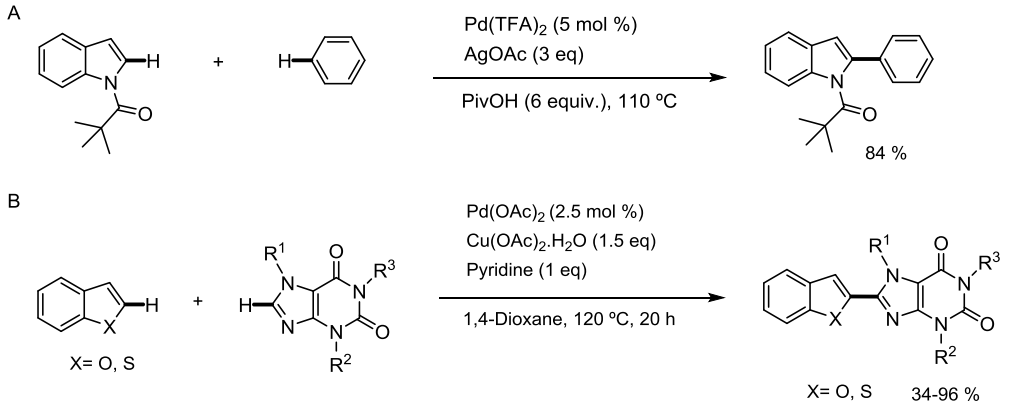
[229] a) Shishilov, O.; Shamsiev, R.; Akhmadullina, N.; Flid, V. *ChemistrySelect* **2020**, *5*, 1080. b) Huang, Q.; Zhang, X.; Qiu, L.; Wu, J.; Xiao, H.; Zhang, X.; Lin, S. *Adv. Synth. Catal.* **2015**, *357*, 3753. c) Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 5525. d) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377. e) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973.

[230] For some selected examples, see: a) Wang, S.; Liu, W.; Cen, J.; Liao, J.; Huang, J.; Zhan, H. *Tetrahedron Lett.* **2014**, *55*, 1589. b) He, C.-Y.; Min, Q.-Q.; Zhang, X. *Organometallics* **2012**, *31*, 1335. c) Malakar, C. C.; Scmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1378. d) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

[231] For some selected homocoupling products, see: a) Li, N. N.; Zhang, Y. L.; Mao, S.; Gao, Y. R.; Guo, D. D.; Wang, Y. Q. *Org. Lett.* **2014**, *16*, 2732. b) Li, Y.; Wang, W. H.; Yang, S. D.; Li, B. J.; Feng, C.; Shi, Z. J. *Chem. Commun.* **2010**, 4553. c) Li, Y.; Jin, J.; Qian, W.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 326. d) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. e) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. f) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074.

[232] a) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

(Scheme 5.7 A). Accordingly, N-pivaloylindole was phenylated with benzene in the presence of a catalytic amount of Pd(II) salt and an excess of silver acetate. It is worth mentioning that, under such conditions, the arylation occurred preferably at the C(2) position of the indole ring, instead of the usually more reactive C(3) position.



Scheme 5.7. Palladium-catalyzed oxidative couplings *via* C-H/C-H dual activation. (A) Heteroarene/arene (indol with benzene). (B) Heteroarene/heteroarene (benzofurane and benzothiophene with xanthines)

Other authors have developed related strategies to carry out the C(2) arylation of indoles and pyrroles by chelation-directed control.[233] For example, You, Hu and co-workers published the first palladium catalyzed C-H/C-H dual coupling of xanthine heteroarenes with five-membered π-electron-rich azoles, like (benzo)furans and (benzo)thiophenes (Scheme 5.7 B)[234] Subsequently, similar couplings have been reported for indoles and pyrroles with different heteroarenes,[235] and for benzothiazole or benzimidazoles with oxygen, nitrogen and sulphur containing heteroarenes.[236]

[233] For some selected examples, see: a) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. *Chem. Eur. J.* **2012**, *18*, 16616. b) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. c) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. d) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. e) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

[234] Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822.

[235] a) Shi, Y.; Wang, Z.; Cheng, Y.; Lan, J.; She, Z.; You, J. *Sci. China Chem*. **2015**, *58*, 1292. b) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5365.

[236] a) Chen, X.; Huang, X.; He, Q.; Xie, Y.; Yang, C. *Chem. Commun.* **2014**, *50*, 3996. b) Fu, X.-P.; Xuan, Q.-Q.; Liu, L.; Wang, D.; Chen, Y.-J.; Li, C.-J. *Tetrahedron* **2013**, *69*, 4436. c) Han, W.; Mayer, P.; Ofial, A. R. *Angew. Chem.* **2011**, *123*, 2226; *Angew. Chem. Int. Ed.* **2011**, *50*, 2178.

5.1.2.2 Heteroaromatic N-oxides in palladium catalyzed coupling reactions with heteroarenes *via* C-H/C-H dual activation

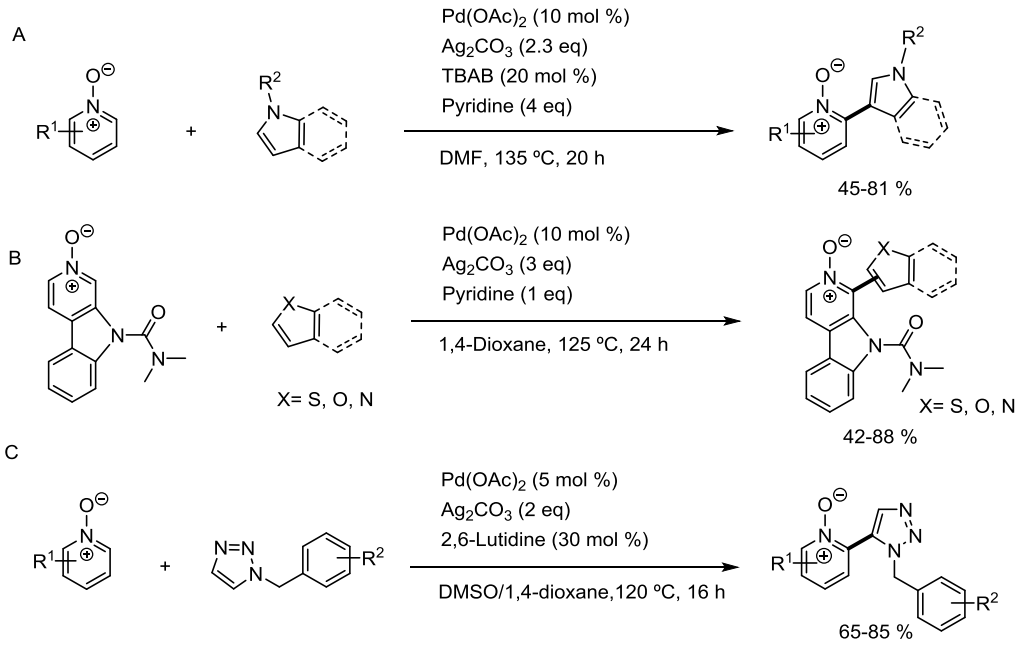
Heteroarene N-oxides are expected to be excellent components for coupling reactions occurring *via* C-H/C-H dual activation, because the presence of the N-oxide moiety enhances the C-H activation and prevents non-productive binding of the palladium catalyst to the nitrogen lone pair favoring π-binding interactions and heteroarene α-metallation. Applying this principle, Li and Zhang developed the first Pd(II)-catalyzed and silver-promoted coupling of pyridine N-oxides with indoles *via* C-H/C-H dual activation (Scheme 5.8 A).[237] Remarkably, the C-C bond formation took place selectively at the C(3) position of the indole ring, in contrast to the analogous indole arylations commented in Scheme 5.7. Other authors have extended this functionalization of pyridine N-oxides to pyrrole, furane and thiophene derivatives or to related N-oxides.[234,235b,238]. For example, You[239] has developed a regioselective C(2) heteroarylation of a pyridine N-oxide using a chelation system strategy (Scheme 5.8 B). Finally, Kuang[240] has reported a highly efficient and regioselective oxidative coupling of pyridine N-oxides with different five membered heteroarenes, including 1-substituted-1*H*-1,2,3-triazoles (Scheme 5.8 C).

[237] Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett*. **2011**, *13*, 1766.

[238] a) Liu, S.; Tzschucke, C. C. *Eur. J. Org. Chem*. **2016**, *21*, 3509. b) Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett.* **2011**, *40*, 555. c) Han, W.; Ofial, A. R. *Synlett* **2011**, *14*, 1951.

[239] Wu, N.; Song, F.; Yan, L.; Li, J.; You, J. *Chem. Eur. J*. **2014**, *20*, 3408.

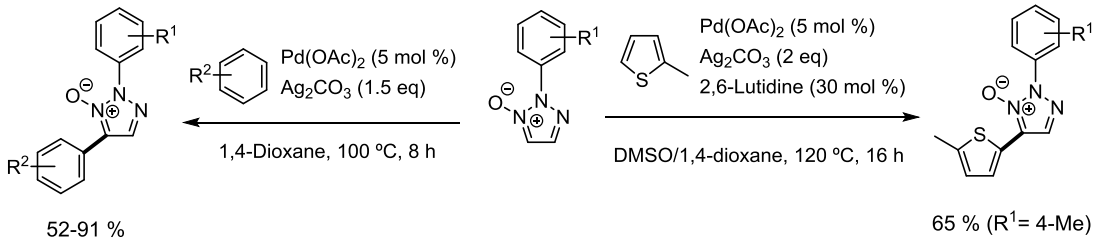
[240] Liu, W.; Yu, X.; Li, Y.; Kuang, C. *Chem. Commun.* **2014**, *50*, 9291.



Scheme 5.8. Pd(II) catalyzed coupling reactions of pyridine N-oxides with heteroarenes *via* CH/CH dual activation.

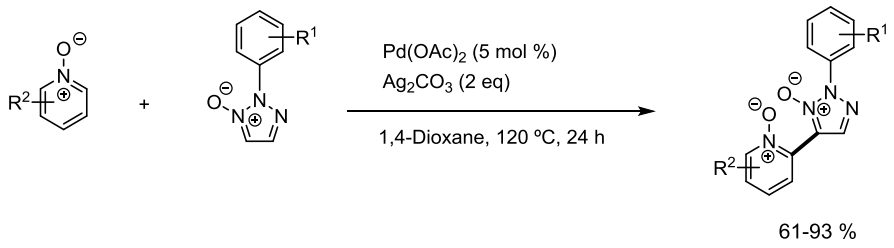
5.1.2.2.1 2*H*-1,2,3-Triazole N-oxides in double C-H activation reactions with (hetero)arenes.

In the realm of palladium-catalyzed coupling reactions of heteroarenes involving C-H/C-H dual activation, 1,2,3-triazole N-oxides are more challenging than simple pyridine and quinoline N-oxides because triazoles possess an additional nitrogen atom that could bind and poison the catalyst. Kuang developed the first protocol for the highly regioselective C(5)-arylation, alkenylation[36b] and heteroarylation[240] of 2-aryl-2*H*-1,2,3-triazoles N-oxides, catalyzed with Pd(II) and promoted by silver carbonate (Scheme 5.9). Interestingly, this author described that similar 2*H*-1,2,3-triazoles, lacking the N-oxide moiety, gave no coupling with alkenes or arenes under identical reaction conditions.



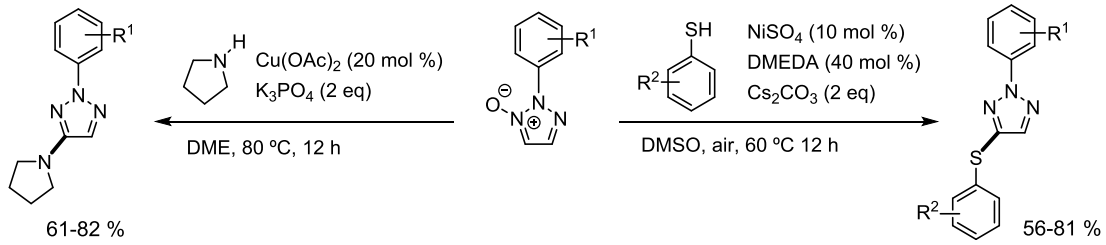
Scheme 5.9. Arylation and heteroarylation of 2-substituted 2*H*-1,2,3-triazole N-oxides *via* C-H/C-H dual activation.

Coupling between two electron-deficient heteroarene components *via* C-H/C-H dual activation can be expected to pose an even greater challenge because of the daunting reduction in reactivity. Nevertheless, the introduction of the N-oxide moiety can increase simultaneously the reactivity and regioselectivity of the oxidative C-H/C-H coupling reaction. Accordingly, Kuang[178b] has developed a highly efficient protocol to couple 2-aryl-2*H*-1,2,3-triazole N-oxides and pyridine N-oxides (Scheme 5.10).



Scheme 5.10. C-H/C-H dual activation of 2*H*-1,2,3-triazole N-oxides and pyridine N-oxides.

Finally, a few examples of alternative heterocoupling reactions occurring *via* C-H/X-H dual activation have been described for 2-aryl-2*H*-1,2,3-triazole N-oxides (Scheme 5.11). These transformations were catalyzed by inexpensive Cu(II) and Ni(II) salts, which efficiently promoted the formation of C-N[178a] or C-S[241] bonds from secondary amines and thiophenols, respectively. Importantly, both reactions occurred with simultaneous deoxygenation of the starting triazole N-oxides.



Scheme 5.11. Cu(II) and Ni(II)-catalyzed deoxygenative heterocoupling of 2-aryl-2*H*-1,2,3-triazole N-oxides *via* C-H/X-H dual activation (X=S, N).

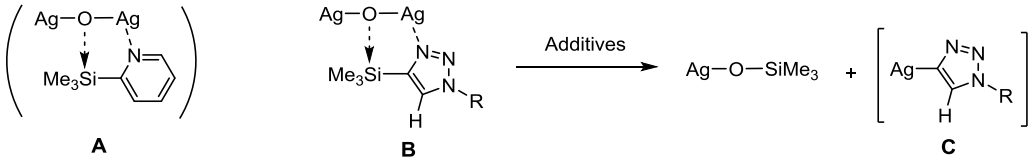
No examples of coupling reactions occurring *via* C-H/C-H or C-H/X-H dual activations and involving 1*H*-1,2,3-triazole N-oxides were reported in the literature. So, we decided to explore the potential reactivity of 1,5-disubstituted 1,2,3-triazole N-oxides previously described in this thesis with various heteroarenes (e.g. indoles, pyrroles, furans or

[241] Zhu, J.; Chen, Y.; Lin, F.; Wang, B.; Chen, Z.; Liu, L. *Org. Biomol. Chem.* **2015**, *13*, 3711.

thiophenes) under Pd(II) and Cu(II)-catalyzed reaction conditions. The details of the results obtained will be disclosed in detail below (sections 5.4.2).

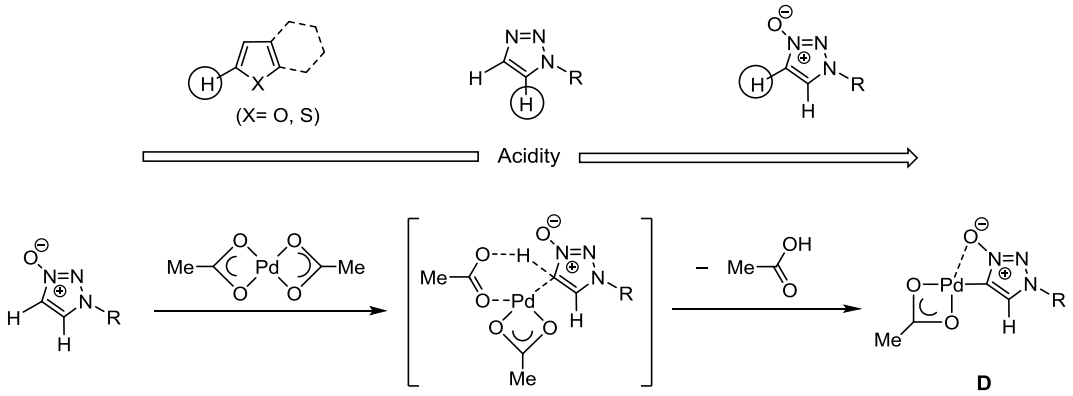
5.2 Hypothesis and objectives

On the basis of the precedent discussion regarding the silver promoted activation of 2-trimethylsilylpyridines *via* interactions of type **A** (see Scheme 5.12), we hypothesized that a similar activation of the C-Si bond with silver oxide or oxygenated silver salts would take place on 4-trimethylsilyl-1*H*-1,2,3-triazoles **B** to provide 4-silver-1,2,3-triazole intermediates **C** that could participate as triazole donors in "Hiyama-like" coupling reactions. In particular, we considered that such silver triazoles generated *in situ* could couple with 1*H*-1,2,3-triazole N-oxides in palladium-catalyzed reactions.



Scheme 5.12. Transmetallation of C-Si bond into C-Ag in 4-trimethylsilyl-1*H*-1,2,3-triazoles promoted by silver oxide.

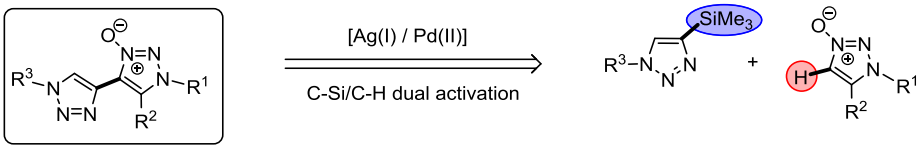
On the other hand, we also considered the convenience of exploring the potential of 1*H*-1,2,3-triazole N-oxides as substrates for palladium-catalyzed coupling reactions with heteroarenes, *via* C-H/C-H dual activation. Our hypothesis was based on the acidity-difference of C-H protons of several types of heterocyclic when compared to 1*H*-1,2,3-triazole N-oxides (Scheme 5.13) and the concerted metalation-deprotonation (CMD)[131] mechanism proposed by Fagnou for pyridine N-oxides to generate palladated heteroarene intermediates **D**. We considered that, under suitable conditions, a sequential C-H palladation of triazole N-oxides and several types of heteroarenes could be achieved in a way that would allow the prevalence of the heterocoupling reactions over the homocoupling reaction.



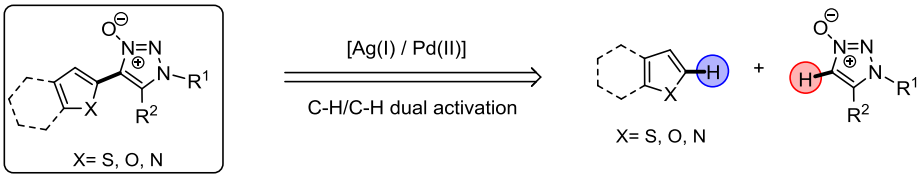
Scheme 5.13. 1*H*-1,2,3-triazole N-oxides for C-H/C-H coupling reactions: (A) Compared acidity of some heteroarenes. (B) Concerted metalation-deprotonation (CMD) model for 1*H*-1,2,3-triazole N-oxides promoted by palladium diacetate (ref.152).

To confirm experimentally the former hypotheses, for the last part of this doctoral thesis work, we selected to achieve the following objectives:

1. A general procedure for the synthesis of polysubstituted bistriazole N-oxides using the C-Si bond of readily accessible 4-trimethylsilyl-1*H*-1,2,3-triazoles as an activation and regiocontrolling element.



2. A general synthesis of nonsymmetric bi-heteroarenes comprising the 1*H*-1,2,3-triazole N-oxide motif, involving coupling reactions occurring *via* C-H/C-H dual activation.



5.3 Results and discussion

To accomplish the last objectives of the thesis, we focused our experimental activity towards the activation of C-Si and C-H bonds in 1*H*-1,2,3-triazole heterocycles, in order to transform them into suitable components for palladium-catalyzed direct heteroarylation reaction. The results obtained are disclosed in the following sections.

5.3.1 Palladium-catalyzed synthesis of non-symmetrically substituted 4,4'-bis(1,2,3-triazole) N-oxides *via* C-Si/C-H coupling reactions

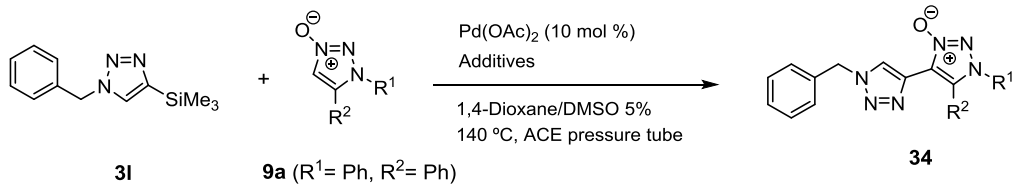
After the encouraging results obtained in our former study on the desilylative N-oxidation of 4-trimethylsilyl-1,2,3-triazoles described in Chapter 2 (Section 2.3.2.2), we decided to explore the unprecedented Hiyama-type coupling of 4-silyl-1,2,3-triazoles with 1*H*-1,2,3-triazole N-oxides.

In order to test the feasibility of the hypothesis and establish the optimized reaction conditions, we reacted one equivalent of the model 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole **3l** and 1.2 equivalents of a few representative 1,2,3-triazole N-oxides (**9a**, **9c**, **4l**) in the presence of a catalytic amount of palladium acetate, different Ag(I) promoters and various additives. All reactions were conducted using ACE pressure tubes in a mixture of 1,4-dioxane and DMSO, which was found to be the best reaction medium after a fast screening of solvents such as toluene, 1,4-dioxane, DMF and DMSO. The results obtained are collected in Table 5.1.

As expected, in the absence of silver oxidants (entry 1) the trimethylsilyl group of **3l** remained unchanged and the starting compounds were totally recovered. Adding 2.3 equivalents of silver acetate (entry 2) and heating the reaction mixture to 120 ºC for 30 h led to a mixture of the coupled bistriazole product **34a** (20 %) and the desilylated 1-benzyl-1,2,3-triazole **3y**. No trace of the starting silyltriazole **3l** could be detected by ^{1}H-NMR analysis in the reaction crude, suggesting that the desilylative formation of the putative 4-silver-1*H*-1,2,3-triazole intermediate was faster than the subsequent transmetallation to the palladium-triazole N-oxide complex. When the temperature was raised to 140 ºC (entry 3), the product was obtained in 50 % isolated yield. Silver carbonate in the presence of 2,6-lutidine or potassium carbonate also afforded the coupling product **34a** in comparable yields (entries 4 and 5). Finally, silver oxide proved to be the most efficient coupling promoter, delivering the desired product in 65 % isolated

yield (entry 6). It should be mentioned that repeating the reaction in the presence of 5 mol % of TBAF, as decribed by Gros[218] for 2-trimethylsilylpyridines, a complex reaction mixture was obtained, containing only minor amounts of the expected coupling product **34a** (not shown in the Table).

Table 5.1. Screening of reaction conditions for the synthesis of 4,4'-bistriazole N-oxides from 4-trimethylsilyl-1*H*-1,2,3-triazole **3l** and 1*H*-1,2,3-triazole N-oxides.



3l **34**

9a (R^1= Ph, R^2= Ph)
9c (R^1= Ph, R^2= 2,6-MePh)
4l (R^1= Ph, R^2= H)

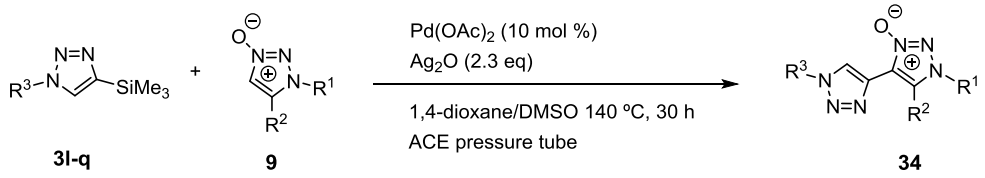
Entry	Substrate[a]	Additives (eq)	Time (h)	Yield[b] (%)
1	**9a**	---	30	0
2	**9a**	AgOAc (2.3)	30	20[c]
3	**9a**	AgOAc (2.3)	30	50
4	**9a**	Ag_2CO_3 (2.3)/Lutidine (0.3)	30	30
5	**9a**	Ag_2CO_3 (2.3)/K_2CO_3 (2.0)	30	40
6	**9a**	Ag_2O (2.3)	30	60
7	**9c**	Ag_2O (2.3)	24	35
8	**9c**	Ag_2O (2.3)	48	50
9	**4l**	Ag_2O (2.3)	24	--[d]
10	**9a**	$Cu(OAc)_2$ (3.0)/Pyr (1.0)	30	--[e]

[a]Molar ratio **3l**/**9**: 1.0/1.2. [b]Yield of pure isolated products. The reaction was monitored by ^{1}H-NMR integration of the C$\underline{H}_2$Ph signals of **34** and 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole **3l** in the reaction crude. [c]Reaction conducted at 120 ºC. [d]The N-oxide **4l** was totally converted to the homocoupling 1,1'-dibenzyl-4,4'-bis(1,2,3-triazole N-oxide). [e]Starting materials recovered unchanged.

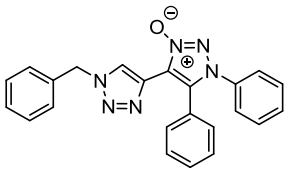
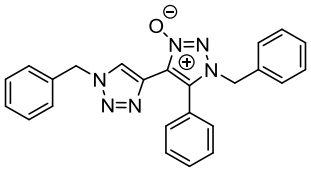
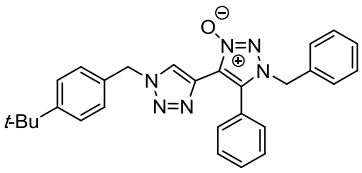
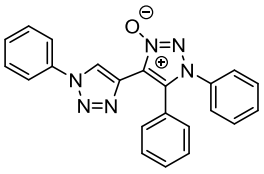
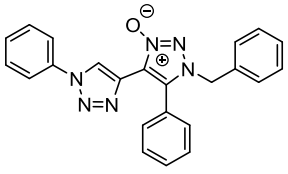
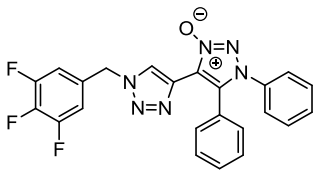
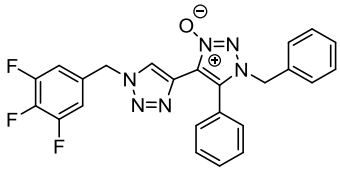
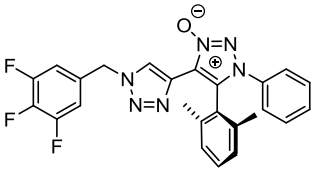
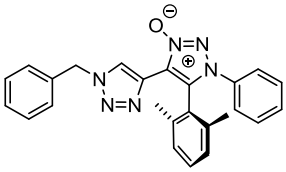
Next, we checked the extension of the method to triazole N-oxides with different steric hindrances, like **9c** and **4l** (entries 7-9). Not surprisingly, the reaction conversion dropped to 35 % for the triazole N-oxide **9c**, which bears a C(5) position was substituted by the highly hindered 2,6-dimethylphenyl group. Nonetheless, extending the reaction time to 48 h ameliorated the yield to 50 % (entry 8). Instead, the use of the unhindered monosubstituted N-oxide **4l** (entry 9) resulted in no heterocoupling, but the total homocoupling of the N-oxide **9a** to 1,1'-dibenzyl-4,4'-bis(1,2,3-triazole N-oxide). Finally, replacing silver oxide by copper(II) acetate also proved to be ineffective in promoting the coupling reaction (entry 10), since the starting 4-trimethylsilyl-triazole **3l** and the N-oxide **9a** were recovered unchanged.

With the reaction conditions optimized and the synthetic limits stablished, we next explored the scope of the Hiyama-type coupling reaction and the results obtained are depicted in Table 5.2.

Table 5.2. Pd-catalyzed coupling reaction of 4-trimethylsilyl-1*H*-1,2,3-triazole N-oxides.



3l-q + **9** → **34**

 **34a** (60 %)	 **34b** (60 %)	 **34c** (56 %)
 **34d** (50 %)	 **34e** (50 %)	 **34f** (50 %)
 **34g** (50 %)	 **34h** (50 %)[b]	 **34i** (50 %)[b]

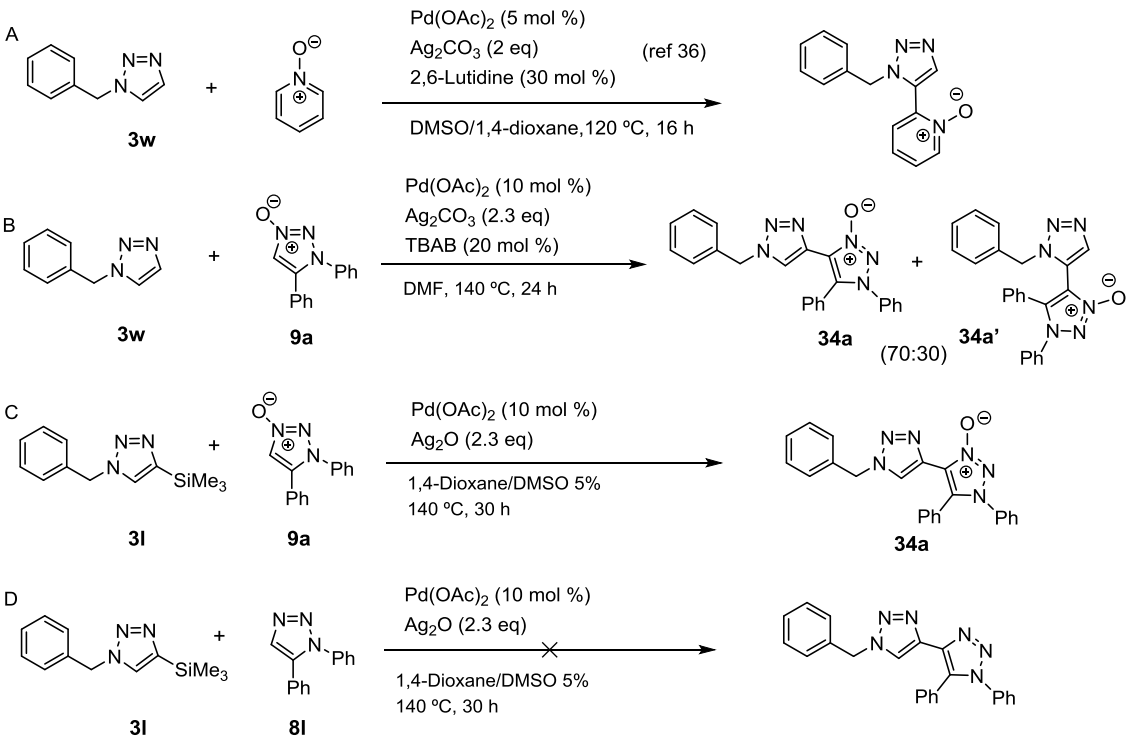
[b] Reaction time extended to 48 hours.

Unprecedented bistriazole N-oxides **34**, nonsymmetrically substituted with aliphatic or aromatic groups, were obtained in moderate to good isolated yields. The presence of highly hindered groups or electron-withdrawing substituents was well tolerated, albeit the exploration of a wider range of substituent groups would be desirable. At this point, in an attemp to widen the scope of the reaction, we tested the reaction of triazole N-oxide **9a** with several 4-trimethylsilyl triazoles bearing two additional substituents at N(1) and C(5) positions (e.g. triazoles **8c** and **8h**, described in section 2.3.2.1, Table 2.5). Unfortunately, all trials met with failure and only the complete desilylation of triazoles **8c**, **8h** and the recovery of the starting N-oxide **9a** were observed.

In order to shed light upon the results described above, we decided to carry out a series of experiments to investigate the role played by the triazole N-oxide moiety on the

activation of the reaction and, more importantly, the contribution of the trimethylsilyl group on the regiochemistry observed during the coupling reactions (Scheme 5.14).

As discussed previously in section 3.4.2.1, monosubstituted 1,2,3-triazoles are preferentially deprotonated at C(5) position by palladium acetate. Therefore, the exclusive C(5) substitution described by Kuang[240] for the palladium-catalyzed coupling of the N-benzyl-1,2,3-triazole **3w** with pyridine N-oxide could be considered as fully predictable (see Scheme 5.14 A). In contrast (see Scheme 5.14 B), triazole **3w** experienced a combination of C(4) and C(5) substitutions with the triazole N-oxide **9a**, which led to a 70:30 mixture of **34a** and **35a'** regiosisomers. According to this result, steric factors would represent a decisive contribution for the stereoisomeric outcome of the reaction. In contrast with this observation, the trimethylsilyl-triazole **3l** cleanly reacted with the N-oxide **9a** to deliver **34a** as the single isomer product (Scheme 5.14 C). This observations clearly confirm the essential role of the trimethylsilyl group to control the coupling reaction regiochemistry. Finally, the activating effect of the N-oxide moiety of **9a** was also assessed by the failure of the coupling reaction shown in Scheme 5.14 D. Actually, replacing the N-oxide **9a** by the parent triazole **8l** while keeping the reaction conditions unchanged, resulted in the desilylation of **3l**, but no conversion to the expected product could be observed.



Scheme 5.14. Test experiments conducted to confirm the activating and regiodirecting effect of the silyl group on cross-coupling reactions of 4-trimethylsilyl-1*H*-1,2,3-triazoles.

In the next part of this section are detailed the spectroscopic and crystallographic details used to characterize the regioisomeric bistriazoles outlined above. Figure 5.1 represents the assigned ^{1}H-NMR spectra of a 70:30 mixture of **34**/**34a'** described in Scheme 5.14 B.

An inspection of the spectrum of the mixture **34a**/**34a'** immediately revealed a very large difference in the chemical shifts of the benzylic methylene proton H1 of **34a**, resonating at 5.52 ppm, and the proton H1' of **34a'** resonating at an abnormally low field of 6.30 ppm. The later signal is fully consistent with a diamagnetic deshielding caused by the spatially close phenyl group attached to the C(5) position of the triazole N-oxide ring.

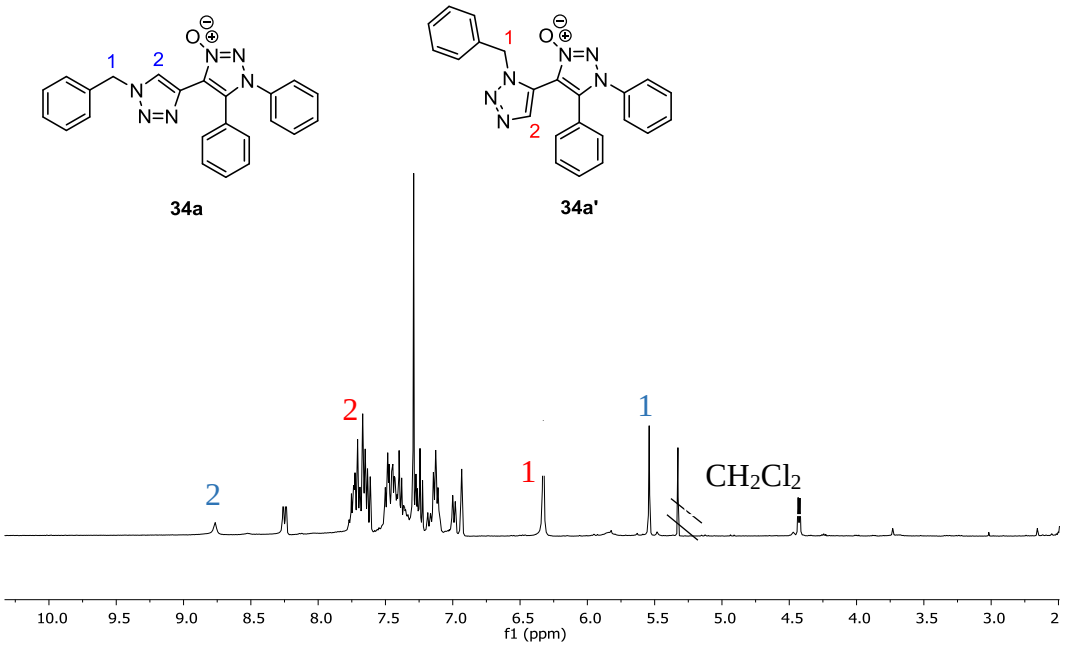


Figure 5.1. ^{1}H-NMR spectrum of a (70:30) mixture of bistriazoles **34a** and **34a'**.

The pure isomer **34a'** was obtained by a careful chromatographic separation from the reaction mixture using CH_2Cl_2/MeOH 95:5 as eluent and its spectrum is shown in Figure 5.2.

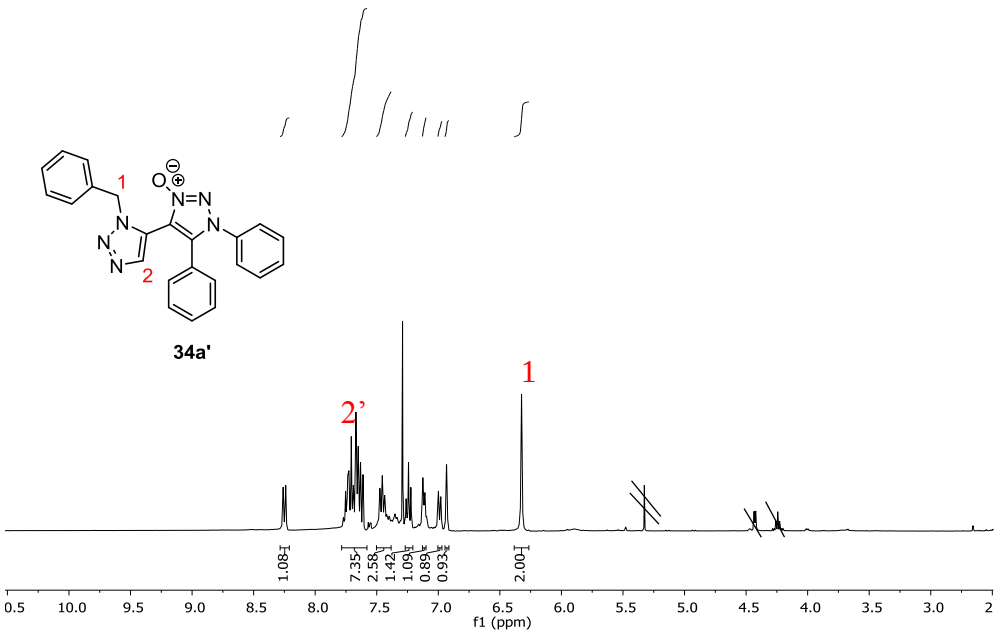


Figure 5.2. ^{1}H-NMR spectrum of bistriazoles **34a'**.

The 4,4'-substitution pattern of compound **34a** was further confirmed by several NMR studies. We first performed a selective NOE experiment saturating the methylene H1 protons and observed the positive NOE over the triazole H2 proton and the benzylic aromatic ring as depicted in Figure 5.3. Obviously, the spatial proximity of these protons was fully compatible with the regioisomer **34a**, but not with **34a'**.

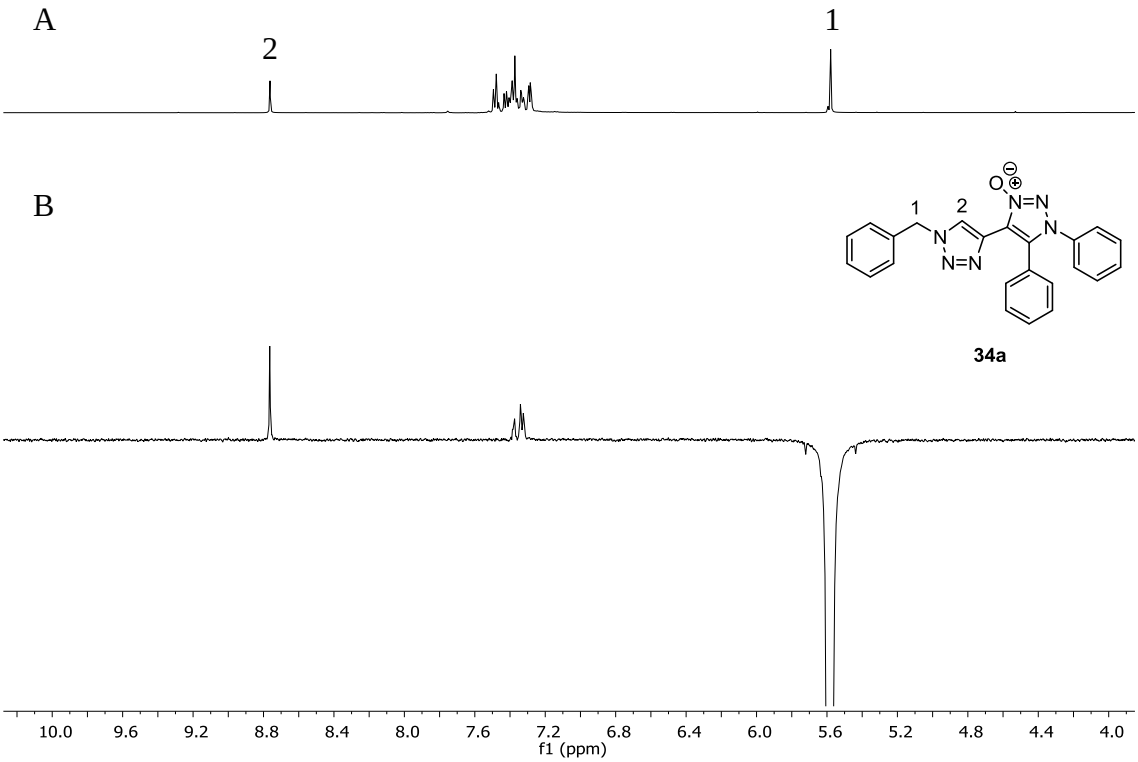


Figure 5.3. Selective NOE experiments recorded for bistriazole **34a**. (A) Regular ^{1}H-NMR spectrum. (B) NOE spectrum with saturation at H1 proton with a positive increase of the signal intensities at H2 and the benzylic aromatic ring.

In order to further ascertain the former observation, we also performed an HMBC experiment shown in Figure 5.4.

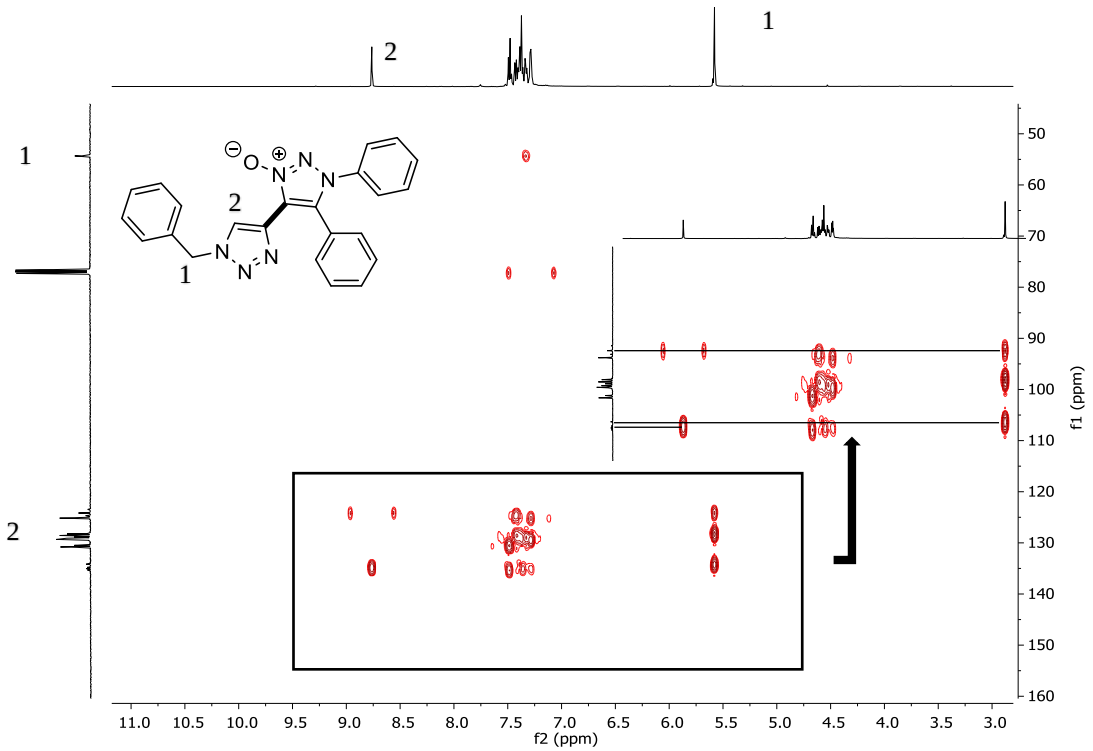


Figure 5.4. HMBC experiment of compound **34a**.

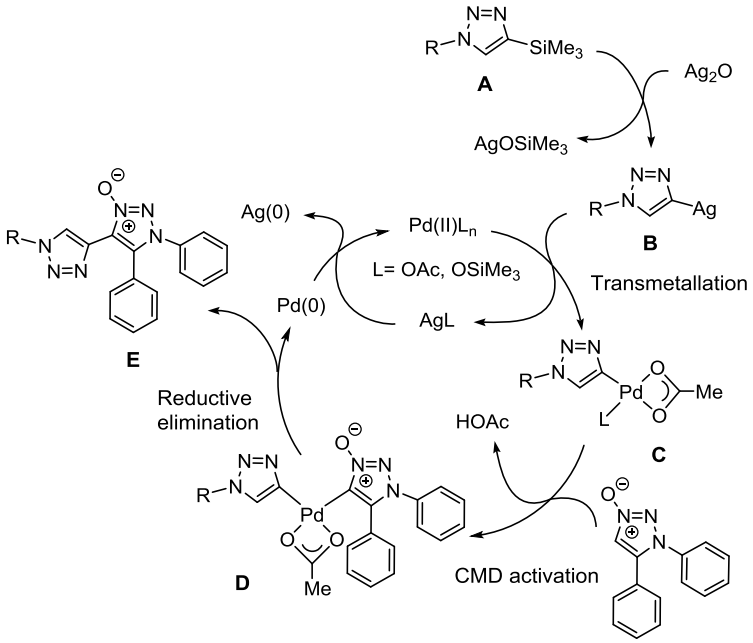
Again, in the spectrum the benzylic proton H1 gives cross-peaks with the triazole carbon attached to H2, but not with the quaternary carbon of the triazole, meaning that only structure possible was the 4,4'-bistriazole N-oxide **34a**.

Finally, a monocrystal of **34a** was obtained and the X-ray crystallogram shown in Figure 5.5 was recorded, which definitively confirmed our previous assignations.

Figure 5.5. X-ray crystallogram of 4,4'-bistriazole N-oxide **34a**.

5.3.1.1 Reaction mechanism

A plausible mechanism for the coupling reaction discussed above is depicted in Scheme 5.15. After the initial cleavage of the C-Si bond in the 4-trimethylsilyl-triazole **A** by Ag_2O, possibly assisted by the triazole N(3) nitrogen coordination, the resulting intermediate 4-silver-1,2,3-triazole **B** undergoes a transmetallation reaction to afford the palladium complex **C**. Then, a concerted metalation-deprotonation (CMD) of the C-H bond at the triazole N-oxide with **C** would lead to the key ditriazolyl complex **D**. Finally, the reductive elimination the later should deliver the coupling product **E**. Additionally, a continuous oxidation of the Pd(0) catalyst generated during the coupling step would be reoxidized to Pd(II) by Ag(I) species present in the medium, thus completing the catalytic cycle.



Scheme 5.15. Mechanistic proposal of the catalytic desilylative coupling reaction of 4-trimethylsilyl-1*H*-1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazole N-oxides.

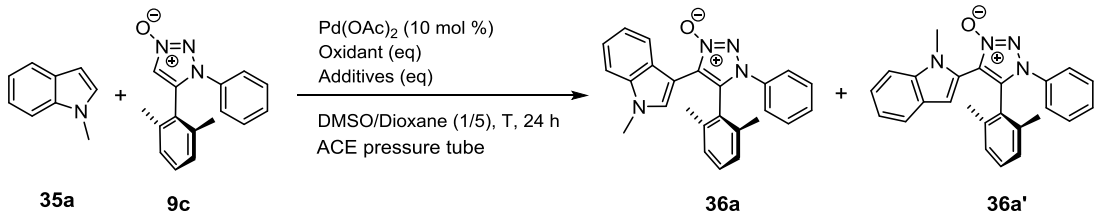
5.3.2 Palladium-catalyzed synthesis of 4-heteroaryl-1*H*-1,2,3-triazole N-oxides *via* C-H/C-H dual activation

Following our working plan, we next addressed the second objective of this chapter, consisting in the investigation of palladium-catalyzed CH/CH oxidative coupling reactions of 1,5-disubstituted 1,2,3-triazole N-oxides with electron-rich heterocycles comprising pyrrole, furan, and thiophene rings.

To check the feasibility of the proposal, we selected the pair formed by N-methyl indole **35a** and the triazole N-oxide **9c** as the workbench model and submitted it to different coupling reaction conditions in the presence of an oxidant promoter and various additives, as shown in Table 5.3. As mentioned in the introduction of this chapter (Section 5.1.2.1), indoles can give coupling products by substitution at C(3) and C(2) positions, although the natural reactivity is C(3). Therefore, we deserved particular attention to the determination of the regioisomer ratios of the coupling products **36a** and **36a'**. Mercifully, the progress of the reaction and the isomer ratio of the products was readily determined by inspecting the relative intensities of the different methyl group peaks in the ^{1}H-NMR spectra of the reaction crudes.

After a quick survey of the literature[36b] we selected palladium(II) acetate as the catalyst and silver carbonate (Ag_2CO_3) as the oxidant of choice. In a first experiment, we performed the reaction using 10 mol % $Pd(OAc)_2$ as catalyst and 2.3 equivalents of Ag_2CO_3 oxidant, in the absence of any added base (entry 1). Under such conditions, a fair 40 % yield of the coupling product **36a** was obtained, together with the corresponding regioisomer **36a'** in a 85:15 proportion, respectively. When 2 equivalents of K_2CO_3 base were added, the same proportion of products was obtained, but the yield improved to 55 % (entry 2). From these results, we concluded that an excess of base was needed to neutralize the acetic acid formed from the deprotonation **35a** and **9c**. Increasing the K_2CO_3 amount to 5 equivalents and lowering the reaction temperature to 100 ºC, resulted in a slight yield drop to 50 % (entry 3). Ultimately, repeating the same experiment at 120 ºC, provided the best result with a yield of 70 % (entry 4). Diminishing the $Pd(OAc)_2$ load to 5 mol % (entry 5) or adding additives like 2,6-lutidine[240] or pyridine[238a] was also detrimental for the reaction yield (entries 6-7). Changing the concentration of the reagents described in the run of entry 4 by increasing or decreasing the solvent mixture proportion or replacing them by alternative solvents only deteriorated the yield (not shown in the table).

Table 5.3. Reaction conditions optimization for the Pd-catalyzed oxidative coupling of N-methylindole **19a** with the model triazole N-oxide **9c**.



35a **9c** **36a** **36a'**

Entry[a]	Oxidant (eq)	Base (eq)	Additives (mol %)	T (°C)	Yield[b] (%)	Isomer ratio (**36a**:**36a'**)
1	Ag_2CO_3 (2.3)	---	-	120	40	85:15
2	Ag_2CO_3 (2.3)	K_2CO_3 (2.0)	--	120	55	88:12
3	Ag_2CO_3 (2.3)	K_2CO_3 (5.0)	--	100	50	90:10
4	Ag_2CO_3 (2.3)	K_2CO_3 (5.0)	--	120	70	90:10
5	Ag_2CO_3 (2.3)	K_2CO_3 (5.0)	--	120	55	90:10
6	Ag_2CO_3 (2.3)	K_2CO_3 (5.0)	2,6-Lutidine (30)	120	40	90:10
7	Ag_2CO_3 (2.3)	K_2CO_3 (5.0)	Pyridine (20)	120	45	90:10
8	$Cu(OAc)_2$ (2.3)	K_2CO_3 (5.0)	--	120	45	50:50

[a]Molar ratio **35a**/**9c**: 1.5/1.0. [b]Yield of isolated isomer mixture. [c]Reaction conducted with 5 mol % of $Pd(OAc)_2$ catalyst.

Finally, replacing the Ag_2CO_3 oxidant by $Cu(OAc)_2$ afforded a decent 45 % yield of the coupling products, albeit in a very poor 50:50 regioisomer ratio (entry 8) as shown in Figure 5.6 A.

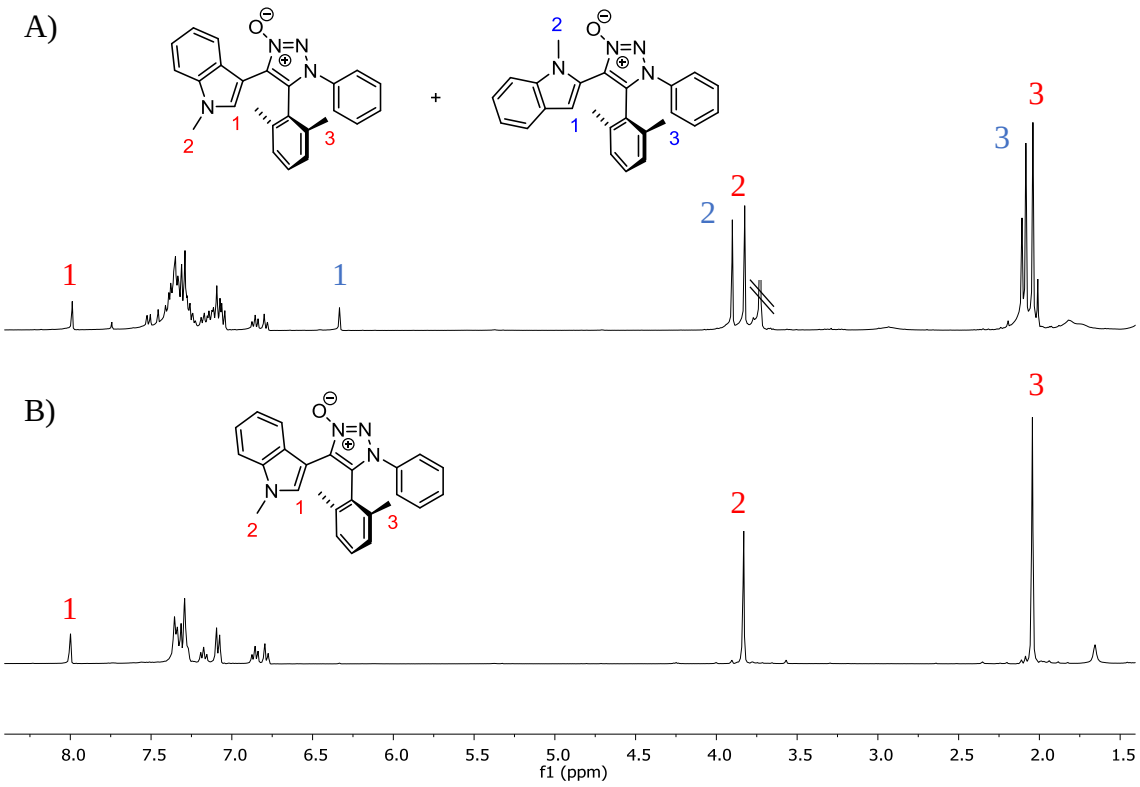
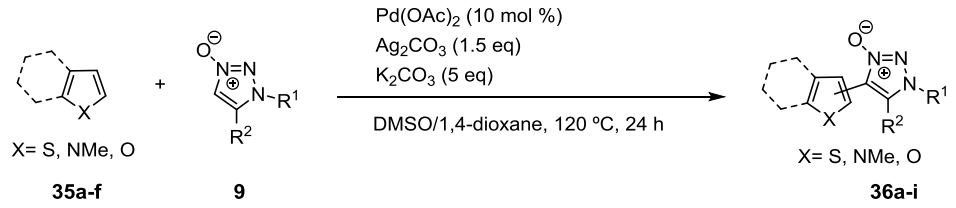


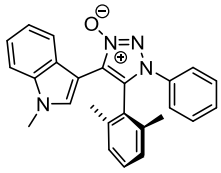
Figure 5.6. Reaction crude of the dual C-H activation utilizing indole and triazole N-oxide (**9c**). (A) Reaction crude when copper (II) acetate was used as oxidant. (B) Pure compound.

With an optimized set of reaction conditions available, we next explored the scope of the oxidative coupling to evaluate the influence of different heterocycles on the outcome of the reaction. The results obtained are collected in Table 5.4.

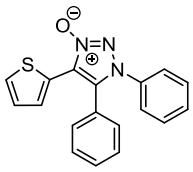
Table 5.4. Reaction scope of the palladium-catalyzed coupling of electron-rich heterocyclic compounds with triazole N-oxides *via* CH dual activation.[a]



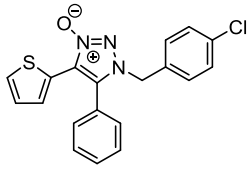
35a-f **9** **36a-i**



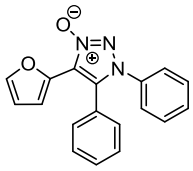
36a (70 %)



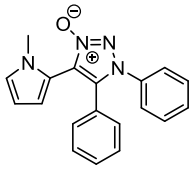
36b (66 %)



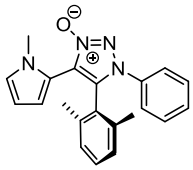
36c (66 %)



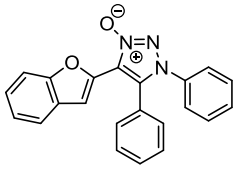
36d (73 %)



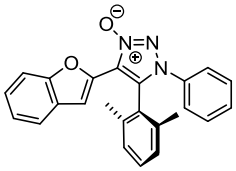
36e (86 %)



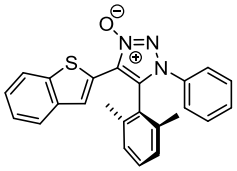
36f (88 %)



36g (80 %)



36h (69 %)



36i (76 %)

[a]Reaction conditions: triazole N-oxide **9** (0.06 mmol), heteroarene **35** (0.09 mmol), $Pd(OAc)_2$ (10 mol %), K_2CO_3 (0.3 mmol), Ag_2CO_3 (2.3 eq) in DMSO/dioxane (1/5, 0.6 mL) at 120 ºC for 24 hours under N_2.

As depicted in table 5.4, different combinations of heteroarenes and triazole N-oxides were reacted to provide uniformly good yields of trisubstituted triazoles **36**. Indeed, aliphatic and aromatic triazole N-oxides **36** were obtained in good isolated yields. It is worth mentioning that only the indole derivative **36a** was coupled from the C(3) position of the heterocyclic substrate, whereas the rest of the heteroarenes generated the new C-C bond in α- to the ring heteroatom, as depicted in the following Figure 5.7.

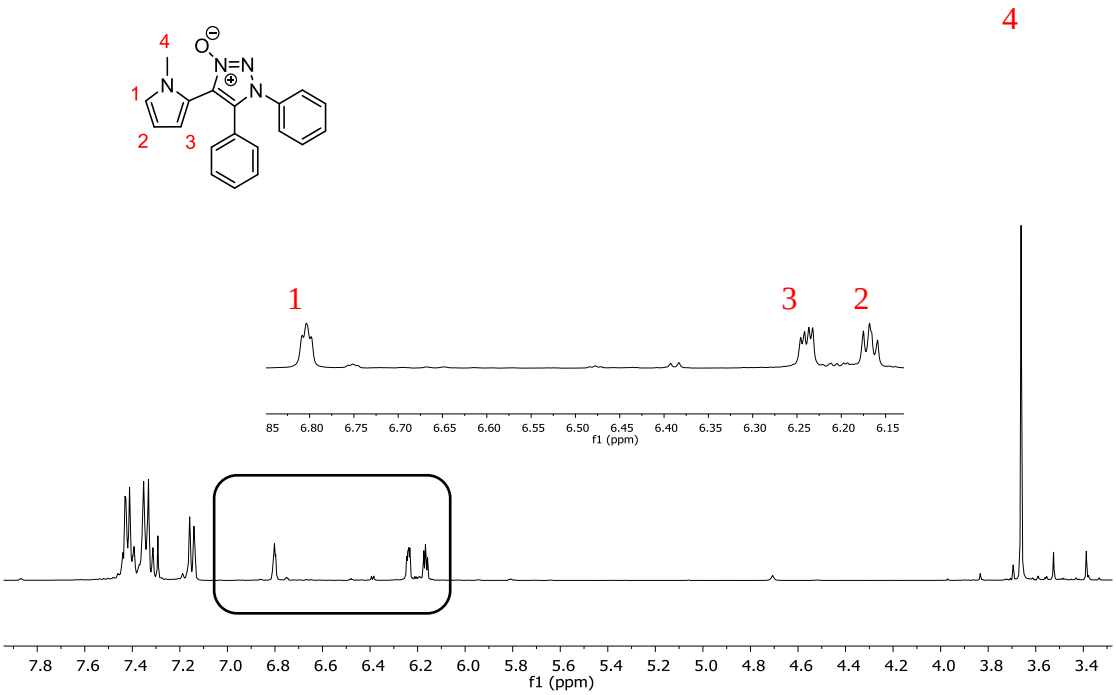
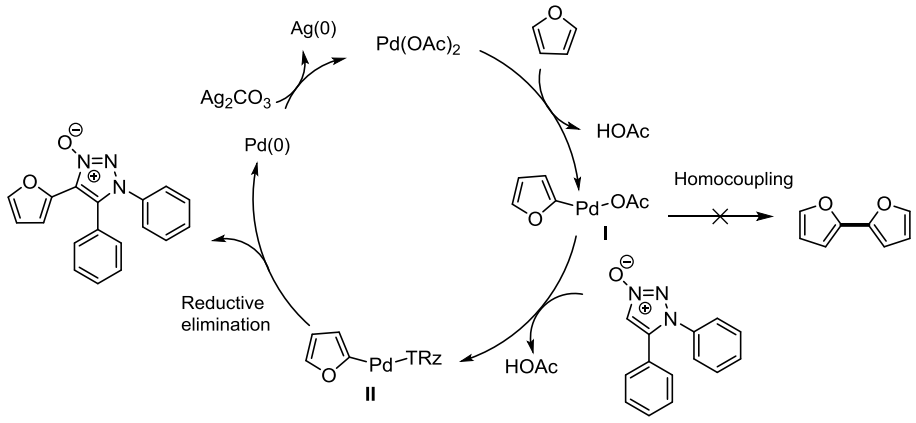


Figure 5.7. Spectrum of 1,5-diphenyl-4-(1-Methylpyrrole-2-yl)-1*H*-1,2,3-triazole N-oxide.

To conclude our investigation, we also attempted the coupling reaction of triazole N-oxides with electron-poor coupling partners, such as, caffeine, pyridine N-oxides or arenes, among other. In all cases, no evidence of coupling product formation could be detected, and we concluded that higher activation energies were necessary to activate such transformations.

5.3.2.1 Reaction mechanism

In view of the previous results, we suggest a plausible mechanism depicted below, in scheme 5.16.



Scheme 5.16. Pausible mechanism for the dual CH activation.

A plausible mechanism could proceed through Pd(0)/Pd(II) catalytic cycle. In the first step a C-H activation at Pd(II) center by electrophilic attack is taking place to afford a cyclopalladated **I**. At that point, two possible activations could occur: another CH activation with furan to afford homocoupled product or the activation of the triazole N-oxide to afford intermediate **II**. We experimentally tested that when reaction media was more concentrated this homocoupling product was afforded in moderate yields. Therefore, this pathway was supressed by diluting the reaction media. Finally, a reductive elimination process is occurring in intermediate **II** and 1,4,5-trisubstituted triazole N-oxide is obtained.

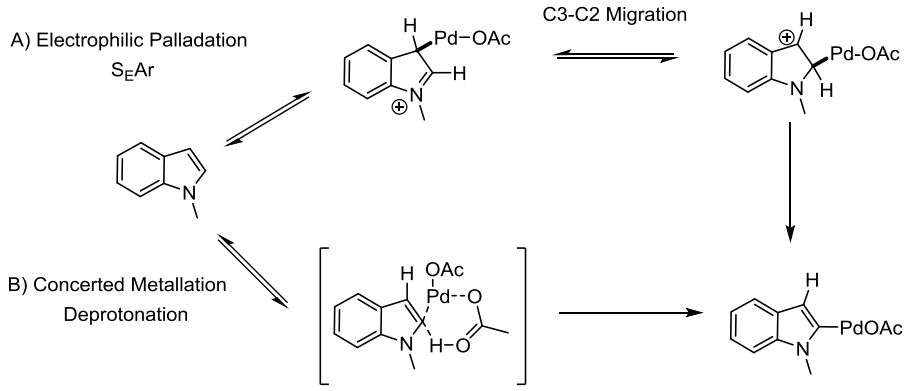
It should be highlight that when copper acetate was used as oxidant, which can also act as weak base, in dual C-H activation between triazole N-oxide and indoles, moderate yields were obtained but low C2/C3 regioselectivity was achieved.[242] This change in regioselectivity could be due to the acetate concentration in the media, that imparts the increased C2 selectivity to the Pd catalyst.[243]

Among the different pathways for C-H activation that have been proposed, electrophilic aromatic substitution and concerted metallated deprotonation have been the most support pathways for electrophilic substitution as shown in the following scheme.[244]

[242] For other example obtaining 1:1 regiomeric mixture employing $Cu(OAc)_2$ as oxidant, see: Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

[243] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.

[244] Lebrasseur, N.; Larrosa, I. *Adv Heterocycl Chem.* **2012**, *105*, 309.



Scheme 5.17. Potential mechanisms for palladation of indole.

In Scheme 5.17 A, a plausible electrophilic aromatic substitution is explained. It involves the initial palladation at the nucleophilic 3-position, after which a 1,2-migration of the metal to the 2-position can be performed. Migration of the palladium center favored in the presence of the weak base, such as, acetate.[245] Alternatively, Fagnou[246] and DeBoef[247] explained that concerted metalation deprotonation process with a six membered transition state could take place (Scheme 5.17 B), in which, some complementary experimental and computational evidence were shown.

5.4 General conclusions

We have developed a general method for the synthesis of 4,4'-polysubstituted triazole N-oxides by CH activation of 1,5-disubstituted triazole N-oxides and 1-substituted-4-silylated-1,2,3-triazoles, although not in total conversion. Moreover, the CH functionalization between 1-substituted triazole and 1,5-disubstituted triazole N-oxides provided a mixture of regioisomers 4,4'- and 4,5'- bistriazole N-oxides while the coupling between 1-substituted-4-trimethylsilyl-1,2,3-triazoles afforded 4,4'-bistriazoles as a sole product. Although, a regioselective way was not achieved for 4,5'- bistriazole N-oxides, we could further continue studying to afford a total regioselective synthesis.

Furthermore, "Click" triazole N-oxides have been demonstrated to be a powerful tool for a double CH activation with heteroarenes and thus, synthesize trisubtituted triazoles by Pd(II)- catalyzed oxidative coupling between 1,5-disubstituted triazoles and

[245] Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929.

[246] Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

[247] Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Andrew, P.; LeBris, A. P.; DeBoef, B. *J. Am.Chem. Soc.* **2010**, *132*, 14676.

functionalized heteroarenes. A broad scope of different hindered triazoles and different heteroarenes has been defined.

Finally, we wanted to expand the application of the use of triazole N-oxides and obtain preliminary results about C-N coupling. We did not find the optimized conditions and it was not wide in scope but we demonstrated that cross-coupling reactions with 1*H*-1,2,3-triazoles is possible

6

General conclusions

6. General conclusions

The N-oxidation of 1*H*-1,2,3-triazoles provide a novel platform to perform cross-coupling or CH functionalization reaction taking advantage of the activation of the N-oxide moiety. This type of heterocycles are more challenging for oxidizing than other heteroaromatic structures, such as, pyridines or quinolones, and so, stronger reaction conditions are required.

1,4- and 1,5-disubstituted triazole N-oxides react with aryl halides or other heteroarenes to afford 1,4,5-trisubstituted triazole N-oxides, while their counterparts did not react under the same reaction conditions.

Moreover, mono substituted triazole N-oxides react with aryl halide to synthesize 1,4-disubstituted triazole N-oxides. In contrast, an inverse in regioselectivity takes place when non-deoxygentated triazoles are used, thus, affording 1,5-disusbtituted triazoles.

A general route to prepare 4,4'- and 5,5'- bistriazoles was developed by CH activation for the first time under copper catalyzed reactions. Normally, bisacetylenes were used for the formation of the 4,4'-bistriazoles and oxidative conditions for cycloaddition reactions for the synthesis of 5,5'-bistriazoles. Herein, we propose homocoupling reactions of 1,5- and 1,4-disubstituted triazole N-oxides to afford 4,4'- and 5,5'- bistriazoles respectively.

Apart from C-C coupling reactions, further studies are currently under way in our group to explore new synthetic opportunities to afford C-heteroatom coupling

7

Experimental

7. Experimental

General considerations

Reagents: All reagents and solvents were obtained from commercial sources (Aldrich, Acros, Alfa Aesar, Merck and Fluka) and were used without further purification unless stated otherwise. Extra pure dichloromethane (CH_2Cl_2), acetonitrile (MeCN), hexane (Hex) and ethyl acetate (EtOAc) were bought from Sharlau.

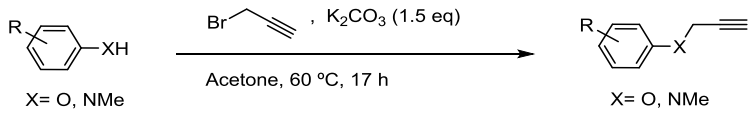
Moisture sensitive reactions were carried out using magnetic stirring under an atmosphere of nitrogen in oven or flame-dried glassware.

Purification of reaction products was carried out by flash chromatography using silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates and visualization was accomplished with UV light (λ = 254 nm). Solvents produced during reaction work up or chromatography were evaporated in Büchi R-210 rotavapors under reduced pressure.

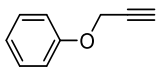
Analytical Methods: Characterization of all new compounds included ^{1}H NMR and ^{13}C NMR spectra as well as IR, HRMS and melting points (where applicable). ^{1}H NMR and ^{13}C NMR spectra were recorded at 20 ºC on Bruker Avance spectrometers operated at 500 MHz and 400 MHz for ^{1}H and at 125 MHz and 101 MHz for ^{13}C, respectively. All ^{1}H NMR spectra were reported in parts per million (ppm) downfield of TMS or were measured relative to the residual signals for $CHCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants, *J*, were reported in Hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. Mass spectra were performed by SGIker and were acquired on a time of flight (TOF) mass spectrometer (SYNAPT G2 HDMS from Waters) equipped with an electrospray source in positive mode (ESI+). Infrared spectra were recorded on a Bruker Alpha P spectrometer. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh).

7.1 Preparation of precursors, reagents and known compounds

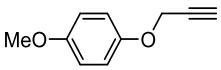
7.1.1 General procedure for the synthesis of alkynes (1)



Propargyl bromide (15 mmol, 1.7 mL; 80 % soln in toluene w/w) was added to a suspension of the corresponding phenol (10.00 mmol) and K_2CO_3 (15.00 mmol, 2.1 g) in acetone (15 mL) cooled to 0 ºC. Then, the resulting mixture was vigorously stirred at 60 ºC for 17 h. After completion of the reaction, the solvent was carefully evaporated, water (15 mL) was added to the residue and the aqueous solution was extracted with EtOAc (30 mL x 2). The combined organic extract was washed with brine (15 mL x 2), dried ($MgSO_4$) and carefully evaporated under reduced pressure. Crude products were often unstable to column chromatography purification conditions, but were pure enough to be used in next transformations as such.



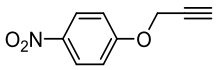
Phenyl propargyl ether.[248] The general procedure 7.1.1 was followed starting from phenol (40 mmol, 3.76 g). Yield: 5.00 g (94 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.41 (t, *J* = 7,9 Hz, 1H), 7.10 (m, *J* = 9Hz, 4H), 4.76 (d, *J* = 2,4 Hz, 2H), 2.61 (t, *J* = 2,3 Hz, 1H).



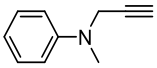
4-Methoxyphenyl propargyl ether.[249] The general procedure 7.1.1 was followed starting from 4-methoxyphenol (20.00 mmol, 2.48 g). The mixture was heated during 17 hours at 60 °C. Yield: 3.50 g (95 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.95 (d, *J* = 9,1Hz, 2H), 6.89 (d, *J* = 9,1Hz, 2H), 4.67 (d, *J* = 2,3Hz, 2H), 3.80 (s, 3H), 2.53 (t, *J* = 2,3 Hz, 1H).

[248] Pal, M.; Parasuraman, K.; Yeleswarapu, K. R. *Org. Lett.* **2003**, *5*, 349.

[249] Ishikawa, T.; Nagai, K.; Ohkubo, N.; Ishii, H. *Heterocycles* **1994**, *39*, 371.

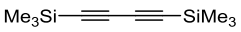


4-Nitrophenyl propargyl ether.[248] The general procedure 7.1.1 was followed starting from 4-nitrophenol (10.00 mmol, 1.39 g). Yield: 1.2 g (87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 4.82 (d, *J* = 1.8 Hz, 2H), 2.61 (t, *J* = 2.4 Hz, 1H).



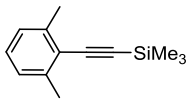
N-Methyl-N-propargylaniline. A suspension of N-methylaniline (5.00 mmol, 0.56 mL), propargyl bromide (5.00 mmol, 0.54 mL, 80 % soln in toluene w/w) and K_2CO_3 (15 mmol, 2.07 g) in DMF (7 mL) and the resulting mixture was stirred at room temperature for 24 hours. On completion, the mixture was quenched with aqueous 1M NaOH and extracted with EtOAc (20 mL x 3). Yield: 650 mg (90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 6.90 – 6.85 (m, 2H), 6.82 (tt, *J* = 7.3, 1.1 Hz, 1H), 4.07 (d, *J* = 2.3 Hz, 2H), 2.99 (s, 3H), 2.59 (t, *J* = 2.4 Hz, 1H).

7.1.1.1 Synthesis of silyl alkynes

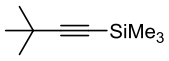


1,4-Bis(trimethylsilyl)buta-1,3-diyne.[250] In a round bottomed 500 mL flask fitted with a rubber stopper, a gas balloon and an efficient stirring bar, a suspension of trimethylsilylacetylene (10.00 mmol, 982 mg), CuI (5.00 mmol, 952 mg), TMEDA (20.00 mmol, 3.0 mL) and $MgSO_4$ (50.00 mmol, 6.0 g) in $CHCl_3$ (75 mL) was placed under O_2 atmosphere. The reaction mixture was stirred at 35 ºC for 150 minutes and was successively washed with 1M HCl (50 mL x 2) and water (50 mL). The organic phase was dried ($MgSO_4$) and was very carefully evaporated under reduced pressure to give the crude product, which was purified by recrystallization in MeOH (approx. 30 mL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 88.0, 85.9, -0.5.

[250] Fateh, V.; Mônica, F.; Hélio, A. *Tetrahedron Lett*. **2009**, *50*, 2636.



[(2,6-Dimethylphenyl)ethynyl]trimethylsilane (7b).[251] To a solution of 2,6-dimethyliodobenzene (15.00 mmol, 2.11 mL), copper (I) iodide (0.39 mmol, 75 mg) and trimethylsilylacetylene (22.5 mmol, 3.15 mL) in diethylamine (28 mL), was added tetrakis(triphenylphosphine)palladium (0.195 mmol, 225 mg) and the mixture was stirred at 50 ºC for 24 hours under nitrogen atmosphere. After removal of the solvent and the addition of water (40 mL), the mixture was extracted with chloroform (50 mL x 3). The organic layer was dried over $MgSO_4$ and the solvent was carefully evaporated under reduced pressure. The product was purified by column chromatography (silica gel, hexane). Yield: 2.7 g (90 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 6.95 (m, 3H), 2.46 (s, 6H), 0.30 (s, 9H).



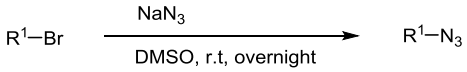
3,3-(Dimethyl)but-1-yn-1-yltrimethylsilane (7c).[252] *n*-BuLi (21.0 mmol, 13.13 mL; 1.6 M in hexanes) was added dropwise to a stirred solution of 3,3-dimethylbut-1-yne (20.4 mmol, 2.54 mL) in anhydrous THF (10 mL) at -78 ºC. Then, Me_3SiCl (20.00 mmol, 2.54 mL) dissolved in THF (10 mL) was added dropwise and the mixture was allowed to warm slowly to room temperature overnight. A saturated solution of ammonium chloride (100 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (50 mL x 2). The combined organic layer was successively washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and very carefully concentrated under reduced pressure. Yield: 2.8 g (89 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J* = 2.3 Hz, 9H), 0.30 – 0.06 (m, 9H).

[251] Saiki, T.; Akine, S.; Goto, K.; Tokito, N.; Kawashima, T.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1893.

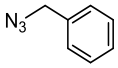
[252] Chun Chen, C.; Waser, J. *Org. Lett.* **2015**, *17*, 736.

7.1.2 Preparation of azides (2)

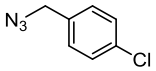
7.1.2.1 General procedure for the synthesis of aliphatic azides



The corresponding alkyl bromide (1.00 mmol) was added to a solution of NaN_3 (1.10 mmol, 71.5 mg) in DMSO (2.2 mL) and the reaction mixture was stirred for 18 hours at ambient temperature. The resulting suspension was quenched with water (5 mL) and the product was extracted with Et_2O (10 mL x 3). The combined organic phase was washed with water (10 mL x 2), dried over $MgSO_4$ and the solvent was carefully evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc).



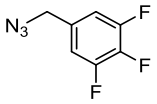
Benzyl azide.[253] The general procedure 7.1.2.1 was followed starting from benzyl bromide (3.00 mmol, 0. 35 mL) and NaN_3 (3.30 mmol, 215 mg) in DMSO (6.6 mL). Yield: 379 mg (95 %).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H, Ar), 4.33 (s, 2H, CH_2).



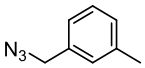
4-Chlorobenzyl azide.[254] The general procedure 7.1.2.1 was followed starting from 4-chlorobenzyl bromide (3.00 mmol, 616 mg) and NaN_3 (3.30 mmol, 215 mg) in DMSO (6.6 mL). Yield: 480 mg (96 %).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.32 – 7.25 (m, 2H), 4.35 (s, 2H).

[253] Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.

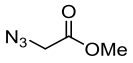
[254] Bochis, R. J.; Chabala, J. C.; Harris, E.; Peterson, L. H.; Barash, L.; Beattie, T.; Brown, J. E.; Graham, D. W.; Waksmunski, F. S.; Tischler, M.; Joshua, H.; Smith, J.; Colwell, L. F.; Wyvratt, M. J.; Jr.; Fisher, M. H. *J. Med. Chem.* **1991**, *34*, 2843.



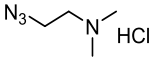
3,4,5-Trifluorobenzylazide.[255] The general procedure 7.1.2.1 was followed starting from 3,4,5-trifluorobenzyl bromide (3.00 mmol, 0.40 mL) and NaN_3 (3.30 mmol, 215 mg) in DMSO (6.6 mL). Yield: 520 mg (93 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.91-7.01 (m, 2 H), 4.32 (s, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -133.10 (d, $^3J_{FF}$ = 20.6 Hz), -160.55 (t, $^3J_{FF}$ = 20.5 Hz).



3-Methylbenzyl azide.[256] The general procedure 7.1.2.1 was followed starting from 3-methylbenzyl bromide (1.50 mmol, 0.20 mL) and NaN_3 (1.70 mmol, 108 mg) in DMSO (3.3 mL). Yield: 190 mg (86 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.13 (m, 4H), 4.32 (s, 2H), 2.39 (s, 3H).



Methyl azidoacetate.[257] A solution of methyl bromoacetate (21.30 mmol, 3.20 g) and sodium azide (22.50 mmol, 1.50 g) in dry DMF (5 mL) was stirred at room temperature for 3 h. The solution was quenched with a mol equivalent of water (21.30 mmol, 0.38 mL) and the resulting mixture was extracted with Et_2O (3 x 10 mL). The combined organic extract was washed with water (10 mL x 3) and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure. Yield: 2.32 g (95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 2H), 3.79 (s, 3H).



2-(N,N'-Dimethylamino)ethylazide hydrochloride. NaN_3 (13.00 mmol, 840 mg), 2-(N,N'-dimethylamino)ethylamine hydrochloride (10.00 mmol, 1.24 g) and NaI (0.65

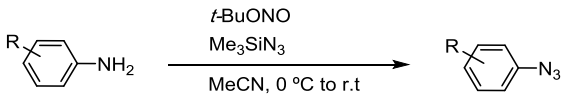
[255] Schreiner, E.; Wilcke, T.; Müller, T. J. J. *Synlett* **2016**, *27*, 379.

[256] Pinto, R. M.; Olariu, R. I.; Lameiras, J.; Martins, F. T.; Dias, A. A.; Langley, G. J.; Rodrigues, P.; Maycock, C. D.; Santos, J. P.; Duarte, M. F.; Fernandez, M. T.; Costa, M. L. *J. Mol. Struct.* **2010**, *980*, 163.

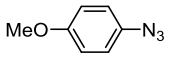
[257] Bonacorsoa, H. G.; Liberoa, F. M.; Dal Fornoa, G. M.; Pittalugaa, E. P.; Backb, D. F.; Hörnerc, M.; Martinsa, M. A. P.; Zanattaa, N. *Tetrahedron Lett.* **2016**, *57*, 4568.

mmol, 97 mg) were dissolved in water (80 mL) and the mixture was heated at 80 ºC for 16 hours. The concentration of the alkyl azide product in the resulting aqueous solution was 1.25 M, as determined by NMR (internal standard). The aqueous solution was used directly in further reactions and could be stored at 0 ºC for months without decomposition. An analytical sample of the free aminoalkyl azide was obtained upon basification of an aqueous hydrochloride solution with sodium carbonate, followed by extraction with CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30 (t, *J* = 6.3 Hz, 2H), 2.45 (t, 2H), 2.23 (s, 6H).

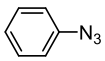
7.1.2.2 General procedure for the synthesis of aromatic azides[258]



To a solution of the corresponding aniline (10.00 mmol) in MeCN (30 mL) cooled at 0 ºC was added *t*-BuONO (20.00 mmol, 2.37 mL) followed by the dropwise addition of Me_3SiN_3 (11.00 mmol, 1.46 mL). The resulting yellow solution was stirred at room temperature for 2 hours and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc).

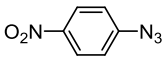


4-Methoxyphenyl azide.[258a] The general procedure 7.1.2.2 was followed starting from 4-methoxyaniline (10.00 mmol, 1.23 g). The crude product was purified by column chromatography (silica gel, Hex/EtOAc 1:10). Yield: 1.47 g (98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H).

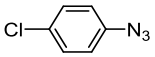


Phenyl azide.[258b] The general procedure 7.1.2.2 was followed starting from aniline (10.00 mmol, 931 mg). The crude product was purified by column chromatography (silica gel, Hex). Yield: 893 mg (75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 2H).

[258] a) Barral, A. K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett*. **2007**, *9*, 1809. b) Liu, Q.; Tor, Y. *Org. Lett*. **2003**, *5*, 2571.

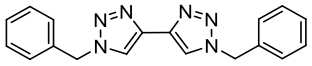


4-Nitrophenyl azide.[44a] The general procedure 7.1.2.2 was followed starting from 4-nitroaniline (10.00 mmol, 1.11 mL). The crude product was purified by column chromatography (silica gel, Hex/EtOAc 1:3). Yield: 1.51 g (92 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.9 Hz, 2H), 7.17 (d, *J* = 8.9 Hz, 2H).



4-Chlorophenyl azide.[259] The general procedure 7.1.2.2 was followed starting from 4-chloroaniline (10.00 mmol, 1.3 g). The crude product was purified by column chromatography (silica gel, Hex/EtOAc 1:4). Yield: 1.3 g (90 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.60 Hz, 2H), 6.92 (d, *J* = 8.60 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 138.7, 130.2, 129.8, 120.3.

7.1.3 Synthesis of symmetrically substituted 4,4'-bis(1*H*-1,2,3-triazoles)

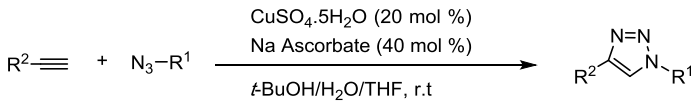


1,1'-Dibenzyl-4,4'-bis(1*H*-1,2,3-triazole) (3k).[260] To a solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne (2.00 mmol, 389 mg) and benzyl azide (4.20 mmol, 559 mg) in H_2O/*t*-BuOH 1:1 (30 mL) were added successively $CuSO_4.5H_2O$ (0.80 mmol, 200 mg), sodium ascorbate (1.60 mmol, 317 mg), K_2CO_3 (4.00 mmol, 553 mg) and pyridine (20.00 mmol, 1.60 mL) and the reaction mixture was stirred vigorously at room temperature for 24 hours. The solvent was evaporated under reduced pressure, the residue was suspended in aqueous 10% NH_3 (10 mL) and extracted with CH_2Cl_2 (15 mL x 2). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc). Yield: 500 mg (80 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 2H), 7.40 (d, *J* = 6.8 Hz, 6H), 7.35 – 7.31 (m, 4H), 5.59 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 134.3, 129.2, 128.9, 128.2, 120.5, 54.4.

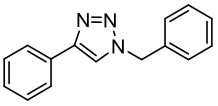
[259] Ankati, H.; Biehl, E. *Tetrahedron Lett.* **2009**, *50*, 4677.

[260] Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007**, 4597.

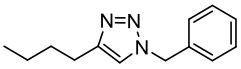
7.1.4 General procedure for the synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles (3)



To a solution of the corresponding azide (1.00 mmol) and alkyne (1.10 mmol) in THF/*t*-BuOH/H_2O 1:1:1 (5 mL), sodium ascorbate (0.40 mmol, 80 mg) and $CuSO_4 \cdot 5H_2O$ (0.20 mmol, 32 mg) were added. The reaction mixture was stirred at room temperature for 18 hours. The organic solvents were evaporated under reduced pressure, aqueous 20 % NH_3 was added to the aqueous residue and it was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, Hex/EtOAc).



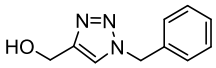
1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3a).[261] The general procedure 7.1.4 was followed starting from benzyl azide (9.35 mmol, 1.25 g) and phenylacetylene (8.5 mmol, 0.94 mL). Yield: 1.76 g (85 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.69 (s, 1H), 7.44 – 7.38 (m, 4H), 7.33 (t, *J* = 5.5 Hz, 4H), 5.58 (s, 2H).



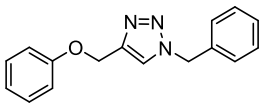
1-Benzyl-4-butyl-1*H*-1,2,3-triazole (3b).[262] The general procedure 7.1.4 was followed starting from benzyl azide (6.60 mmol, 800 mg) and 1-hexyne (6.00 mmol, 543 mg). Yield: 1.76 g (99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.08 (m, 6H), 5.51 (s, 2H), 2.71 (t, *J* = 7.8 Hz, 2H), 1.64 (p, *J* = 7.6 Hz, 2H), 1.38 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 134.9, 128.9, 128.5, 127.9, 120.4, 53.9, 31.4, 25.3, 22.3, 13.7.

[261] Jlalia, I.; Meganem, F.; Herscovici, J.; Girard, C. *Molecules* **2009**, *14*, 528.

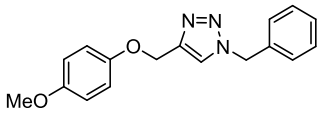
[262] Candelon, N.; Lastécouères, D.; Diallo, A. K.; Aranzaes, J. R.; Astruc, D.; Vincent, J.-M. *Chem. Commun.* **2008**, 741.



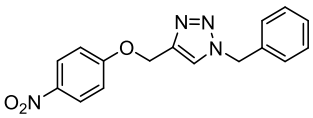
1-Benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (3c).[263] The general procedure 7.1.4 was followed starting from benzyl azide (10.00 mmol, 1.33 g) and propargyl alcohol (11.00 mmol, 0.64 mL). Yield: 1.65 g (87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.38-7.28 (m, 5H), 5.51 (s, 2H), 4.76 (s, 2H), 3.29 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 134.7, 129.3, 129.0, 128.3, 121.9, 56.5, 54.4.



1-Benzyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole (3d).[54] The general procedure 7.1.4 was followed starting from benzyl azide (4.80 mmol, 577.5 mg) and phenyl propargyl ether (4.40 mmol, 573 mg). Yield: 973 mg (80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.41 (dd, *J* = 5.8, 1.6 Hz, 3H), 7.36 – 7.26 (m, 4H), 6.99 (dt, *J* = 6.7, 2.8 Hz, 3H), 5.56 (s, 2H), 5.22 (s, 2H).



1-Benzyl-4-(4-methoxyphenoxymethyl)-1*H*-1,2,3-triazole (3e).[264] The general procedure 7.1.4 was followed starting from 4-methoxyphenyl propargyl ether (4.34 mmol, 704 mg), benzyl azide (4.8 mmol, 577 mg). Yield: 1.2 g (94 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.40 (dd, *J* = 5.7, 1.7 Hz, 2H), 7.34 – 7.25 (m, 3H), 6.93 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 5.56 (s, 2H), 5.16 (s, 2H), 3.79 (s, 3H).



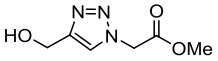
1-Benzyl-4-(4-nitrophenoxymethyl)-1*H*-1,2,3-triazole (3f).[265] The general procedure 7.1.4 was followed starting from benzyl azide (4.80 mmol, 577 mg) and 4-nitrophenyl

[263] Girard, C.; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett*. **2006**, *8*, 1689.

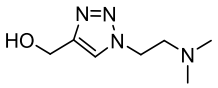
[264] Buckley, B. R.; Dann, S. E.; Heaney, H. *Chem. Eur. J.* **2010**, *16*, 6278.

[265] Jiang, Y.; Kong, D.; Zhao, J.; Zhang, W.; Xu, W.; Li, W.; Xu, G. *Tetrahedron Lett.* **2014**, *55*, 2410.

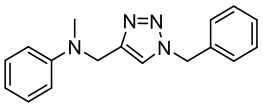
propargyl ether (4.34 mmol, 768 mg). Yield: 1.2 g (89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2 Hz, 2H), 7.62 (s, 1H), 7.43 – 7.26 (m, 5H), 7.21 – 6.98 (m, 2H), 5.57 (s, 2H), 5.28 (s, 2H).



4-Hydroxymethyl-1-methoxycarbonylmethyl-1*H*-1,2,3-triazole (3g).[266] In a flame-dried flask fitted with magnetic stirring and nitrogen atmosphere, propargyl alcohol (2.00 mmol, 112 mg), methyl azidoacetate (2.00 mmol, 230 mg) and CuI (2.00 mmol, 381 mg) were suspended in MeCN (10 mL). DIPEA (6.00 mmol, 1.04 mL) was added and the reaction mixture was stirred at room temperature for 5 h. The mixture was filtered through a pad of celite and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to provide the product as yellow oil. Yield: 147 mg (86 % yield); yellow oil. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.95 (s, 1H), 5.33 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H).



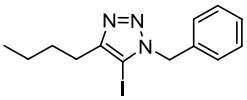
1-[2-(N,N'-Dimethylamino)ethyl]-4-hydroxymethyl-1*H*-1,2,3-triazole (3h). The general procedure 7.1.4 was starting from 2-(N,N'-dimethylamino) ethyl azide (4.38 mmol, 500 mg), propargyl alcohol (4.80 mmol, 0.3 mL). Yield: 447 mg (60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 4.77 (s, 2H), 4.45 (t, *J* = 6.3 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.29 (s, 6H).



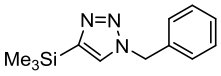
1-Benzyl-4-(N-methyl-N-phenylaminomethyl)-1*H*-1,2,3-triazole (3i).[267] The general procedure 7.1.4 was followed starting from N-methyl-N-phenylpropargyl amine (1.37 mmol, 200 mg), benzyl azide (1.50 mmol, 185 mg). Yield: 286 mg (75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.11 (m, 8H), 6.90 – 6.60 (m, 3H), 5.49 (s, 2H), 4.65 (s, 2H), 3.00 (s, 3H).

[266] Buckley, B. R.; Dann, S. E.; Heaney, H.; Stubbs, E. C. *Eur. J. Org. Chem*. **2011**, 770.

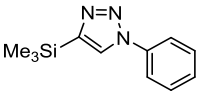
[267] Okuda, Y.; Imafuku, K.; Tsuchida, Y.; Seo, T.; Akashi, H.; Orita, A. *Org. Lett.* **2020**, *22*, 5099.



1-Butyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (3j).[92a] A solution of N-bromosuccinimide (8.19 mmol, 1.46 g) in anhydrous MeCN (20 mL) was added under nitrogen atmosphere to a suspension of CuI (7.51 mmol, 1.43 g) in MeCN (20 mL) and the mixture was stirred 5 min at room temperature. Then, benzyl azide (7.51 mmol, 1.0 g), 1-hexyne (6.83 mmol, 561 mg) and DIPEA (7.51 mmol, 0.97 g) were subsequently added and the resulting reaction mixture was stirred at room temperature overnight. On completion, 10 % aqueous HCl and aqueous saturated NH_4Cl (2 mL) were added and the mixture was evaporated at reduced pressure to eliminate the organic solvent. The resulting aqueous residue was extracted with CH_2Cl_2 (10 mL x 3) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2). Yield: 1.72 g (74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.07 (m, 5H), 5.59 (s, 2H), 2.79 – 2.60 (m, 2H), 1.78 – 1.61 (m, 2H), 1.40 (h, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 134.5, 128.8, 128.3, 127.7, 80.0, 54.2, 30.9, 25.8, 22.3, 13.8.



1-Benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (3l).[268] The general procedure 7.1.4 was followed starting from benzyl azide (4.80 mmol, 577 mg) and trimethylsilylacetylene (4.40 mmol, 0.6 mL). Yield: 915 mg (90 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.39–7.34 (m, 3H), 7.29–7.25 (m, 2H), 5.54 (s, 2H), 0.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 134.9, 129.0, 128.7, 128.5, 128.0, 53.4, -1.2.

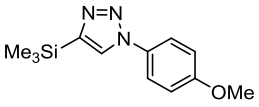


1-Phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (3m).[269] The general procedure 7.1.4 was followed starting from phenyl azide (4.00 mmol, 476 mg) and trimethylsilylacetylene (9.00 mmol, 882 mg). Yield: 750 mg (86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.73-7.75 (m, 2H), 7.49-7.54 (m, 2H), 7.40-7.45 (m, 1H), 0.39 (s, 9H).^{13}C NMR (100

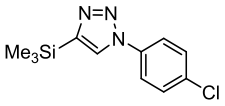
[268] Jeong, Y.; Ryu, J.-S. *J. Org. Chem.* **2010**, *75*, 4183.

[269] Fletcher, J. T.; Walz, S. E.; Keeney, M. E. *Tetrahedron Lett.* **2008**, *49*, 7030.

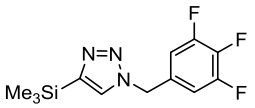
MHz, $CDCl_3$): δ 147.4, 137.2, 129.8, 128.6, 127.3, 120.9, -1.0.



1-(4-Methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (3n).[270] The general procedure 7.1.4 was followed starting from 4-methoxyphenyl azide (4.8 mmol, 715 mg) and trimethylsilylacetylene (4.40 mmol, 0.6 mL). Yield: 1.0 g (90 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 6.89 (m, 5H), 3.89 (s, 3H), 0.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 147.1, 130.7, 127.4, 122.5, 114.8, 55.7, -1.0.



1-(4-Chlorophenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (3o).[271] The general procedure 7.1.4 was followed starting from 4-chlorophenyl azide (3.00 mmol, 460 mg) and trimethylsilylacetylene (3.50 mmol, 0.48 mL). Yield: 650 mg (87 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.69 (d, *J* = 6.9 Hz, 2H), 7.48 (d, *J* = 6.8 Hz, 2H), 0.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 135.7, 134.3, 129.9, 127.1, 122.04, –1.03.

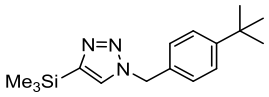


1-(3,4,5-Trifluorobenzyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (3p). The general procedure 7.1.4 was followed starting from 3,4,5-trifluorobenzyl azide (4.00 mmol, 748 mg) and trimethylsilylacetylene (6.00 mmol, 588 mg) The crude product was used without further purification. Yield: 1.0 g (87 %). Mp 56-57 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.04 – 6.73 (m, 2H), 5.52 (s, 2H), 0.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (ddd, $^1J_{CF}$ = 251.3 Hz,$^2J_{CF}$ = 10.1 Hz, $^3J_{CF}$ = 4.0 Hz), 147.7,139.0 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 15.2 Hz), 131.2 (td, $^3J_{CF}$ = 7.2 Hz, $^4J_{CF}$ = 4.7 Hz), 128.9, 112.1 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 7.8 Hz), 52.09, -1.20. IR (cm^{-1}) 3434, 1530, 1046, 835, 758.

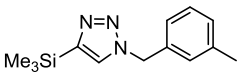
[270] Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. *Angew. Chem. Int. Ed*. **2015**, *54*, 2467.

[271] Panja, C.; Puttaramu, J. V.; Chandran, T. K.; Nimje, R. Y.; Kumar, H.; Gupta, A.; Arunachalam, P. N.; Corte, J. R.; Mathur, A. *J. Fluor. Chem.* **2020**, *236*, 109516.

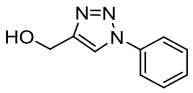
HRMS calculated for $C_{12}H_{14}N_3SiF_3$ 285,0909; found: 285,0906.



1-(4-*tert*-Butylbenzyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (3q).[272] The general procedure 7.1.4 was followed starting from 4-*tert*-butyl benzyl azide (4.00 mmol, 756 mg) and trimethylsilylacetylene (6.00 mmol, 588 mg). The crude product was used without further purification. Yield: 1.00 g (87 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.44 – 7.39 (m, 2H), 7.27 – 7.19 (m, 2H), 5.55 (s, 2H), 1.34 (s, 9H), 0.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 147.2, 132.2, 129.0, 128.1, 126.2, 53.5, 34.9, 31.5, -0.8.



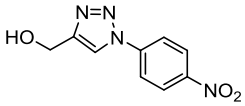
1-(3-Methylbenzyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (3r). The general procedure 7.1.4 was followed starting from 3-methyl benzyl azide (2.7 mmol, 400 mg) and trimethylsilylacetylene (10.9 mmol, 1.1 g). The crude product was used without further purification. Yield: 590 mg (89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.36 – 7.24 (m, 1H), 7.20 (s, 1H), 7.19 – 7.05 (m, 2H), 5.54 (s, 2H), 2.37 (s, 3H), 0.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 139.2, 135.0, 129.7, 129.2, 129.2, 129.0, 125.5, 53.8, 21.6, -0.8.



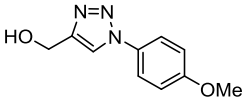
1-Phenyl-4-hydroxymethyl-1*H*-1,2,3-triazole (3s).[273] The general procedure 7.1.4 was followed starting from phenyl azide (7.61 mmol, 907 mg), propargyl alcohol (8.36 mmol, 0.49 mL), $CuSO_4 \cdot 5H_2O$ (1.52 mmol, 380 mg) and sodium ascorbate (3.04 mmol, 602 mg). Yield: 988 mg (74 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.79 – 7.72 (m, 2H), 7.60 – 7.44 (m, 3H), 4.93 (d, *J* = 5.7 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 137.3, 130.0, 129.1, 120.8, 120.3, 56.8.

[272] Han, X.; Weng, Z.; Young, D. J.; Jin, G.-X.; Hor, T. S. A. *Dalton Trans.* **2014**, *43*, 1305.

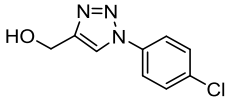
[273] Stefani, H. A.; Canduzini, H. A.; Manarin, F. *Tetrahedron Lett.* **2011**, *52*, 6086.



1-(4-Nitrophenyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (3t).[274] The general procedure 7.1.4 was followed starting from 4-nitrophenyl azide (1.22 mmol, 200 mg), propargyl alcohol (1.34 mmol, 0.09 mL), $CuSO_4 \cdot 5H_2O$ (0.24 mmol, 59.4 mg) and sodium ascorbate (0.49 mmol, 99.23 mg). Yield: 184 mg (70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.2 Hz, 2H), 8.09 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 2H), 4.93 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 149.8, 146.5, 140.9, 125.5, 121.3, 120.4, 54.8.



1-(4-Methoxyphenyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (3u).[275] The general procedure 7.1.4 was followed starting from 4-methoxyphenyl azide (1.34 mmol, 200 mg), propargyl alcohol (1.47 mmol, 0.1 mL), $CuSO_4 \cdot 5H_2O$ (0.27 mmol, 65.2 mg) and sodium ascorbate (0.54 mmol, 109 mg). Yield: 240 mg (87 %). ^{1}H NMR (400 MHz, DMSO) δ 8.64 (s, 1H), 7.88–7.92 (m, 2H), 4.72 (d, *J* = 5.5 Hz, 2H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d6) δ: 55.1, 55.6, 115.0, 121.0, 121.8, 130.3, 148.9, 159.3.

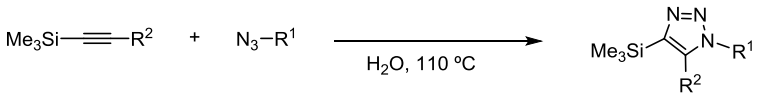


1-(4-Chlorophenyl)-4-hydroxymethyl-1*H*-1,2,3-triazole (3v).[274] The general procedure 7.1.4 was followed starting from 4-chlorophenyl azide (1.31 mmol, 200 mg), propargyl alcohol (1.41 mmol, 0.1 mL), $CuSO_4 \cdot 5H_2O$ (0.27 mmol, 65.2 mg) and sodium ascorbate (0.54 mmol, 109 mg). Yield: 240 mg (84 %). ^{1}H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 7.92 (d, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 9.1 Hz, 2H), 5.33 (t, *J* = 3.3 Hz, 1H), 4.63 (d, *J* = 3.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d6) δ 55.0, 121.1, 121.6, 129.9, 132.8, 135.6, 149.4.

[274] Boechat, N.; Ferreira, V. F.; Ferreira, S. B.; Ferreira, M. L. G.; da Silva, F. C.; Bastos, M. M.; Costa, M. S.; Lourenço, M. C. S.; Pinto, A. C.; Krettli, A. U.; Aguiar, A. C.; Teixeira, B. M.; da Silva, N. V.; Martins, P. R. C.; Bezerra, F. A. F. M.; Camilo, A. L. S.; da Silva, G. P.; Costa, C. C. P. *J. Med. Chem.* **2011**, *54*, 5988.

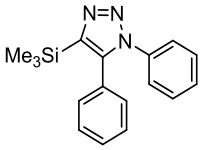
[275] Gonzaga, D.; Senger, M. R.; de Carvalho da Silva, F.; Ferreira, V. F.; Silva, F. P, Jr. *Eur. J. Med. Chem.* **2014**, *74*, 461.

7.1.5 General procedure for the synthesis of 1,5-disubsituted 4-trimethylsilyl-1*H*-1,2,3-triazoles[58]



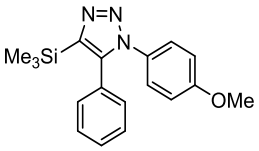
A) A solution of the corresponding azide (1.50 mmol) and the trimethylsilylalkyne (1.00 mmol) in toluene (0.5 mL) was heated in a sealed tube under microwave irradiation at 130 ºC for 2.5 hours. Then, the solvent was evaporated under pressure and the crude product was purified by column chromatography (silica gel, Hex/EtOAc).

B) In a sealed ACE tube a mixture of the corresponding azide (1.00 mmol), the trimethylsilylalkyne (1.00 mmol) and water (2 mL) was heated at 90-120 ºC with vigorous stirring for 24-48 hours. The mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 mL x 2). The combined extract was dried ($MgSO_4$) and carefully evaporated at reduced pressure. The crude product was purified by column chromatography. (Silica gel, Hex/EtOAc).

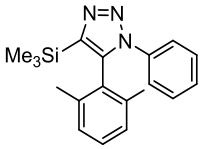


1,5-Diphenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8a).[276] The general procedure 7.1.5 B was followed starting from phenyl azide (1.00 mmol, 125 mg) and 1-phenyl-2-trimethylsilyl-acetylene (0.70 mmol, 117 mg) during a reaction of 48 h. The crude product was purified by column chromatography (Hex/EtOAc 5:1). Yield: 123 mg (60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 6H), 7.30 – 7.26 (m, 2H), 7.22 – 7.15 (m, 2H), 0.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 143.5, 136.7, 130.2, 129.4, 129.2, 128.9, 128.8, 128.7, 125.1, -0.5.

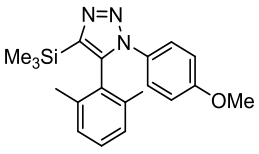
[276] Morozova, M. A.; Yusubov, M. S.; Kratochvil, B.; Eigner, V.; Bondarev, A. A.; Yoshimura, A.; Saito, A.; Zhdankin, V. V.; Trusova, M. E.; Postnikov, P. S. *Org. Chem. Front.* **2017**, *4*, 978.



1-(4-Methoxyphenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8b). The general procedure 7.1.5 A was followed starting from 4-methoxyphenyl azide (1.00 mmol, 150 mg) and 1-phenyl-2-trimethylsilyl-acetylene (0.70 mmol, 117 mg). The crude product was purified by column chromatography (Hex/EtOAc 10:1). Yield: 130 mg (60 %). Mp 84-85 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 6.68 (m, 9H), 3.80 (s, 3H), 0.23 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.1, 142.9, 129.5, 128.9, 128.6, 128.3, 127.9, 125.8, 113.7, 54.9, -1.2. IR (cm^{-1}) 3051, 1513, 1244, 830. HRMS calculated for $C_{18}H_{21}N_3OSi$: 323.1454; found: 323.1455.

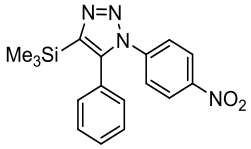


5-(2,6-Dimethylpenyl)-1-phenyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole (8c). The general procedure 7.1.5 A was followed starting from phenyl azide (1.30 mmol, 150 mg) and 1-(2,6-dimethylphenyl)-2-trimethylsilyl-acetylene (0.85 mmol, 172 mg). The crude product was purified by column chromatography (Hex/EtOAc 5:1). Yield: 164 mg (60 %). Mp 109-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 1.0 Hz, 5H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 1.98 (s, 6H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 141.2, 137.8, 136.7, 129.5, 129.0, 128.3, 128.2, 127.5, 122.9, 20.2,-1.6. IR (cm^{-1}) 2954, 1599, 1243, 838. HRMS calculated for $C_{19}H_{23}N_3Si$: 321.1661; found: 321.1661.

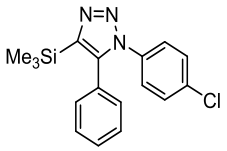


5-(2,6-Dimethylphenyl)-1-(4-methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (8d). The general procedure 7.1.5 A was followed starting from 4-methoxyphenyl azide (1.30 mmol, 185 mg) and 1-(2,6-dimethylphenyl)-2-trimethylsilyl-acetylene (0.85 mmol, 172 mg). The crude product was purified by column chromatography (Hex/EtOAc 5:1). Yield: 265 mg (60 %). Mp 162-163 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 6.79 (m, 7H), 3.80 (s, 3H), 1.98 (s, 6H), 0.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 144.3,

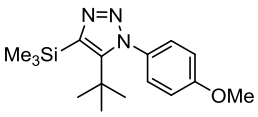
141.3, 137.8, 129.9, 129.4, 128.2, 127.5, 124.5, 114.2, 55.4, 20.3, -1.5. IR (cm^{-1}) 2956, 1511, 1243, 837. HRMS calculated for $C_{20}H_{25}N_3OSi$: 351.1767; found: 351.1769.



1-(4-Nitrophenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8e). The general procedure 7.1.5 B was followed starting from 4-nitrophenyl azide (2.00 mmol, 328 mg) and 1-phenyl-2-trimethylsilyl-acetylene (3.20 mmol, 558 mg) during a reaction time of 48 h. The crude product was purified by column chromatography (EtOAc/Hex 1:4). Yield: 473 mg (70 %). Mp 91-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.16 (m, 2H), 7.58 – 7.38 (m, 5H), 7.32 – 7.15 (m, 2H), 0.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 146.2, 143.3, 141.3, 129.9, 129.9, 128.9, 128.0, 124.8, 124.6, -0.9. IR (cm^{-1}) 3075, 1513, 1338, 834. HRMS calculated for $C_{17}H_{18}N_4O_2Si$: 338.1199; found: 338.1202.

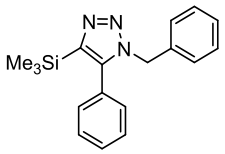


1-(4-Chlorophenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8f). The general procedure 7.1.5 B was followed starting from 4-chlorophenyl azide (2.61 mmol, 400 mg) and 1-phenyl-2-trimethylsilyl-acetylene (3.20 mmol, 558 mg) during a reaction time of 48 h. The crude product was purified by column chromatography (EtOAc/Hex 1:4). Yield: 600 mg (70 %). Mp 90-93 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 3H), 7.33 – 7.28 (m, 2H), 7.21 (ddd, *J* = 17.8, 8.3, 1.8 Hz, 4H), 0.22 (d, *J* = 1.8 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 143.1, 134.9, 134.4, 129.9, 129.3, 129.2, 128.5, 128.3, 125.9, -0.9. IR (cm^{-1}) 3070, 1496, 1248, 832. HRMS calculated for $C_{17}H_{18}ClN_3OSi$: 327.0959; found: 327.0959.

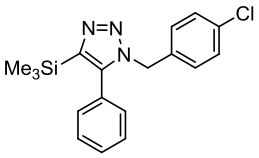


5-*tert*-Butyl-1-(4-methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (8g). The general procedure 7.1.5 B was followed starting from 4-methoxyphenyl azide (2.10 mmol, 313 mg) and 1-*tert*-butyl-2-trimethylsilyl-acetylene (4.00 mmol, 616 mg) during

a reaction time of 48 h. A mixture of 1,4- and 1,5- isomers was obtained (45:55 respectively). The crude product was used in subsequent reaction without purification. Yield: 200 mg (40 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 6.79 (m, 4H), 3.87 (s, 3H), 1.26 (s, 9H), 0.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 131.9, 129.0, 128.3, 114.0, 113.9, 55.6, 31.82, 31.5, 1.2.

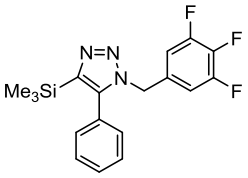


1-Benzyl-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8h).[277] The general procedure 7.1.5 B was followed starting from benzyl azide (2.00 mmol, 266 mg) and 1-phenyl-2-trimethylsilyl-acetylene (3.2 mmol, 558 mg) during a reaction time of 48 h. The crude product was purified by column chromatography. (EtOAc/Hex 1:5). Yield: 553.4 mg (90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.37 (m, 3H), 7.32 – 7.23 (m, 3H), 7.13 – 6.98 (m, 4H), 5.40 (s, 2H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 135.8, 130.3, 129.6, 128.8, 128.7, 128.3, 128.2, 127.8, 126.7, 51.6, -0.6.



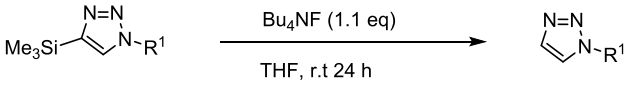
1-(4-Chlorobenzyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (8i). The general procedure 7.1.5 B was followed starting from *p*-chlorobenzyl azide (2.00 mmol, 335 mg) and 1-phenyl-2-trimethylsilyl-acetylene (3.20 mmol, 558 mg) during a reaction time of 48 h. The crude product was purified by column chromatography (Hex/EtOAc 5:1). Yield: 581 mg (85 %). Mp 86 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.40 (m, 3H), 7.28 – 7.19 (m, 2H), 7.14 – 7.08 (m, 2H), 7.01 – 6.92 (m, 2H), 5.36 (s, 2H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 143.5, 134.0, 133.9, 129.9, 129.6, 129.0, 128.8, 128.6, 128.3, 50.7, -0.9. IR (cm^{-1}) 2958, 808. HRMS calculated for $C_{18}H_{20}ClN_3Si$: 341.1115; found: 341.1111.

[277] Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2009**, 436.

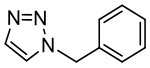


5-Phenyl-1-(3,4,5-trifluorobenzyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (8j). The general procedure 7.1.5 B was followed starting from 3,4,5-trifluorobenzyl azide (2.00 mmol, 374 mg) and 1-phenyl-2-trimethylsilyl-acetylene (3.20 mmol, 558 mg) during a reaction time of 48 h. The crude product was purified by column chromatography (EtOAc/Hex 1:4). Yield: 350 mg (50 %). Mp 111.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.41 (m, 3H), 7.20 – 7.08 (m, 2H), 6.79 – 6.55 (m, 2H), 5.31 (s, 2H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 ($^{1}J_{CF}$ = 251.3 Hz, $^{2}J_{CF}$ = 10.5 Hz, $^{3}J_{CF}$ = 3.8 Hz), 145.2, 143.5, 139.4 (dt, $^{1}J_{CF}$ = 255.2 Hz, $^{2}J_{CF}$ = 15.4 Hz), 131.5 (td, $^{3}J_{CF}$ = 7.2 Hz, $^{4}J_{CF}$ = 4.8 Hz), 129.8, 129.7, 128.7, 128.0, 112.0 (dd, $^{2}J_{CF}$ = 22.6 Hz, $^{3}J_{CF}$ = 6.5 Hz), 50.0, -1.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.82 (d, *J* = 20.2 Hz), -160.12 (t, *J* = 20.5 Hz). IR (cm^{-1}) 2957, 1620, 1529, 836. HRMS calculated for $C_{18}H_{18}F_3N_3Si$: 361.1222; found 361.1222.

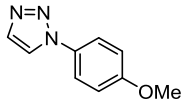
7.1.6 General procedure for the synthesis of 1-substituted 1,2,3-triazoles



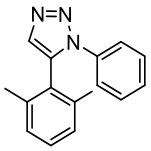
In a round bottomed flask, a solution of the corresponding 4-trimethylsilyl-1,2,3-triazole (1.00 mmol) and TBAF (1.10 mmol, 1.1 mL; 1.0 M in THF) in THF (5 mL) was stirred at room temperature for 24 hours. Upon completion (TLC), H_2O (7 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 2). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to provide a crude product, which was purified by column chromatography (Hex:EtOAc).



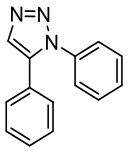
1-Benzyl-1,2,3-triazole (3w).[268] The general procedure 7.1.6 was followed starting from 1-benzyl-4-trimethylsilyl-1,2,3-triazole (**3l**) (0.43 mmol, 100 mg) and TBAF (0.47 mmol, 0.47 mL). Yield: 55 mg (80 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 7.47 (s, 1H), 7.34-7.39 (m, 3H), 7.26-7.27 (m, 2H), 5.57 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 134.6, 134.1, 129.0, 128.6, 127.9, 123.3, 53.8.



1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole (3x).[278] The general procedure 7.1.6 was followed starting from 1-(4-Methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole **(3n)** (0.20 mmol, 50 mg) and TBAF (0.19 mmol, 0.19 mL). Yield: 26 mg (75 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91(d, *J* = 1.1 Hz, 1H), 7.82 (d, *J* = 1.1 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H).



5-(2,6-Dimethylpenyl)-1-phenyl-1*H*-1,2,3-triazole (8k). The general procedure 7.1.6 was followed starting from 5-(2,6-Dimethylpenyl)-1-phenyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole **(8c)** (0.19 mmol, 60 mg) and TBAF (0.23 mmol, 0.23 mL). Yield: 33 mg (70 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (s, 1H), 7.41 – 7.20 (m, 6H), 7.10 (d, J = 7.6 Hz, 2H), 2.00 (s, 6H).

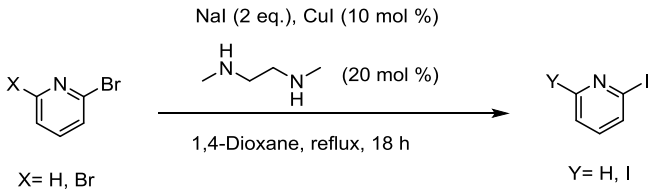


1,5-Diphenyl-1,2,3-triazole (8l).[279] The general procedure 7.1.6 was followed starting from 1,5-diphenyl-4-trimethylsilyl-1,2,3-triazole (**8a**) (0.43 mmol, 126 mg) and TBAF (0.47 mmol, 0.47 mL). Yield: 65 mg (70 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.9 (s, 1H), 7.50-7.44 (m, 3H), 7.44-7.36 (m, 5H), 7.31-7.22 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.7, 136.6, 133.4, 129.4, 129.3, 129.2, 128.9, 128.6, 126.8, 125.2.

[278] Wu, L.; Yan, B.; Yang, G.; Chen, Y. *Heterocycl. Commun.* **2013**, *19*, 397.

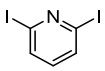
[279] Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928.

7.1.7 General procedure for the synthesis of pyridyl iodides



A reported procedure was followed to prepare pyridil iodides from the commercially available pyridyl bromides[280]. The reaction was carried out under argon using standard Schlenk techniques. A two-neck pear-shaped flask equipped with a reflux condenser was charged with the corresponding pyridyl bromide (1.00 mmol), NaI (2 mmol per bromine to exchange), and CuI (10 mol % per bromine to exchange). *N*,*N*′-Dimethylethylenediamine (20 mol % per bromine to exchange) and anhydrous 1,4-dioxane (0.5 mL per mmol of NaI used) were added. The resulting suspension was heated to 110 °C for 18 h. After cooling to r.t., the mixture was poured into aq 25% NH_3 solution. The blue solution was diluted to a doubled volume with H_2O and was extracted three times with CH_2Cl_2. Finally, the product was purified by column chromatography.

2-Iodopyridine. The general procedure 7.1.7 was followed starting from 2-bromopyridine (42.00 mmol, 4 mL), CuI (4.20 mmol, 800 mg), NaI (8.40 mmol, 1.26 g) and N,N'-Dimethylethylenediamine (8.40 mmol, 1,06 mL) in dioxane (40 mL). The product was purified by column chromatography (Hex/EtOAc 4:1). The analytical data were in accordance with the literature data[281]



2,5-Diiodopyridine.[282] The general procedure 7.1.7 was followed starting from 2,5-dibromopyridine (2.98 mmol, 700 mg), NaI (11.8 mol, 1.77 g), CuI (0.60 mmol, 114 mg)

[280] Meyer-Eppler, G.; Küchler, L.; Tenten, C.; Benkhäuser, C.; Brück, S.; Lützen, A. *Synthesis.* **2014**, *46*, 1085.

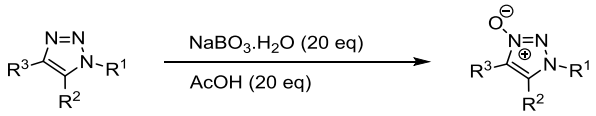
[281] Chau, N. T. T.; Meyer, M.; Komagawa, S.; Chevallier, F.; Fort, Y.; Uchiyama, M.; Mongin, F.; Gros, P. C. *Chem. Eur. J.* **2010**, *16*, 12425.

[282] Yang, H.; Rys, A. Z.; McLaughlin, C. K.; Sleiman, H. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 9919.

and N,N'-dimethylethylenediamine (0.59 mmol, 0.13 mL) in dioxane (3 mL). The product was purified by column chromatography (Hex/EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 2H), 6.97 (t, *J* = 7.7 Hz, 1H).

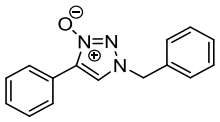
7.2 Experimental section of chapter 2

7.2.1 General procedure for the synthesis of 1*H*-1,2,3-triazole N-oxides

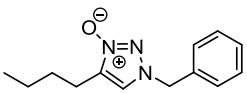


Sodium perborate monohydrate (20.0 mmol, 2.00 g) was added to a solution of the corresponding 1*H*-1,2,3-triazole (1.00 mmol) in AcOH (20 mL). The reaction mixture was heated at 90 ºC for 24 hours. Then, the resulting mixture was filtered through a celite pad and was extensively extracted with CH_2Cl_2. The combined extract was washed with saturated $NaHCO_3$ solution (15 mL x 2). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product which was purified by column chromatography. (silica gel, Hex/EtOAc).

7.2.1.1 Oxidation of 1,4-disubstituted 1*H*-1,2,3-triazoles

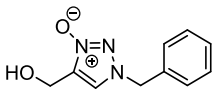


1-Benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (4a). The general procedure 7.2.1 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**3a**) (0.43 mmol, 100 mg). The product was purified by column chromatography (EtOAc/Hex 10:1) Yield: 48.6 mg (45 %). Mp 190-193 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.73 (s, 1H), 7.49 – 7.28 (m, 8H), 5.29 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 131.5, 129.6, 129.5, 129.4, 128.9, 128.9, 126.6, 125.6, 122.2, 55.8. IR (cm^{-1}) 3034, 1726, 1390, 701. HRMS calculated for $C_{15}H_{13}N_3O$: 251.1059; found: 251.1061.

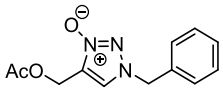


1-Benzyl-4-butyl-1*H*-1,2,3-triazole N-oxide (4b). The general procedure 7.2.1 was followed starting from 1-benzyl-4-butyl-1*H*-1,2,3-triazole (**3b**) (0.46 mmol, 100 mg). The

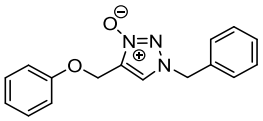
crude product was purified by column chromatography (EtOAc). Yield: 69 mg (65 %). Mp 64-67 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.04 (m, 6H), 5.24 (s, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.58 (q, *J* = 7.7 Hz, 2H), 1.37 (q, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 133.0, 129.1, 129.1, 128.3, 122.2, 55.2, 28.6, 22.2, 22.1, 13.6. IR (cm^{-1}) 3345, 1723, 1388, 705. HRMS calculated for $C_{13}H_{17}N_3O$: 231.1372; found: 231.1373.



1-Benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole N-oxide (4c). The general procedure 7.2.1 was followed starting from 1-benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (**3c**) (0.53 mmol, 100 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 70 mg (65 %). Mp 90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.31 (m, 6H), 5.29 (s, 2H), 4.67 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4, 131.7, 129.5, 129.3, 128.6, 122.7, 55.5, 53.2. IR (cm^{-1}) 3291, 1683, 1403, 1030, 662. HRMS calculated for $C_{10}H_{11}N_3O_2$: 205.0851; found: 205.0854.

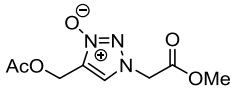


4-(Acetoxymethyl)-1-benzyl-1,2,3-triazole N-oxide (4c'). The general procedure 7.2.1 was followed starting from 1-benzyl-4-hydroxymethyl-1*H*-1,2,3-triazole (**3c**) (0.53 mmol, 100 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 45 mg (35 %). Mp 60 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.45 – 7.23 (m, 5H), 5.27 (s, 2H), 5.10 (s, 2H), 2.03 (d, *J* = 2.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 132.5, 129.2, 129.1, 128.5, 127.4, 125.7, 55.4, 53.1, 20.5. IR (cm^{-1}) 3105, 1739, 1395, 1220, 705. HRMS calculated for $C_{12}H_{13}N_3O_3$: 247.0957; found: 247.0957.

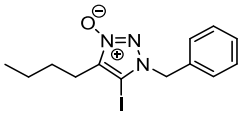


1-Benzyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole N-oxide (4d). The general procedure 7.2.1 was followed starting from 1-benzyl-4-phenoxymethyl-1*H*-1,2,3-triazole (**3d**) (0.19 mmol, 50 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 30 mg (55 %). Mp 91 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ

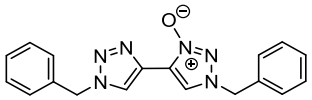
7.55 (s, 1H), 7.44 – 7.25 (m, 7H), 7.05 – 6.92 (m, 3H), 5.27 (s, 2H), 5.14 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 132.9, 129.9, 129.6, 129.5, 129.3, 128.8, 124.3, 121.9, 114.8, 58.7, 55.8. IR (cm^{-1}) 3385, 1741, 1594, 1222, 1008, 692. HRMS calculated for $C_{16}H_{15}N_3O_2$: 281.1164; found: 281.1161.



4-Acetoxymethyl-1-methoxycarbonylmethyl-1*H*-1,2,3-triazole N-oxide (4g). The general procedure 7.2.1 was followed starting from 4-hydroxymethyl-1-methoxycarbonylmethyl-1*H*-1,2,3-triazole (**3g**) (0.53 mmol, 100 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 61 mg (50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 5.25 (s, 2H), 5.20 (s, 2H), 3.83 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 166.5, 143.2, 125.1, 57.4, 53.1, 50.6, 20.8.

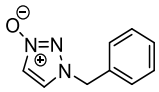


1-Benzyl-4-butyl-5-iodo-1*H*-1,2,3-triazole N-oxide (4j). The general procedure 7.2.1 was followed starting from 1-benzyl-5-iodo-4-butyl-1*H*-1,2,3-triazole (**3j**) (0.30 mmol, 100 mg) The crude product was purified by column chromatography (EtOAc/Hex 10:1). Yield: 41 mg (40 %). Mp 169.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.34 (s, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.65 (tt, *J* = 7.8, 6.4 Hz, 2H), 1.36 (dt, *J* = 14.7, 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 133.3, 128.9, 128.8, 128.0, 79.2, 55.3, 28.5, 23.1, 22.3, 13.7. IR (cm^{-1}) 1727, 1673, 1339. HRMS calculated for $[2M]^+$ $C_{13}H_{16}IN_3O$: 357.0338; found: 715.1991.

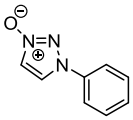


1,1'-Dibenzyl-1*H*,1'*H*-[4,4'-bi(1,2,3-triazole)] N-oxide (4k). The general procedure 7.2.1 was followed starting from 1,1'-dibenzyl-4,4'-bis(1*H*-1,2,3-triazole) (**3k**) (0.3 mmol, 100 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:5) Yield: 70 mg (70 %). Mp 245.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.97 (s, 1H), 7.53 – 7.19 (m, 10H), 5.59 (s, 2H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 134.1, 132.3, 129.5, 129.3, 129.1, 128.9, 128.7, 128.1, 125.5, 122.6, 121.3, 55.7,

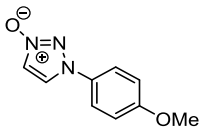
54.4. IR (cm^1) 3135, 3108, 2922, 1441, 1350, 704. HRMS calculated for $C_{18}H_{16}N_6O$: 332.1386; found: 332.1381.



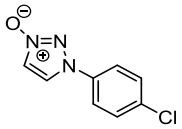
1-Benzyl-1*H*-1,2,3-triazole N-oxide (4l). The general procedure 7.2.1 was followed starting from 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3l**) (1.73 mmol, 400 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 220 mg (73 %). Mp 133.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 3H), 7.37 – 7.31 (m, 4H), 5.29 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.6, 129.3, 129.3, 128.5, 124.9, 120.2, 55.5. IR (cm^{-1}) 1518, 1412, 1327, 706. HRMS calculated for $C_9H_9N_3O$: 175.0746; found: 175.0751.



1-Phenyl-1*H*-1,2,3-triazole N-oxide (4m). The general procedure 7.2.1 was followed starting from 1-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3m**) (2.10 mmol, 450 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 280 mg (82 %). Mp 79-81 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.4 Hz, 1H), 7.67 (dd, *J* = 8.6, 1.2 Hz, 3H), 7.60 – 7.53 (m, 2H), 7.53 – 7.44 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 130.1, 129.1, 122.7, 121.8, 119.4. IR (cm^{-1}) 1502, 1228, 682. HRMS calculated for $C_8H_7N_3O$: 161.0589; found: 161.0595.

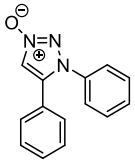


1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole N-oxide (4n). The general procedure 7.2.1 was followed starting from 1-(4-methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (**3n**) (0.40 mmol, 129 mg). The product was purified by column chromatography (Hex/EtOAc 1:10). Yield: 75.6 mg (70 %). Mp 207-208 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.2 Hz, 1H), 7.55 (m, 3H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 129.2, 122.8, 121.2, 121.1, 114.9, 55.6. IR (cm^{-1}) 3068, 1506, 1241, 1022, 835, 759. HRMS calculated for $C_9H_9N_3O_2$: 267.1008; found: 267.1008.

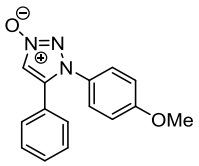


1-(4-Chlorophenyl)-1*H*-1,2,3-triazole N-oxide (4o). The general procedure 7.2.1 was followed starting from 1-(4-chlorophenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (**3o**) (1.60 mmol, 400 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 160 mg (51 %). Mp >250 ºC. ^{1}H NMR (500 MHz, DMSO) δ 8.97 (q, *J* = 1.6 Hz, 1H), 7.96 (q, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.72 – 7.61 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 135.1, 132.9, 130.3, 125.9, 122.2, 121.1. IR (cm^1) 3085, 1527, 1426, 815, 767. HRMS calculated for $C_8H_6ClN_3O$: 195.0199; found: 195.0203.

7.2.1.2 Oxidation of 1,5-disubstituted 1*H*-1,2,3-triazoles

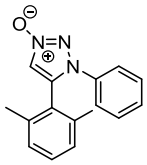


1,5-Diphenyl-1*H*-1,2,3-triazole N-oxide (9a). The general procedure 7.2.1 was followed starting from 1,5-diphenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8a**) (0.68 mmol, 150 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 114 mg (70 %). Mp 202.5 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.46 – 7.41 (m, 6H), 7.37 – 7.33 (m, 2H), 7.26 (t, *J* = 1.3 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) 139.0, 135.1, 130.6, 129.6, 129.5, 129.2, 128.7, 125.2, 124.5, 119.4. IR (cm^{-1}) 3150, 3058, 1588, 1498, 1488, 755. HRMS calculated for $C_{14}H_{11}N_3O$: 237.0902; found: 237.0901.

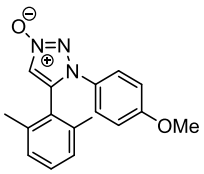


1-(4-Methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (9b). The general procedure 7.2.1 was followed starting from 1-(4-methoxyphenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8b**) (1.05 mmol, 260 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:10) Yield: 100 mg (50 %). Mp 192.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.45 – 7.32 (m, 3H), 7.25 – 7.17 (m, 4H), 6.92 – 6.84 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 139.0, 130.3, 129.0, 128.5, 127.8,

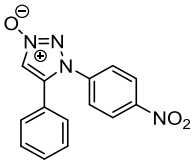
126.6, 124.4, 118.9, 114.5, 55.4. IR (cm^{-1}) 3076, 1522, 1397, 1246, 752. HRMS calculated for $C_{15}H_{13}N_3O_2$: 191.0695; found: 191.0695.



5-(2,6-Dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (9c). The general procedure 7.2.1 was followed starting from 5-(2,6-dimethylpenyl)-1-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8c**) (0.5 mmol, 150 mg). The crude product was purified by column chromatography (EtOAc). Yield: 85 mg (65 %). Mp 178.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.07 (m, 9H), 2.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.2, 135.5, 130.9, 129.4, 129.0, 128.1, 124.0, 122.6, 120.6, 20.2. IR (cm^{-1}) 3154, 2921, 1701, 1459, 785. HRMS calculated for $C_{16}H_{15}N_3O$: 265.1215; found: 265.1215.

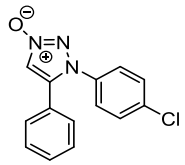


5-(2,6-Dimethylphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole N-oxide (9d). The general procedure 7.2.1 was followed starting from 5-(2,6-dimethylphenyl)-1-(4-methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (**8d**) (0.65 mmol, 230 mg). The crude product was purified by column chromatography (EtOAc). Yield: 134 mg (70 %). Mp 194.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.37 – 7.26 (m, 1H), 7.23 – 7.05 (m, 4H), 6.91 – 6.73 (m, 2H), 3.80 (s, 3H), 2.11 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.0, 137.1, 130.8, 128.5, 128.1, 124.3, 124.1, 120.3, 114.5, 55.5, 20.2. IR (cm^{-1}) 3102, 1509, 1251, 737. HRMS calculated for $C_{17}H_{17}N_3O_2$: 295.1321; found: 295.1319.

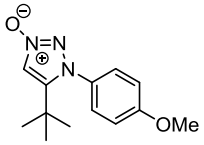


1-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (9e). The general procedure 7.2.1 was followed starting from 1-(4-nitrophenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8e**) (1.00 mmol, 338 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5) Yield: 197.1 mg (70 %). Mp 199.6 ºC. ^{1}H NMR

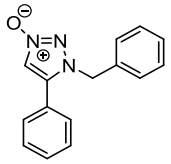
(400 MHz, $CDCl_3$) δ 8.34 – 8.27 (m, 2H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.61 – 7.46 (m, 5H), 7.34 – 7.29 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 139.7, 139.6, 131.4, 129.6, 128.8, 125.2, 125.0, 123.7, 120.8. IR (cm^{-1}) 3067, 1593, 1441, 1341, 694. HRMS calculated for $C_{14}H_{10}N_4O_3$: 282.0753; found: 282.0757.



1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (9f). The general procedure 7.2.1 was followed starting from 1-(4-chlorophenyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8f**) (1.48 mmol, 400 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5) Yield: 250 mg (63 %). Mp 160 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.32 – 7.25 (m, 1H), 7.25 – 7.12 (m, 4H), 7.12 – 6.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 135.7, 133.4, 130.8, 129.8, 129.3, 128.7, 126.3, 124.0, 119.8. IR (cm^{-1}) 3365, 3165, 1658, 1396, 766. HRMS calculated for $C_{14}H_{10}ClN_3O$: 271.0512; found: 271.0520.

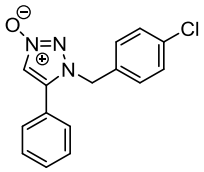


5-*tert*-Butyl-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole N-oxide (9g). The general procedure 7.2.1 was followed starting from 5-*tert*-butyl-1-(4-methoxyphenyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (**8g**) (0.09 mmol, 20 mg). The crude product was purified by column chromatography (CH_2Cl_2/ MeOH 95:5). Yield: 134.5 mg (70 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 3H), 7.02 (dd, *J* = 8.4, 1.4 Hz, 2H), 3.91 (d, *J* = 1.1 Hz, 3H), 1.25 (d, *J* = 1.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 130.7, 129.2, 129.1, 114.1, 114.0, 55.6, 30.8, 30.1. IR (cm^{-1}) 2966, 2929, 1514, 1252, 1236, 839. HRMS calculated for $[M - CH_3]^+$ $C_{12}H_{14}N_3O_2$: 233.1298; found: 233.1370.

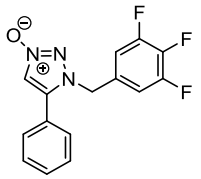


1-Benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (9h). The general procedure 7.2.1 was

followed starting from 1-benzyl-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8h**) (1.30 mmol, 400 mg) in AcOH (26 mL). The crude product was purified by column chromatography (EtOAc). Yield: 225 mg (70 %). Mp 135.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 1H), 7.55 – 7.50 (m, 3H), 7.37 – 7.31 (m, 5H), 7.17 (dd, *J* = 6.7, 2.9 Hz, 2H), 5.33 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 133.7, 131.0, 129.4, 129.0, 129.1, 128.8, 127.5, 124.1, 119.1, 52.7. IR (cm^{-1}) 3298, 2214, 1466, 767. HRMS calculated for $C_{15}H_{13}N_3O$: 251.1059; found: 251.1055.



1-(4-Chlorobenzyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (9i). The general procedure 7.2.1 was followed starting from 1-(4-chlorobenzyl)-5-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**8i**) (1.30 mmol, 400 mg). The crude product was purified by column chromatography (EtOAc). Yield: 134.5 mg (70 %). Mp 96 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.51 (m, 3H), 7.49 (s, 1H), 7.36 – 7.30 (m, 4H), 7.12 – 7.08 (m, 2H), 5.29 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 134.9, 132.2, 131.1, 129.5, 129.3, 129.0, 128.9, 124.1, 119.1, 51.8. IR (cm^{-1}) 2201, 1989, 1402, 773. HRMS calculated for $C_{15}H_{12}ClN_3O$: 285.0669; found: 285.0675.

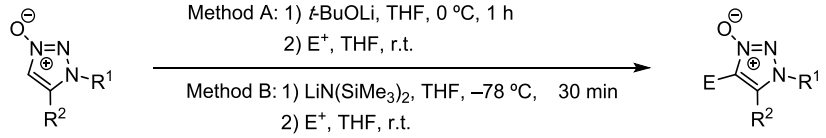


5-Phenyl-1-(3,4,5-trifluorobenzyl)-1*H*-1,2,3-triazole N-oxide (9j). The general procedure 7.2.1 was followed starting from 5-phenyl-1-(3,4,5-trifluorobenzyl)-4-trimethylsilyl-1*H*-1,2,3-triazole (**8j**) (0.55 mmol, 198 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 85 mg (50 %). Mp 165.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.51 (m, 3H), 7.44 (s, 1H), 7.34 (dt, *J* = 6.8, 1.5 Hz, 2H), 6.80 (dd, *J* = 7.5, 6.1 Hz, 2H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (ddd, $^{1}J_{CF}$ = 254.8 Hz, $^{2}J_{CF}$ = 10.6 Hz, $^{3}J_{CF}$ = 4.2 Hz), 140.2, 139.8 (dt, $^{1}J_{CF}$ = 252.4 Hz, $^{2}J_{CF}$ =15.3 Hz), 131.2, 129.9 (td, $^{3}J_{CF}$ = 7.2 Hz, $^{4}J_{CF}$ = 4.6 Hz), 129.6, 128.8, 123.8, 119.0, 112.0 ($^{2}J_{CF}$ = 22.2 Hz, $^{3}J_{CF}$ = 6.6 Hz), 50.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -131.70 (d, *J* = 20.2 Hz), -158.72 (t, *J* = 20.5 Hz). IR (cm^{-1}) 1618, 1532, 1035, 752. HRMS

calculated for $C_{15}H_{10}F_3N_3O$: 305.0776; found: 305.0775.

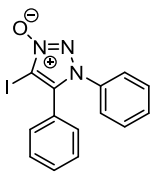
7.3 Experimental section of chapter 3

7.3.1 Base-promoted electrophilic substitution of 1,5-disubstituted 1,2,3-triazole N-oxides (18)



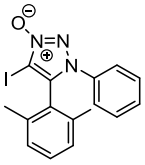
METHOD A: In a sealed tube, the corresponding triazole N-oxide (1.00 mmol) was dissolved in anhydrous THF (20 mL) under nitrogen atmosphere. The solution was cooled to 0 ºC, potassium *tert*-butoxide was added (8.00 mmol, 900 mg) and the mixture was stirred for 30 min at the same temperature. Then, the corresponding electrophile (3.00 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. On completion, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and the organic solvent was evaporated. The residue was extracted with CH_2Cl_2 (15 mL x 3), the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (DCM/MeOH 95:5).

METHOD B: In a sealed tube, the corresponding triazole N-oxide (1.00 mmol) was dissolved in anhydrous THF (20 mL) under nitrogen atmosphere. The solution was cooled to -78 ºC, a 1M solution of lithium bis(trimethylsilyl)amide in hexane was added (1.30 mmol, 1.30 mL) and the reaction mixture was stirred at the same temperature for 15 min. Then, the corresponding electrophile (1.30 mmol) was added, the mixture was stirred for a further 15 min at -78 ºC and finally was warmed to room temperature within 1 h. On completion, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and the organic solvent was evaporated. The residue was extracted with CH_2Cl_2 (15 mL x 3), the combined organic phases were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (DCM:MeOH 95:5).

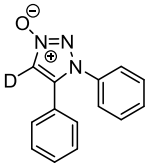


1,5-Diphenyl-4-iodo-1,2,3-triazole N-oxide (18a). The general procedure 7.3.1 A was

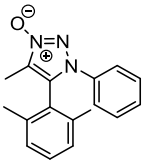
followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and iodine (0.18 mmol, 40 mg). The product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 18 mg (86 %). Mp 212 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.37 (m, 6H), 7.36 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 135.3, 130.8, 129.7, 129.6, 129.4, 129.1, 125.0, 124.7, 79.6. IR (cm^{-1}) 1590, 1312, 765, 69. HRMS calculated for $C_{14}H_{10}IN_3O$: 362.9869; found: 362.9864.



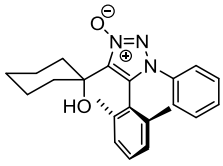
5-(2,6-Dimethylphenyl)-4-iodo-1-phenyl-1,2,3-triazole N-oxide (18b). The general procedure 7.3.1 A was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and iodine (0.18 mmol, 40 mg). The product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 21.11 mg (90 %). Mp 213.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 6.98 (m, 8H), 2.09 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 137.9, 135.8, 131.2, 129.5, 129.2, 128.2, 124.4, 122.3, 80.4, 19.9. IR (cm^{-1}) 2926, 2855, 1594, 1494, 1371, 777, 737. HRMS calculated for $C_{16}H_{14}IN_3O$: 391.0182; found: 391.0180.



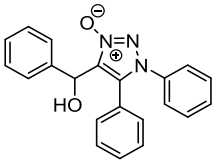
1,5-Diphenyl-4-d-1,2,3-triazole N-oxide (18c). The general procedure 7.3.1 B was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and deuterium oxide (0.16 mmol, 11 µL) was added. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 14 mg (98 %). Mp 198.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.38 (m, 6H), 7.34 (dt, *J* = 6.6, 1.7 Hz, 2H), 7.28 – 7.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 135.0, 130.6, 129.7, 129.5, 129.4, 129.2, 128.7, 125.2, 124.4. IR (cm^{-1}) 2363, 1482, 1429, 759, 693. HRMS calculated for $C_{14}H_{10}DN_3O$: 238.0965; found: 238.0961.



5-(2,6-Dimethylphenyl)-4-methyl-1-phenyl-1,2,3-triazole N-oxide (18d). The general procedure 7.3.1 B, was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and iodomethane (0.16 mmol, 4 µL). The product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 14.5 mg (87 %). Mp 168.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 4H), 7.28 – 7.18 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 2.19 (s, 3H), 2.04 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 135.8, 134.4, 130.8, 129.4, 128.7, 128.2, 124.6, 122.6, 122.3, 19.9, 7.4. IR (cm^{-1}) 2924, 2855, 1591, 1494, 1396, 1377, 789, 777. HRMS calculated for $C_{17}H_{17}N_3O$: 279.1372; found: 279.1367.

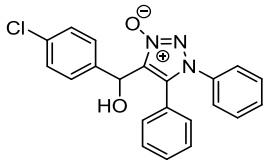


5-(2,6-Dimethylphenyl)-4-(1-hydroxycyclohexyl)-1-phenyl-1,2,3-triazole N-oxide (18e). The general procedure 7.3.1 B was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and cyclohexanone (0.16 mmol, 6 µL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 15.3 mg (70 %). Mp 190.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.21 – 7.15 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 2.12 (s, 6H), 1.90 – 1.72 (m, 3H), 1.72 – 1.61 (m, 1H), 1.43 (dt, *J* = 13.7, 3.4 Hz, 2H), 1.23 (td, *J* = 13.4, 4.4 Hz, 3H), 1.05 (d, *J* = 13.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 135.6, 134.9, 132.8, 131.1, 129.6, 129.5, 128.3, 125.8, 123.8, 69.7, 34.4, 25.7, 20.9, 20.7. IR (cm^{-1}) 3511, 2926, 2854, 1369, 1334, 971, 778, 754. HRMS calculated for $C_{22}H_{25}N_3O_2$: 363.1947; found: 363.1948.

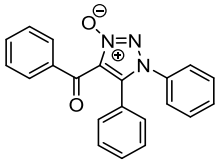


4-[Hydroxy(phenyl)methyl]-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (18f). The general procedure 7.3.1 B was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.12 mmol, 28 mg), benzaldehyde (0.16 mmol, 0.016 mL) was added. The crude

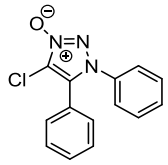
product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 30 mg (73 %). Mp 210 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.19 (m, 13H), 7.18 – 7.01 (m, 2H), 5.88 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 136.0, 135.2, 131.1, 130.8, 130.0, 129.8, 129.7, 129.4, 128.9, 128.4, 126.7, 125.2, 124.5, 67.6. IR (cm^{-1}) 3159, 1592, 1405, 740, 693. HRMS calculated for $C_{21}H_{17}N_3O_2$: 343.1321; found: 343.1326.



4-[4-Chlorophenyl(hydroxyl)methyl]-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (18g). The general procedure 7.3.1 B was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.12 mmol, 28 mg), and p-chlorobenzaldehyde (0.16 mmol, 22 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 32.4 mg (72 %). Mp 209.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.36 (qd, *J* = 7.2, 6.8, 3.6 Hz, 7H), 7.24 (dt, *J* = 7.7, 4.0 Hz, 4H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.90 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 135.8, 134.7, 133.8, 130.6, 130.5, 129.7, 129.5, 129.4, 129.0, 128.6, 127.7, 124.8, 124.1, 66.5. IR (cm^{-1}) 3143, 1594, 1491, 775, 732. HRMS calculated for $C_{21}H_{16}ClN_3O_2$: 377.0931; found: 377.0935.

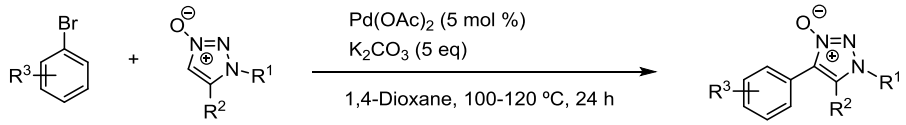


4-Benzoyl-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (18h). The general procedure 7.3.1 B was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and benzoyl chloride (0.16 mol, 0.009 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5).Yield: 14 mg (70 %). Mp 186.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.40 (m, 6H), 7.39 – 7.28 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.8, 139.8, 135.6, 134.7, 134.3, 130.8, 130.0, 129.9, 129.8, 129.5, 128.9, 128.6, 127.9, 125.2, 123.9. IR (cm^{-1}) 3057, 1661, 1493, 1387, 693. HRMS calculated for $C_{21}H_{15}N_3O_2$: 341.1164; found: 341.1164.

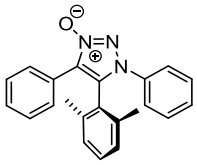


4-Chloro-1,5-diphenyl 1,2,3-triazole N-oxide (18i). The general procedure 7.3.1 B was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.12 mmol, 28 mg), and 2-nitrobenzenesulfonyl chloride (0.16 mmol, 30 mg). Yield: 20 mg (62 %). Mp >150 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.39 (m, 6H), 7.36 – 7.29 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 134.5, 130.9, 129.7, 129.6, 129.3, 129.2, 124.9, 123.6, 120.6. HRMS calculated for $C_{14}H_{10}ClN_3O$: 271.0512; found: 271.0506.

7.3.2 Palladium-catalyzed cross-coupling arylation of 1,5-disubstituted 1,2,3-triazole N-oxides (19)

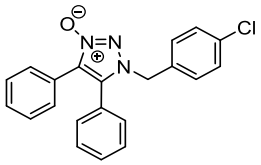


A mixture of the corresponding triazole N-oxide (1.00 mmol), aryl bromide (1.30 mmol), $Pd(OAc)_2$ (0.05 mol, 11 mg), K_2CO_3 (5.0 mmol, 0.7 g) in 1,4-dioxane (5.0 mL) was stirred at 100-120 ºC for 24 h in a sealed tube under Schlenk conditions. The mixture was diluted with CH_2Cl_2 (5 mL) and filtered. The organic phase was dried over anhydrous $MgSO_4$ filtered and concentrated under vacuo. The resulting residue was purified by column chromatography.

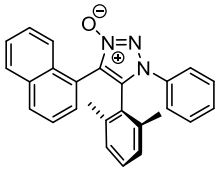


5-(2,6-Dimethylphenyl)-1,4-diphenyl-1*H*-1,2,3-triazole N-oxide (19a). The general procedure 7.3.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole 3-oxide (**9c**) (0.06 mmol, 15 mg) and bromobenzene (0.074 mmol, 56 µL). The reaction mixture was stirred at 100 ºC for 24 h. The crude product was purified by column chromatography (EtOAc). Yield: 15.3 mg (80 %). Mp >254 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.44 – 7.24 (m, 9H), 7.12 (d, *J* = 7.6 Hz, 2H), 2.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 135.5, 133.9, 130.9, 129.3, 129.1,

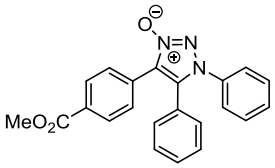
128.9, 128.5, 128.4, 127.4, 125.2, 125.1, 123.1, 123.0, 19.9. IR (cm^{-1}) 3060, 1592, 1357, 688. HRMS calculated for $C_{22}H_{19}N_3O$: 341.1528; found: 341.1523.



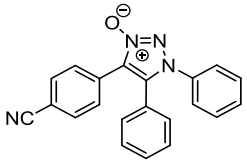
1-(4-Chlorobenzyl)-4,5-diphenyl-1*H*-1,2,3-triazole N-oxide (19b). The general procedure 7.3.2 was followed starting from 1-(4-chlorobenzyl)-5-phenyl-1*H*-1,2,3-triazole 3-oxide (**9i**) (0.06 mmol, 17 mg) and bromobenzene (0.078 mmol, 0.06 mL). The reaction mixture was stirred at 100 ºC for 24 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 17.8 mg (83 %). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.47 (m, 5H), 7.44 – 7.16 (m, 7H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.20 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 134.7, 132.4, 130.8, 129.9, 129.5, 129.3, 129.1, 129.0, 128.9, 128.5, 128.3, 125.3, 124.9, 51.6. IR (cm^{-1}) 3051, 1491, 1385. HRMS calculated for $C_{21}H_{16}ClN_3O$: 361.0982; found: 361.0989.



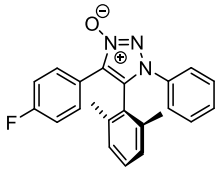
5-(2,6-Dimethylphenyl)-4-(naphthalen-1-yl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (19c). The general procedure 7.3.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole 3-oxide (**9c**) (0.045 mmol, 12 mg) and 1-bromonaphthalene (0.059 mmol, 49 mg). The reaction mixture was stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 12 mg (70 %). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.4, 5.9 Hz, 3H), 7.69 – 7.49 (m, 3H), 7.44 – 7.11 (m, 7H), 6.99 (d, *J* = 27.0 Hz, 2H), 2.16 – 1.90 (m, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 135.9, 133.7, 131.2, 131.1, 130.7, 130.5, 129.4, 129.2, 128.8, 128.5, 128.2, 128.1, 127.0, 126.4, 125.6, 124.9, 124.6, 122.8, 122.2, 20.2. IR (cm^{-1}) 3060, 1591, 1383, 751. HRMS calculated for $C_{26}H_{21}N_3O$: 391.1685; found: 391.1684.



4-[4-(methoxycarbonyl)phenyl]-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (19d). The general procedure 7.3.2 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole 3-oxide (**9a**) (0.06 mmol, 14 mg) and methyl-4-bromobenzoate (0.074 mmol, 16.8 mg). The reaction mixture stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 20 mg (90 %). Mp 195.1 ºC ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.34 (m, 5H), 7.33 – 7.26 (m, 2H), 7.26 – 7.15 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 136.3, 135.3, 130.9, 130.6, 130.2, 129.8, 129.8, 129.7, 129.6, 129.5, 129.2, 129.0, 125.5, 125.4, 52.5. IR (cm^{-1}) 2226, 1725, 1492, 1272, 724. HRMS calculated for $C_{22}H_{17}N_3O_3$: 371.1269; found: 371.1268.

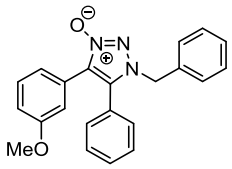


4-(4-Cyanophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (19e). The general procedure 7.3.2 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole 3-oxide (**9a**) (0.06 mmol, 14 mg) and 4-bromobenzonitrile (0.074 mmol, 14.2 mg). The reaction mixture was stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (Hex/EtOAc 1:1).Yield. 19 mg (94 %). Mp 183.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.41 (dt, *J* = 9.3, 7.0 Hz, 5H), 7.28 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.24 – 7.16 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 134.7, 133.6, 132.1, 130.9, 129.8, 129.6, 129.6, 129.4, 129.3, 127.7, 125.1, 124.8, 118.3, 112.5. IR (cm^{-1}) 2229, 1605, 1495, 1384, 836, 776. HRMS calculated for $C_{21}H_{14}N_4O$: 338.1168; found: 338.1174.

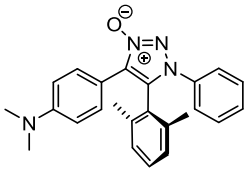


5-(2,6-Dimethylphenyl)-4-(4-fluorophenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (19f). The general procedure 7.3.2 was followed starting from 5-(2,6-dimethylphenyl)-1-

phenyl-1*H*-1,2,3-triazole 3-oxide (**9c**) (0.06 mmol, 15 mg) and 4-bromo-fluorobromobenzene (0.074 mmol, 9 µL). The reaction mixture was stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 14 mg (65 %). Mp 219 ºC ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 3H), 7.35 (dt, *J* = 9.0, 3.8 Hz, 3H), 7.28 – 7.23 (m, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.06 – 6.99 (m, 2H), 2.01 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, $^{1}J_{C\text{-}F}$ = 252 Hz), 138.3, 135.8, 134.2, 131.4, 129.7, 129.6, 129.3, 128.8, 125.2, 123.3, 121.8, 121.7, 116.0 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 20.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.69. IR (cm^{-1}) 3067, 2210, 1593, 1382. HRMS calculated for $C_{22}H_{18}FN_3O$: 359.1434; found: 359.1425.

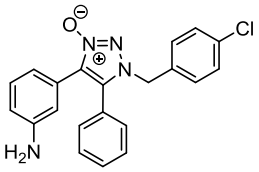


1-Benzyl-4-(3-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (19g). The general procedure 7.3.2 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole 3-oxide (**9h**) (0.06 mmol, 15 mg) and 3-bromoanisole (0.074 mmol, 0.01 mL). The mixture was stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 19 mg (84 %). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.44 (m, 3H), 7.37 – 6.99 (m, 10H), 6.86 (ddd, *J* = 8.1, 2.7, 1.1 Hz, 1H), 5.20 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 136.5, 135.1, 132.7, 131.1, 130.3, 129.8, 129.6, 129.6, 129.4, 129.1, 126.4, 125.7, 121.1, 115.7, 113.6, 55.4, 51.9. IR (cm^{-1}) 3050, 1578, 1382, 766. HRMS calculated for $C_{22}H_{19}N_3O_2$: 391.11; found: 391.1088.



4-[4-(N,N-Dimethylamino)phenyl]-5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (19h). The general procedure 7.3.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole 3-oxide (**9c**) (0.06 mmol, 15 mg) and 4-bromo-N,N-dimethylaniline (0.074 mmol, 62 mg). The reaction mixture was stirred at 120 ºC for 24 h. The product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 17 mg (89 %). Mp 238.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.23 (m, 6H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 2.96 (s, 6H),

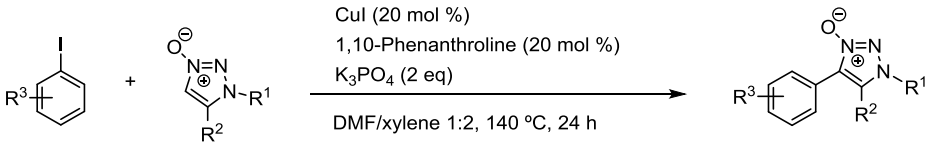
2.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 138.2, 135.8, 132.6, 130.8, 130.6, 129.2, 128.6, 128.3, 128.3, 125.7, 122.9, 111.8, 111.7, 40.1, 20.0. IR (cm^{-1}) 1379, 1355, 777. HRMS calculated for $C_{24}H_{24}N_4O$: 384.1950; found: 384.1948.



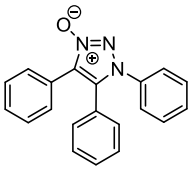
4-(3-Aminophenyl)-1-(4-chlorobenzyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (19i). The general procedure 7.3.2 was followed starting from 1-(4-chlorobenzyl)-5-phenyl-1*H*-1,2,3-triazole 3-oxide (**9i**) (0.06 mmol, 17 mg), 3-bromoaniline (0.074 mmol, 0.0085 mL). The reaction mixture was stirred at 120 ºC for 24 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield:11 mg (50 %). ^{1}H NMR (400 MHz, $CDCl_3$) 7.70 – 7.42 (m, 3H), 7.27 (dq, *J* = 16.0, 7.9, 7.2 Hz, 5H), 7.16 – 6.90 (m, 3H), 6.76 – 6.52 (m, 2H), 5.19 (d, *J* = 4.0 Hz, 2H), 3.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 136.5, 135.1, 132.8, 131.0, 130.3, 130.2, 129.7, 129.6, 129.4, 129.3, 126.1, 125.8, 119.1, 116.0, 115.5, 51.9. IR (cm^{-1}) 3308, 3209, 1604, 1385, 692. HRMS calculated for $C_{21}H_{18}N_4O$: 376.11; found: 376.1091.

7.3.3 Copper-catalyzed cross-coupling arylation of 1*H*-1,2,3-triazole N-oxides

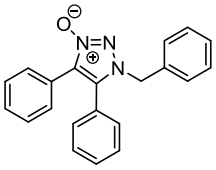
7.3.3.1 Copper-catalyzed cross-coupling arylation of 1,5-disubstituted triazole N-oxides (23)



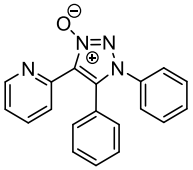
A flame-dried Schlenk test tube with a magnetic stirring bar was charged under N_2 with CuI (0.024 mmol, 4.6 mg), 1,10-phenanthroline (0.024 mmol, 4.3 mg), K_3PO_4 (0.24 mmol, 51 mg), the corresponding triazole N-oxide (0.12 mmol), the selected aryl or heteroaryl halide (0.14 mmol) and DMF/xylene (1:2, 0.2 mL). The reaction mixture was stirred at 140 ºC for 24 hours. Upon completion, it was cooled to ambient temperature, 3-4 mL of CH_2Cl_2 were added and after a 5 min stirring, the resulting suspension was filtered through a celite pad. The filtrate was evaporated at reduced pressure and the crude product was purified by column chromatography on silica gel.



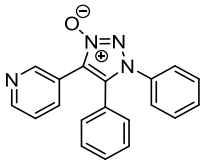
1,4,5-Triphenyl-1*H*-1,2,3-triazole N-oxide (23a). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl triazole N-oxide (**9a**) (0.06 mmol, 15 mg), and iodobenzene (0.07 mmol, 8 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2) Yield: 15 mg (80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.48 – 7.35 (m, 8H), 7.33 – 7.30 (m, 3H), 7.21 – 7.17 (m, 2H).



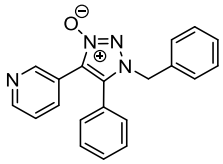
1-Benzyl-4,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23b). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl triazole N-oxide (**9h**) (0.06 mmol, 15 mg), and iodobenzene (0.07 mmol, 8 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2) Yield: 14.8 mg (75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.52 – 7.41 (m, 3H), 7.34 – 7.23 (m, 6H), 7.20 – 7.14 (m, 2H), 7.10 – 7.02 (m, 2H), 5.3 (s, 2H).



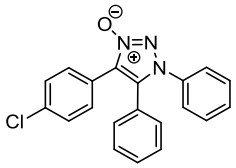
1,5-Diphenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (23c). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl triazole N-oxide (**9a**) (0.12 mmol, 28 mg), and 2-iodopyridine (0.14 mmol, 15 µL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5) Yield: 37 mg (98 %). Mp 212 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.84 (td, *J* = 7.8, 1.8 Hz, 1H), 7.46 – 7.21 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 145.0, 137.0, 136.2, 134.7, 130.1, 129.7, 129.0, 128.9, 128.7, 128.1, 125.1, 124.9, 124.4, 123.3. IR (cm^{-1}) 1589, 1493, 1391, 777, 701. HRMS calculated for $C_{19}H_{14}N_4O$: 314.1168; found: 314.1178.



1,5-Diphenyl-4-(pyridin-3-yl)-1*H*-1,2,3-triazole N-oxide (23d). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 3-iodopyridine (0.095 mmol, 20 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15.2 mg (84 %). Mp 225.8 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.36 (m, 8H), 7.36 – 7.27 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.23 – 7.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 134.9, 134.8, 130.9, 130.5, 129.8, 129.6, 129.5, 129.3, 129.1, 128.6, 125.2, 125.1, 124.7, 124.4. IR (cm^{-1}) 3073, 1720, 1383, 685. HRMS calculated for $C_{19}H_{14}N_4O$: 314.1168; found: 314.1169.

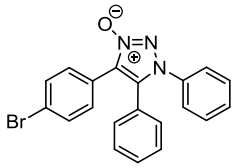


1-Benzyl-5-phenyl-4-(pyridin-3-yl)-1*H*-1,2,3-triazole N-oxide (23e). The general procedure 7.3.3.1 was following starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 3-iodopyridine (0.09 mmol, 20 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 11.5 mg (60 %) brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.64 – 7.48 (m, 4H), 7.33 (dd, *J* = 5.1, 2.0 Hz, 4H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.15 (dt, *J* = 7.4, 3.6 Hz, 3H), 5.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 133.7, 131.2, 130.9, 129.9, 129.8, 129.3, 129.0, 128.9, 128.8, 128.7, 127.9, 127.4, 124.7, 118.8, 52.6. IR (cm^{-1}) 3392, 3052, 1719, 1385, 703. HRMS calculated for $C_{20}H_{16}N_4O$: 328.1324; found: 328.1309.

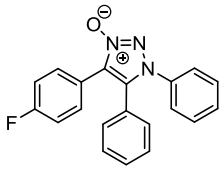


4-(4-Chlorophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23f). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 1-chloro-4-iodobenzene (0.03 mmol, 22.5 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 12 mg (60 %). Mp 210 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.48 (t, *J* = 7.5

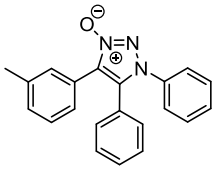
Hz, 1H), 7.38 (dd, *J* = 18.4, 7.7 Hz, 7H), 7.32 – 7.26 (m, 2H), 7.22 – 7.16 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 134.9, 130.6, 130.5, 129.9, 129.7, 129.4, 129.3, 129.3, 129.2, 128.7, 125.3, 125.2, 123.3. IR (cm^{-1}) 3088, 1721, 1379, 761. HRMS calculated for $C_{20}H_{14}ClN_3O$: 347.0825; found: 347.0825.



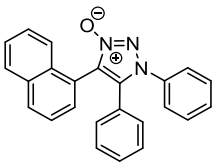
4-(4-bromophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23g). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 1-bromo-4-iodobenzene (0.095 mmol, 27 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 14 mg (60 %). Mp 192 ºC. ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.72 (d, *J* = 8.2 Hz, 1H), 7.51 (m, 3H), 7.44 – 7.35 (m, 6H), 7.31 – 7.27 (m, 2H), 7.23 – 7.16 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 135.8, 135.2, 132.0, 131.0, 130.9, 130.8, 130.2, 129.7, 125.4, 124.7, 124.1, 123.8, 95.8. IR (cm^{-1}) 3063, 1719, 1479, 1372, 765, 662. HRMS calculated for $C_{20}H_{14}BrN_3O$: 391.0320; found: 391.0320.



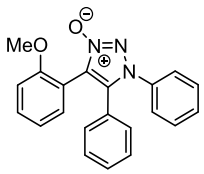
4-(4-Fluorophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23h). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 1-fluoro-4-iodobenzene (0.095 mmol, 11 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 10.6 mg (56 %). Mp 244 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.53 – 7.34 (m, 6H), 7.33 – 7.26 (m, 2H), 7.24 – 7.16 (m, 2H), 7.08 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{C\text{-}F}$ = 252.5 Hz), 134.99, 131.3 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 130.5, 129.9, 129.3, 129.2, 129.1, 128.5, 125.3, 125.1, 124.9, 120.9 (d, $^4J_{C\text{-}F}$ = 2 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 22 Hz). IR (cm^{-1}) 3055, 1719, 1383, 1231, 837, 685. HRMS calculated for $C_{20}H_{14}FN_3O$; 331.1121; found: 331.1120.



1,5-Diphenyl-4-(*m*-tolyl) 1*H*-1,2,3-triazole N-oxide (23i). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 3-iodotoluene (0.03 mmol, 12 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 7 mg (42 %). Mp 211 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.47 – 7.17 (m, 13H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 134.8, 130.2, 130.2, 129.9, 129.8, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 128.2, 126.6, 125.6, 125.5, 21.4. IR (cm^{-1}) 3058, 1720, 1493, 750. HRMS calculated for $C_{21}H_{17}N_3O$: 327.1372; found: 327.1369.

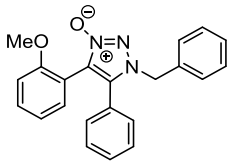


4-(Naphthalen-1-yl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23j). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg), 1-iodonaphthalene (0.095 mmol, 14 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 19.3 mg (84 %). Mp 217 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dt, *J* = 19.6, 5.0 Hz, 2H), 7.83 – 7.75 (m, 1H), 7.48 (ddt, *J* = 24.2, 11.4, 5.0 Hz, 9H), 7.30 (q, *J* = 5.5, 3.5 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 135.3, 133.7, 131.9, 130.7, 130.4, 130.0, 129.9, 129.6, 129.5, 129.4, 129.3, 129.2, 128.8, 128.5, 127.0, 126.3, 125.2, 125.1, 122.2. IR (cm^{-1}) 3045, 1722, 1392, 773, 690. HRMS calculated for $C_{24}H_{17}N_3O$; 363.1372; found: 363.1371.

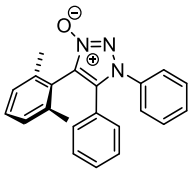


4-(2-Methoxyphenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23k). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.12 mmol, 28 mg) and 2-iodoanisole (0.14 mmol, 0.02 mL). The reaction was

conducted at 140 ºC for 30 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 30 mg (72 %). Mp 204.5 ºC .^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.45 – 7.32 (m, 7H), 7.30 – 7.23 (m, 2H), 7.14 – 7.04 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 136.62, 135.5, 132.3, 131.4, 129.7, 129.2, 129.0, 128.9, 128.6, 127.6, 126.4, 125.1, 120.8, 113.8, 111.3, 55.0. IR (cm^{-1}) 1505, 1380, 1026, 758, 702. HRMS calculated for $C_{21}H_{17}N_3O_2$: 343.1321; found: 343.1330.

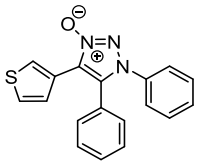


1-Benzyl-4-(2-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23l). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.12 mmol, 30 mg) and 2-iodoanisole (0.14 mmol, 0.02 mL). The reaction was conducted at 140 ºC for 30 h. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 26 mg (60 %). Mp 167.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.48 – 7.31 (m, 7H), 7.21 (ddd, *J* = 13.4, 7.9, 2.6 Hz, 4H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.82 (dd, *J* = 8.4, 0.9 Hz, 1H), 5.31 (s, 2H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 137.8, 134.3, 132.2, 131.2, 129.9, 129.1, 128.9, 128.8, 128.5, 127.8, 126.7, 126.3, 120.6, 113.8, 111.1, 54.8, 52.4. IR (cm^{-1}) 1435, 1022, 696. HRMS calculated for $C_{22}H_{19}N_3O_2$: 357.1477; found: 357.1490.

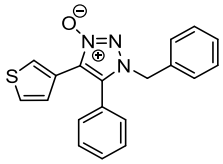


4-(2,6-Dimethylphenyl)-1,5-diphenyl-1*H*-1,2,3-triazole (23m). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl triazole N-oxide (**9a**) (0.12 mmol, 28 mg) and 2-iodo-1,3-dimethylbenzene (0.14 mmol, 0.02 mL). The crude product was purified by column chromatography (EtOAc) Yield: 20 mg (50 %). Mp 202 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.32 (m, 6H), 7.31 – 7.21 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.04 – 6.97 (m, 2H), 2.17 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 136.1, 135.4, 130.2, 130.1, 129.8, 129.4, 129.2, 129.0, 128.7, 127.8, 125.4, 125.0, 123.8, 20.0. IR (cm^{-1}

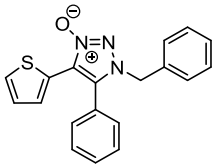
[1]) 1491, 1385, 1348, 774, 736. HRMS calculated for $C_{22}H_{19}N_3O$: 341.1528; found: 341.1542.



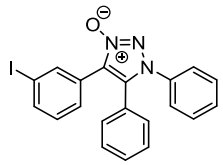
1,5-Diphenyl-4-(thiophen-3-yl)-1*H*-1,2,3-triazole N-oxide (23n). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 3-iodothiophene (0.095 mmol, 10 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 11.2 mg (60 %). Mp 234 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.28 (m, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.36 (m, 3H), 7.28 (td, *J* = 13.0, 11.5, 6.0 Hz, 5H), 7.02 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 134.3, 130.7, 130.2, 129.4, 129.3, 129.2, 128.9, 126.3, 125.8, 125.7, 125.2, 125.0, 124.7. IR (cm^{-1}) 3050, 1719, 1493, 1392, 701. HRMS calculated for $C_{18}H_{13}N_3OS$: 319.0779; found: 319.0781.



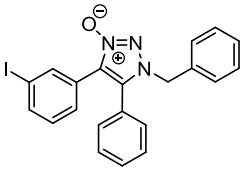
1-Benzyl-5-phenyl-4-(thiophen-3-yl)-1*H*-1,2,3-triazole N-oxide (23o). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg), 3-iodothiophene (0.09 mmol, 10 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 10 mg (50 %). Mp 229.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.28 (m, 5H), 7.19 (d, *J* = 4.7 Hz, 1H), 7.11 (dd, *J* = 7.0, 2.5 Hz, 2H), 6.92 (d, *J* = 5.1 Hz, 1H), 5.23 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 131.0, 130.2, 129.5, 128.8, 128.7, 128.7, 127.8, 127.4, 125.7, 125.5, 125.3, 125.1, 124.9, 52.5. IR (cm^{-1}) 3100, 1719, 1415, 701. HRMS calculated for $C_{19}H_{15}N_3OS$: 333.0936; found: 333.0933.



1-Benzyl-5-phenyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazole N-oxide (23p). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 2-iodothiophene (0.09 mmol, 10.5 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 11 mg (50 %). Mp 176.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.33 (q, *J* = 7.0, 6.1 Hz, 6H), 7.10 (dt, *J* = 5.9, 2.6 Hz, 3H), 6.94 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.22 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 133.7, 131.3, 130.3, 129.8, 129.7, 128.9, 128.8, 127.9, 127.1, 126.4, 125.9, 125.5, 124.9, 52.8. IR (cm^{-1}) 3029, 1721, 1389, 694. HRMS calculated for $C_{19}H_{15}N_3OS$: 333.0936; found: 333.0939.

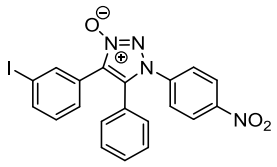


4-(3-Iodophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23q). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 1,3-diiodobenzene (0.05 mmol, 16.5 mg). The crude product was purified by column chromatography (EtOAc then, CH_2Cl_2/MeOH 95:5). Yield: 14 mg (54 %). Mp 204.5 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, *J* = 1.8 Hz, 1H), 7.71 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.40 (m, 5H), 7.32 – 7.27 (m, 2H), 7.21 – 7.16 (m, 2H), 7.09 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 138.1, 136.1, 135.3, 130.9, 130.3, 130.2, 129.8, 129.7, 129.6, 129.5 128.6, 127.3, 125.4, 125.4, 94.2. IR (cm^{-1}) 3052, 1719, 1375, 702. HRMS calculated for $C_{20}H_{14}IN_3O$: 439.0182; found: 439.0194.

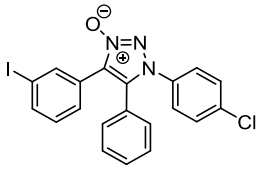


1-Benzyl-4-(3-iodopenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23r). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 1,3-diiodobenzene (0.09 mmol, 30 mg). The crude

product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 14 mg (50 %). Mp 173.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.69 – 7.43 (m, 5H), 7.33 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.26 – 7.20 (m, 2H), 7.14 (dd, *J* = 6.7, 2.7 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 1H), 5.26 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 137.1, 133.8, 131.0, 129.9, 129.8, 129.6, 129.5 128.9, 128.8, 127.9, 127.8, 127.6, 126.9, 124.9, 93.8, 52.6. IR (cm^{-1}) 3062, 1376, 698. HRMS calculated for $C_{21}H_{16}IN_3O$: 453.0338; found: 453.0335.

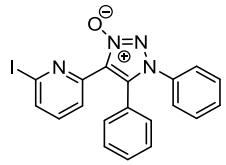


4-(3-Iodophenyl)-1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23s). The general procedure 7.3.3.1 was followed starting from 1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9e**) (0.11 mmol, 30 mg) and 1,3-diiodobenzene (0.10 mmol, 60 mg). The crude product was purified by column chromatography (EtOAc/Hex 1:1). Yield: 34 mg (65 %). Mp 130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.19 (m, 2H), 7.99 (t, *J* = 1.7 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.63 – 7.52 (m, 1H), 7.52 – 7.42 (m, 5H), 7.32 – 7.21 (m, 2H), 7.08 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 139.6, 138.4, 137.7, 136.1, 131.3, 130.0, 129.8, 129.8, 129.2, 128.2, 126.2, 125.0, 124.8, 124.5, 93.9. IR (cm^{-1}) 3061, 1593, 1521, 1339, 840, 707. HRMS calculated for $C_{20}H_{13}IN_4O_3$: 484.0032; found: 484.0014.

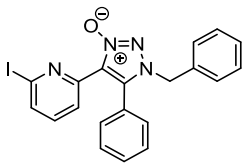


4-(3-Iodophenyl)-1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23t). The general procedure 7.3.3.1 was followed starting from 1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9f**) (0.11 mmol, 30 mg) and 1,3-diiodobenzene (0.17 mmol, 56 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 38 mg (73 %). Mp 209.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 1.7 Hz, 1H), 7.70 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.33 (m, 2H), 7.26 – 7.16 (m, 4H), 7.07 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 137.9, 136.1, 135.6, 133.7, 131.1, 130.3, 130.1, 129.9, 129.8, 128.6, 128.5, 126.9,

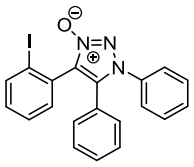
126.5, 125.0, 94.2. IR (cm^{-1}) 3109, 1490, 1380, 831, 716. HRMS calculated for $C_{20}H_{13}ClIN_3O$: 472.9796; found: 472.9796.



4-(6-Iodopyridin-2-yl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23u). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 2,6-diiodopyridine (0.08 mmol, 27 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 18 mg (70 %). Mp 169.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.64 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.49 – 7.37 (m, 9H), 7.33 – 7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 137.9, 135.0, 134.4, 130.8, 130.7, 130.1, 129.4, 129.3, 128.3, 127.7, 125.3, 125.2, 122.7, 116.1. IR (cm^{-1}) 3059, 1716, 1372, 1156, 745. HRMS calculated for $C_{19}H_{13}IN_4O$: 440.0134; found: 440.0133.

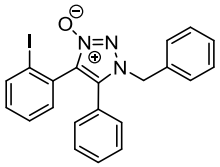


1-Benzyl-4-(6-iodopyridin-2-yl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23v). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 2,6-diiodopyridine (0.09 mmol, 30 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 17 mg (63 %). Mp 118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 7.8 Hz, 1H), 7.63 – 7.49 (m, 4H), 7.47 – 7.27 (m, 6H), 7.22 – 7.05 (m, 2H), 5.25 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 138.6, 137.8, 134.1, 133.7, 130.4, 129.7, 128.9, 128.7, 128.5, 127.9, 127.0, 125.4, 121.8, 116.0, 52.5. IR (cm^{-1}) 3540, 3060, 1368, 657. HRMS calculated for $C_{20}H_{15}IN_4O$: 454.0291; found: 454.0290.

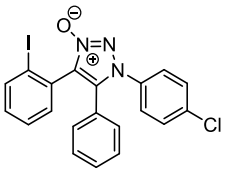


4-(2-Iodophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (23w). The general

procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 14 mg) and 1,2-diiodobenzene (0.095 mmol, 12.4 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15.4 mg (56 %). Mp 208.5 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.36 (m, 8H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 136.2, 135.2, 132.9, 131.5, 130.7, 130.2, 129.9, 129.4, 129.3, 129.2, 128.9, 128.4, 125.1, 125.0, 101.1. IR (cm^{-1}) 3052, 1718, 1492, 1389, 761. HRMS calculated for $C_{20}H_{14}IN_3O$: 439.0182; found: 439.0183.

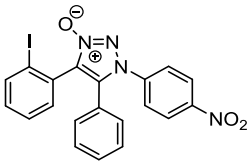


4-(2-Iodophenyl)-1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (23x). The general procedure 7.3.3.1 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and 1,2-diiodobenzene (0.095 mmol, 12.4 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 23 mg (83 %). Mp 165.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.43 – 7.31 (m, 6H), 7.25 – 7.19 (m, 4H), 7.13 (td, *J* = 7.6, 1.8 Hz, 2H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 134.5, 132.9, 131.4, 130.5, 130.3, 129.4, 129.1, 128.9, 128.5, 128.4, 128.3, 127.4, 126.0, 124.8, 101.4, 52.4. IR (cm^{-1}) 3066, 1560, 1367, 696. HRMS calculated for $C_{21}H_{16}IN_3O$: 453.0338; found: 453.0337.

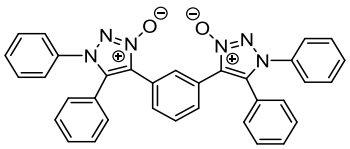


4-(2-Iodophenyl)-1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23y). The general procedure 7.3.3.1 was followed starting from 1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9f**) (0.11 mmol, 30 mg) and 1,2-diiodobenzene (0.17 mmol, 40 µL). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield 31 mg (59 %). Mp 104.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.37 (m, 5H), 7.33 (td, *J* = 8.2, 7.5, 5.1 Hz, 4H), 7.20 – 7.16 (m, 1H), 7.15 – 7.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.4, 135.3, 133.7, 133.3, 132.9, 131.6,

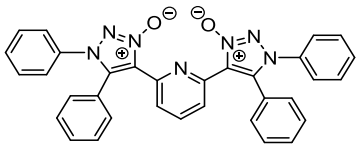
130.5, 129.7, 129.4, 129.2, 129.1, 128.5, 126.2, 124.7, 101.0. IR (cm^{-1}) 3053, 1492, 1388, 1089, 1011, 724. HRMS calculated for $C_{20}H_{13}ClIN_3O$: 472.9792; found: 472.9793.



4-(2-Iodophenyl)-1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (23z). The general procedure 7.3.3.1 was followed starting from 1-(4-nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9e**) (0.11 mmol, 30 mg) and 1,2-diiodobenzene (0.10 mmol, 24 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 38 mg (72 %). Mp 119 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.41 (dt, *J* = 30.7, 7.8 Hz, 5H), 7.20 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 139.8, 139.5, 136.8, 134.3, 132.9, 131.8, 130.9, 129.9, 129.4, 129.4, 128.5, 124.9, 124.9, 124.4, 100.9. IR (cm^{-1}) 3056, 1593, 1521, 1339, 724. HRMS calculated for $C_{20}H_{13}IN_4O_3$: 484.0032; found: 484.0011.



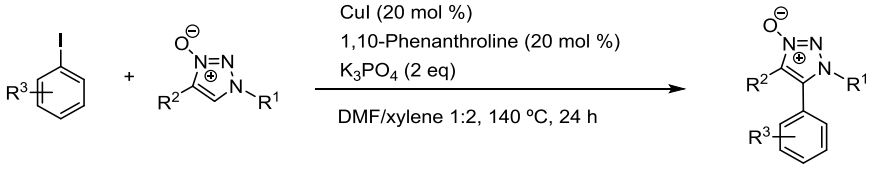
1,3-Bis(1,5-diphenyl-3-oxo-1*H*-1,2,3-triazol-4-yl)benzene (23aa). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**9a**) (0.12 mmol, 28 mg) and 1,3-dibromobenzene (0.048 mmol, 16 mg). The reaction was stirred at 140 ºC for 48 hours. On completion, the solvent was evaporated, the crude was dispersed with EtOAc. Yield: 20 mg (76 %). Mp 218 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, *J* = 1.8 Hz, 1H), 7.44 (m, 15H), 7.34 – 7.15 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.1, 130.5, 130.4, 130.0, 129.9, 129.7, 129.4, 129.3, 129.2, 128.6, 125.2, 125.1, 125.0. IR (cm^{-1}) 3227, 1591, 1383, 1076, 707. HRMS calculated for $C_{34}H_{24}N_6O_2$: 548.1961; found: 548.1969.



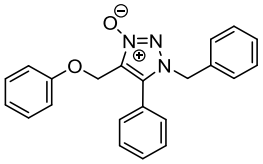
2,6-Bis(1,5-diphenyl-3-oxo-1*H*-1,2,3-triazol-4-yl)pyridine (23ab). The general procedure 7.3.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole N-oxide

(**9a**) (0.06 mmol, 14 mg) and 2,6-diiodopyridine (0.03 mmol, 10.4 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 11 mg (65 %). Mp >250 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.9 Hz, 2H), 8.00 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.27 (m, 9H), 7.27 – 7.17 (m, 8H), 6.96 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 137.3, 137.2, 135.0, 130.4, 129.9, 129.4, 129.3, 128.4, 128.4, 125.2, 124.9, 124.9. IR (cm^{-1}) 3065, 1719, 1493, 1353, 762. HRMS calculated for $C_{33}H_{23}N_7O_2$: 549.1913; found: 549.1917.

7.3.3.2 Copper-catalyzed cross-coupling arylation of 1,4-Disubstituted triazole N-oxides (24)

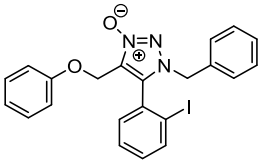


A flame-dried Schlenk test tube with a magnetic stirring bar was charged under N_2 with CuI (0.024 mmol, 4.6 mg), 1,10-phenanthroline (0.024 mmol, 4.3 mg), K_3PO_4 (0.24 mmol, 51 mg), the corresponding triazole N-oxide (0.12 mmol), the selected aryl or heteroaryl halide (0.14 mmol) and DMF/xylene (1:2, 0.2 mL). The reaction mixture was stirred at 140 ºC for 24 hours. Upon completion, it was cooled to ambient temperature, 3-4 mL of CH_2Cl_2 were added and after a 5 min stirring, the resulting suspension was filtered through a celite pad. The filtrate was evaporated at reduced pressure and the crude product was purified by column chromatography on silica gel.

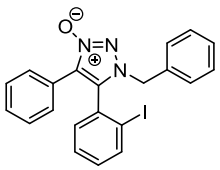


1-Benzyl-4-phenoxymethyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (24a). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenoxymethyl-1*H*-1,2,3-triazole N-oxide (**4d**) (0.053 mmol, 15 mg) and iodobenzene (0.24 mmol, 28 µL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 13 mg (73 %). Mp 120 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.43 (m, 3H), 7.39 – 7.22 (m, 7H), 7.21 – 7.10 (m, 2H), 7.04 – 6.89 (m, 3H), 5.26 (s, 2H), 5.08 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 139.2, 133.9, 130.9, 129.7, 129.5, 129.2, 128.9, 128.7, 127.6, 126.1, 124.3, 121.4, 114.9, 57.4, 52.4. IR (cm^{-1}) 3090, 1717, 1586, 1407, 1224, 670.

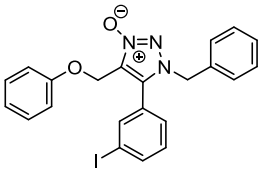
HRMS calculated for $C_{22}H_{19}N_3O_2$: 357.1477; found: 357.1480.



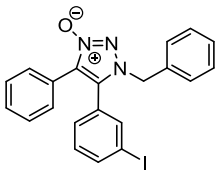
1-Benzyl-5-(2-iodophenyl)-4-phenoxymethyl-1*H*-1,2,3-triazole N-oxide (24b). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenoxymethyl-1,2,3-triazole N-oxide (**4d**) (0.053 mmol, 15 mg) and 1,2-diiodobenzene (0.07 mmol, 10 µL). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 2:1). Yield: 13 mg (52 %). Mp 90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.39 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 – 7.18 (m, 7H), 7.05 – 6.97 (m, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 2H), 5.49 – 5.22 (m, 2H), 5.11 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 139.5, 132.3, 131.9, 130.1, 129.7, 129.6, 129.4, 129.2, 128.8, 128.4, 128.3, 127.7, 121.3, 114.6, 99.1, 52.9, 42.7. IR (cm^{-1}) 3384, 1719, 1488, 1225, 688. HRMS calculated for $C_{22}H_{18}IN_3O_2$: 453.0338; found: 453.0318.



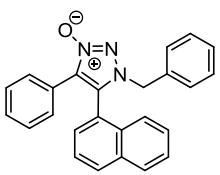
1-Benzyl-5-(2-iodophenyl)-4-phenyl-1*H*-1,2,3-triazole N-oxide (24c). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 1,2-diiodobenzene (0.08 mmol, 12 µL). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 2:1). Yield: 17 mg (60 %). Mp 170 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.65 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36 – 7.20 (m, 7H), 7.07 (dd, *J* = 7.6, 1.7 Hz, 3H), 5.29 (d, *J* = 14.8 Hz, 1H), 5.03 (d, *J* = 14.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 137.2, 133.1, 132.3, 132.3, 130.9, 129.4, 129.1, 128.8, 128.8, 128.8, 128.5, 128.4, 127.9, 124.9, 100.0, 53.3. IR (cm^{-1}) 3058, 1719, 1383, 692. HRMS calculated for $C_{21}H_{16}IN_3O$: 453.0338; found: 453.0318.



1-Benzyl-5-(3-iodophenyl)-4-phenoxymethyl-1*H*-1,2,3-triazole N-oxide (24d). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenoxymethyl-1*H*-1,2,3-triazole N-oxide (**4d**) (0.053 mmol, 15 mg) and 1,3-diiodobenzene (0.07 mmol, 23 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 15 mg (53 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.61 (t, *J* = 1.8 Hz, 1H), 7.37 (p, *J* = 3.5, 3.0 Hz, 3H), 7.33 – 7.28 (m, 3H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.03 – 6.92 (m, 3H), 5.23 (s, 2H), 5.11 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 139.9, 138.5, 137.5, 133.7, 130.6, 129.7, 129.6, 129.1, 128.9, 128.9, 127.7, 126.1, 121.7, 114.9, 94.3, 57.4, 52.8. IR (cm^{-1}) 3393, 3057, 1719, 1406, 1221, 752. HRMS calculated for $C_{22}H_{18}IN_3O_2$: 483.0444; found: 483.0425.

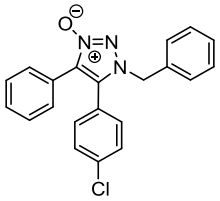


1-Benzyl-5-(3-iodophenyl)-4-phenyl-1*H*-1,2,3-triazole N-oxide (24e). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 1,3-diiodobenzene (0.12 mmol, 40 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 10 mg (40 %). Mp 183 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.85 (m, 1H), 7.66 – 7.56 (m, 2H), 7.53 (s, 1H), 7.37 (dd, *J* = 7.8, 4.2 Hz, 6H), 7.19 (q, *J* = 5.5, 4.2 Hz, 4H), 5.28 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.6, 134.4, 133.7, 130.9, 129.3, 129.2, 129.1, 128.9, 128.7, 128.6, 128.5, 127.9, 127.3, 124.6, 94.6, 52.9. IR (cm^{-1}) 3117, 1386, 703. HRMS calculated for $C_{21}H_{16}IN_3O$: 453.0338; found: 453.0323.

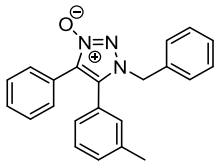


1-Benzyl-5-(naphthalene-1-yl)-4-phenyl-1*H*-1,2,3-triazole N-oxide (24f). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-

oxide (**4a**) (0.06 mmol, 15 mg) and 1-iodonaphthalene (0.09 mmol, 14 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15.4 mg (70 %). Mp 135 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.50 (m, 4H), 7.48 – 7.33 (m, 3H), 7.23 – 7.12 (m, 6H), 6.90 (d, *J* = 7.4 Hz, 2H), 5.21 (d, *J* = 14.5 Hz, 1H), 4.99 (d, *J* = 14.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 133.5, 133.4, 131.5, 131.4, 129.7, 129.5, 128.8, 128.7, 128.6, 128.2, 128.1, 128.0, 127.8, 127.0, 126.9, 125.3, 124.9, 124.0, 122.6, 52.8. IR (cm^{-1}) 3056, 1719, 1380, 770, 691. HRMS calculated for $C_{25}H_{19}N_3O$: 377.1528; found: 377.1525.

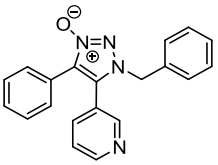


1-Benzyl-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole N-oxide (24g). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 1-chloro-4-iodobenzene (0.09 mmol, 22.5 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 3 mg (14 %). Mp 180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.41 – 7.29 (m, 6H), 7.17 (d, *J* = 7.9 Hz, 4H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 133.9, 131.4, 129.9, 129.8, 129.4, 129.1, 129.0, 128.9, 128.5, 128.4, 127.8, 127.7, 123.7, 52.9. IR (cm^{-1}) 3065, 1717, 1389, 691. HRMS: calculated for $C_{21}H_{16}ClN_3O$: 361.0982; found: 361.0964.

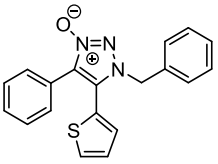


1-Benzyl-4-phenyl-5-(*m*-tolyl)-1*H*-1,2,3-triazole N-oxide (24h). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 3-iodotoluene (0.09 mmol, 12 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15.7 mg (77 %). Mp 173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.59 (m, 2H), 7.44 – 7.26 (m, 8H), 7.17 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.08 – 6.95 (m, 2H), 5.24 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 136.3, 134.1, 131.4, 130.5, 129.2, 128.9, 128.8, 128.7, 128.6,

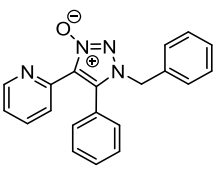
128.5, 128.2, 127.9, 127.1, 125.2, 125.0, 52.5, 21.3. IR (cm^{-1}) 3054, 1720, 1385, 695. HRMS calculated for $C_{22}H_{19}N_3O$: 341.1528; found: 341.1527.



1-Benzyl-4-phenyl-5-(pyridin-3-yl)-1*H*-1,2,3-triazole N-oxide (24i). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 3-iodopyridine (0.09 mmol, 20 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 7.3 mg (40 %). Mp >160 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.43 (m, 5H), 7.42 – 7.28 (m, 7H), 7.21 – 7.05 (m, 2H), 5.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 150.1, 137.5, 133.6, 133.0, 130.0, 129.7, 129.6, 129.3, 129.1, 128.9, 128.7, 128.6, 127.6, 124.4, 52.9. IR (cm^{-1}) 3381, 1716, 1387, 1261, 695. HRMS calculated for $C_{20}H_{16}N_4O$: 328.1324; found: 328.1324.

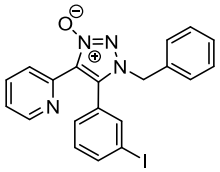


1-Benzyl-4-phenyl-5-(thiophen-2-yl)-1*H*-1,2,3-triazole N-oxide (24j). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-phenyl-1*H*-1,2,3-triazole N-oxide (**4a**) (0.06 mmol, 15 mg) and 2-iodothiophene (0.09 mmol, 10.5 µL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 12 mg (64 %). Mp 175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.70 (s, 2H), 7.53 – 7.29 (m, 9H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.7, 129.5, 129.4, 129.3, 129.2, 129.2, 129.1, 128.8, 128.7, 128.6, 128.6, 126.5, 125.0, 121.6, 55.6. IR (cm^{-1}) 3088, 1720, 1393, 758, 701. HRMS calculated for $C_{19}H_{15}N_3OS$: 333.0936; found: 333.0945.

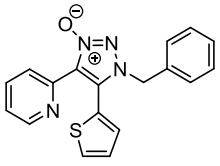


1-Benzyl-5-phenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (24k). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole

N-oxide (0.06 mmol, 15 mg) and iodobenzene (0.24 mmol, 28 µL) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 15 mg (73 %). Mp 148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.74 – 7.52 (m, 3H), 7.40 (ddd, *J* = 6.4, 5.2, 2.2 Hz, 4H), 7.33 – 7.16 (m, 5H), 7.05 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 145.6, 137.0, 134.3, 133.8, 129.7, 129.5, 129.5, 129.4, 128.7, 128.5, 128.2, 125.5, 124.9, 124.5, 53.0. IR (cm^{-1}) 3382, 3057, 1719, 1719, 1386, 694. HRMS calculated for $C_{20}H_{16}N_4O$: 328.1324; found: 328.1322.

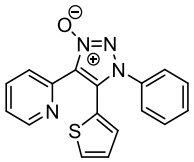


1-Benzyl-5-(3-iodophenyl)-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (24l). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-(pyridine-2-yl)-1*H*-1,2,3-triazole N-oxide (0.06 mmol, 15 mg), 1,3-diiodobenzene (0.24 mmol, 106 mg) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15 mg (55 %) as an yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (ddd, *J* = 4.9, 1.8, 0.9 H, 1H), 7.97 (t, *J* = 1.7 Hz, 1H), 7.77-7.63 (m, 2H), 7.53 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.44 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.24-7.02 (m, 4H), 5.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 145.1, 138.4, 137.9, 137.2, 134.1, 134.1, 130.2, 128.7, 128.6, 128.6, 128.2, 128.1, 126.8, 125.5, 124.8, 94.1, 53.1. IR (cm^{-1}) 3065, 1720, 1378, 784. HRMS calculated for $C_{20}H_{15}IN_4O$; 454.0291; found: 454.0290.

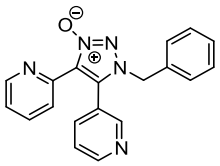


1-Benzyl-4-(pyridin-2-yl)-5-(thiophen-2-yl)-1*H*-1,2,3-triazole N-oxide (24m). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (0.04 mmol, 10 mg), 2-iodothiophene (0.16 mmol, 19 µL) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 7 mg (52 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 8.89 (m, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.7, 4.9, 1.0 Hz, 1H), 7.44

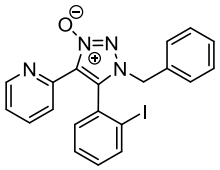
(dd, *J* = 5.1, 1.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.25 (dt, *J* = 5.2, 1.4 Hz, 4H), 7.15 – 7.09 (m, 2H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.54 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 145.2, 137.3, 133.8, 132.4, 128.8, 128.6, 128.0, 127.8, 126.8, 126.5, 126.1, 125.3, 125.3, 125.2, 53.1. IR (cm^{-1}) 3433, 3061, 1420, 696. HRMS calculated for $C_{18}H_{14}N_4OS$: 334.0888; found: 334.0889.



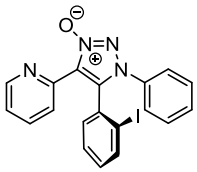
1-Phenyl-4-(pyridin-2-yl)-5-(thiophen-2-yl)-1*H*-1,2,3-triazole N-oxide (24n). The general procedure 7.3.3.2 was followed starting from 1-phenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (0.04 mmol, 10 mg), 2-iodothiophene (0.16 mmol, 19 µL) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 9 mg (67 %). Mp 203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (dt, *J* = 4.9, 1.3 Hz, 1H), 7.81 (td, *J* = 7.7, 1.8 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.42 – 7.31 (m, 7H), 7.03 (dd, *J* = 5.1, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 145.6, 137.3, 135.2, 132.3, 130.8, 129.4, 129.3, 129.2, 127.8, 126.8, 126.5, 125.1, 124.9, 124.9. IR (cm^{-1}) 3055, 1493, 1390, 704. HRMS calculated for $C_{17}H_{12}N_4OS$: 320.0732; found: 320.0731.



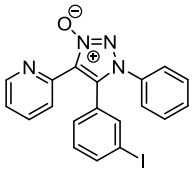
1-Benzyl-4-(pyridin-2-yl)-5-(pyridin-3-yl)-1*H*-1,2,3-triazole N-oxide (24o). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-(pyridyn-2-yl)-1*H*-1,2,3-triazole N-oxide (0.06 mmol, 15 mg) and 3-iodopyridine (0.24 mmol, 54 mg) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 13 mg (66 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 – 8.84 (m, 1H), 8.62 (s, 2H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.70 (td, *J* = 7.8, 1.8 Hz, 1H), 7.54 – 7.36 (m, 2H), 7.32 – 7.24 (m, 4H), 7.19 (dd, *J* = 6.7, 2.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 5.66 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 149.5, 148.9, 144.9, 137.5, 137.2, 134.4, 133.9, 129.7, 129.6, 128.8, 128.7, 128.2, 126.5, 125.3, 125.0, 53.1. IR (cm^{-1}) 3394, 1718, 1387, 704. HRMS calculated for $C_{19}H_{15}N_5O$: 329.1277; found: 329.1276.



1-Benzyl-5-(2-iodophenyl)-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (24p). The general procedure 7.3.3.2 was followed starting from 1-benzyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (0.08 mmol, 20 mg) and 1,2-diiodobenzene (0.12 mmol, 15 µL) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (EtOAc/Hex 1:1 then EtOAc). Yield: 19 mg (52 %). Mp 169 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.58 (q, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.35 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 5H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 5.96 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 145.1, 139.8, 137.1, 132.7, 131.6, 129.5, 129.5, 128.8, 128.7, 128.6, 128.3, 128.2, 128.0, 124.4, 124.2, 101.0, 53.5. IR (cm^{-1}) 3056, 1586, 1389, 699. HRMS calculated for $C_{20}H_{15}IN_4O$: 454.0291; found: 454.0298.



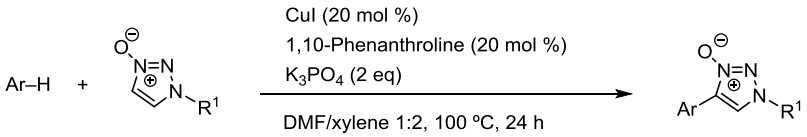
1-Phenyl-5-(2-iodophenyl)-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (24q). The general procedure 7.3.3.2 was followed starting from 1-phenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (0.08 mmol, 20 mg) and 1,2-diiodobenzene (0.12 mmol, 15 µL) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (EtOAc/Hex 1:1 then EtOAc). Yield: 21.1 mg (60 %). Mp 196.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dt, *J* = 4.8, 1.3 Hz, 1H), 8.02 – 7.93 (m, 1H), 7.65 (td, *J* = 7.8, 1.8 Hz, 1H), 7.54 – 7.38 (m, 7H), 7.29 (d, *J* = 3.3 Hz, 1H), 7.25 – 7.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 144.9, 139.6, 136.9, 135.7, 135.1, 133.6, 133.0, 131.6, 130.4, 129.3, 129.2, 128.5, 125.1, 125.0, 124.5, 100.7. IR (cm^{-1}) 3054, 1495, 1383, 766, 679. HRMS calculated for $C_{19}H_{13}IN_4O$: 440.0134; found: 440.0141.



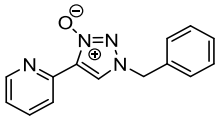
1-Phenyl-5-(3-iodophenyl)-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (24r). The general procedure 7.3.3.2 was followed starting from 1-phenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (0.08 mmol, 20 mg) and 1,3-diiodobenzene (0.12 mmol, 40 mg) in DMF/xylene 1/2 (0.6 mL). The crude product was purified by column chromatography (EtOAc/Hex 1:1 then EtOAc). Yield: 20 mg (57 %). Mp 213 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.08 (t, *J* = 1.7 Hz, 1H), 7.72 (m, 2H), 7.63 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.43 – 7.37 (m, 4H), 7.35 – 7.30 (m, 2H), 7.21 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 145.2, 138.3, 137.9, 137.1, 135.2, 134.7, 129.9, 129.4, 129.3, 129.1, 128.4, 126.6, 125.9, 124.9, 124.9, 93.9. IR (cm^{-1}) 3053, 1496, 1380, 684. HRMS calculated for $C_{19}H_{13}IN_4O$: 440.0134; found: 440.0138.

7.4 Experimental section of chapter 4

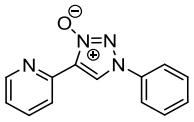
7.4.1 General procedure for the synthesis of 1,4-disubstituted 1*H*-1,2,3-triazole N-oxides from 1-substituted 1*H*-1,2,3-triazole N-oxides (25)



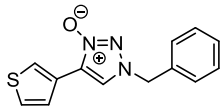
A flame-dried Schlenk test tube with a magnetic stirring bar was charged under N_2 with CuI (0.013 mmol, 2.4 mg), 1,10-phenanthroline (0.013 mmol, 2.3 mg), K_3PO_4 (0.07 mmol, 14.7 mg), the corresponding 1*H*-1,2,3-triazole N-oxide (0.063 mmol), the selected aryl halide (0.63 mmol) and DMF/xylene (1:2) (0.9 mL). The reaction mixture was stirred at 100 ºC for 24 hours. The reaction mixture was then cooled to ambient temperature, diluted with 3-4 mL of EtOAc and extracted with water. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography.



1-Benzyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (25a). The general procedure 7.4.1 was followed starting from 1-benzyl-1*H*-1,2,3-triazole N-oxide (**4l**) (0.62 mmol, 100 mg) and 2-iodopyridine (0.62 mmol., 66 µl). The crude product was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5). Yield: 90 mg (60 %). Mp 176 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dt, *J* = 4.9, 1.2 Hz, 1H), 7.84 (td, *J* = 7.8, 1.8 Hz, 1H), 7.68 (s, 1H), 7.51 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (ddd, *J* = 7.7, 4.8, 1.1 Hz, 1H), 7.38 – 7.21 (m, 5H), 5.96 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 144.7, 137.5, 136.7, 134.7, 128.6, 128.4, 128.2, 124.6, 123.3, 118.6, 53.6. IR (cm^{-1}) 3136, 1587, 1401, 1042, 781, 693. HRMS calculated for $C_{14}H_{12}N_4O$: 252.1011; found: 252.1013.

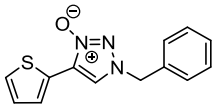


1-Phenyl-4-(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (25b). The general procedure 7.4.1 was followed starting from 1-phenyl-1*H*-1,2,3-triazole N-oxide (**4m**) (0.62 mmol, 100 mg) and 2-iodopyridine (0.62 mmol., 66 µl) were added. The crude product was purified by column chromatography (EtOAc then, CH_2Cl_2/MeOH 95:5). Yield: 73 mg (50 %). Mp 158 ºC. ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.62 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.81 (s, 1H), 7.71 (td, *J* = 7.8, 1.8 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.41 – 7.33 (m, 3H), 7.21 (dt, *J* = 8.0, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 144.1, 138.3, 136.9, 135.4, 129.9, 129.4, 125.5, 124.7, 123.5, 120.4. IR (cm^{-1}) 3077, 1500, 1402, 1035, 758. HRMS calculated for $C_{13}H_{10}N_4O$: 238.0855; found: 238.0860.

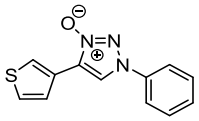


1-Benzyl-4-(thiophen-3-yl)-1*H*-1,2,3-triazole-N-oxide (25c). The general procedure 7.4.1 was followed starting from 1-benzyl-1*H*-1,2,3-triazole N-oxide (**4l**) (0.18 mmol, 30 mg) and 3-iodothiophene (0.18 mmol, 20 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 30 mg (65 %). Mp 175.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.46 (s, 1H), 7.41 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.35 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.17 (dd, *J* = 6.9, 2.6 Hz, 2H), 7.08 (dd, *J* = 5.1,

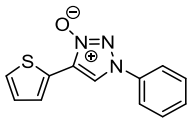
1.3 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.9, 129.1, 128.7, 128.0, 127.3, 127.0, 126.9, 124.0, 118.7, 52.5. IR (cm^{-1}) 3156, 1721, 1497, 1422, 695. HRMS calculated for $C_{13}H_{11}N_3OS$: 257.0623; found: 257.0624.



1-Benzyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (25d). The general procedure 7.4.1 was followed starting from 1-benzyl-1,2,3-triazole N-oxide (**4l**) (0.09 mmol, 15 mg) and 2-iodothiophene (0.09 mmol, 10 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15 mg (63 %). Mp 118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 4.5, 1.8 Hz, 1H), 7.44 (s, 1H), 7.36 (dd, *J* = 5.2, 1.8 Hz, 3H), 7.27 – 7.05 (m, 4H), 5.44 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7, 133.5, 130.3, 129.7, 129.0, 128.7, 128.3, 127.2, 123.4, 119.1, 52.6. IR (cm^{-1}) 3389, 3141, 1594, 1399, 748. HRMS calculated for $C_{13}H_{11}N_3OS$: 257.0623; found: 257.0629.



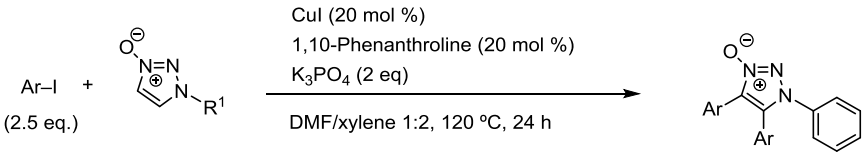
1-Phenyl-4-(thiophen-3-yl)-1*H*-1,2,3-triazole-N-oxide (25e). The general procedure 7.4.1 was followed starting from 1-phenyl-1,2,3-triazole N-oxide (**4m**) (0.12 mmol, 19 mg) and 3-iodothiophene (0.09 mmol, 10 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 17 mg (59 %). Mp 191.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 – 7.48 (m, 4H), 7.41 (dp, *J* = 8.1, 3.1 Hz, 3H), 6.90 (dd, *J* = 5.1, 1.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 134.8, 130.1, 129.7, 127.5, 126.9, 126.6, 125.6, 124.3, 118.8. IR (cm^{-1}) 3386, 1720, 1418, 1017, 702. HRMS calculated for $C_{12}H_9N_3OS$: 243.0466; found: 243.0469.



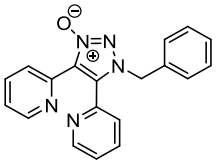
1-Phenyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (25f). The general procedure 7.4.1 was followed starting from 1-phenyl-1*H*-1,2,3-triazole N-oxide (**4m**) (0.09 mmol, 14 mg) and 2-iodothiophene (0.09 mmol, 10 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 12 mg (55 %). Mp 155 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.61 – 7.50 (m, 3H), 7.49 – 7.41 (m, 4H), 7.11 – 6.99 (m,

1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 134.0, 130.6, 129.9, 129.7, 129.5, 127.9, 126.3, 124.2, 118.7. IR (cm^{-1}) 3090, 1493, 1403, 681. HRMS calculated for $C_{12}H_9N_3OS$: 243.0466; found: 243.0474.

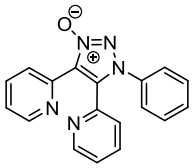
7.4.2 General procedure for the synthesis of 1,4,5-trisubstituted 1*H*-1,2,3-triazole N-oxides from 1-substituted 1*H*-1,2,3-triazole N-oxides (26)



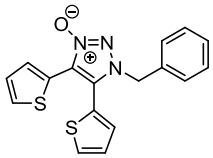
A flame-dried Schlenk test tube with a magnetic stirring bar was charged under N_2 with CuI (0.013 mmol, 2.4 mg), 1,10-phenanthroline (0.013 mmol, 2.3 mg), K_3PO_4 (0.14 mmol, 29 mg), triazole N-oxide (0.063 mmol), aryl halide (0.63 mmol) and DMSO/xylene (1:2) (0.2 mL). The reaction mixture was stirred at 120 ºC for 24 hours. The reaction mixture was then cooled to ambient temperature, diluted with 3-4 mL of EtOAc and extracted with water. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography.



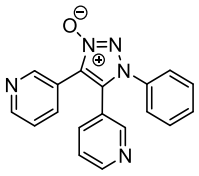
1-Benzyl-4,5-di(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (26a). The general procedure 7.4.2 was followed starting from 1-benzyl-1*H*-1,2,3-triazole N-oxide (**4l**) (0.18 mmol, 30 mg), 2-iodopyridine (0.41 mmol, 44 µL). The crude product was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5). Yield: 27 mg (67 %). Mp 140 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dt, *J* = 4.8, 1.5 Hz, 1H), 8.53 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.40 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.81 (td, *J* = 7.8, 1.9 Hz, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.40 (dd, *J* = 7.6, 5.0 Hz, 2H), 7.23 (qd, *J* = 4.4, 1.8 Hz, 4H), 7.18 – 7.10 (m, 2H), 5.64 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 148.9, 145.7, 145.5, 136.5, 136.2, 135.4, 134.0, 128.6, 128.4, 128.3, 128.1, 126.9, 124.4, 124.3, 123.6, 52.9. IR (cm^{-1}) 3041, 1588, 1389, 787, 700. HRMS calculated for $C_{19}H_{15}N_5O$: 329.1277; found: 329.1286.



1-Phenyl-4,5-di(pyridin-2-yl)-1*H*-1,2,3-triazole N-oxide (26b). The general procedure 7.4.2 was followed starting from phenyl-1*H*-1,2,3-triazole N-oxide (**4m**) (0.18 mmol, 28 mg) and 2-iodopyridine (0.41 mmol, 44 µL). The crude was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5) Yield: 45 mg (80%). Mp 201.5 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.0 Hz, 1H), 8.57 (dt, *J* = 4.9, 1.2 Hz, 1H), 8.42 – 8.35 (m, 1H), 7.83 (td, *J* = 7.8, 1.8 Hz, 1H), 7.74 (td, *J* = 7.8, 1.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.29 (m, 6H), 7.24 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 149.0, 145.8, 145.3, 136.4, 136.3, 136.1, 135.3, 129.7, 129.2, 129.1, 126.7, 125.0, 124.3, 124.1, 123.5. IR (cm^{-1}) 3063, 1583, 1389, 705. HRMS calculated for $C_{18}H_{13}N_5O$: 315.1120; found: 315.1117.

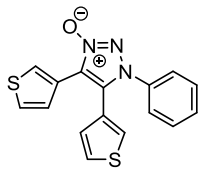


1-Benzyl-4,5-di(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (26c). The general procedure 7.4.2 was followed starting from 1-benzyl-1,2,3-triazole N-oxide (**4l**) (0.09 mmol, 15 mg) and 2-iodothiophene (0.21 mmol, 23 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 15 mg (50 %). Mp 165.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 5.1 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.29 – 7.22 (m, 2H), 7.21 – 7.14 (m, 3H), 7.00 (dd, *J* = 4.9, 3.1 Hz, 1H), 5.30 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 132.5, 131.1, 129.0, 128.9, 128.8, 128.3, 127.8, 127.3, 126.7, 126.5, 126.0, 125.4, 123.5, 52.7. IR (cm^{-1}) 3086, 1604, 1385, 700. HRMS calculated for $C_{17}H_{13}N_3OS_2$: 339.0500; found: 339.0504.

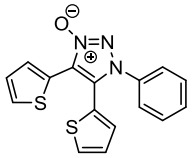


1-Phenyl-4,5-di(pyridin-3-yl)-1*H*-1,2,3-triazole-N-oxide (26d). The general procedure 7.4.2 was followed starting from 1-phenyl-1,2,3-triazole N-oxide (**4m**) (0.09 mmol, 14 mg) and 3-iodopyridine (0.21 mmol, 41 mg). The crude was purified column

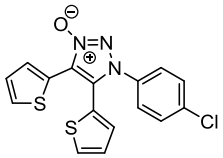
chromatography (Acetone/CH_2Cl_2 1:2). Yield: 14 mg (50 %). Mp 217 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 34.5, 13.5 Hz, 3H), 8.49 (s, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.57 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.53 – 7.26 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 150.1, 149.8, 148.8, 137.2, 137.1, 134.4, 133.0, 130.1, 129.8, 127.5, 125.4, 125.3, 124.0, 121.5, 119.3. IR (cm^{-1}) 3380, 1495, 1382, 703, 685. HRMS calculated for $C_{18}H_{13}N_5O$: 315.1120; found: 315.1123.



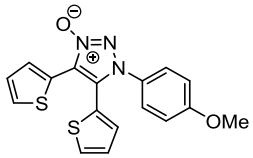
1-Phenyl-4,5-di(thiophen-3-yl)-1*H*-1,2,3-triazole-N-oxide (26e). The general procedure 7.4.2 was followed starting from 1-phenyl-1,2,3-triazole N-oxide (**4m**) (0.09 mmol, 14 mg) and 2-iodothiophene (0.21 mmol, 23 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 23 mg (85 %). Mp 216 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 3.1 Hz, 1H), 7.48 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.45 – 7.37 (m, 4H), 7.31 (td, *J* = 6.8, 6.1, 2.5 Hz, 3H), 7.11 (d, *J* = 5.2 Hz, 1H), 7.00 (d, *J* = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 129.9, 129.4, 129.3, 128.7, 127.9, 127.7, 126.5, 125.8, 125.4, 125.2, 124.9, 124.6, 119.2. IR (cm^{-1}) 3088, 1590, 1413, 711. HRMS calculated for $C_{16}H_{11}N_3OS_2$: 325.03441; found: 325.0346.



1-Phenyl-4,5-di(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (26f). The general procedure 7.4.2 was followed starting from 1-phenyl-1*H*-1,2,3-triazole N-oxide (**4m**) (0.09 mmol, 14 mg) and 2-iodothiophene (0.21 mmol, 23 µL). The crude product was purified column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 18 mg (60 %). Mp 210 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 5.0 Hz, 1H), 7.48 – 7.33 (m, 7H), 7.29 (d, *J* = 4.0 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.1 Hz, 1H), 7.05 (t, *J* = 4.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 132.4, 130.9, 129.6, 129.3, 128.1, 127.7, 126.9, 126.6, 126.6, 125.1, 125.0, 124.4, 119.3. IR (cm^{-1}) 3075, 1590, 1492, 707. HRMS calculated for $C_{16}H_{11}N_3OS_2$: 325.0344; found: 325.0345.



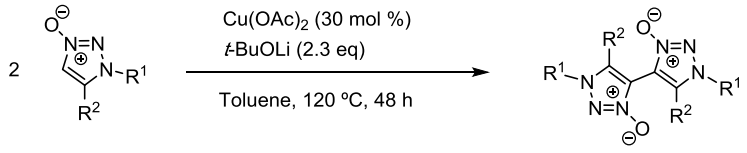
1-(4-Chlorophenyl)-4,5-di(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (26g). The general procedure 7.4.2 was followed starting from 1-(4-chlorophenyl)-1*H*-1,2,3-triazole N-oxide (**4o**) (0.077 mmol, 15 mg) and 2-iodothiophene (0.19 mmol, 21 µL). The crude product was purified column chromatography (Hex/EtOAc 1:1). Yield: 17 mg (61 %). Mp 178 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.18 (m, 4H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 133.6, 132.8, 131.4, 129.9, 128.6, 128.1, 127.3, 127.3, 126.9, 126.9, 126.2, 125.3, 124.4. IR (cm^{-1}) 3081, 1491, 1423, 833, 700. HRMS calculated for $C_{16}H_{10}ClN_3OS_2$: 358.9954; found: 358.9959.



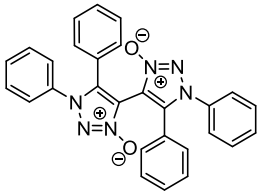
1-(4-Methoxyphenyl)-4,5-di(thiophen-2-yl)-1*H*-1,2,3-triazole-N-oxide (26h). The general procedure 7.4.2 was followed starting from 1-(4-methoxyphenyl)-1,2,3-triazole N-oxide (**4n**) (0.08 mmol, 15 mg) and 2-iodothiophene (0.19 mmol, 21 µL). The crude product was purified column chromatography (Hex/EtOAc 1:1). Yield: 16 mg (57 %). Mp 201.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.46 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.41 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.19 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.8 Hz, 1H), 6.96 – 6.85 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 132.6, 131.1, 128.4, 128.1, 127.9, 127.6, 127.1, 127.0, 126.9, 126.8, 125.6, 124.8, 114.8, 55.9. IR (cm^{-1}) 3081, 1491, 1423, 833, 700. HRMS calculated for $C_{17}H_{13}N_3O_2S_2$: 355.0449; found: 355.0446.

7.4.3 Synthesis of homocoupled 1*H*-1,2,3-triazole N-oxides

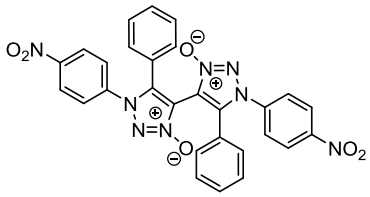
7.4.3.1 General procedure for the synthesis of 4,4'-bis(1*H*-1,2,3-triazole) N-oxides (28)



In an ACE tube or a sealed tube, the corresponding 1*H*-1,2,3-triazole N-oxide (1.00 mmol) in toluene (10 mL), $Cu(OAc)_2$ (30 %) and Li^{t}BuO (2.5 mmol, 200 mg) were added and the mixture was heated at 120 ºC for 48 hours. Then, the solvent was evaporated under pressure. Ethyl acetate was added and the organic phase was washed with ammonia solution. The organic layers were collected, dried and evaporate under reduced pressure. The crude was purified by column chromatography.

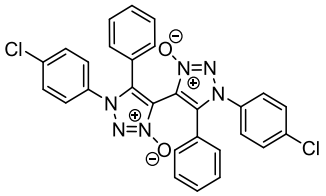


1,1',5,5'-Tetraphenyl-1*H*,1'*H*-[4,4'-bi(1,2,3-triazole)] N,N'-dioxide (28a). The general procedure 7.4.3.1 was followed starting from 1,5-diphenyl-1*H*-1,2,3-triazole 3-oxide (**9a**) (0.15 mmol, 40 mg). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 1:1). Yield: 50 mg (70 %). Mp 248.6 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 6.68 (m, 20H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 135.3, 131.0, 129.8, 129.7, 129.6, 129.5, 125.3, 124.6, 117.8. IR (cm^{-1}) 3050, 1590, 1428, 1401, 702. HRMS calculated for $C_{28}H_{20}N_6O_2$: 472.1648; found: 472.1641.

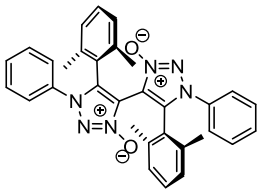


1,1'-Bis(4-nitrophenyl)-5,5'-diphenyl-1*H*, 1'*H*-[4,4'-bi(1,2,3-triazole)] N,N'-dioxide (28b). The general procedure 7.4.3.1 was followed starting from 1-(4-nitrophenyl)-5-phenyl-1,2,3-triazole N-oxide (**9e**) (0.05 mmol, 15 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 9 mg (64 %). Mp 129 ºC. ^{1}H

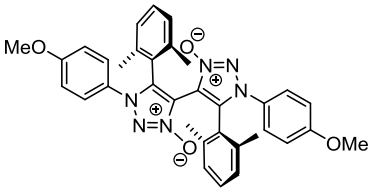
NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.2 Hz, 4H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 4H), 7.35 (d, *J* = 7.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 141.4, 139.4, 131.6, 129.8, 129.2, 125.0, 124.9, 123.6, 118.2. IR (cm^{-1}) 3427, 1594, 1523, 1342, 1038, 824. HRMS calculated for $C_{28}H_{18}N_8O_6$: 562.1345; found: 562.1345.



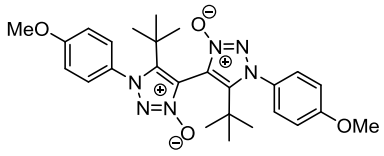
1,1'-Bis(4-chlorophenyl)-5,5'-diphenyl-1*H*, 1'*H*-[4,4'-bi(1,2,3-triazole)] N,N'-dioxide (28c). The general procedure 7.4.3.1 was followed starting from 1-(4-chlorophenyl)-5-phenyl-1,2,3-triazole N-oxide (**9f**) (0.08 mmol, 20 mg). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 12 mg (56 %). Mp >230 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.41 – 7.30 (m, 12H), 7.27 – 7.22 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 135.6, 133.3, 131.0, 129.7, 129.4, 129.2, 126.1, 123.9, 117.5. IR (cm^{-1}) 3056, 1670, 1493, 1389, 1089, 831. HRMS calculated for $C_{28}H_{18}Cl_2N_6O_2$: 540.0848; found: 540.0867.



5,5'-Bis(2,6-dimethylphenyl)-1,1'-diphenyl-1*H*,1'*H*-[4,4'-bi(1,2,3-triazole)]N,N'-dioxide (28d). The general procedure 7.4.3.1 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (**9c**) (0.23 mmol, 61.0 mg). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 1:1). Yield: 50 mg (80 %). Mp >254 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 13H), 6.93 (d, *J* = 7.7 Hz, 3H), 1.67 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 138.8, 135.7, 131.3, 129.7, 129.3, 128.2, 123.6, 122.9, 118.6, 19.6. IR (cm^{-1}) 3068, 1494, 1459, 1392, 774. HRMS calculated for $C_{32}H_{28}N_6O_2$: 528.2274; found: 528.2270.

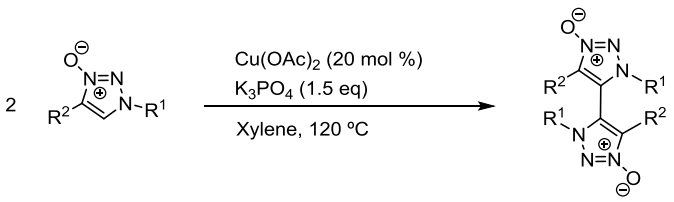


5,5'-Bis(2,6-dimethylphenyl)-1,1'-bis(4-methoxyphenyl)-1*H*,1'*H*-[4,4'-bi(1,2,3-triazole)] N,N'-dioxide (28e). The general procedure 7.4.3.1 was followed starting from 5-(2,6-dimethylphenyl)-1-methoxy-phenyl-1*H*-1,2,3-triazole 3-oxide (**9d**) (0.20 mmol, 60 mg). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 1:1). Yield: 45 mg (75 %). Mp >254 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 9.1 Hz, 4H), 6.92 (d, *J* = 7.7 Hz, 3H), 6.77 (d, *J* = 9.1 Hz, 4H), 3.77 (s, 6H), 1.67 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 138.9, 138.3, 130.9, 128.4, 127.8, 124.3, 123.4, 117.9, 114.4, 55.5, 19.3. IR (cm^{-1}) 1609, 1512, 1257, 826. HRMS calculated for $C_{34}H_{32}N_6O_4$: 588.2485; found: 588.2481.



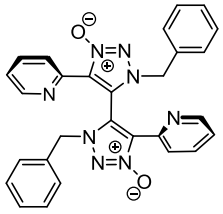
5,5'-Di-tert-butyl-1,1'-bis(4-methoxyphenyl)-1*H*, 1'*H*-[4,4'-bi(1,2,3-triazole)] N,N'-dioxide (28f). The general procedure 7.4.3.1 was followed starting from 5-(*tert*-butyl)-1-(4-methoxy-phenyl)-1*H*-1,2,3-triazole 3-oxide (**9g**) (0.08 mmol, 20 mg). The crude product was purified by column chromatography (CH_2Cl_2/Acetone 1:1). Yield: 12.0 mg (60 %). Mp 200.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 6H), 7.02 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 6H), 1.24 (s, 18H).^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 149.7, 129.9, 128.9, 118.0, 114.3, 55.7, 31.7, 29.7. IR (cm^{-1}) 3135, 1514, 1253, 1028, 846. HRMS calculated for $C_{26}H_{32}N_6O_4$: 492.2485; found: 247.1320.

7.4.3.2 General procedure for the synthesis of 5,5'-bistriazole N-oxides (29)

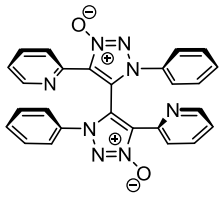


Triazole N-oxide (0,06 mmol), $Cu(OAc)_2$ (20 mmol %), K_3PO_4 (1.5 eq.) were solved in Xylene (0.1 mL) and the reaction mixture was heated between 120-140 ºC for 24 hours

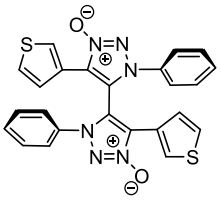
under oxygen atmosphere. Then, the mixture was cooled down and the solvent was filtered and evaporated under pressure. The crude was purified by column chromatography.



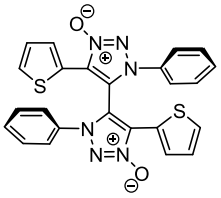
1,1'-Dibenzyl-4,4'-pyridil-1,2,3-bistriazole N-dioxide (29a). The general procedure 7.4.3.2 was starting from 1-benzyl,4-pyridil-1,2,3-triazole N-oxide (0.06 mmol, 15 mg) (**25a**) in xylene (0.2 mL) at 120 ºC. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 11 mg (65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dt, *J* = 4.9, 1.3 Hz, 2H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.78 (td, *J* = 7.8, 1.8 Hz, 2H), 7.42 – 7.21 (m, 12H), 5.75 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 144.2, 138.8, 138.2, 133.7, 128.8, 128.6, 128.4, 125.7, 125.1, 116.5, 53.6. IR (cm^{-1}) 3150, 3060, 1420, 705. HRMS calculated for $C_{28}H_{22}N_8O_2$: 502.1866; found: 502.1852.



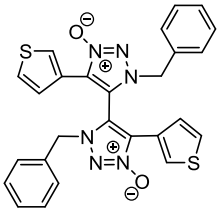
1,1'-Diphenyl-4,4'-pyridil-1,2,3-bistriazole N-dioxide (29b). The general procedure 7.4.3.2 was starting from 1-phenyl,4-pyridil triazole N-oxide (**25b**) (0.063 mmol, 15 mg) in xylene (0.2 mL) at 120 ºC. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 12 mg (80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.9, 1.6 Hz, 2H), 8.07 (d, *J* = 7.8 Hz, 2H), 7.81 (td, *J* = 7.8, 1.8 Hz, 2H), 7.48 – 7.31 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 144.2, 139.2, 137.6, 135.4, 129.6, 129.3, 125.7, 125.1, 125.0, 117.9. IR (cm^{-1}) 3060, 1415, 1035, 720. HRMS calculated for $C_{26}H_{18}N_8O_2$: 474.1553; found: 474.1553.



1,1'-Diphenyl-5,5'-di(thiophen-3-yl)-3*H*-3'*H*-[4,4'-bi(1,2,3-triazole)]-N-dioxide (29c). The general procedure 7.4.3.2 was starting from 1-phenyl-4-(thiophene-3-yl)-triazole N-oxide (**25e**) (0.04 mmol, 10 mg) in xylene (0.1 mL) at 140 ºC. The crude product was purified by column chromatography (CH_2Cl_2/Acetone 2:1). Yield: 7 mg (72 %). Mp 190 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.9 Hz, 2H), 7.52 – 7.45 (m, 6H), 7.44 – 7.40 (m, 4H), 7.29 – 7.26 (m, 2H), 6.83 – 6.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 135.1, 130.9, 130.4, 129.9, 129.6, 128.8, 127.2, 125.3, 123.9. IR (cm^{-1}) 3392, 3072, 1725, 1493, 1402, 695. HRMS calculated for $C_{24}H_{16}N_6O_2S_2$: 484.0776; found: 484.0782.



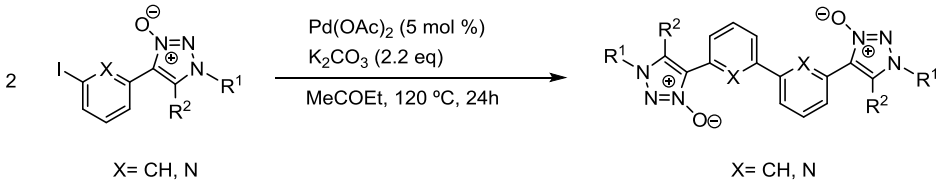
1,1'-Diphenyl-5,5'-di(thiophen-2-yl)-3*H*-3'*H*-[4,4'-bi(1,2,3-triazole)]-N-dioxide (29d). The general procedure 7.4.3.2 was starting from 1-phenyl-4-(thiophene-2-yl)-triazole N-oxide (**25f**) (0.04 mmol, 10 mg) in xylene (0.1 mL) at 140 ºC. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 8 mg (83 %). Mp 116 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 10H), 7.49 – 7.42 (m, 2H), 7.35 (dd, *J* = 3.8, 1.2 Hz, 2H), 7.05 (dd, *J* = 5.1, 3.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.8, 131.9, 130.5, 130.4, 129.6, 129.5, 128.1, 126.2, 123.6. IR (cm^{-1}) 3432, 3071, 1494, 1391, 683. HRMS calculated for $C_{24}H_{16}N_6O_2S_2$: 484.0776; found: 484.0780.



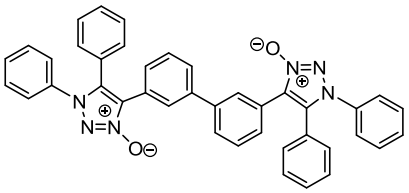
1,1'-Dibenzyl-5,5'-di(thiophen-3-yl)-3*H*-3'*H*-[4,4'-bi(1,2,3-triazole)]-N-dioxide (29e). The general procedure 7.4.3.2 was starting from 1-benzyl-4-(thiophene-3-yl)-triazole N-oxide (**25d**) (0.027 mmol, 7 mg) in xylene (0.1 mL) at 140 ºC. The crude

product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 5 mg (72 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.74 (s, 1H), 7.55 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.39 (ddd, *J* = 9.0, 4.9, 1.8 Hz, 5H), 7.20 (dt, *J* = 5.7, 3.5 Hz, 4H), 7.13 (ddd, *J* = 9.3, 5.0, 1.3 Hz, 2H), 5.43 (s, 2H), 5.32 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 129.5, 129.4, 129.0, 128.0, 127.7, 127.48, 127.4, 127.4, 125.2, 53.3. IR (cm^{-1}) 3050, 1710, 1402, 1076. HRMS calculated for $C_{26}H_{20}N_6O_2S_2$: 512.1089; found: 512.1100.

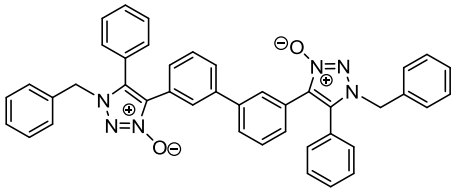
7.4.3.3 General procedure for the biaryl coupling (32)



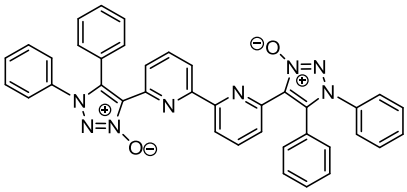
Following a reported procedure[199a], in which, a flame-dried Schlenk test tube with a magnetic stirring bar was charged with $Pd(OAc)_2$ (5 mol %), K_2CO_3 (2.2 equiv), aryl iodide (0.1 mmol) in 2-butanone (0.25 mL) and the reaction mixture was heated at 120 ºC for 24 hours under nitrogen atmosphere. The resulting mixture was diluted with CH_2Cl_2 and filtered through celite path. The crude was purified by column chromatography.



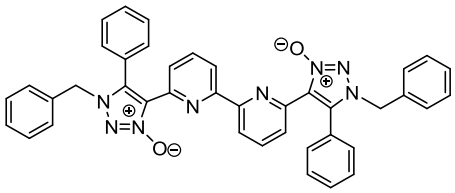
4,4'- (1,1'-Biphenyl)-3-3'diyl)bis(1,5-diphenyl)-1*H*-1,2,3-triazole N-oxide) (32a). The general procedure 7.4.3.3 was followed starting from 4-(2-iodophenyl)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**23o**) (0.034 mmol, 15 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 8 mg (80 %). Mp 97 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.54 – 7.31 (m, 22H), 7.23 (d, *J* = 7.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 135.8, 135.1, 130.7, 130.5, 130.0, 129.4, 129.4, 129.2, 128.9, 128.3, 128.2, 128.1, 125.3, 125.2, 125,0. IR (cm^{-1}) 3407, 1719, 1493, 1379, 693. HRMS calculated for $C_{40}H_{28}N_6O_2$: 624.2274; found: 624.2274.



4,4'- (1,1'-Dibenzyl)-3-3'diyl)bis(1,5-diphenyl)-1*H*-1,2,3-triazole N-oxide) (32b). The general procedure 7.4.3.3 was starting from 4-(2-iodophenyl)-1,benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**23p**) (0.034 mmol, 15 mg). The crude product was purified by column chromatography (EtOAc then CH_2Cl_2/MeOH 95:5). Yield: 10 mg (90 %). Mp 144.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.0 Hz, 2H), 7.56 – 7.47 (m, 9H), 7.36 – 7.32 (m, 6H), 7.29 – 7.23 (m, 7H), 7.17 (dd, *J* = 6.6, 3.0 Hz, 4H), 5.28 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 136.5, 133.9, 130.8, 130.0, 129.9, 129.5, 129.0, 128.9, 128.8, 128.7, 127.8, 127.6, 127.4, 125.3, 125.2, 52.6. IR (cm^{-1}) 3358, 1375, 696. HRMS calculated for $C_{42}H_{32}N_6O_2$: 652.2587; found: 652.2579.

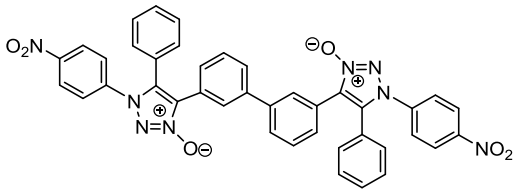


4,4'-[(2,2'-Bipyridine)-6,6'-diyl]bis(1,5-diphenyl-1*H*-1,2,3-triazole N-oxide) (32c). The general procedure 7.4.3.3 was starting from 4-(2-iodopyridil)-1,5-diphenyl-1*H*-1,2,3-triazole N-oxide (**23s**) (0.034 mmol, 15 mg). The crude product was purified by column chromatography (Acetone/CH_2Cl_2 1:2). Yield: 8 mg (76 %). Mp >200 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 7.8 Hz, 2H), 7.67 – 7.19 (m, 22H), 6.85 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 144.6, 137.5, 137.2, 134.9, 130.2, 129.7, 129.4, 129.3, 128.9, 128.8, 127.0, 125.3, 123.3, 120.4. IR (cm^{-1}) 3060, 1719, 1428, 703. HRMS calculated for $C_{38}H_{26}N_8O_2$: 626.2179; found: 626.2175.

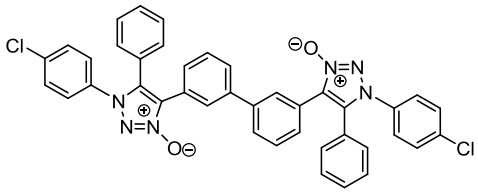


4,4'-[(2,2'-Bipyridine)-6,6'-diyl]bis(1,5-benzyl-1*H*-1,2,3-triazole N-oxide) (32d). The general procedure 7.4.3.3 was starting from 4-(2-iodopyridil)-1,5-dibenzyl-1*H*-1,2,3-triazole N-oxide (**23t**) (0.044 mmol, 20 mg). The crude product was purified by column

chromatography (EtOAc then, CH_2Cl_2/MeOH 95:5). Yield: 10 mg (77 %). Mp >190 ºC.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.66 – 7.58 (m, 3H), 7.50 (dt, *J* = 10.6, 7.8 Hz, 7H), 7.31 (dd, *J* = 5.4, 1.7 Hz, 8H), 7.17 – 7.09 (m, 4H), 6.63 (dd, *J* = 8.0, 1.0 Hz, 2H), 5.22 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 144.6, 137.9, 137.1, 133.7, 130.0, 129.9, 129.1, 128.9, 128.8, 128.4, 127.9, 127.1, 122.5, 120.1, 52.5. IR (cm^{-1}) 3031, 1591, 697. HRMS calculated for $C_{40}H_{30}N_8O_2$: 654.2492; found: 654.2492.

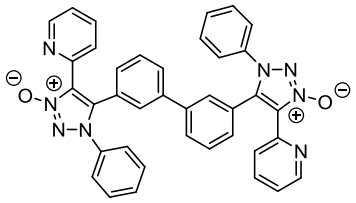


4,4'- (1,1'-Bi(4-nitrophenyl)-3-3'diyl)bis(1,5-diphenyl)-1*H*-1,2,3-triazole N-oxide) (32e). The general procedure 7.4.3.3 was starting from 4-(3-iodophenyl)-1,5-di(4-nitrophenyl)-1*H*-1,2,3-triazole N-oxide (**23q**) (0.044 mmol, 20 mg). The crude product was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5). Yield: 10 mg (80 %). Mp 167.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.24 (m, 4H), 7.84 (d, *J* = 1.7 Hz, 2H), 7.58 – 7.38 (m, 18H), 7.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 140.6, 139.7, 136.0, 131.2, 130.7, 130.0, 129.9, 129.0, 128.3, 128.3, 128.1, 124.9, 124.9, 124.8, 124.7. IR (cm^{-1}) 3077, 1593, 1339, 709. HRMS calculated for $C_{40}H_{26}N_8O_6$: 714.1975; found 714.1968.



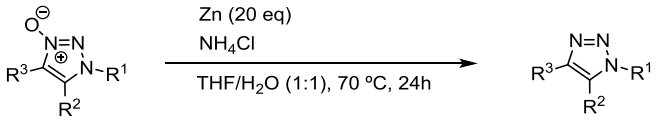
4,4'- (1,1'-Bi(4-chlorophenyl)-3-3'diyl)bis(1,5-diphenyl)-1*H*-1,2,3-triazole N-oxide (32f). The general procedure 7.4.3.3 was starting from 4-(3-iodophenyl)-1,5-di(4-chlorophenyl)-1*H*-1,2,3-triazole N-oxide (**23r**) (0.042 mmol, 20 mg). The crude product was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5). Yield: 12.6 mg (82 %). Mp >220 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (t, *J* = 1.8 Hz, 2H), 7.52 – 7.35 (m, 15H), 7.32 – 7.19 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 135.8, 135.4, 133.5, 130.9, 130.7, 129.9, 129.7, 129.5, 128.9, 128.8, 128.3, 128.2, 128.1, 126.2, 125.0.

IR (cm^{-1}) 3056, 1492, 1382, 718. HRMS calculated for $C_{40}H_{26}Cl_2N_6O_2$: 692.1494; found: 692.1491.

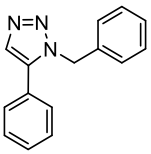


5,5'- [(1,1'-Biphenyl)-3,3'-diyl)]bis(1-benzyl-4-(pyridine-2-yl)1*H*-1,2,3-triazole N-oxide) (32g). The general procedure 7.4.3.3 was starting from 4-(3-iodophenyl)-1-benzyl-5-pyridil 1*H*-1,2,3-triazole N-oxide (**24r**) (0.033 mmol, 15 mg). The crude product was purified by column chromatography (EtOAc, then, CH_2Cl_2/MeOH 95:5). Yield: 13 mg (63 %). Mp 205 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.8 Hz, 2H), 7.89 (s, 2H), 7.75 (td, *J* = 7.8, 1.7 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.37 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 145.3, 140.6, 138.5, 137.3, 135.4, 134.8, 130.7, 130.1, 129.4, 129.3, 129.0, 128.5, 128.3, 126.1, 125.0, 124.9. IR (cm^{-1}) 3061, 1496, 1356, 678. HRMS calculated for $C_{38}H_{26}N_8O_2$: 626.2179; found: 626.2186.

7.4.4 General procedure for desoxygenation reaction (33)

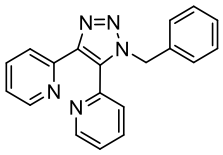


In a round bottom flask triazole N-oxide (1.0 mmol), zink powder (10 mmol, 650 mg) in NH_4Cl:THF (1:1, 14 mL) was added and the reaction mixture was heated at 70 ºC for 24 hours. After the complexion of the reaction, the reaction mixture was filtered through a celite path and extracted with CH_2Cl_2. The reaction mixture was dried and evaporated and in case of necessary, the crude was purified by column chromatography.

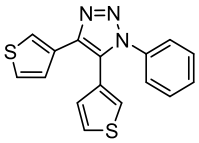


1-Benzyl-5-phenyl-1,2,3-triazole (33a).[57] The general procedure 7.4.4 was followed starting from 1-benzyl-5-phenyl-1*H*-1,2,3-triazole N-oxide (**9h**) (0.20 mmol, 50 mg). Yield: 42 mg (90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.38-7.48 (m, 3H),

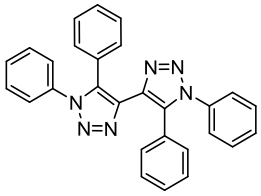
7.22-7.33 (m, 5H), 7.05-7.12 (m, 2H), 5.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 135.4, 133.2, 129.4, 128.9, 128.8, 128.7, 128.1, 127.1, 126.9, 51.8.



1-Benzyl-(4,5-bipyridil)-1,2,3-triazole (33b). The general procedure 7.4.4 was followed starting from 1-benzyl-(4,5-bipyridil)-1,2,3-triazole N-oxide (**26a**) (0.024 mmol, 8 mg). Yield: 6 mg (79 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (m, 1H), 8.53 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 6.7 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 6.6 Hz, 1H), 7.28 – 7.17 (m, 4H), 7.07 (dt, *J* = 8.1, 3.8 Hz, 2H), 5.87 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 149.5, 148.9, 147.3, 144.6, 137.1, 136.5, 135.1, 133.9, 128.5, 128.0, 127.7, 127.6, 126.9, 123.8, 123.0, 52.8. IR (cm^{-1}) 3417, 3053, 1587, 1422, 1007, 730. HRMS calculated for $C_{19}H_{15}N_3$: 313.1327; found: 313.1332.

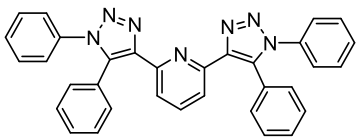


1-Phenyl-[4,5-(3-thiophene)]-1,2,3-triazole (33c). The general procedure 7.4.4 was followed starting from 1-phenyl-[4,5-(3-thiophene)]-1,2,3-triazole N-oxide (**26e**) (0.021 mmol, 7 mg). Yield: 6 mg (92 %). Mp 141.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.47 – 7.42 (m, 4H), 7.41 – 7.34 (m, 4H), 7.31 – 7.30 (m, 1H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 136.5, 131.5, 129.2, 129.1, 128.2, 127.1, 127.0, 126.5, 125.7, 124.8, 123.9, 122.2, 120.5. IR (cm^{-1}) 3097, 1495, 786. HRMS calculated for $C_{16}H_{11}N_3S_2$: 309.0394; found: 309.0400.

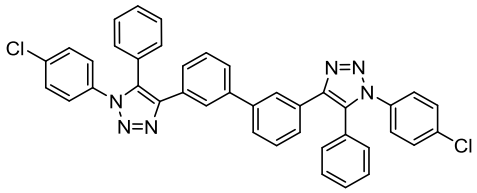


1,1',5,5'-Tetraphenyl-1*H*,1*H'*-4,4'-bi(1,2,3-triazole) (33d). The general procedure 7.4.4 was followed starting from 1,1',5,5'-tetraphenyl-1*H*,1*H'*-4,4'-bi(1,2,3-triazole N-oxide) (**28a**) (0.016 mmol, 8 mg). Yield: 6.0 mg (86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.40 (dt, *J* = 5.8, 3.1 Hz, 6H), 7.38 – 7.30 (m, 5H), 7.27 – 7.16 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.6, 136.5, 130.1, 129.2, 129.1, 129.0, 128.4, 126.4, 125.0. IR (cm^{-1}) 3057, 1592, 1495, 763. HRMS calculated for $C_{28}H_{20}N_6$: 440.1749; found: 440.1747.



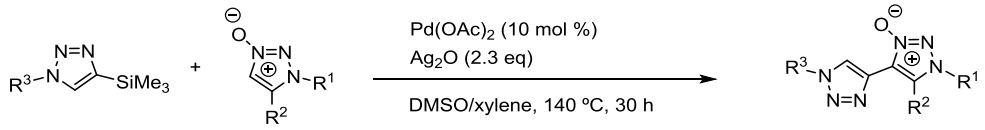
2,6-Bis(1,5-diphenyl-1,2,3-triazole-4-yl)pyridine (33e). The general procedure 7.4.4 was followed starting from 2,6-bis(1,5-diphenyl-1,2,3-triazole N-oxide-4-yl)pyridine (**23ab**) (0.016 mmol, 8.0 mg). Yield: 7.2 mg (85 %). Mp 115 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.76 (m, 2H), 7.65 – 7.55 (m, 2H), 7.49 – 7.37 (m, 7H), 7.37 – 7.26 (m, 6H), 7.25 – 7.20 (m, 3H), 7.19 – 7.12 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 131.0, 130.7, 129.9, 129.3, 129.2, 129.1, 128.4, 126.7, 125.3, 124.9, 122.1, 119.2. IR (cm^{-1}) 3500, 3059, 1496, 689. HRMS calculated for $C_{33}H_{23}N_7$: 517.2015; found: 517.2018.



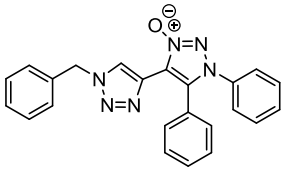
3,3'-Bis(1-(4-chlorophenyl)-5-phenyl-1*H*-1,2,3-triazol-4-yl)-1,1'-biphenyl (33f). The general procedure 7.4.4 was followed starting from compound **32f** (0.007 mmol, 5 mg). The crude was purified by column chromatography (Hex/EtOAc 1:1). Yield: 4.0 mg (87 %). Mp >240 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, *J* = 1.8 Hz, 2H), 7.53 – 7.42 (m, 8H), 7.42 – 7.37 (m, 6H), 7.37 – 7.30 (m, 6H), 7.28 – 7.25 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 140.9, 134.9, 134.9, 133.8, 130.9, 130.8, 130.1, 129.7, 129.4, 129.3, 128.9, 127.3, 126.6, 126.2, 126.1. IR (cm^{-1}) 3066, 1495, 994, 678. HRMS calculated for $C_{40}H_{26}Cl_2N_6$: 660.1596; found: 660.1598.

7.5 Experimental section of chapter 5

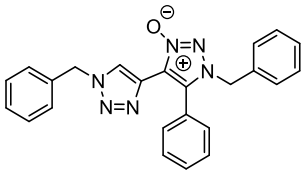
7.5.1 General procedure for the synthesis of polysubstituted 4,4'-bis(1*H*-1,2,3-triazole) N-oxides (34)



A mixture of the corresponding 1,5-disubstituted triazole N-oxide (0.06 mmol), 4-trimethylsilyl- triazole (0.06 mmol), $Pd(OAc)_2$ (0.006 mmol, 1.4 mg), Ag_2O (0.14 mmol, 32 mg) in DMSO/dioxane (1/5, 0.16 mL) was stirred at 140 ºC for 30 h in a sealed tube under nitrogen atmosphere. The mixture was diluted with CH_2Cl_2 and filtered through a pad of celite. The filtrate was evaporated and the resulting crude product was purified by column chromatography (EtOAc/Hex 1:1).

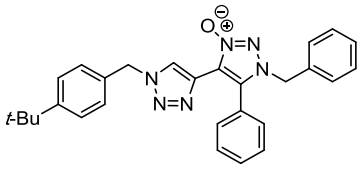


1'-Benzyl-1,5-diphenyl-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34a). The general procedure 7.5.1 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and 1-benzyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole (**3l**) (0.06 mmol, 13.9 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 13.0 mg (60 %). Mp 200.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.54 – 7.45 (m, 3H), 7.46 – 7.36 (m, 7H), 7.36 – 7.31 (m, 2H), 7.32 – 7.26 (m, 3H), 5.58 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 135.0, 134.8, 134.2, 130.8, 130.5, 129.4, 129.3, 129.1, 128.8, 128.6, 128.3, 125.2, 124.7, 124.2, 123.5, 54.3. IR (cm^1) 3148, 1410, 772, 862. HRMS calculated for $C_{23}H_{18}N_6O$: 394.1542; found: 394.1543.

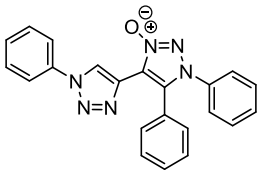


1,1'-Dibenzyl-5-phenyl-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)] N-oxide (34b). The general procedure 7.5.1 was followed starting from 1-benzyl-5-phenyl triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3l**) (0.06

mmol, 13.9 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 13.0 mg (60 %). Mp 168.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.62 – 7.49 (m, 3H), 7.45 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.39 – 7.25 (m, 8H), 7.14 – 7.08 (m, 2H), 5.54 (s, 2H), 5.26 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 134.9, 134.2, 133.8, 130.8, 130.5, 129.0, 128.9, 128.9, 128.8, 128.7, 128.2, 127.8, 124.6, 123.7, 122.9, 54.2, 52.5. IR (cm^{1}) 3146, 1399, 696. HRMS calculated for $C_{24}H_{20}N_6O$: 408.1699; found: 408.1703.

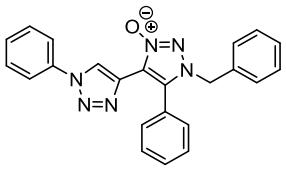


1-Benzyl-1'-[4-(tert-butyl)benzyl]-5-phenyl-1*H*,1'*H*-4,4'-bi(1,2,3-triazole) N-oxide (34c). The general procedure 7.5.1 was followed starting from 1-benzyl-5-phenyl-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 1-[4-(*tert*-butyl)benzyl]-4-trimethylsilyl-1*H*-1,2,3-triazole (**3q**) (0.06 mmol, 17 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 15 mg (56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.62 – 7.50 (m, 3H), 7.47 – 7.42 (m, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.28 (m, 3H), 7.27 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 5.50 (s, 2H), 5.25 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 135.8, 135.0, 133.9, 131.2, 130.7, 130.5, 128.9, 128.8, 128.7, 128.1, 127.7, 126.0, 124.7, 123.5, 122.8, 54.0, 52.4, 34.6, 31.2. IR (cm^{1}) 1433, 1051, 697. HRMS calculated for $C_{28}H_{28}N_6O$: 464.2325; found: 464.2325.

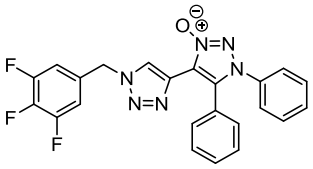


1,1',5-Triphenyl-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34d). The general procedure 7.5.1 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and 1-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3m**) (0.06 mmol, 13.0 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 12 mg (55 %). Mp >250 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.88 – 7.83 (m, 2H), 7.61 – 7.51 (m, 5H), 7.48 (td, *J* = 7.8, 1.6 Hz, 3H), 7.45 – 7.38 (m, 3H), 7.34 (dd, *J* = 8.1, 1.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 135.6, 135.2, 135.1, 130.8, 130.6, 129.8, 129.5, 129.4, 128.9, 128.7, 125.2, 124.7, 123.3, 122.0, 120.4. IR (cm^{-}

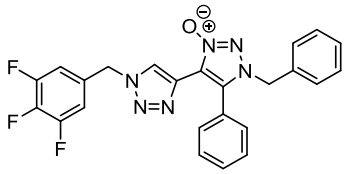
[1]) 2925, 1493, 1407, 750. HRMS calculated for $C_{22}H_{16}N_6O$: 380.1386; found: 380.1388.



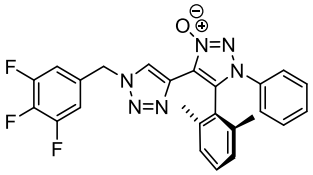
1-Benzyl-1',5'-diphenyl-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34e). The general procedure 7.5.1 was followed starting from 1-benzyl-5-phenyl-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 1-phenyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3m**) (0.06 mmol, 13.0 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 11.0 mg (50 %). Mp 202.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.67 – 7.30 (m, 11H), 7.16 (dd, *J* = 6.6, 2.9 Hz, 2H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 136.2, 135.4, 133.8, 130.9, 130.5, 129.8, 128.9, 128.9, 128.9, 128.8, 127.9, 124.6, 122.7, 121.5, 120.4, 52.7. IR (cm^1) 3133, 1420, 1037, 655. HRMS calculated for $C_{23}H_{18}N_6O$: 394.1542; found:394.1542.



1,5-Diphenyl-1'-(3,4,5-trifluorobenzyl)-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34f). The general procedure 7.5.1 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and 3,4,5-trifluorobenzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3p**) (0.06 mmol, 17 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 12.0 mg (50 %). Mp 202 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.63 – 7.18 (m, 10H), 7.11 – 6.84 (m, 2H), 5.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (ddd, $^1J_{CF}$ = 246.1 Hz, $^2J_{CF}$ = 10.1 Hz, $^3J_{CF}$ = 4.0 Hz), 139.8 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 15.2 Hz), 135.5, 135.3, 135.0, 130.8, 130.6, 129.5, 129.4, 128.6, 125.2, 124.9, 124.6, 124.3, 123.2, 112.1 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 7.8 Hz), 52.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ 132.09 (d, *J* = 20.2 Hz), -159.18 (t, *J* = 20.5 Hz). IR (cm^{-1}) 3064, 1530, 1408, 1043, 685. HRMS calculated for $C_{23}H_{15}F_3N_6O$: 448.1259; found: 448.1262.

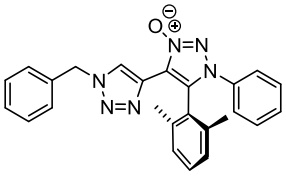


1-Benzyl-5'-phenyl-1'-(3,4,5-trifluorobenzyl)-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34g). The general procedure 7.5.1 was followed starting from 1-benzyl-5-phenyl-1,2,3-triazole N-oxide (**9h**) (0.06 mmol, 15 mg) and 3,4,5-trifluorobenzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3p**) (0.06 mmol, 17 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 11.0 mg (50 %). Mp >240 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.63 – 7.52 (m, 3H), 7.49 – 7.43 (m, 2H), 7.35 – 7.28 (m, 3H), 7.15 – 7.08 (m, 2H), 6.93 (t, *J* = 6.8 Hz, 2H), 5.49 (s, 2H), 5.27 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (ddd, $^1J_{CF}$ = 251.3 Hz, $^2J_{CF}$ = 10.1 Hz, $^3J_{CF}$ = 4.0 Hz), 139.9 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 15.2 Hz), 136.3, 135.9, 135.6, 133.8, 130.9, 130.4, 129.5, 129.1, 128.9, 128.8, 127.8, 124.6, 123.6, 112.1 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 7.8 Hz), 52.78, 52.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.16 (d, *J* = 20.2 Hz), -159.28 (t, *J* = 20.4 Hz). IR (cm^1) 1531, 1410, 1043, 696. HRMS calculated for $C_{24}H_{17}F_3N_6O$: 462.1416; found: 462.1431.



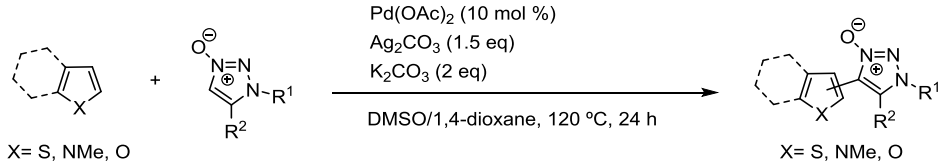
5-(2,6-Dimethylphenyl)-1-phenyl-1'-(3,4,5-trifluorobenzyl)-1*H*,3'*H*-3λ^4-[4,4'-bi(1,2,3-triazole)]-N-oxide (34h). The general procedure 7.5.1 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and 3,4,5-trifluorobenzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3p**) (0.06 mmol, 17 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 11.0 mg (50 %). Mp 170.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.41 – 7.32 (m, 4H), 7.30 (d, *J* = 1.7 Hz, 1H), 7.29 (d, *J* = 3.4 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.97 (dd, *J* = 7.4, 6.1 Hz, 2H), 5.50 (s, 2H), 2.08 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (ddd, $^1J_{CF}$ = 246.1 Hz, $^2J_{CF}$ = 10.1 Hz, $^3J_{CF}$ = 4.0 Hz), 139.0 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 15.2 Hz), 138.2, 135.4, 135.3, 134.0, 130.9, 130.1 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 15.2 Hz), 129.4, 129.2, 128.5, 128.0, 124.6, 123.7, 123.1, 112.1 (dd, $^2J_{CF}$ = 21.8 Hz, $^3J_{CF}$ = 7.8 Hz), 52.9, 20.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -132.09 (d, *J* = 20.3 Hz), -159.18 (t, *J* = 20.4 Hz). IR (cm^1) 3134, 1530, 1410, 1042, 750, 665. HRMS calculated for $C_{25}H_{19}F_3N_6O$:

448.1259; found: 448.1263.

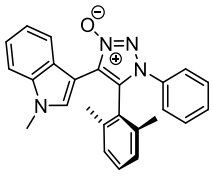


5-(2,6-Dimethylphenyl)-1-phenyl-1'-benzyl-1*H*,3'*H*-3λ⁴-[4,4'-bi(1,2,3-triazole)]-N-oxide (34i). The general procedure 7.5.1 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and 1-benzyl-4-trimethylsilyl-1*H*-1,2,3-triazole (**3l**) (0.06 mmol, 17 mg). The crude product was purified by column chromatography (Hex/EtOAc 1:1). Yield: 13.0 mg (50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.37 (m, 8H), 7.22 (m, 3H), 7.15 – 7.11 (m, 2H), 5.54 (s, 2H), 2.09 (s, 6H).

7.5.2 General procedure for CH activation of 1,5-disubstituted 1*H*-1,2,3-triazole N-oxides with heteroarenes (36)

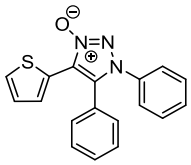


A mixture of the corresponding 1,5-disubstituted triazole (0.06 mmol), the heteroarene (0.09 mmol), $Pd(OAc)_2$ (0.006 mmol, 1.4 mg), Ag_2CO_3 (0.09 mmol, 24.8 mg), K_2CO_3 (0.3 mmol, 42 mg) in DMSO/dioxane (1/5, 0.15 mL) was stirred at 120 ºC for 24 h in a sealed tube under nitrogen atmosphere. The mixture was diluted with CH_2Cl_2 and filtered through a pad of celite. The filtrate was evaporated and the resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5).

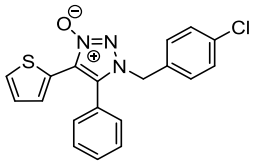


4-(1-Methyl-1*H*-indol-3-yl)-1-(phenyl)-5-(2,6-dimethylphenyl)-1,2,3-triazole N-oxide (36a). The general procedure 7.5.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and N-methylindole (0.09 mmol, 0.013 mL). The crude product was purified by column

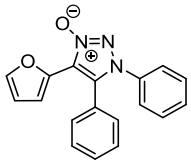
chromatography (CH_2Cl_2/MeOH 95:5). Yield: 16 mg (70 %). Mp >255 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.00 (s, 1H), 7.37 – 7.27 (m, 7H), 7.21 – 7.15 (m, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 3.83 (d, *J* = 2.5 Hz, 3H), 2.05 (d, *J* = 2.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 136.9, 136.4, 132.6, 131.1, 131.0, 129.6, 128.9, 128.5, 128.2, 126.3, 125.9, 123.4, 122.2, 120.6, 120.4, 109.6, 99.5, 33.5, 20.5. IR (cm^{-1}) 3060, 1628, 1493, 1391, 1311, 780, 748. HRMS calculated for $C_{25}H_{22}N_4O$: 394.1794; found: 394.1796.



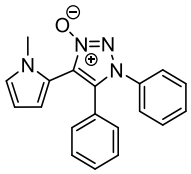
1,5-Diphenyl-4-(thiophen-3-yl)-1,2,3-triazole N-oxide (36b). The general procedure 7.5.2 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg), thiophene (0.09 mmol, 0.01 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 10 mg (66 %). Mp 227.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 3H), 7.46 – 7.26 (m, 9H), 7.01 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4, 133.7, 131.2, 130.7, 129.9, 129.6, 129.6, 127.6, 126.7, 126.3, 126.1, 125.9, 125.2, 77.6. IR (cm^{-1}) 3087, 1589, 1493, 1390, 746, 688. HRMS calculated for $C_{18}H_{13}N_3OS$: 319.0779; found: 319.0780.



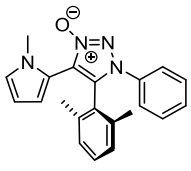
1-(4-Chlorobenzyl)-5-phenyl-4-(thiophen-3-yl)-1,2,3-triazole N-oxide (36c). The general procedure 7.5.2 was followed starting from 1-(4-chlorobenzyl)-5-phenyl-1,2,3-triazole N-oxide (**9i**) (0.06 mmol, 15 mg) and thiophene (0.09 mmol, 0.01 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 13 mg (66 %). Mp 102.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dq, *J* = 21.1, 7.2, 6.8 Hz, 3H), 7.31 (dt, *J* = 20.5, 7.1 Hz, 5H), 7.21 – 6.62 (m, 4H), 5.16 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 134.0, 132.6, 131.6, 130.5, 130.1, 129.6, 129.4, 127.2, 126.7, 126.4, 126.2, 125.7, 125.4, 52.1. IR (cm^{-1}) 2234, 1492, 1409, 720, 705. HRMS calculated for $C_{19}H_{14}ClN_3OS$: 367.0546; found: 367.0541.



4-(Furan-2-yl)-1,5-diphenyl-1,2,3-triazole N-oxide (36d). The general procedure 7.5.2 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and furane (0.017 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 14.4 mg (73 %). Mp 162.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.00 (m, 12H), 6.56 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 140.8, 135.4, 134.1, 130.8, 130.6, 129.6, 129.6, 128.9, 125.5, 125.4, 123.9, 112.7, 111.7. IR (cm^{-1}) 3051, 1494, 1371, 761, 701. HRMS calculated for $C_{18}H_{13}N_3O_2$: 303.108; found: 304.1081.

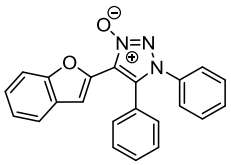


4-(1-Methylpyrrole-2-yl)-1,5-diphenyl-1,2,3-triazole N-oxide (36e). The general procedure 7.5.2 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and 1-methylpyrrole (0.09 mmol, 0.009 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 13 mg (86 %). Mp 199.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (ddt, *J* = 7.0, 5.1, 2.4 Hz, 3H), 7.39 (t, *J* = 1.3 Hz, 1H), 7.36 – 7.33 (m, 3H), 7.31 (d, *J* = 1.2 Hz, 1H), 7.22 – 7.06 (m, 2H), 6.80 (t, *J* = 2.1 Hz, 1H), 6.24 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.17 (dd, *J* = 3.8, 2.7 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 135.7, 130.5, 129.9, 129.7, 129.6, 129.2, 125.4, 125.3, 116.2, 114.5, 113.7, 108.7, 107.8, 35.4. IR (cm^{-1}) 2224, 1596, 1424, 1408, 767, 667. HRMS calculated for $C_{19}H_{16}N_4O$: 316.1324: found: 316,1327.

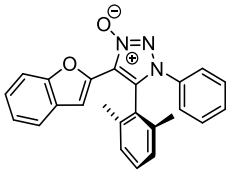


5-(2,6-Dimethylphenyl)-4-(1-methylpyrrole-2-yl)-1-phenyl-1,2,3-triazole N-oxide (36f). The general procedure 7.5.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1*H*-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and 1-methylpyrrole (0.09 mmol, 0.009 mL). The crude product was purified by column chromatography

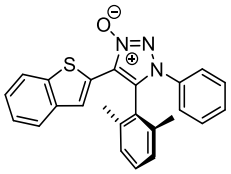
(CH_2Cl_2/MeOH 95:5). Yield: 17 mg (88 %). Mp 198.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.31 – 7.25 (m, 4H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.86 – 6.74 (m, 1H), 6.13 – 6.00 (m, 1H), 5.97 (dd, *J* = 3.8, 1.8 Hz, 1H), 3.81 (d, *J* = 2.2 Hz, 3H), 2.05 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 136.3, 136.1, 130.9, 129.7, 129.2, 128.4, 126.0, 125.6, 125.1, 123.0, 116.2, 113.2, 108.7, 35.6, 20.3. IR (cm^{-1}) 2921, 2211, 1493, 1424, 727. HRMS calculated for $C_{21}H_{20}N_4O$: 344.1637; found: 344.1638.



4-(Benzofuran-3-yl)-1,5-diphenyl-1,2,3-triazole N-oxide (36g). The general procedure 7.5.2 was followed starting from 1,5-diphenyl-1,2,3-triazole N-oxide (**9a**) (0.06 mmol, 15 mg) and benzofurane (0.09 mmol, 0.01 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 17 mg (80 %). Mp 201.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.03 (s, 1H), 7.69 – 7.66 (m, 1H), 7.54 (t, *J* = 6.8 Hz, 1H), 7.48 – 7.22 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 142.7, 135.3, 130.9, 130.8, 129.7, 129.7, 129.3, 129.1, 129.1, 128.8, 128.2, 125.5, 123.6, 122.1, 121.4, 111.3, 108.7. IR (cm^{-1}) 3055, 1590, 1492, 1418, 761. HRMS calculated for $C_{22}H_{15}N_3O_2$: 353.120; found: 354.1240.



4-(Benzofuran-3-yl)-5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (36h). The general procedure 7.5.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg), benzofurane (0.09 mmol, 0.011 mL). The product was purified by (CH_2Cl_2/MeOH 95:5). Yield: 16 mg (69 %). Mp >180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 5.7 Hz, 1H), 7.73 – 7.57 (m, 1H), 7.49 – 6.97 (m, 11H), 2.31 – 1.87 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 142.8, 138.7, 135.7, 133.6, 131.1, 129.7, 129.5, 129.1, 128.7, 128.2, 125.4, 125.3, 123.6, 123.4, 122.1, 111.4, 108.1, 20.5. IR (cm^{-1}) 3066, 2957, 1724, 1493, 1421, 1251, 750. HRMS calculated for $C_{24}H_{19}N_3O_2$: 381.1477; found: 381.1481.

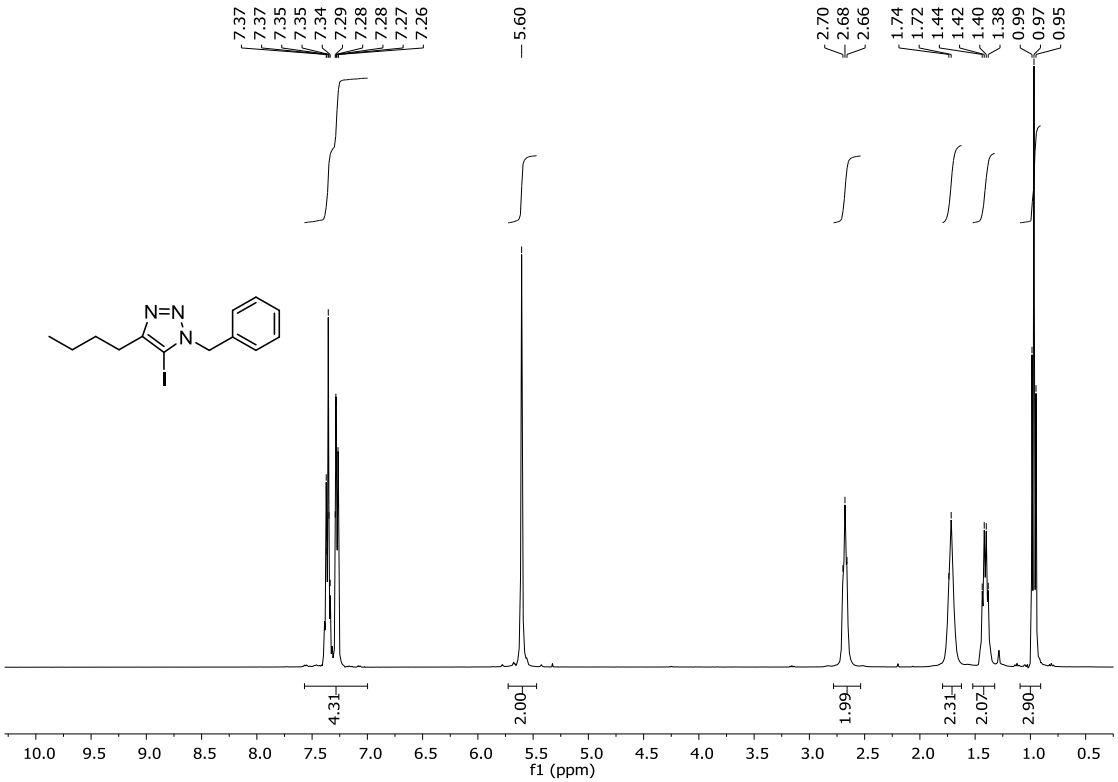


4-(Benzo[*b*]thiohen-3-yl)-5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (36i). The general procedure 7.5.2 was followed starting from 5-(2,6-dimethylphenyl)-1-phenyl-1,2,3-triazole N-oxide (**9c**) (0.06 mmol, 15 mg) and benzothiophene (0.02 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 17.5 mg (76 %). Mp 204.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 1H), 7.81 – 7.77 (m, 1H), 7.76 – 7.71 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.40 – 7.30 (m, 7H), 7.25 (d, *J* = 7.7 Hz, 2H), 2.11 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 138.8, 138.7, 135.4, 133.1, 131.6, 129.5, 129.2, 128.6, 126.3, 125.9, 125.0, 124.6, 124.5, 124.0, 122.9, 122.5, 121.9, 19.9. IR (cm^{-1}) 3060, 1591, 1458, 752. HRMS calculated for $C_{24}H_{19}N_3OS$: 397.1249; found: 397.1251.

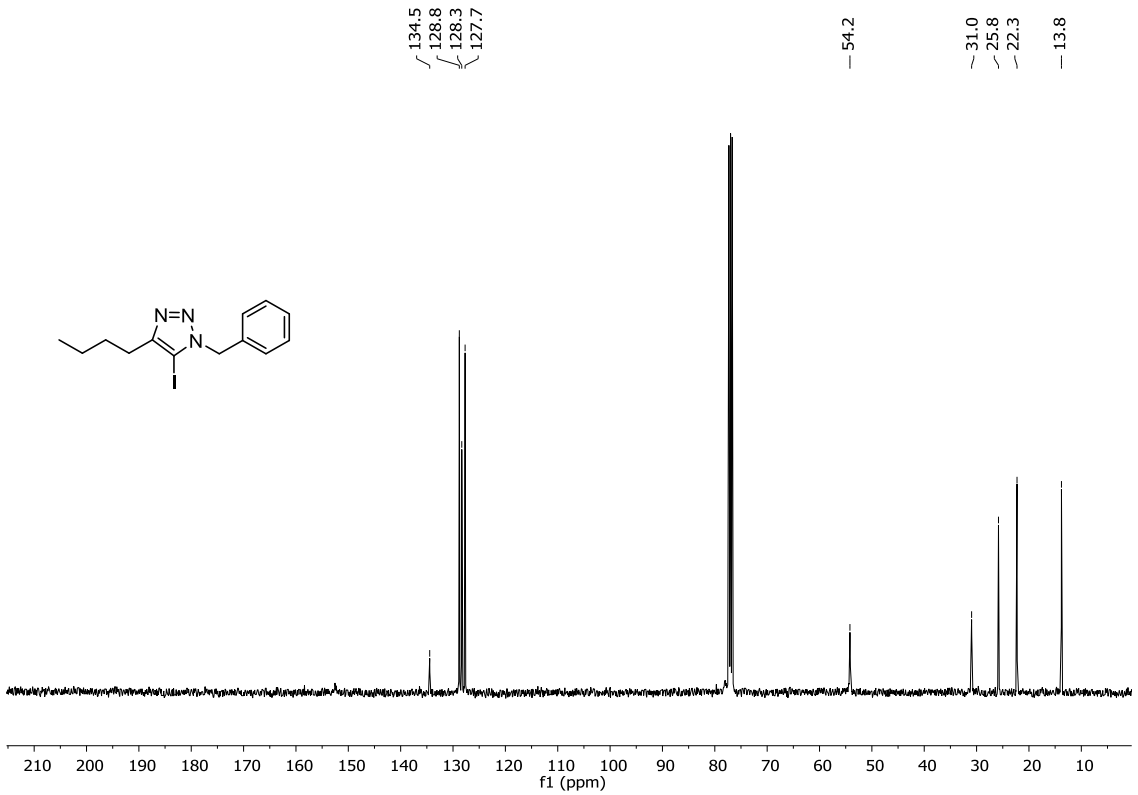
8

APPENDIX

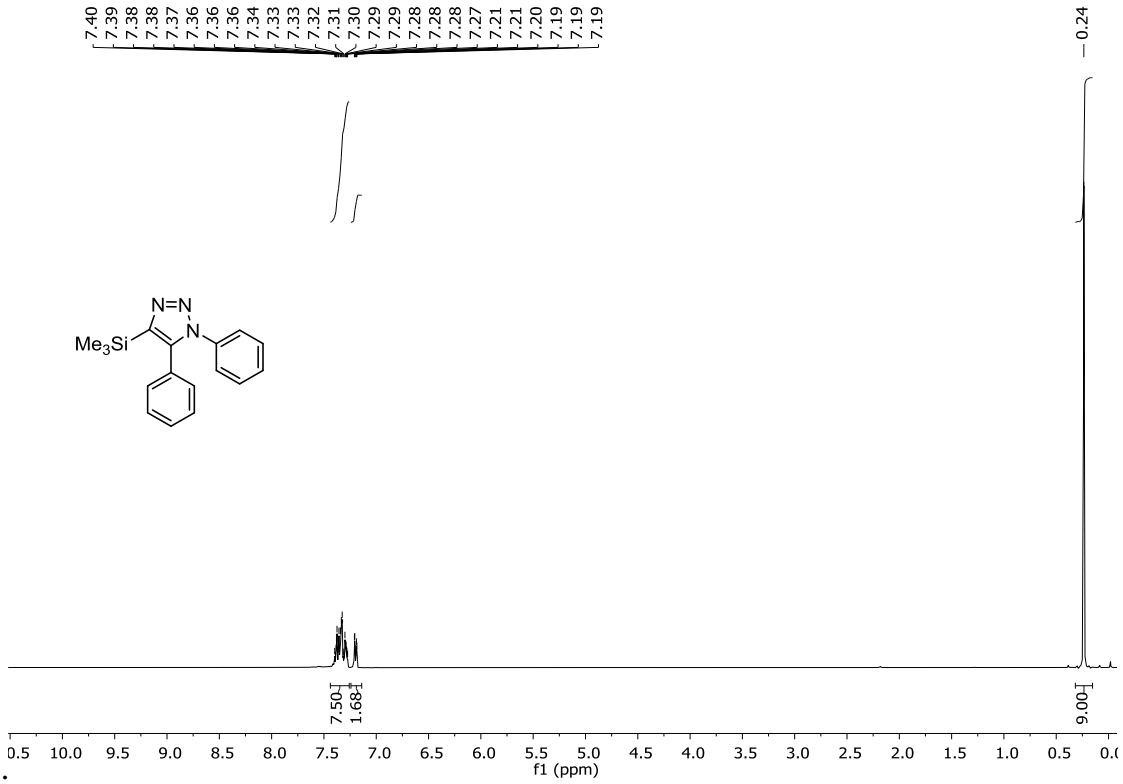
APPENDIX 1: ^{1}H NMR and ^{13}C NMR Spectra



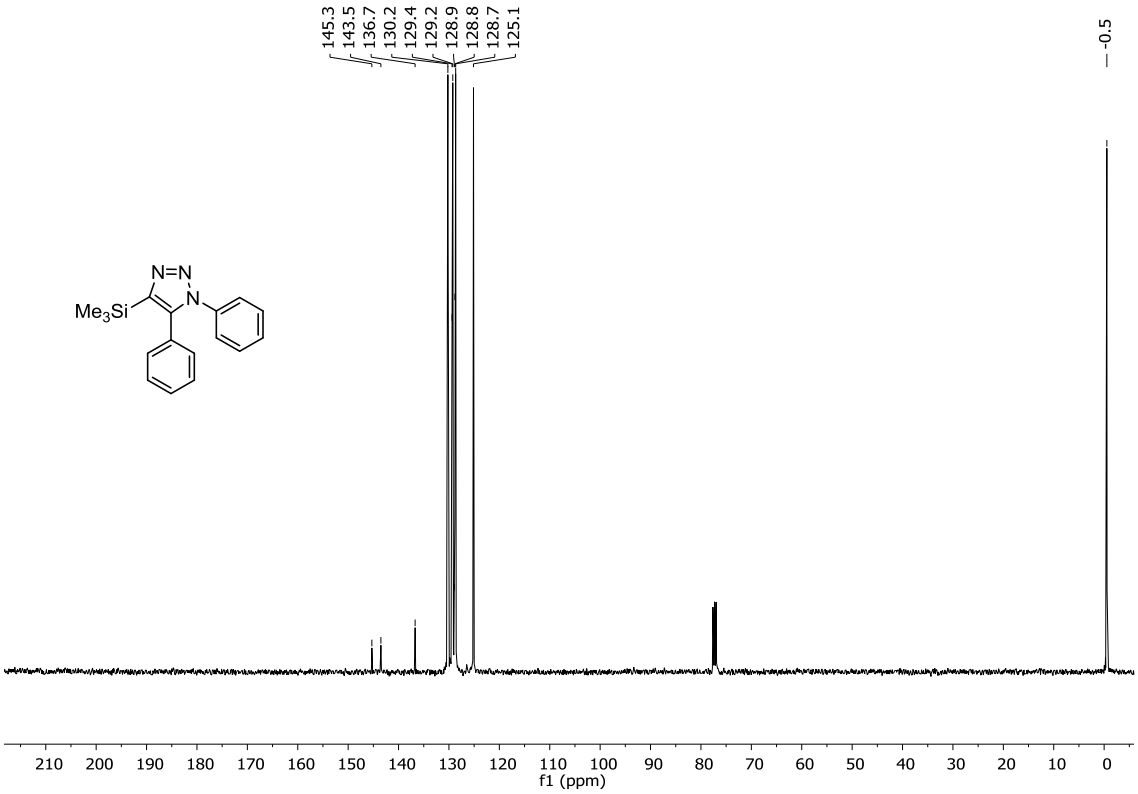
Spectrum 8.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3j**.



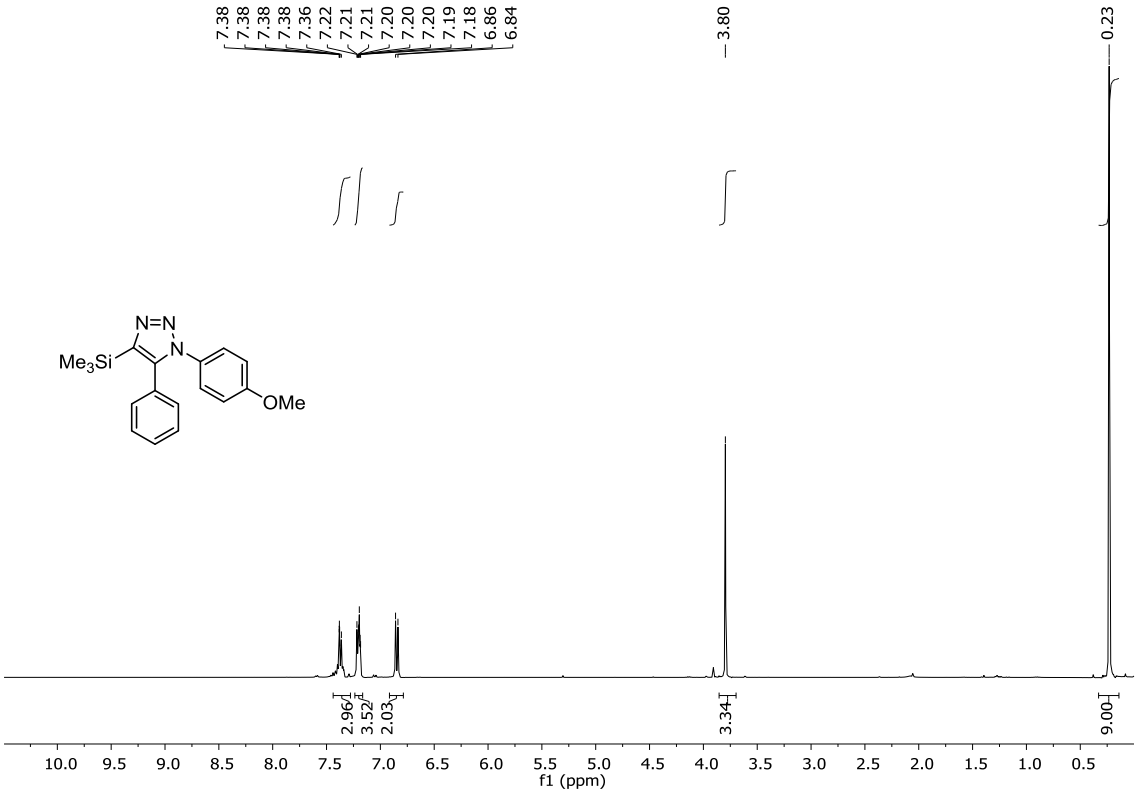
Spectrum 8.2. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3j**.



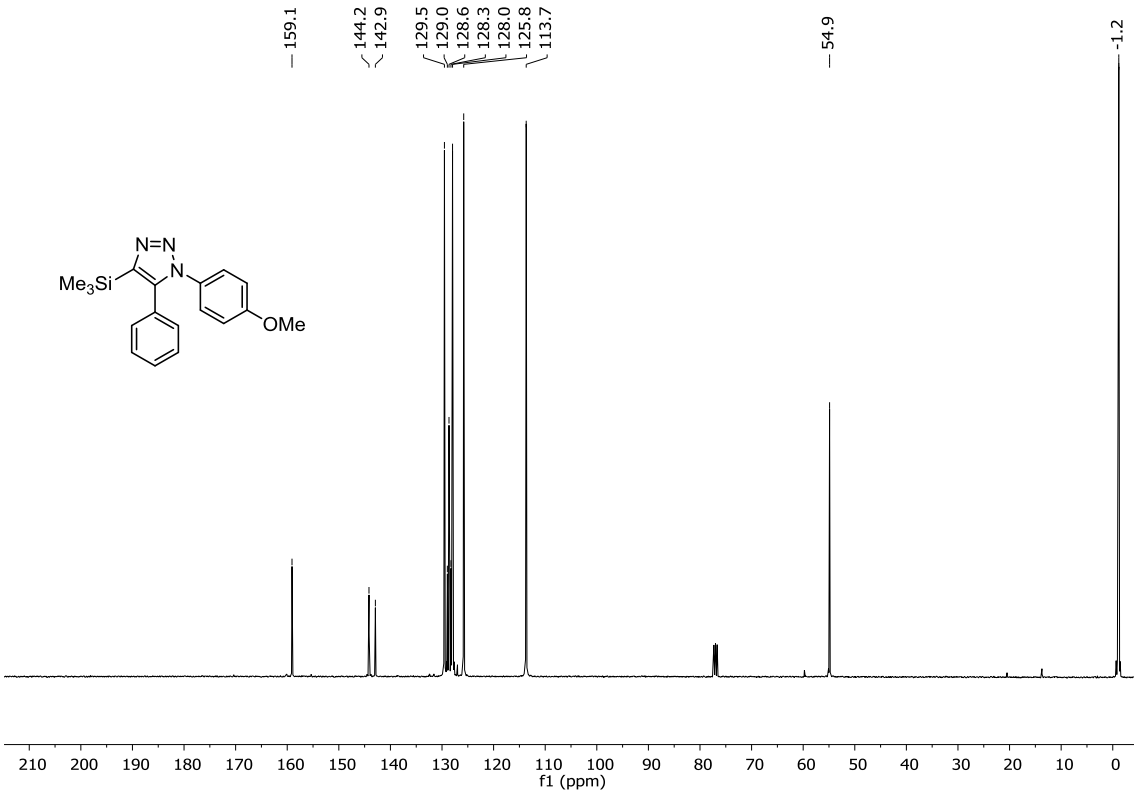
Spectrum 8.3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8a**.



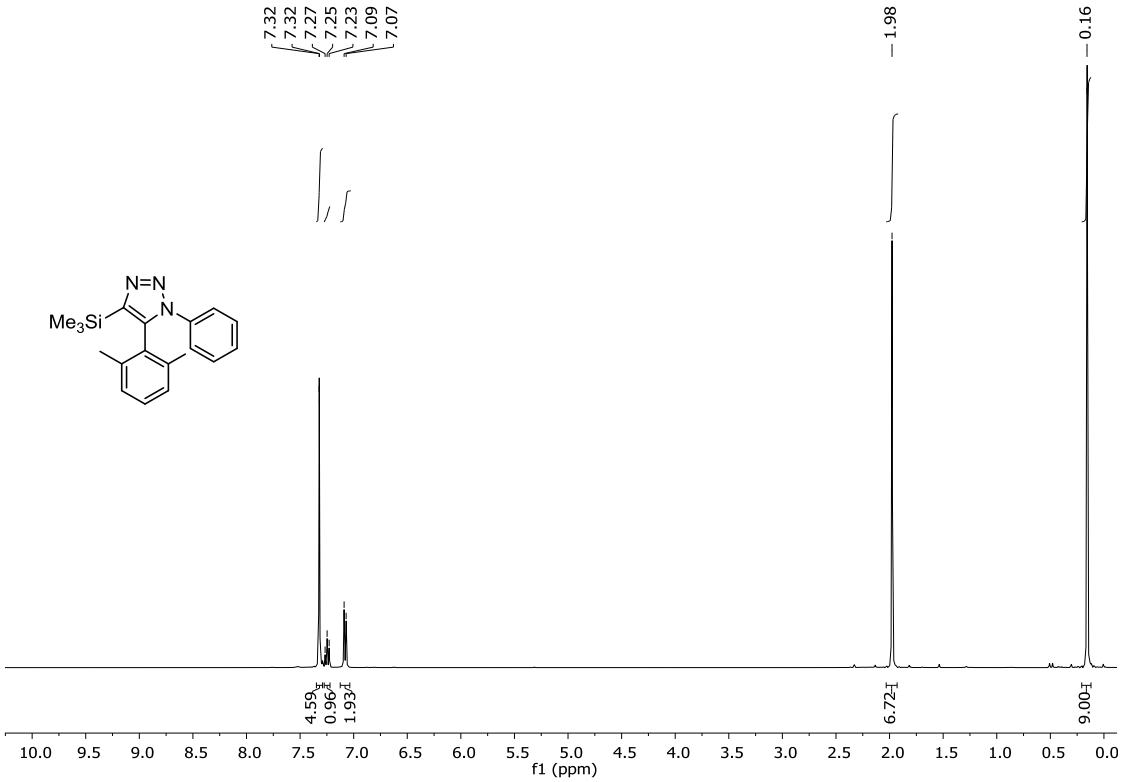
Spectrum 8.4. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8a**.



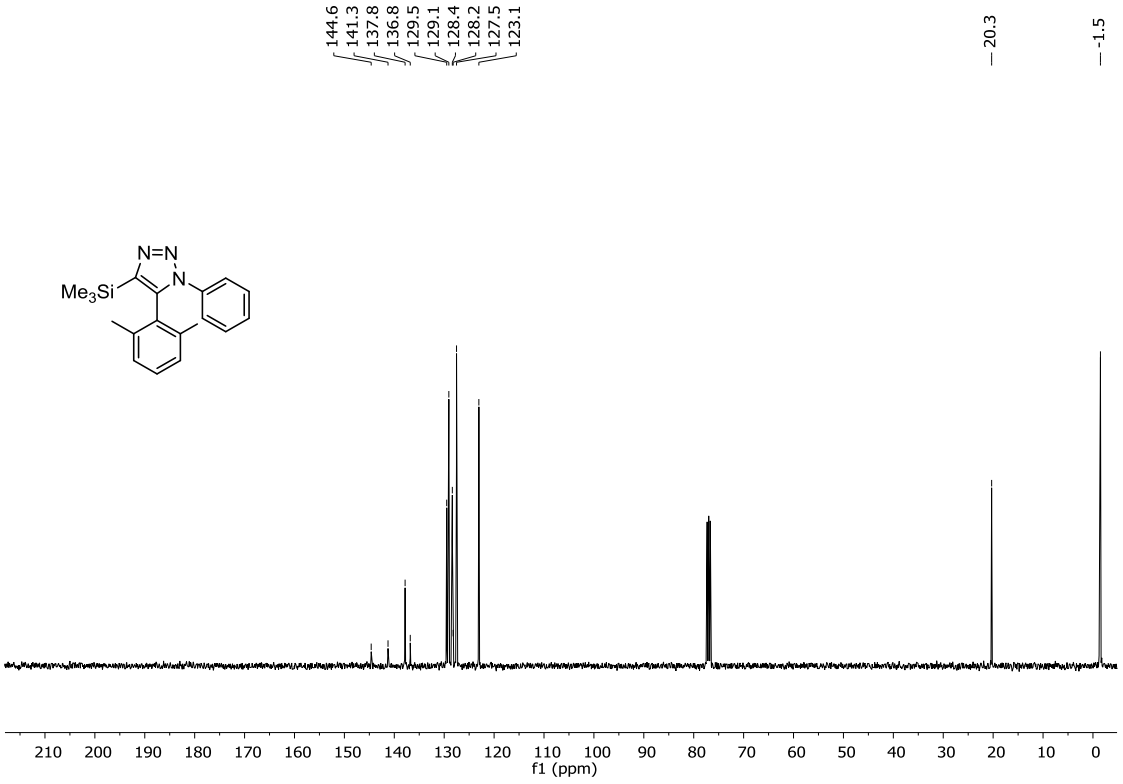
Spectrum 8.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8b**.



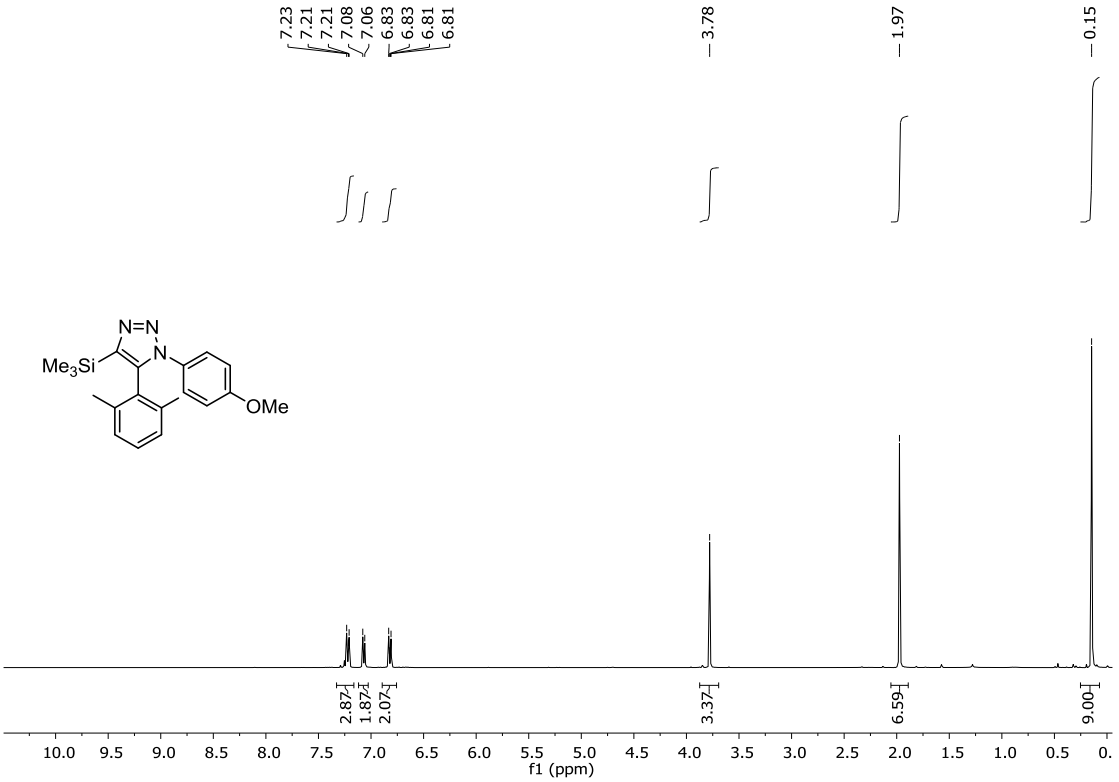
Spectrum 8.6. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8b**.



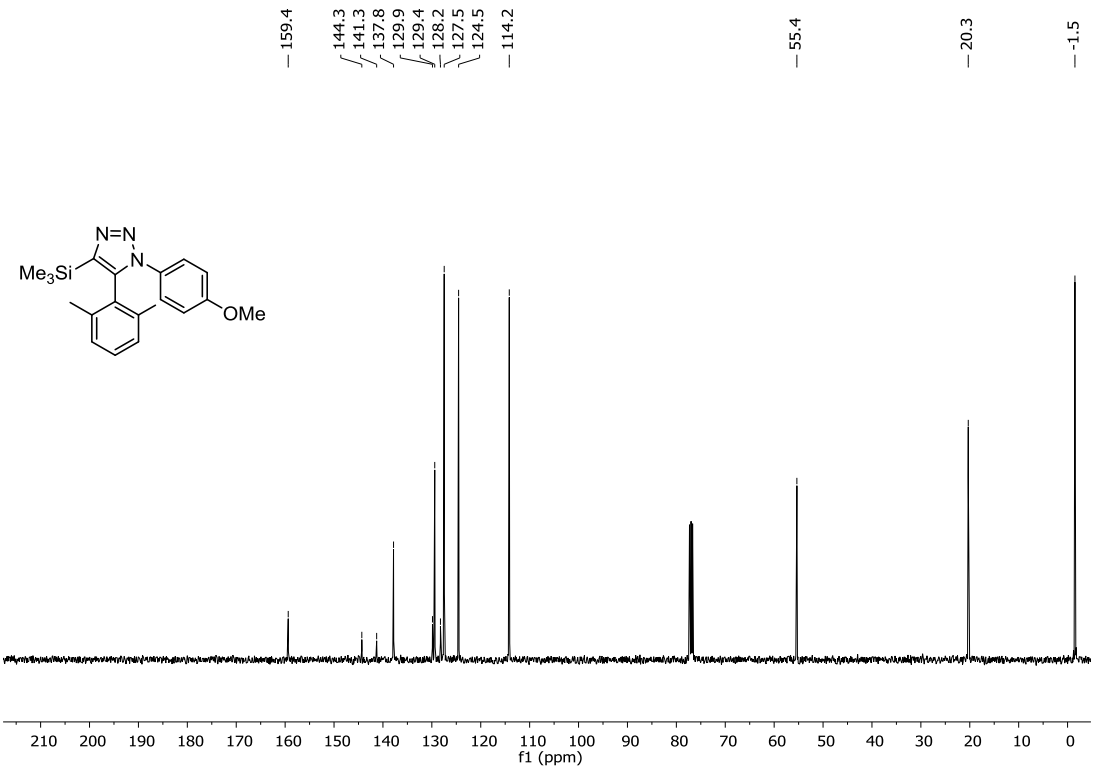
Spectrum 8.7. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8c**.



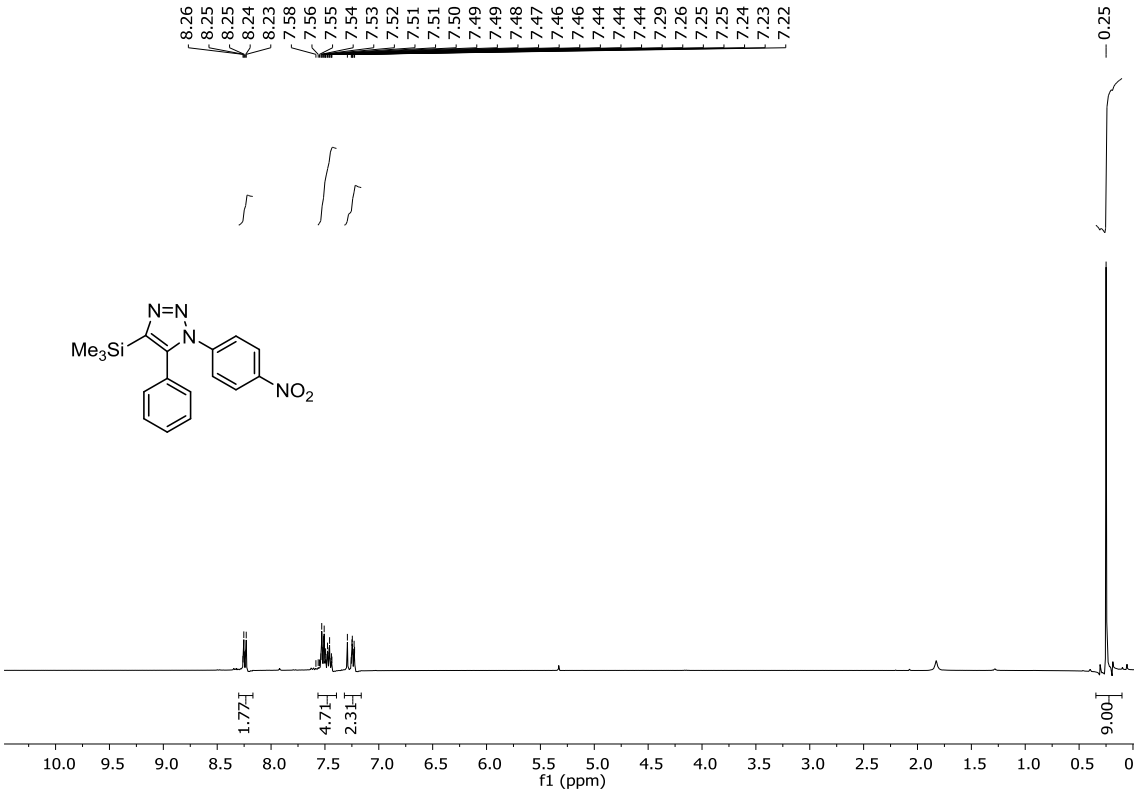
Spectrum 8.8. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8c**.



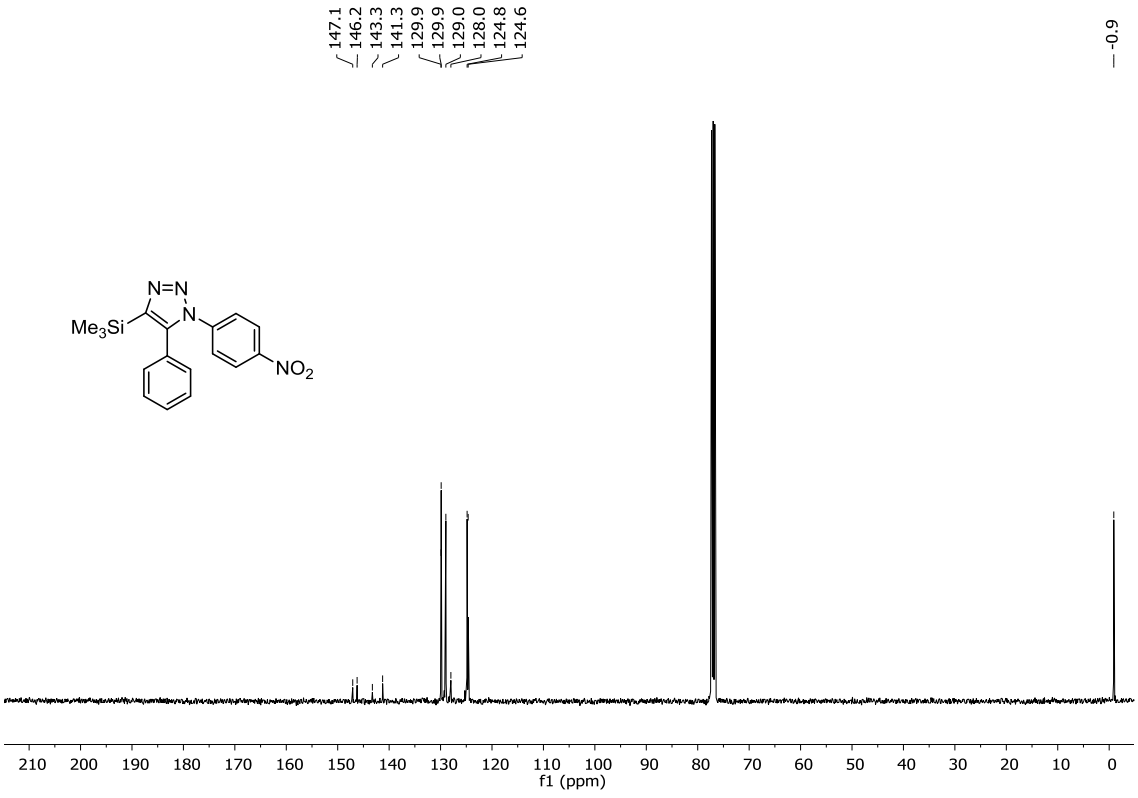
Spectrum 8.9. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8d**.



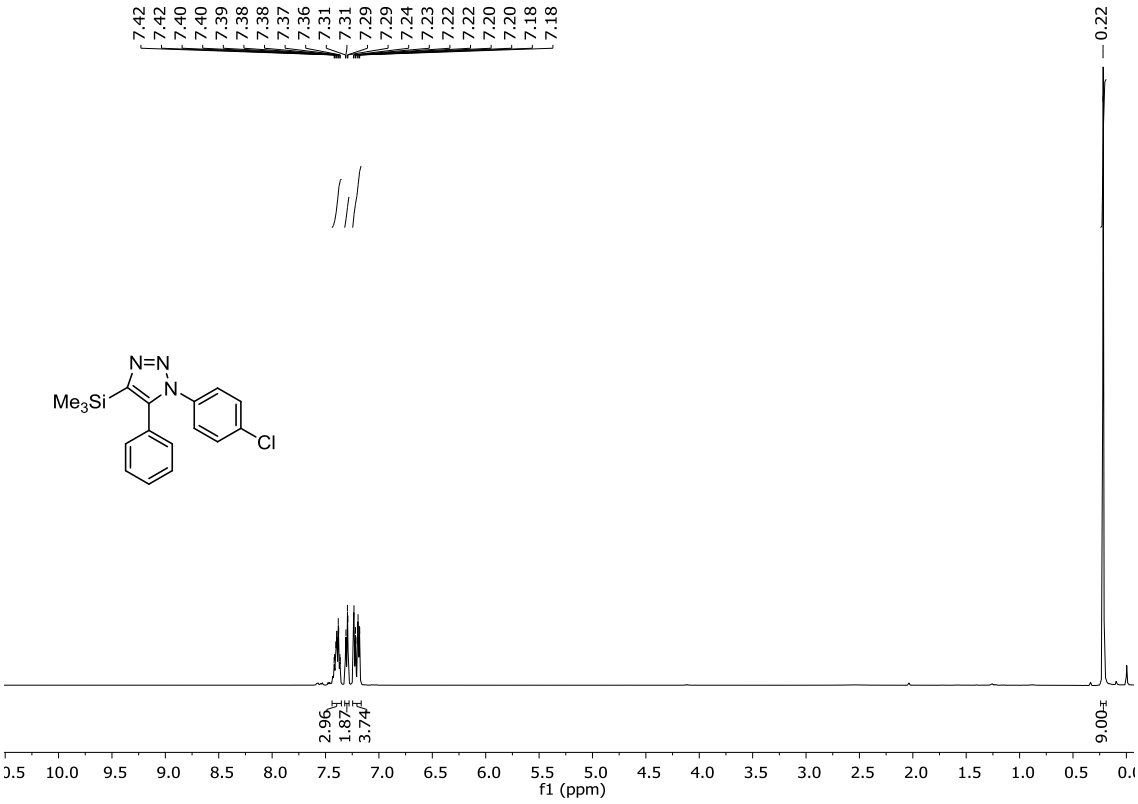
Spectrum 8.10. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8d**.



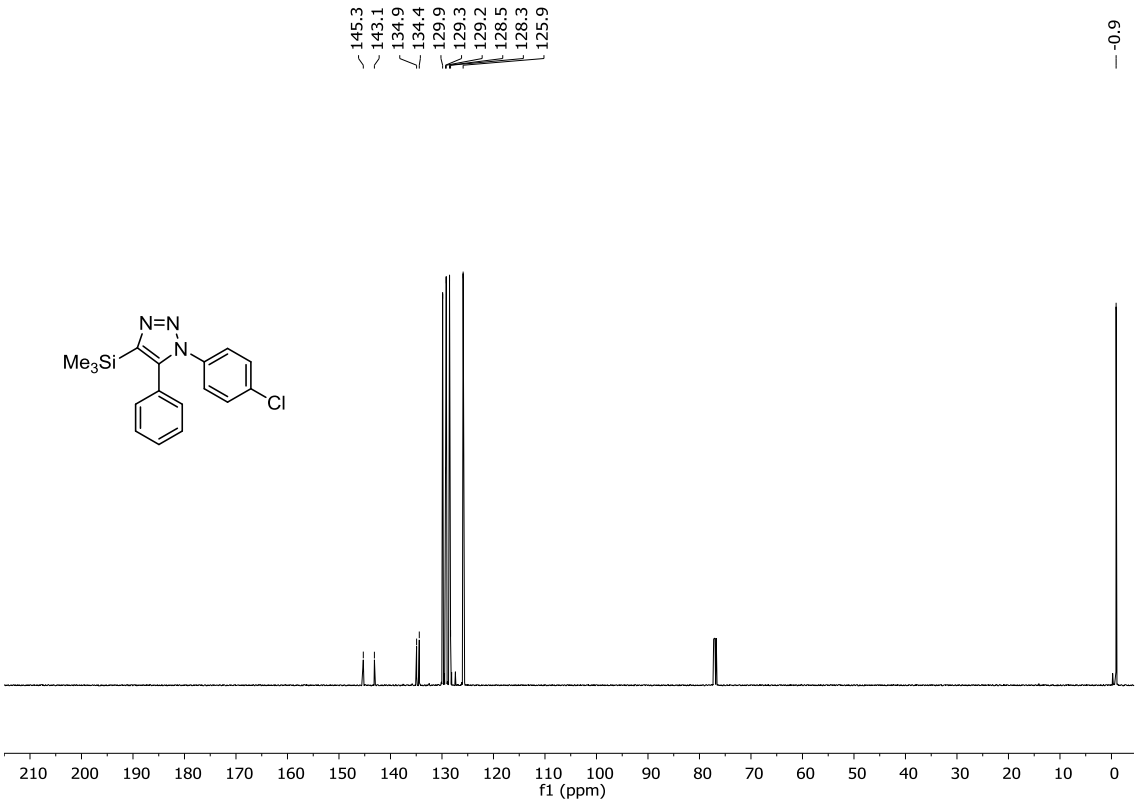
Spectrum 8.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8e**.



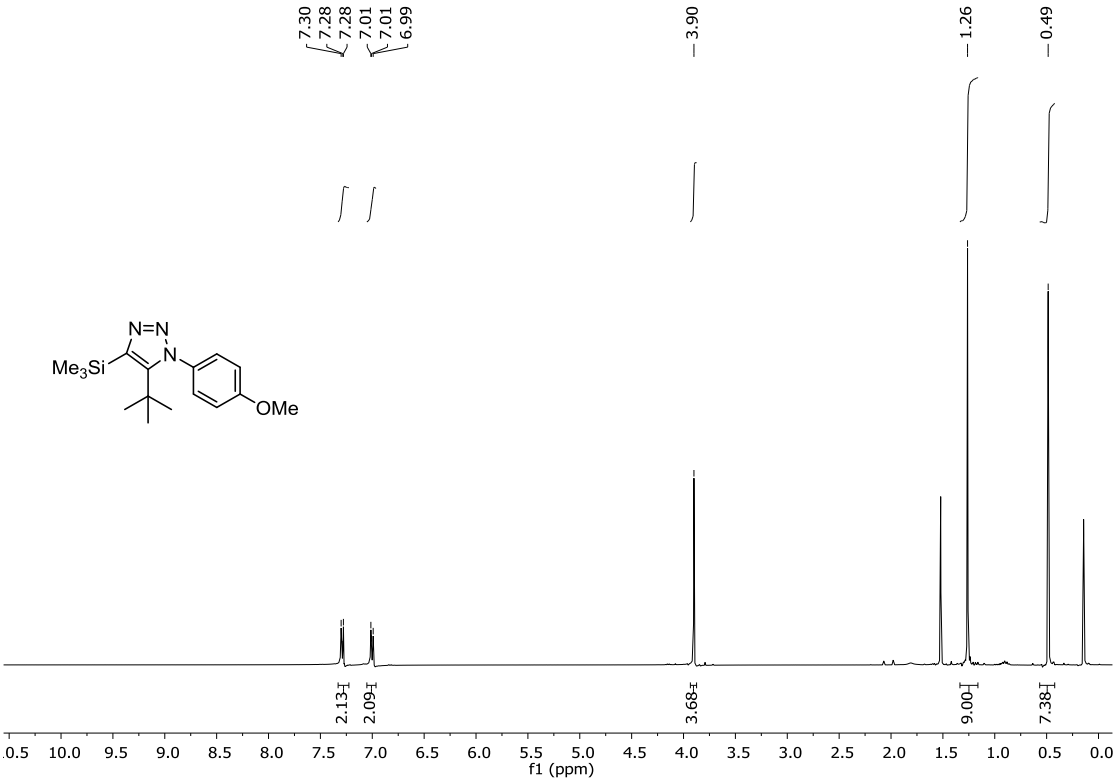
Spectrum 8.12. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8e**.



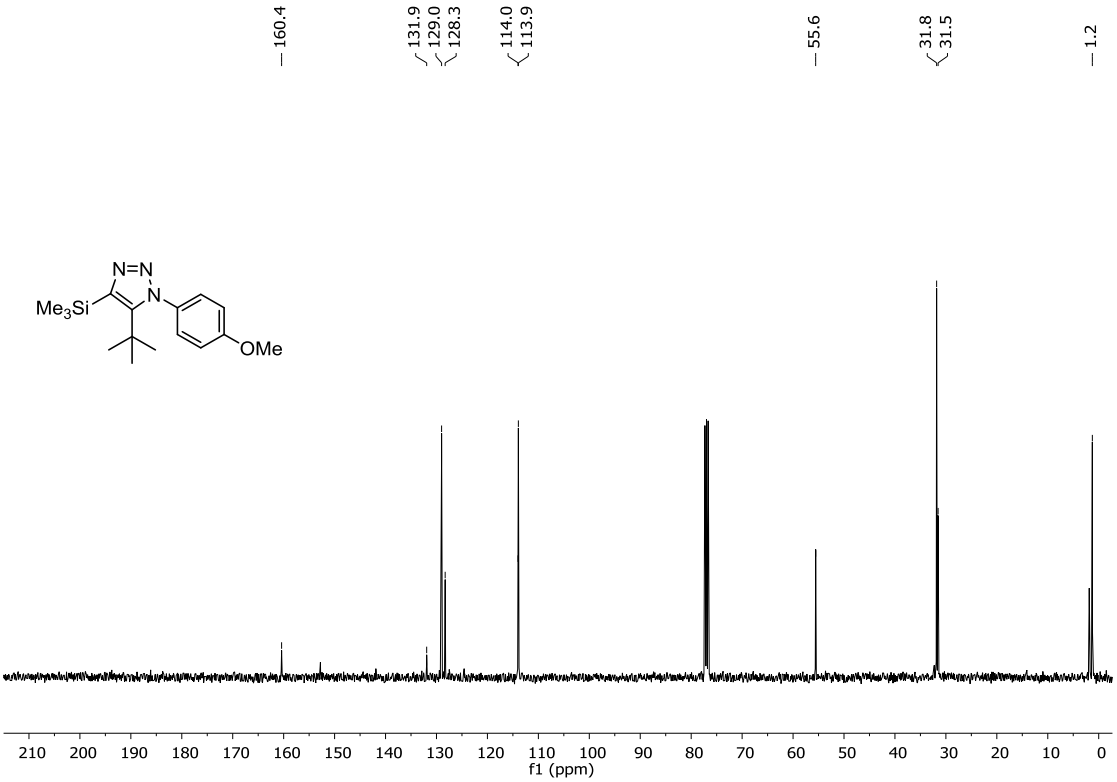
Spectrum 8.13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8f**.



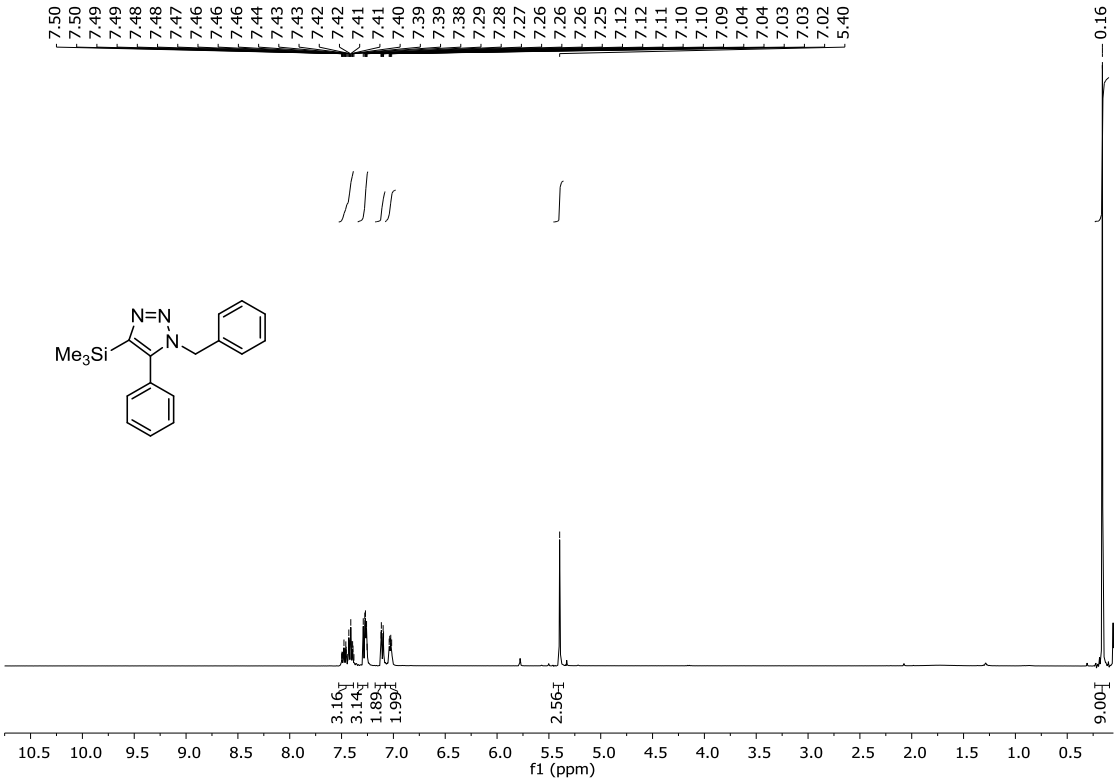
Spectrum 8.14. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8f**.



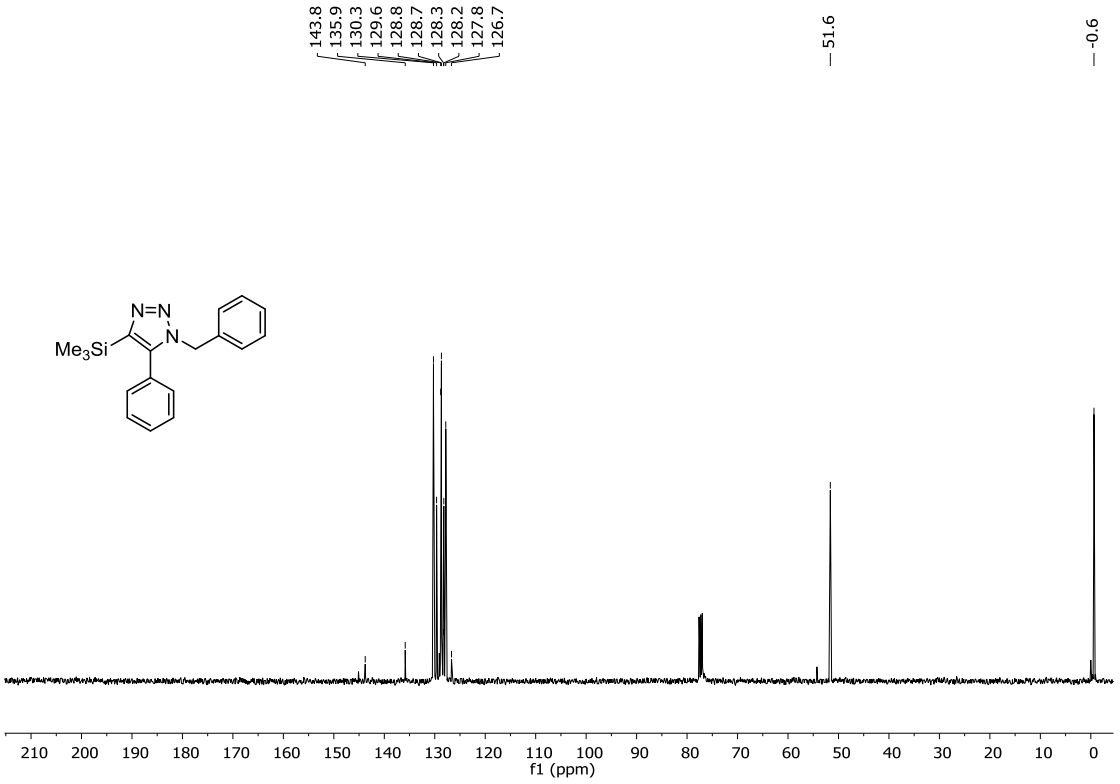
Spectrum 8.15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8g**.



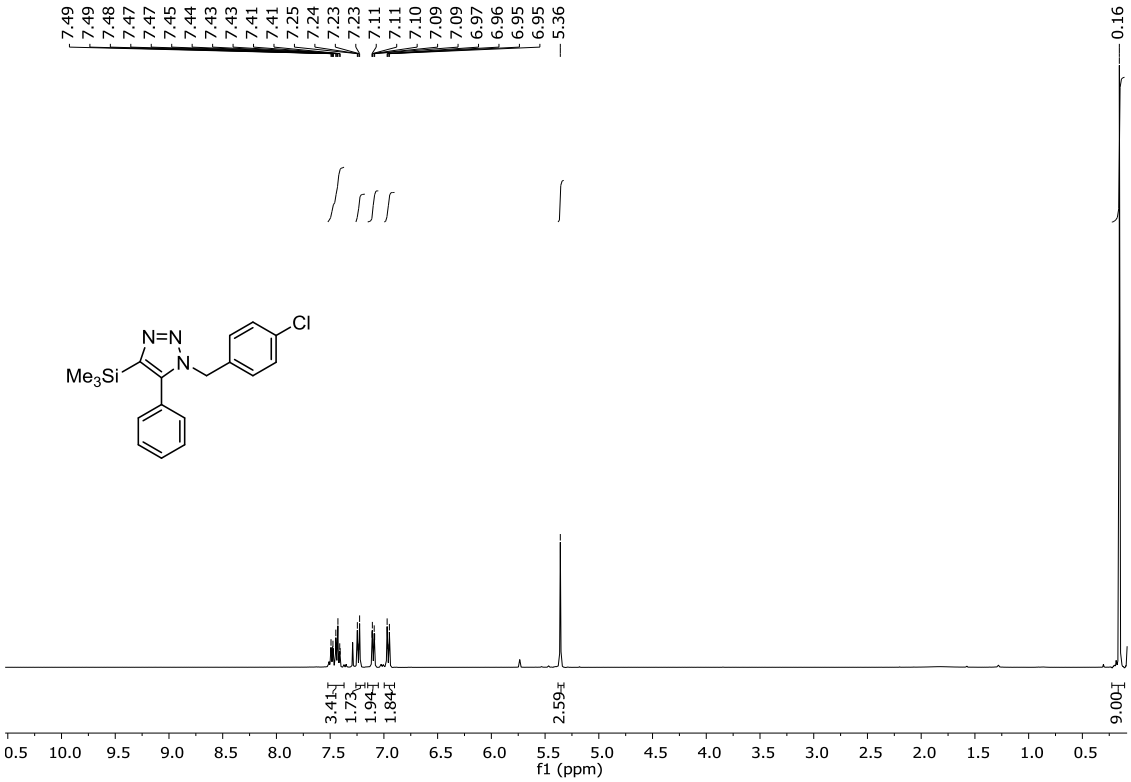
Spectrum 8.16. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8g**.



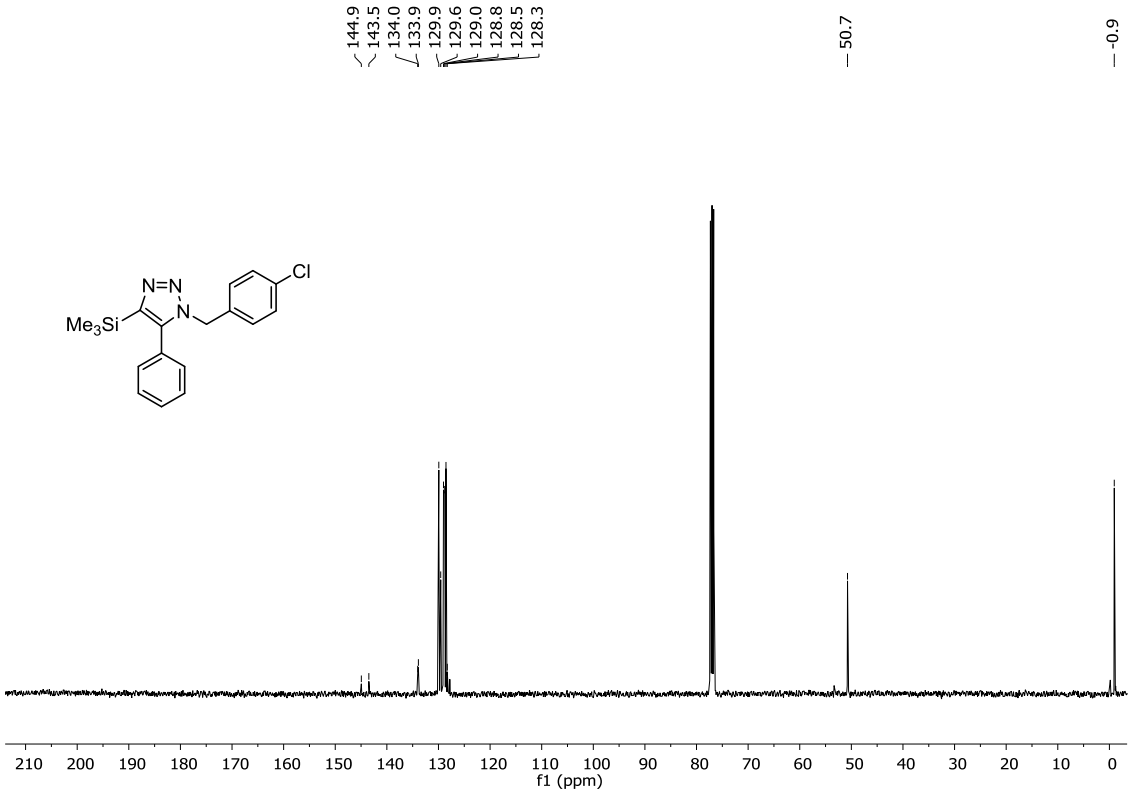
Spectrum 8.17. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8h**.



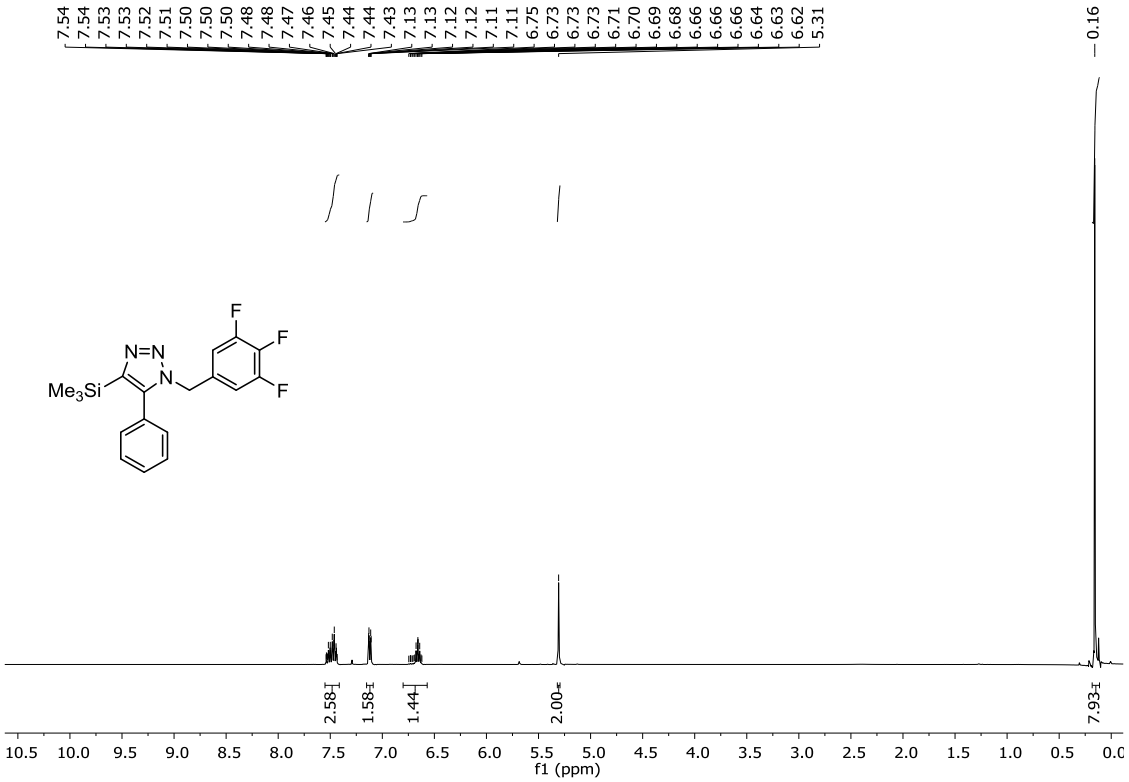
Spectrum 8.18. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8h**.



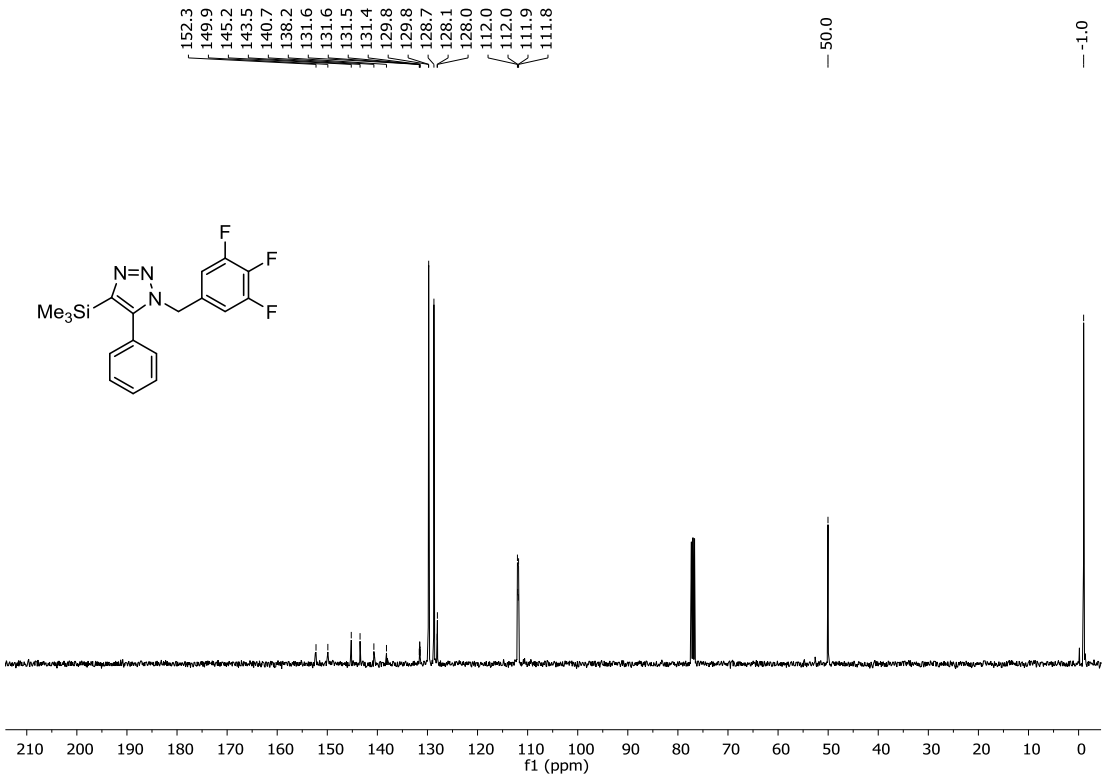
Spectrum 8.19. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8i**.



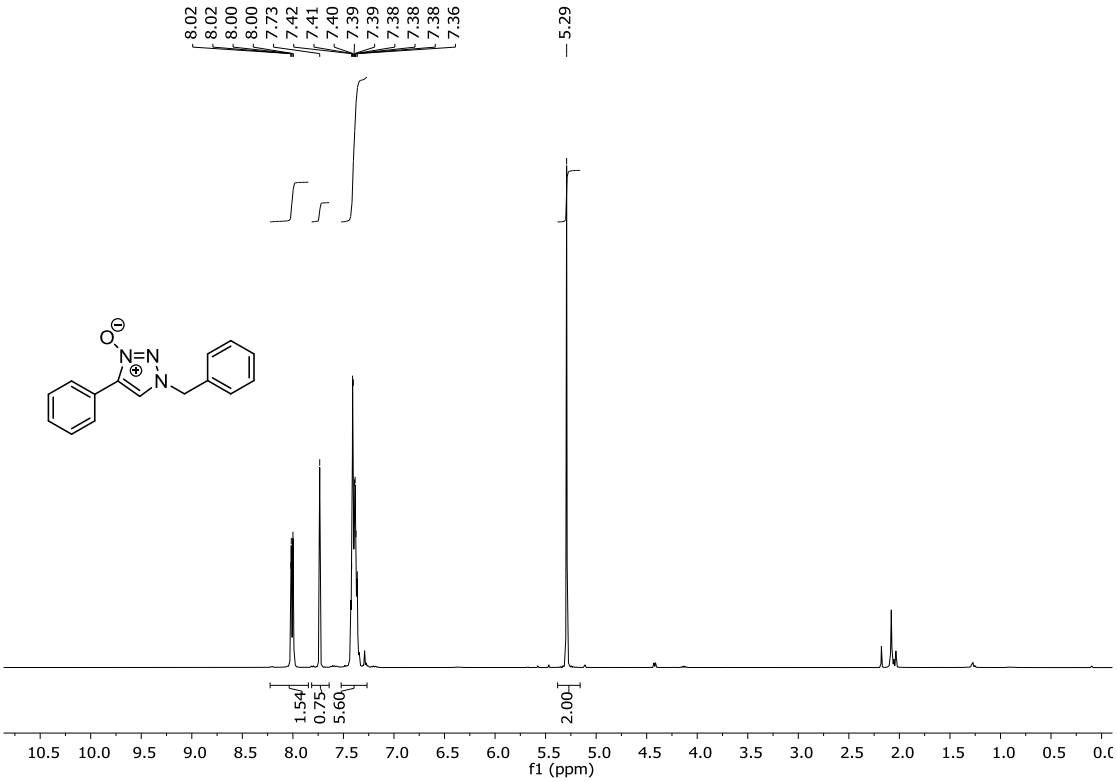
Spectrum 8.20. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8i**.



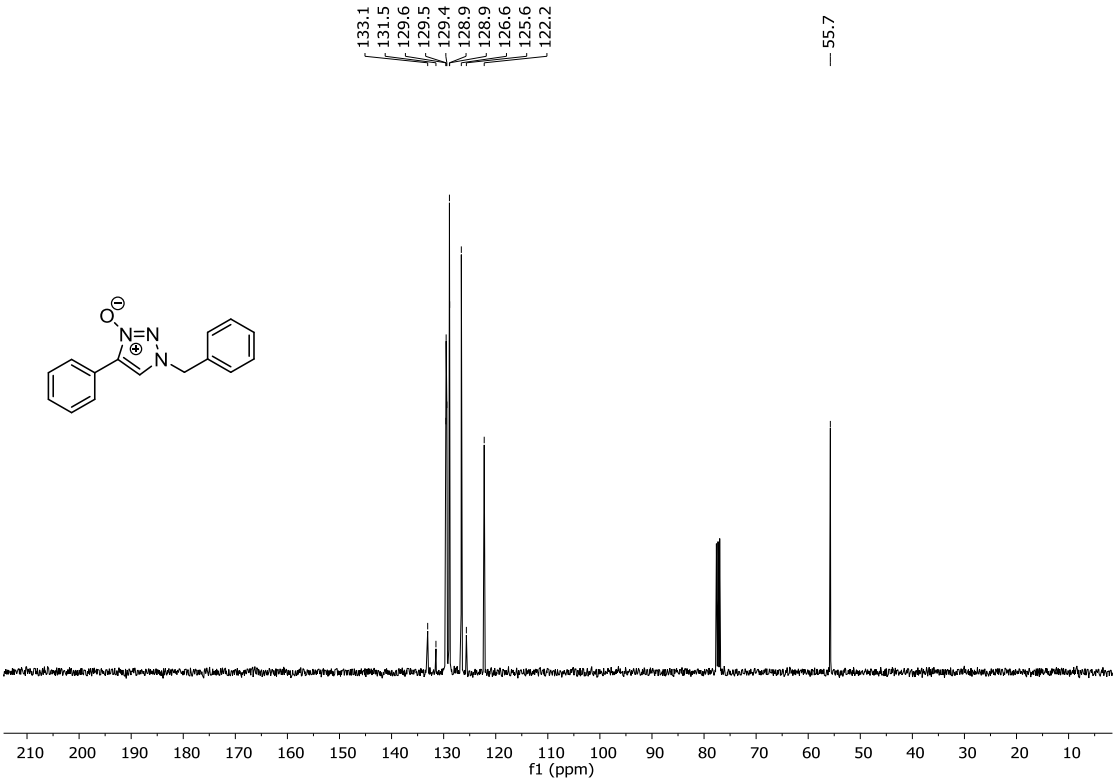
Spectrum 8.21. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8j**.



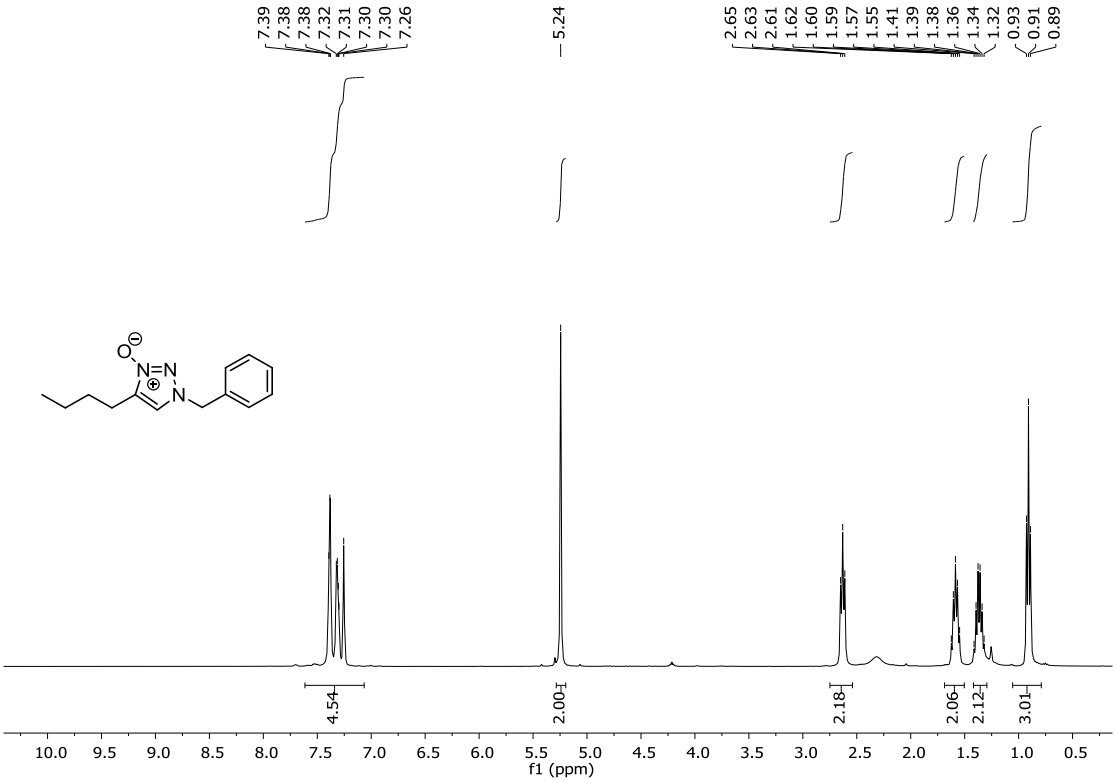
Spectrum 8.22. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **8j**.



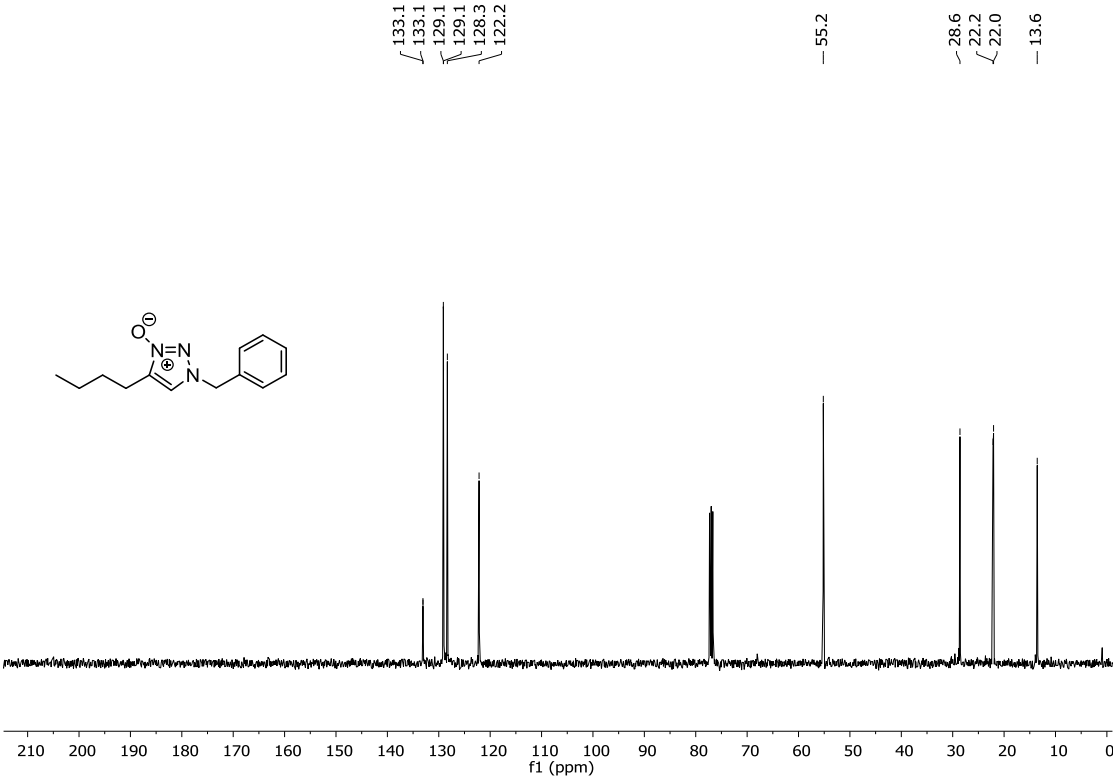
Spectrum 8.23. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**.



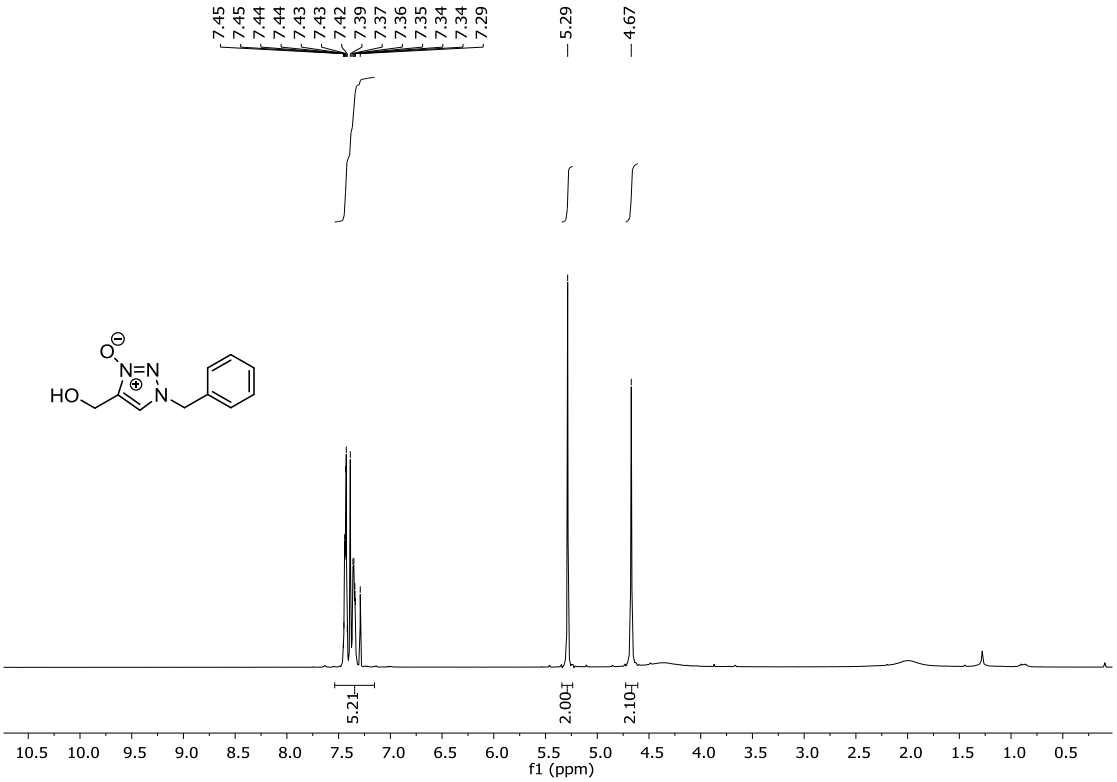
Spectrum 8.24. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4a**.



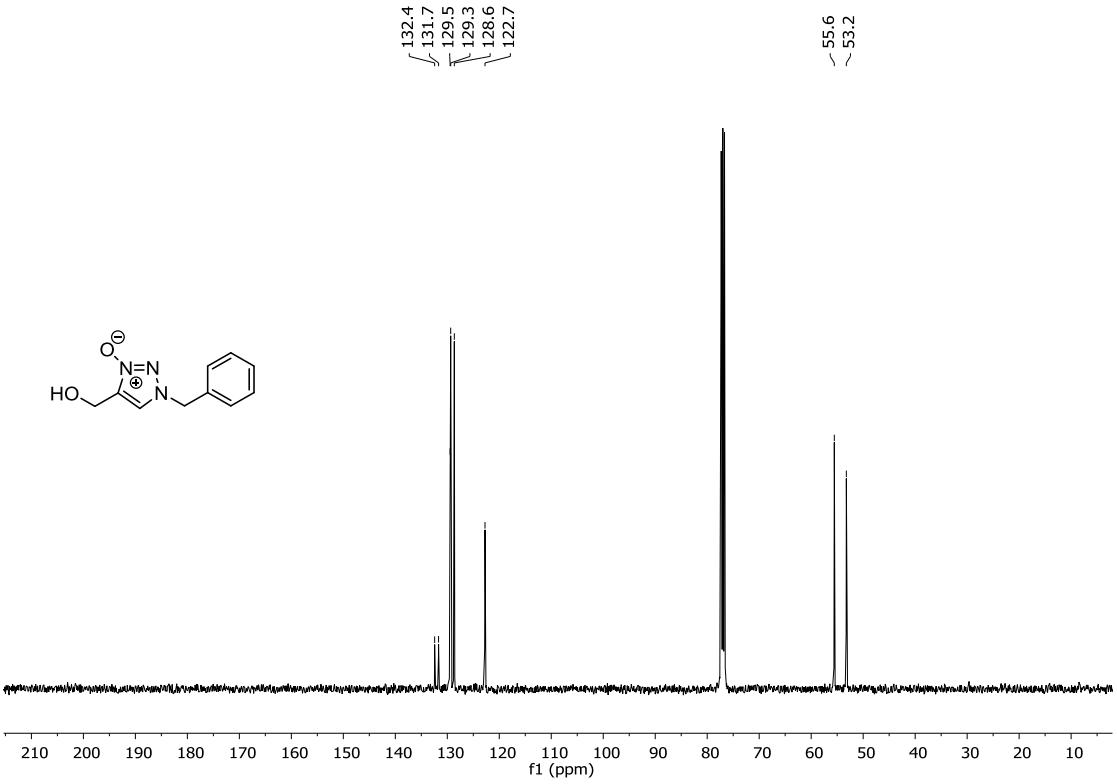
Spectrum 8.25. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4b**.



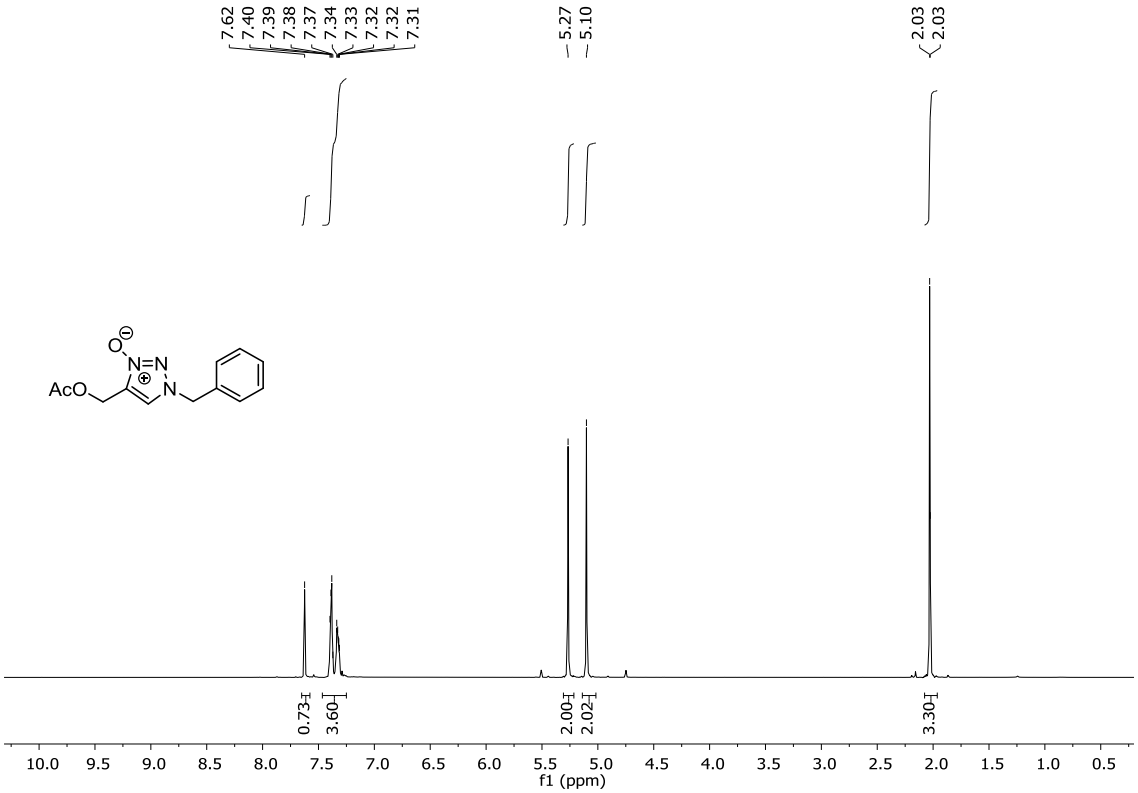
Spectrum 8.26. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4b**.



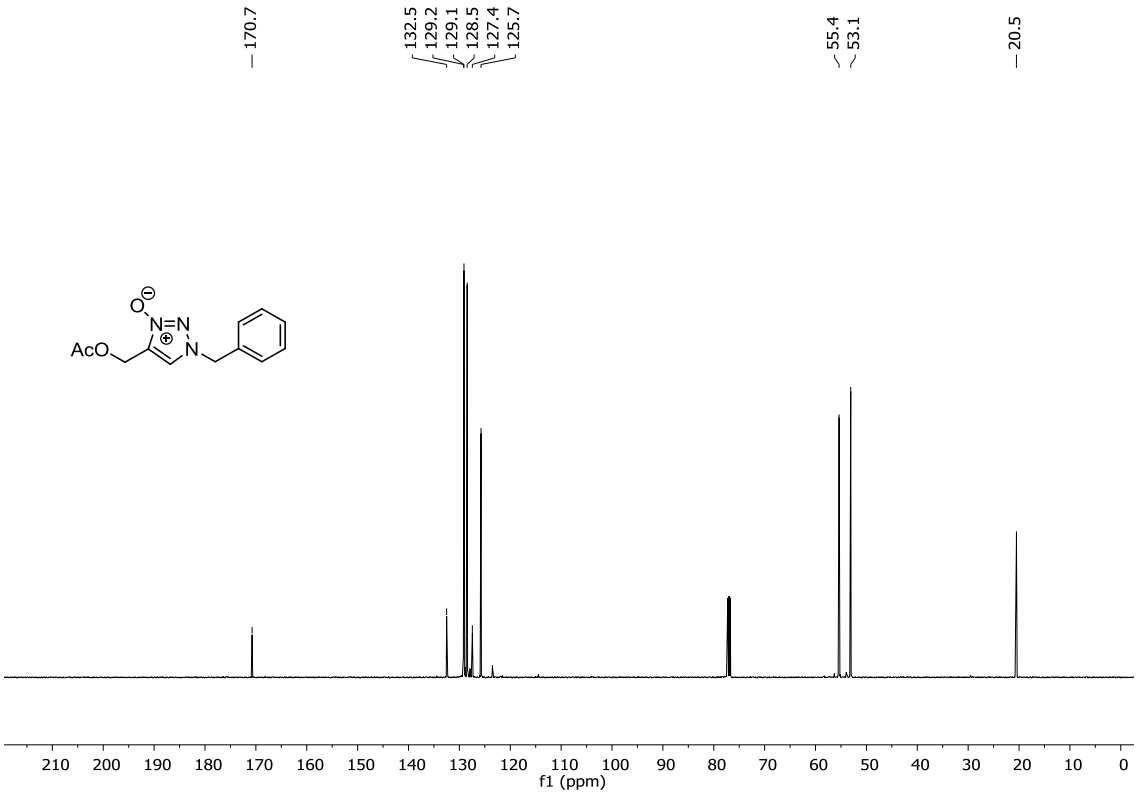
Spectrum 8.27. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4c**.



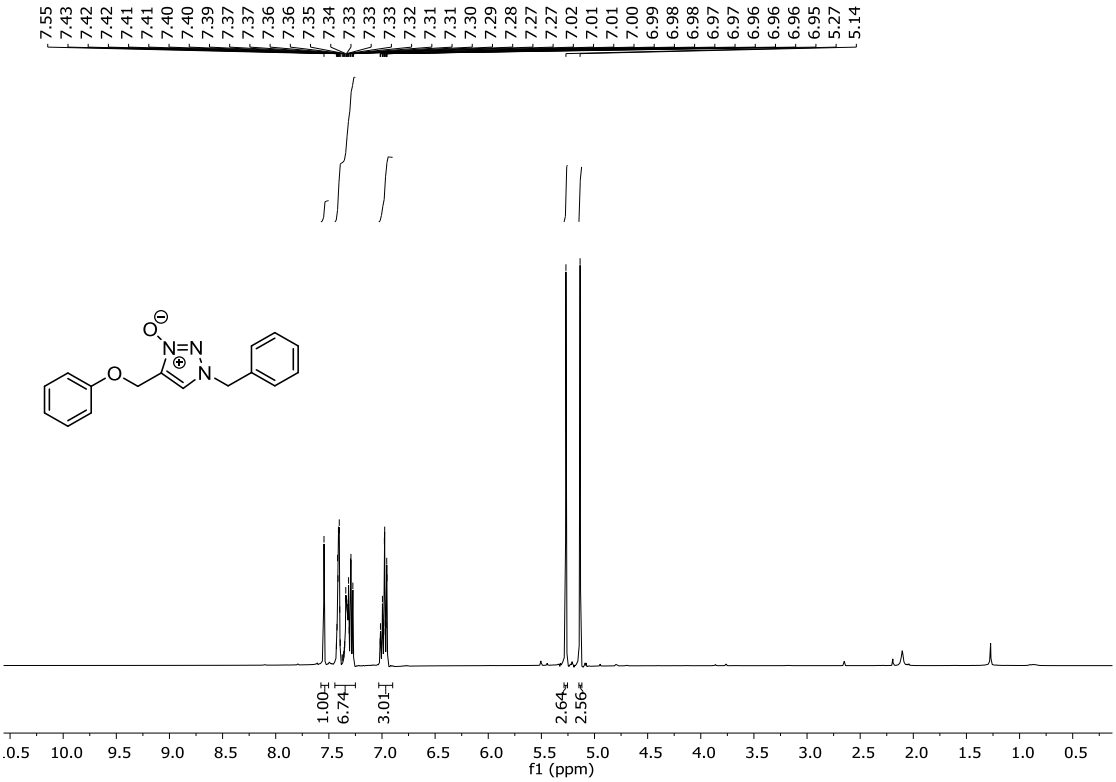
Spectrum 8.28. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4c**.



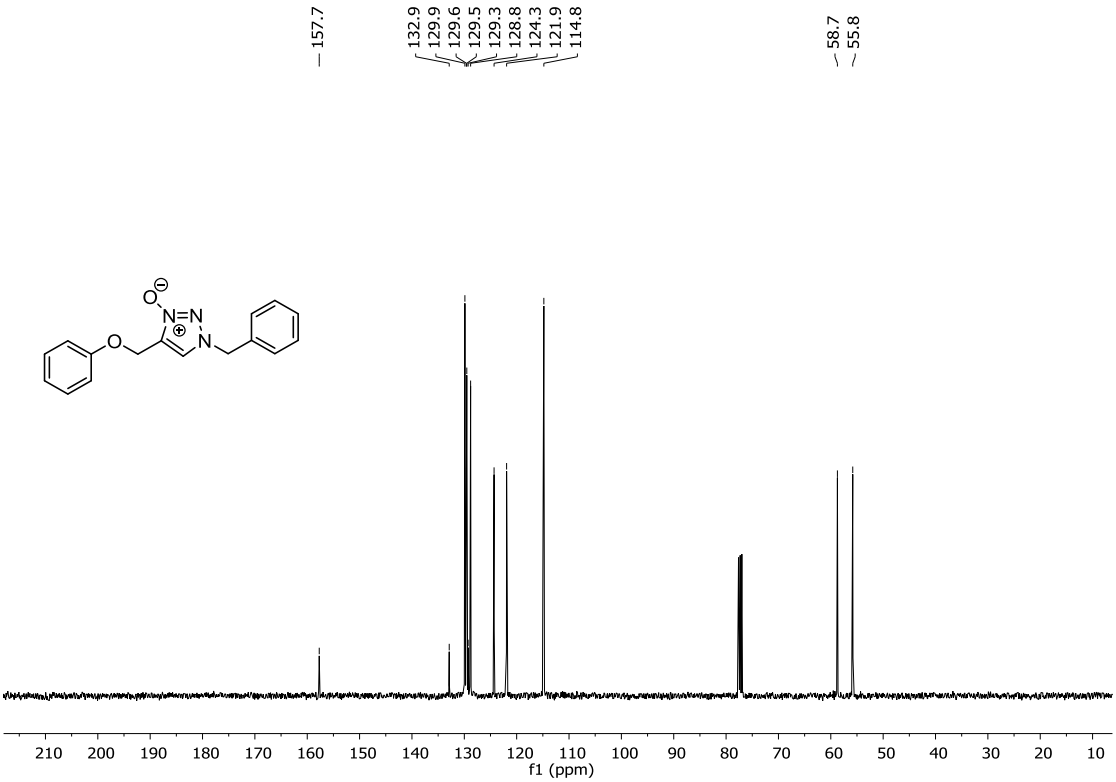
Spectrum 8.29. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4c'**.



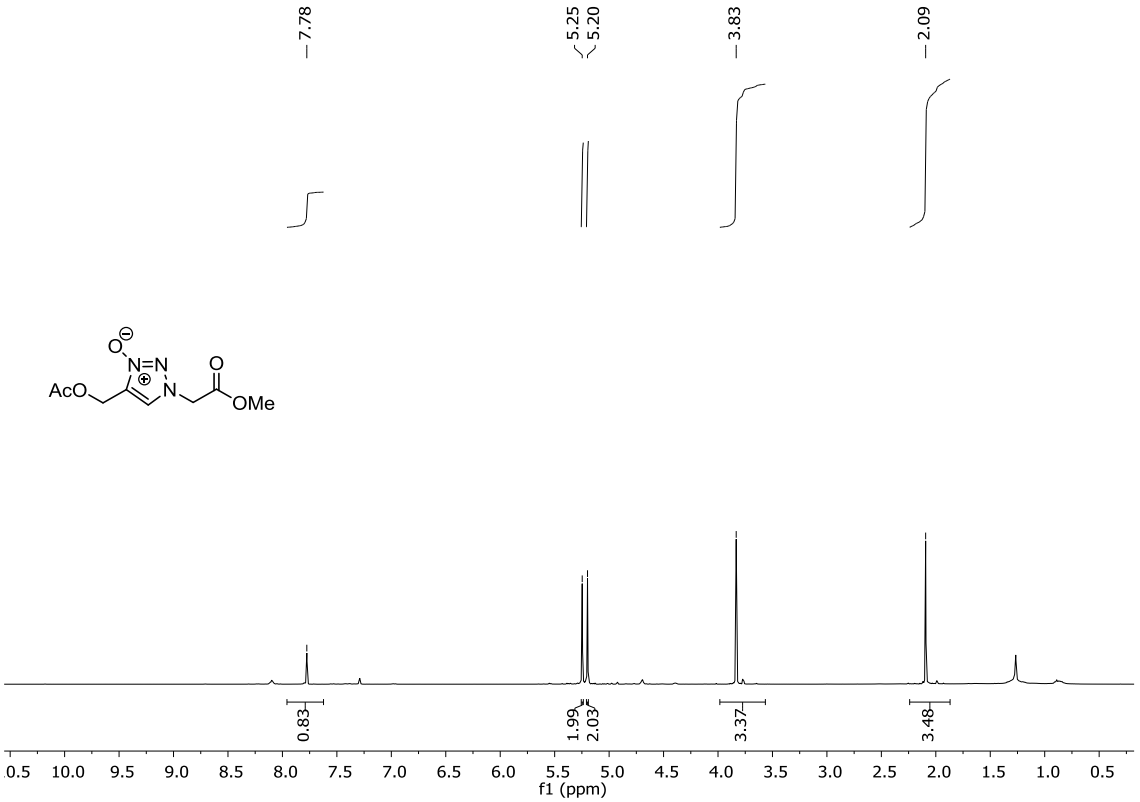
Spectrum 8.30. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4c'**.



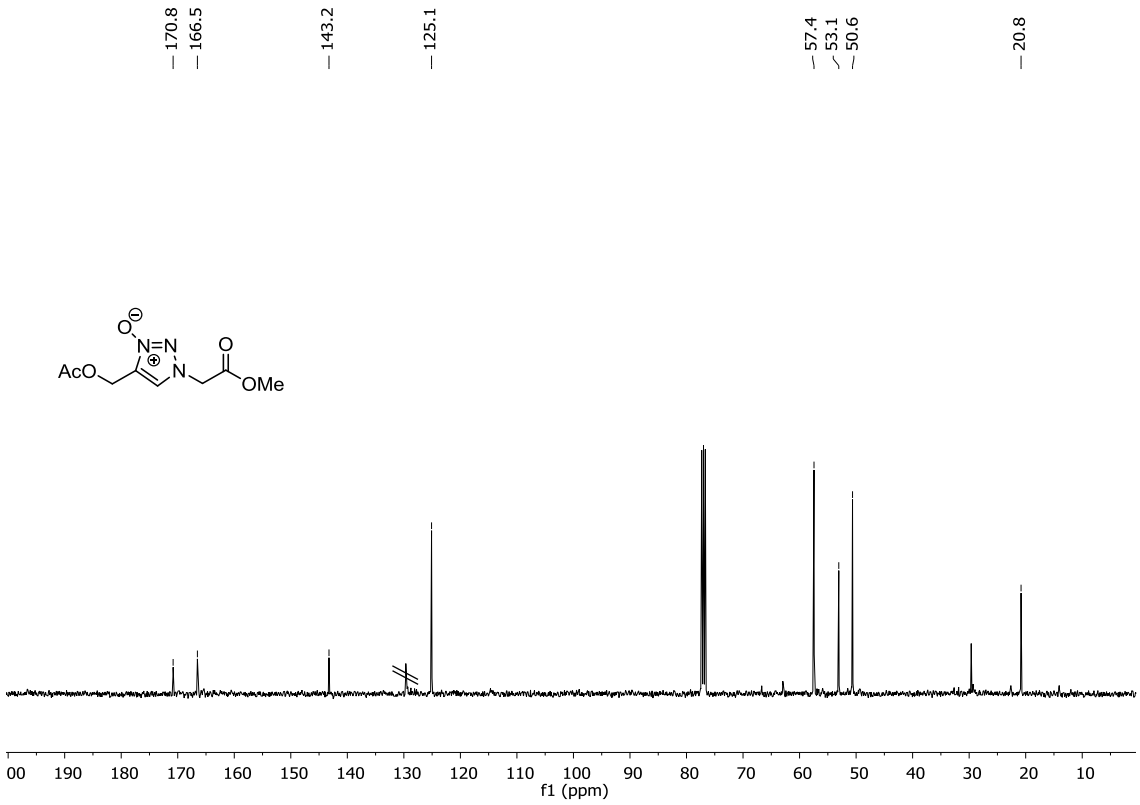
Spectrum 8.31. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4d**.



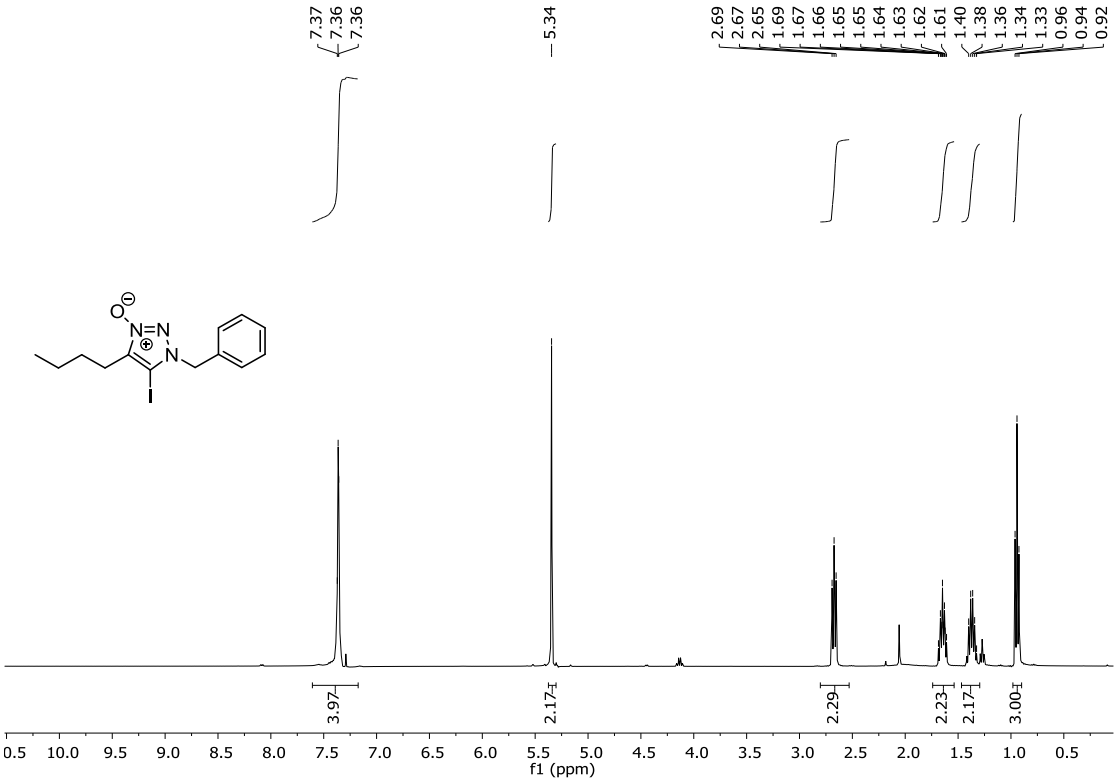
Spectrum 8.32. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4d**.



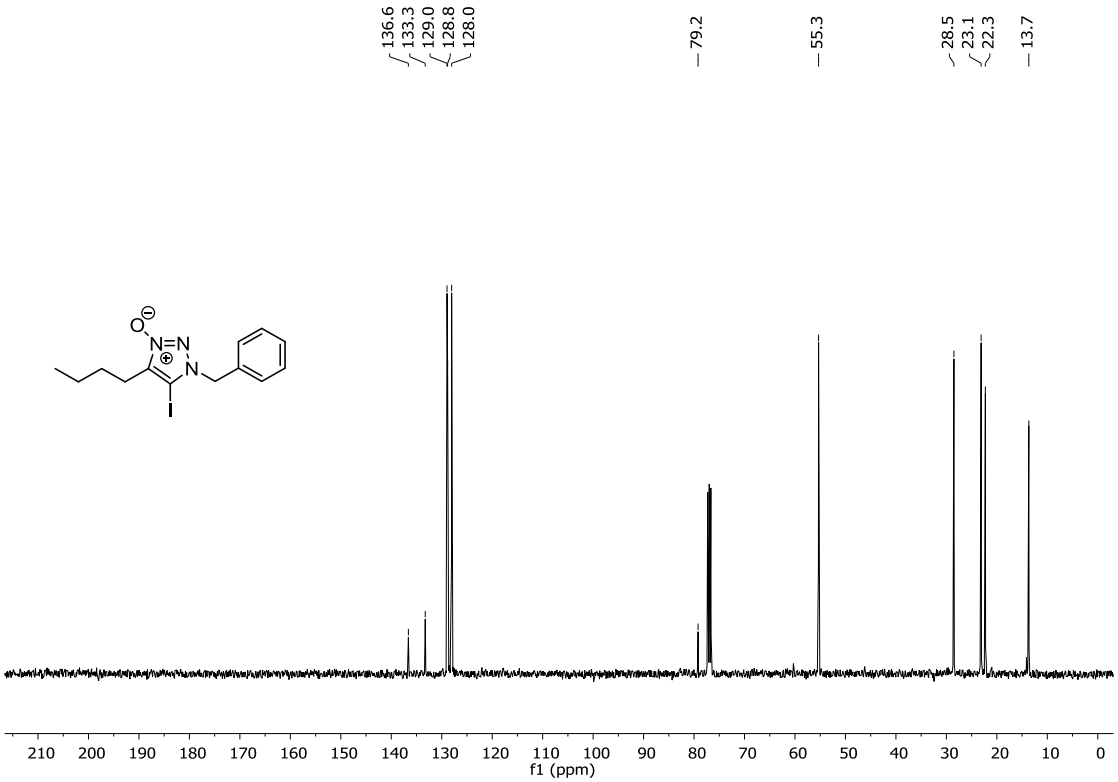
Spectrum 8.33. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4g**.



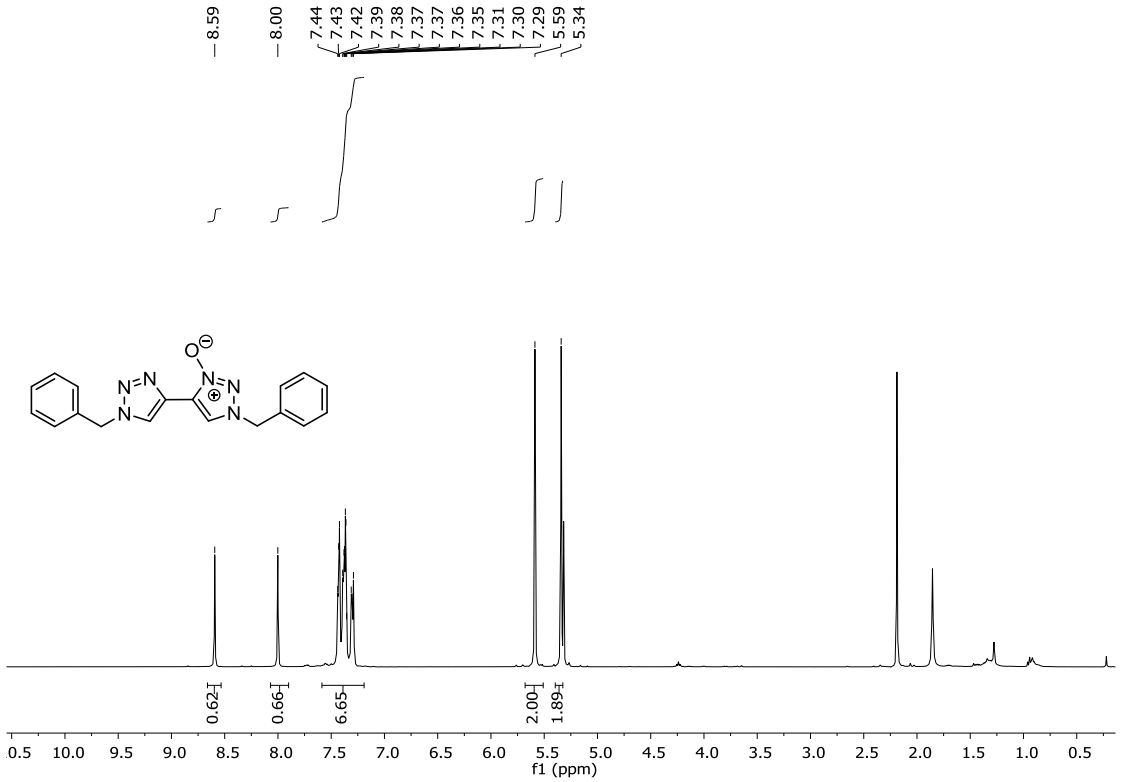
Spectrum 8.34. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4g**.



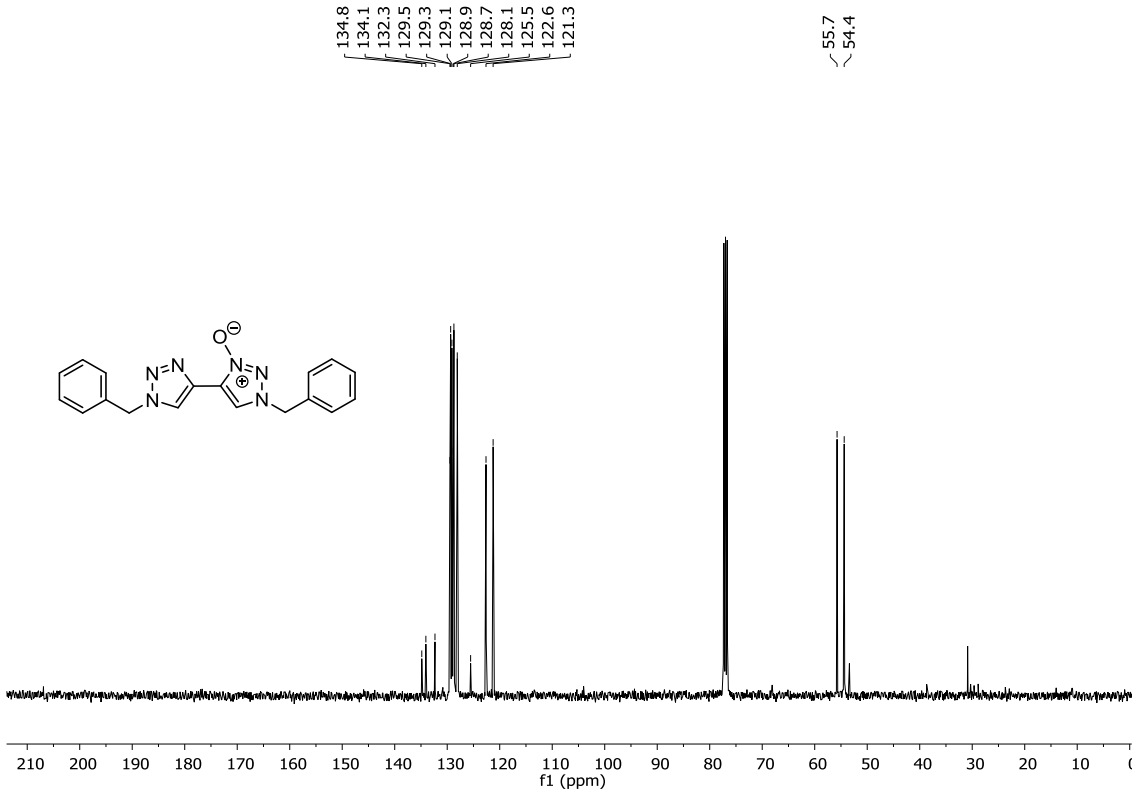
Spectrum 8.35. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4j**.



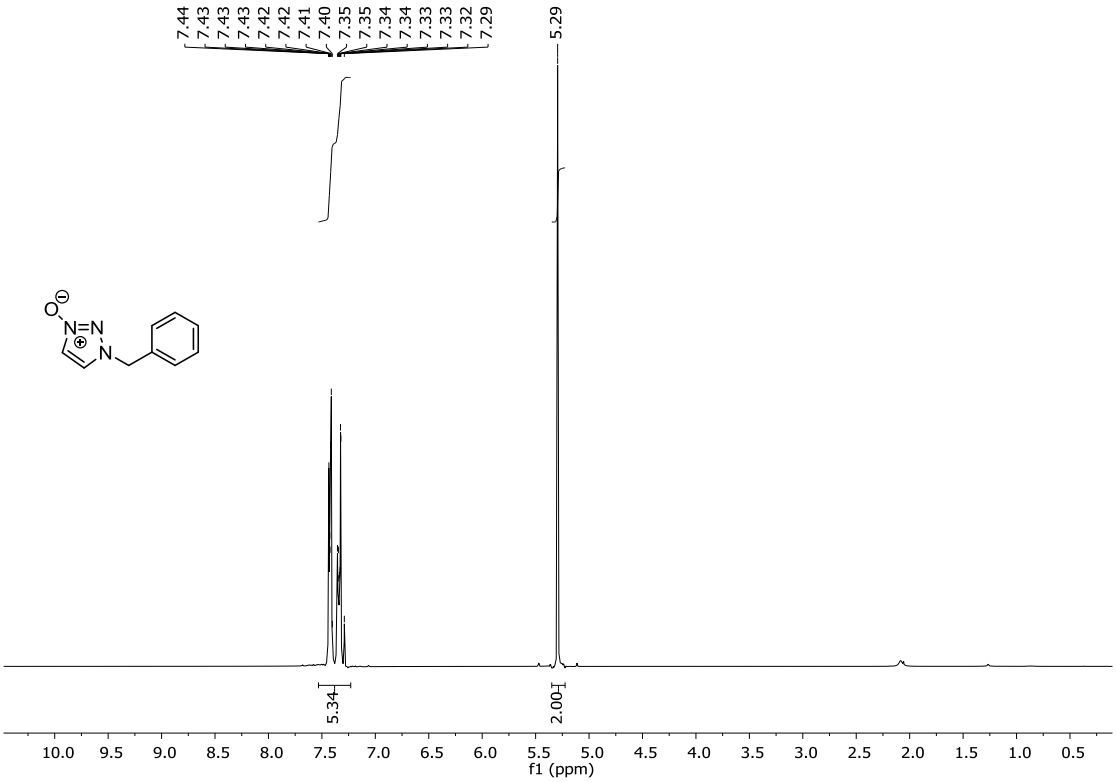
Spectrum 8.36. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4j**.



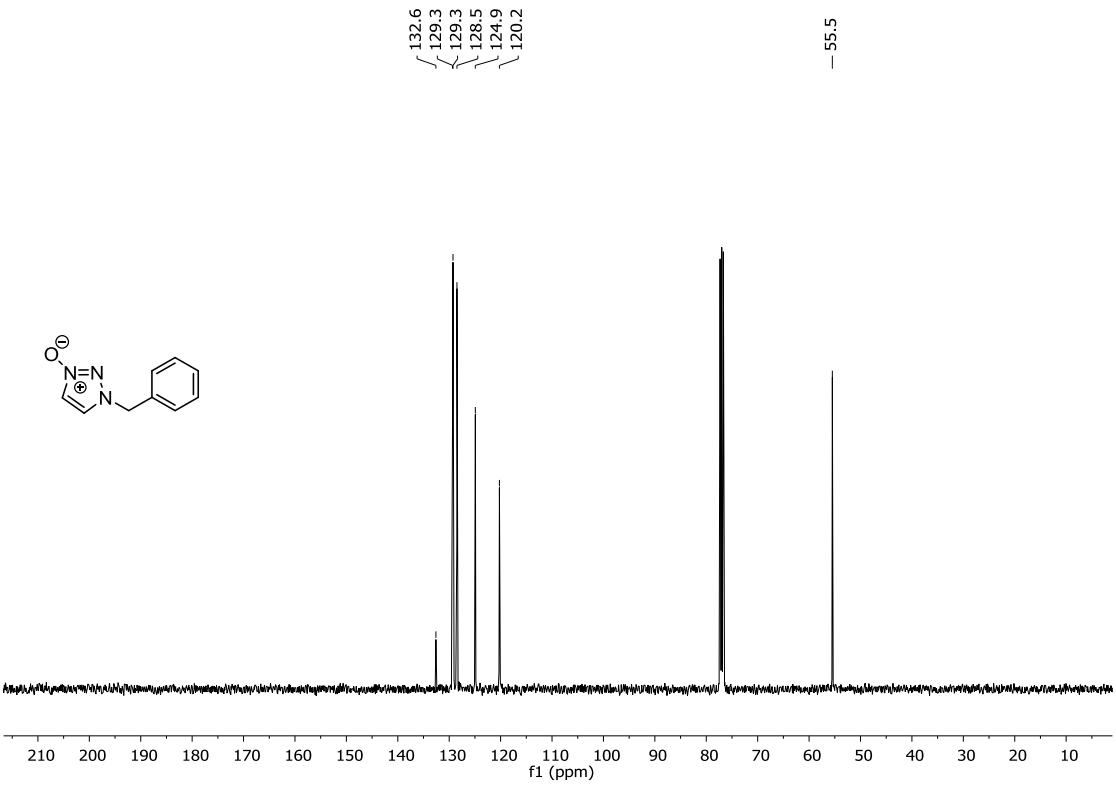
Spectrum 8.37. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4k**.



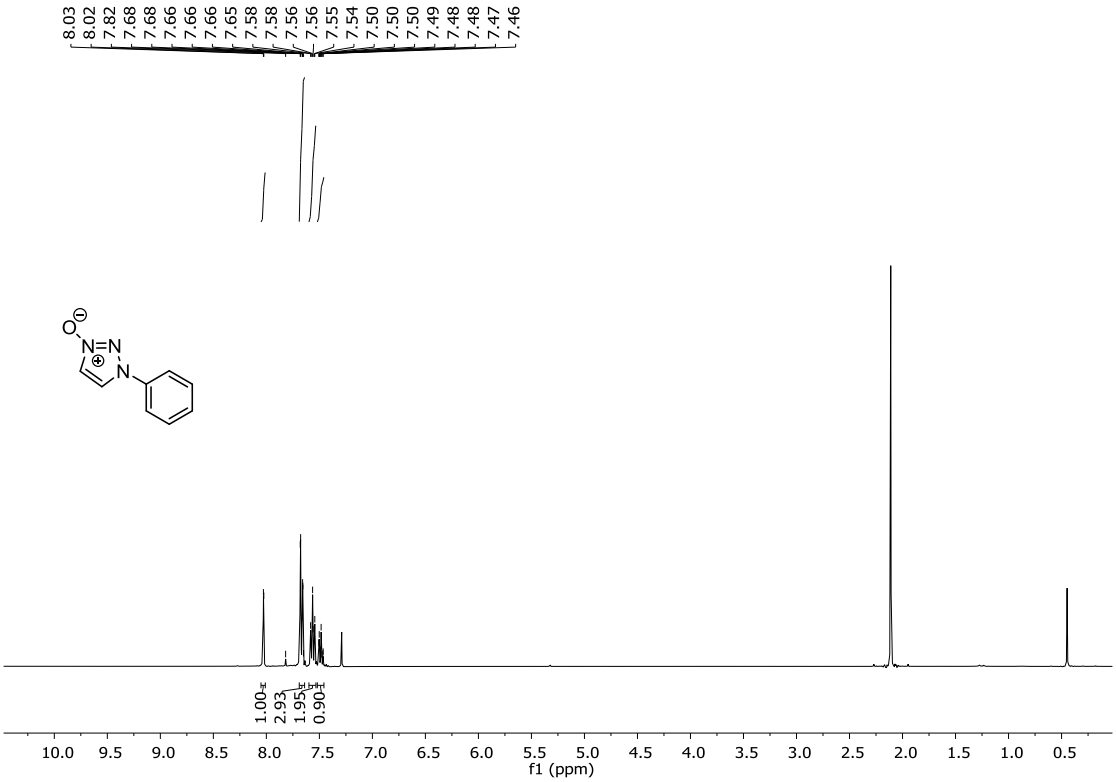
Spectrum 8.38. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4k**.



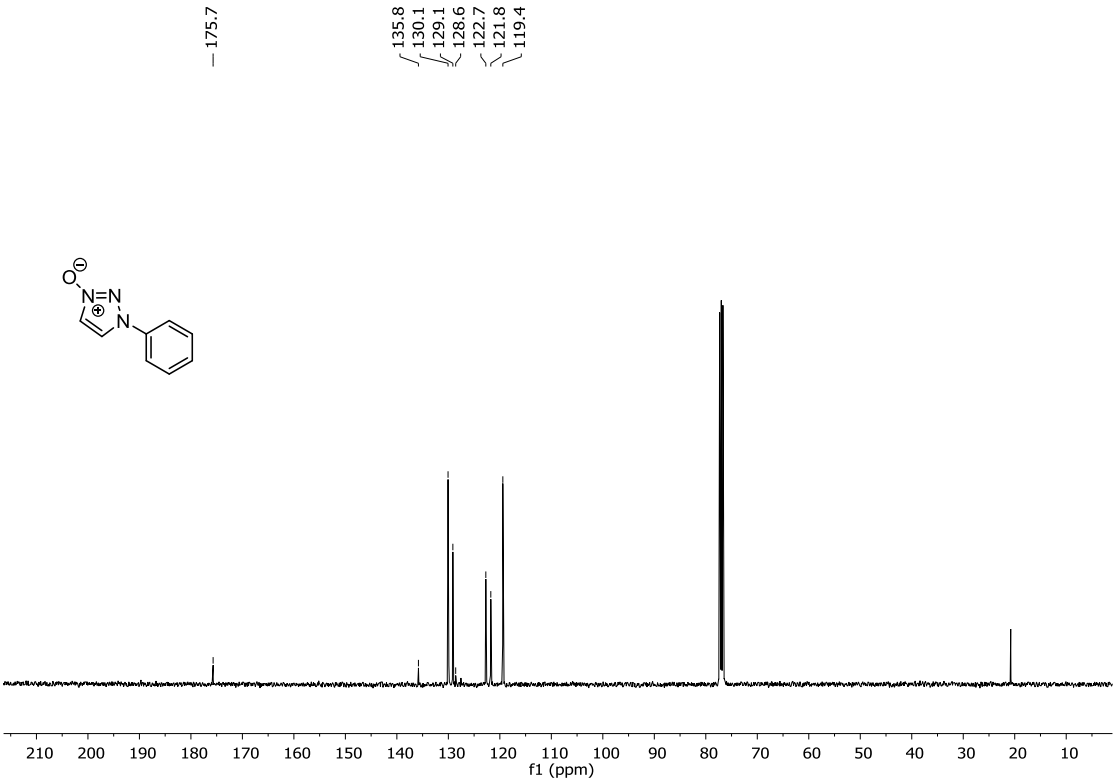
Spectrum 8.39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4l**.



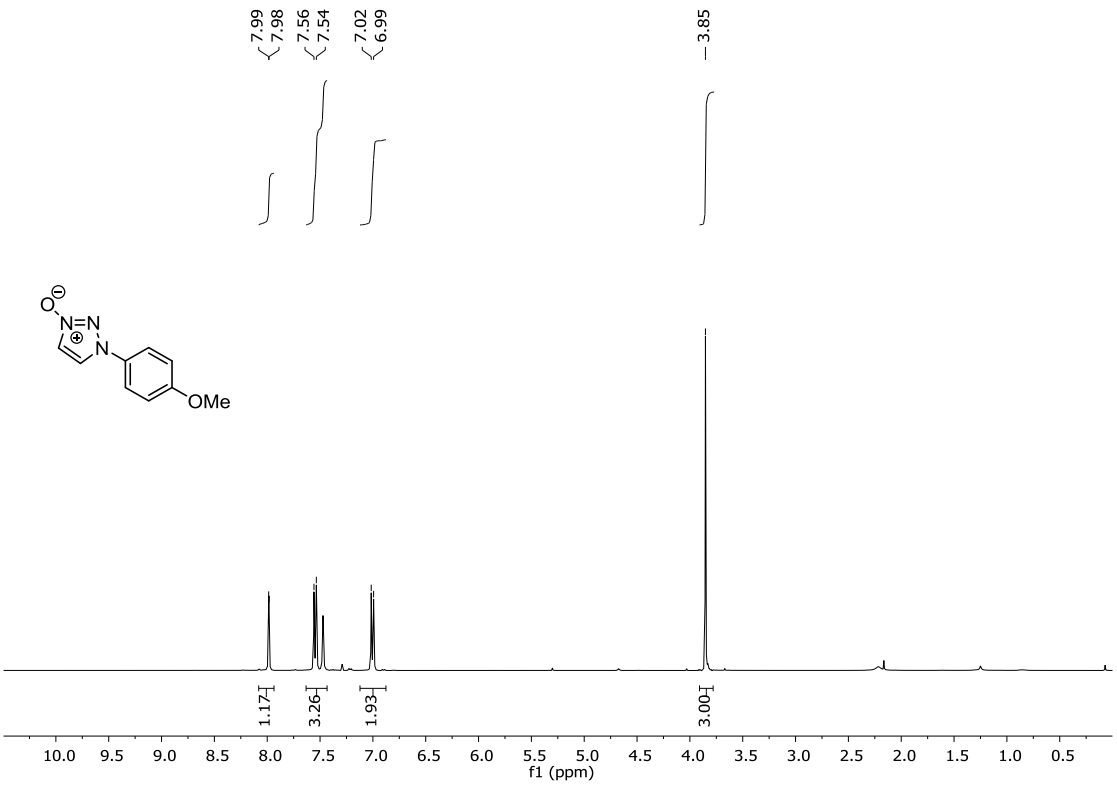
Spectrum 8.40. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4l**.



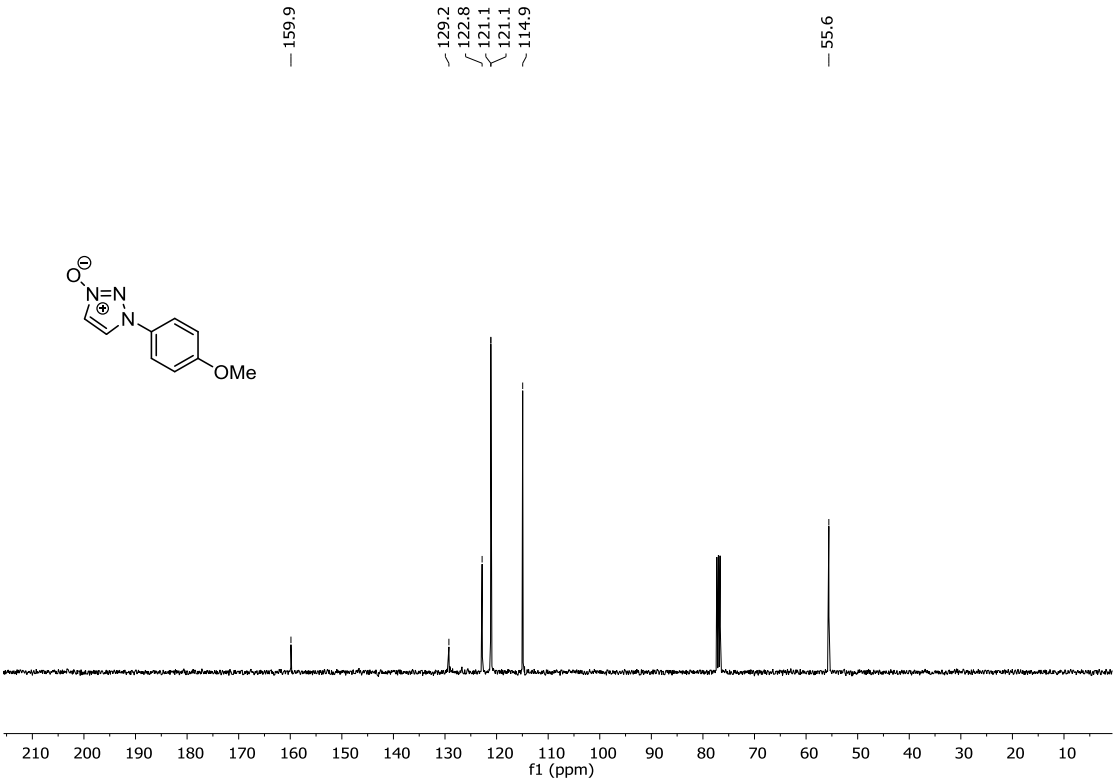
Spectrum 8.41. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4m**.



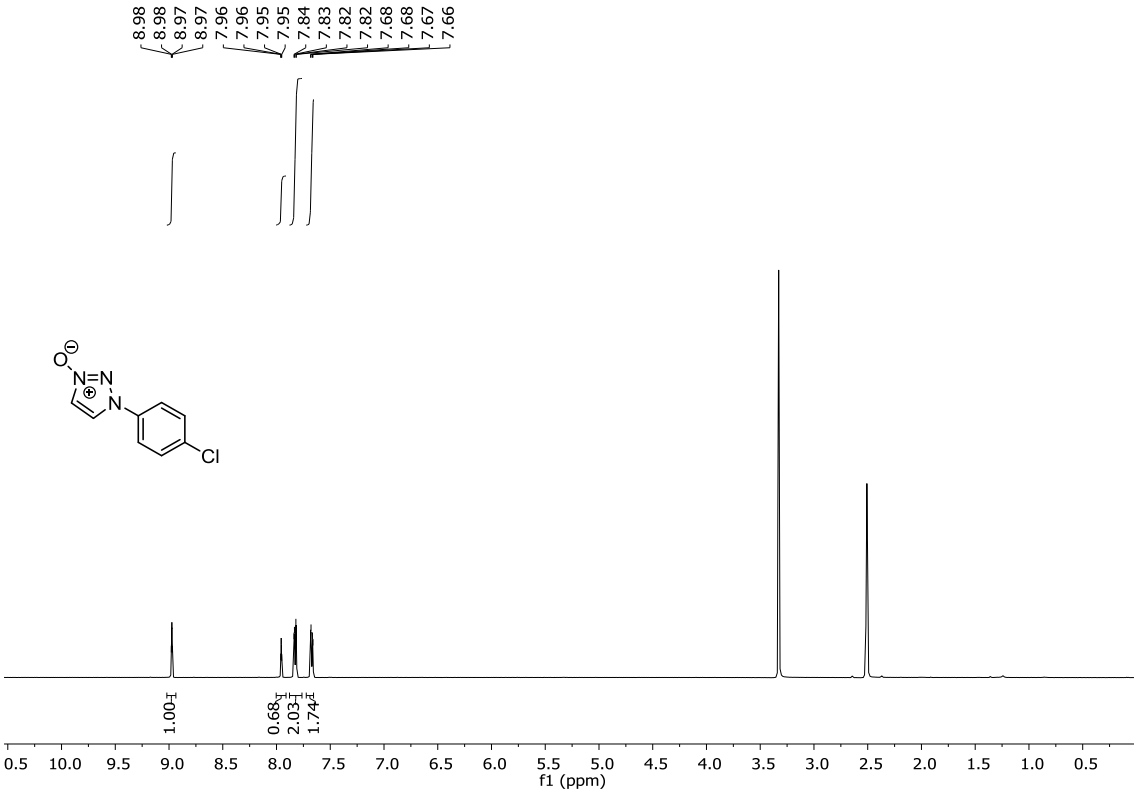
Spectrum 8.42. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4m**.



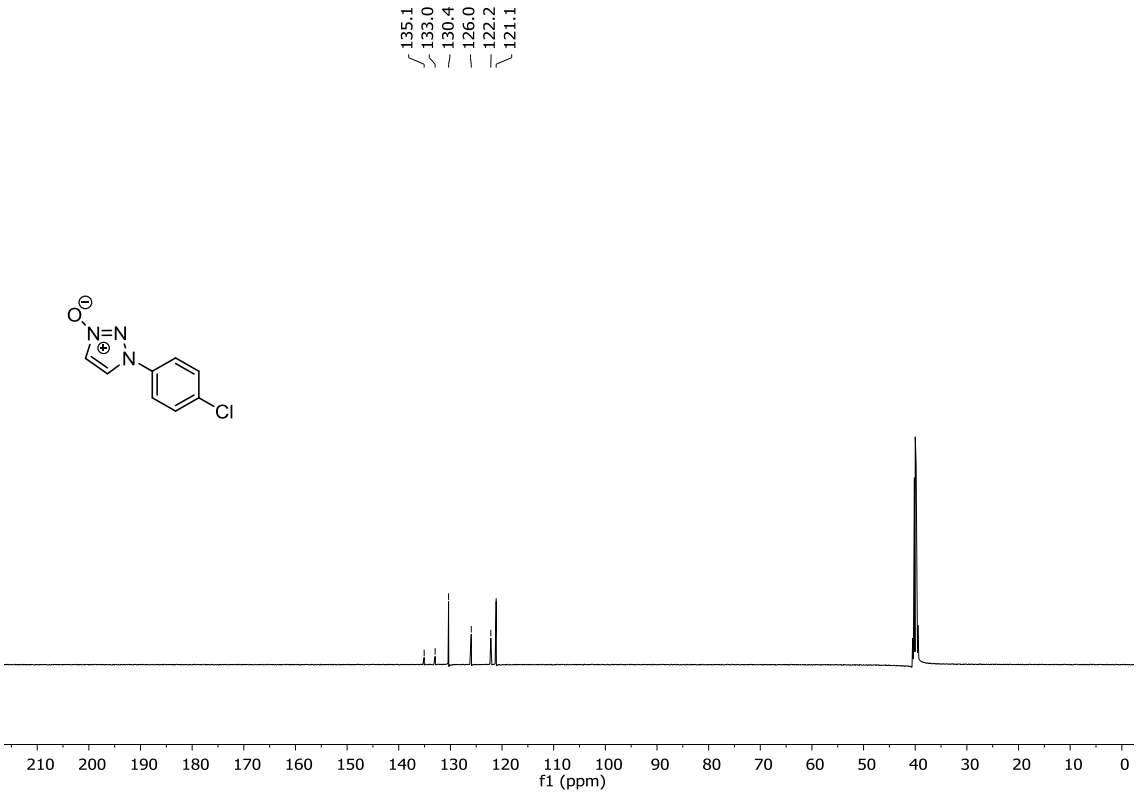
Spectrum 8.43. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4n**.



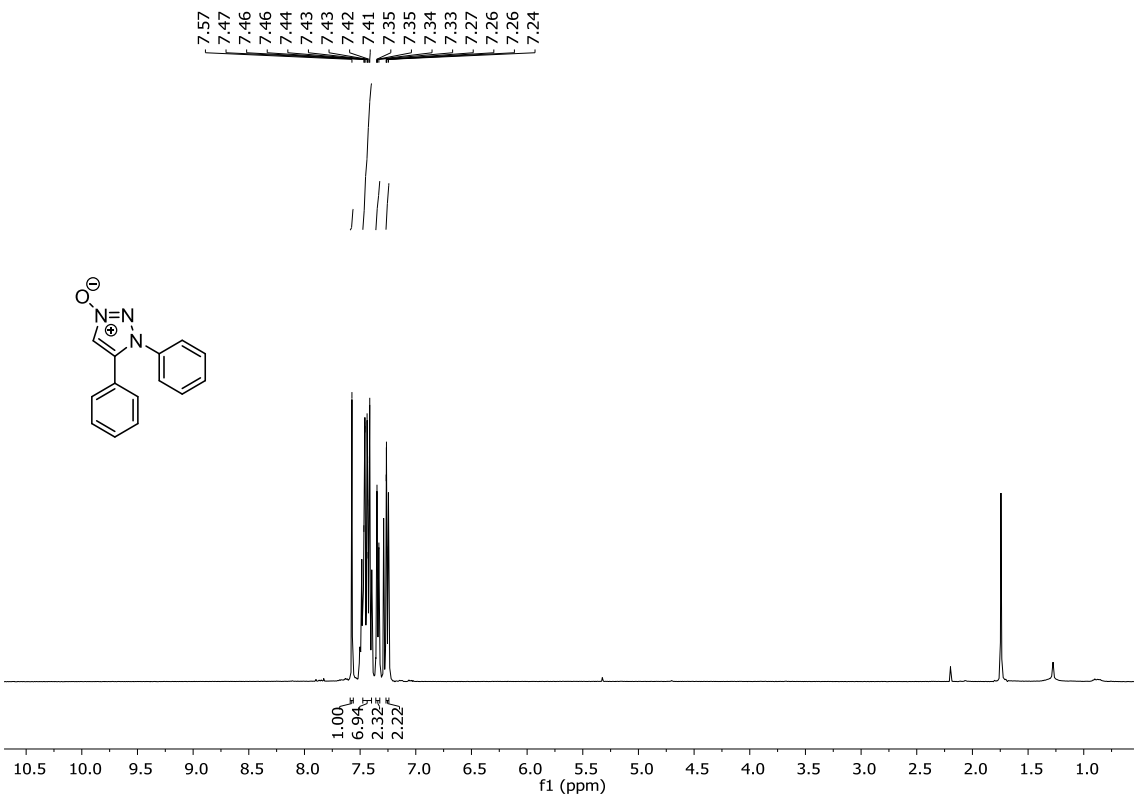
Spectrum 8.44. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4n**.



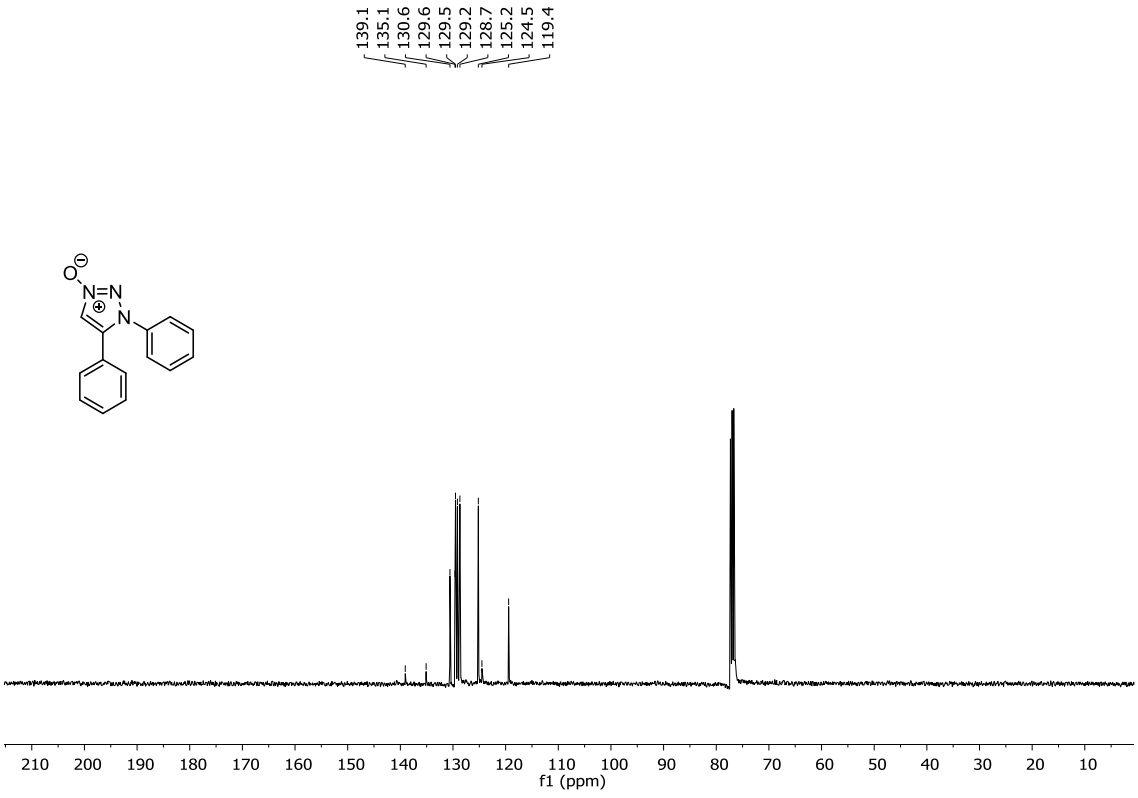
Spectrum 8.45. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4o**.



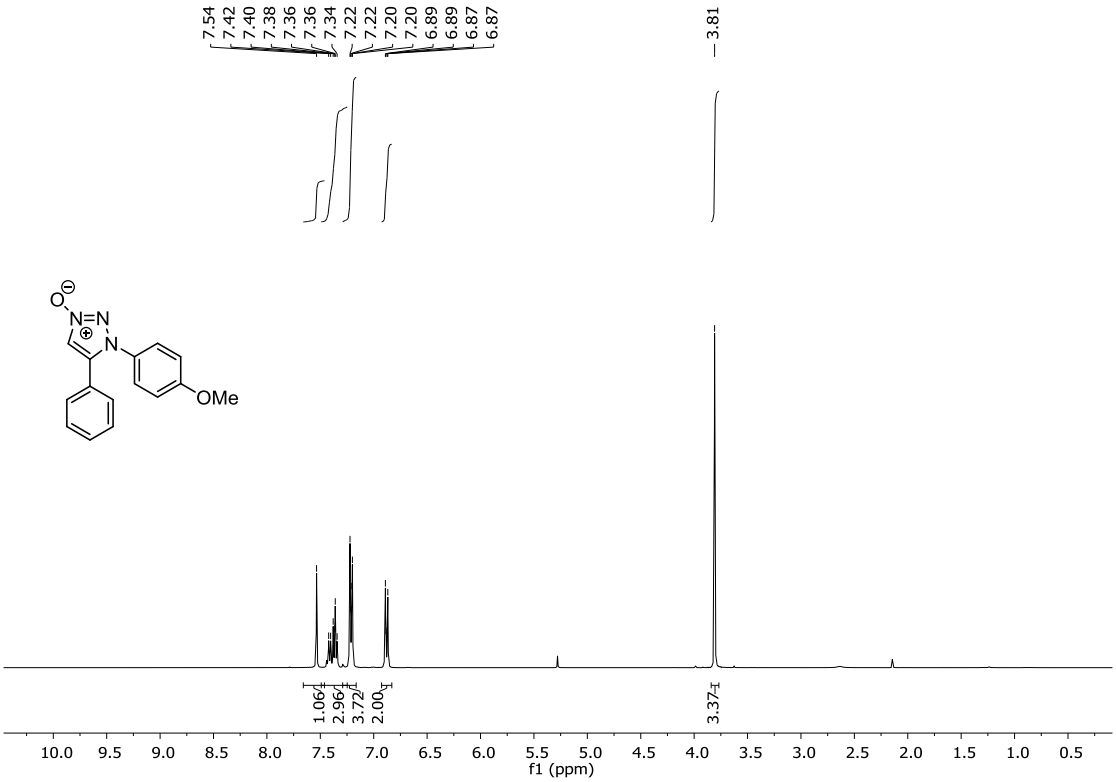
Spectrum 8.46. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4o**.



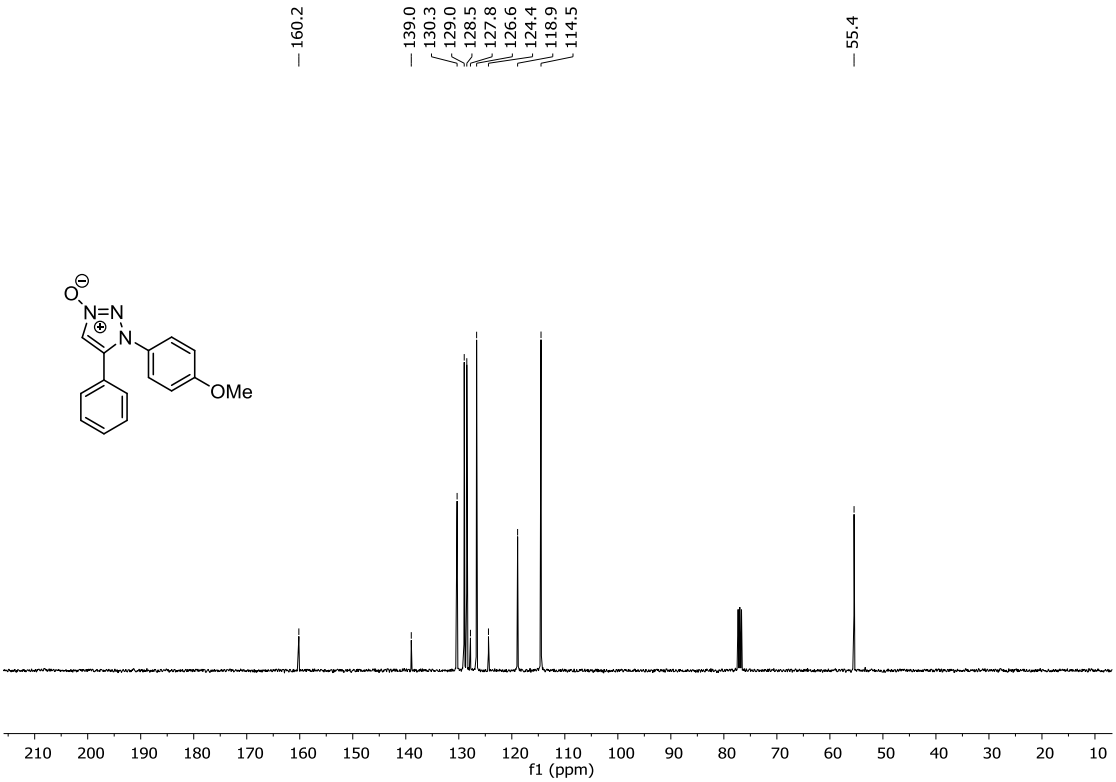
Spectrum 8.47. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9a**.



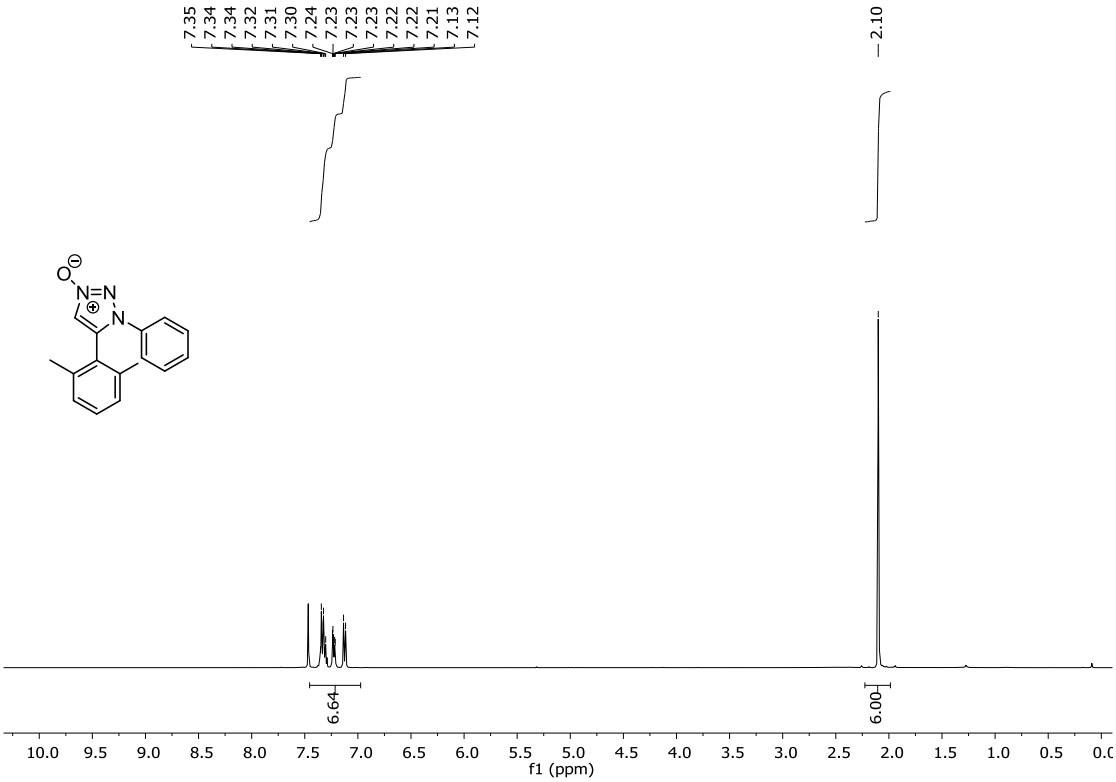
Spectrum 8.48. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9a**.



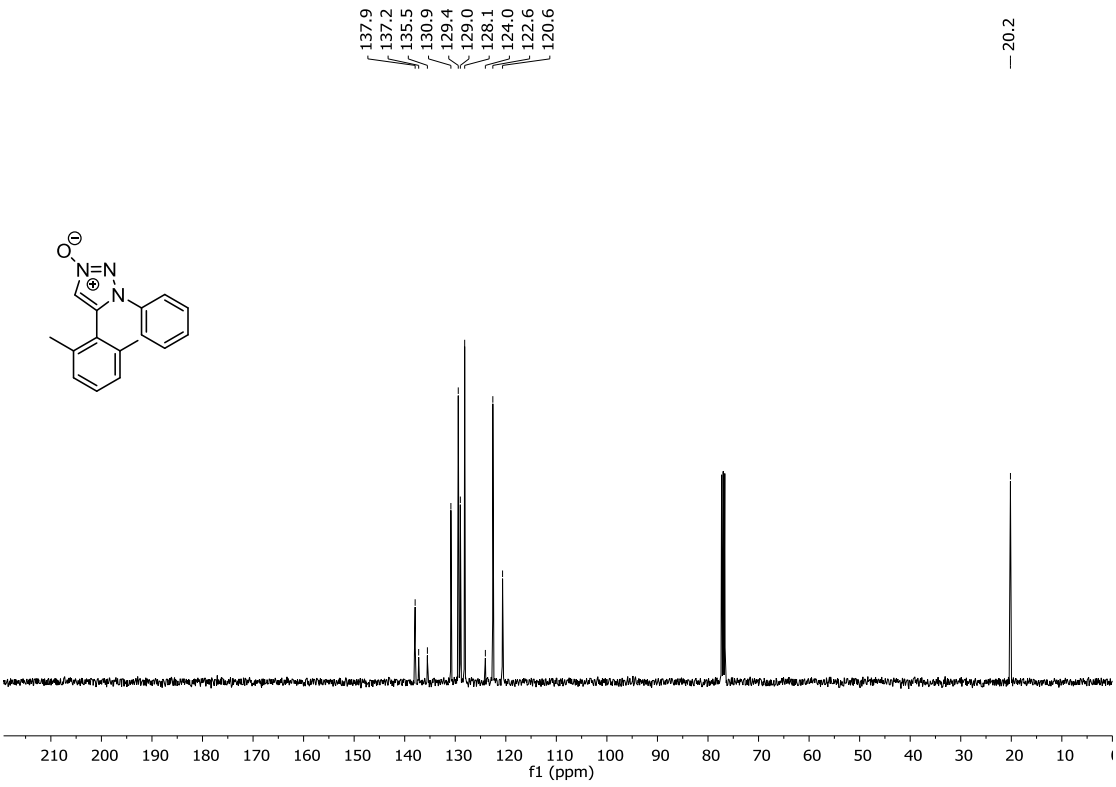
Spectrum 8.49. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9b**.



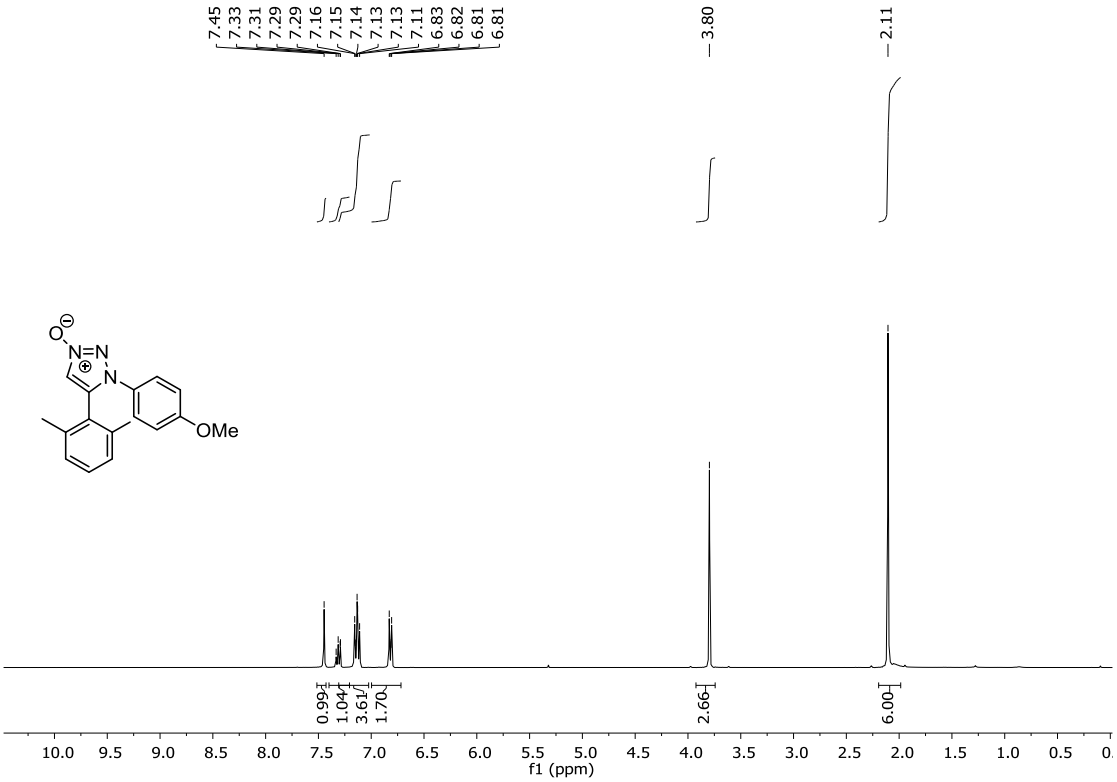
Spectrum 8.50. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9b**.



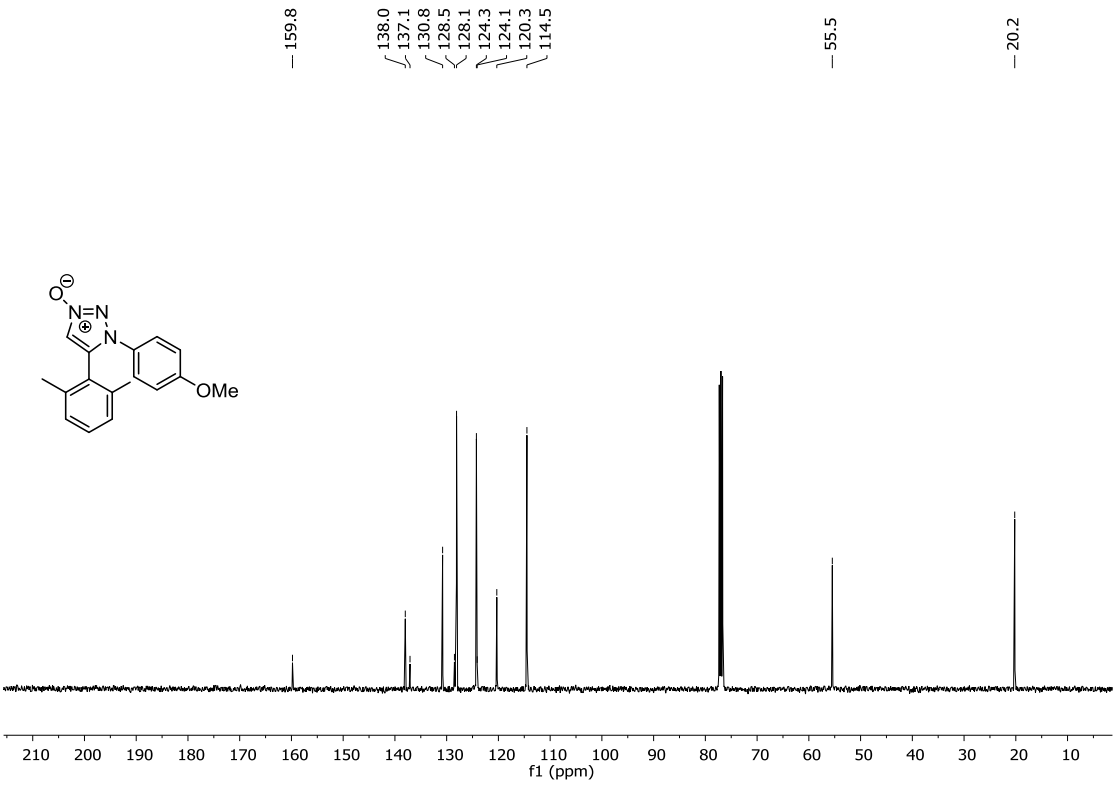
Spectrum 8.51. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9c**.



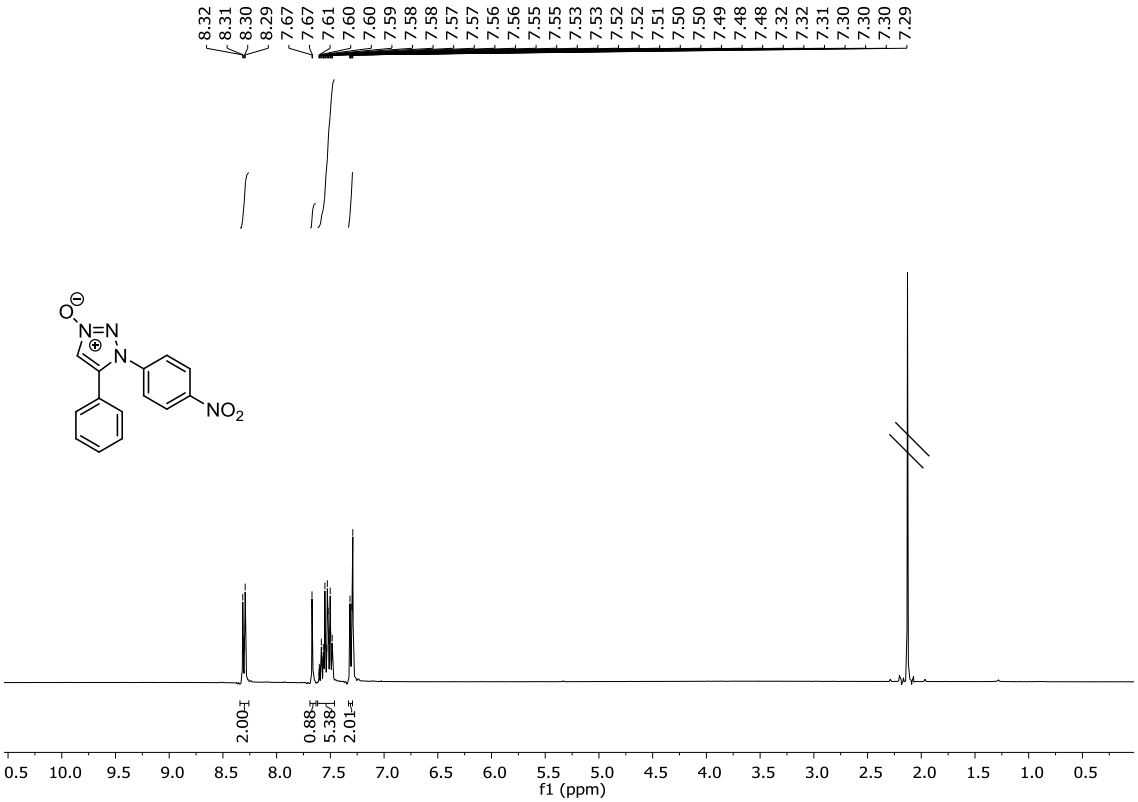
Spectrum 8.52. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9c**.



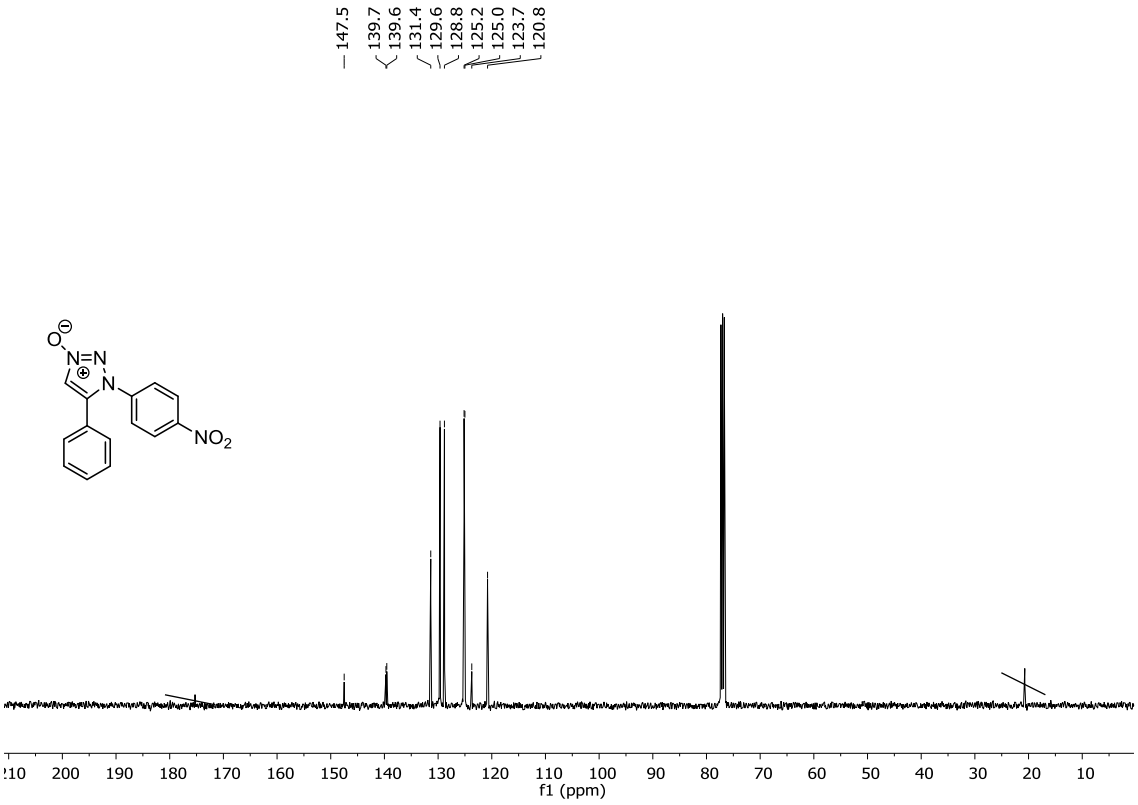
Spectrum 8.53. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9d**.



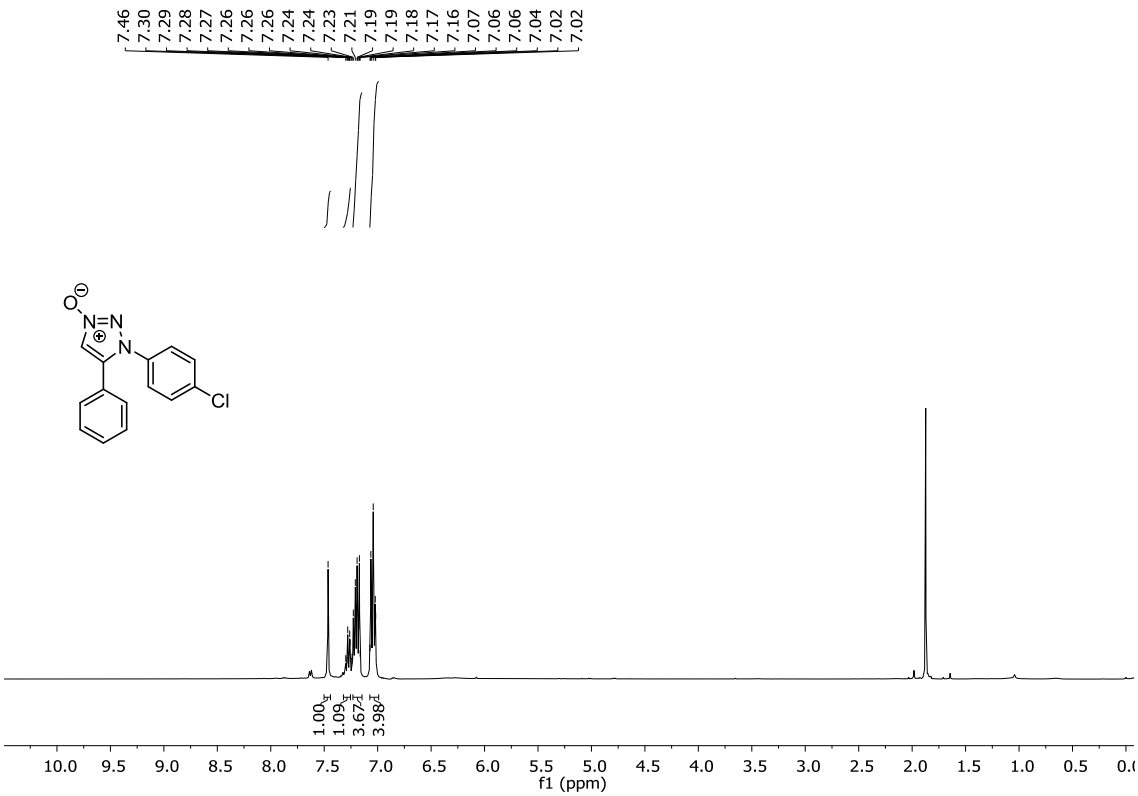
Spectrum 8.54. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9d**.



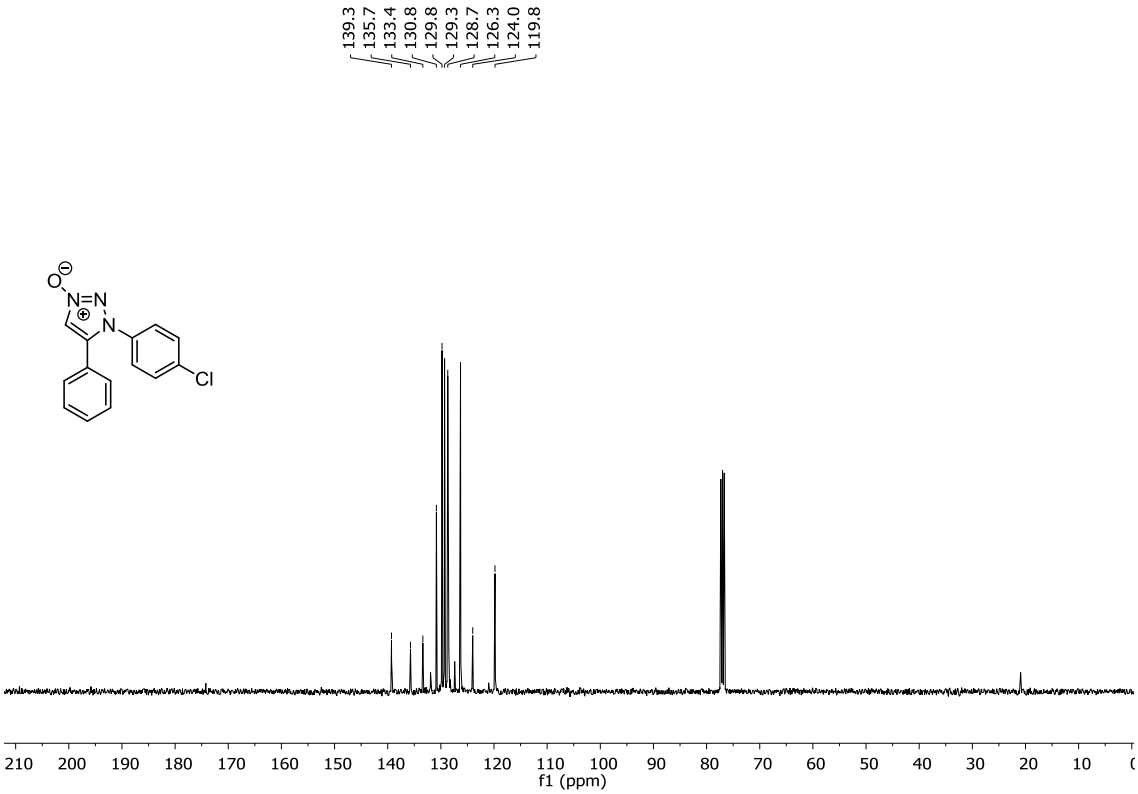
Spectrum 8.55. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9e**.



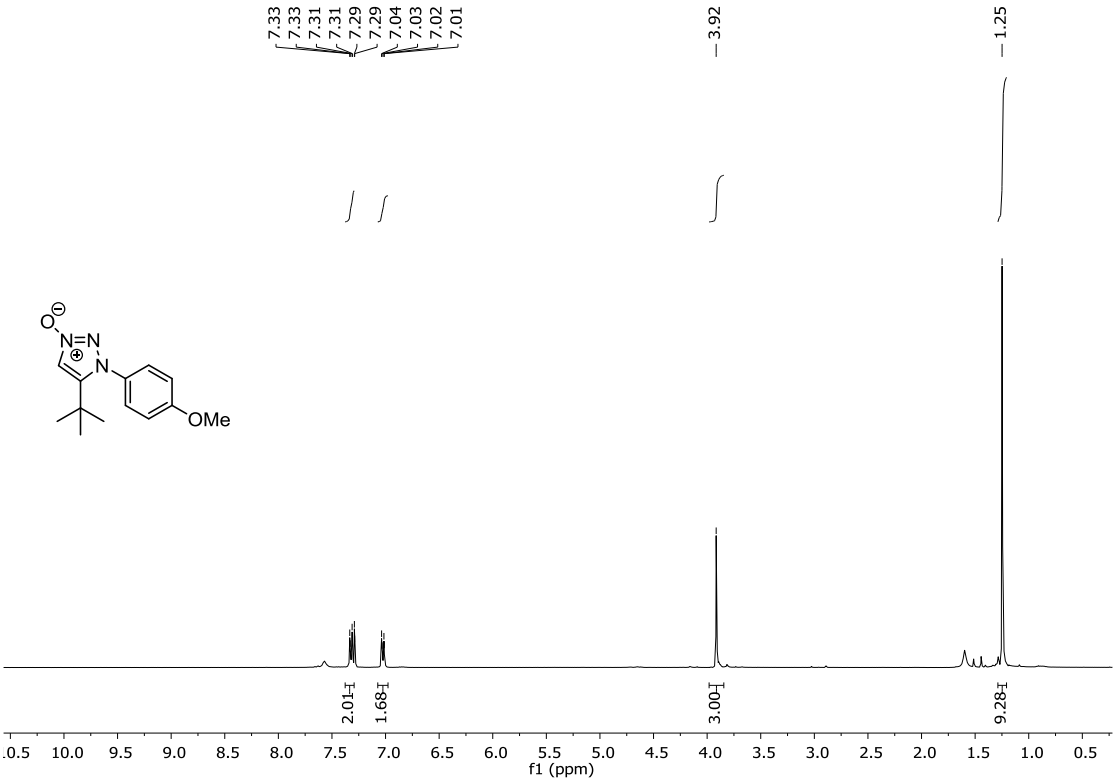
Spectrum 8.56. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9e**.



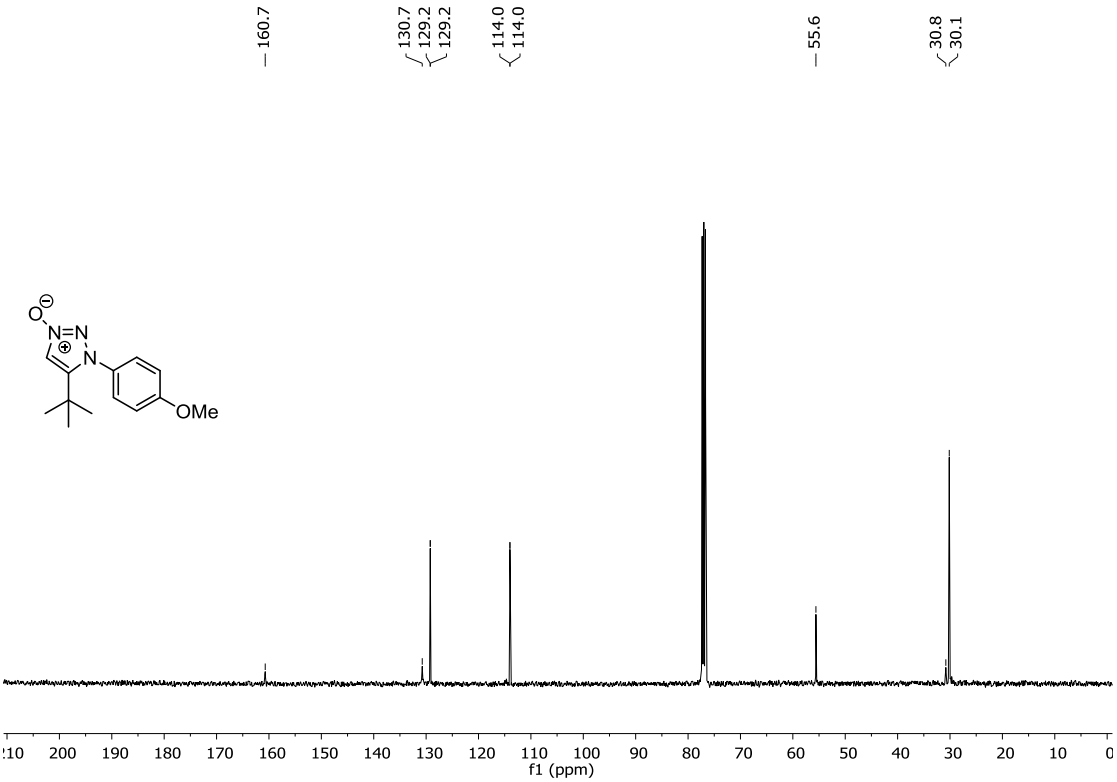
Spectrum 8.57. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9f**.



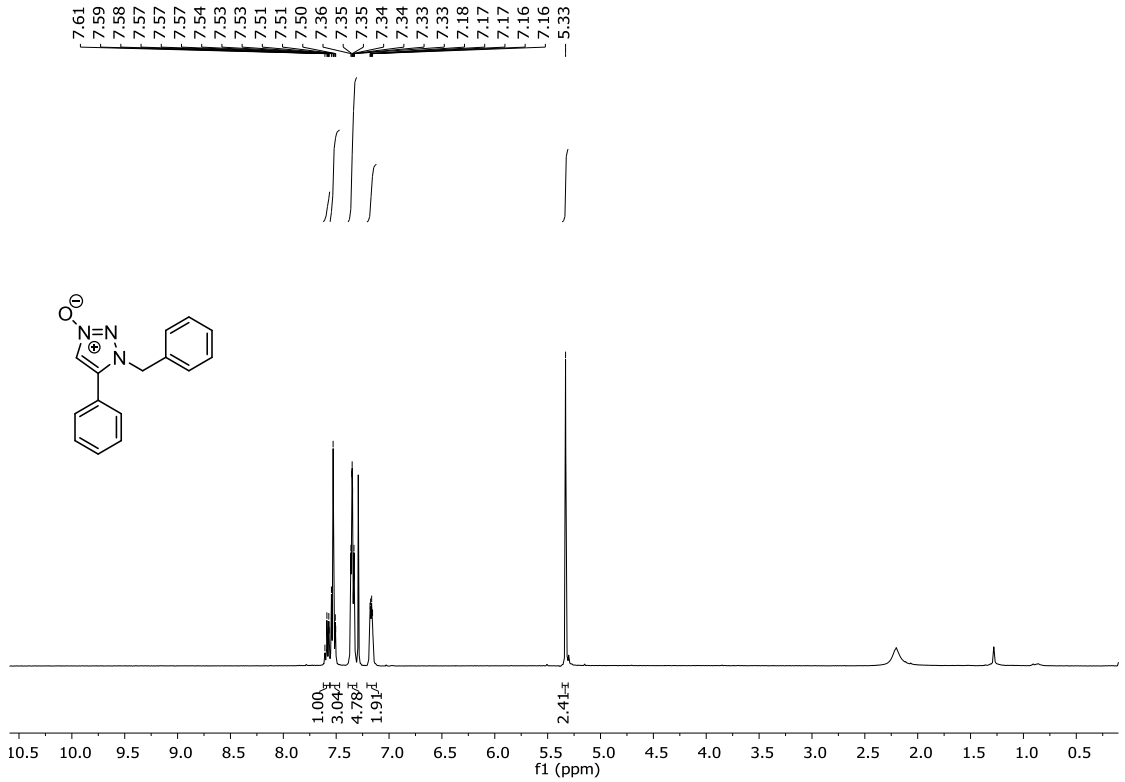
Spectrum 8.58. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9f**.



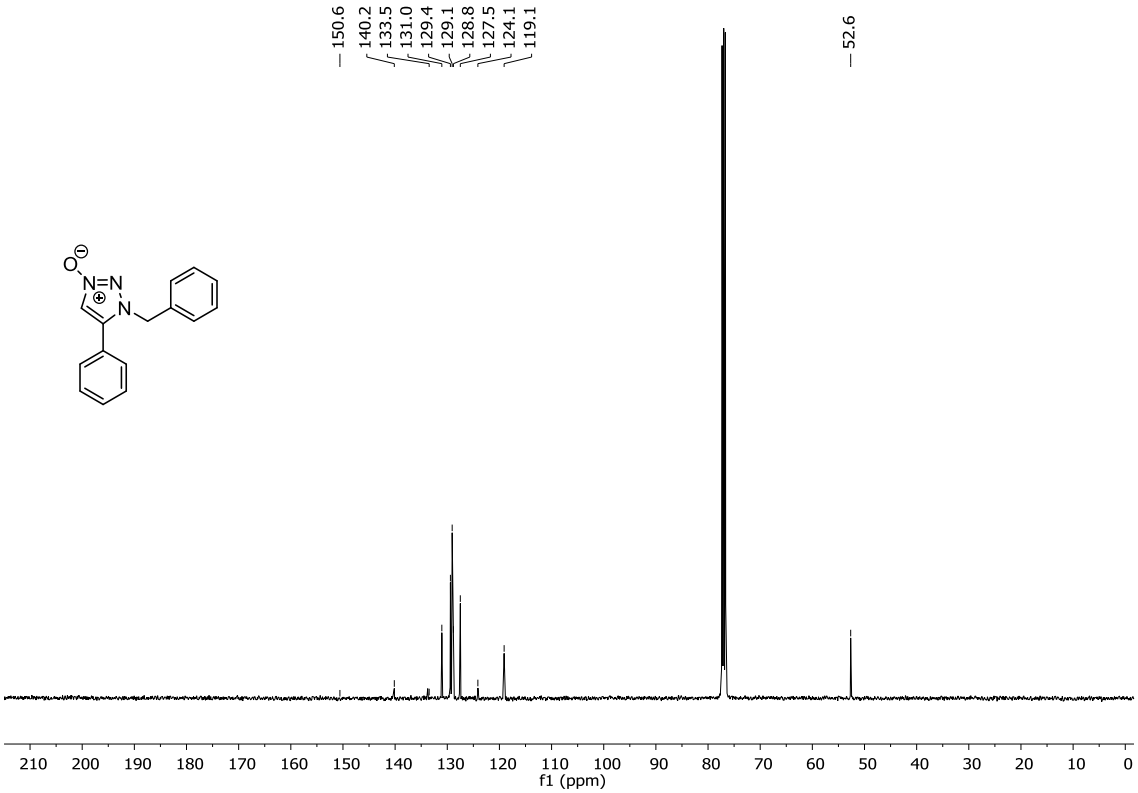
Spectrum 8.59. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9g**.



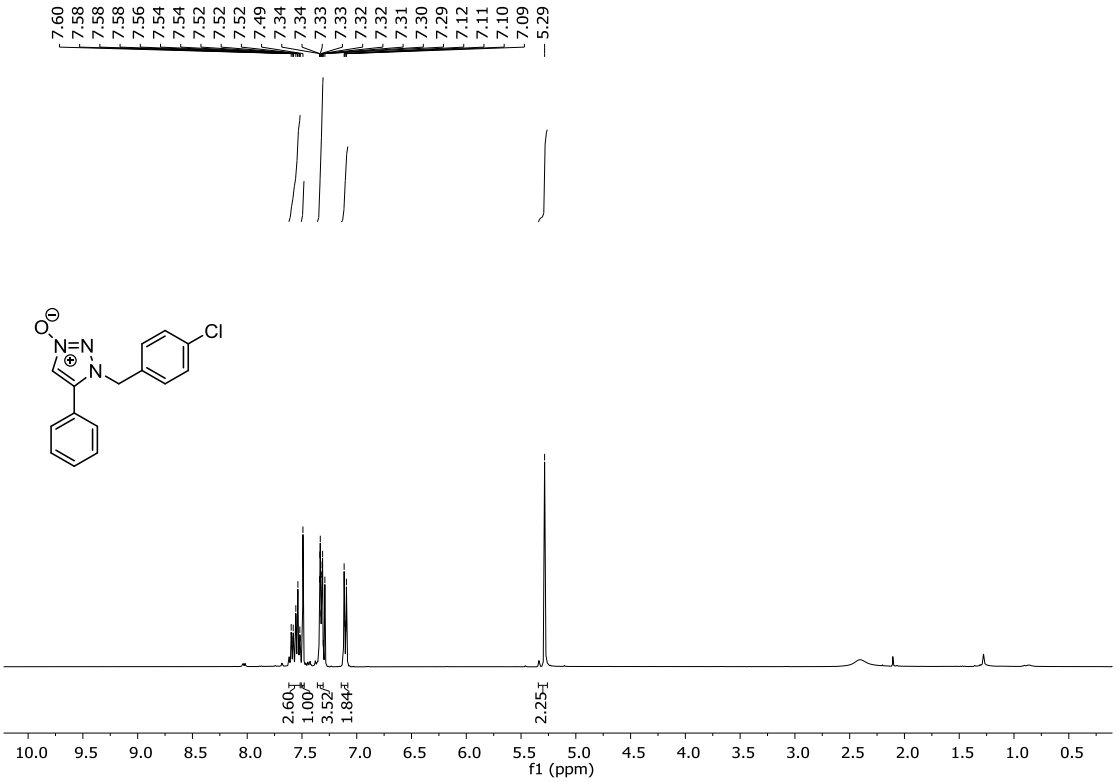
Spectrum 8.60. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9g**.



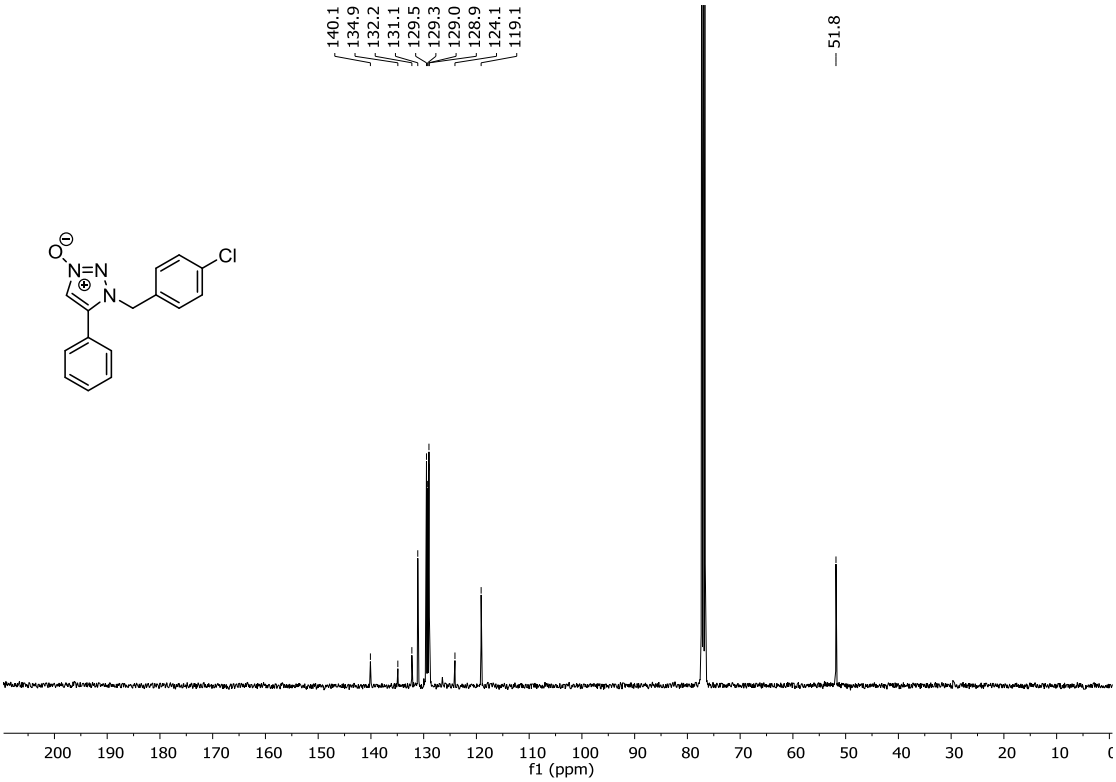
Spectrum 8.61. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9h**.



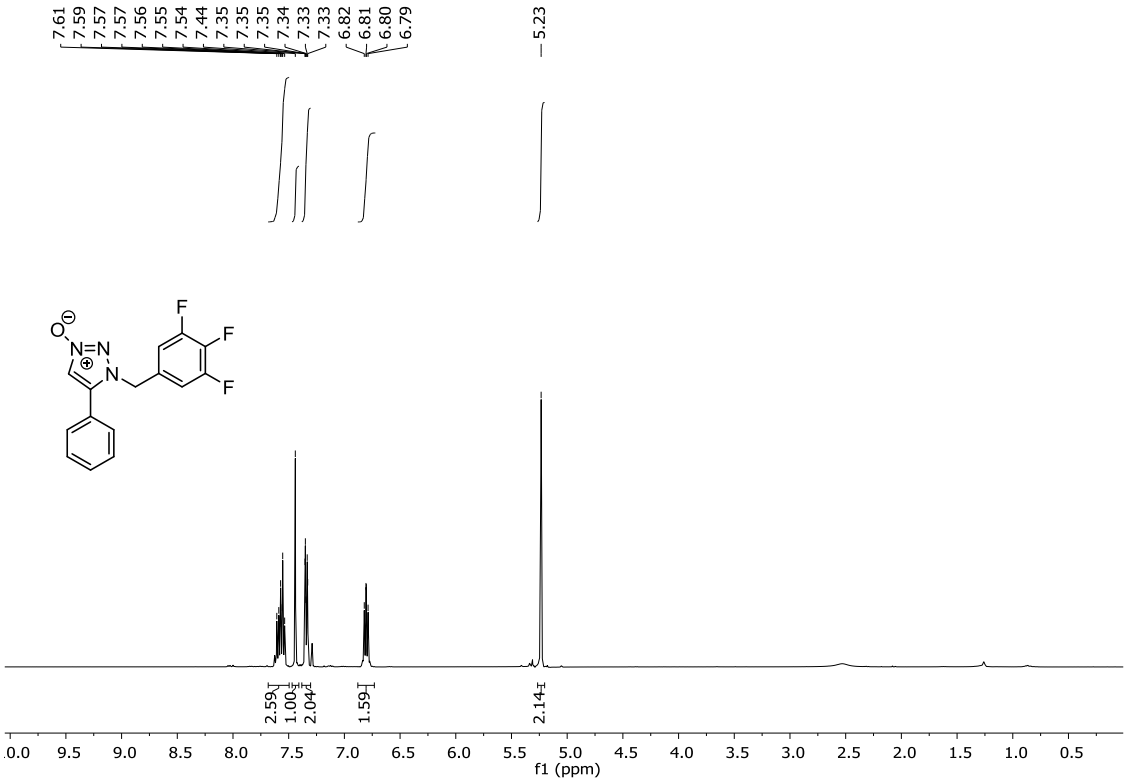
Spectrum 8.62. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9h**.



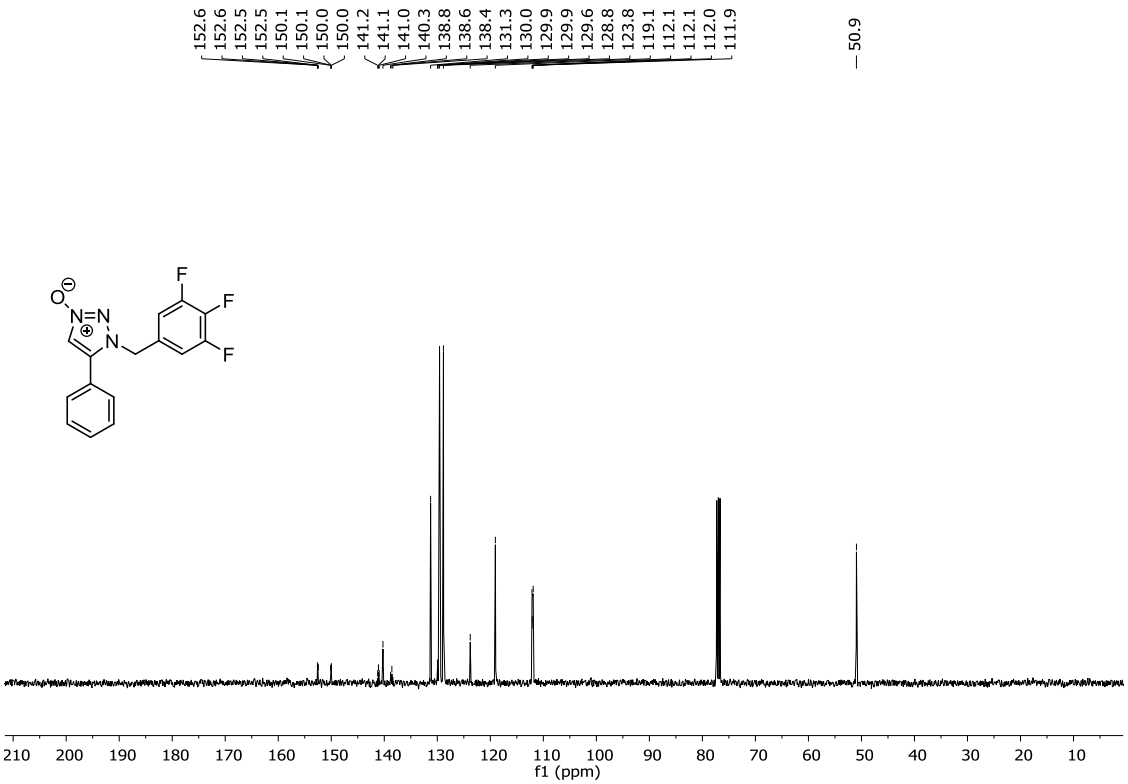
Spectrum 8.63. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9i**.



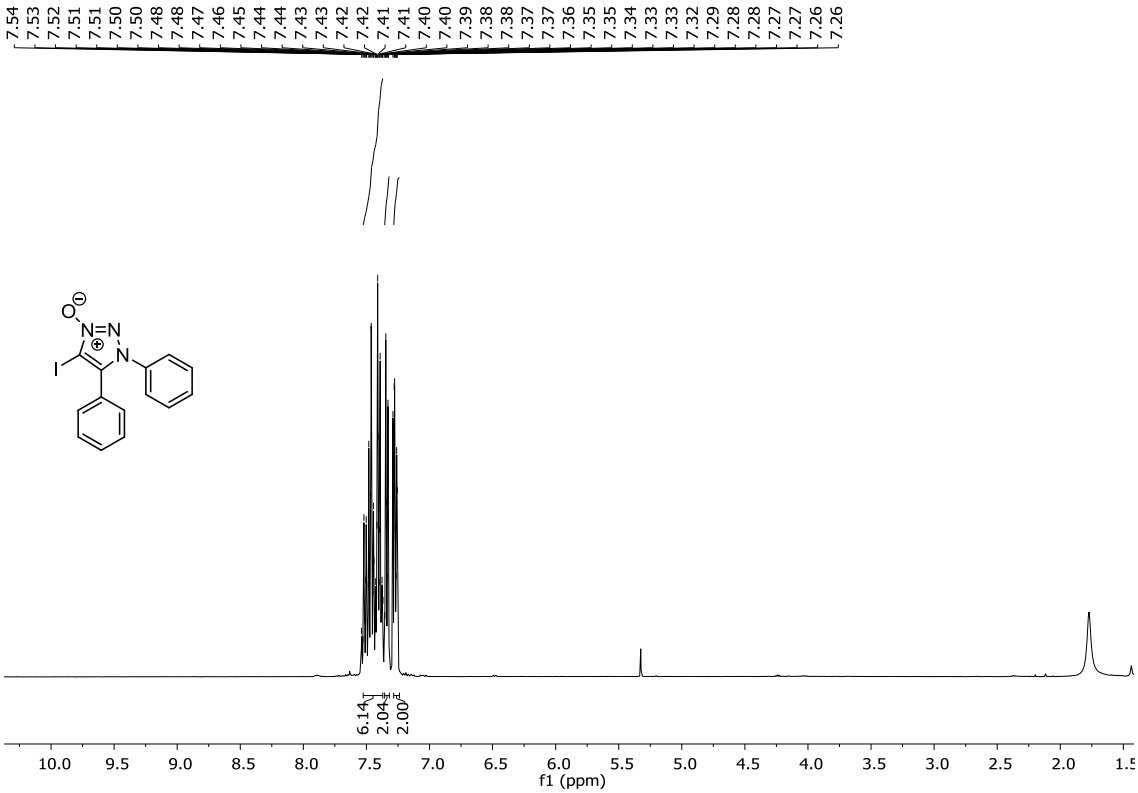
Spectrum 8.64. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9i**.



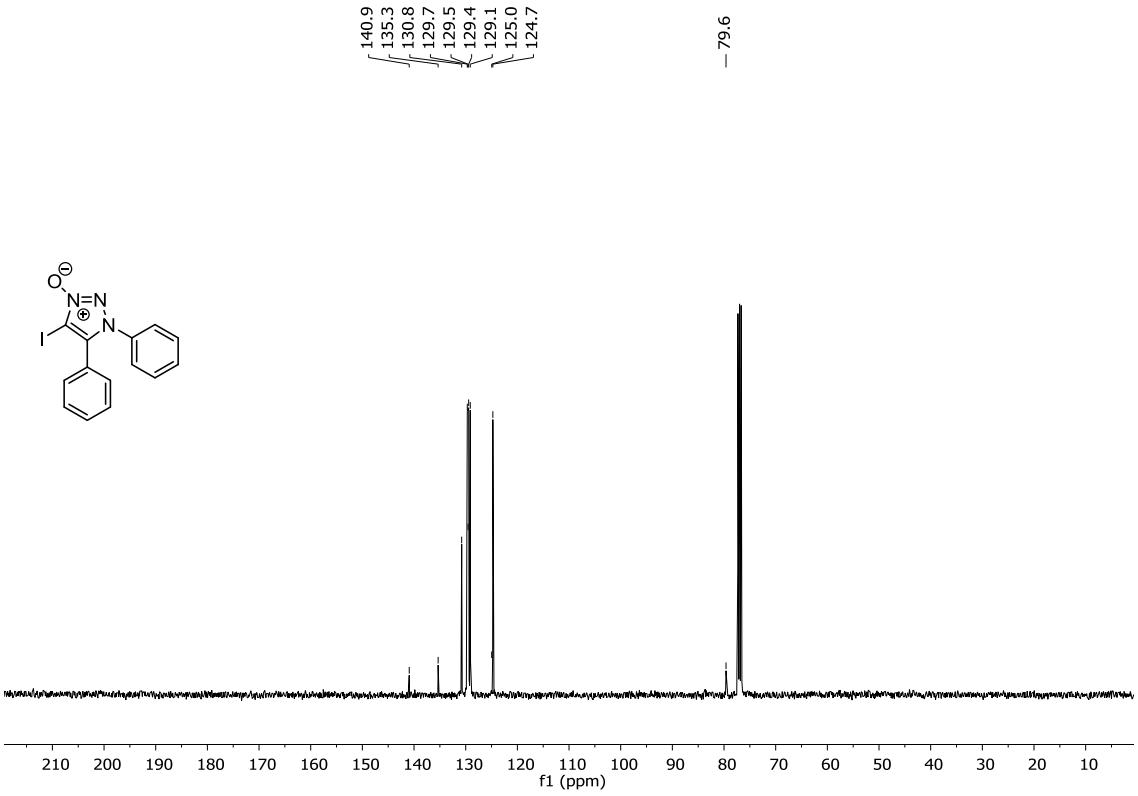
Spectrum 8.65. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9j**.



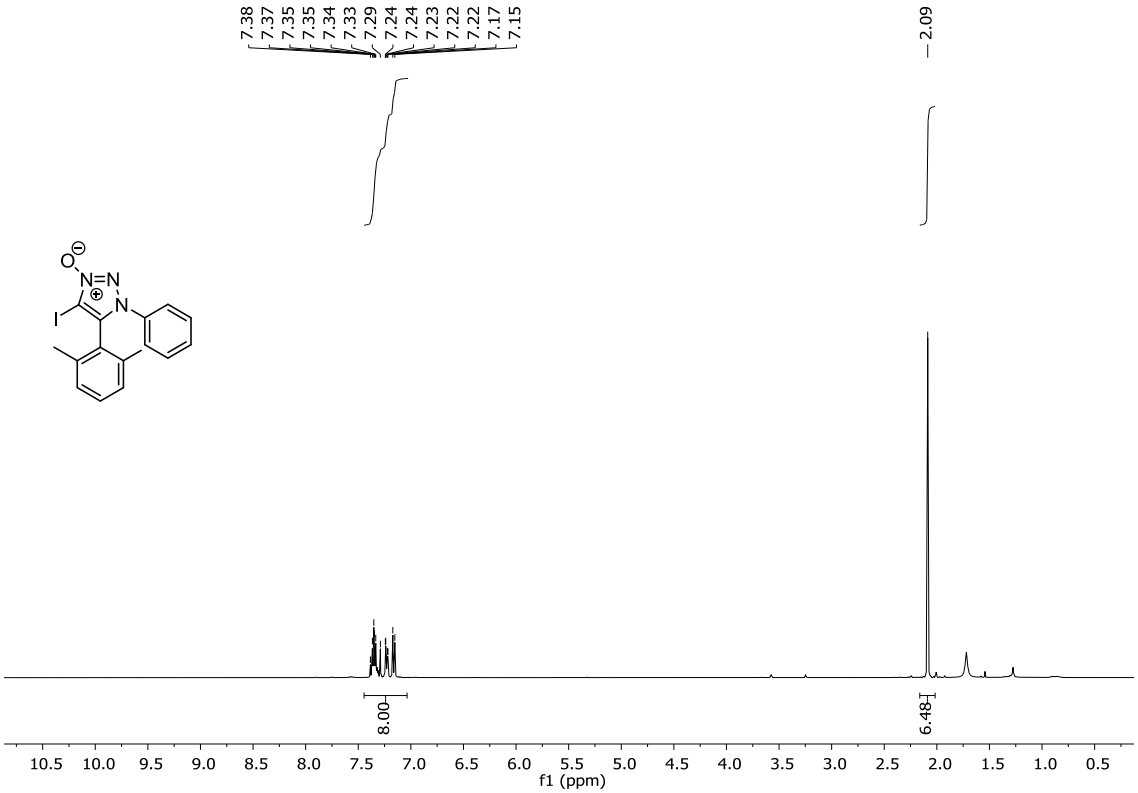
Spectrum 8.66. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9j**.



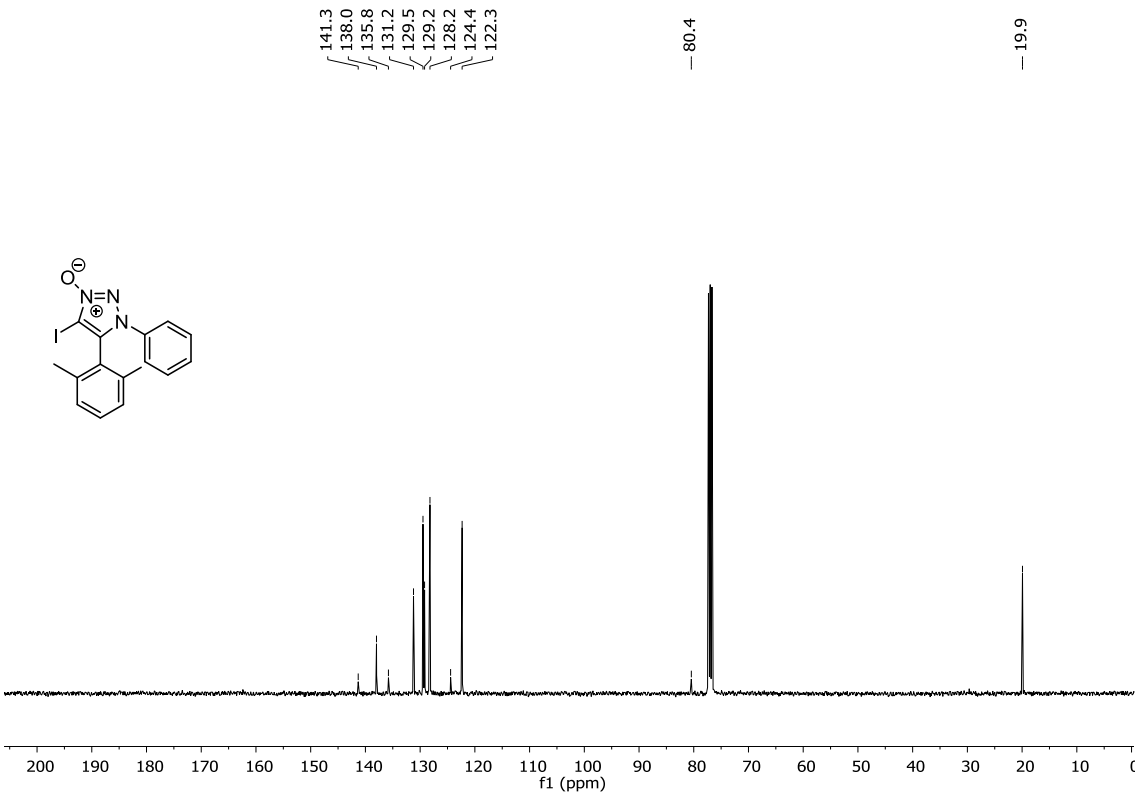
Spectrum 8.67. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18a**.



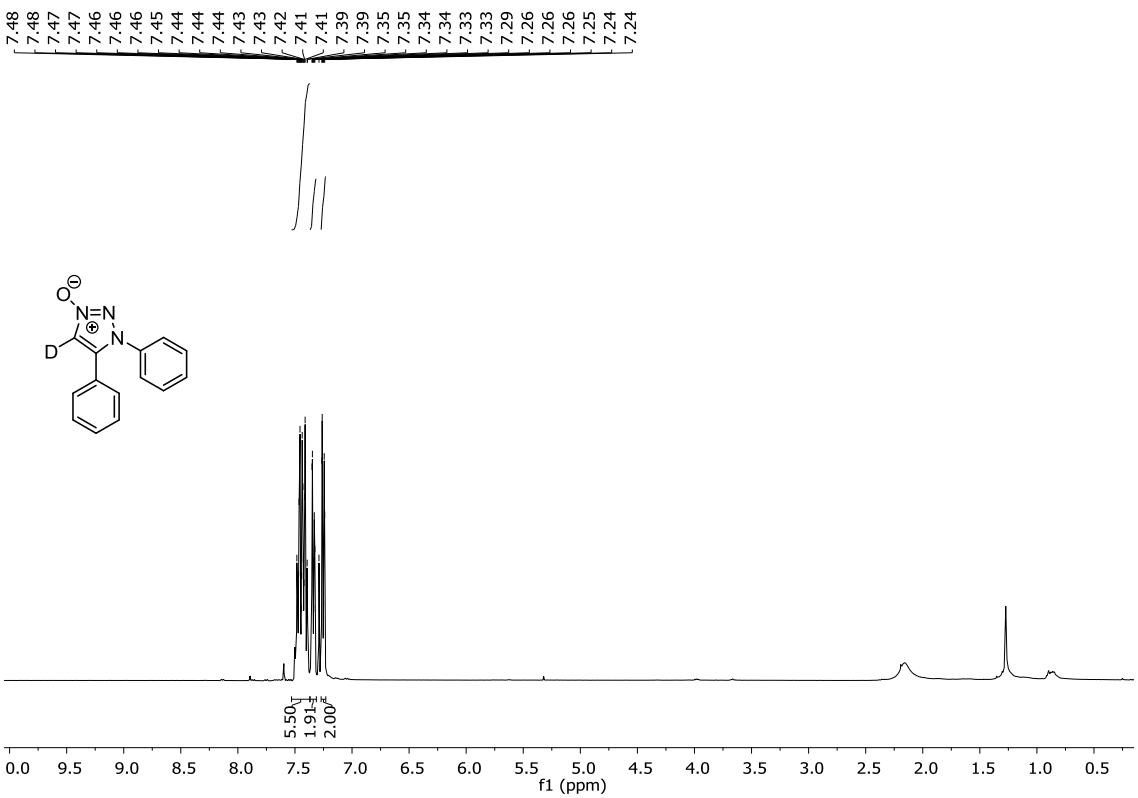
Spectrum 8.68. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18a**.



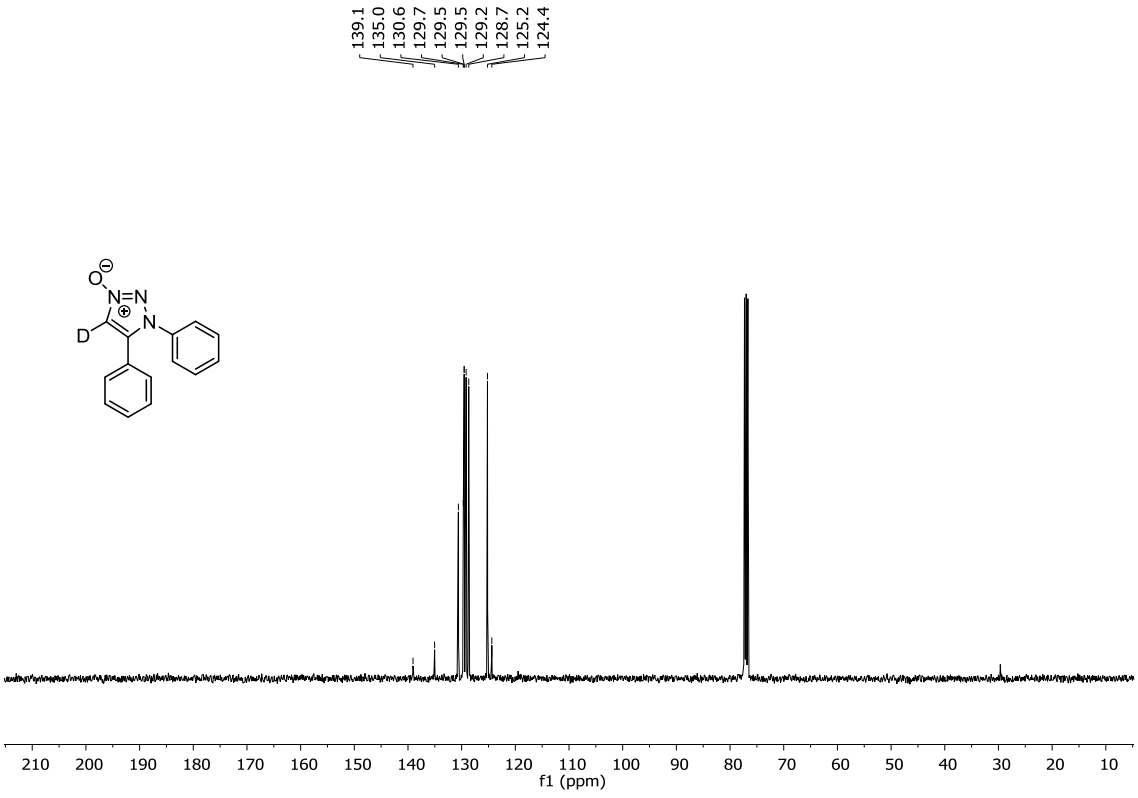
Spectrum 8.69. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18b**.



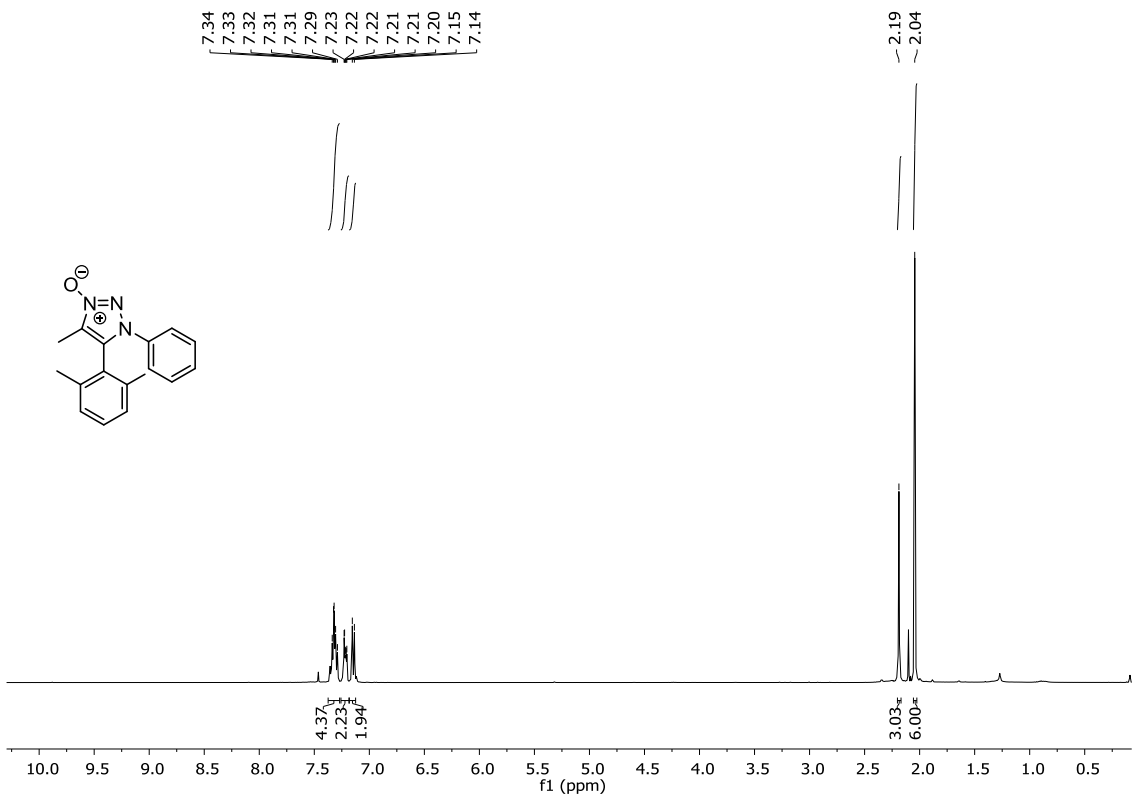
Spectrum 8.70. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18b**.



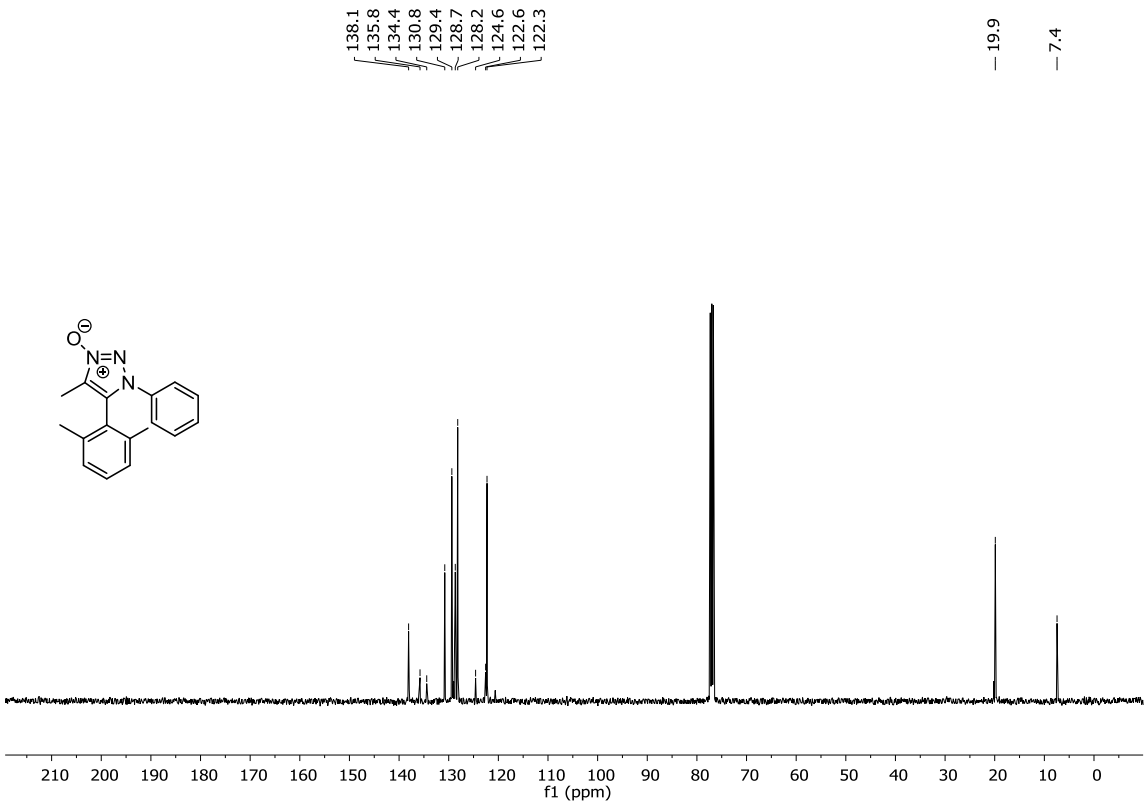
Spectrum 8.71. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18c**.



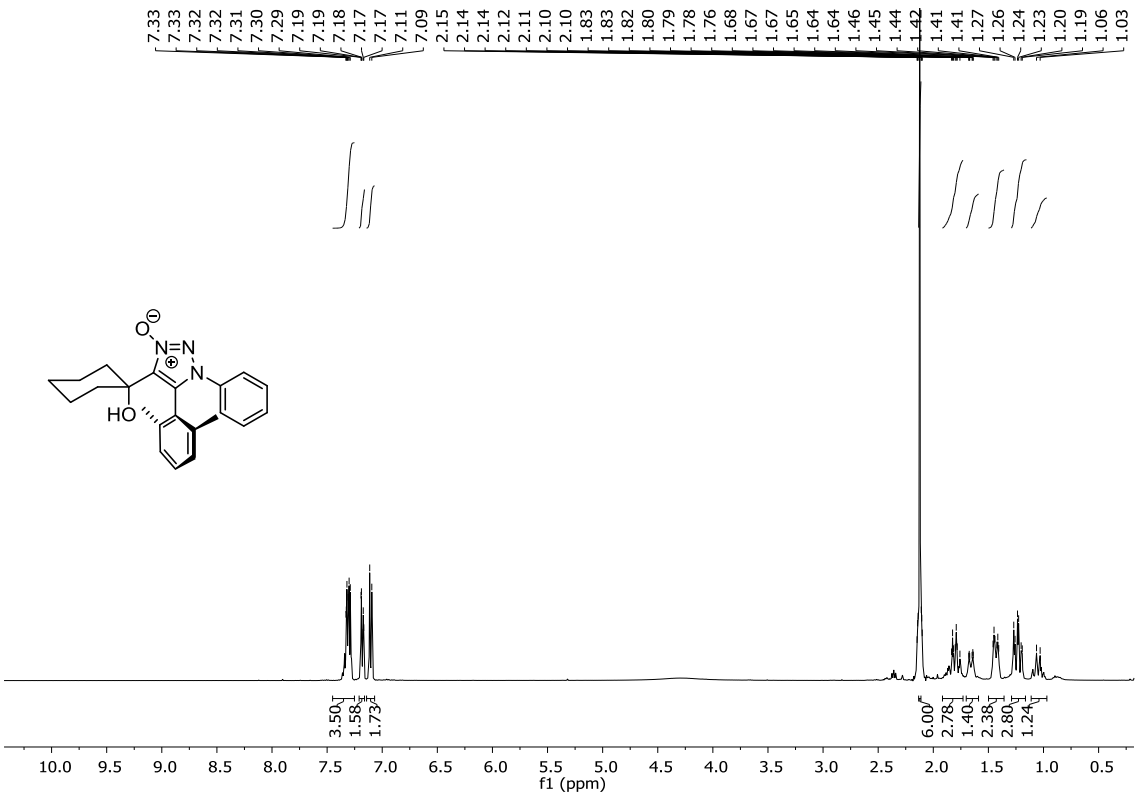
Spectrum 8.72. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18c**.



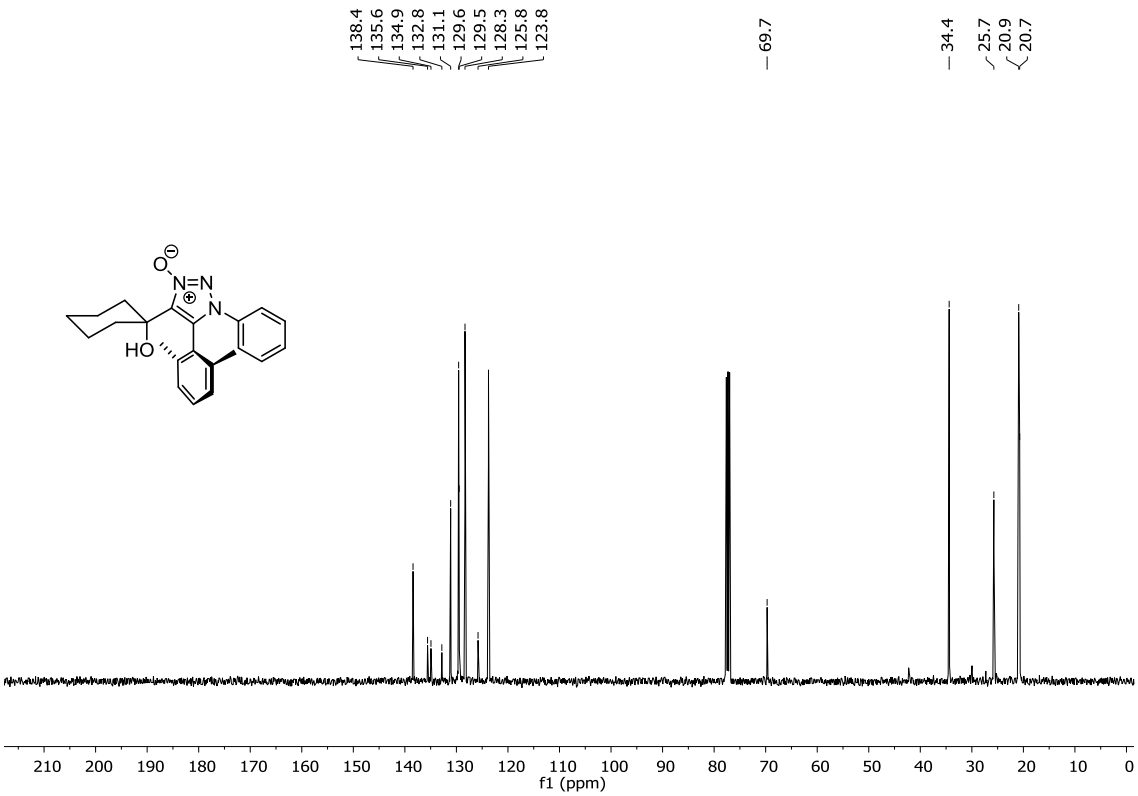
Spectrum 8.73. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18d**.



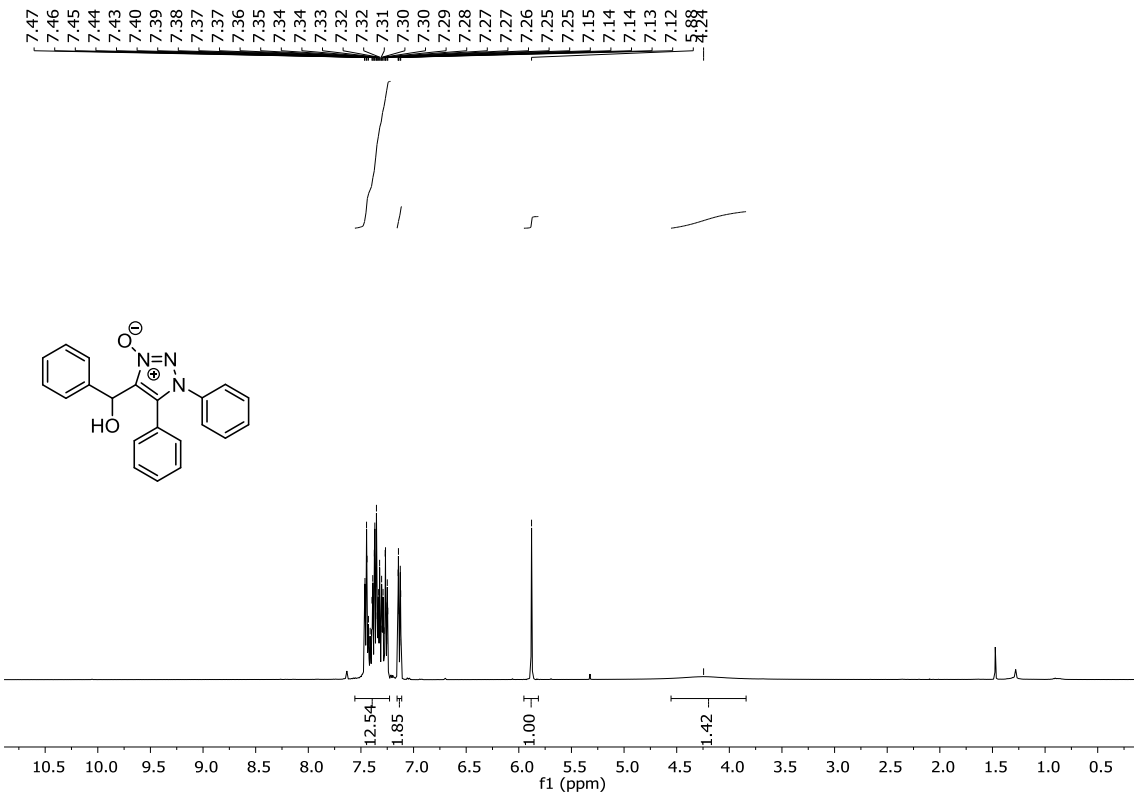
Spectrum 8.74. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18d**.



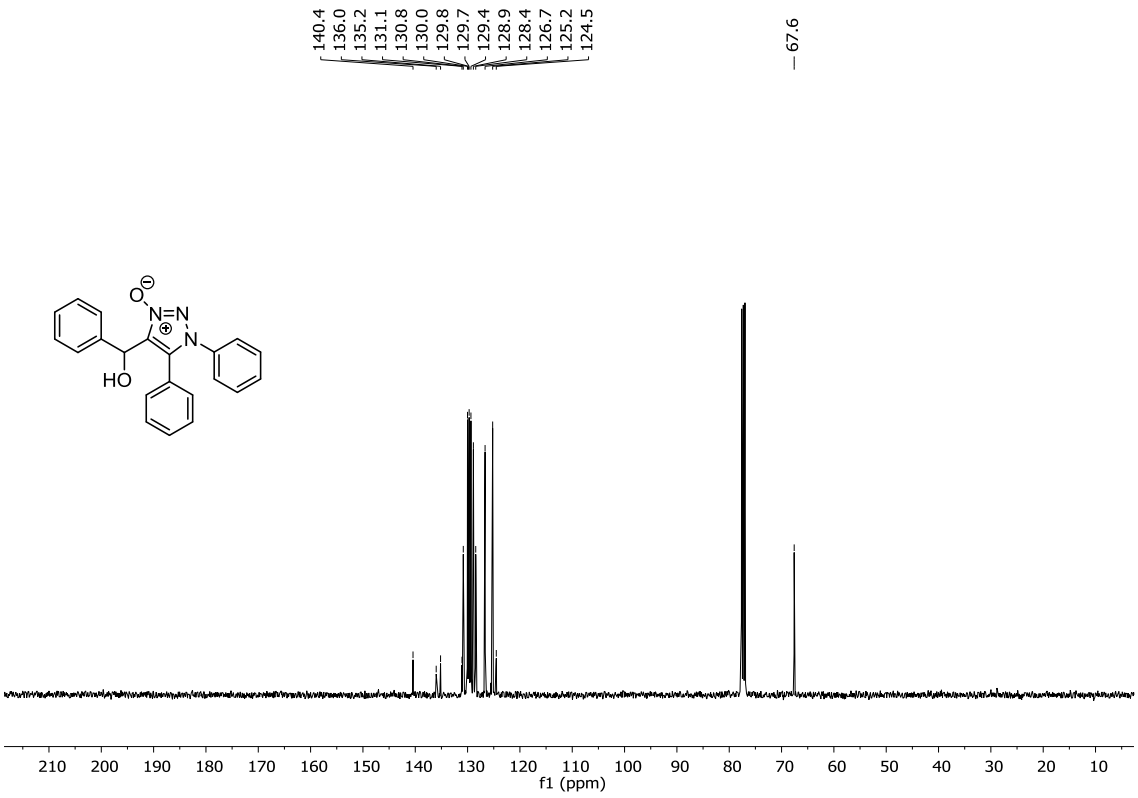
Spectrum 8.75. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18e**.



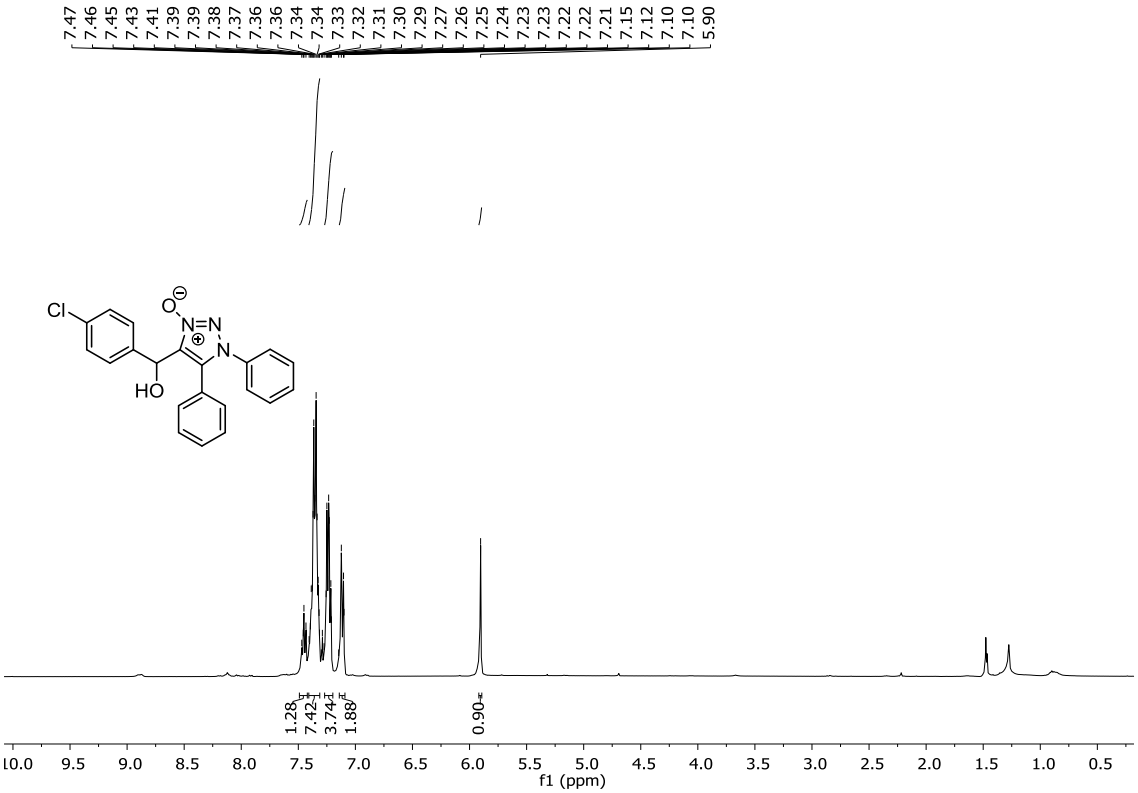
Spectrum 8.76. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18e**.



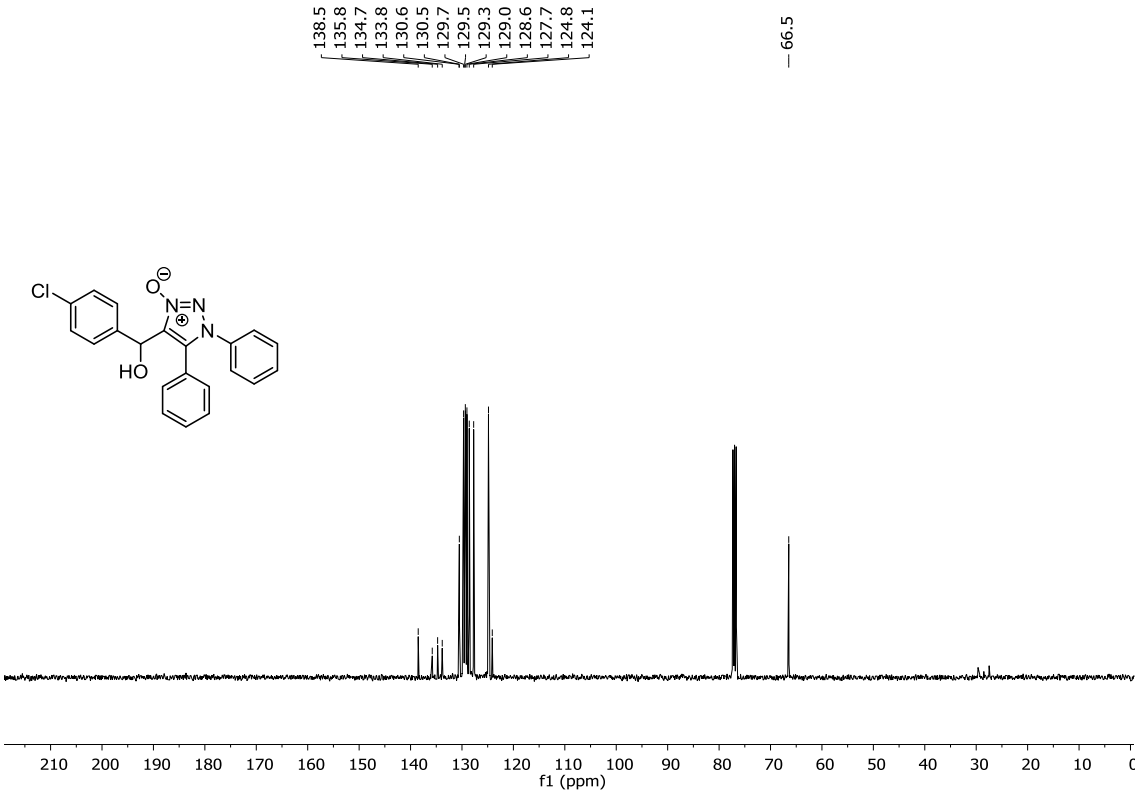
Spectrum 8.77. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18f**.



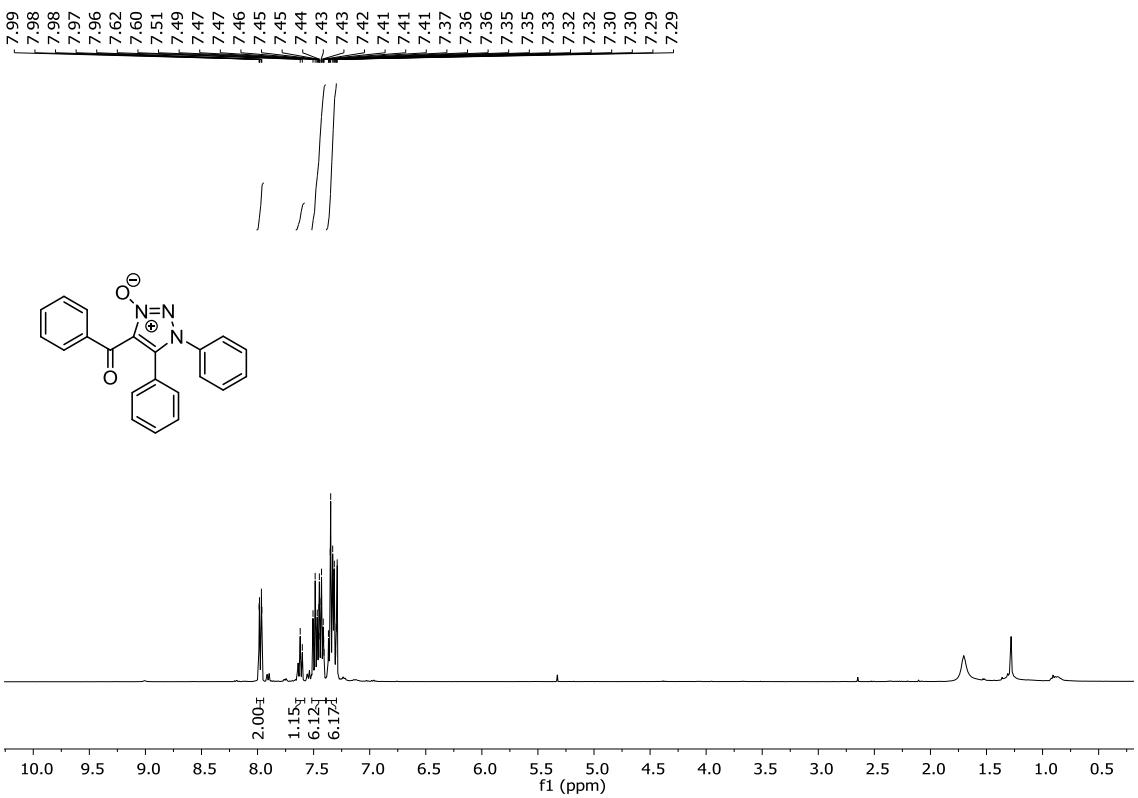
Spectrum 8.78. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18f**.



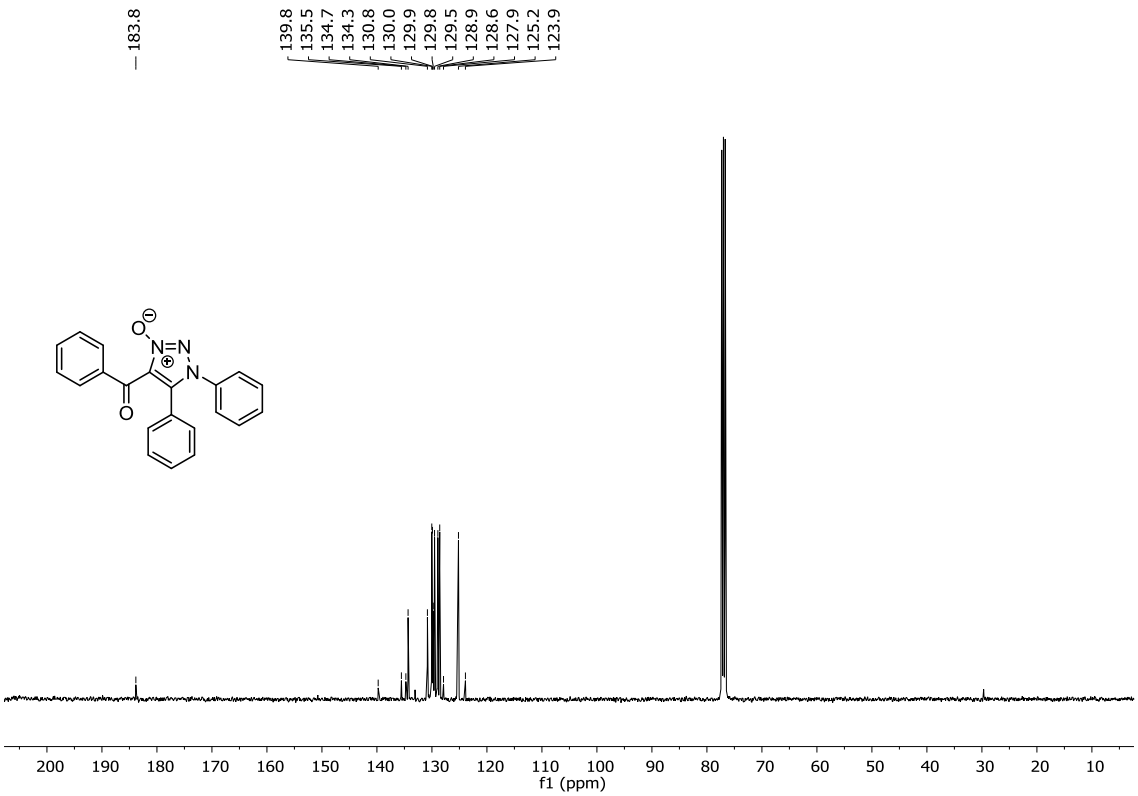
Spectrum 8.79. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18g**.



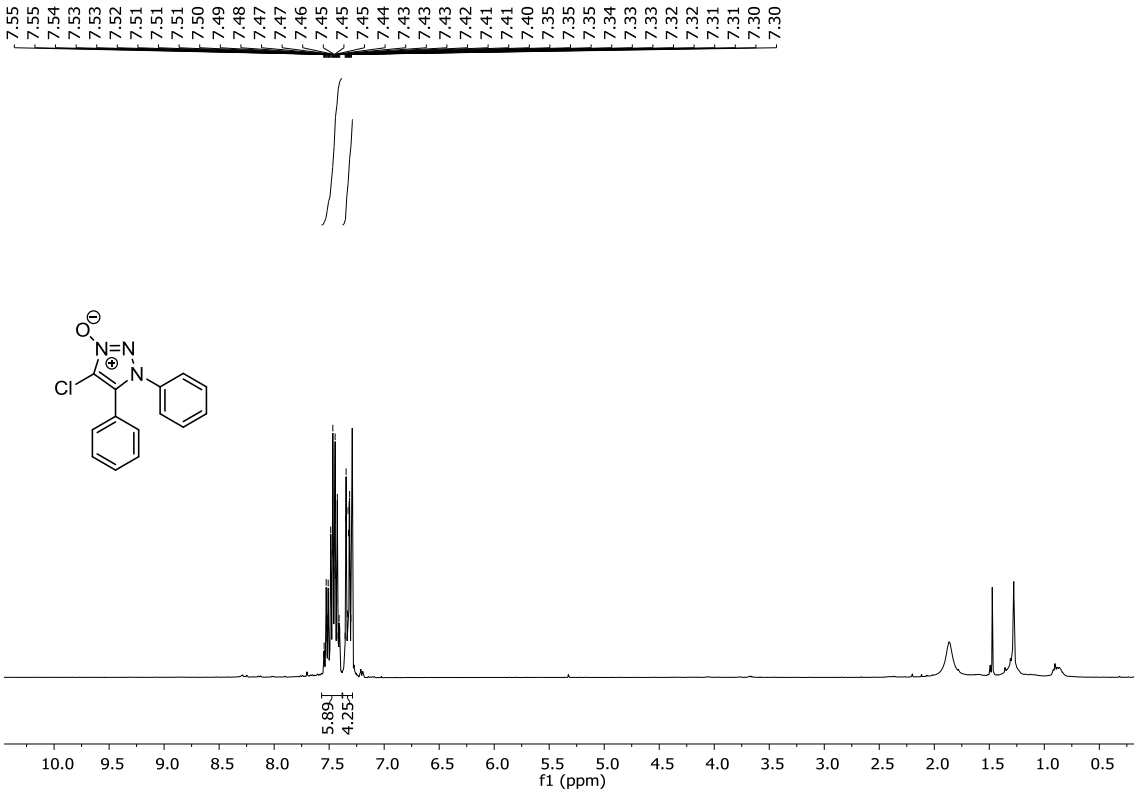
Spectrum 8.80. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18g**.



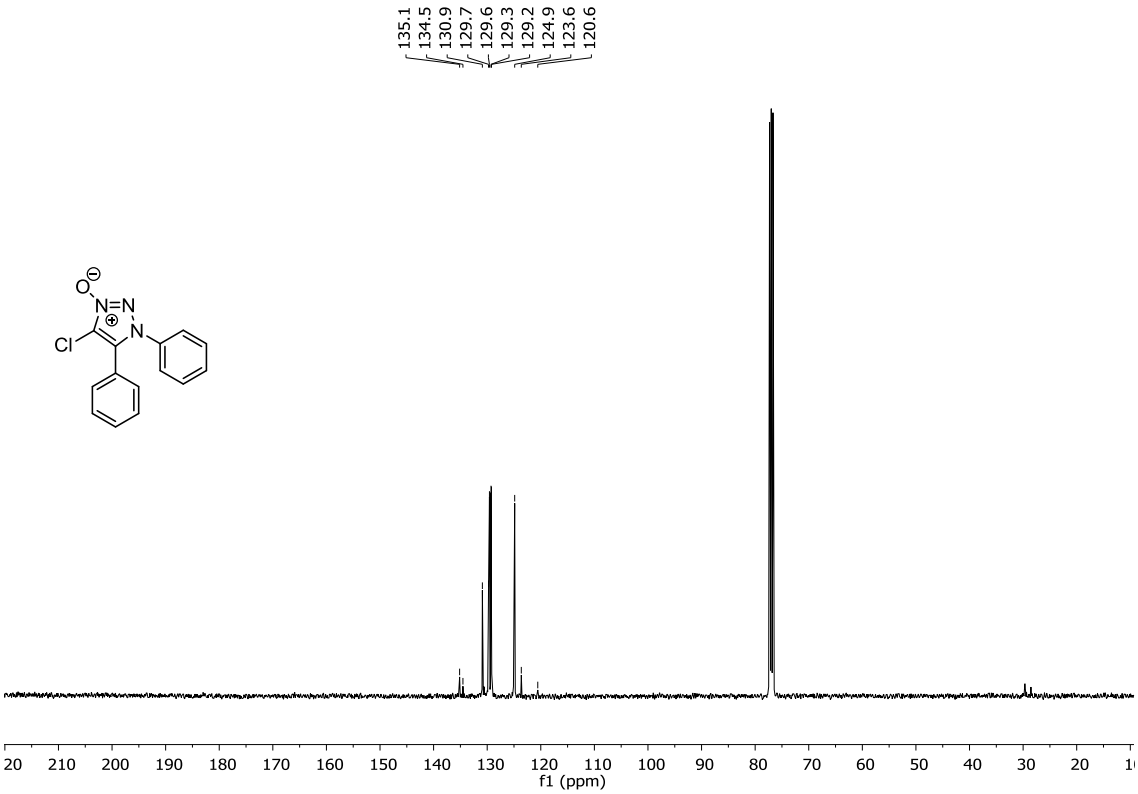
Spectrum 8.81. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18h**.



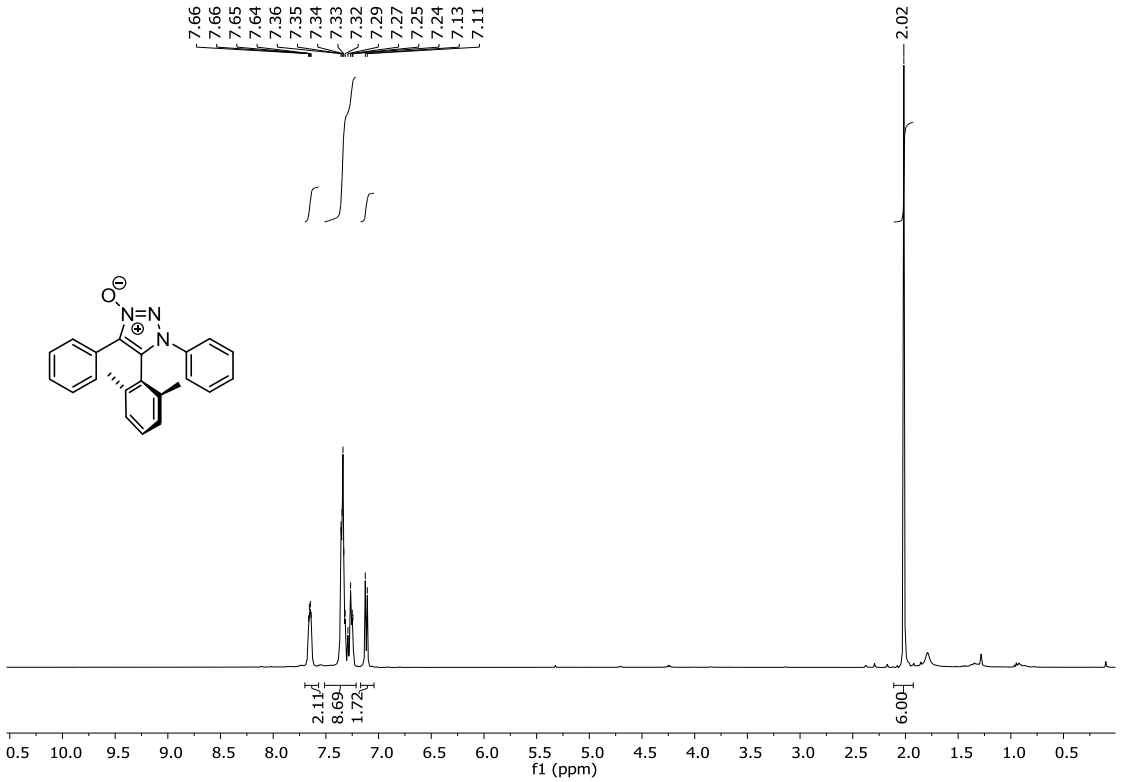
Spectrum 8.82. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18h**.



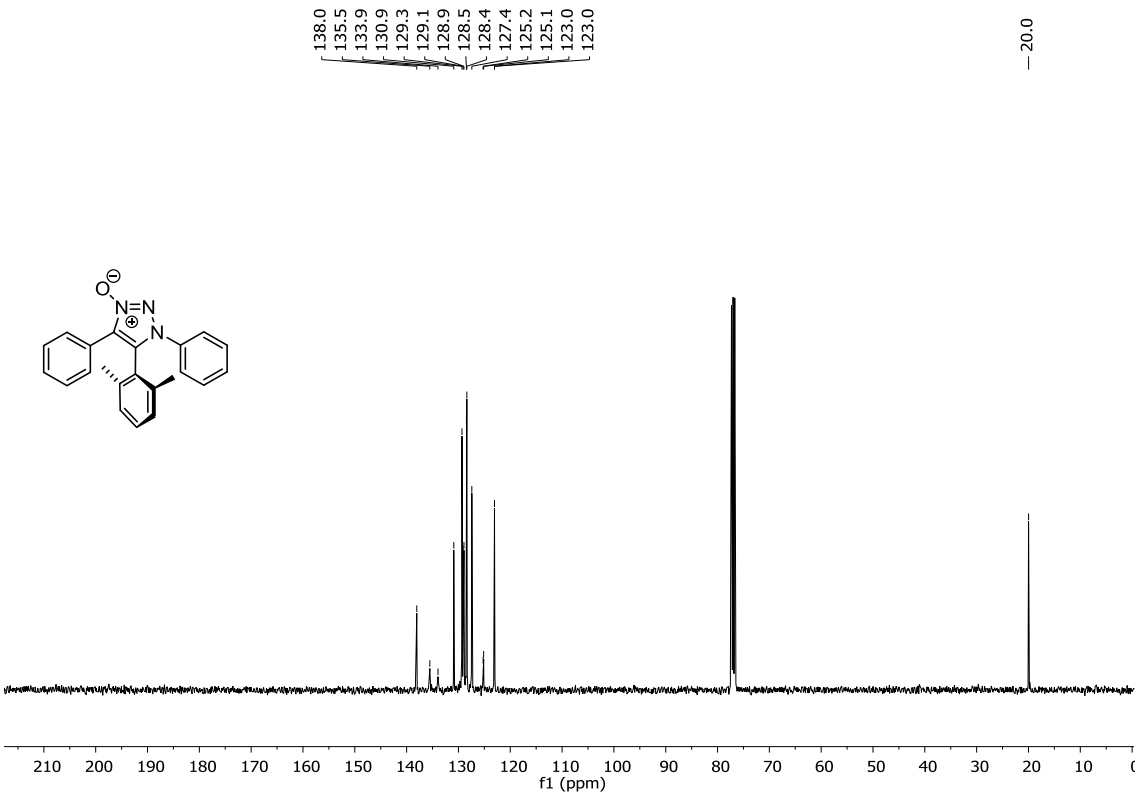
Spectrum 8.83. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **18i**.



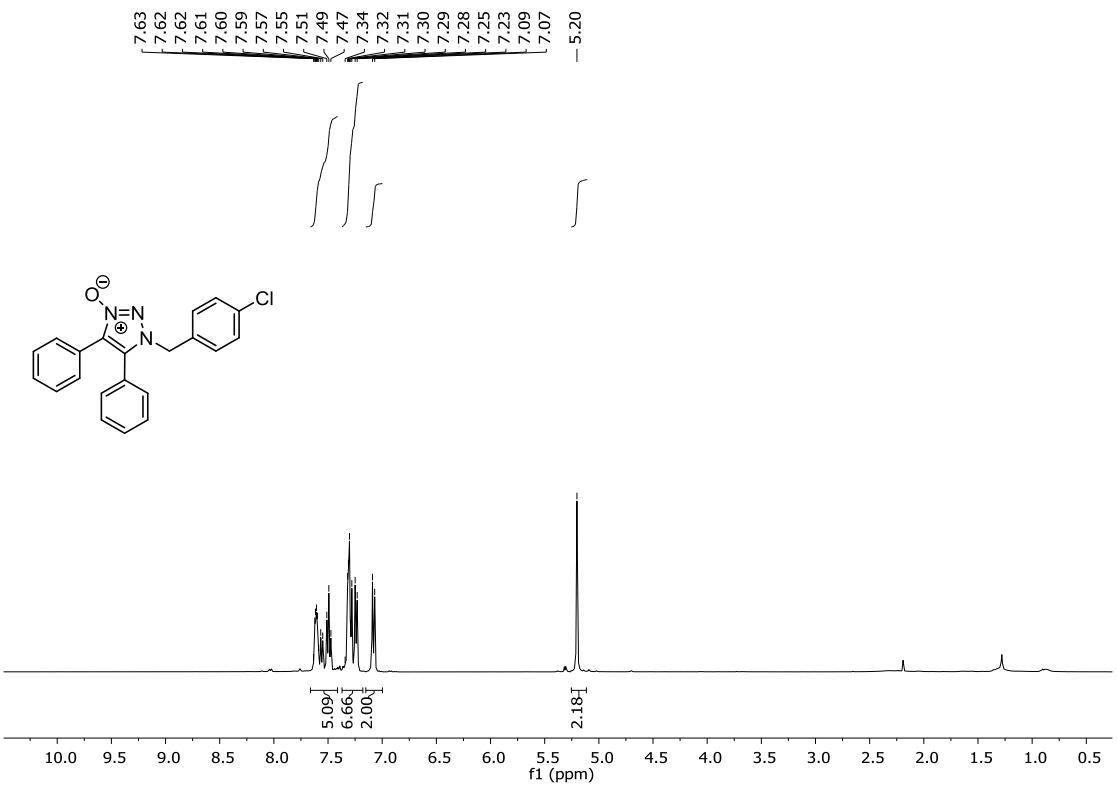
Spectrum 8.84. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **18i**.



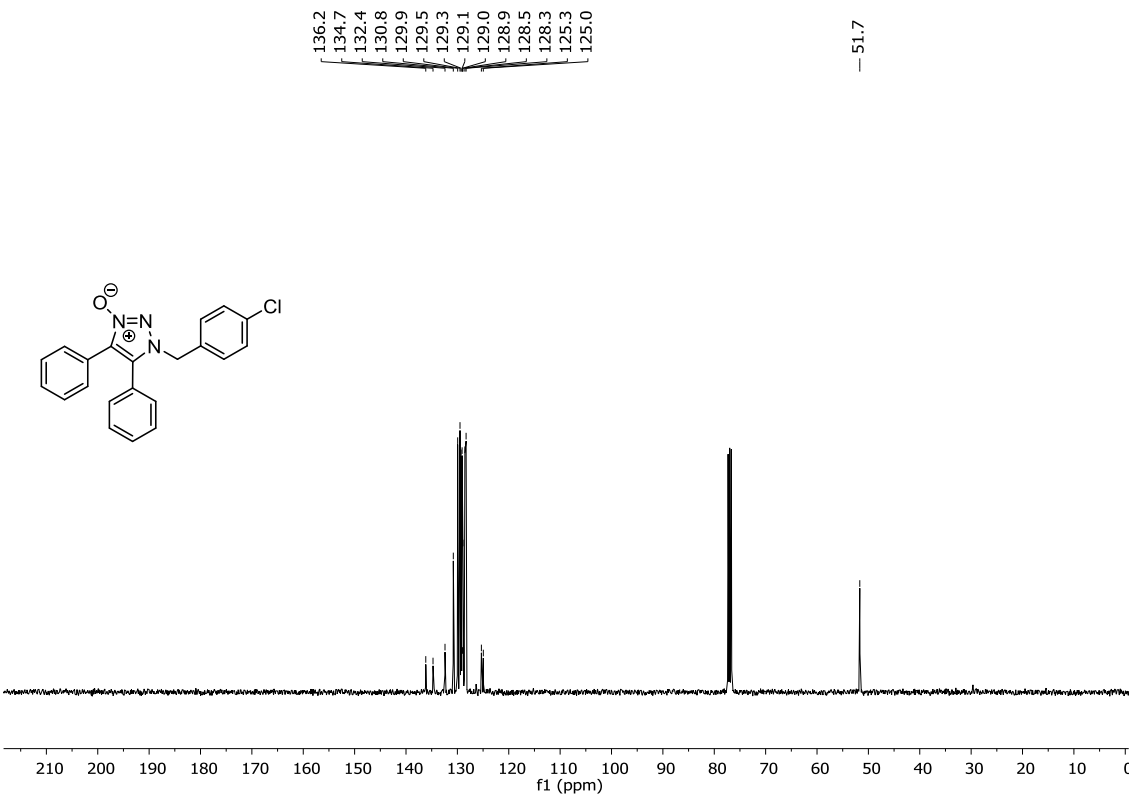
Spectrum 8.85. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19a**.



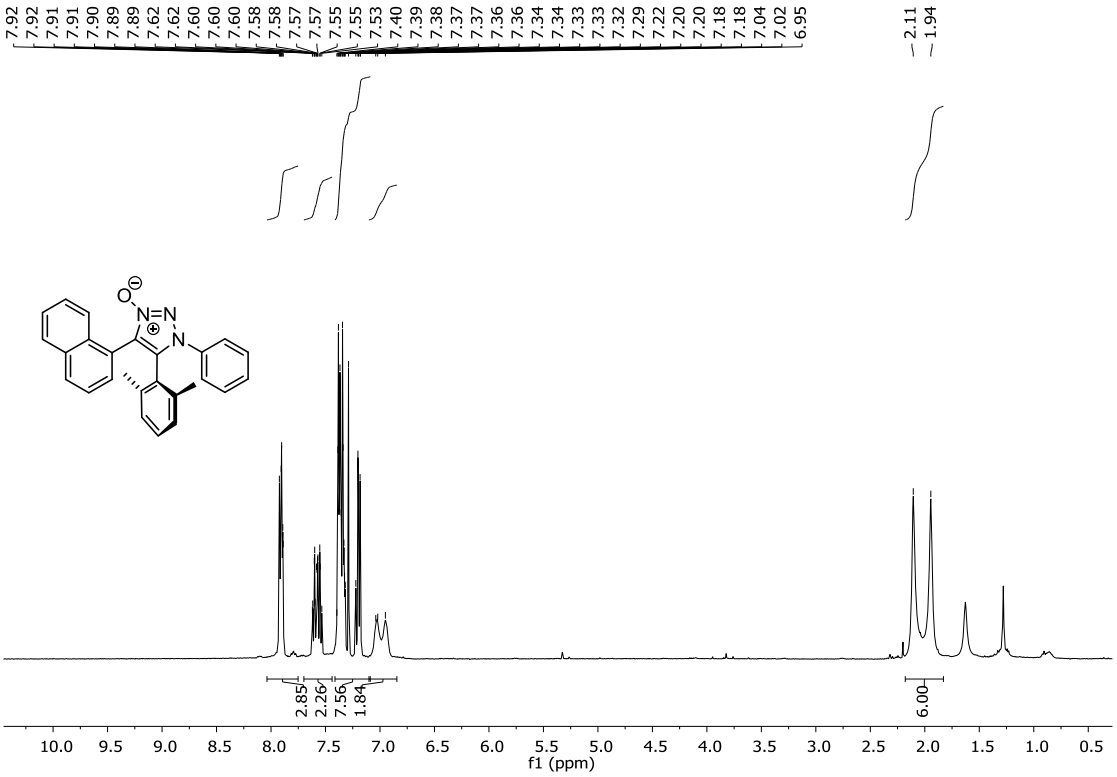
Spectrum 8.86. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19a**.



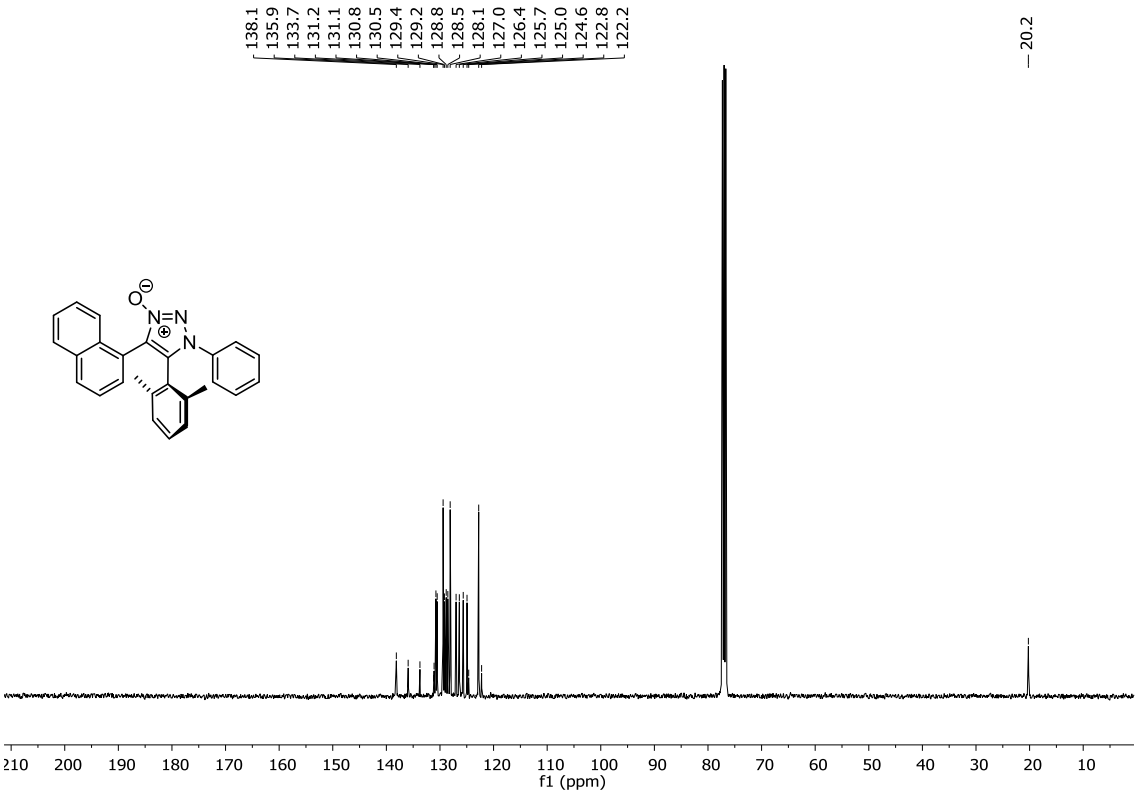
Spectrum 8.87. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19b**.



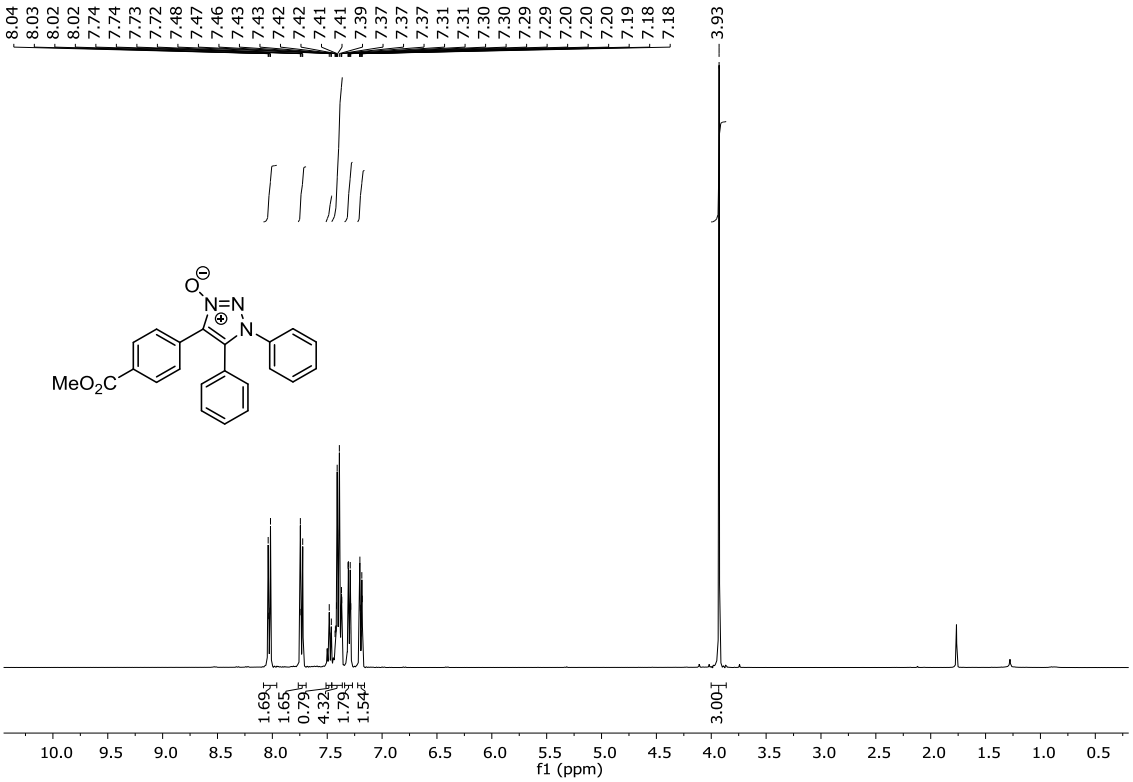
Spectrum 8.88. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19b**.



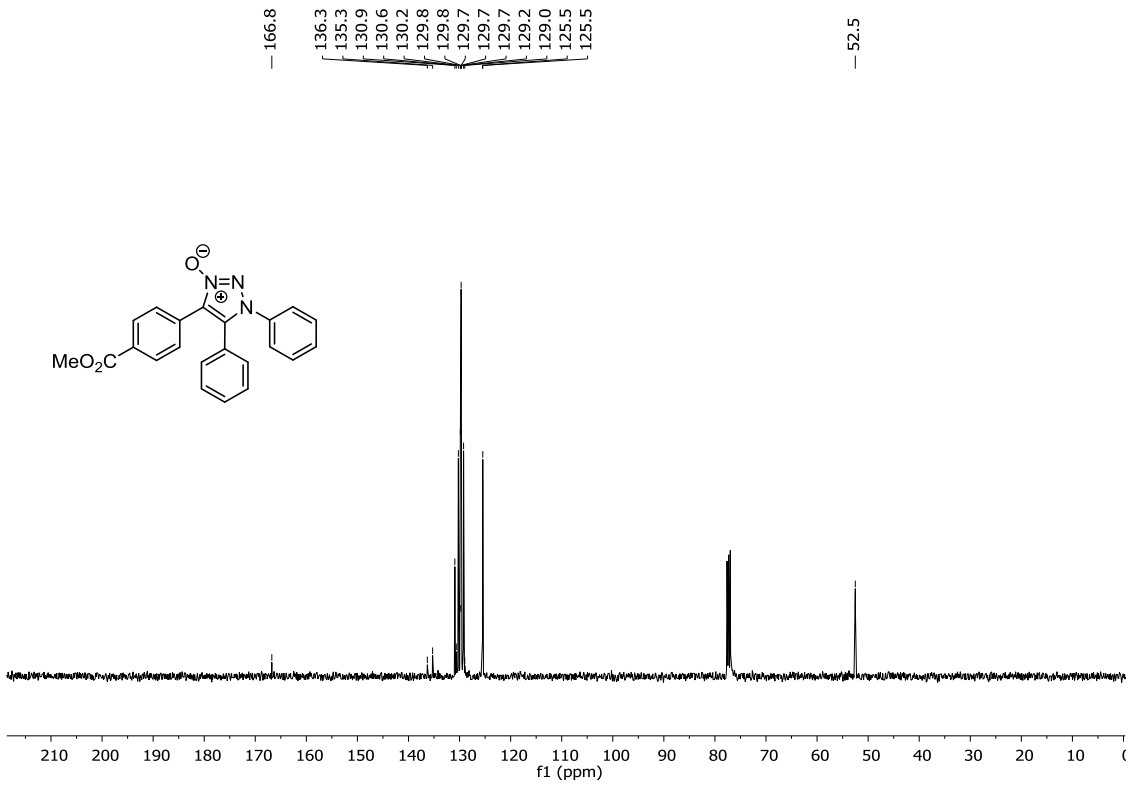
Spectrum 8.89. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19c**.



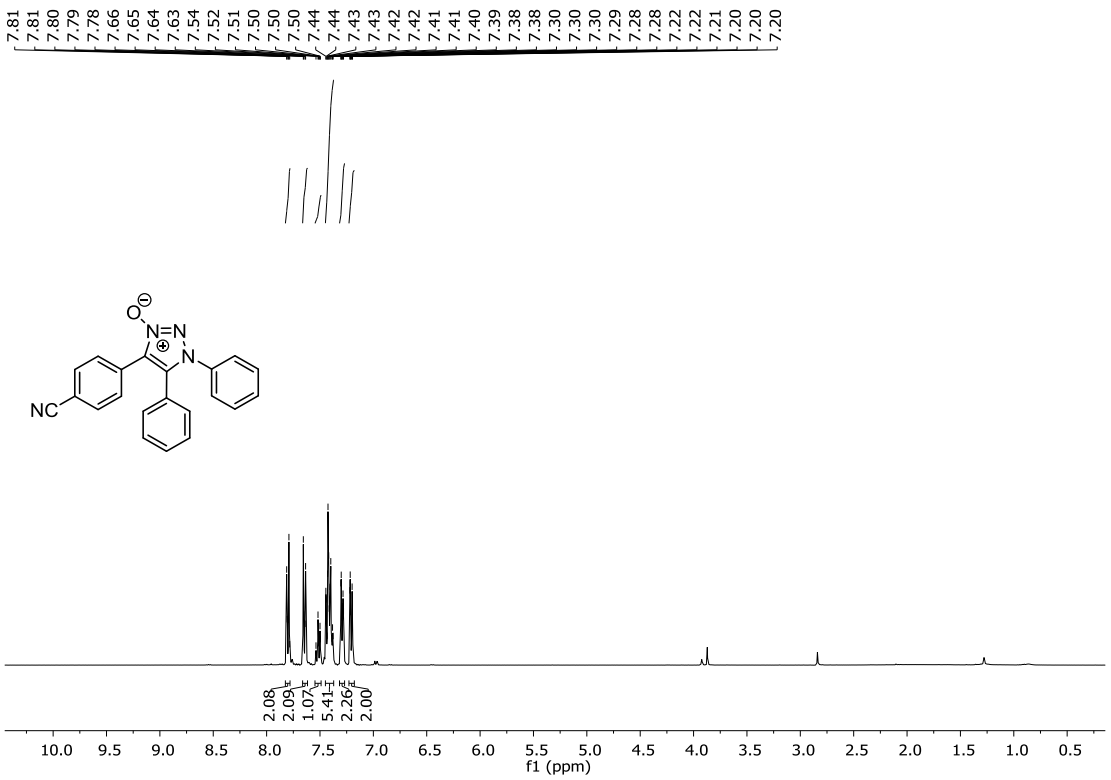
Spectrum 8.90. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19c**.



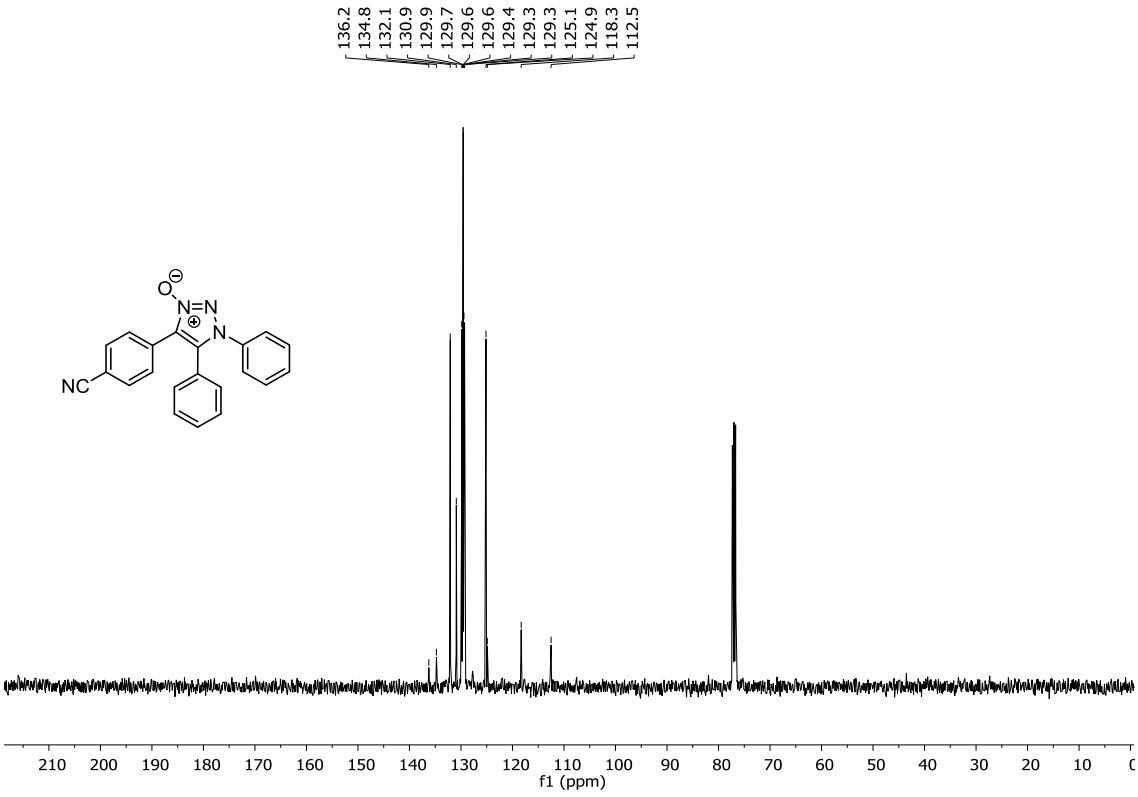
Spectrum 8.91. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19d**.



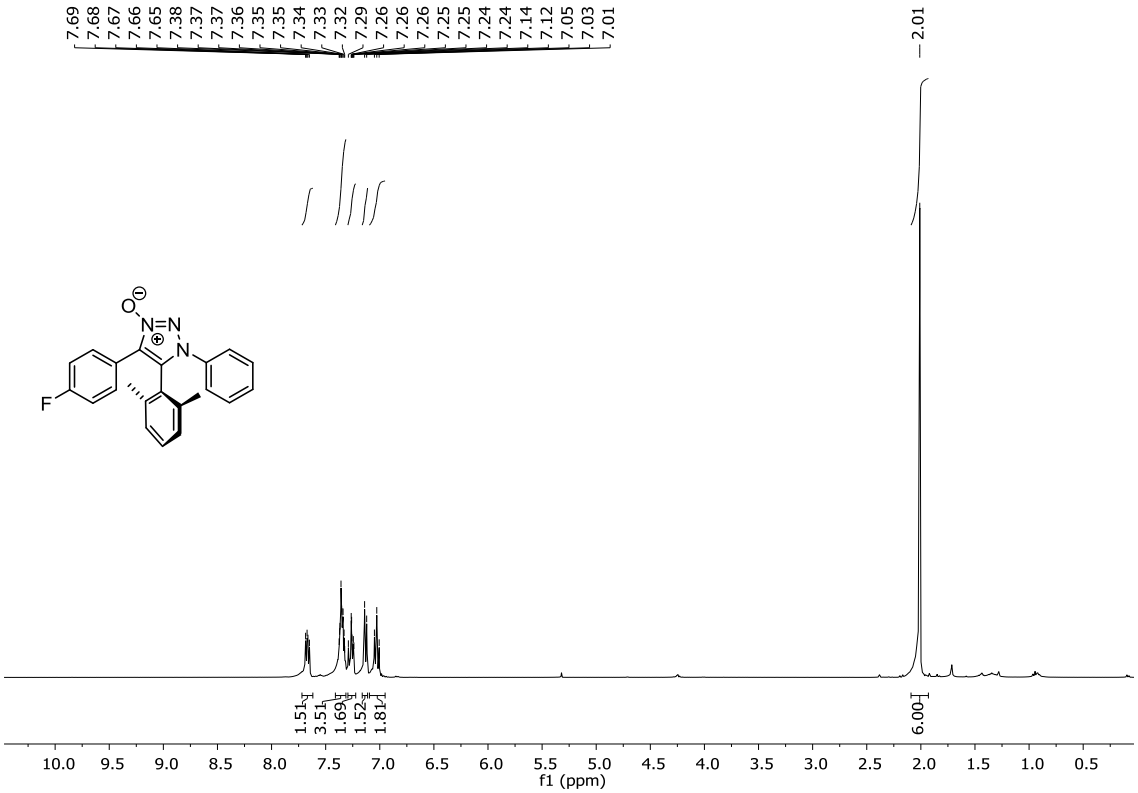
Spectrum 8.92. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19d**.



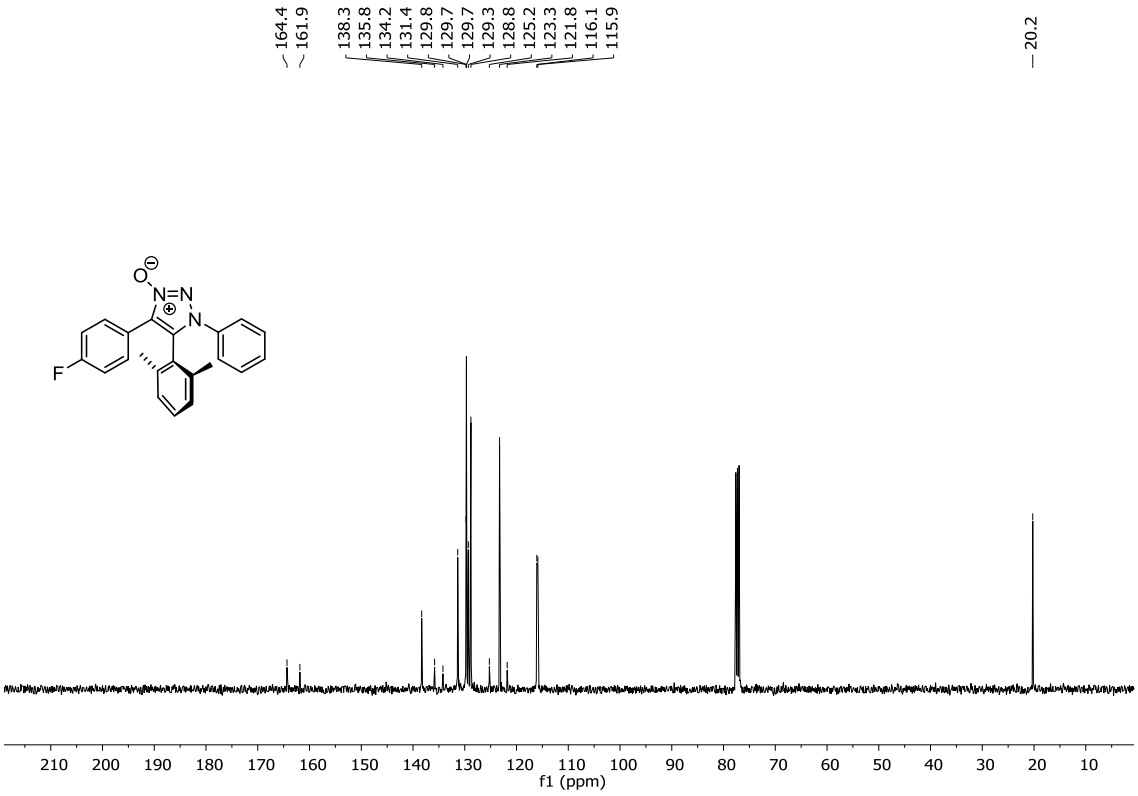
Spectrum 8.93. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19e**.



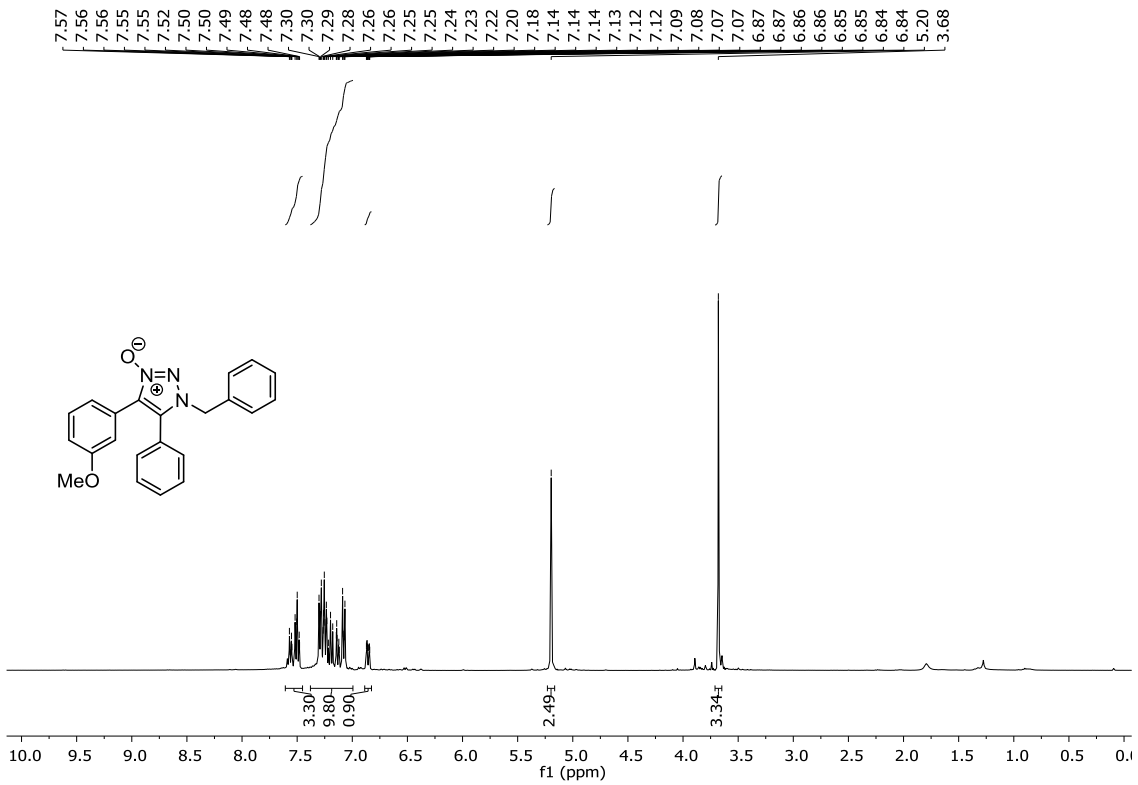
Spectrum 8.94. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19e**.



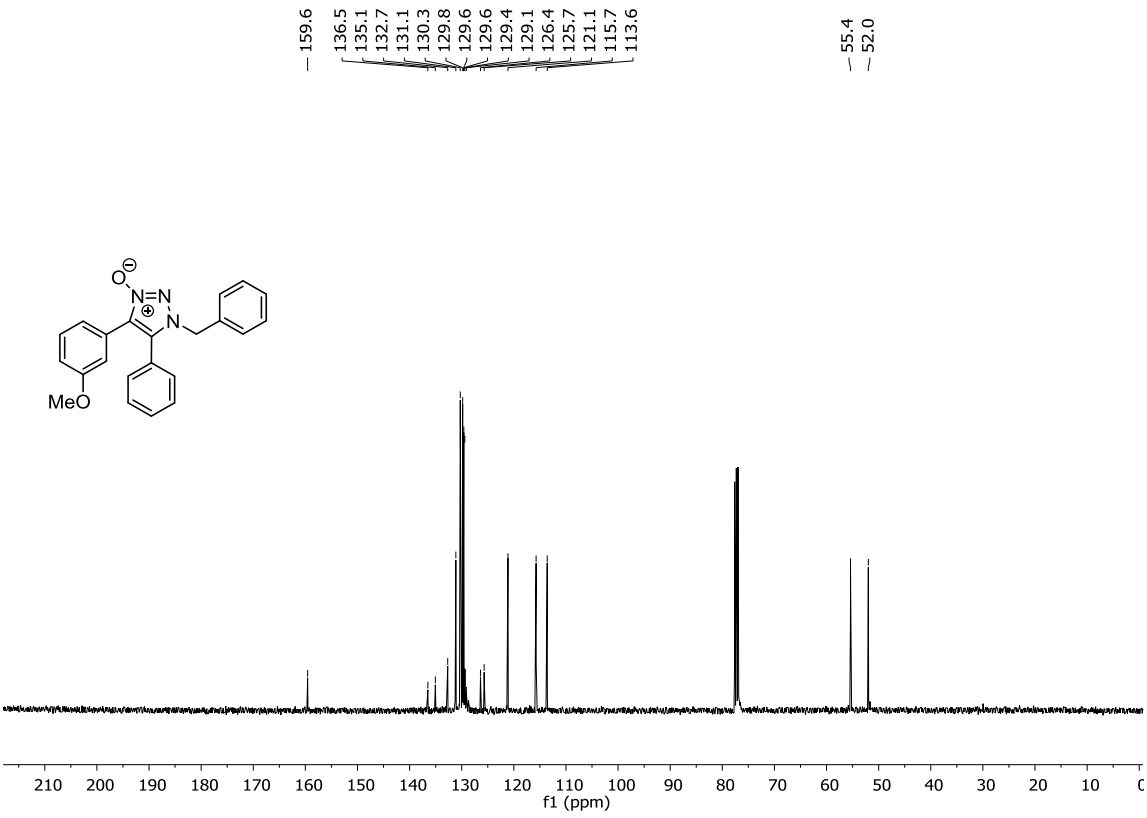
Spectrum 8.95. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19f**.



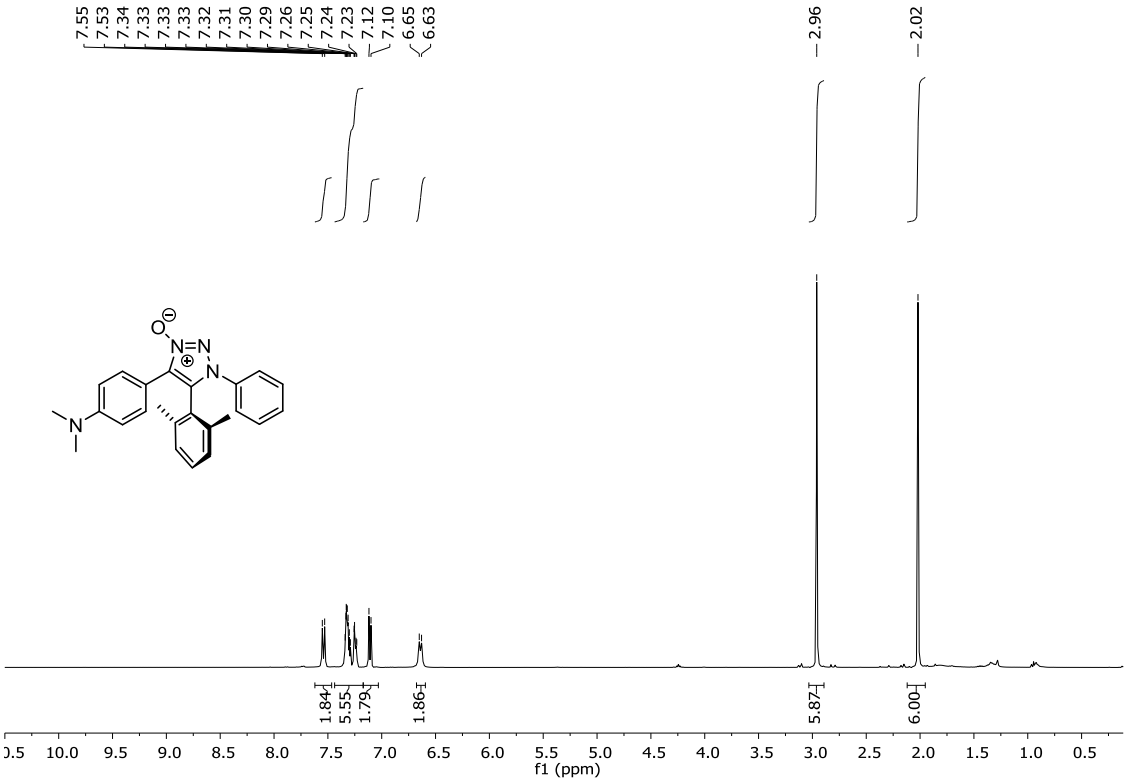
Spectrum 8.96. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19f**.



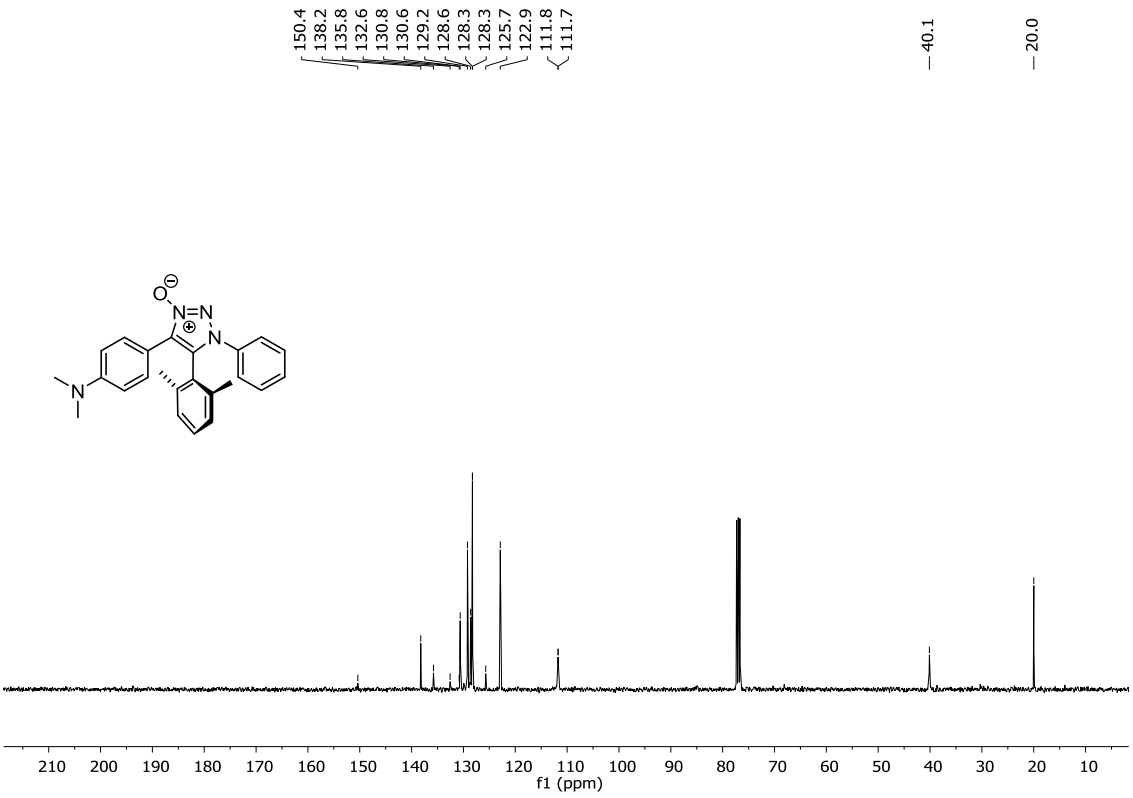
Spectrum 8.97. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19g**.



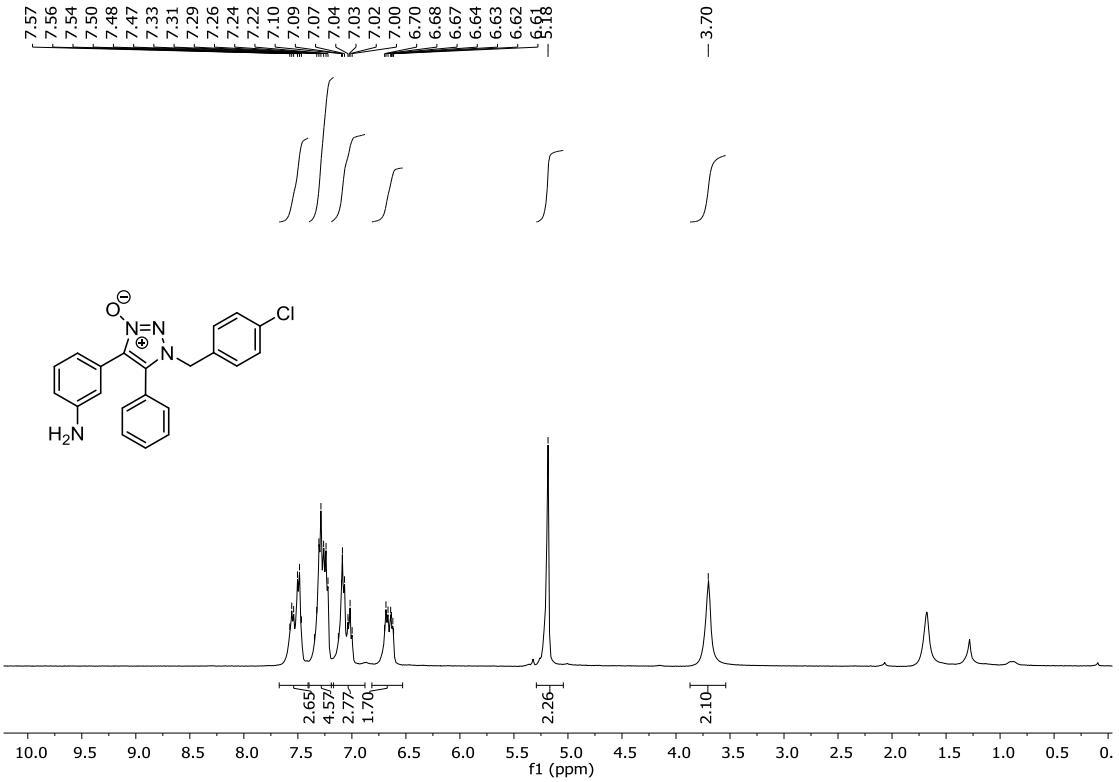
Spectrum 8.98. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19g.**



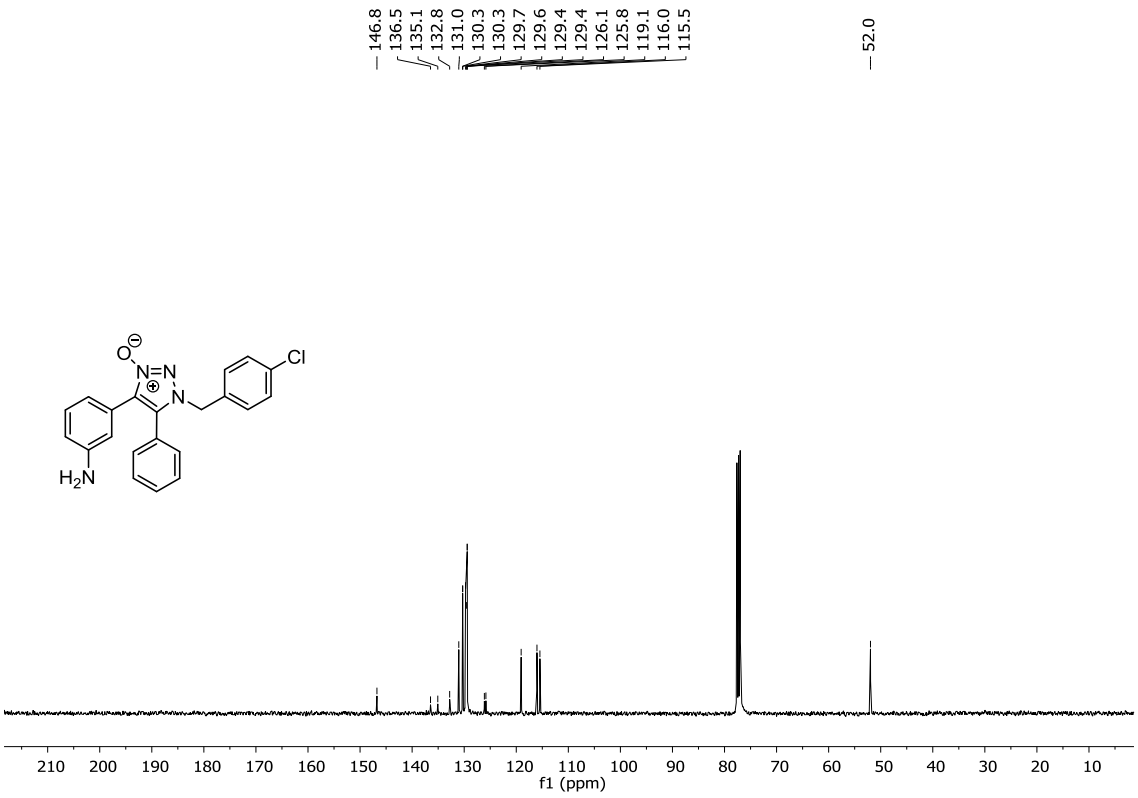
Spectrum 8.99. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19h**.



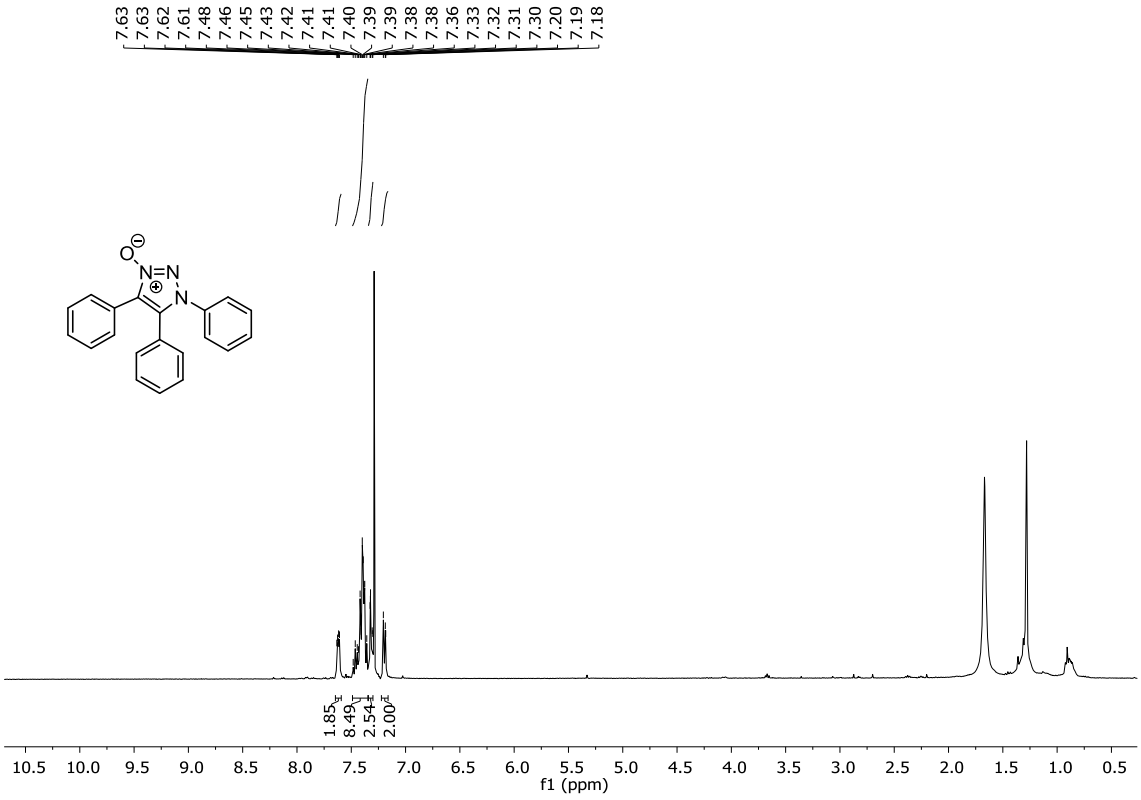
Spectrum 8.100. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19h**.



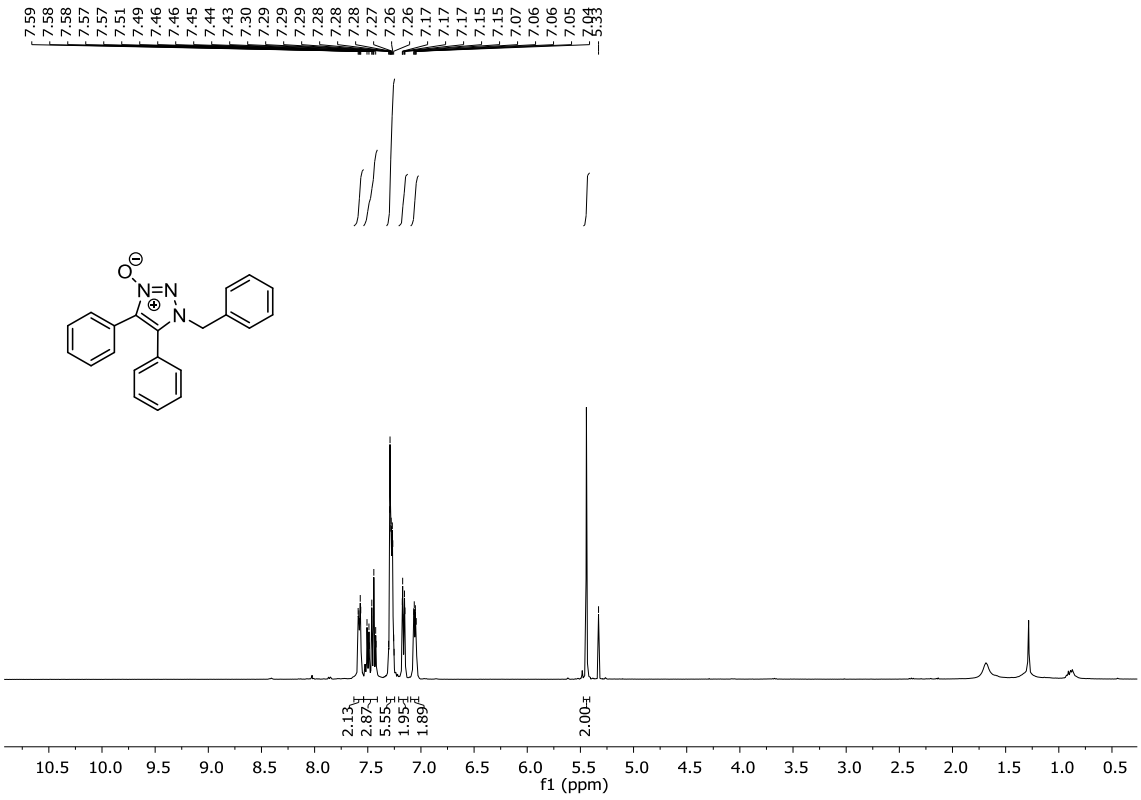
Spectrum 8.101. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **19i**.



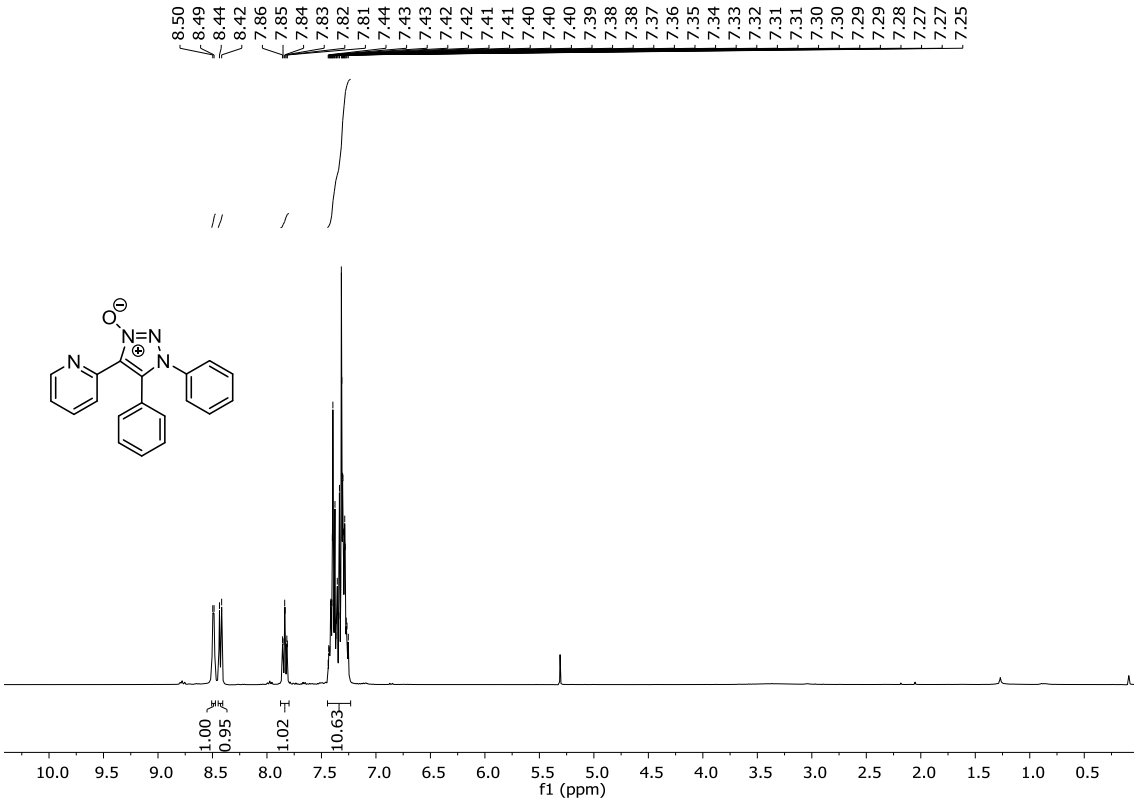
Spectrum 8.102. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **19i.**



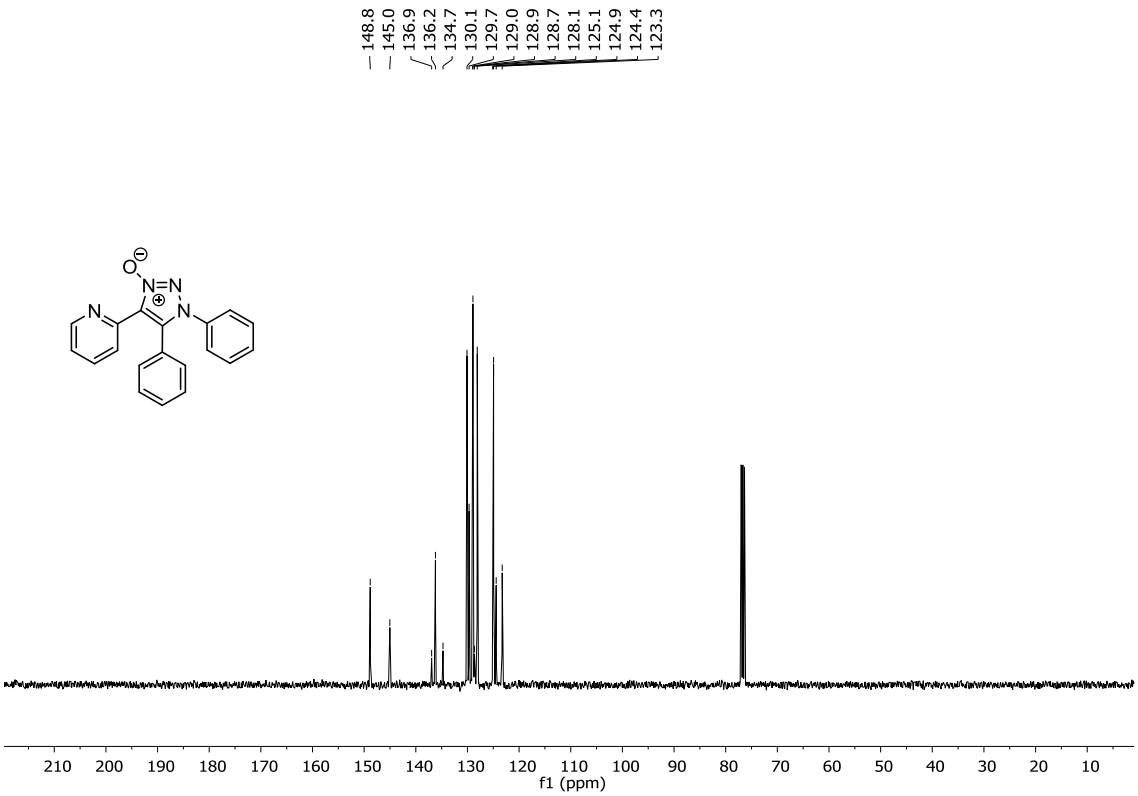
Spectrum 8.103. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23a**.



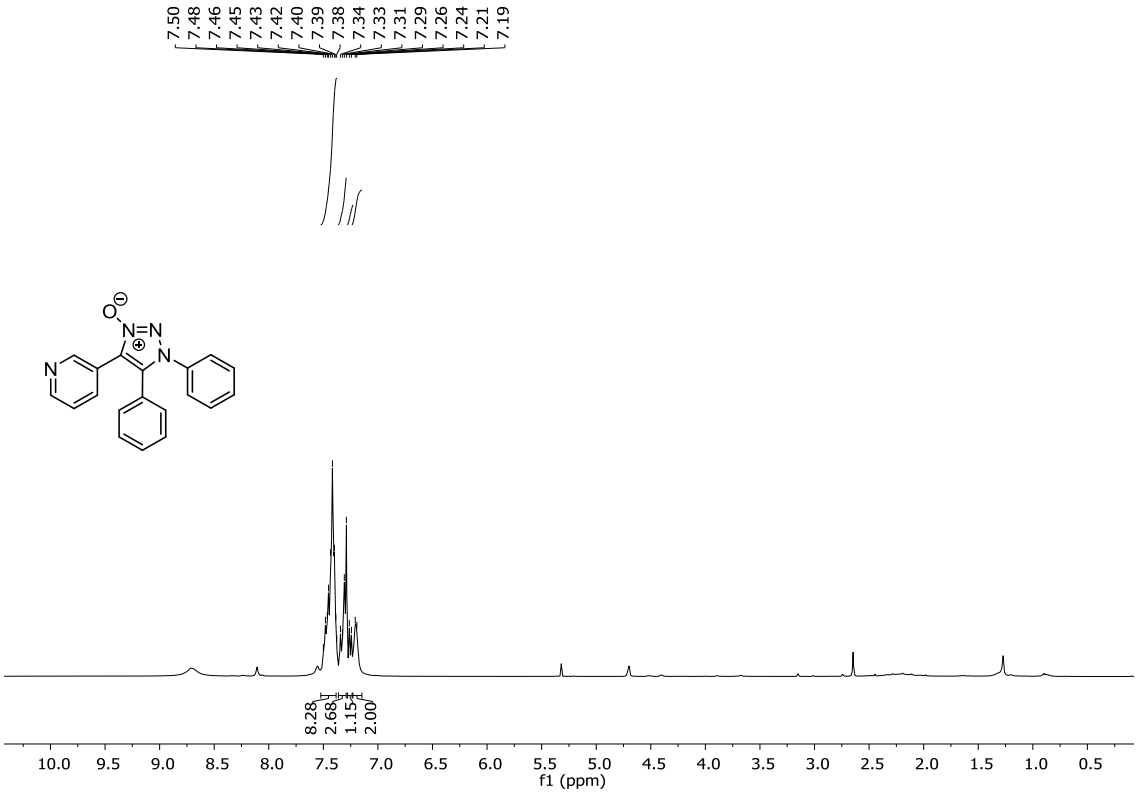
Spectrum 8.104. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23b**.



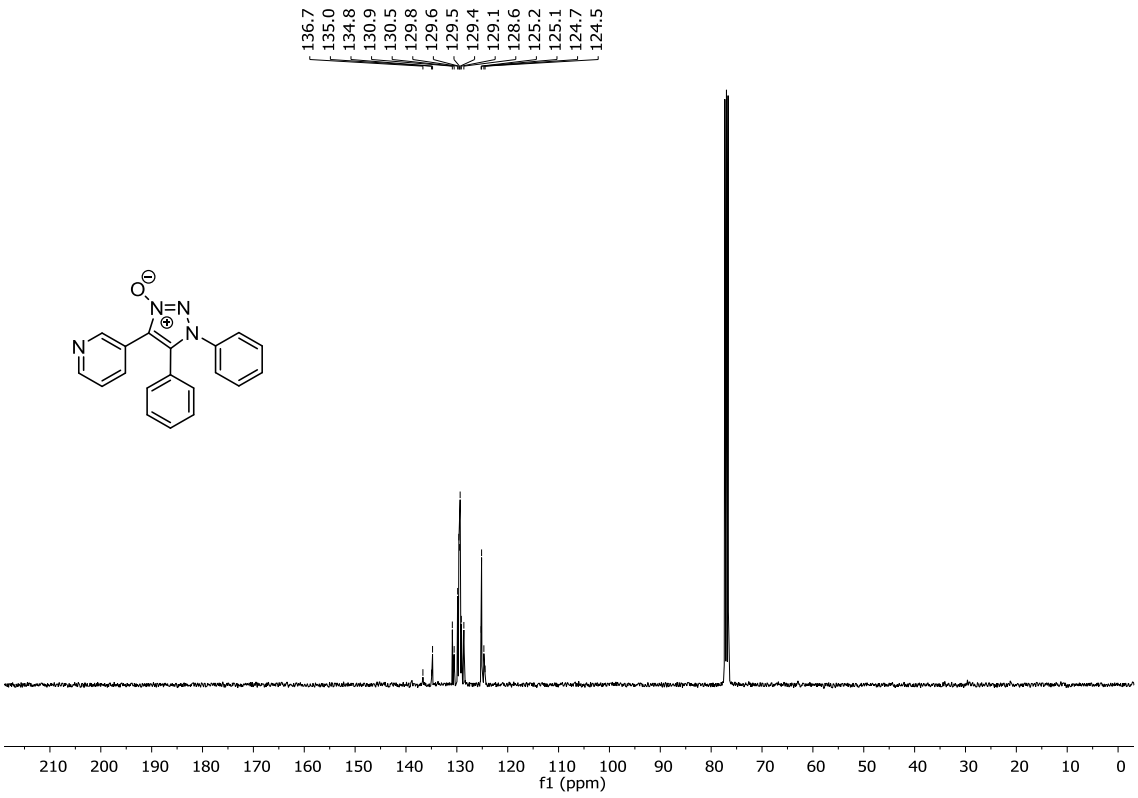
Spectrum 8.105. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23c**.



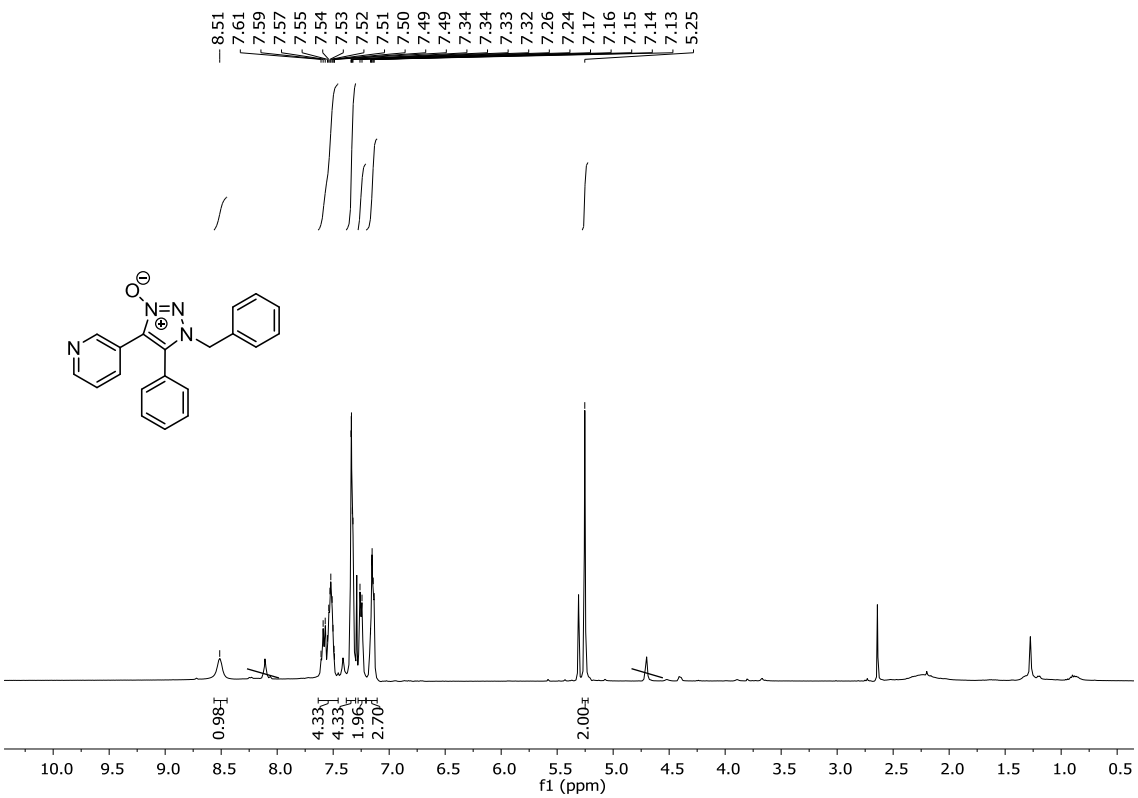
Spectrum 8.106. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23c**.



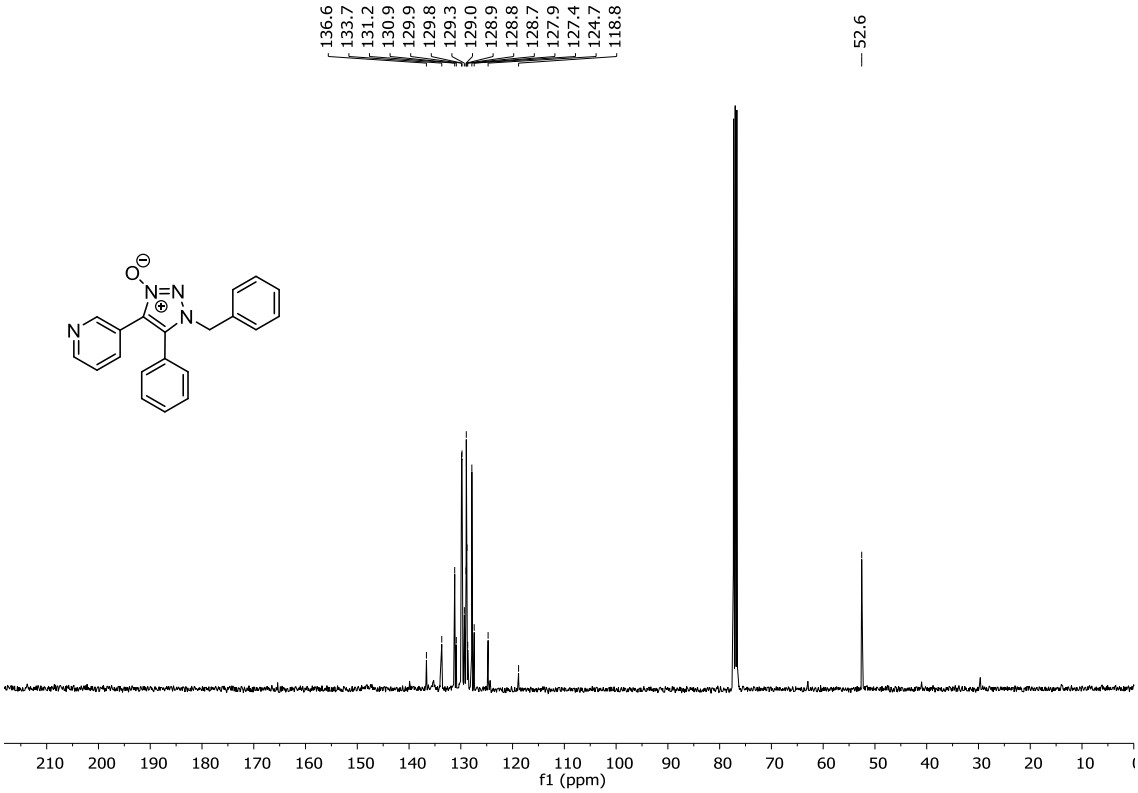
Spectrum 8.107. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23d**.



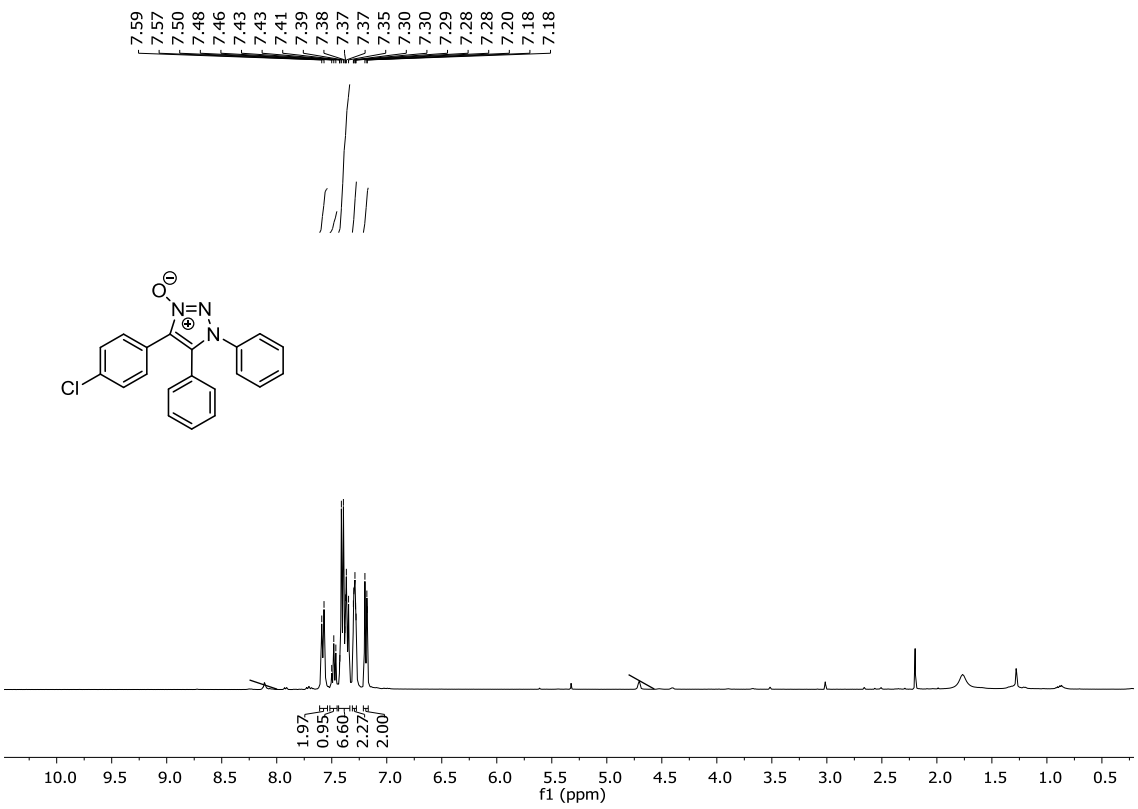
Spectrum 8.108. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23d**.



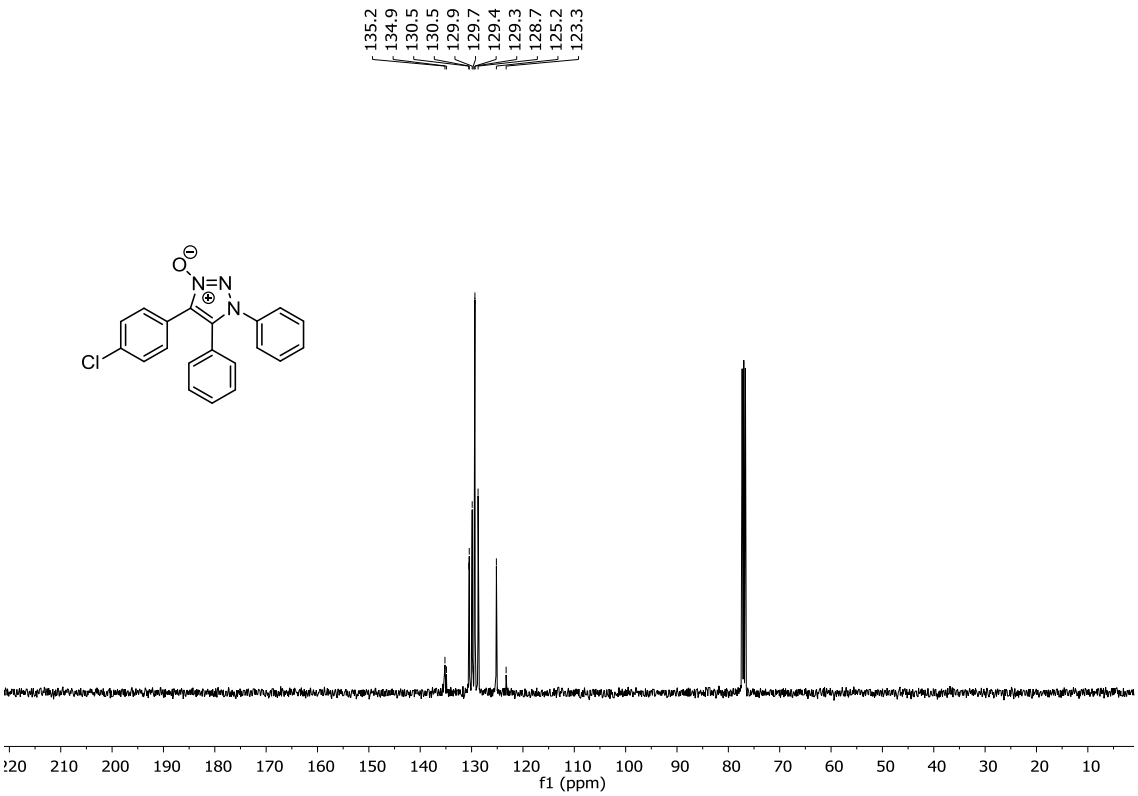
Spectrum 8.109. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23e**.



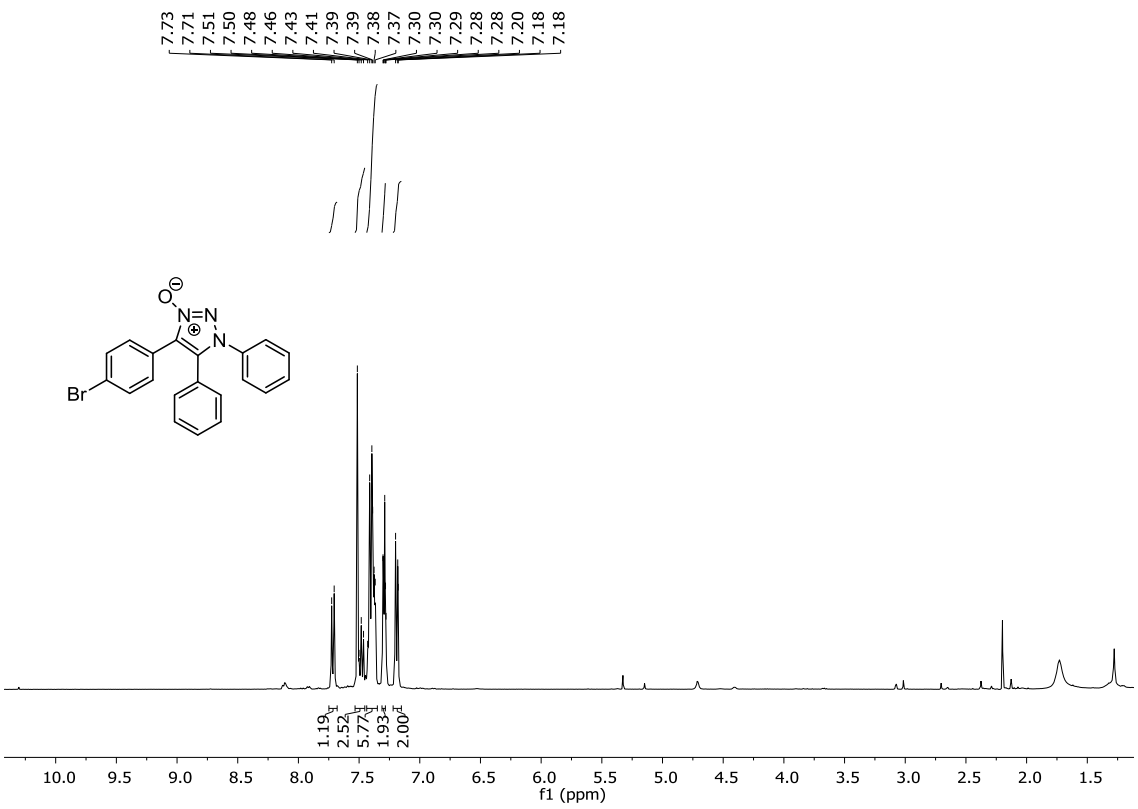
Spectrum 8.110. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23e**.



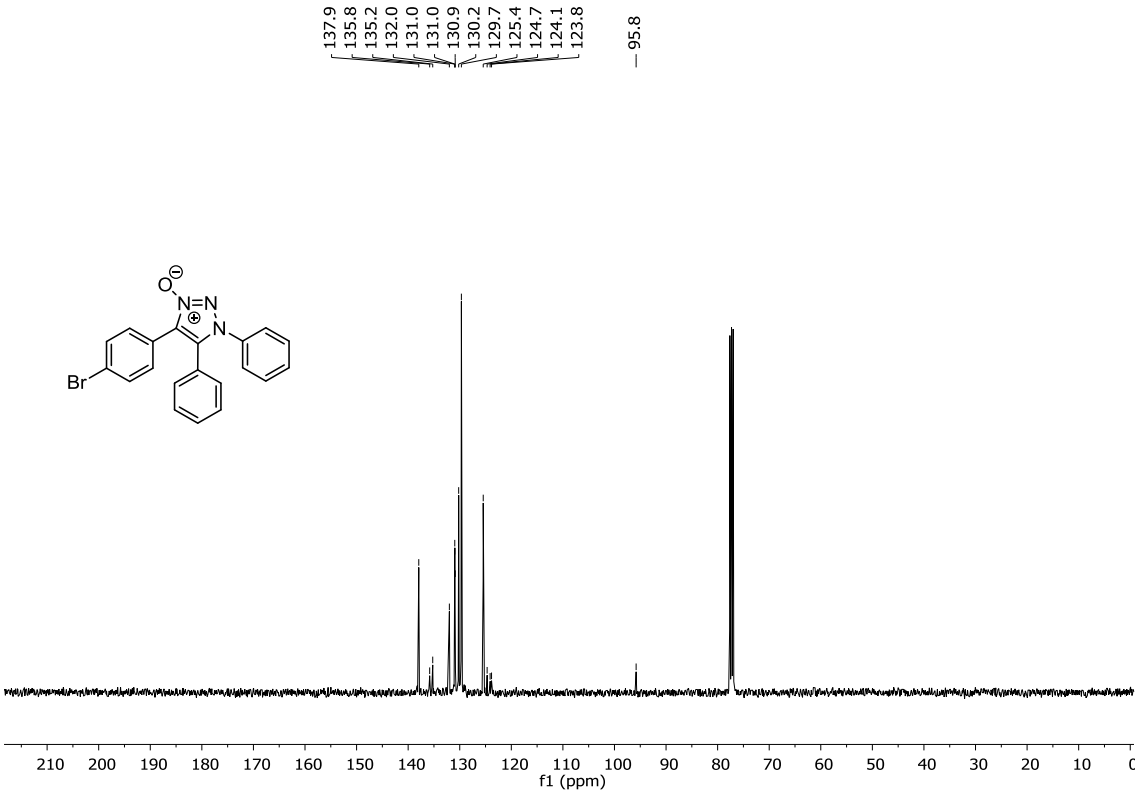
Spectrum 8.111. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23f**.



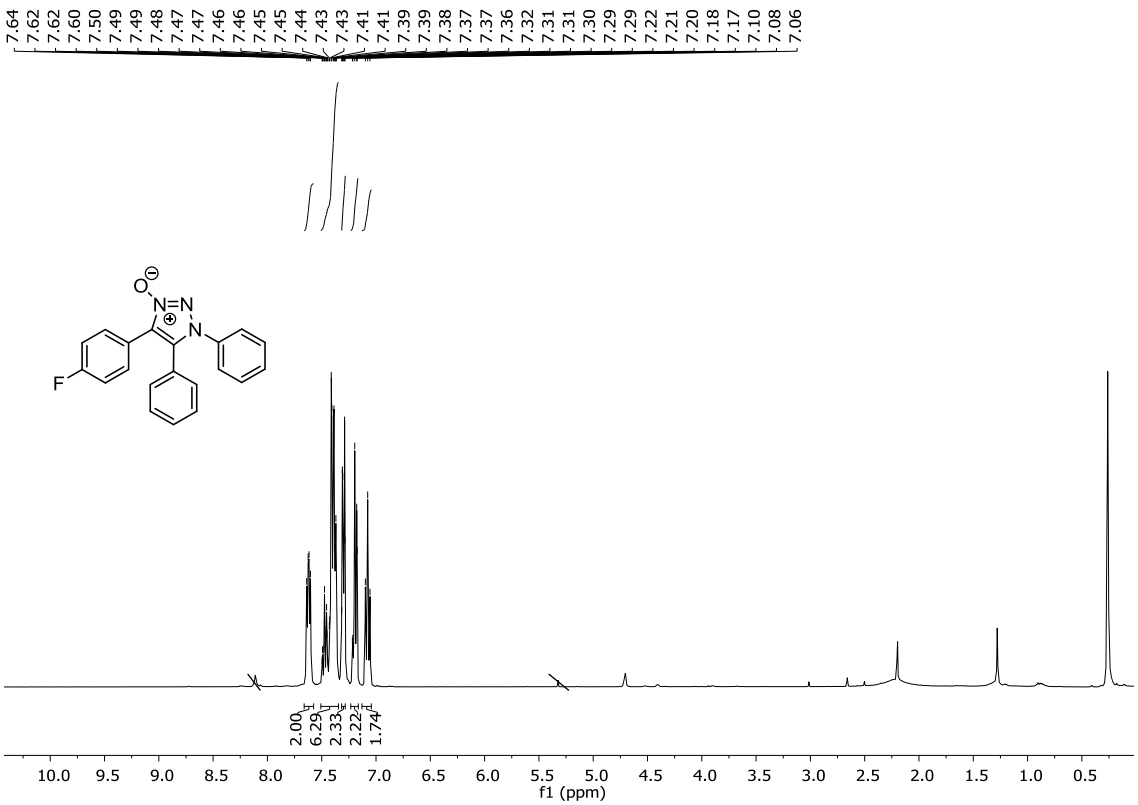
Spectrum 8.112. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23f**.



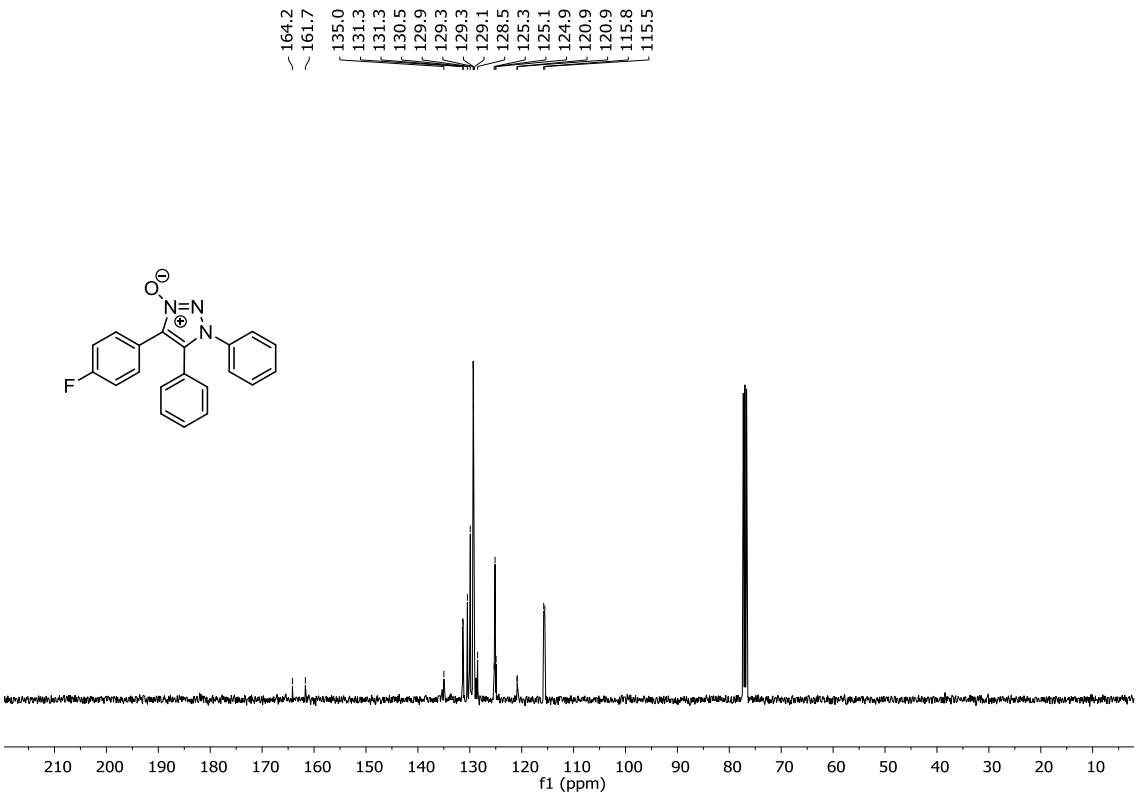
Spectrum 8.113. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23g**.



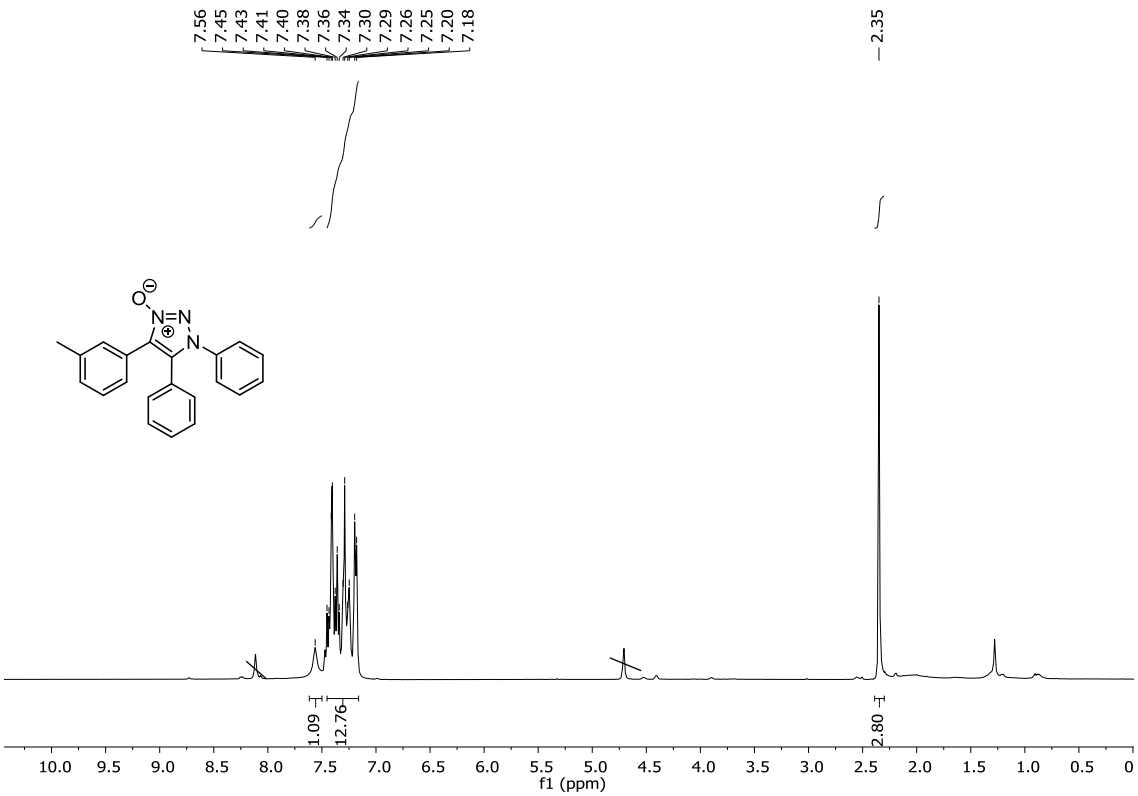
Spectrum 8.114. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23g**.



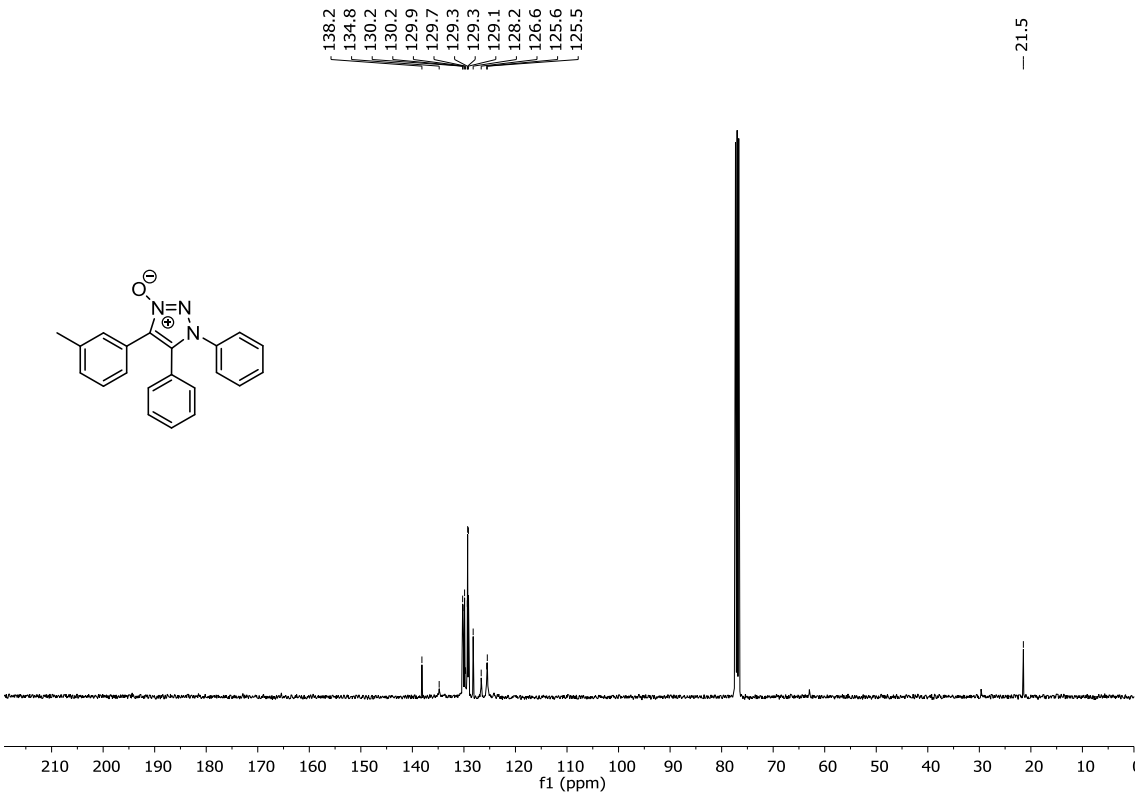
Spectrum 8.115. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23h**.



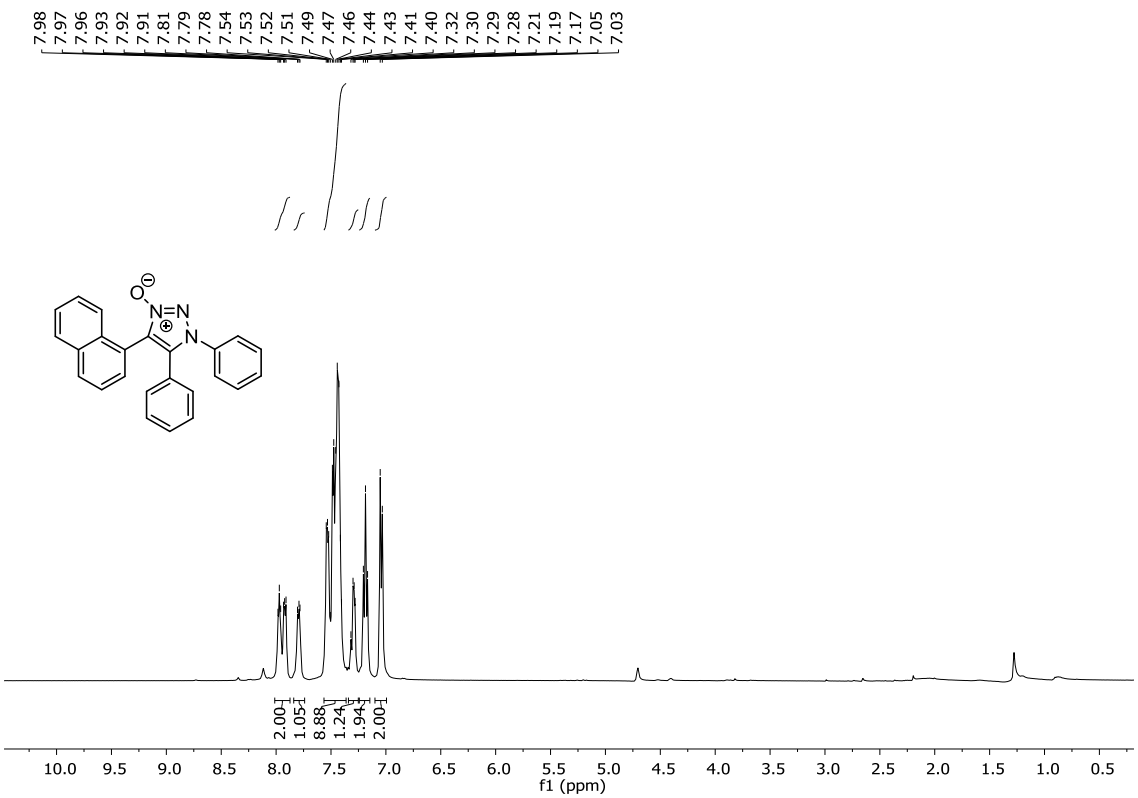
Spectrum 8.116. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23h**.



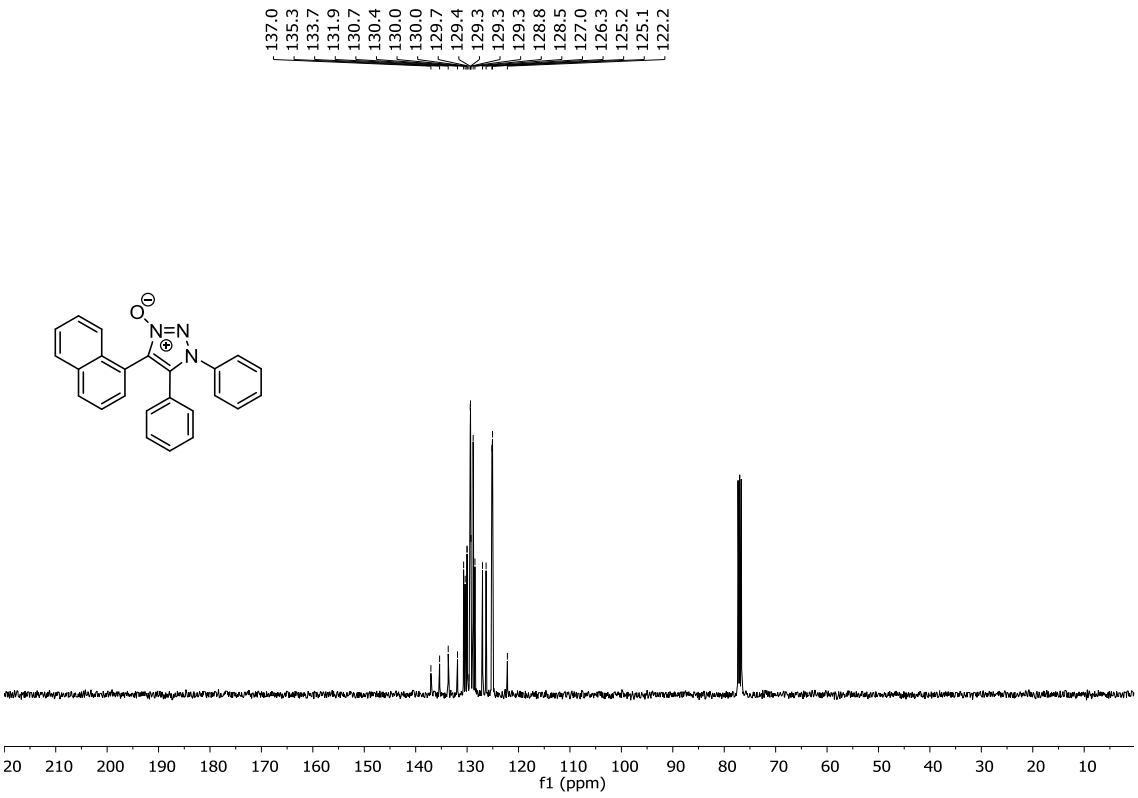
Spectrum 8.117. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23i**.



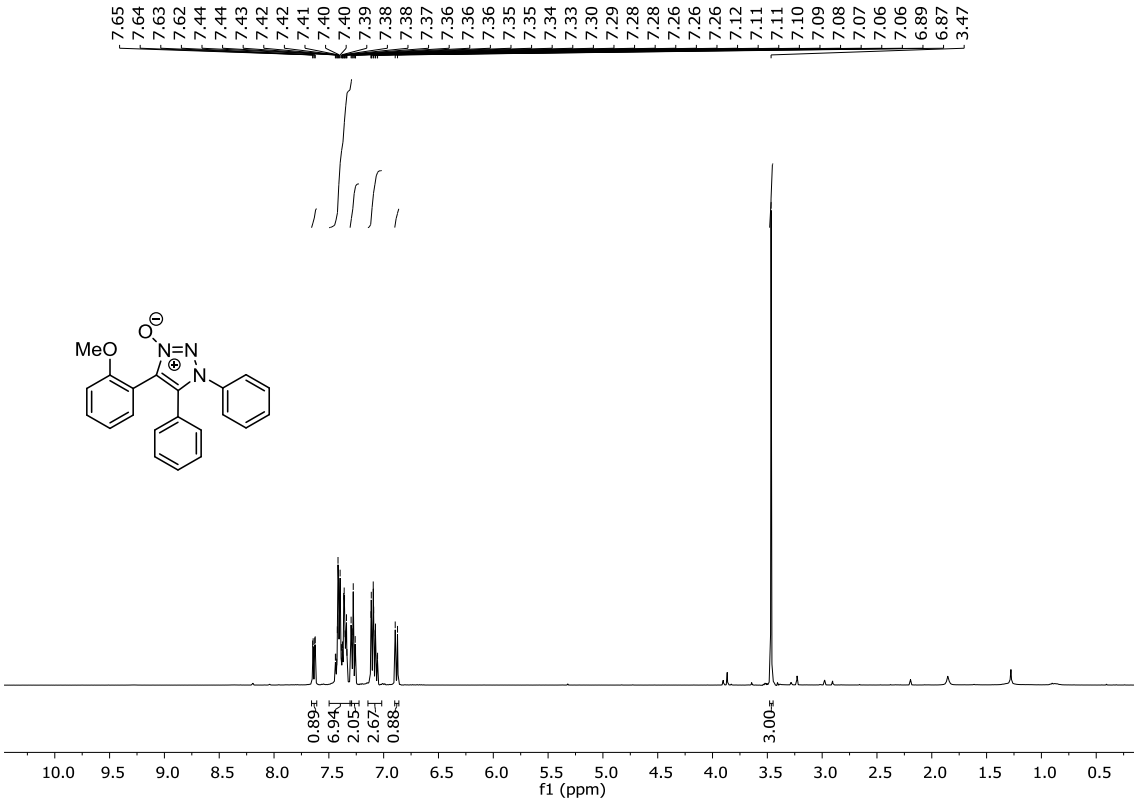
Spectrum 8.118. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23i**.



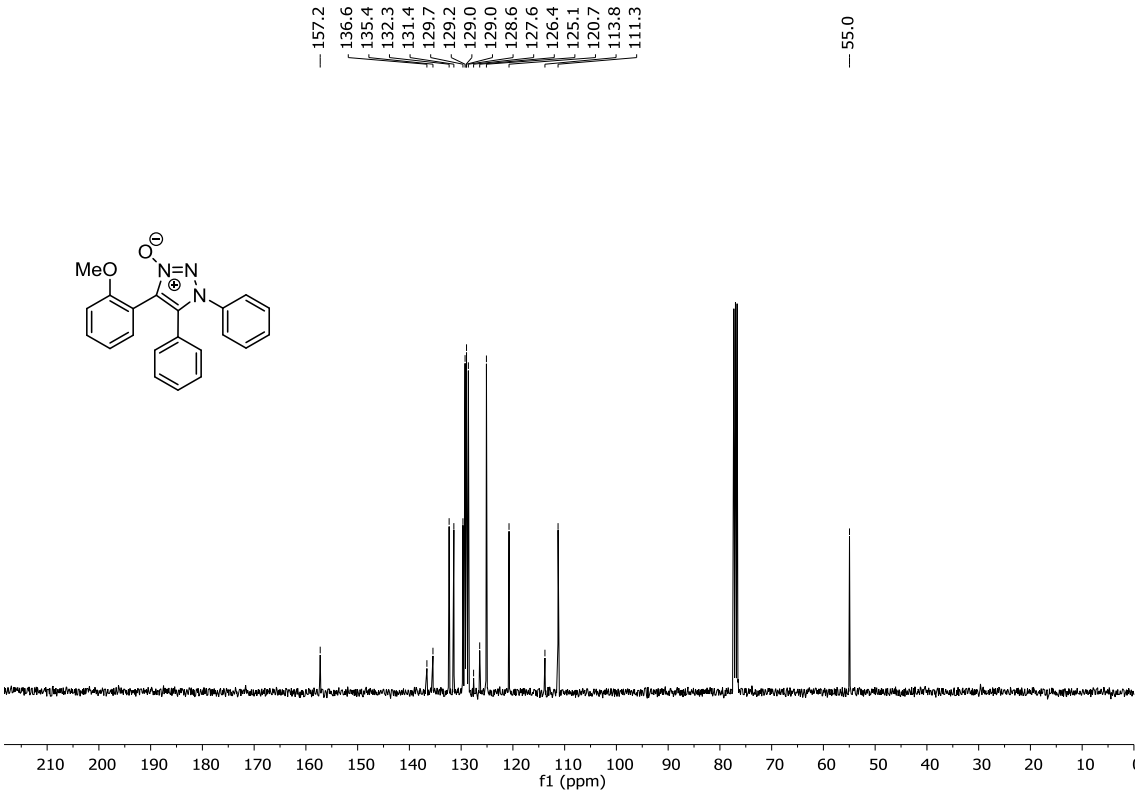
Spectrum 8.119. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23j**.



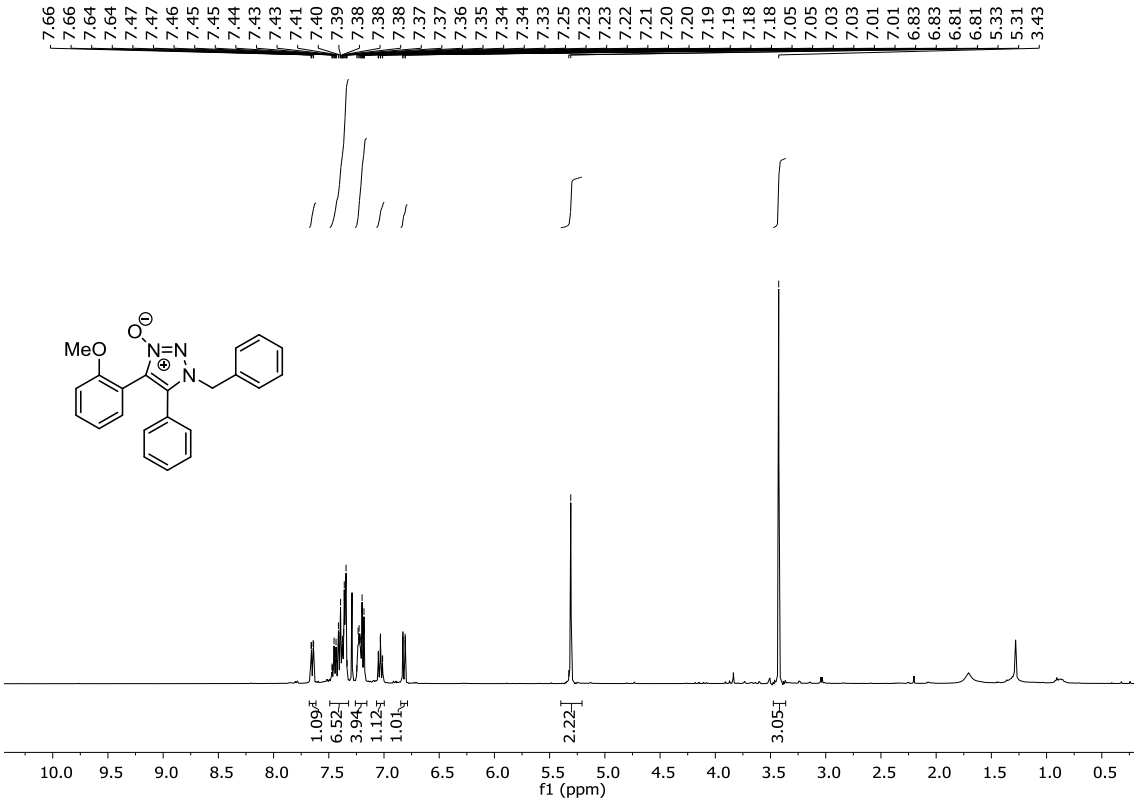
Spectrum 8.120. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23j**.



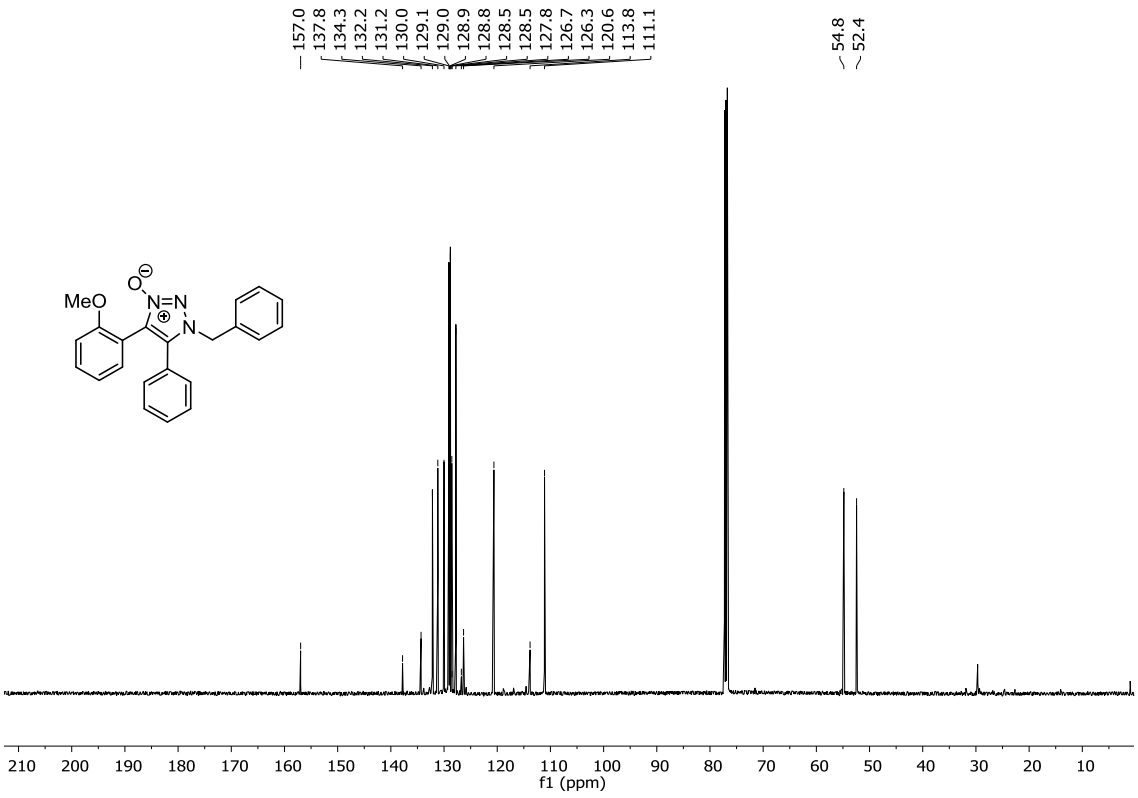
Spectrum 8.121. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23k**.



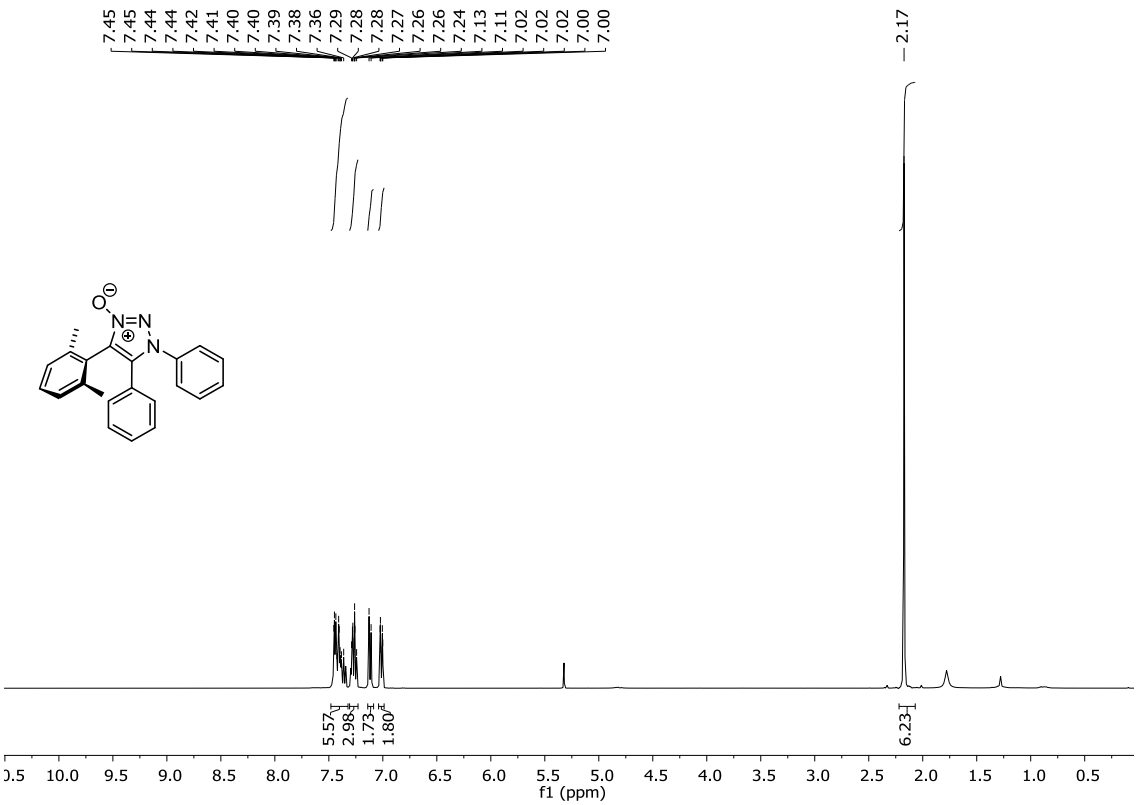
Spectrum 8.122. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23k**.



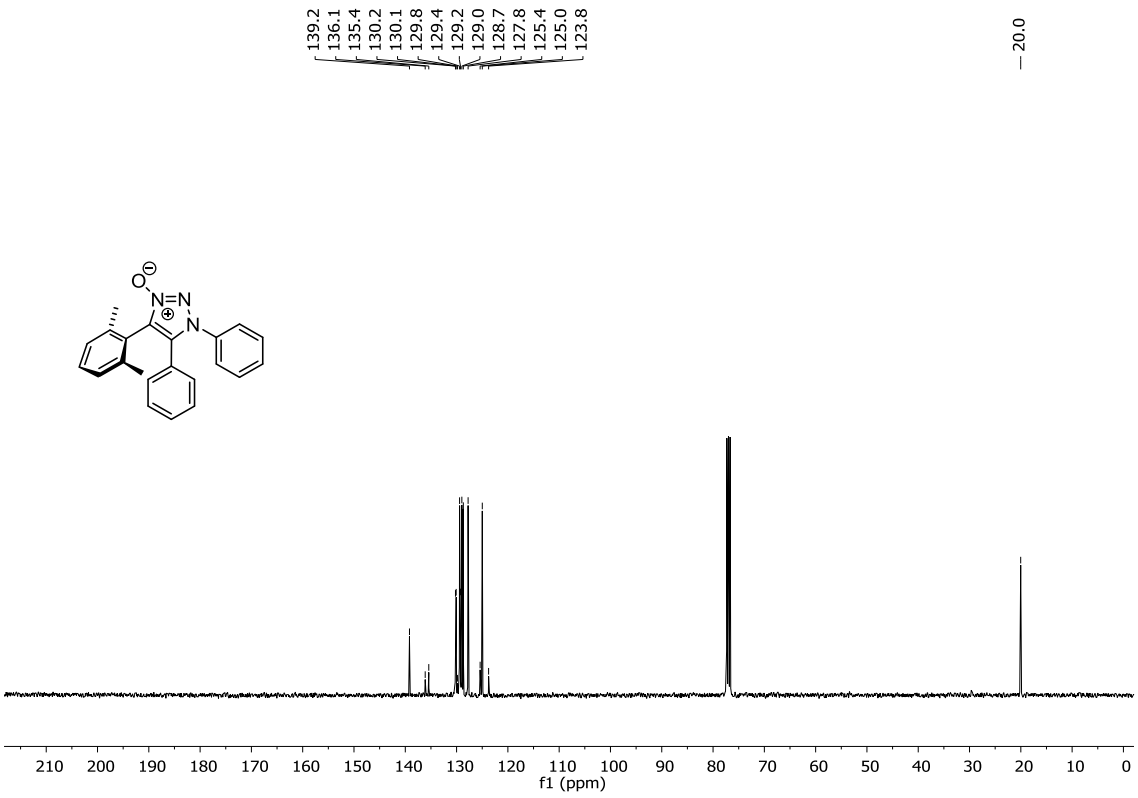
Spectrum 8.123. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23l**.



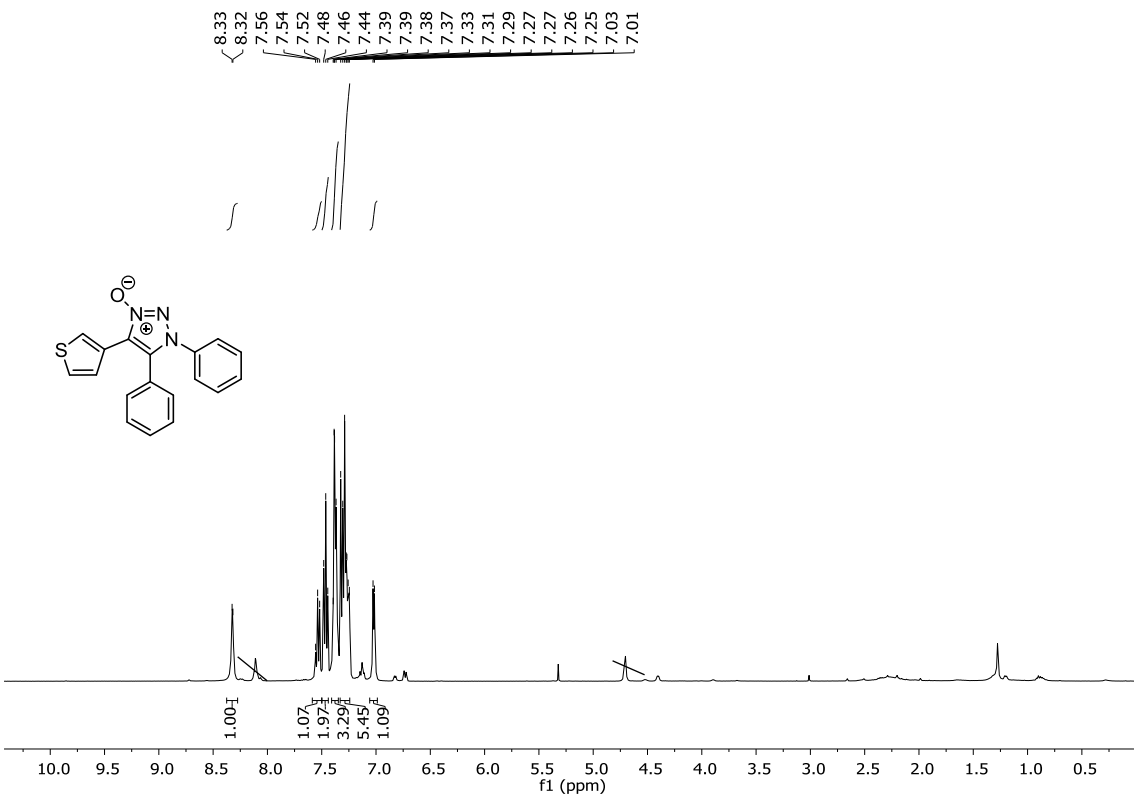
Spectrum 8.124. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23l**.



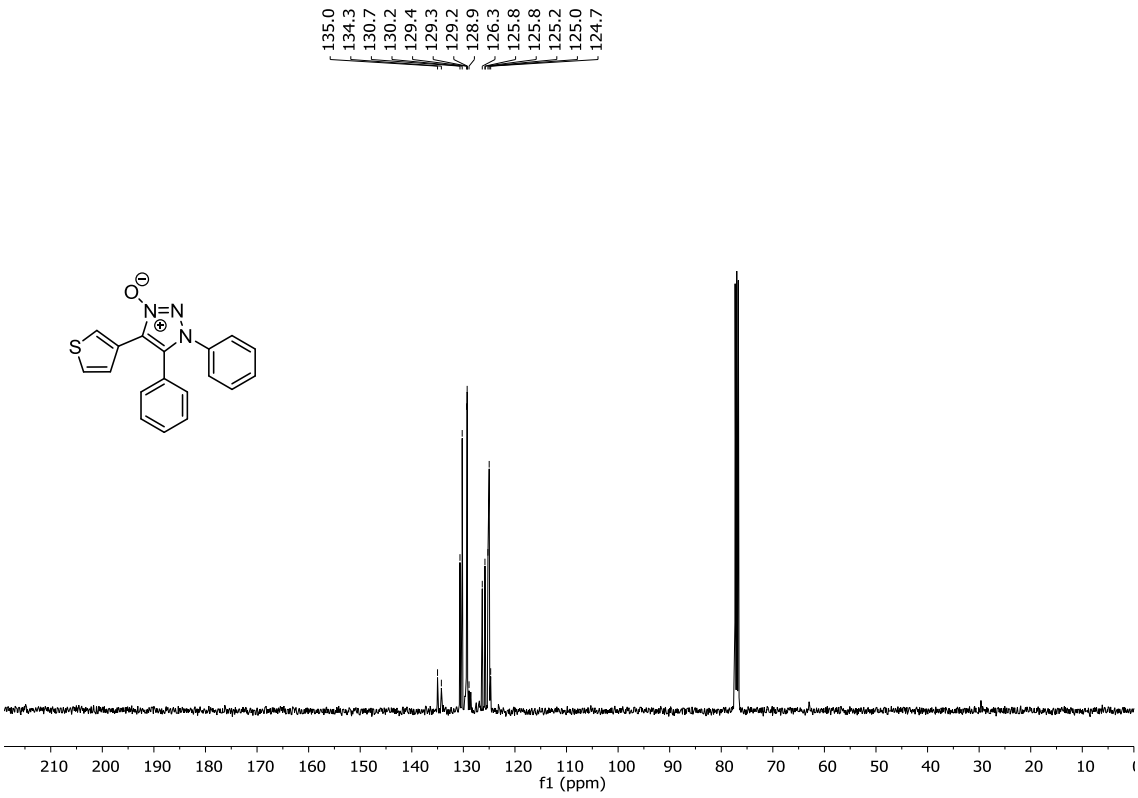
Spectrum 8.125. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23m**.



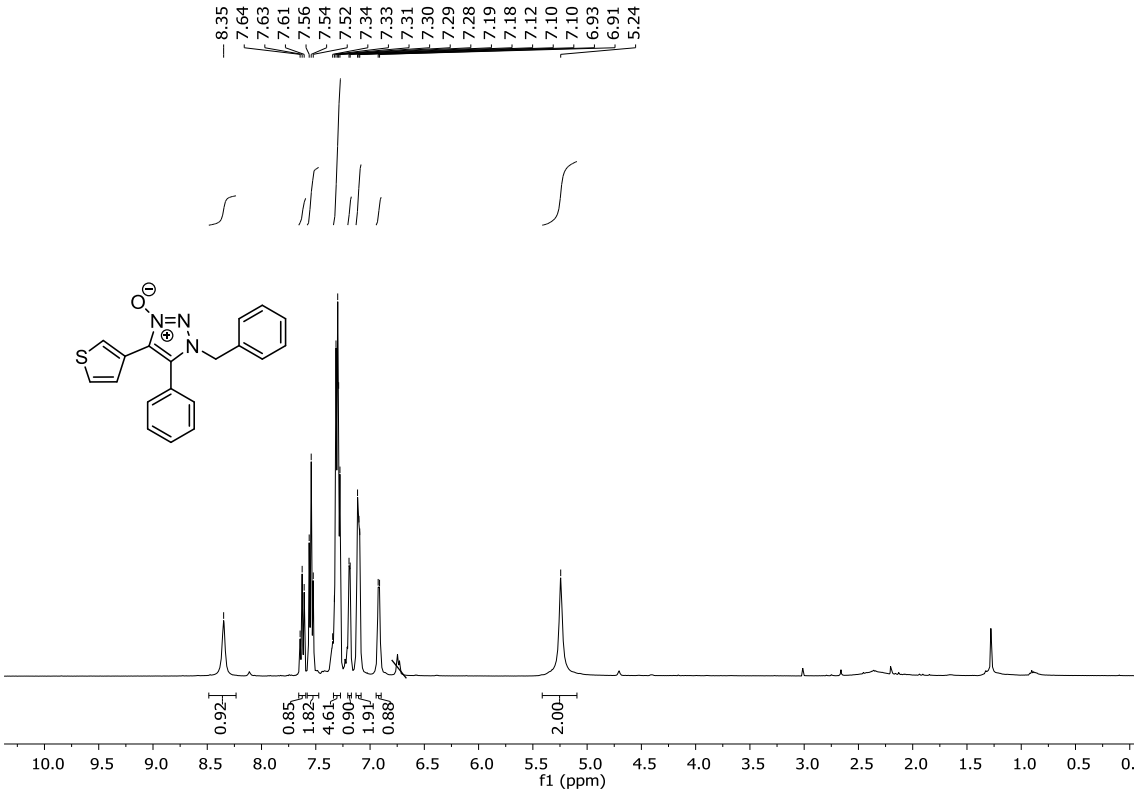
Spectrum 8.126. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23m**.



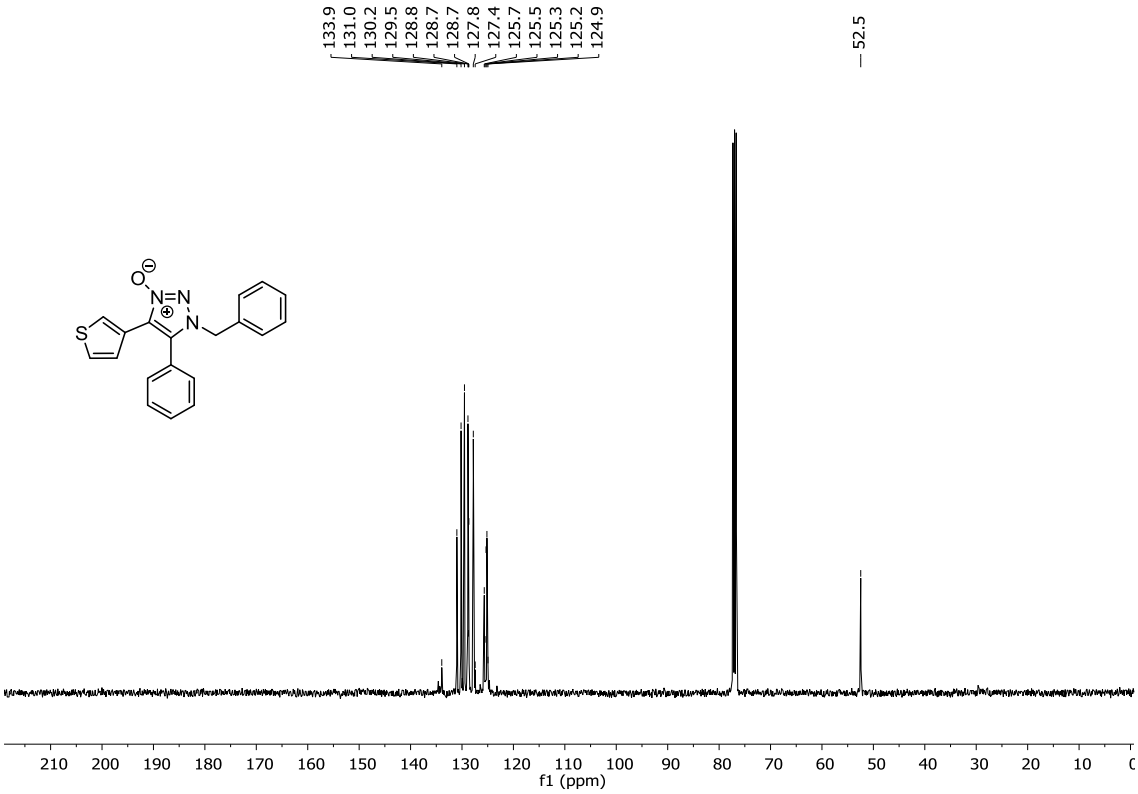
Spectrum 8.127. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23n**.



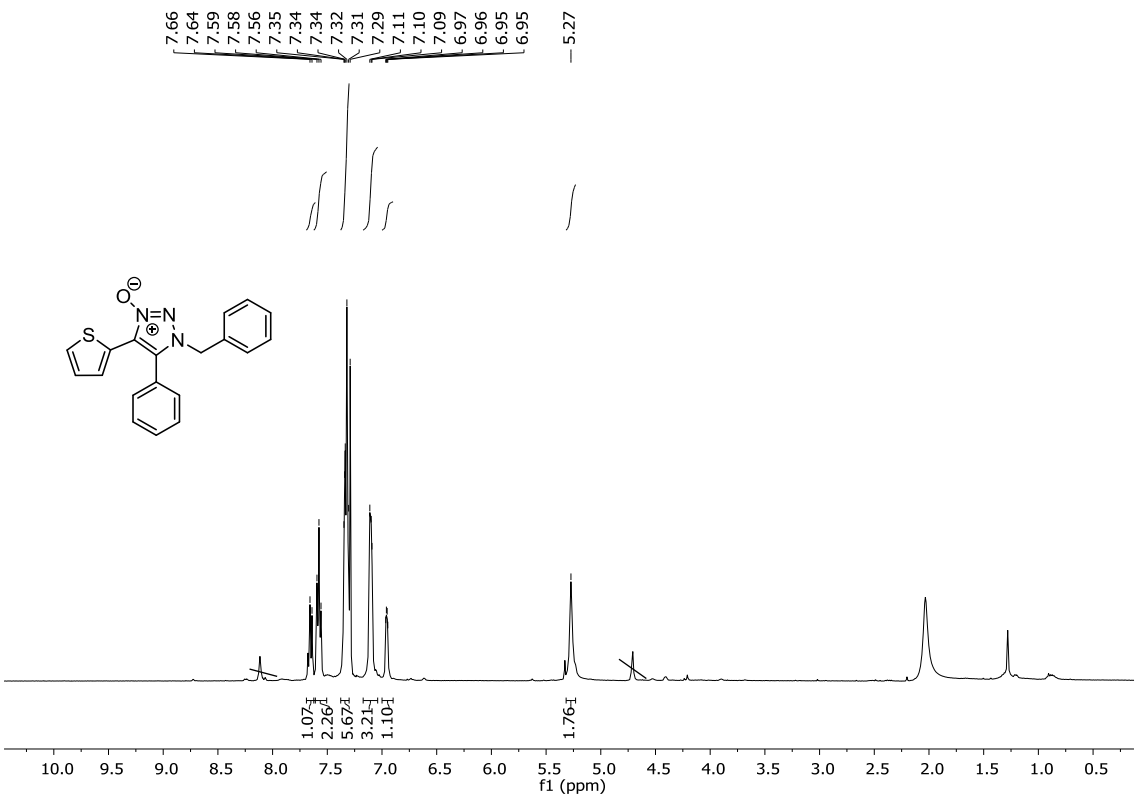
Spectrum 8.128. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23n**.



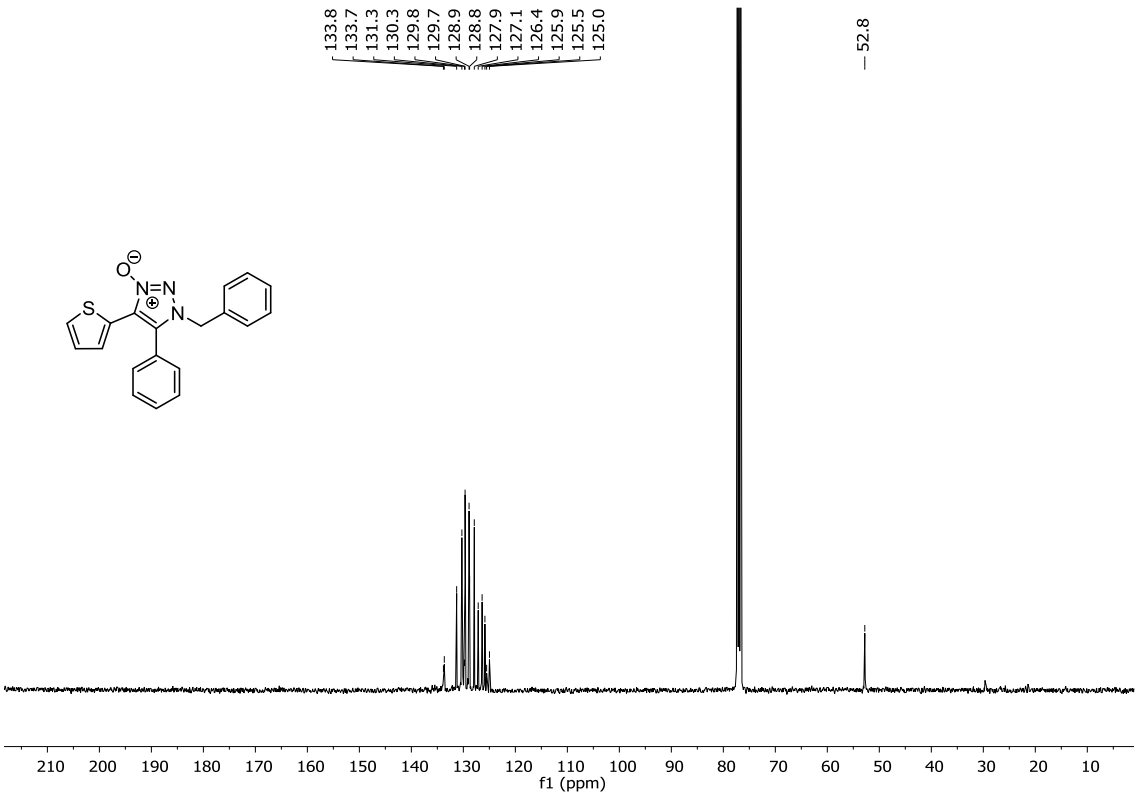
Spectrum 8.129. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23o**.



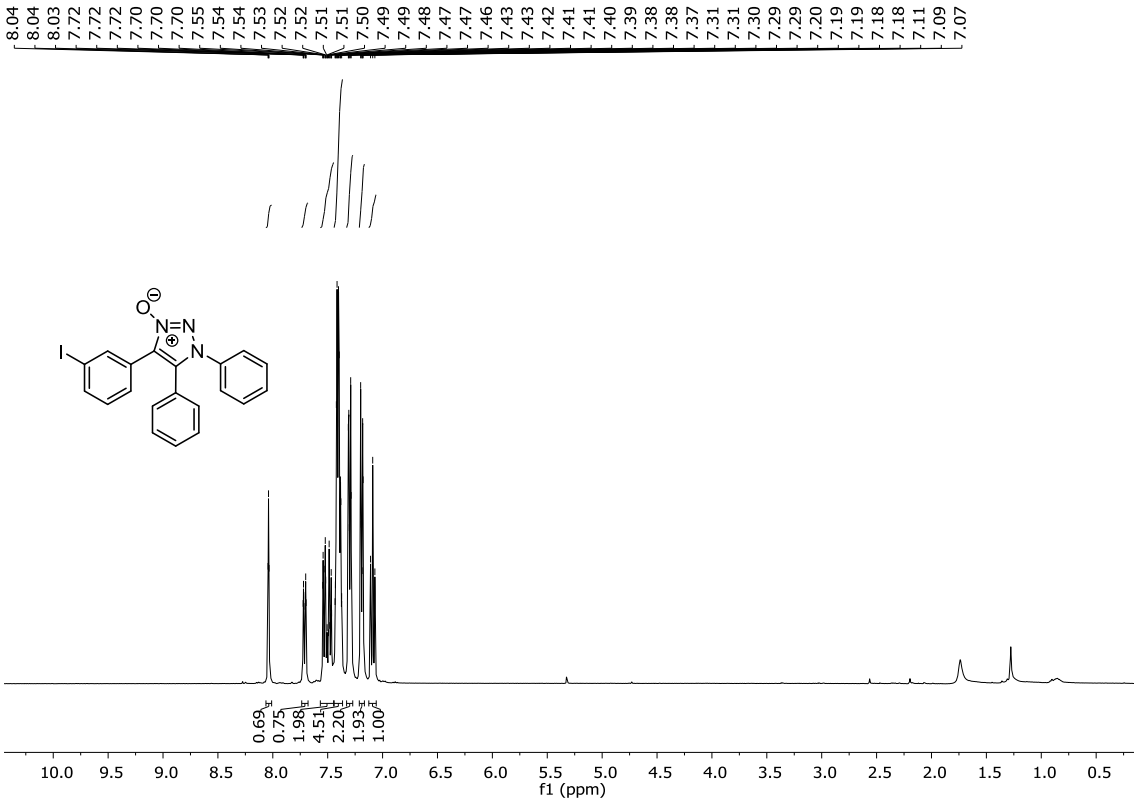
Spectrum 8.130. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23o**.



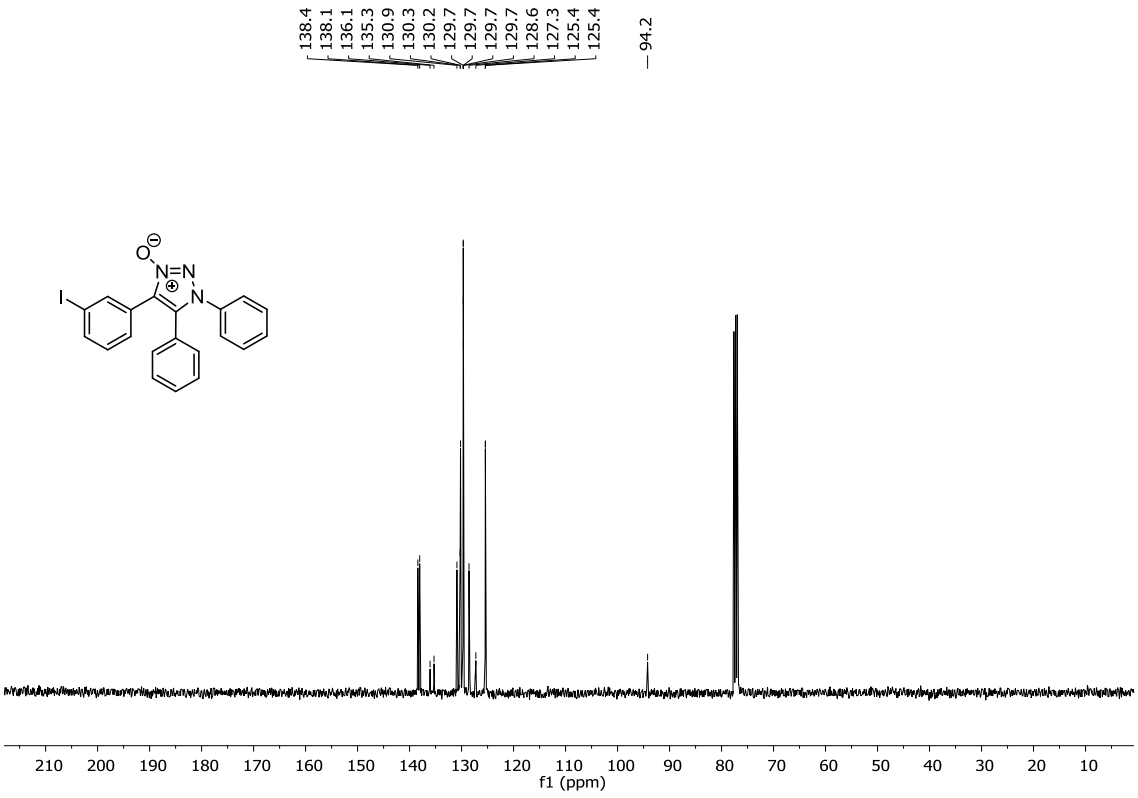
Spectrum 8.131. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23p**.



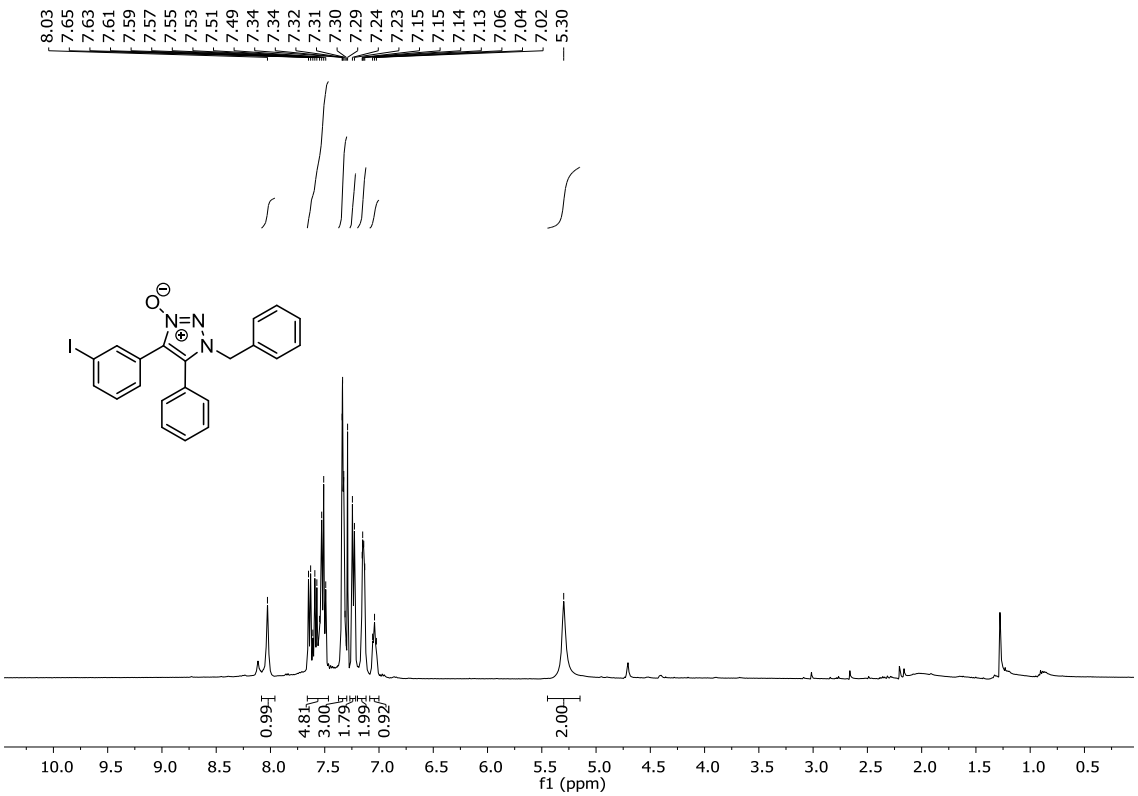
Spectrum 8.132. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23p**.



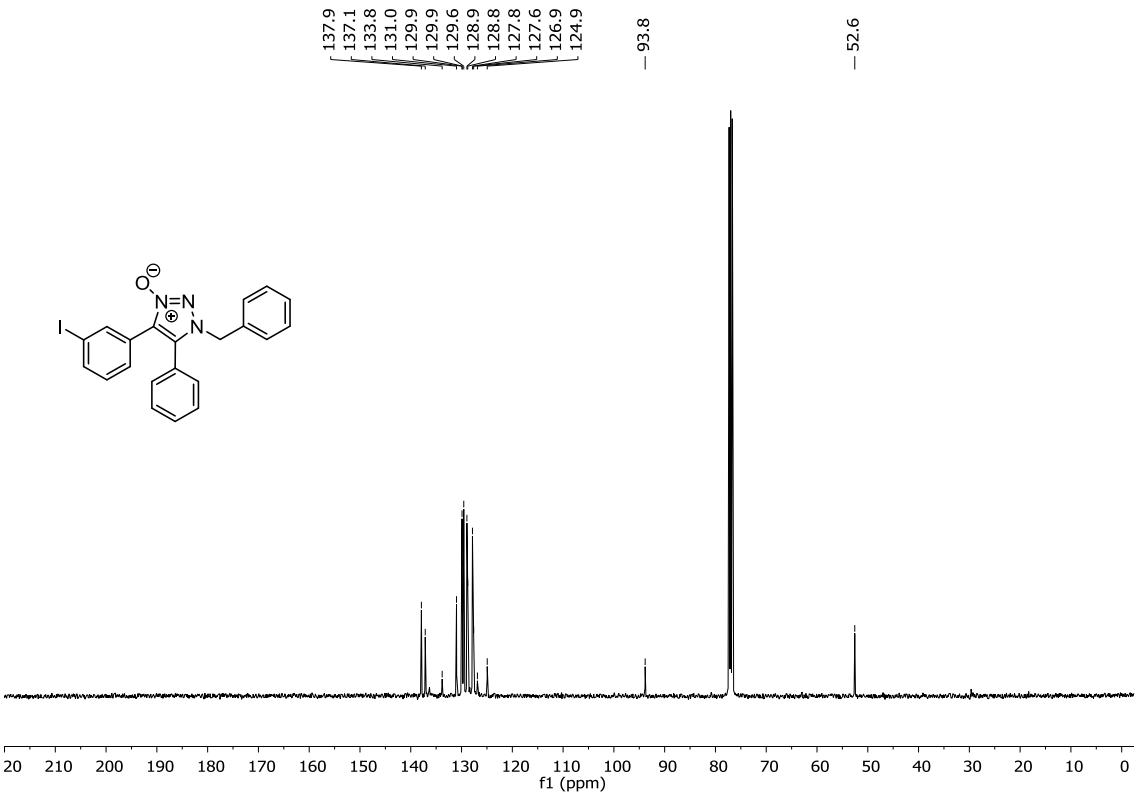
Spectrum 8.133. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23q**.



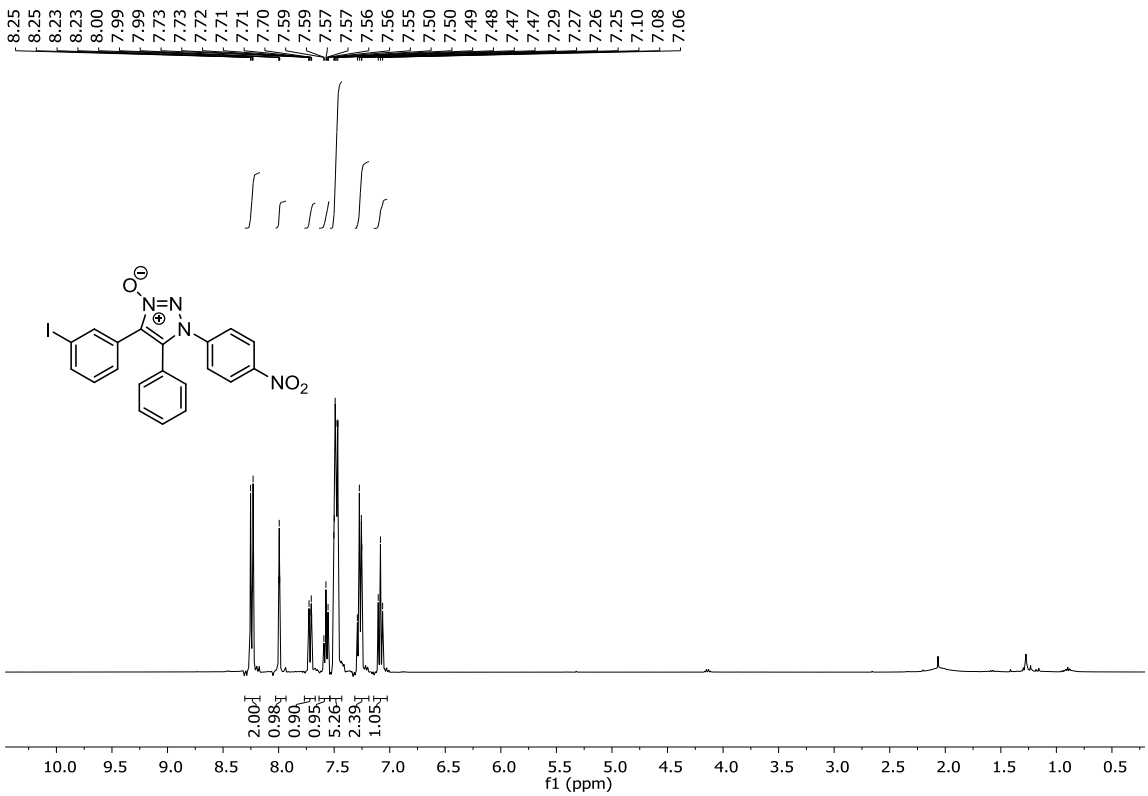
Spectrum 8.134. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23q**.



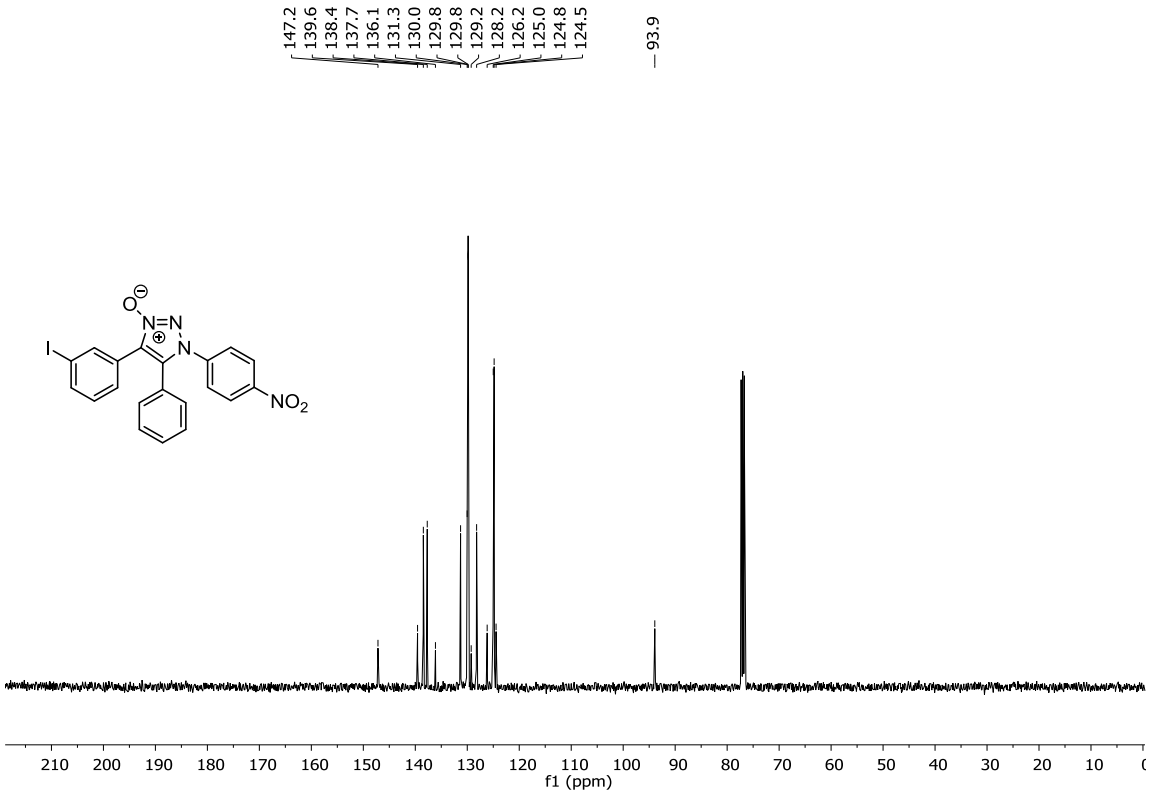
Spectrum 8.135. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23r**.



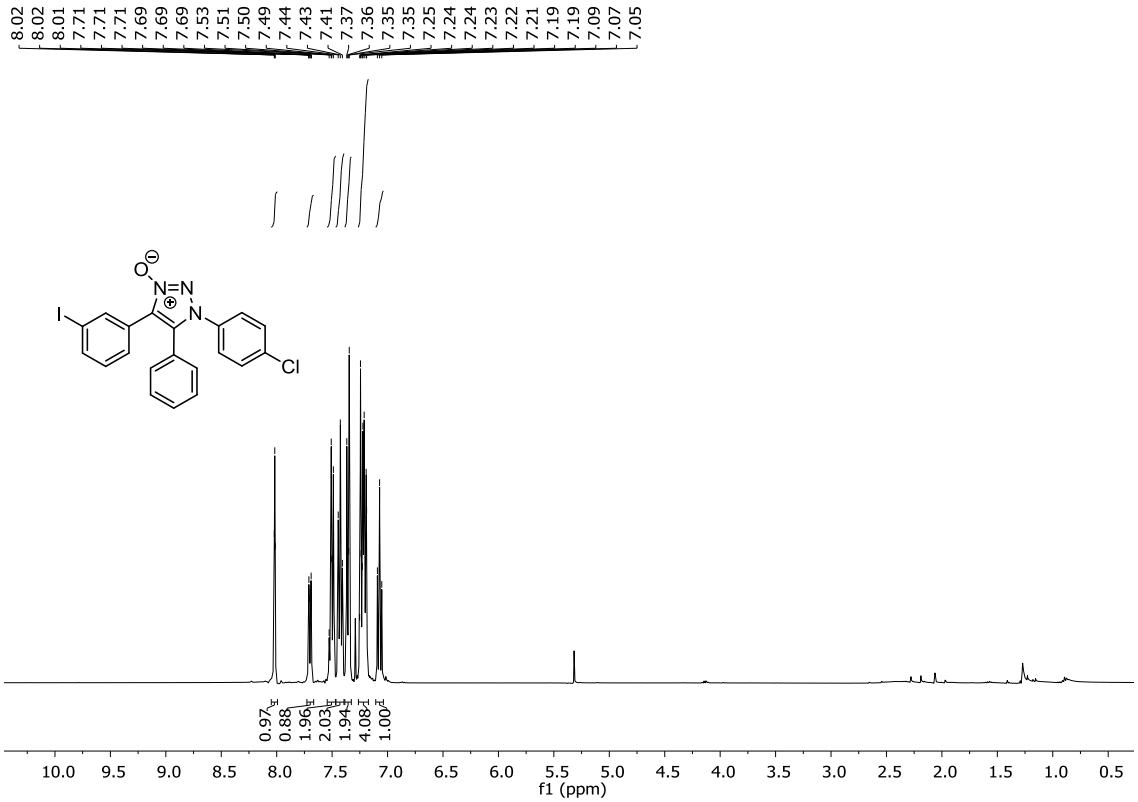
Spectrum 8.136. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23r**.



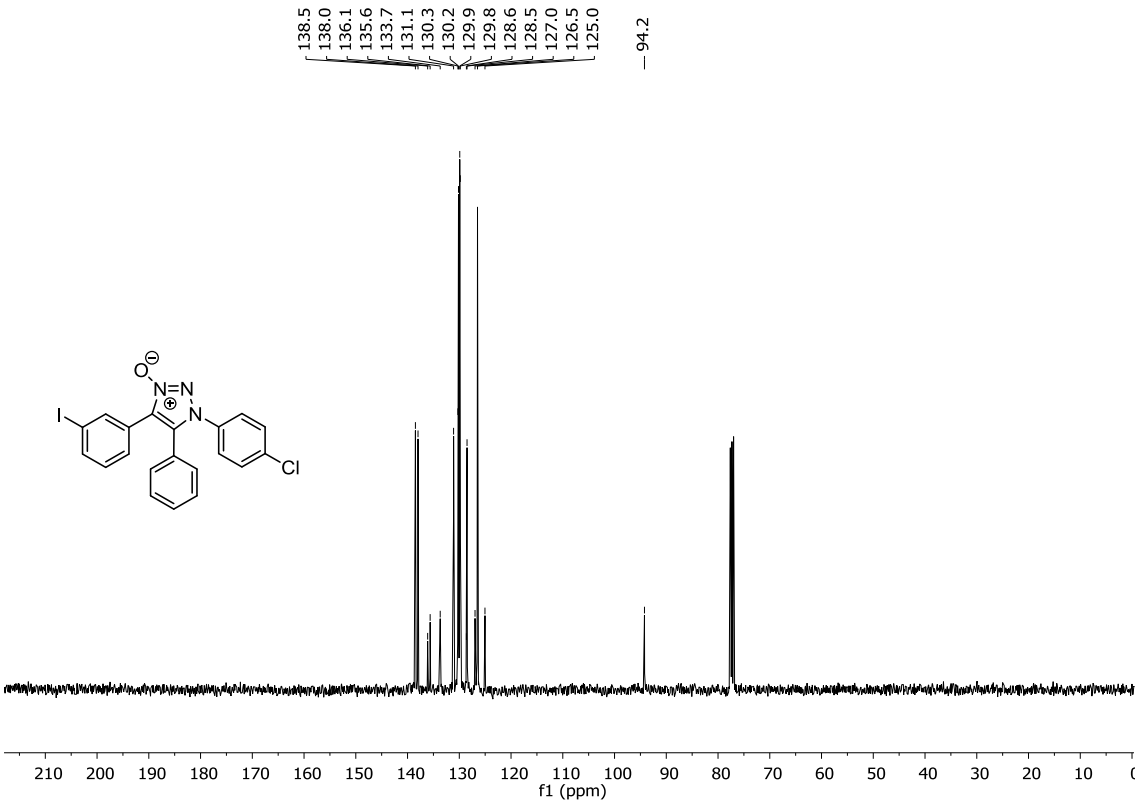
Spectrum 8.137. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23s**.



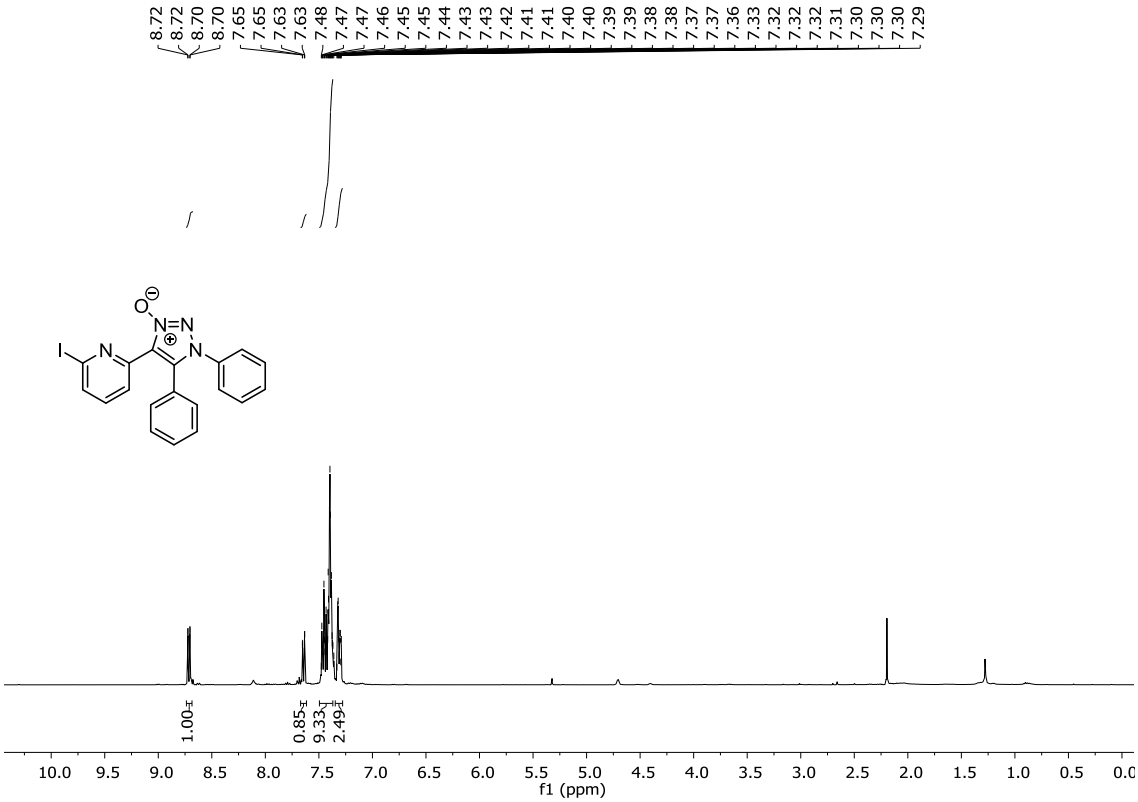
Spectrum 8.138. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23s**.



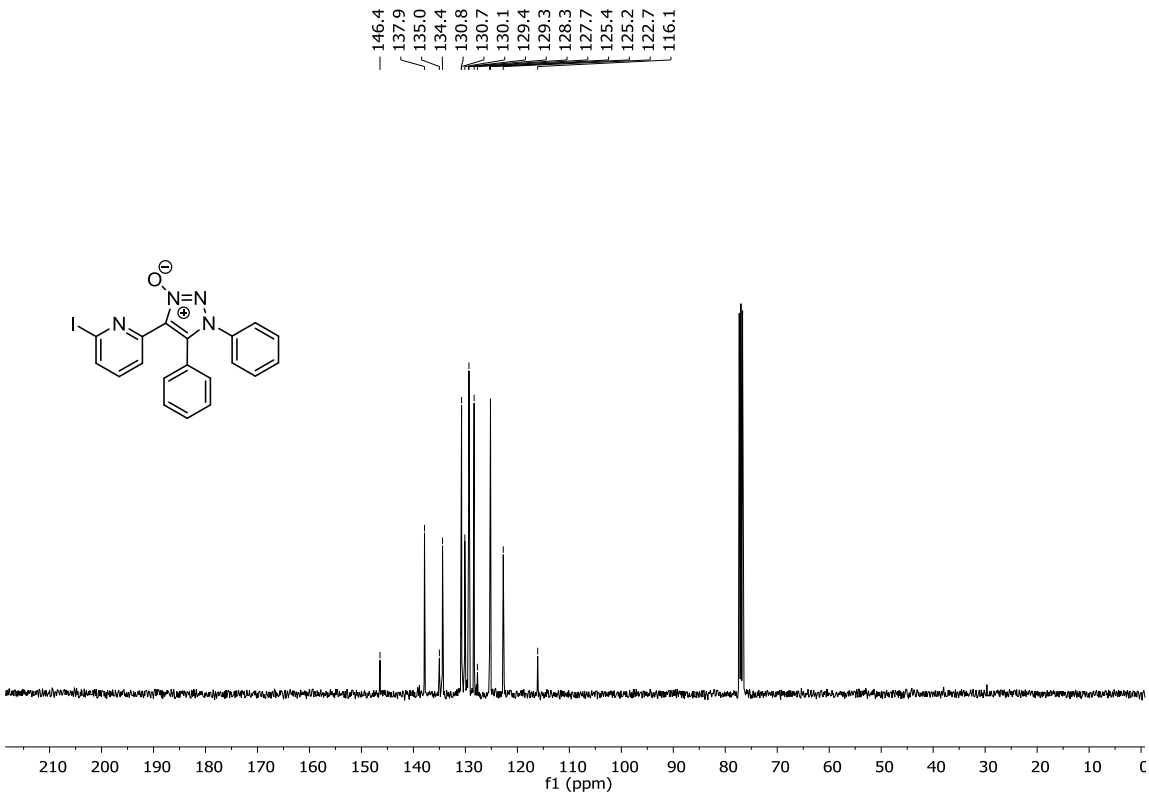
Spectrum 8.139. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23t**.



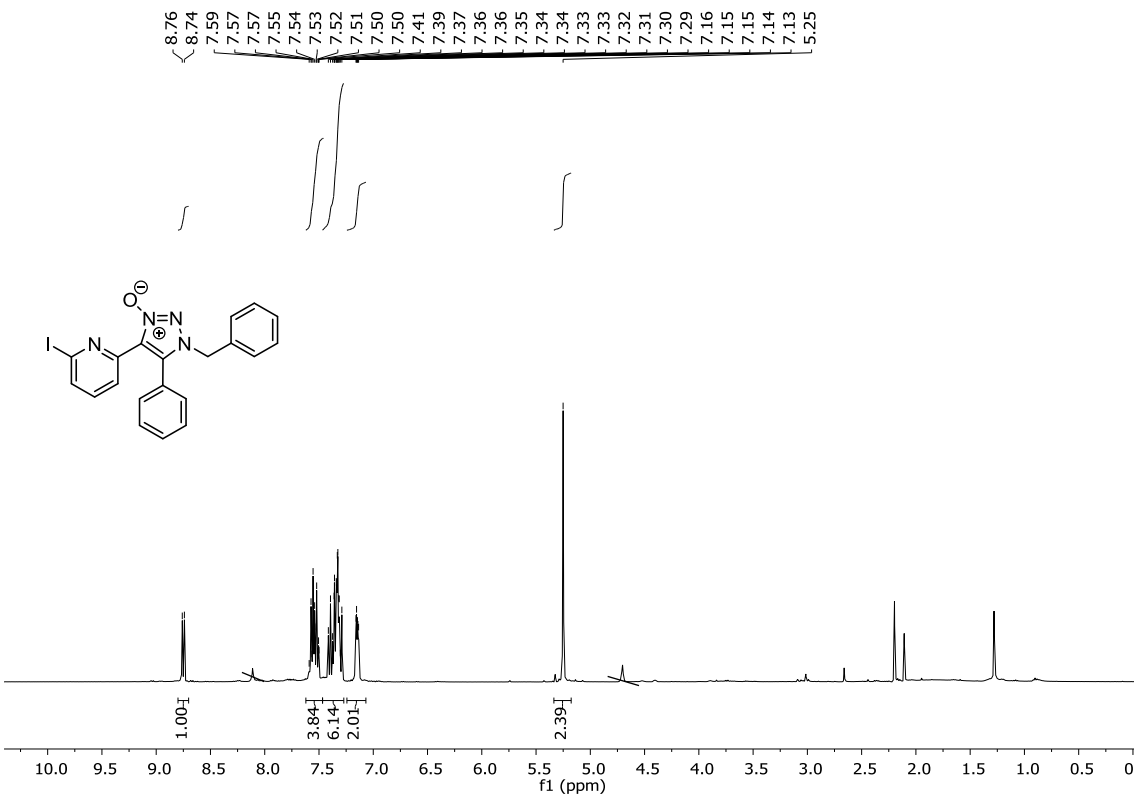
Spectrum 8.140. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23t**.



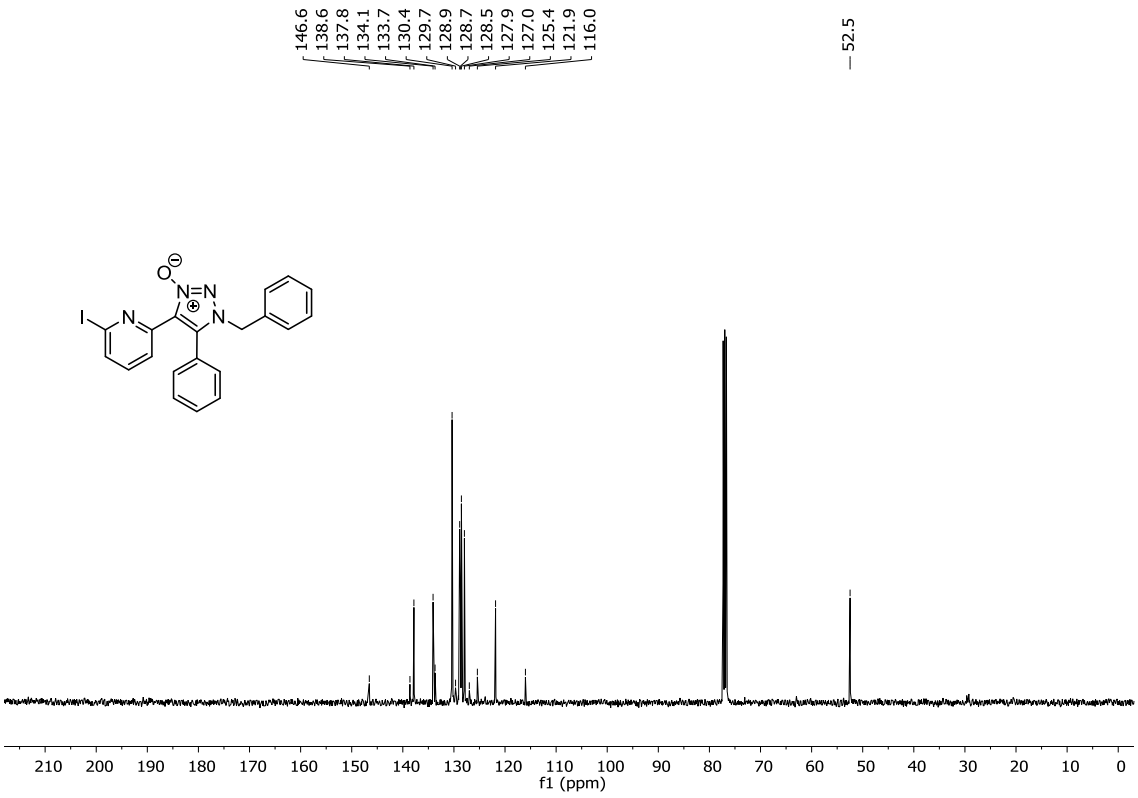
Spectrum 8.141. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23u**.



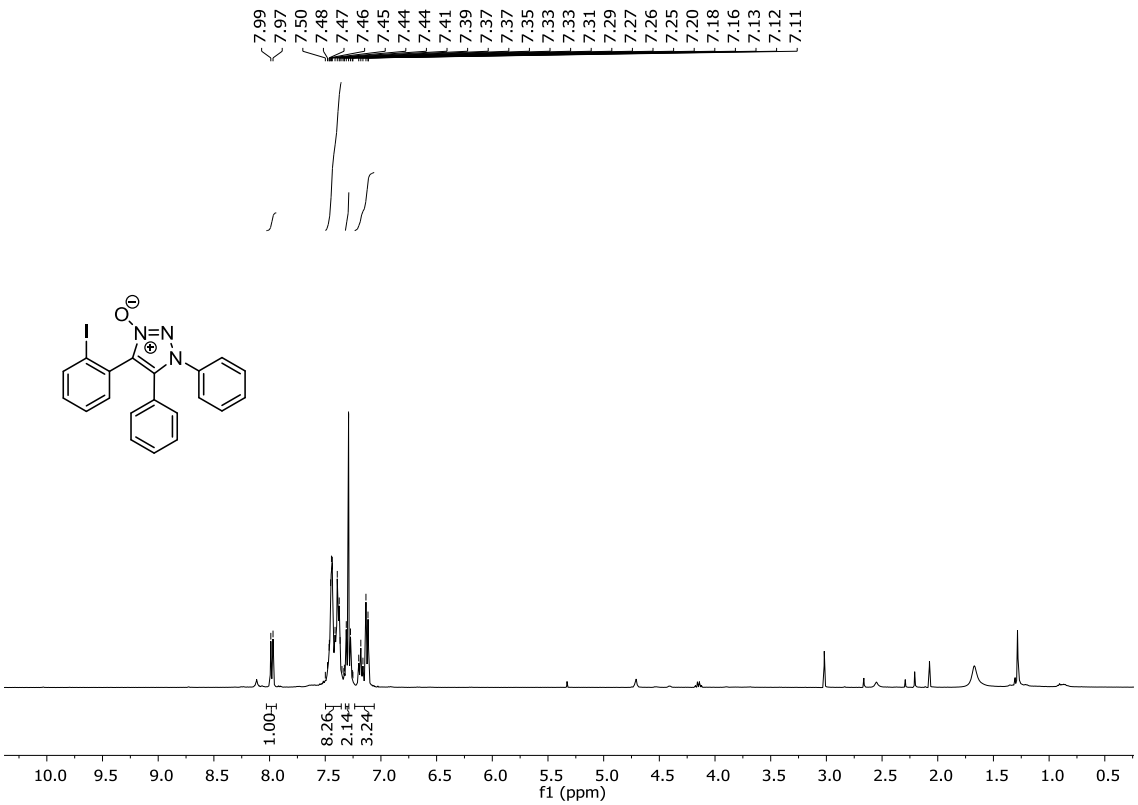
Spectrum 8.142. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23u**.



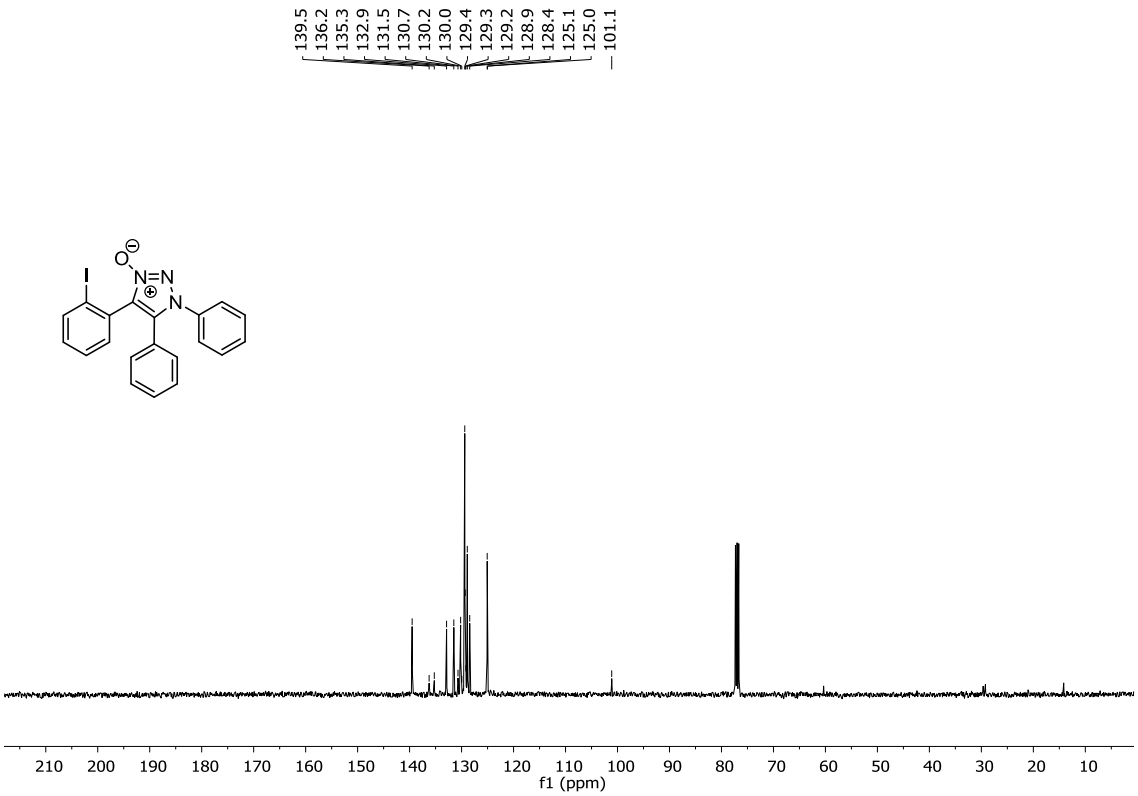
Spectrum 8.143. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23v**.



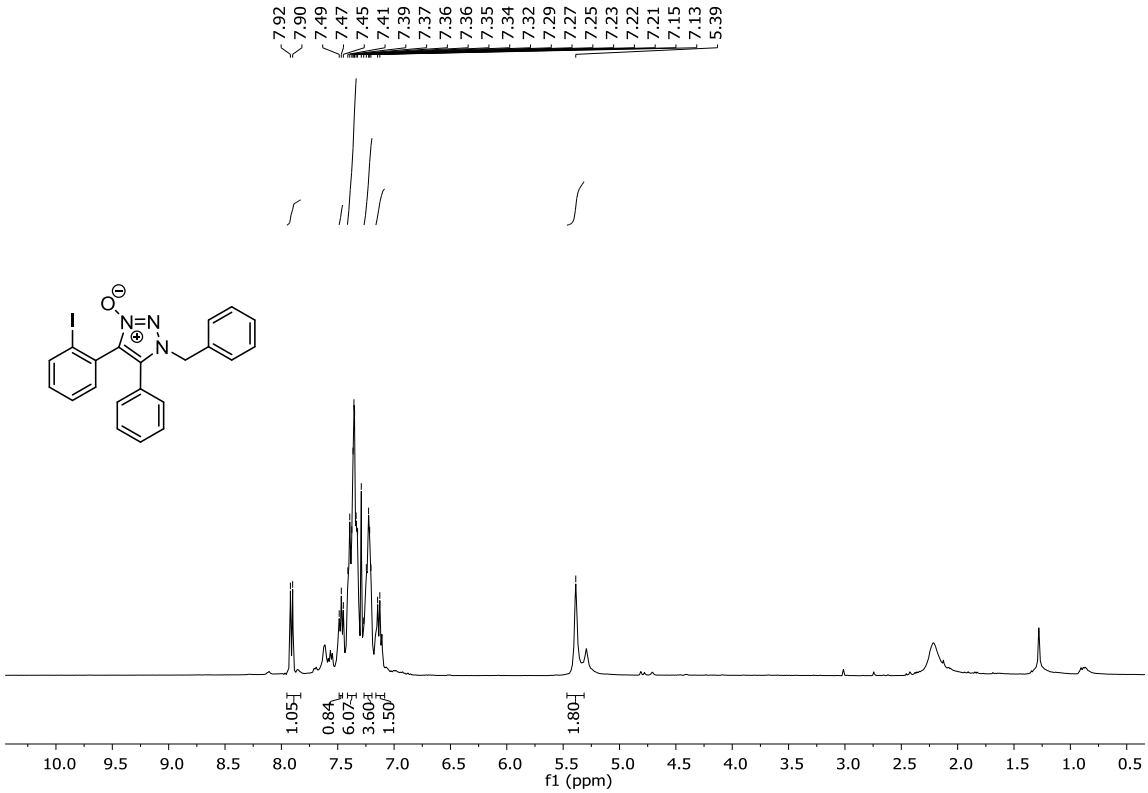
Spectrum 8.144. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23v**.



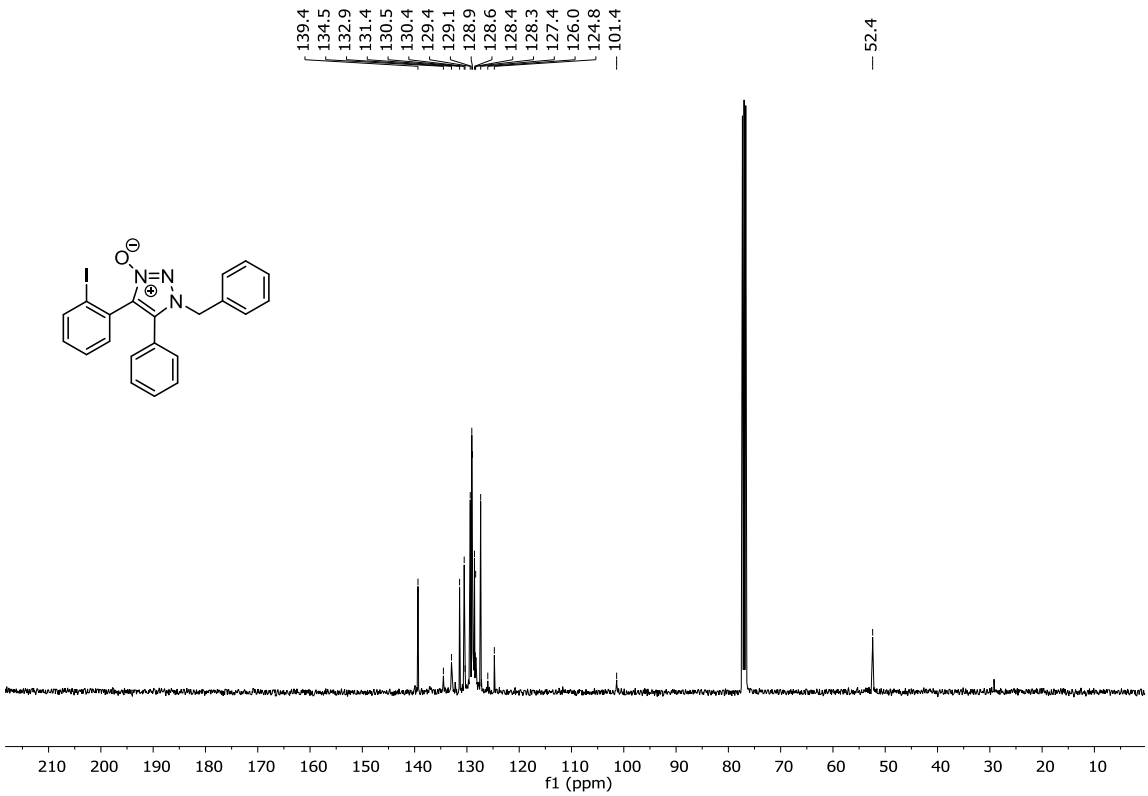
Spectrum 8.145. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23w**.



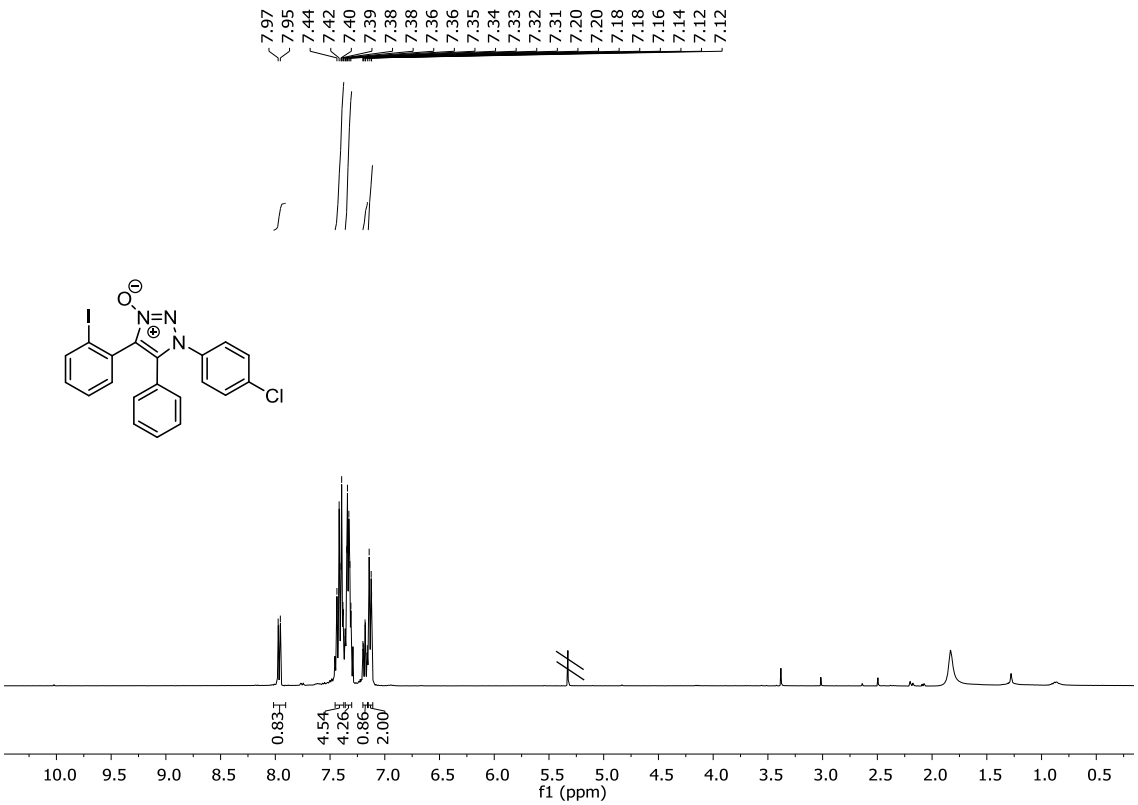
Spectrum 8.146. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23w**.



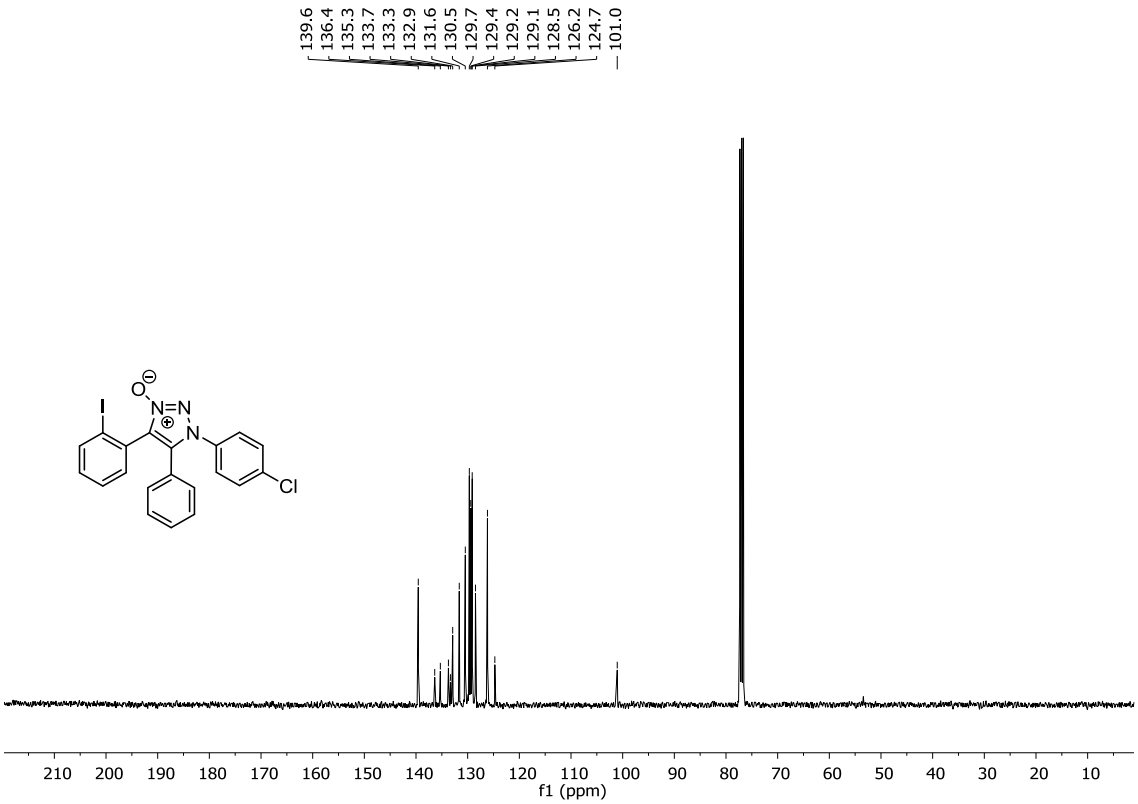
Spectrum 8.147. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23x**.



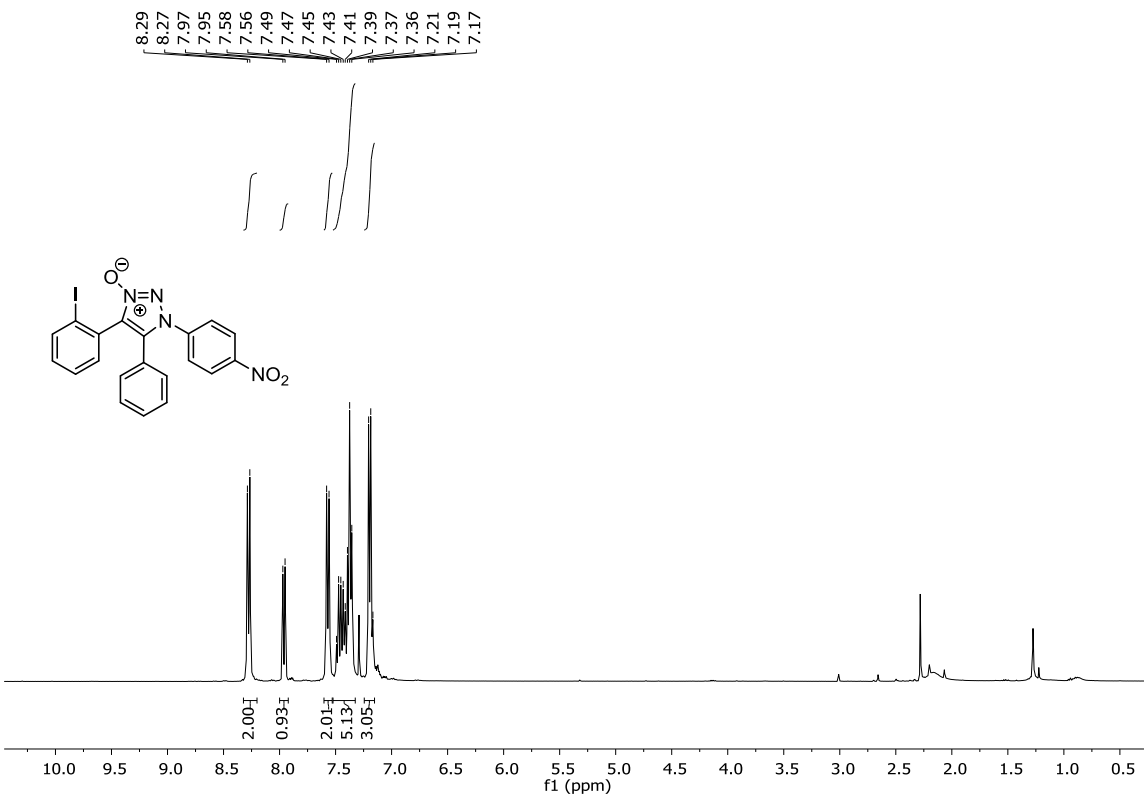
Spectrum 8.148. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23x**.



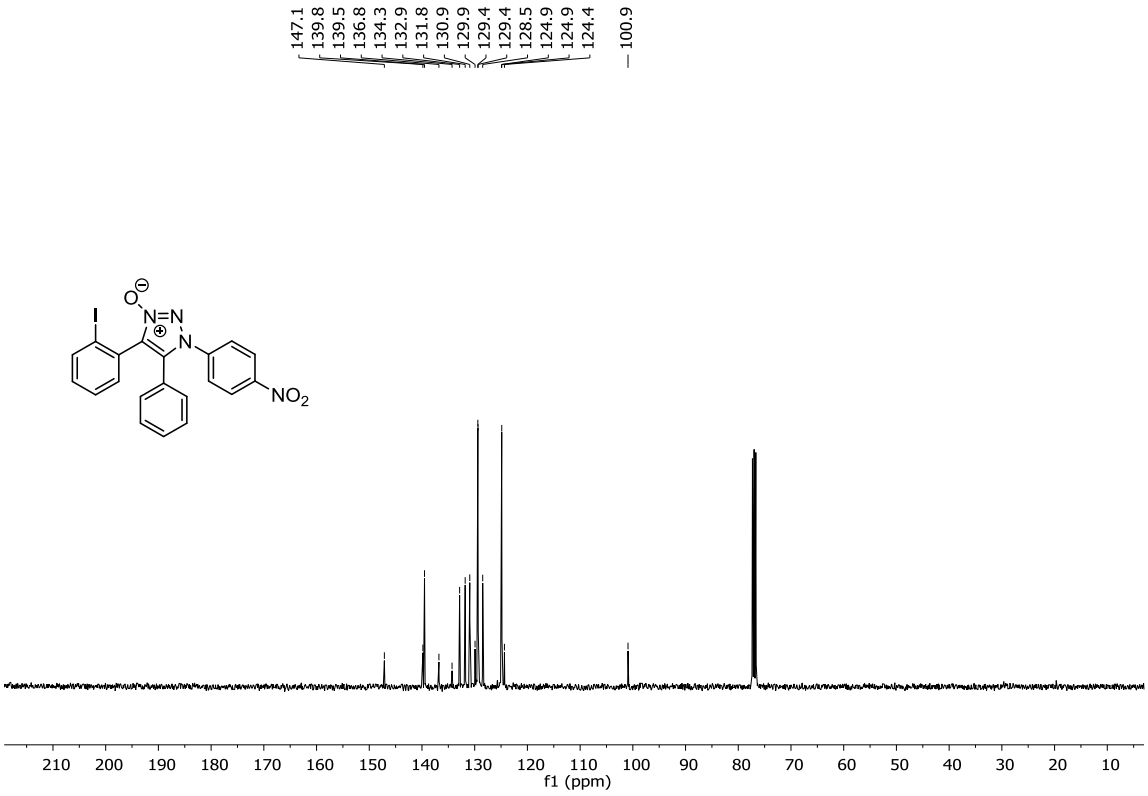
Spectrum 8.149. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23y**.



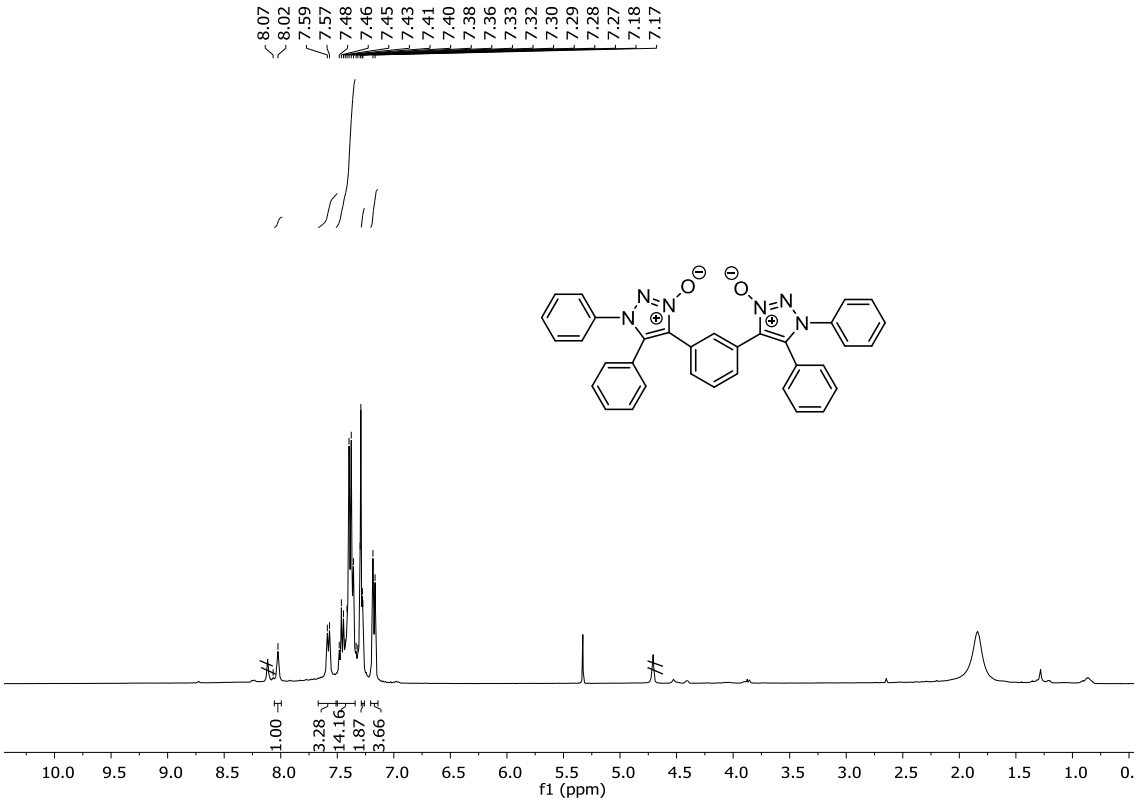
Spectrum 8.150. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23y**.



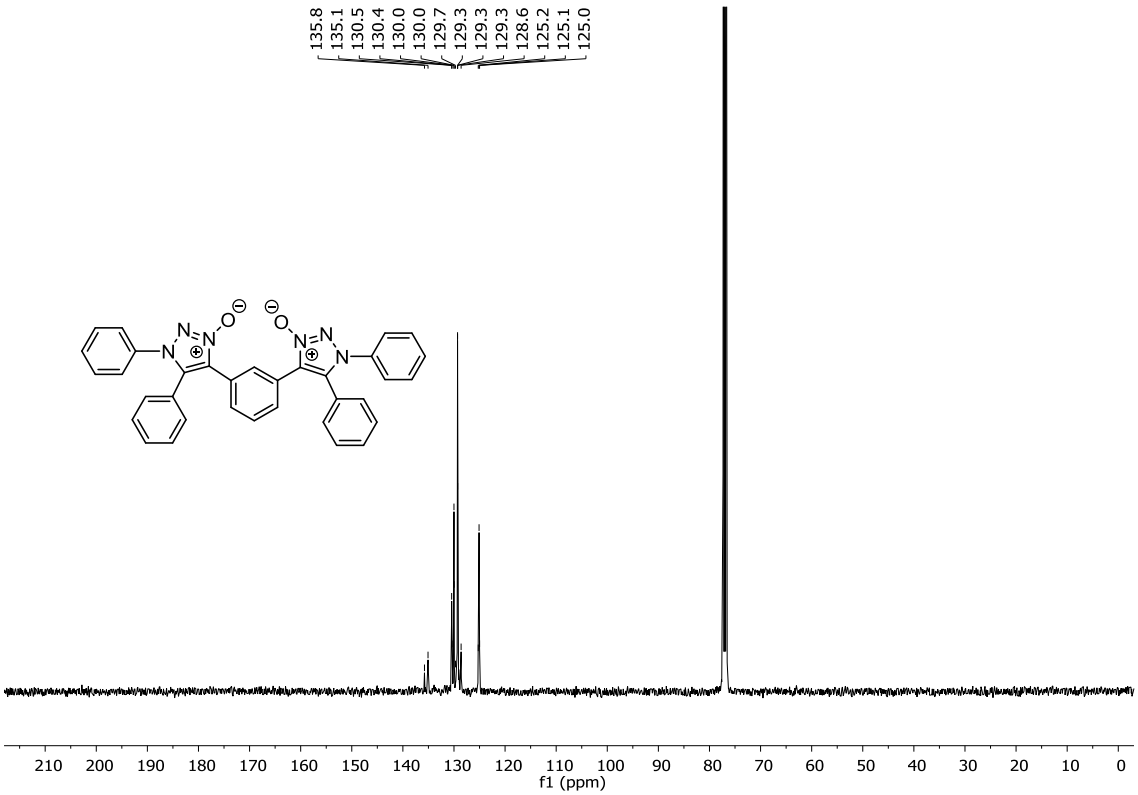
Spectrum 8.151. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23z**.



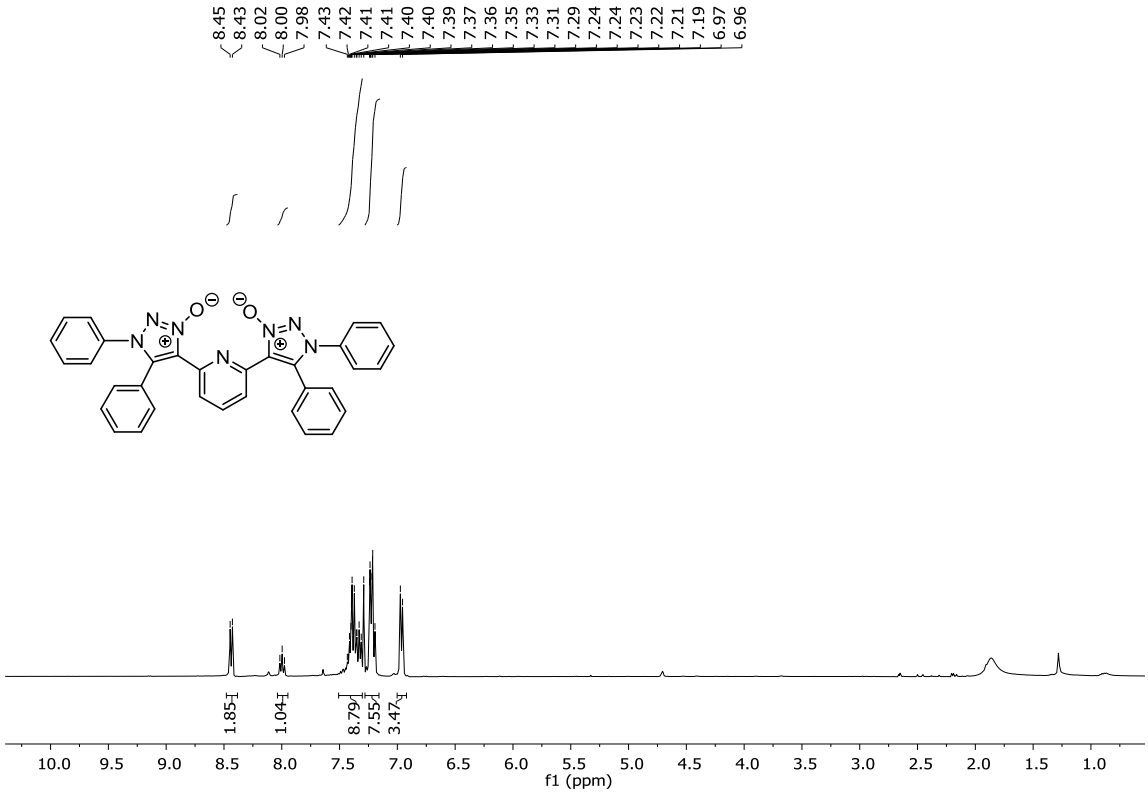
Spectrum 8.152. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23z**.



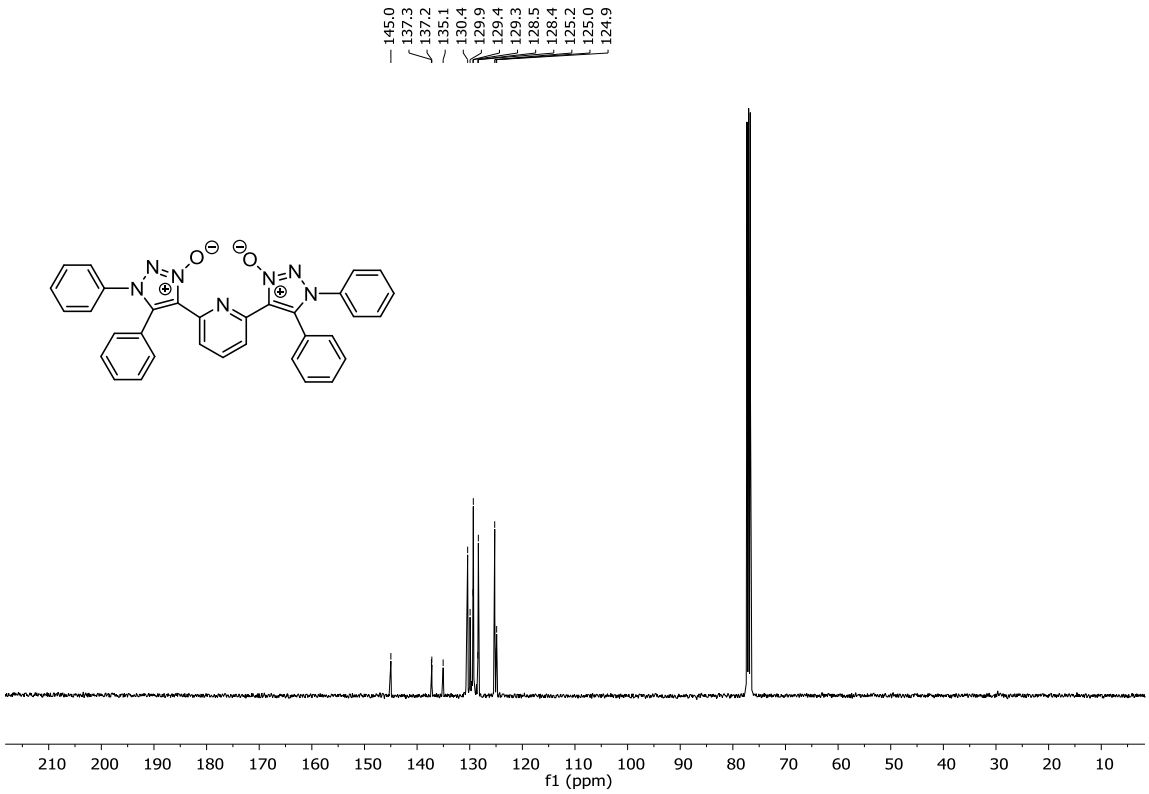
Spectrum 8.153. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23aa**.



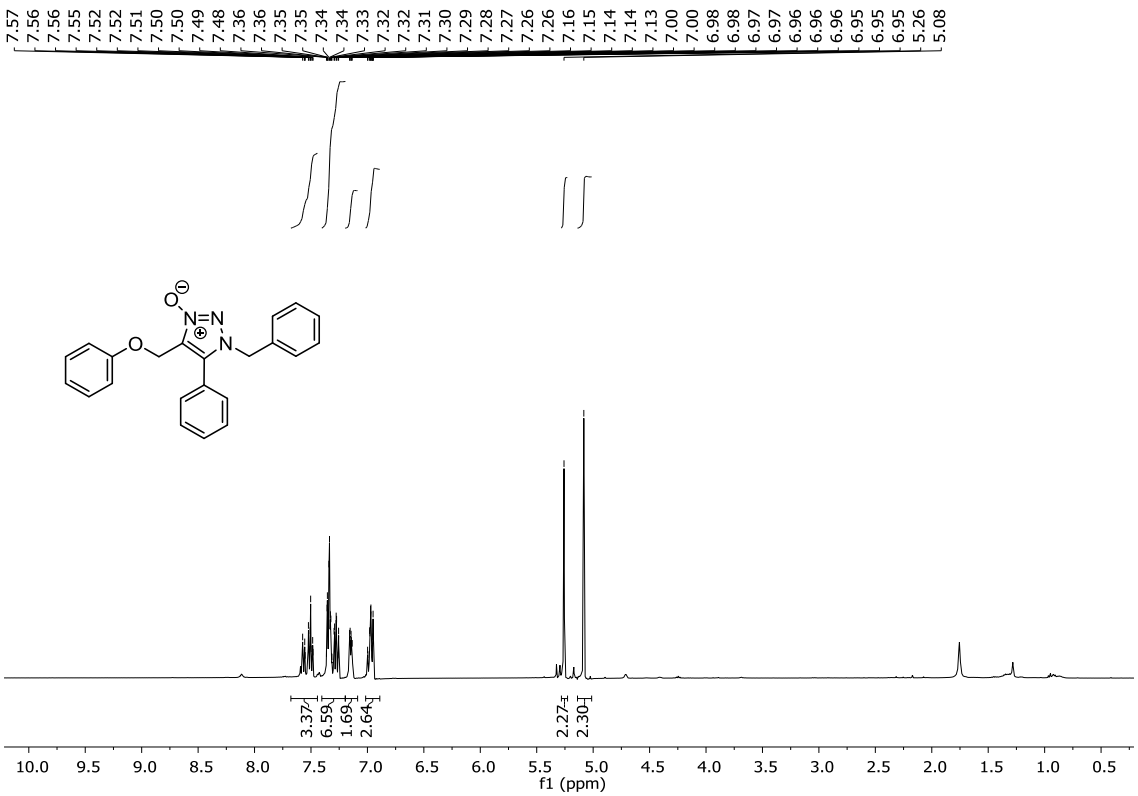
Spectrum 8.154. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23aa**.



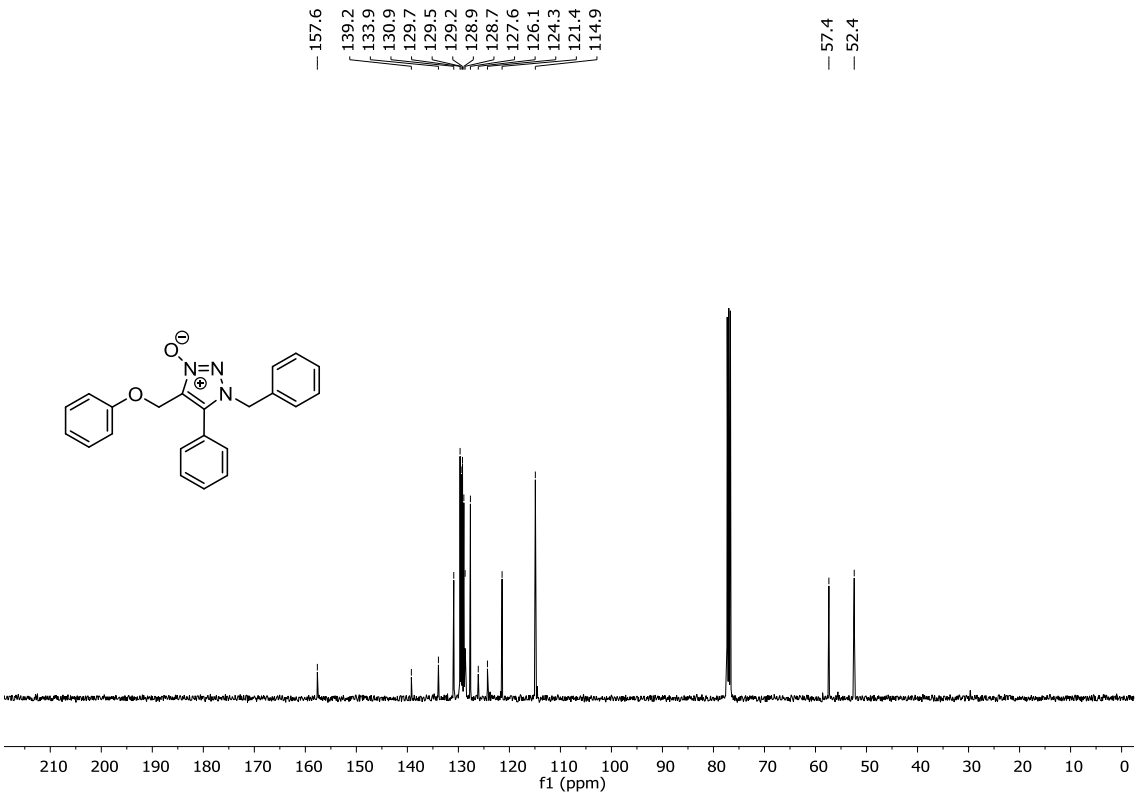
Spectrum 8.155. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **23ab**.



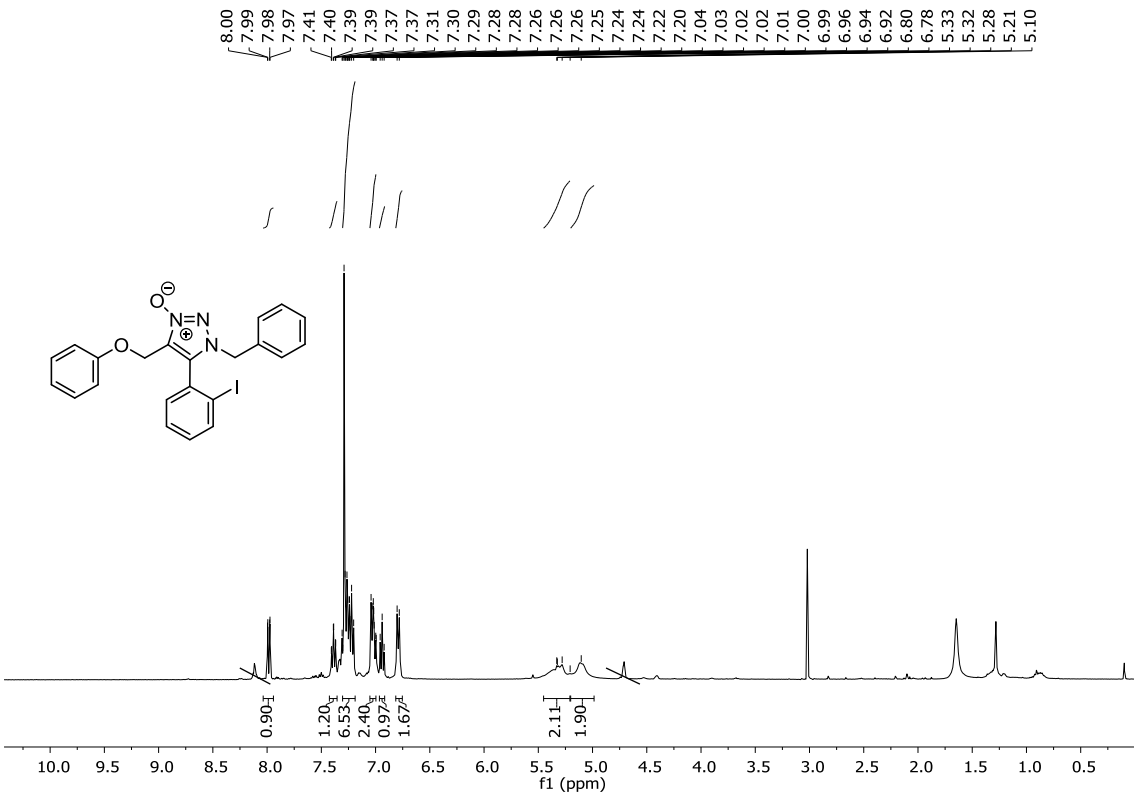
Spectrum 8.156. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **23ab**.



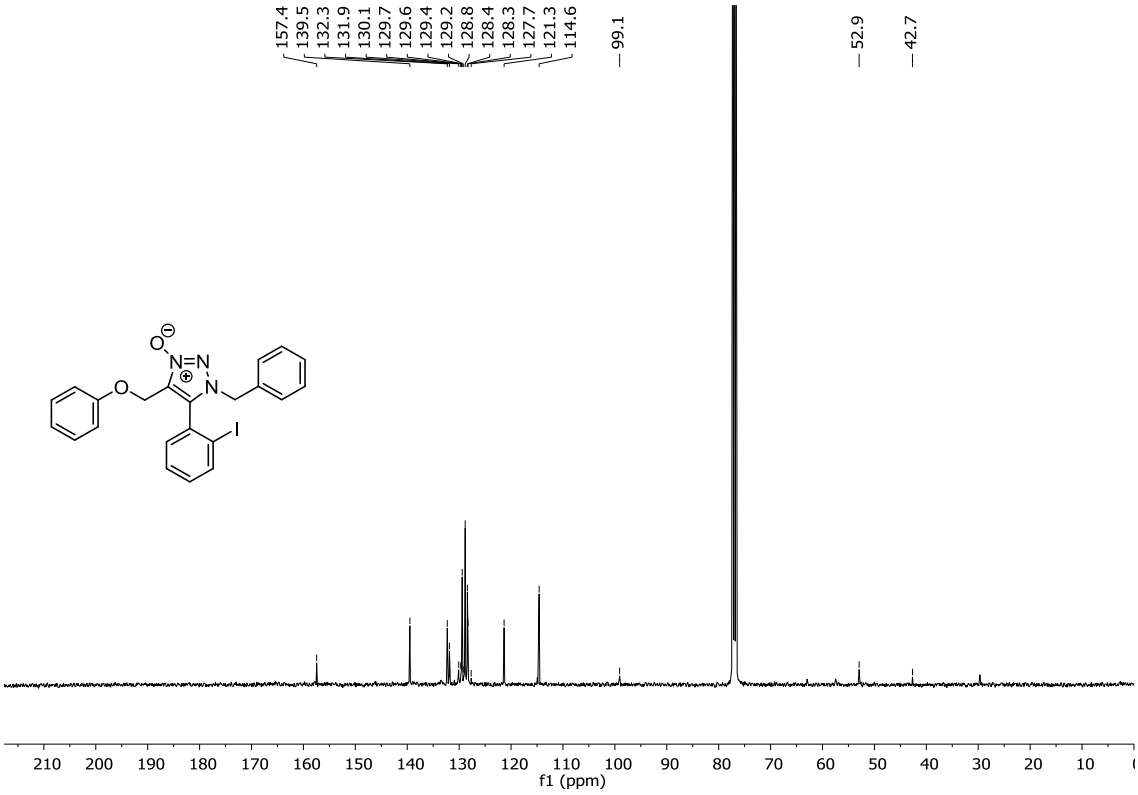
Spectrum 8.157. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24a**.



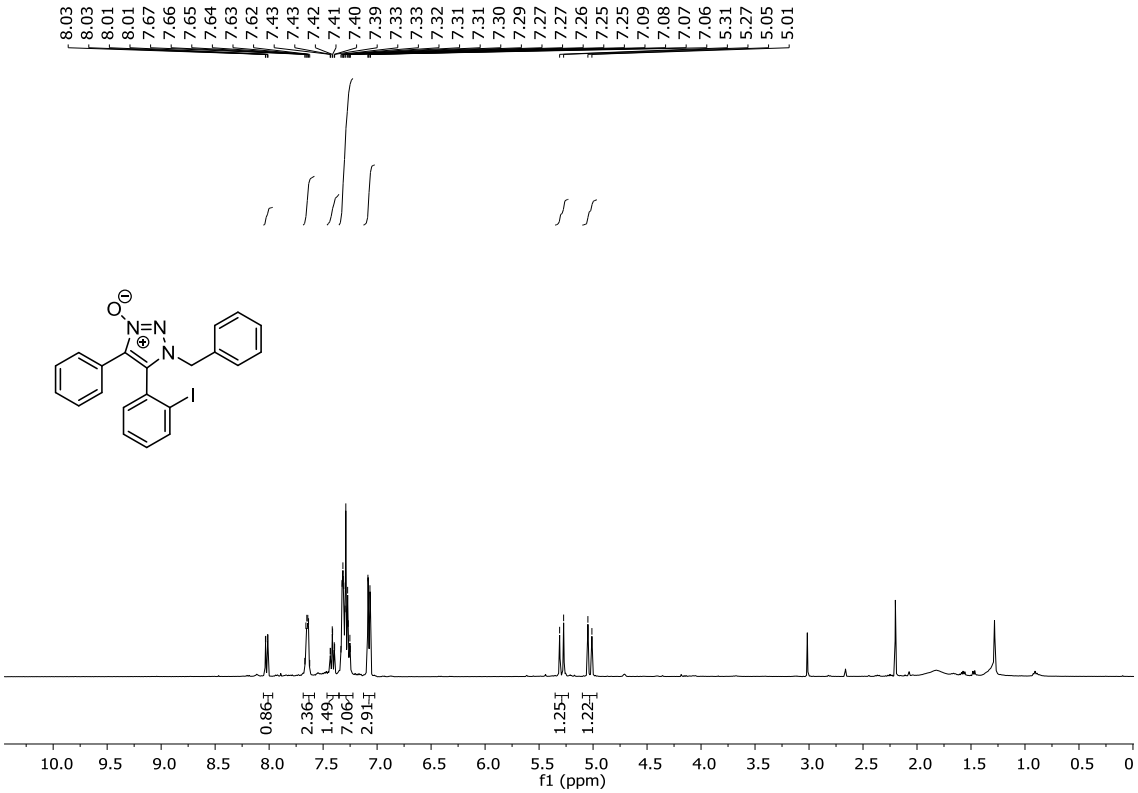
Spectrum 8.158. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24a**.



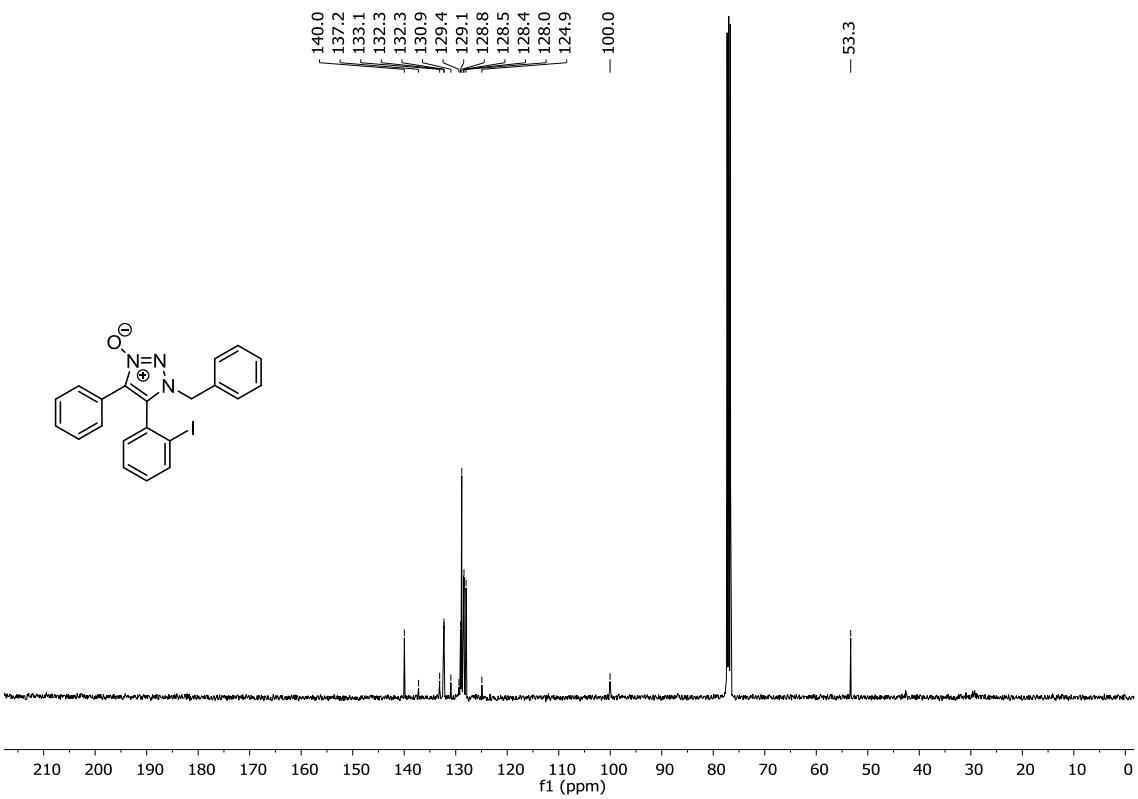
Spectrum 8.159. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24b**.



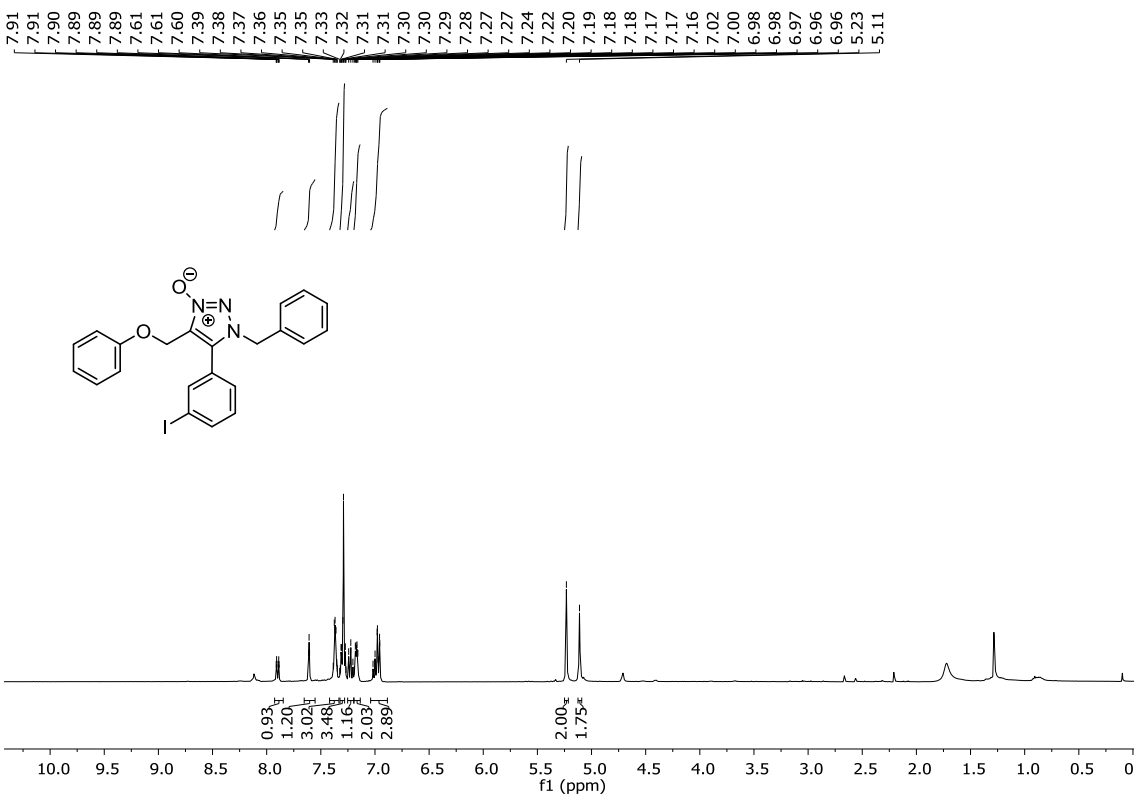
Spectrum 8.160. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24b**.



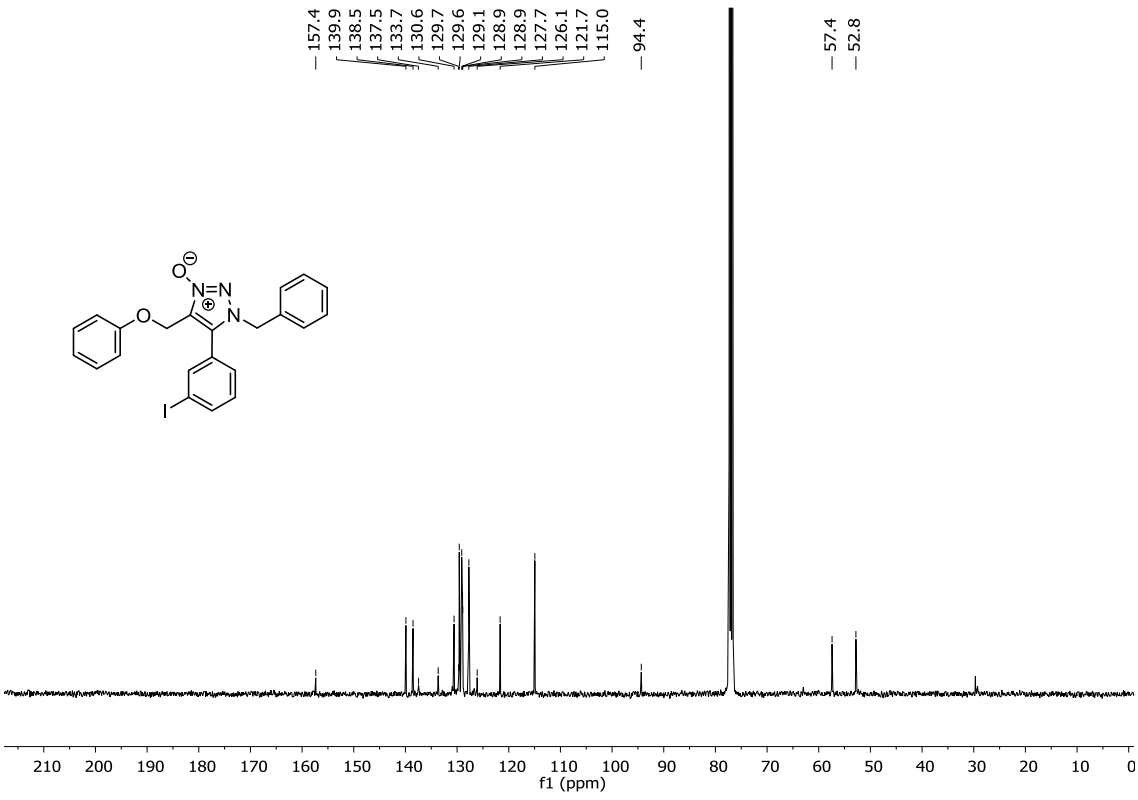
Spectrum 8.161. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24c**.



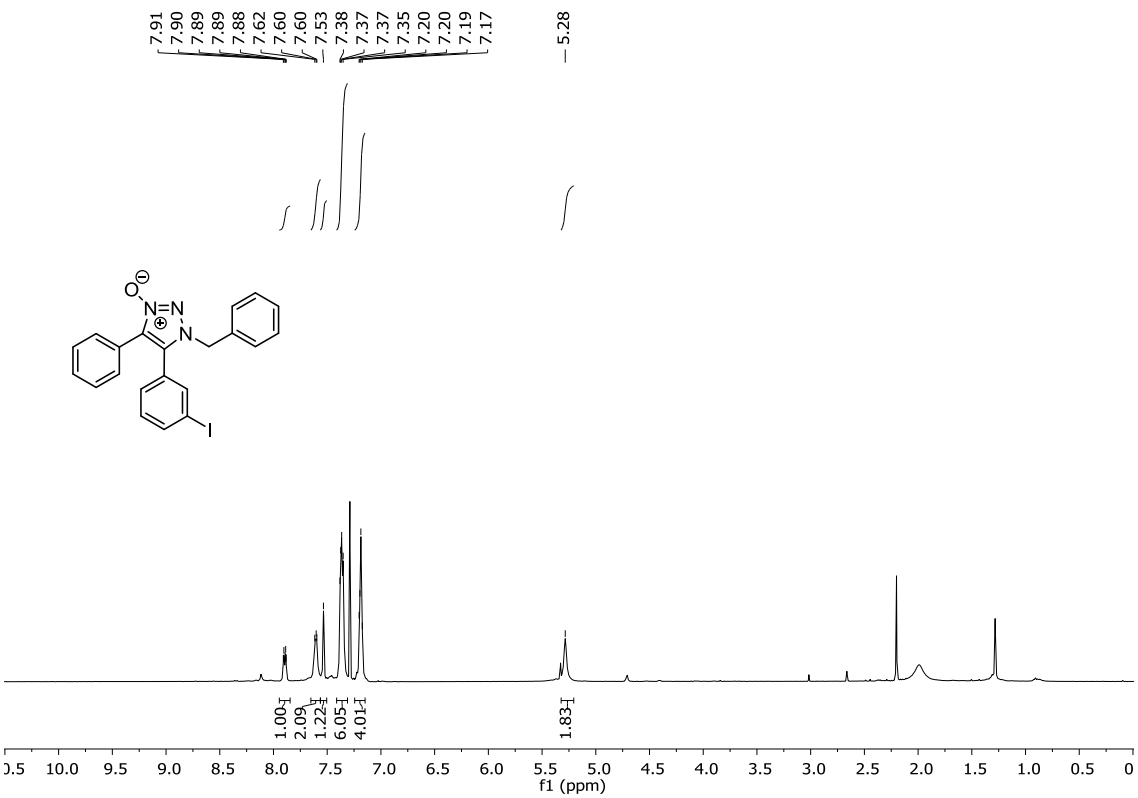
Spectrum 8.162. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24c**.



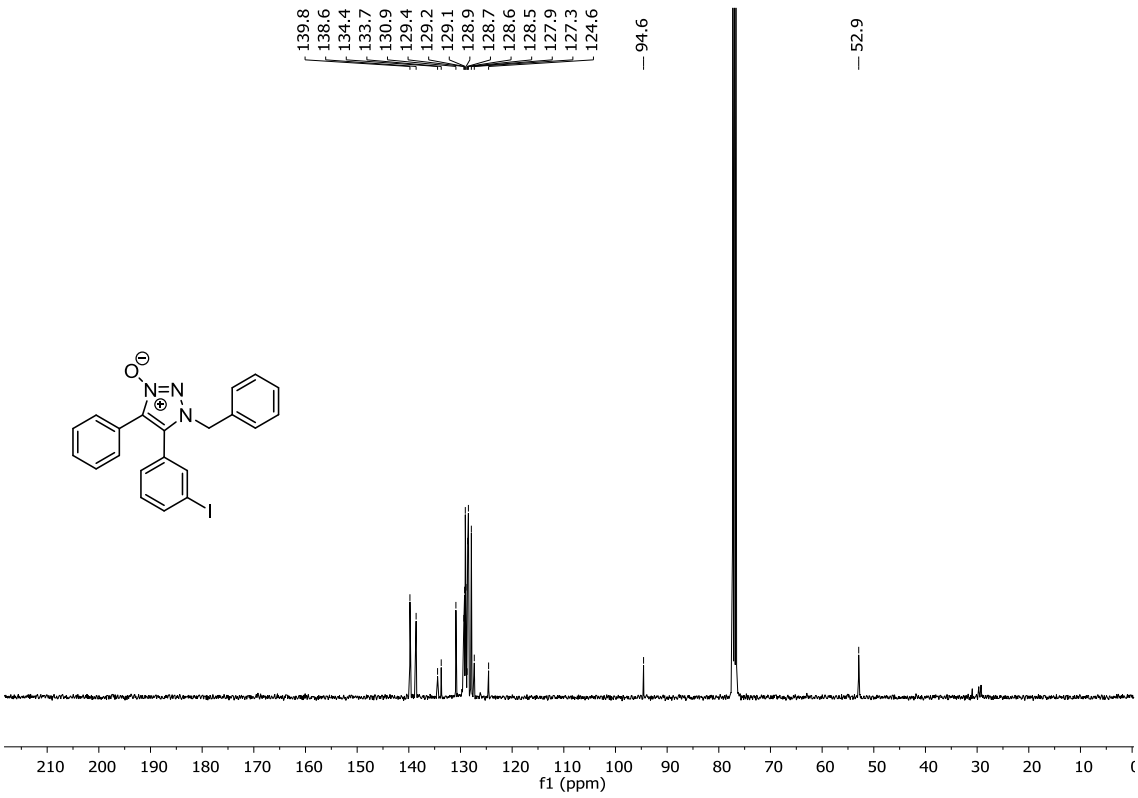
Spectrum 8.163. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24d**.



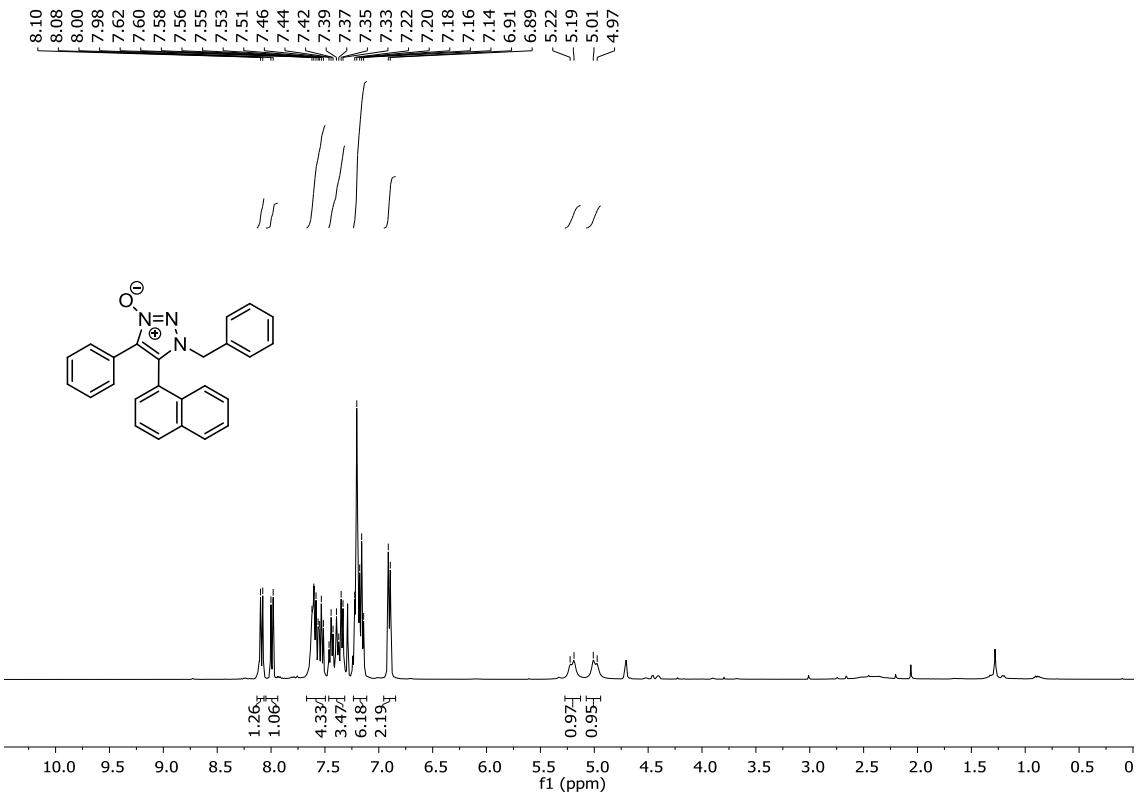
Spectrum 8.164. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24d**.



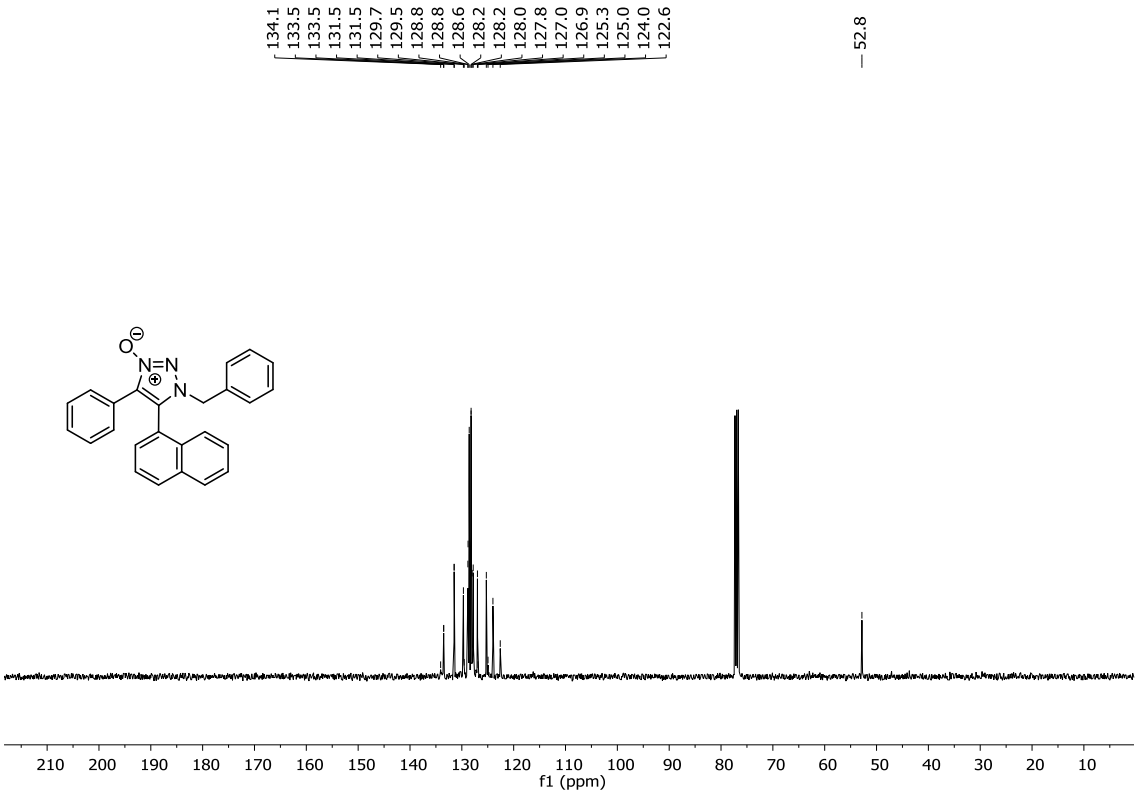
Spectrum 8.165. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24e**.



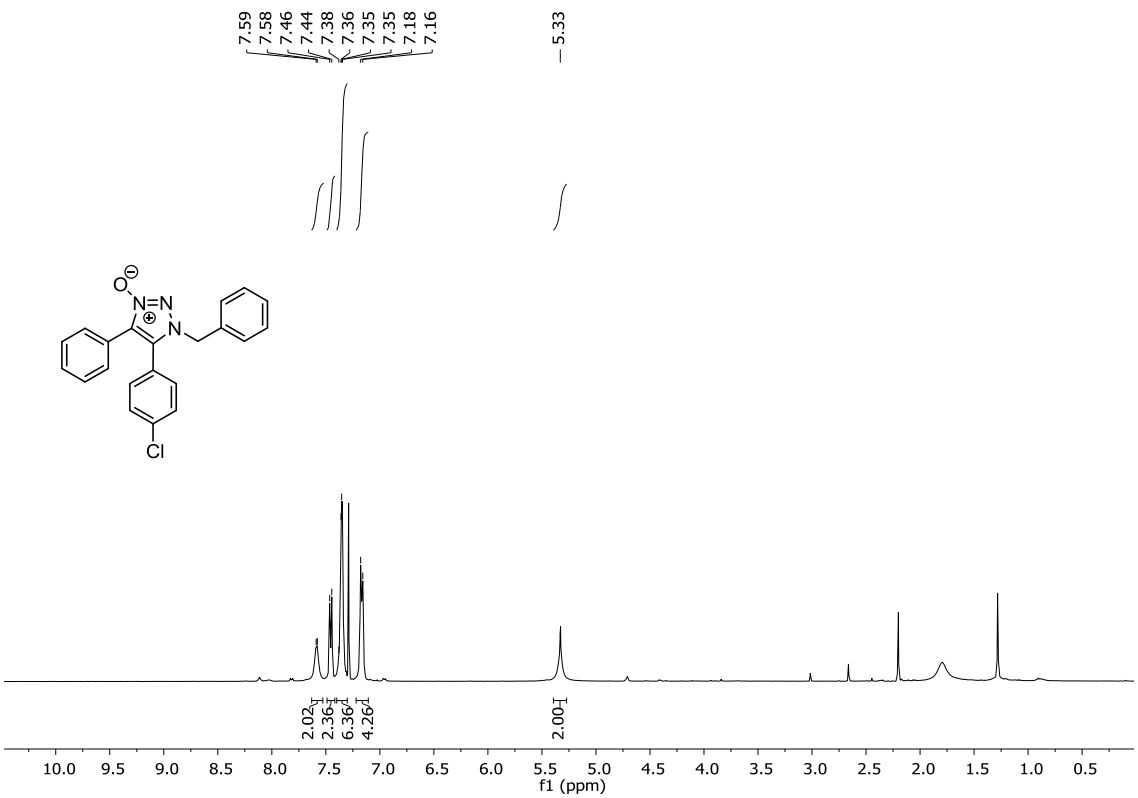
Spectrum 8.166. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24e**.



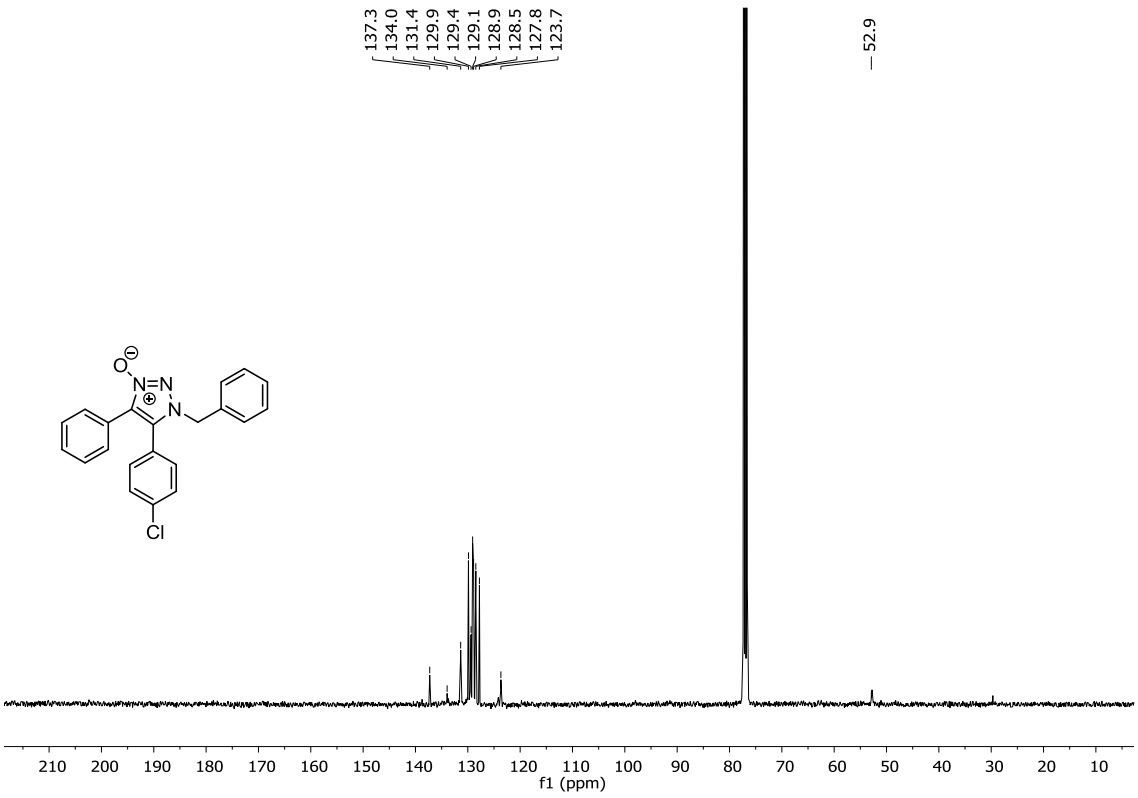
Spectrum 8.167. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24f**.



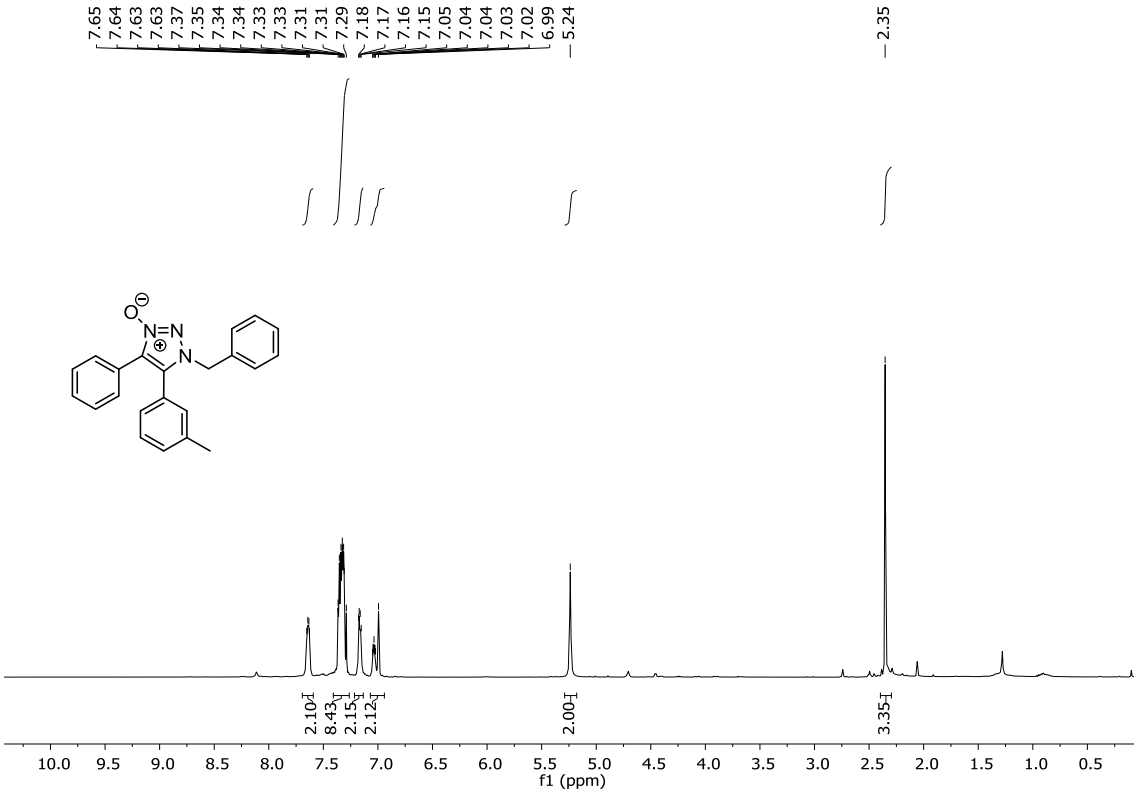
Spectrum 8.168. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24f**.



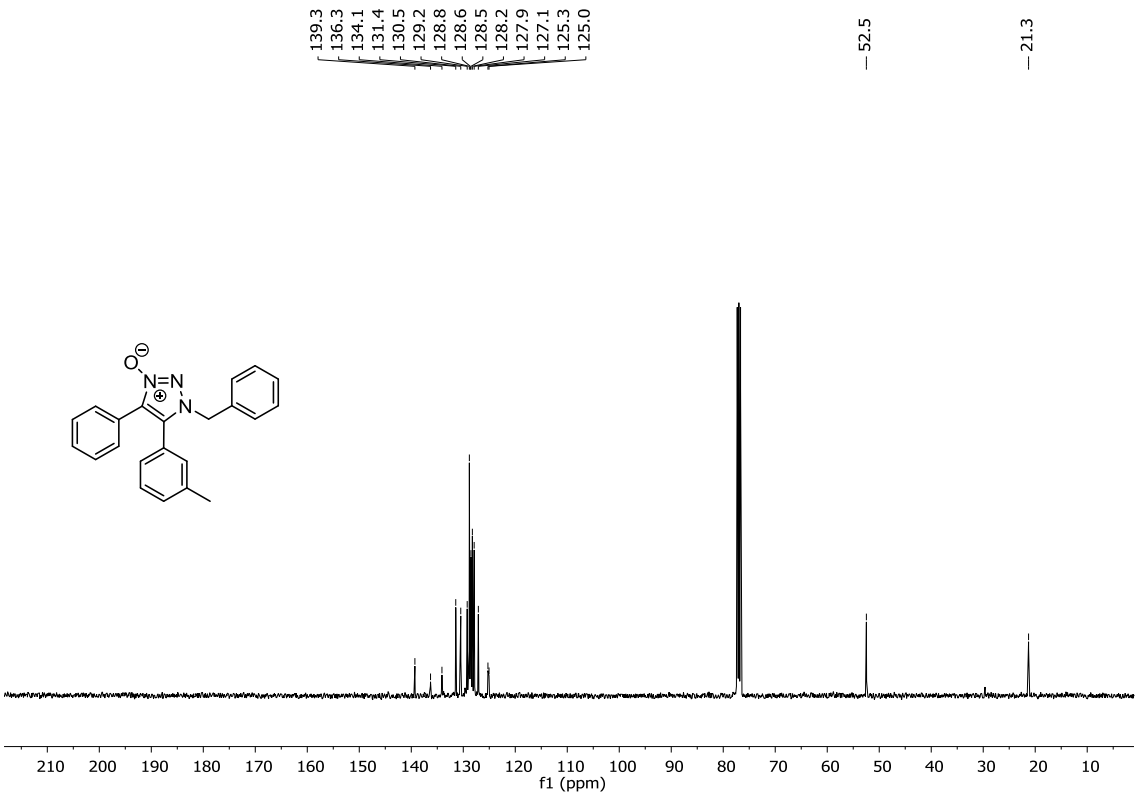
Spectrum 8.169. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24g**.



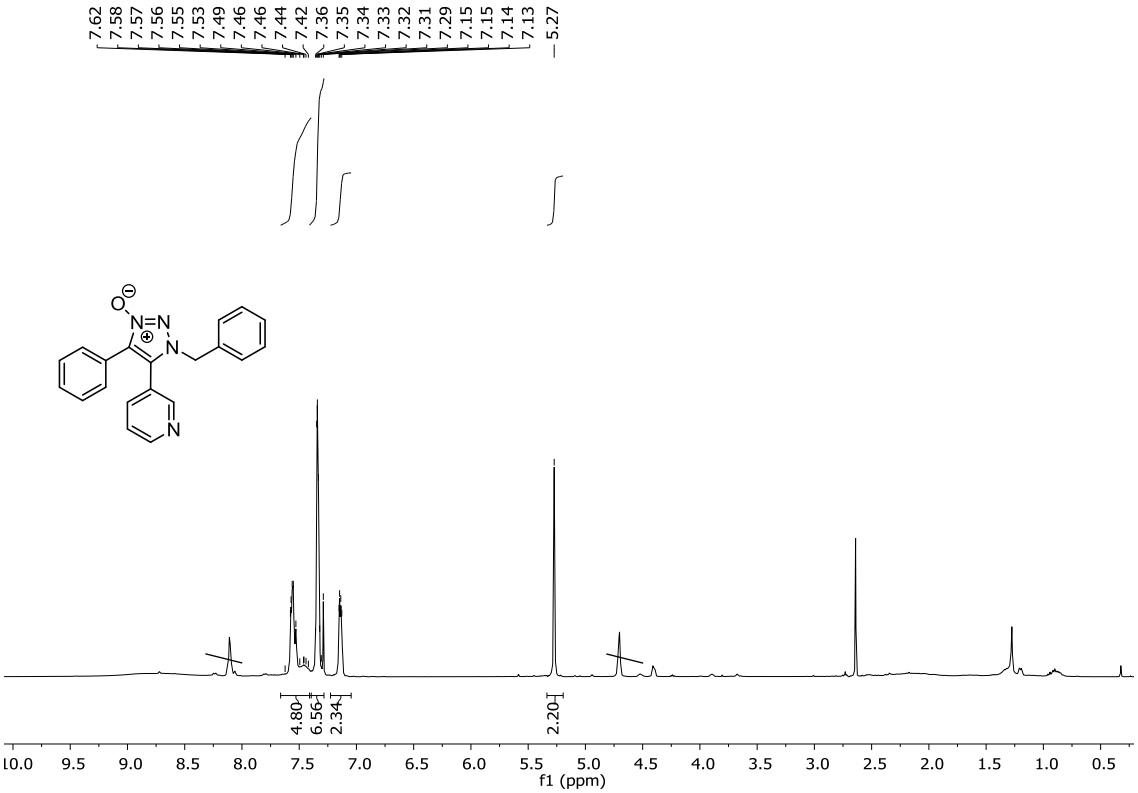
Spectrum 8.170. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24g**.



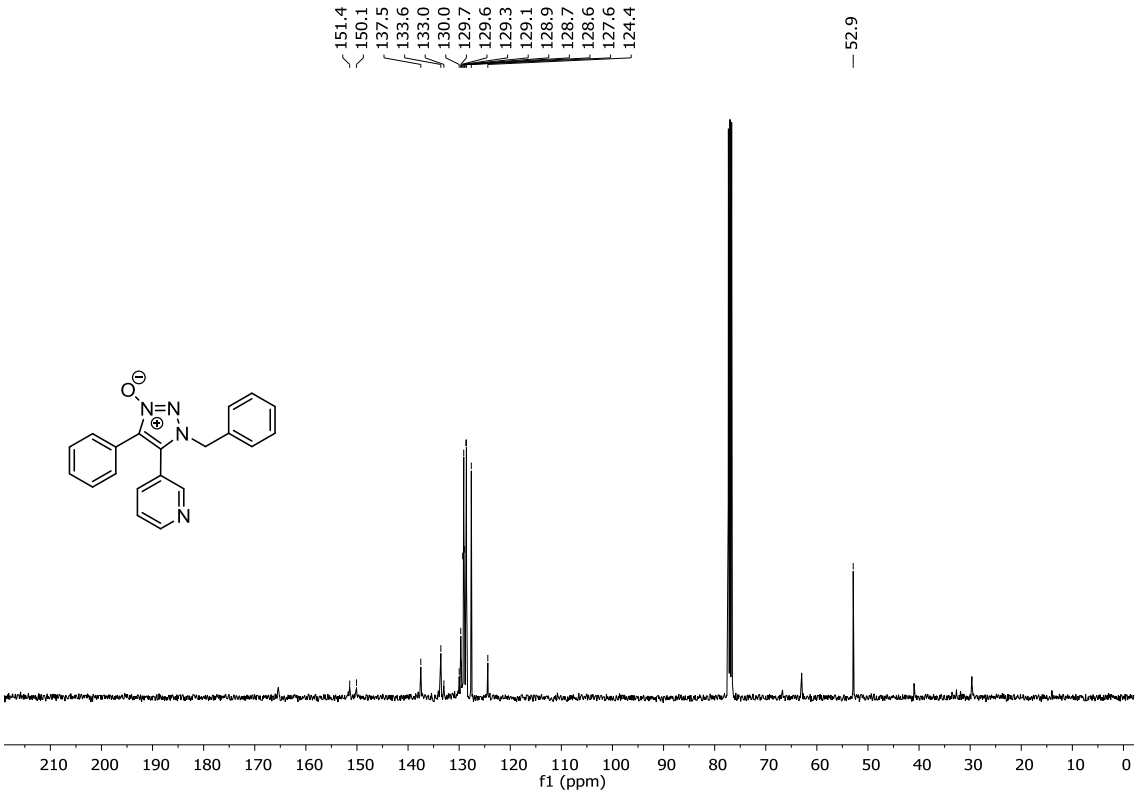
Spectrum 8.171. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24h**.



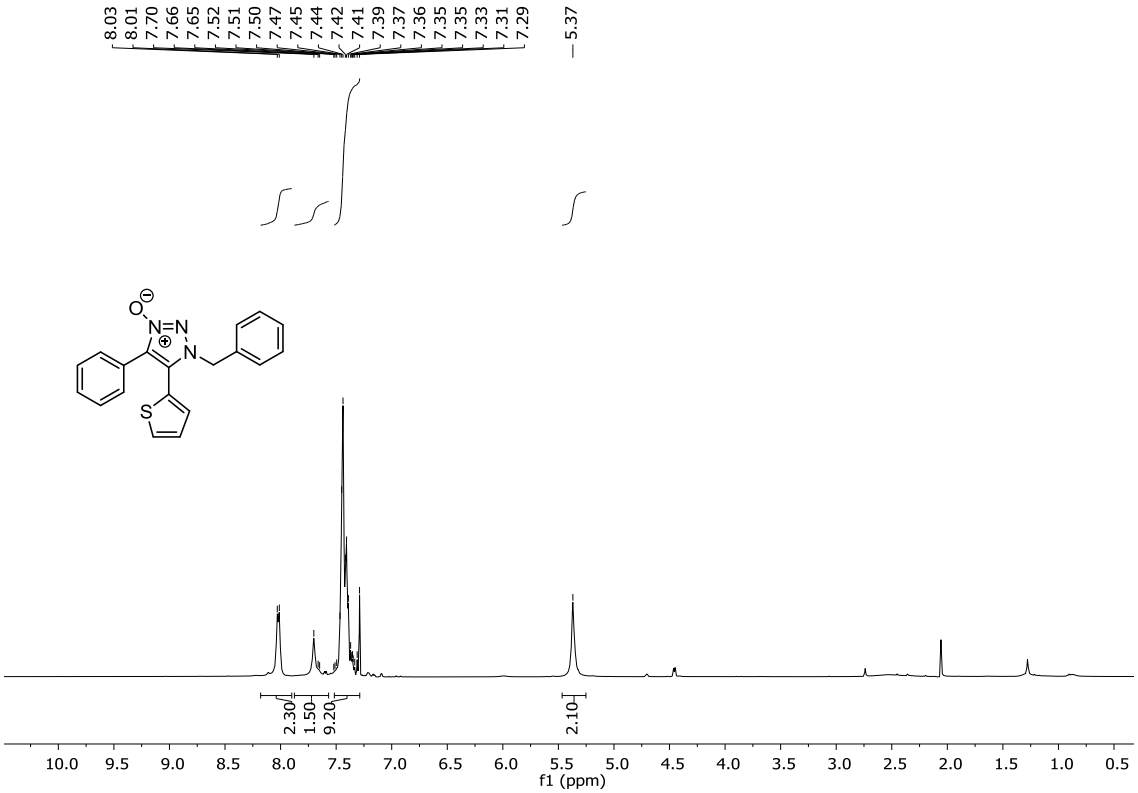
Spectrum 8.172. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24h**.



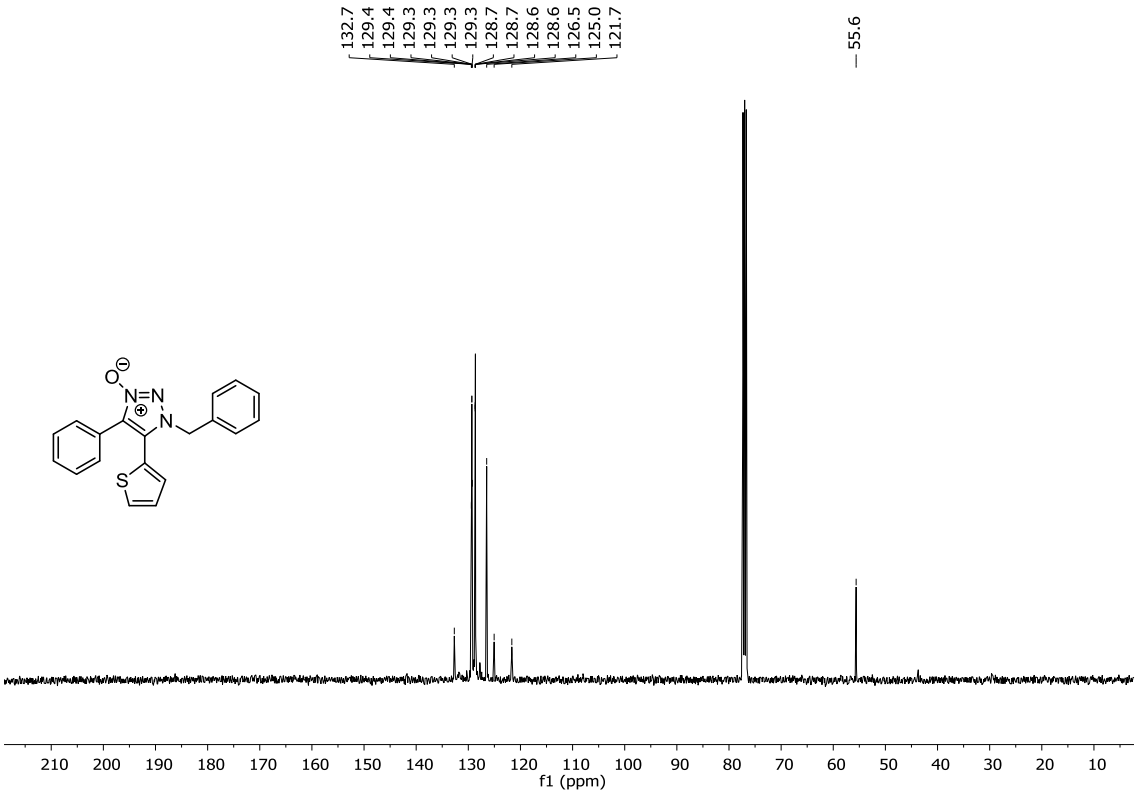
Spectrum 8.173. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24i**.



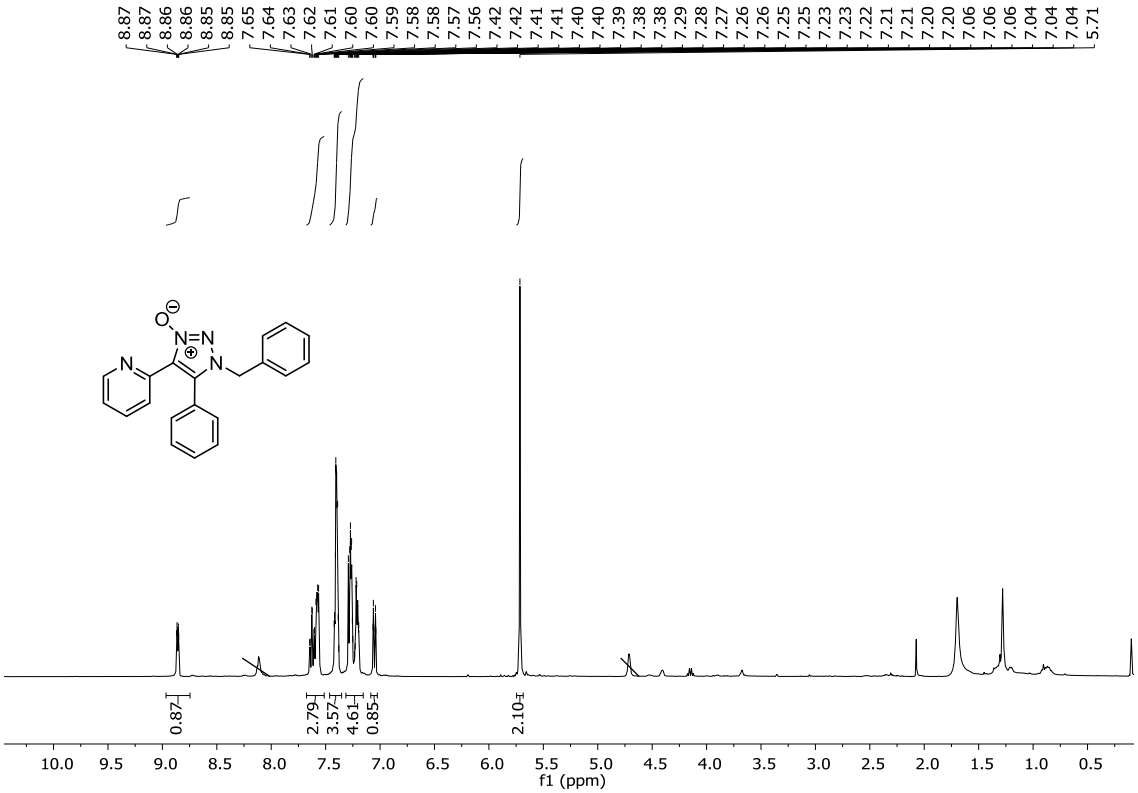
Spectrum 8.174. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24i**.



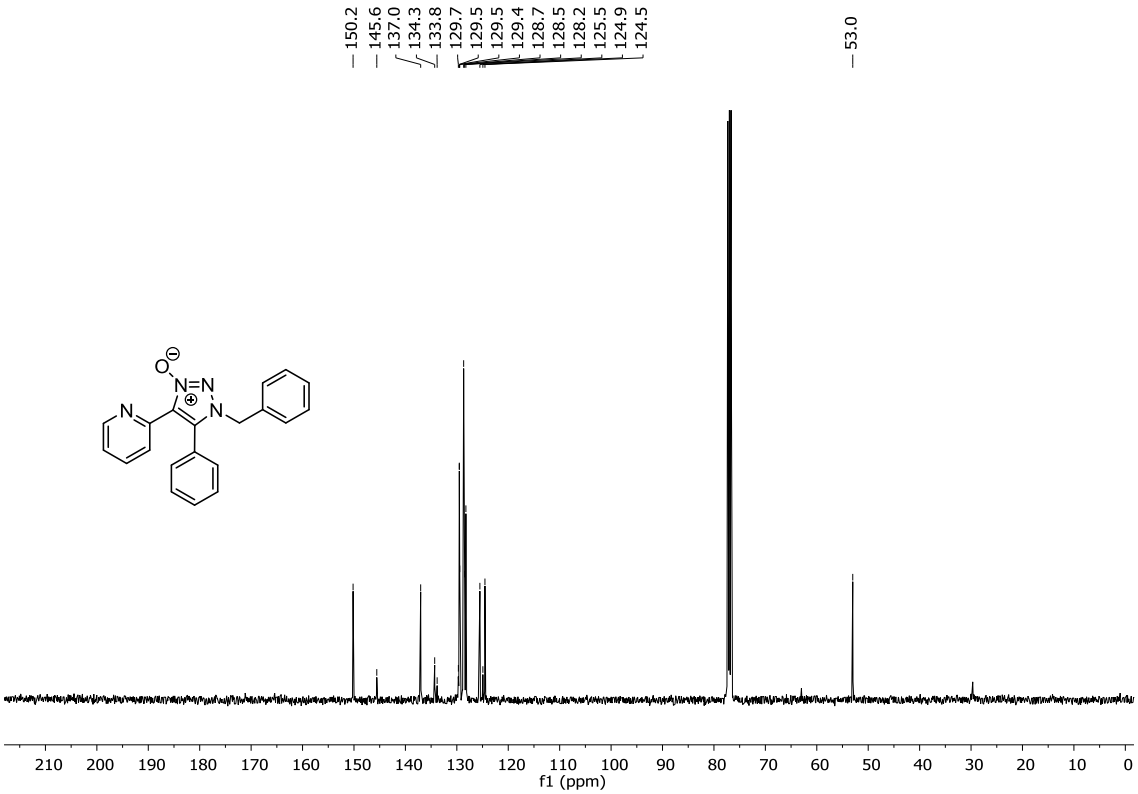
Spectrum 8.175. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24j**.



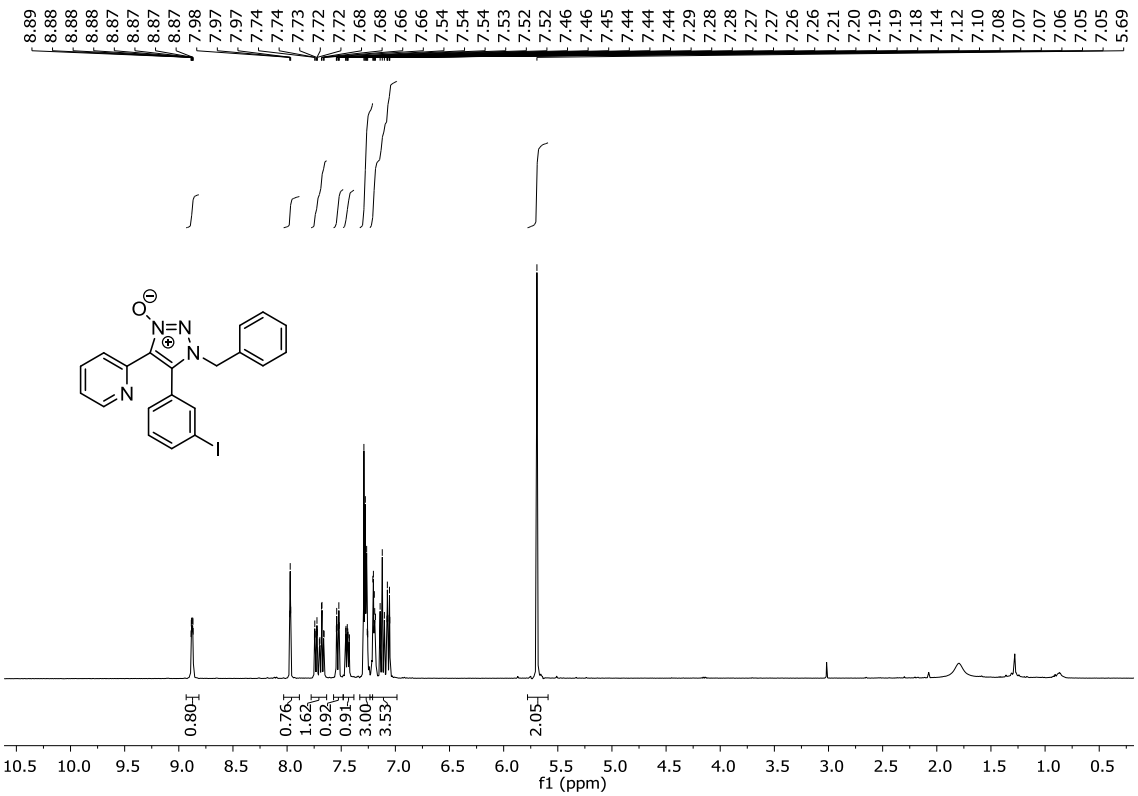
Spectrum 8.176. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24j**.



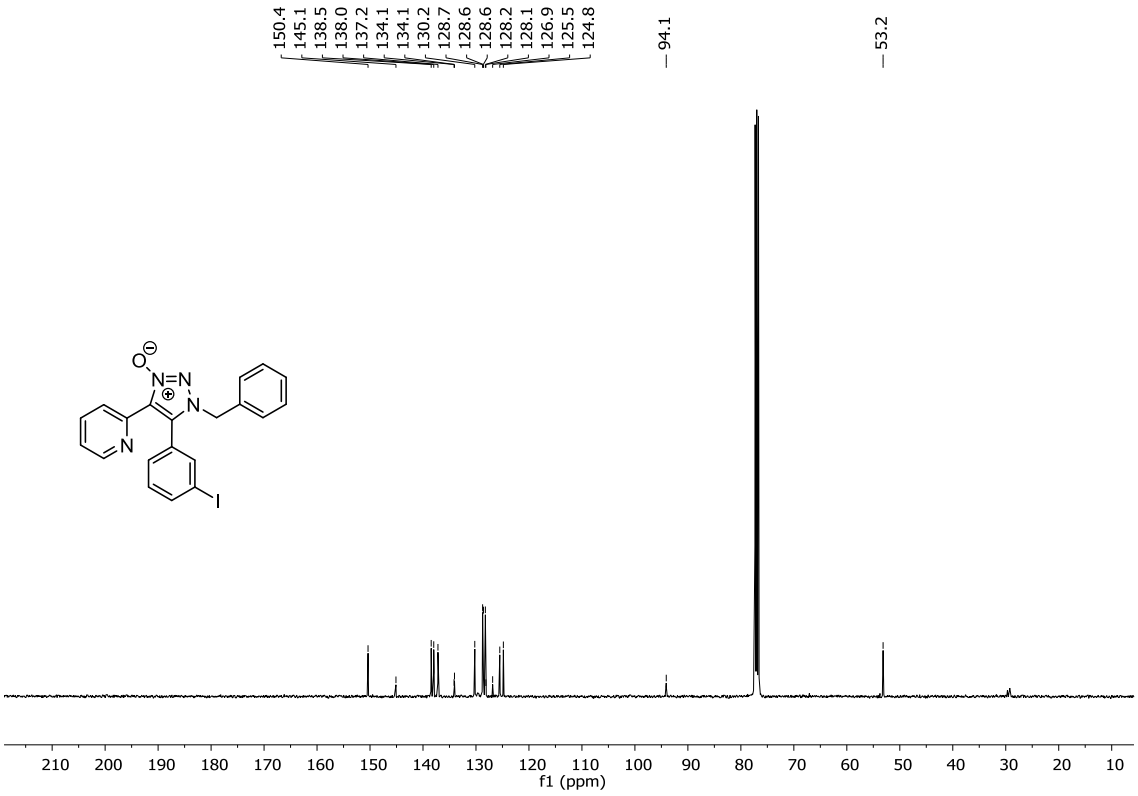
Spectrum 8.177. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24k**.



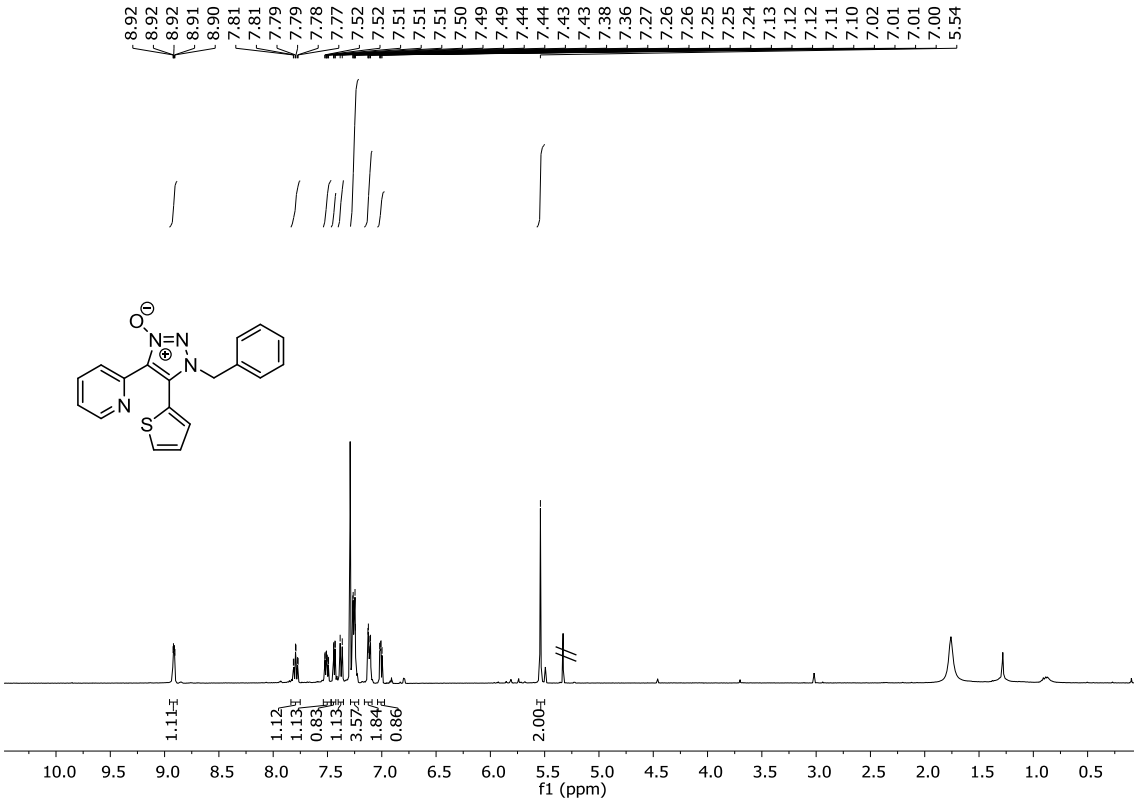
Spectrum 8.178. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24k**.



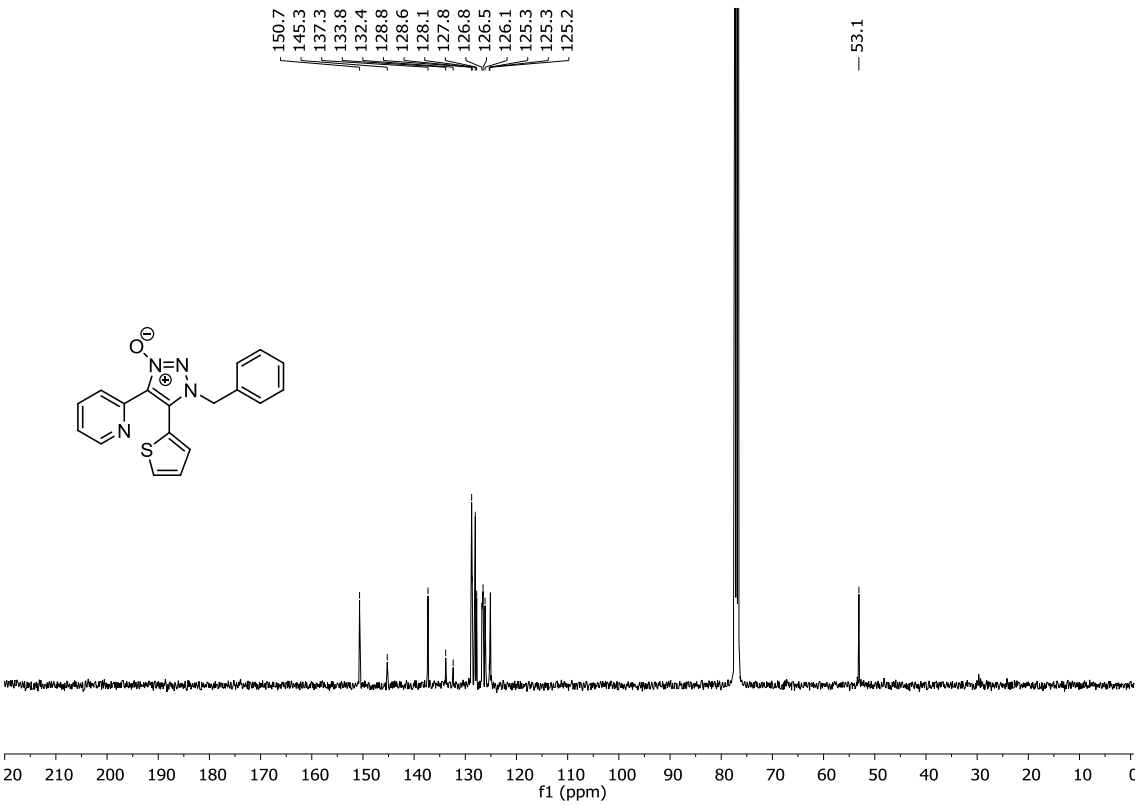
Spectrum 8.179. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24l**.



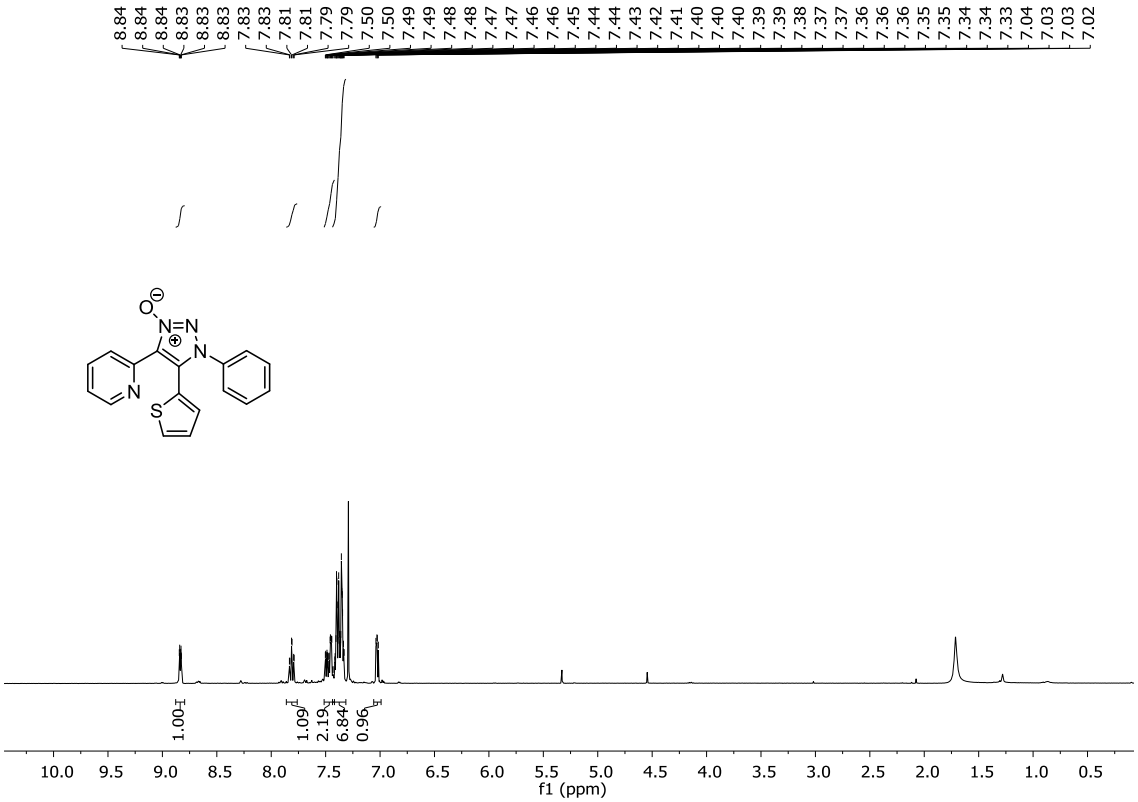
Spectrum 8.180. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24l**.



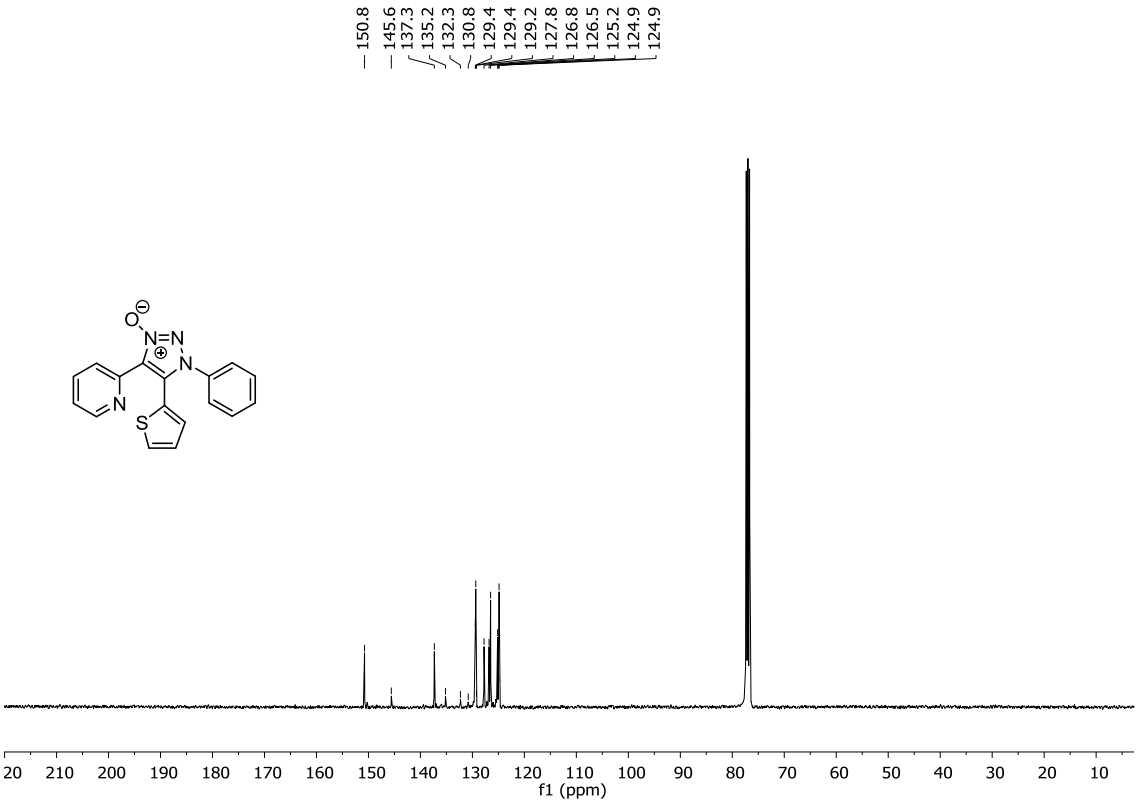
Spectrum 8.181. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24m**.



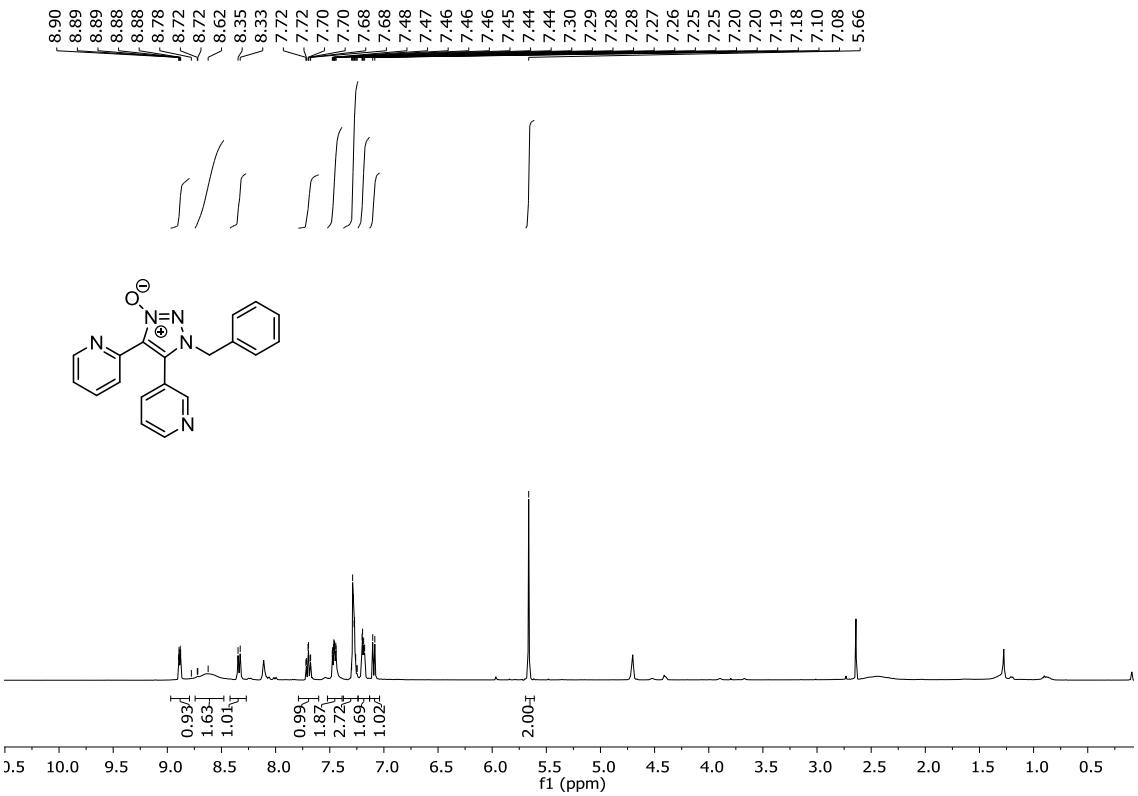
Spectrum 8.182. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24m**.



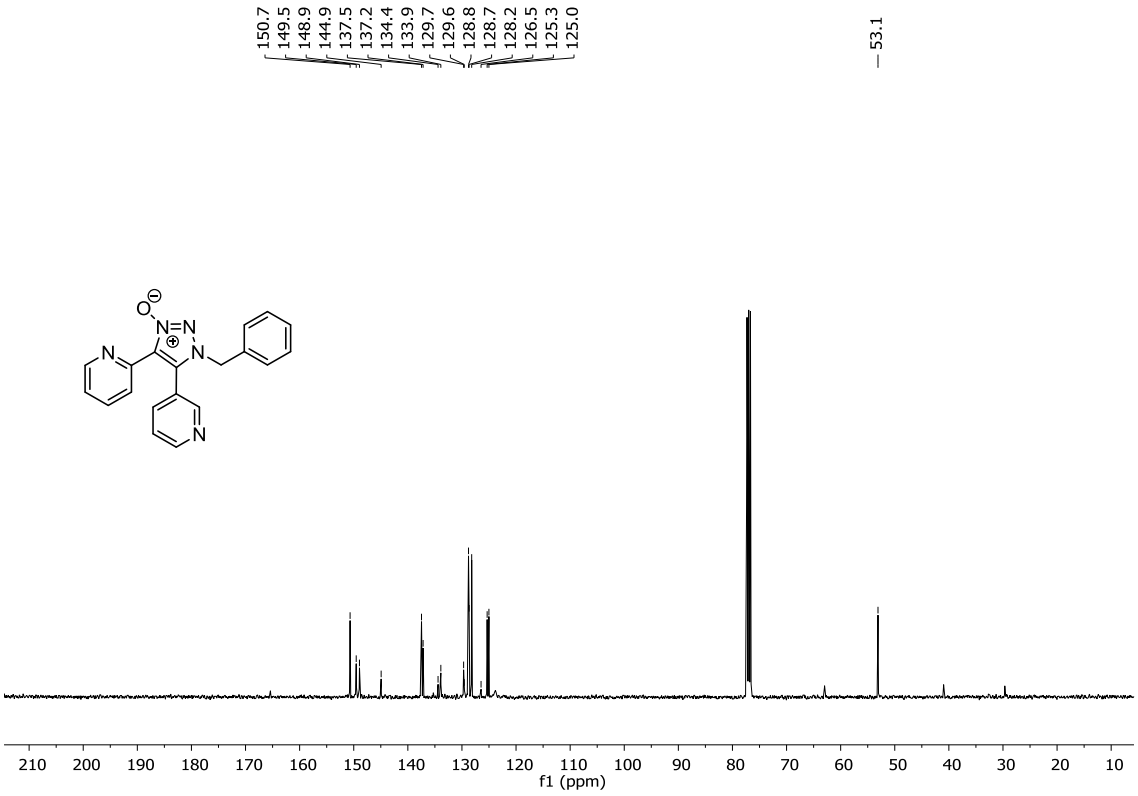
Spectrum 8.183. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24n**.



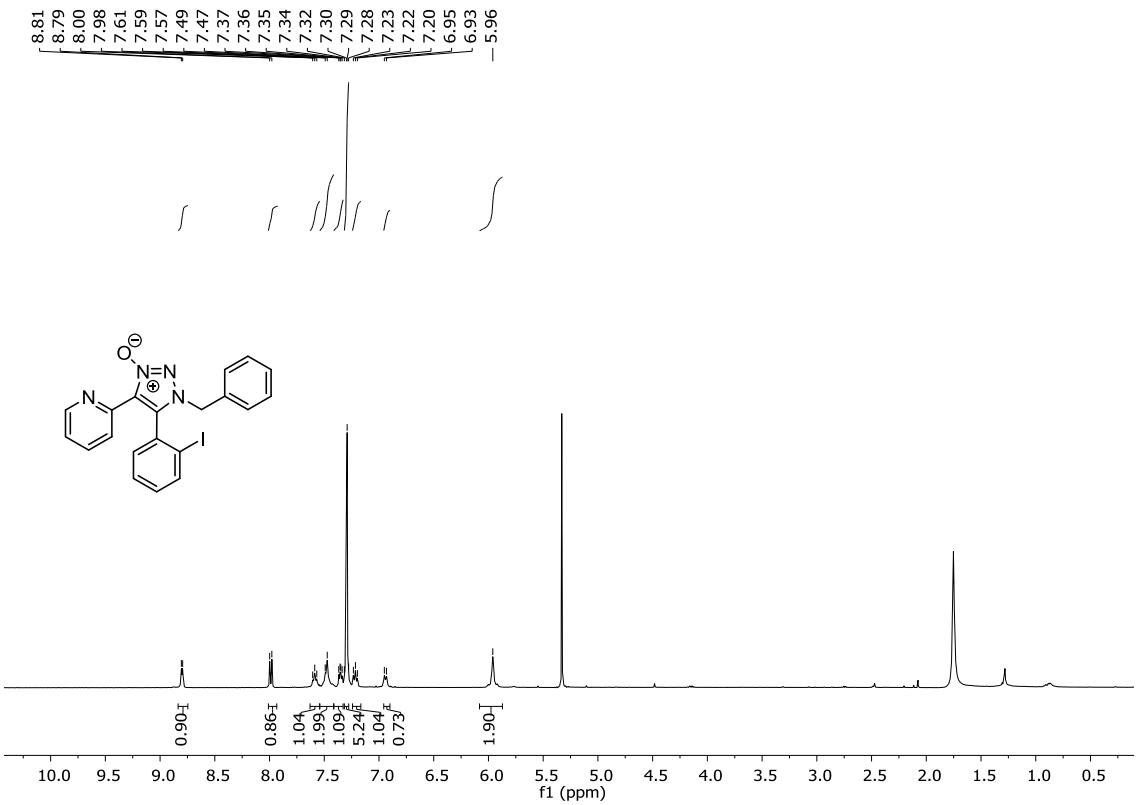
Spectrum 8.184. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24n**.



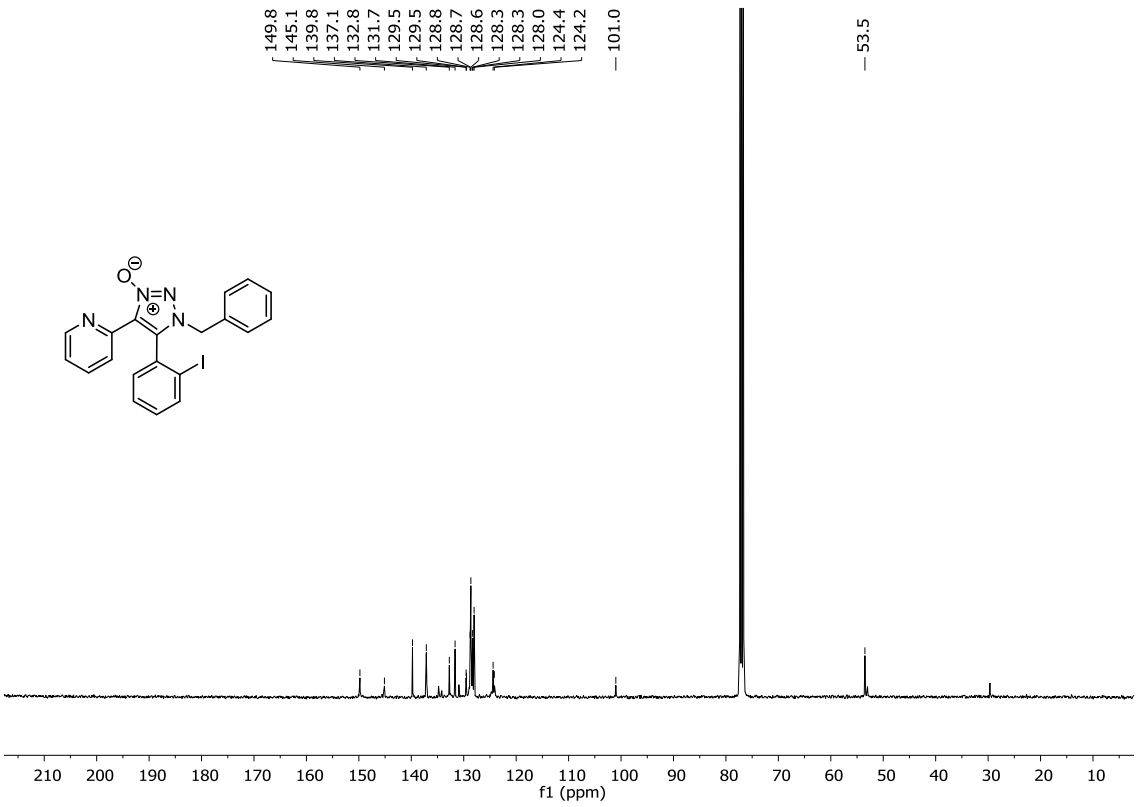
Spectrum 8.185. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24o**.



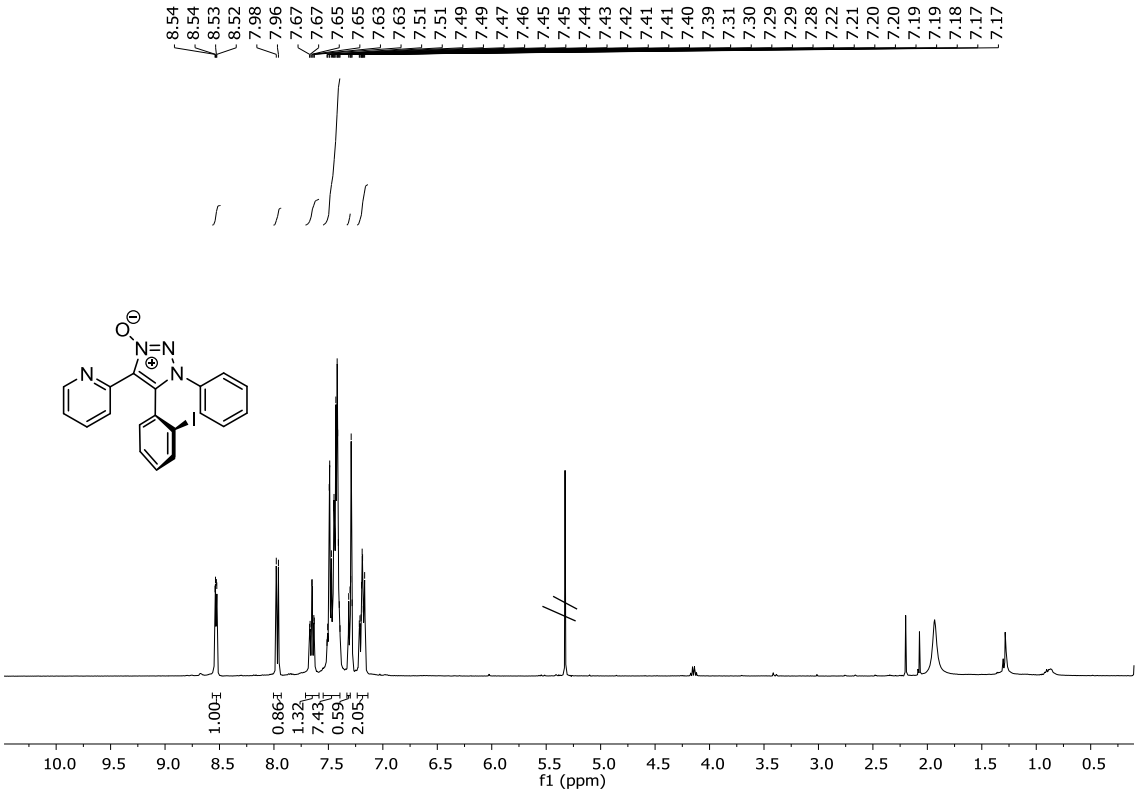
Spectrum 8.186. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24o**.



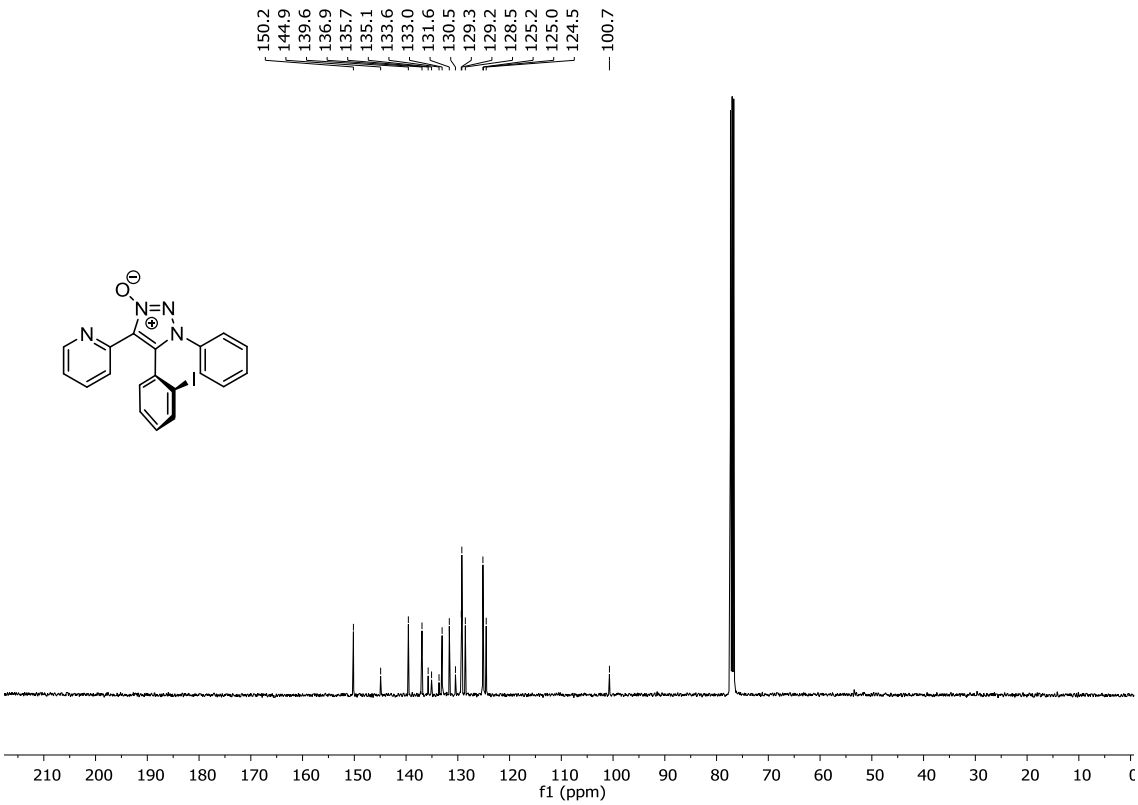
Spectrum 8.187. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24p**.



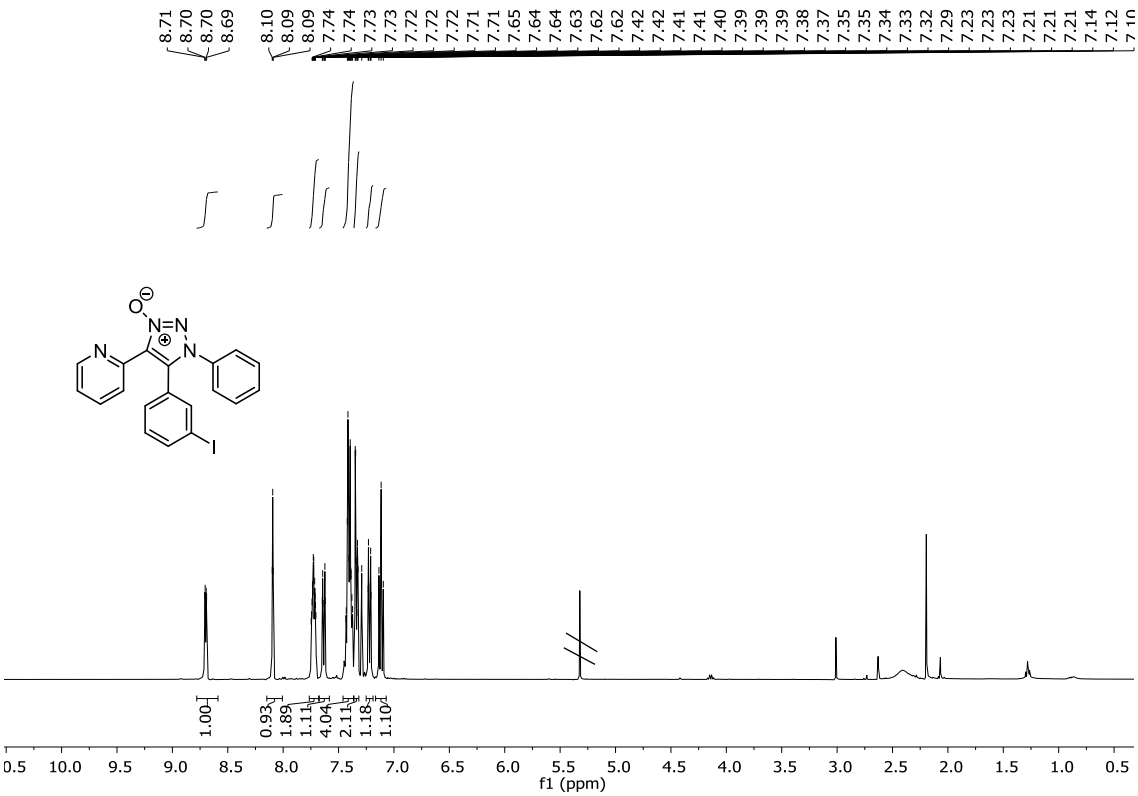
Spectrum 8.188. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24p**.



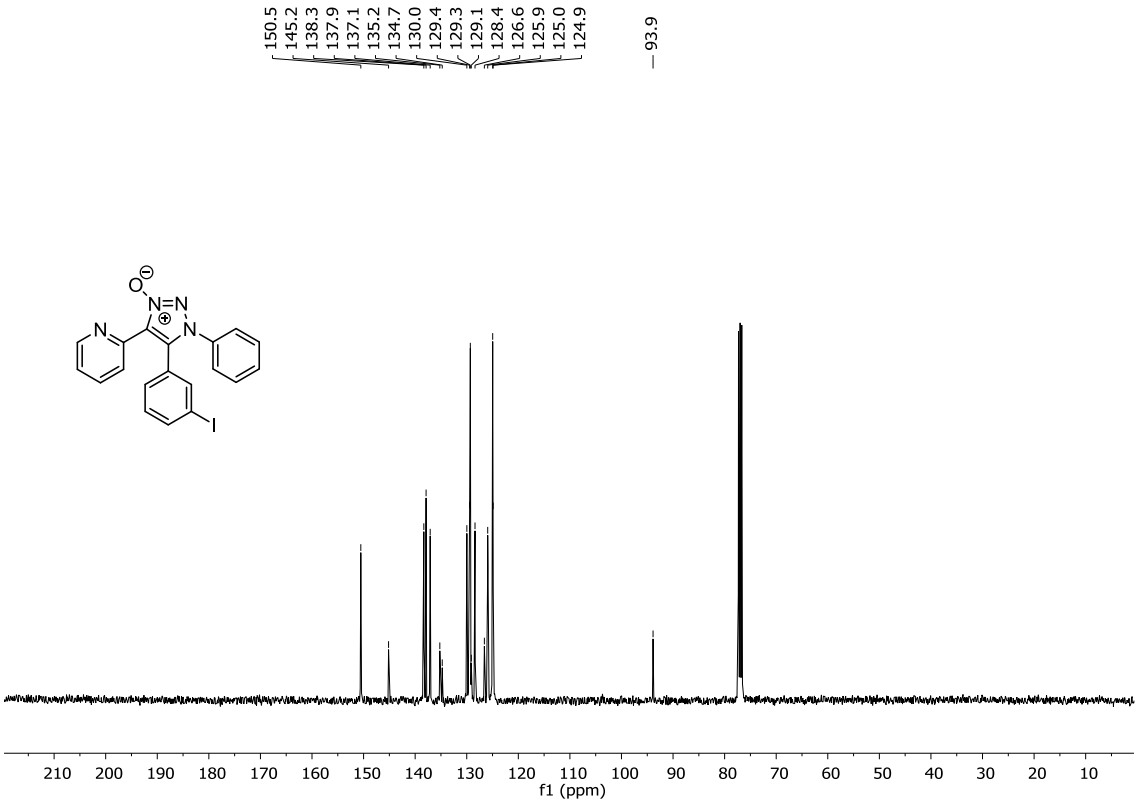
Spectrum 8.189. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24q**.



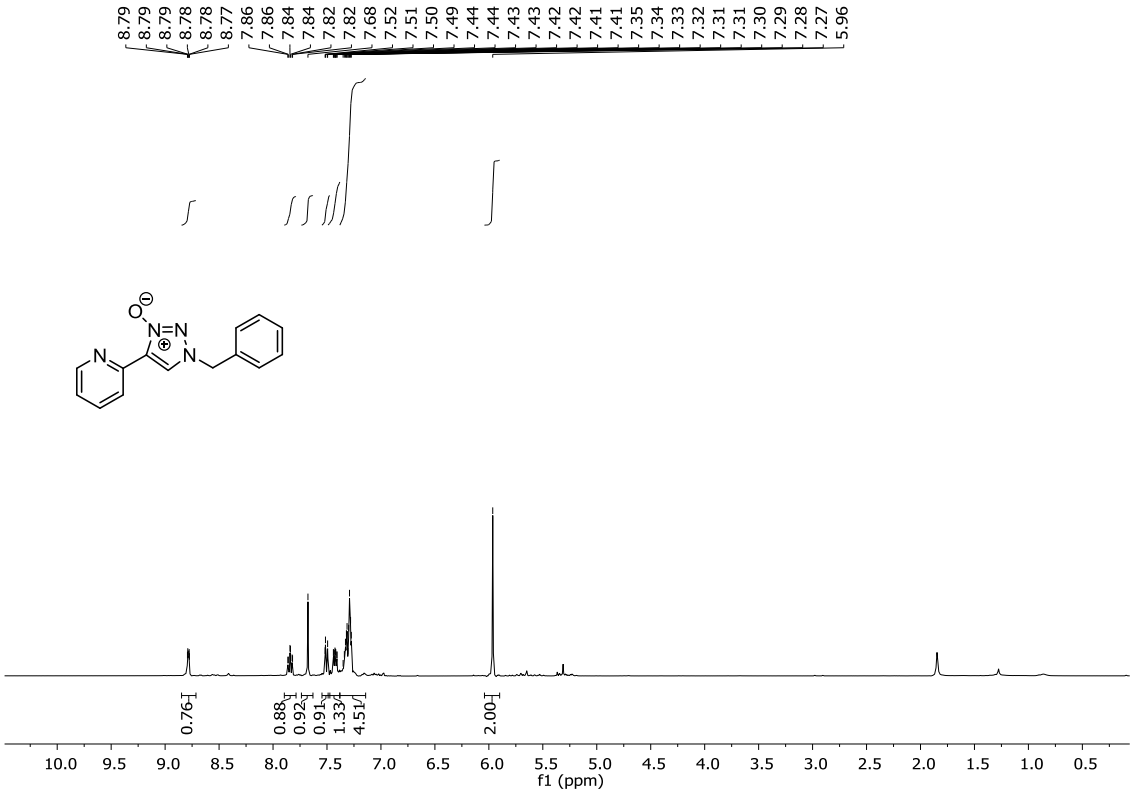
Spectrum 8.190. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24q**.



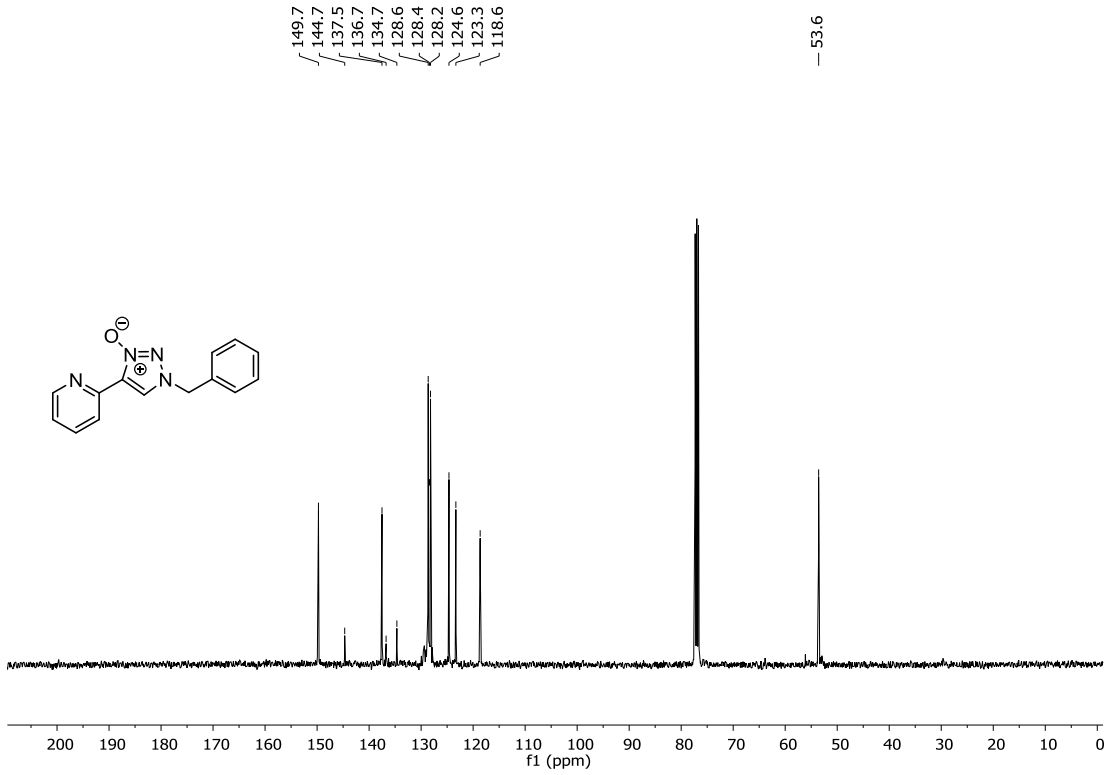
Spectrum 8.191. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24r**.



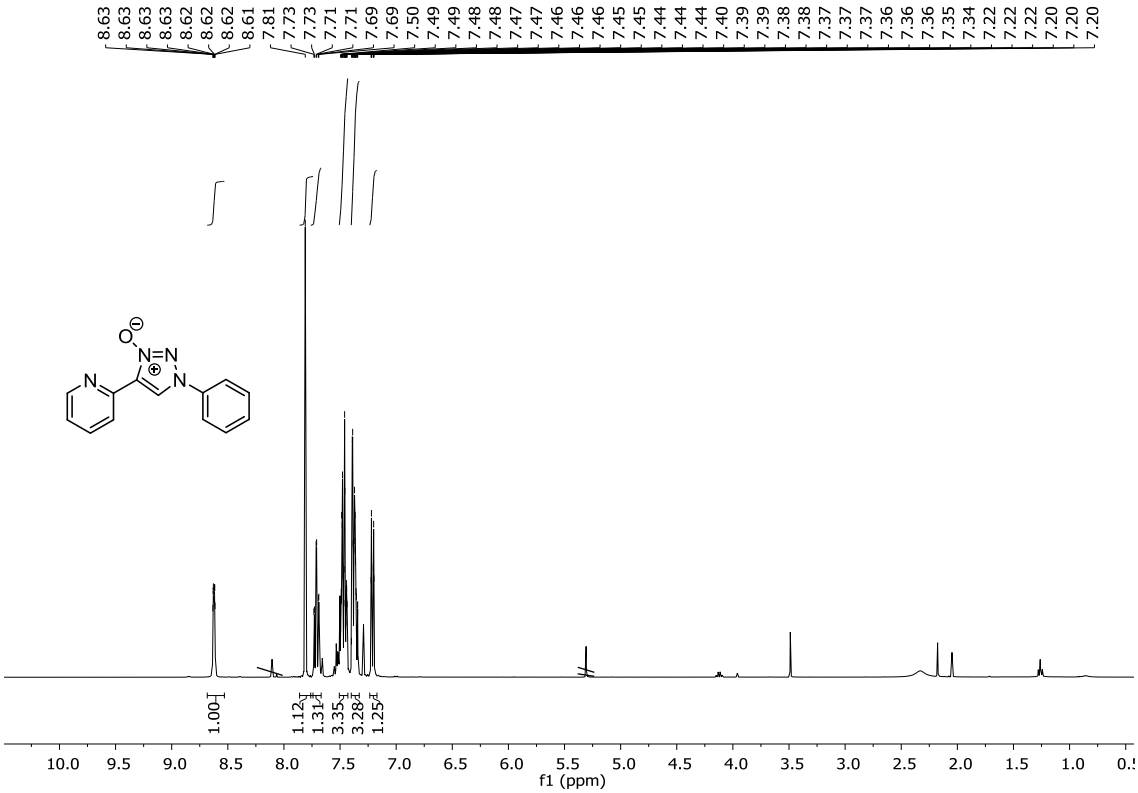
Spectrum 8.192. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **24r**.



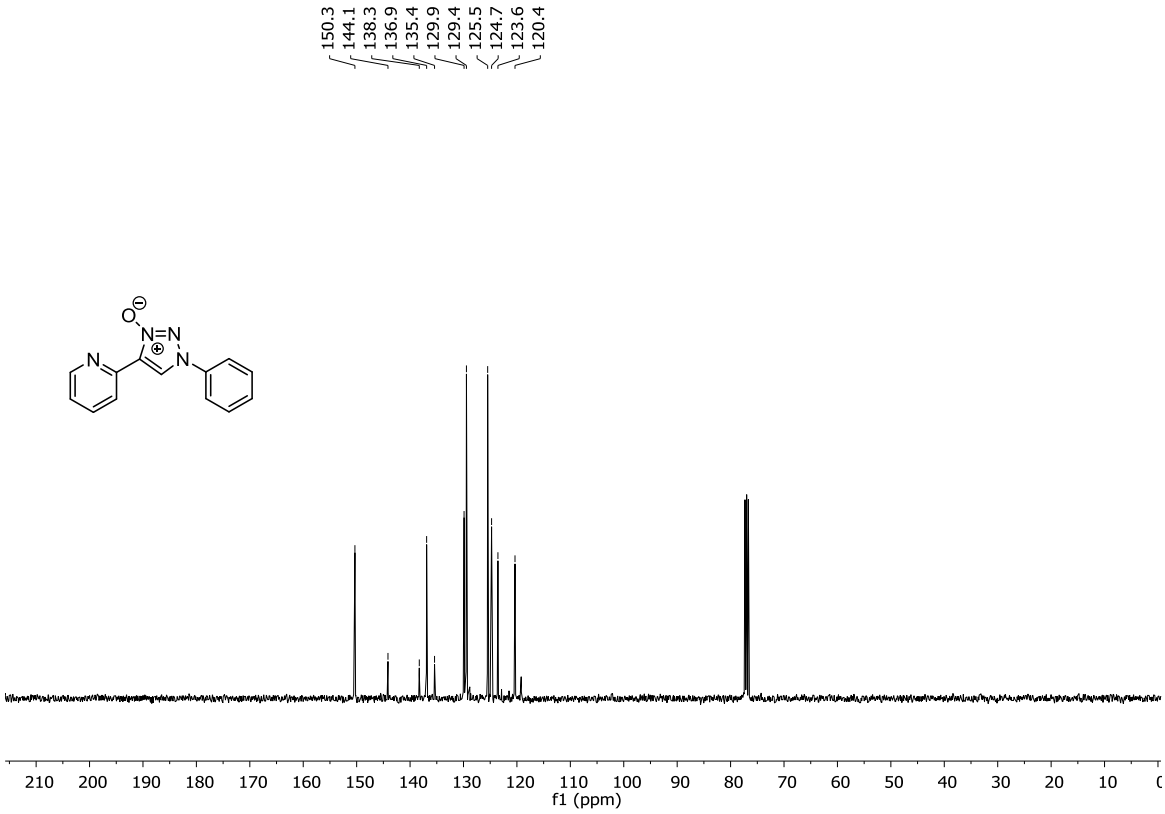
Spectrum 8.193. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25a**.



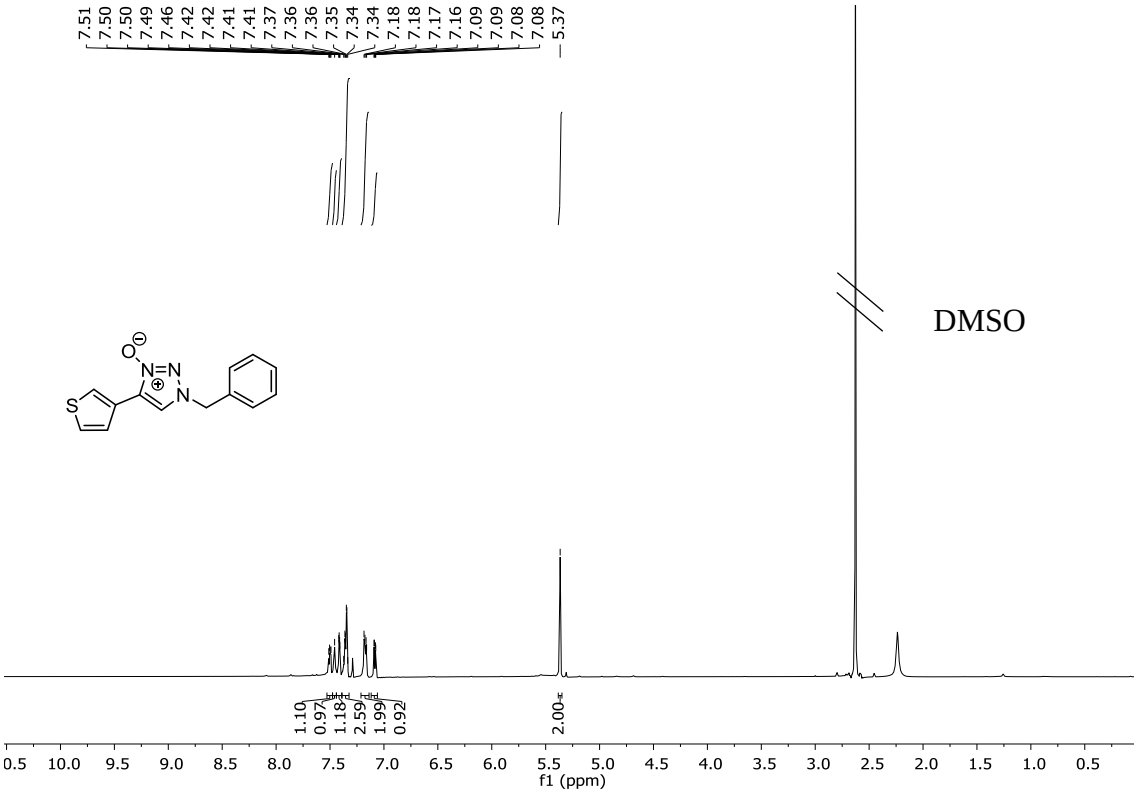
Spectrum 8.194. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25a**.



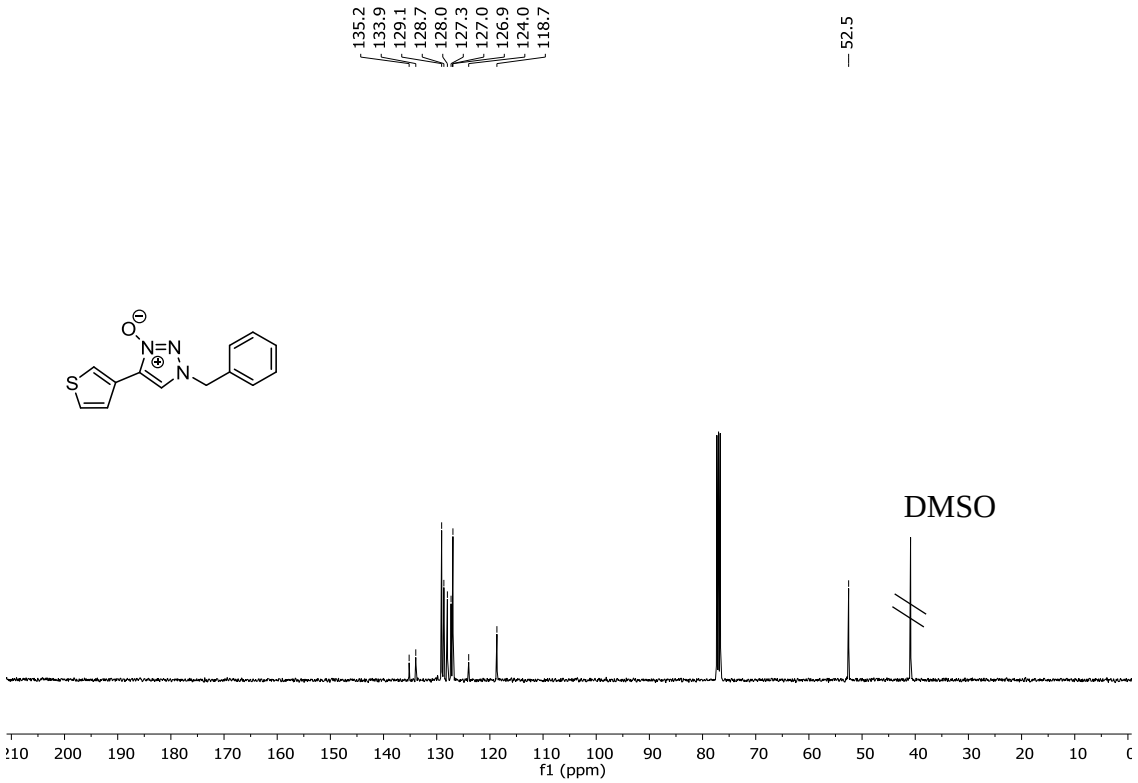
Spectrum 8.195. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25b**.



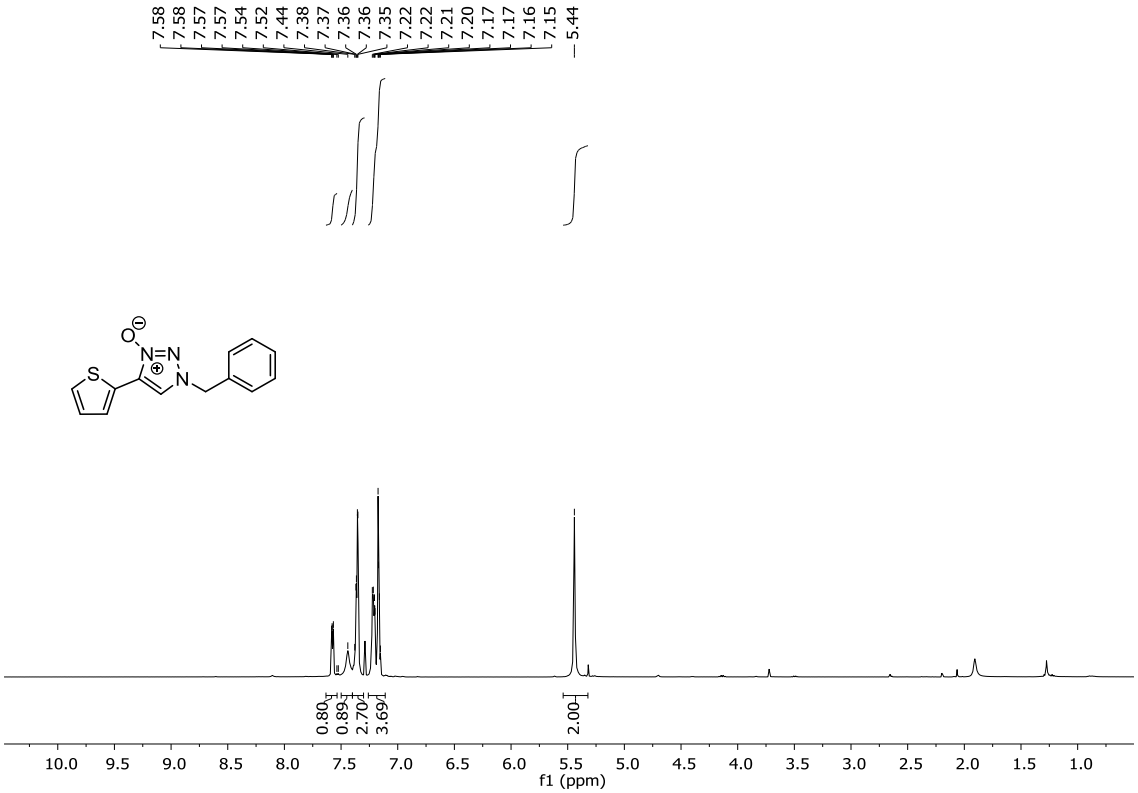
Spectrum 8.196. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25b**.



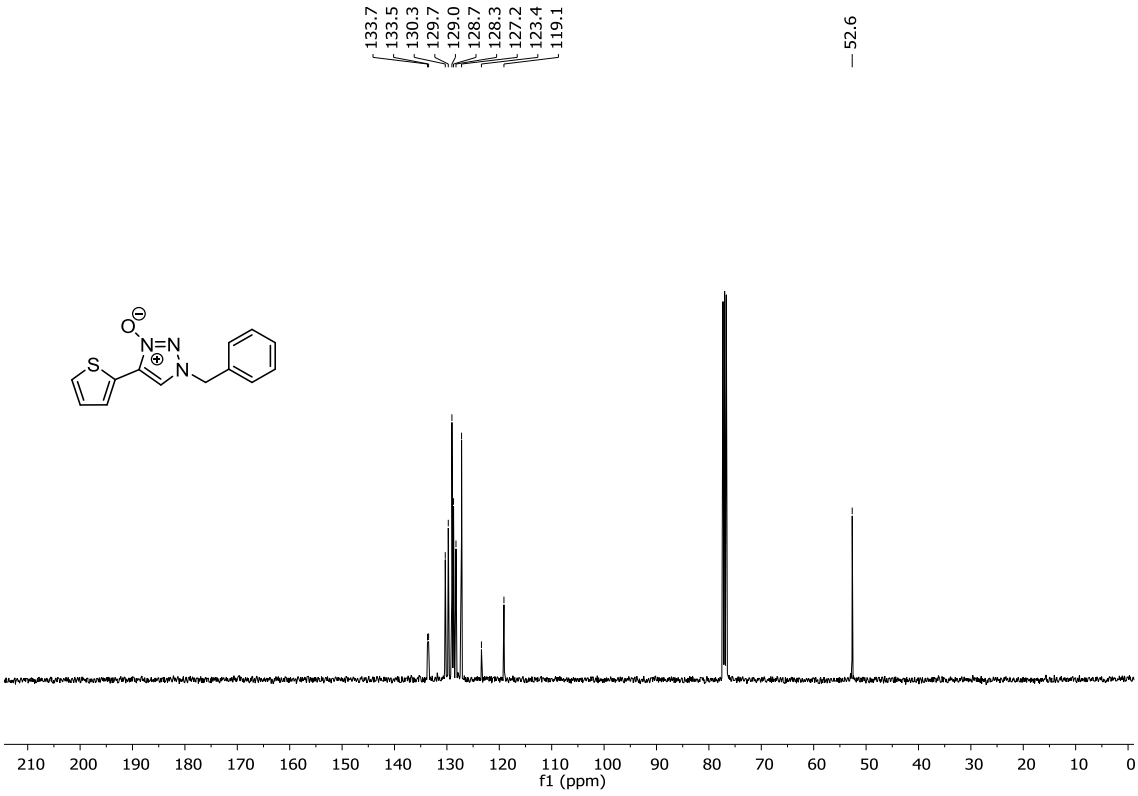
Spectrum 8.197. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25c**.



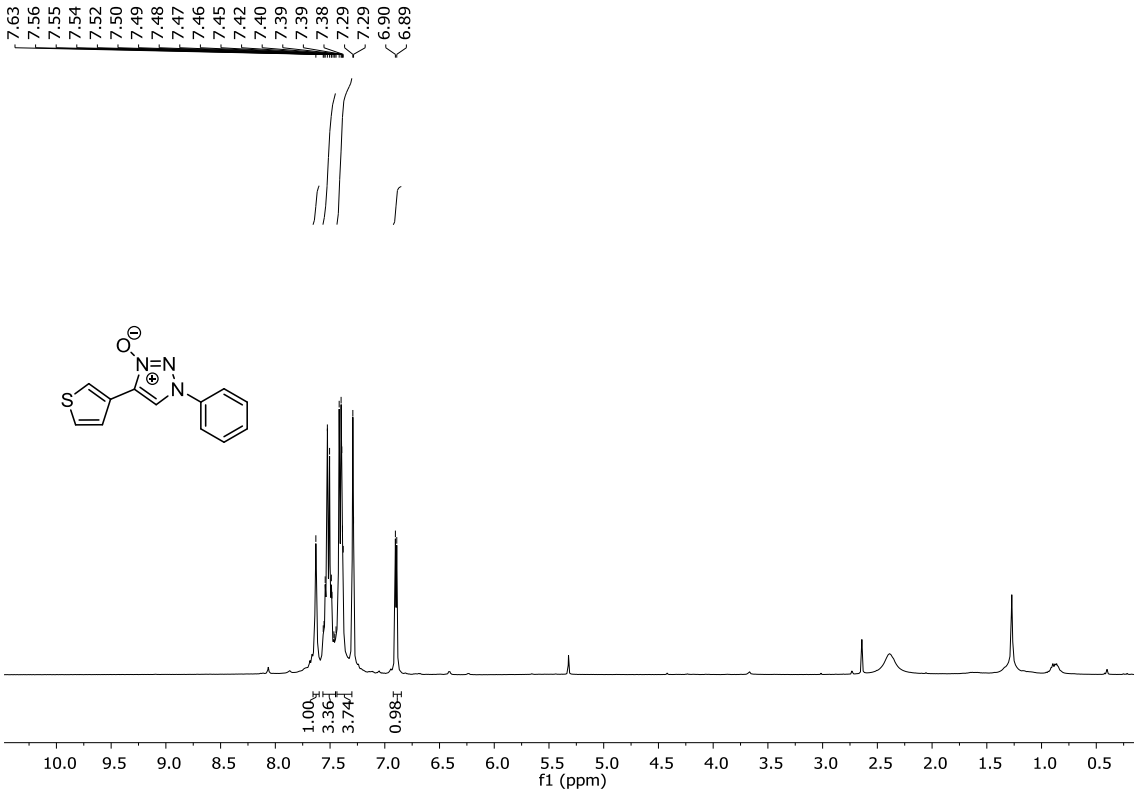
Spectrum 8.198. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25c**.



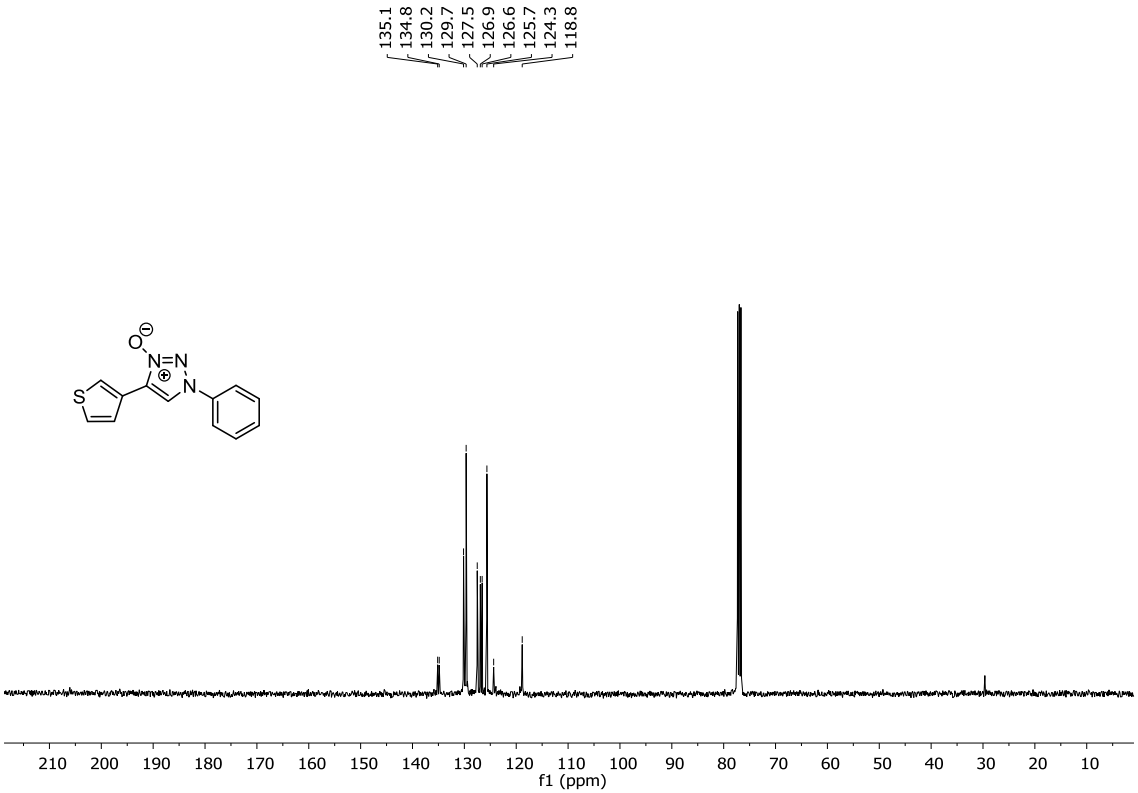
Spectrum 8.199. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25d**.



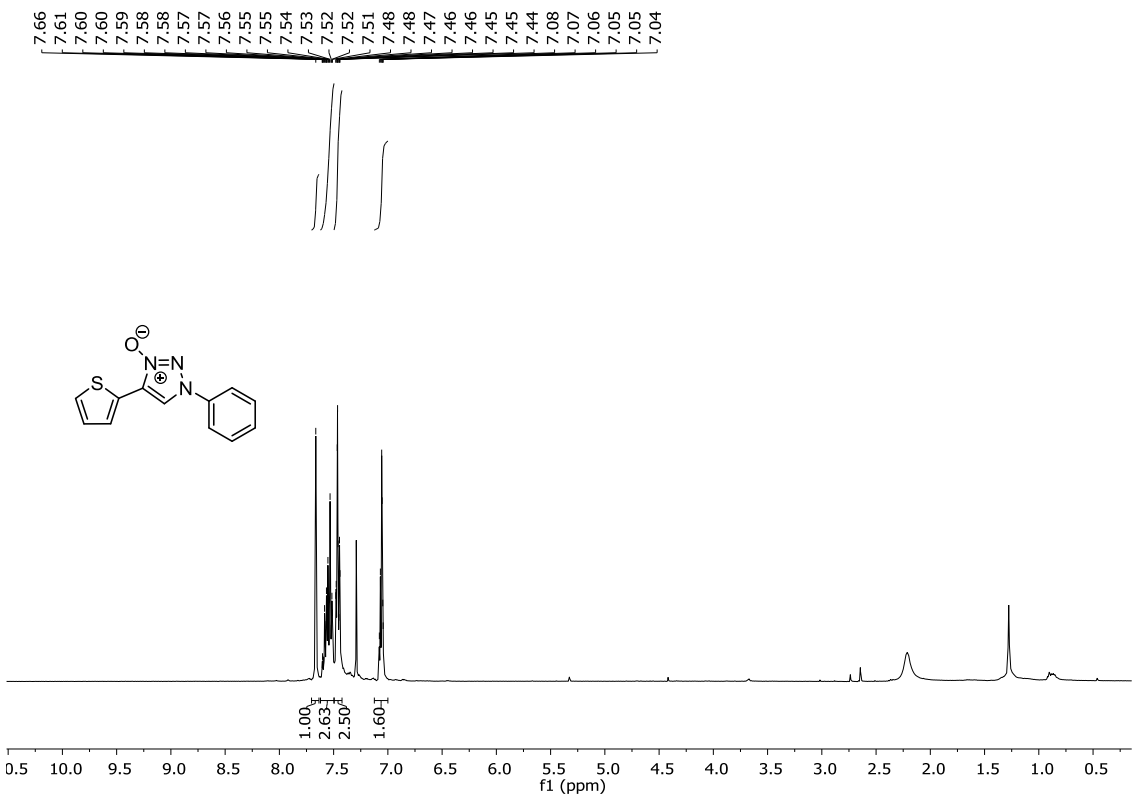
Spectrum 8.200. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25d**.



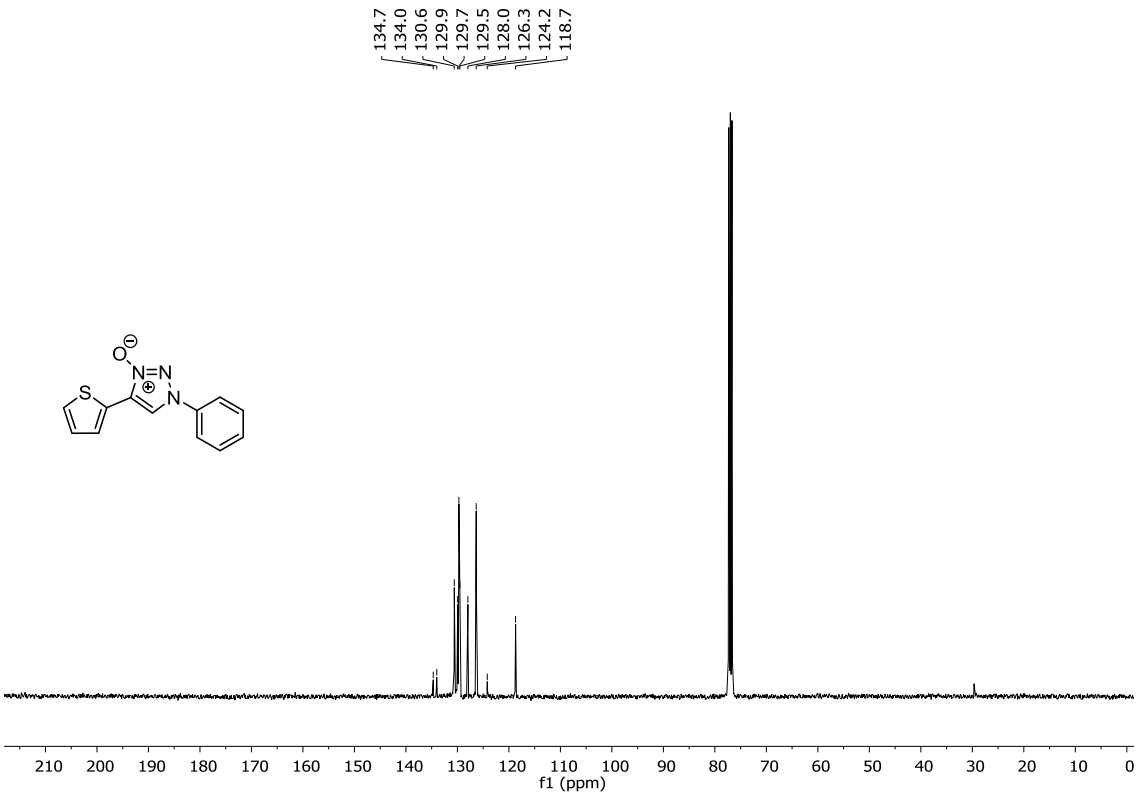
Spectrum 8.201. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25e**.



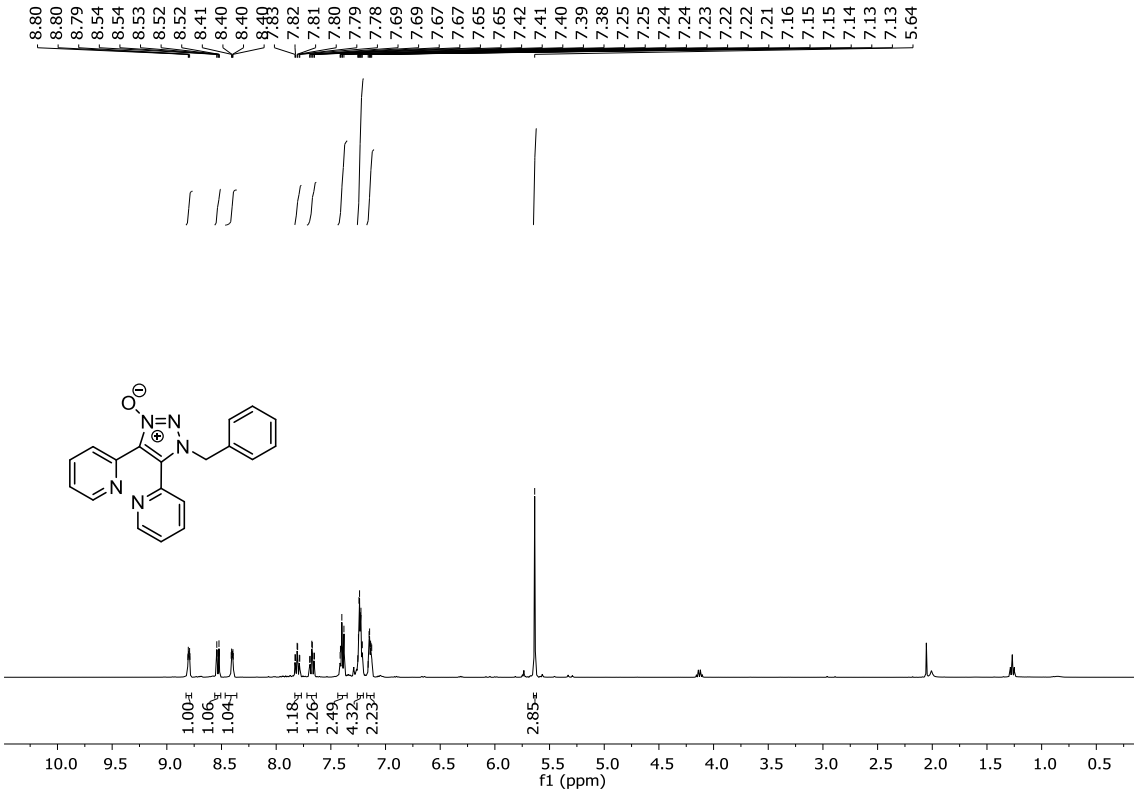
Spectrum 8.202. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25e**.



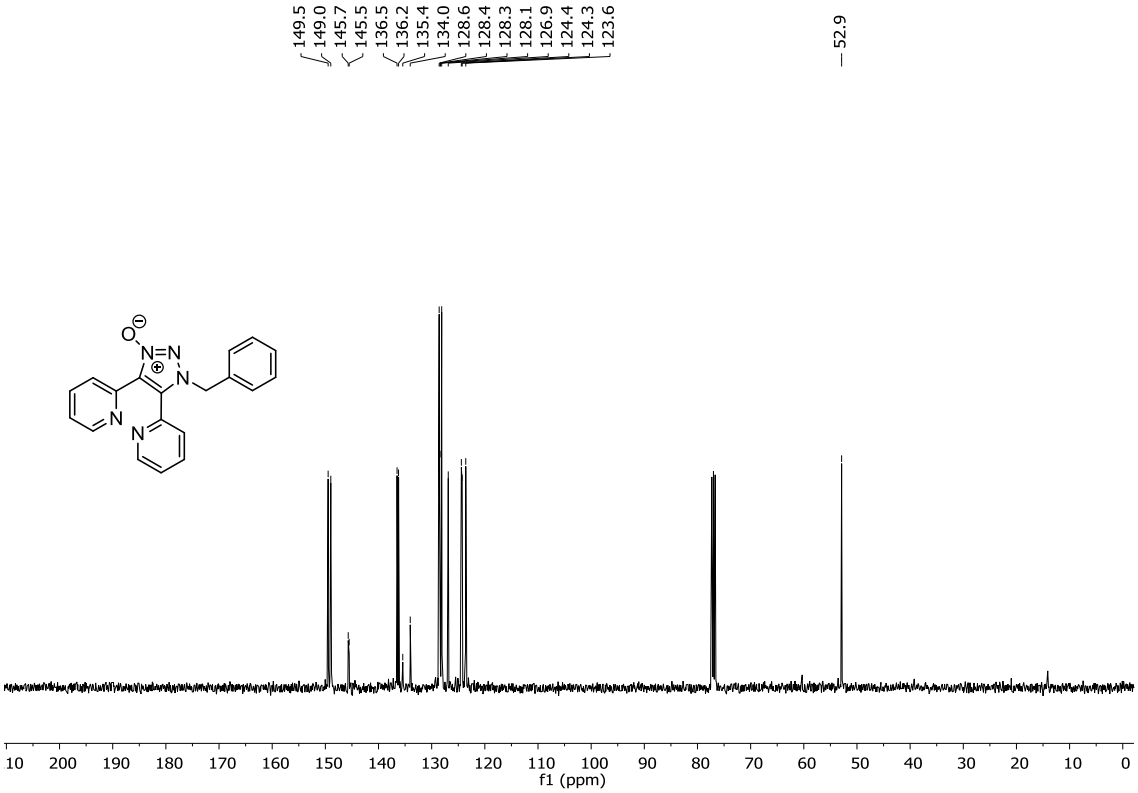
Spectrum 8.203. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **25f**.



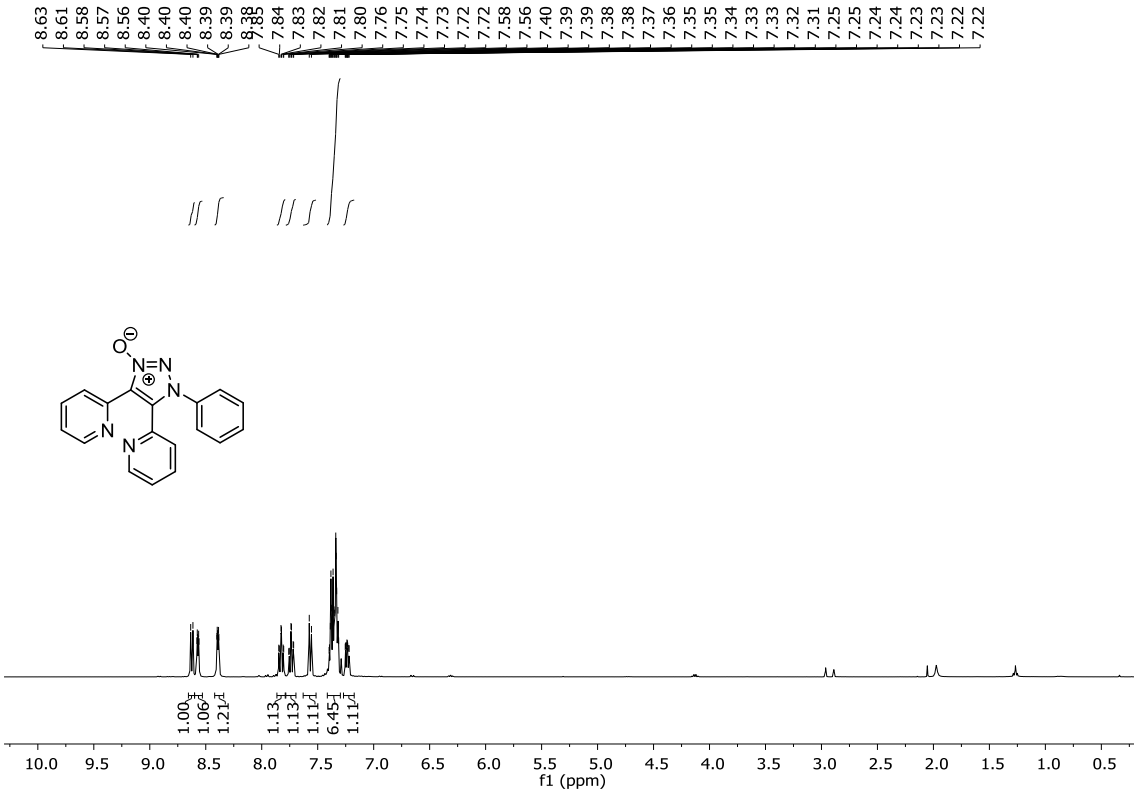
Spectrum 8.204. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **25f**.



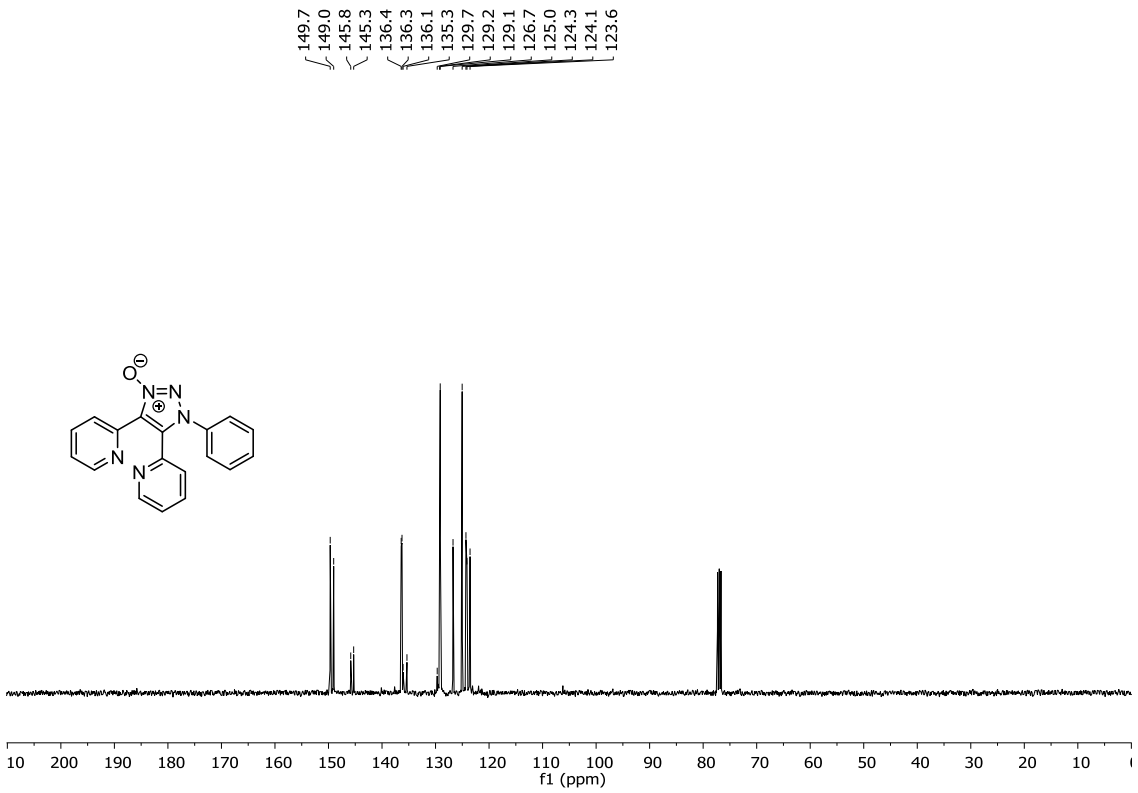
Spectrum 8.205. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26a**.



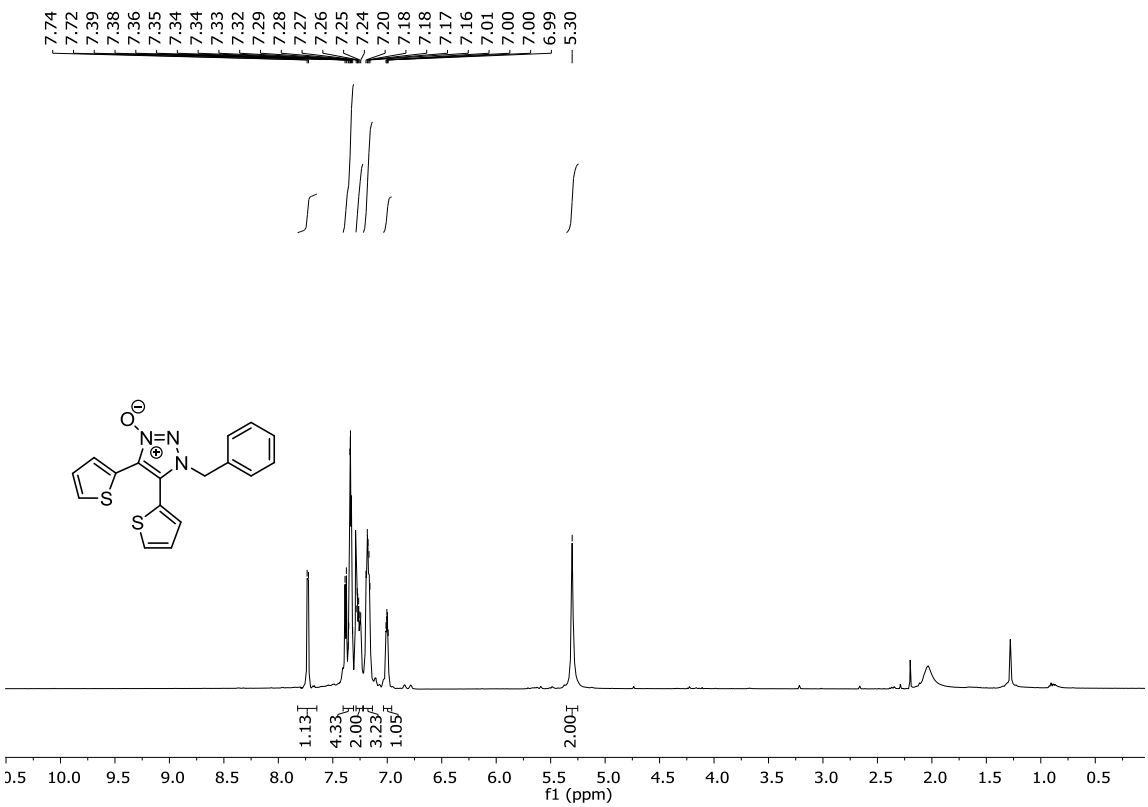
Spectrum 8.206. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26a**.



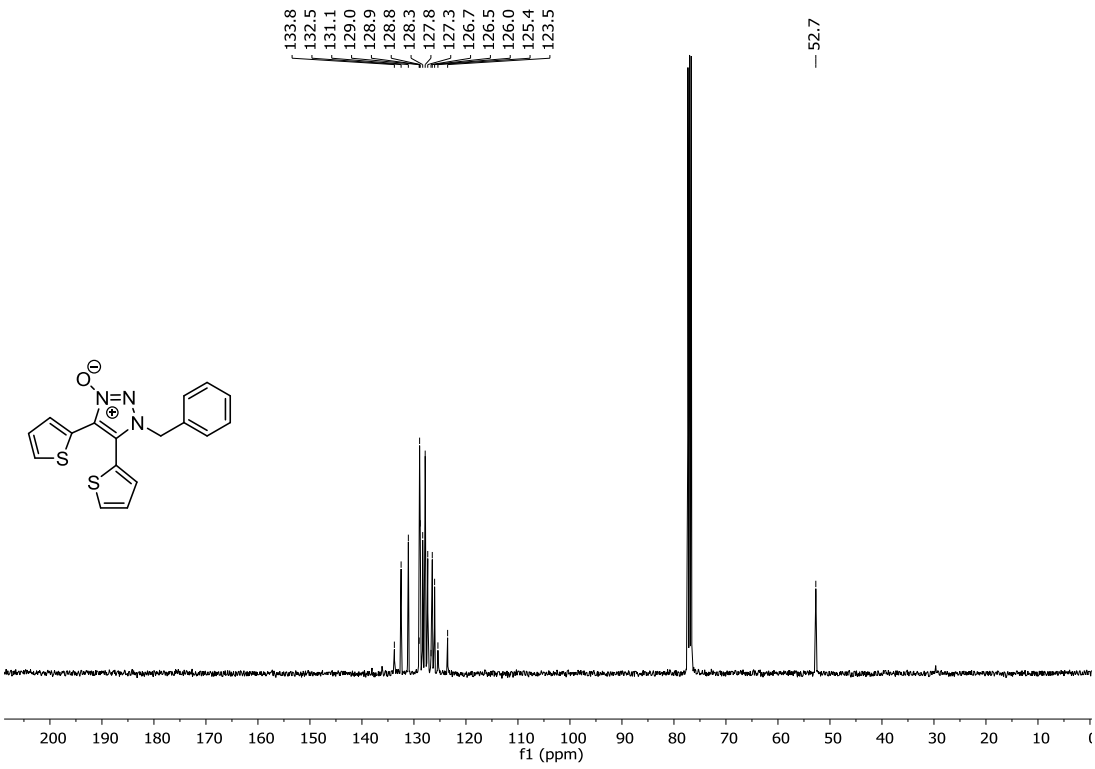
Spectrum 8.207. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26b**.



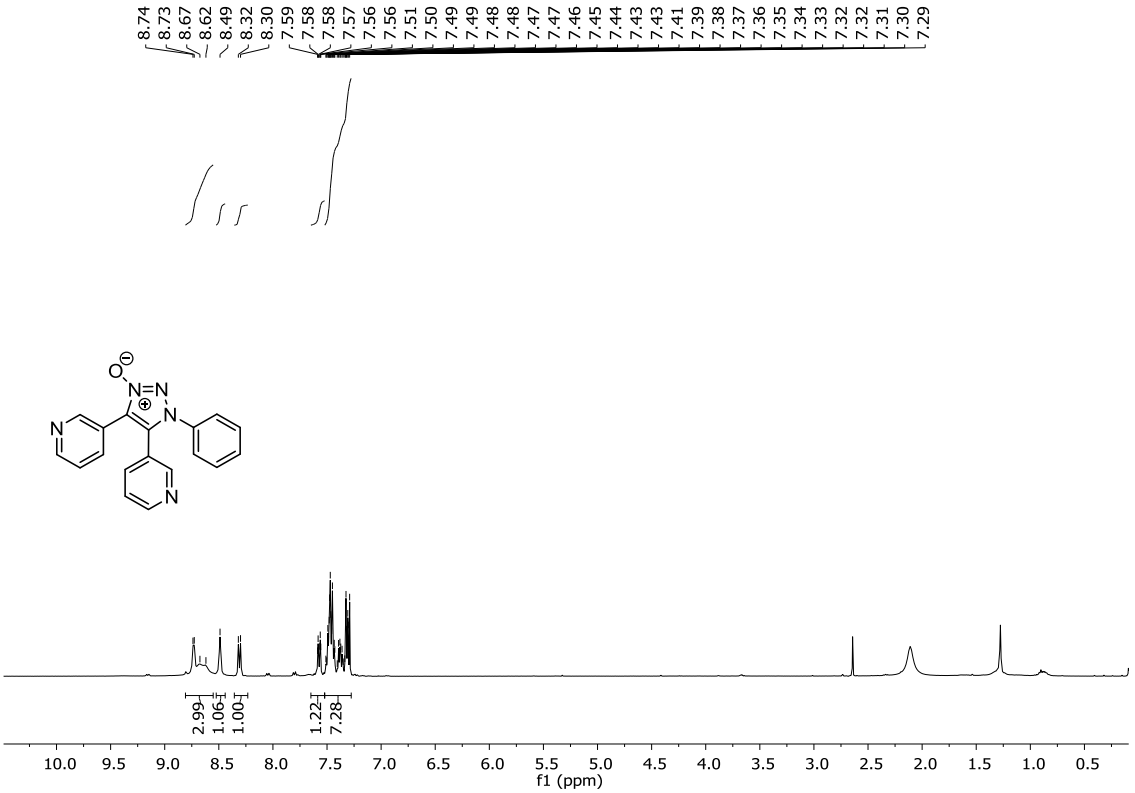
Spectrum 8.208. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26b**.



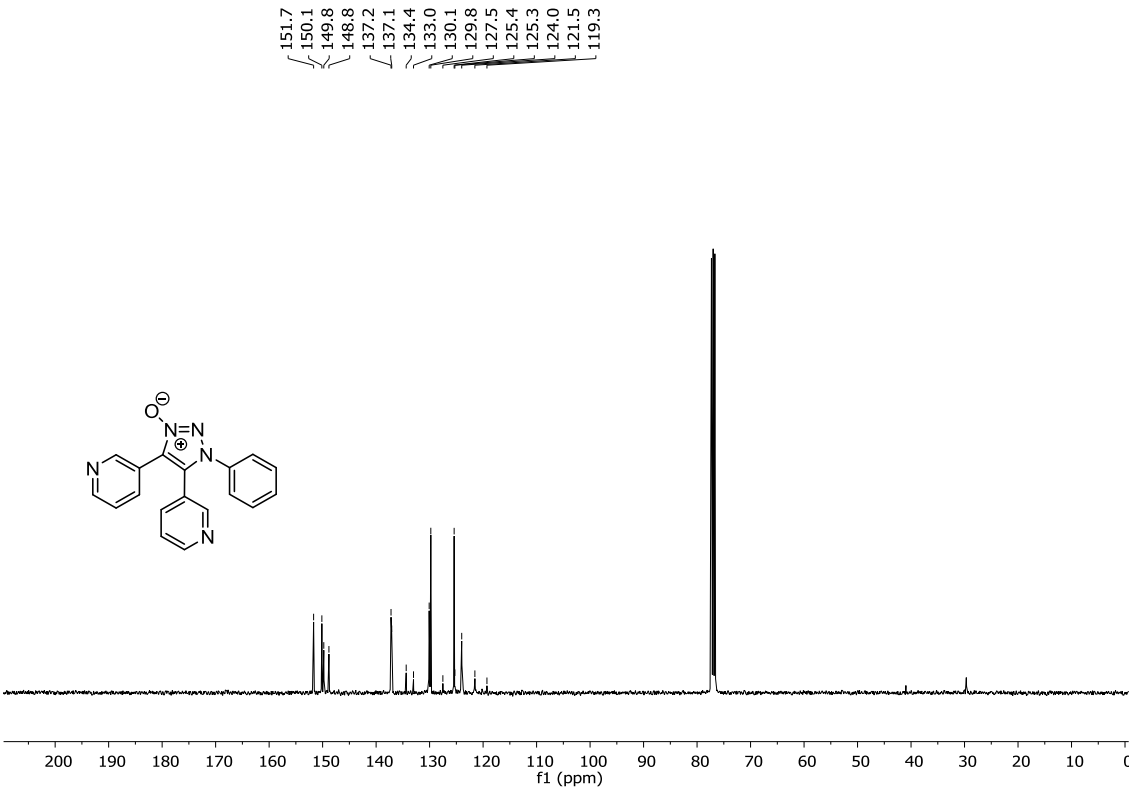
Spectrum 8.209. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26c**.



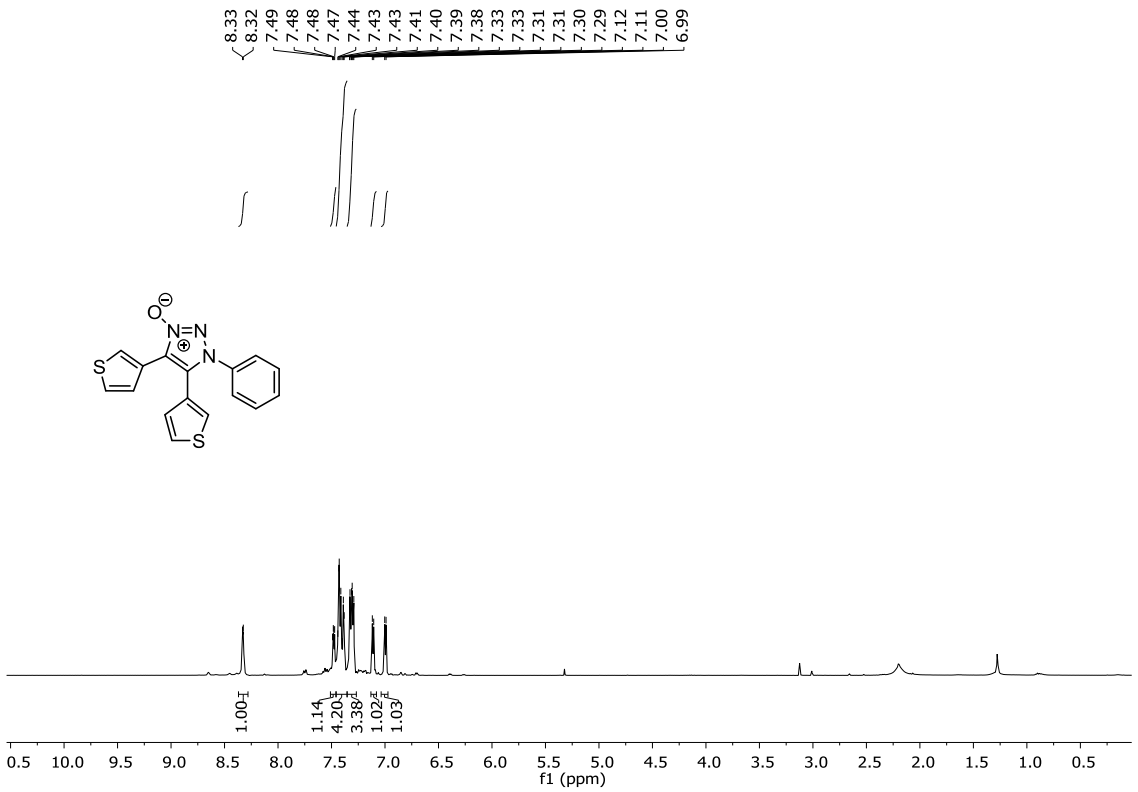
Spectrum 8.210. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26c**.



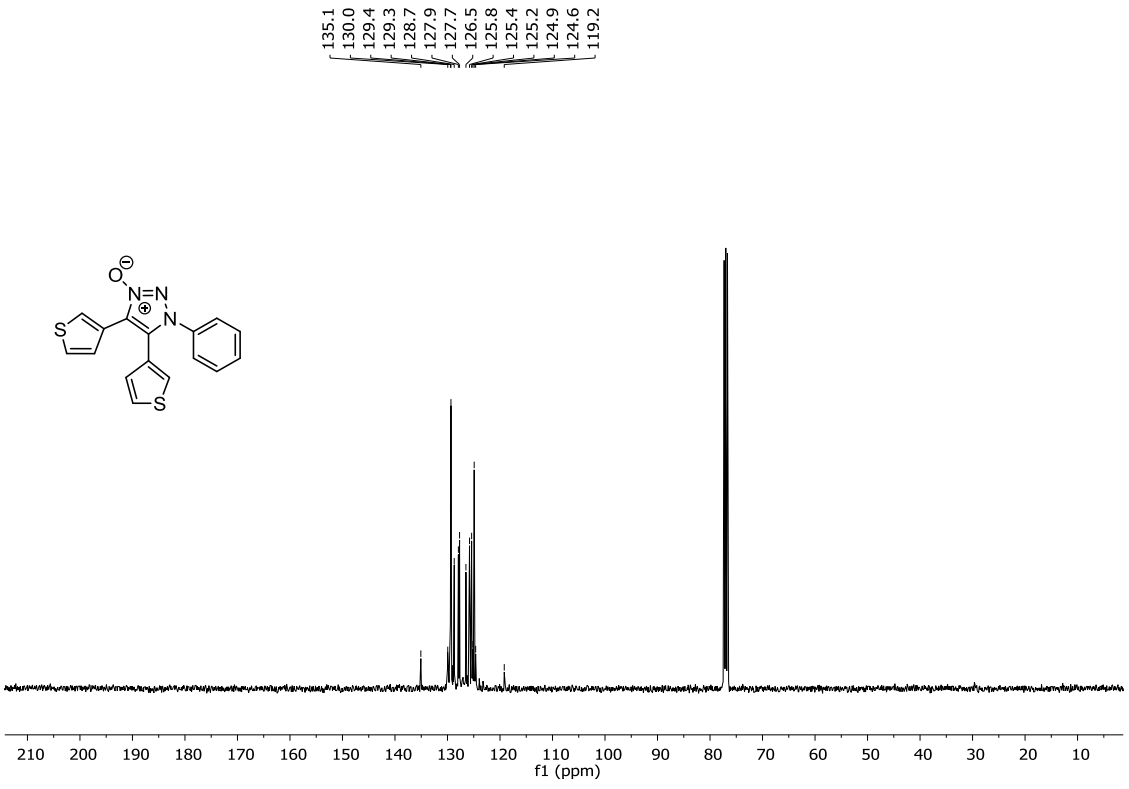
Spectrum 8.211. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26d**.



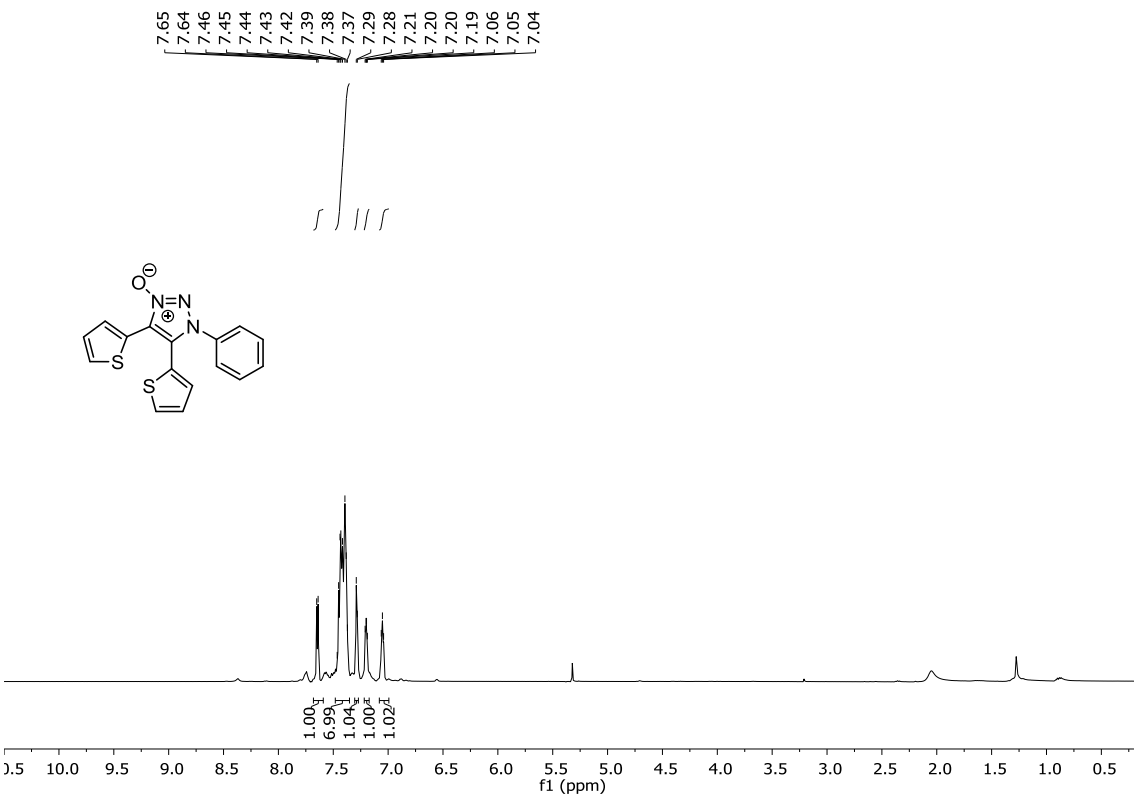
Spectrum 8.212. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26d**.



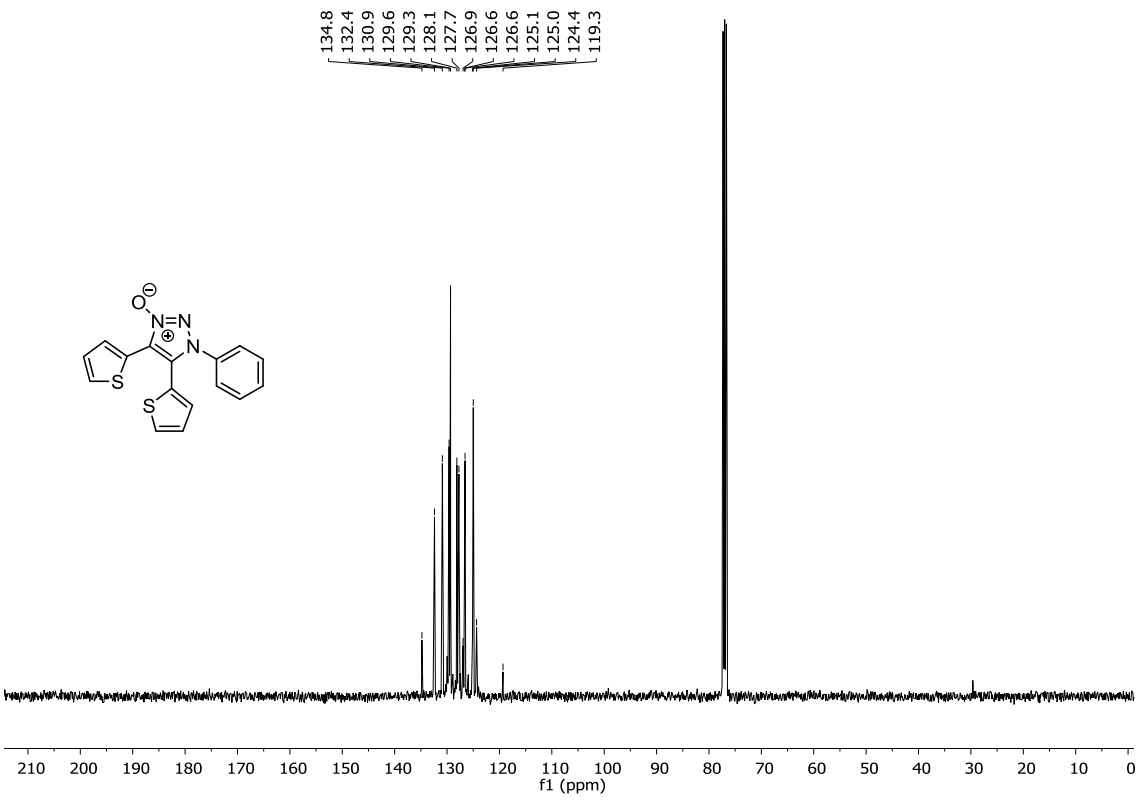
Spectrum 8.213. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26e**.



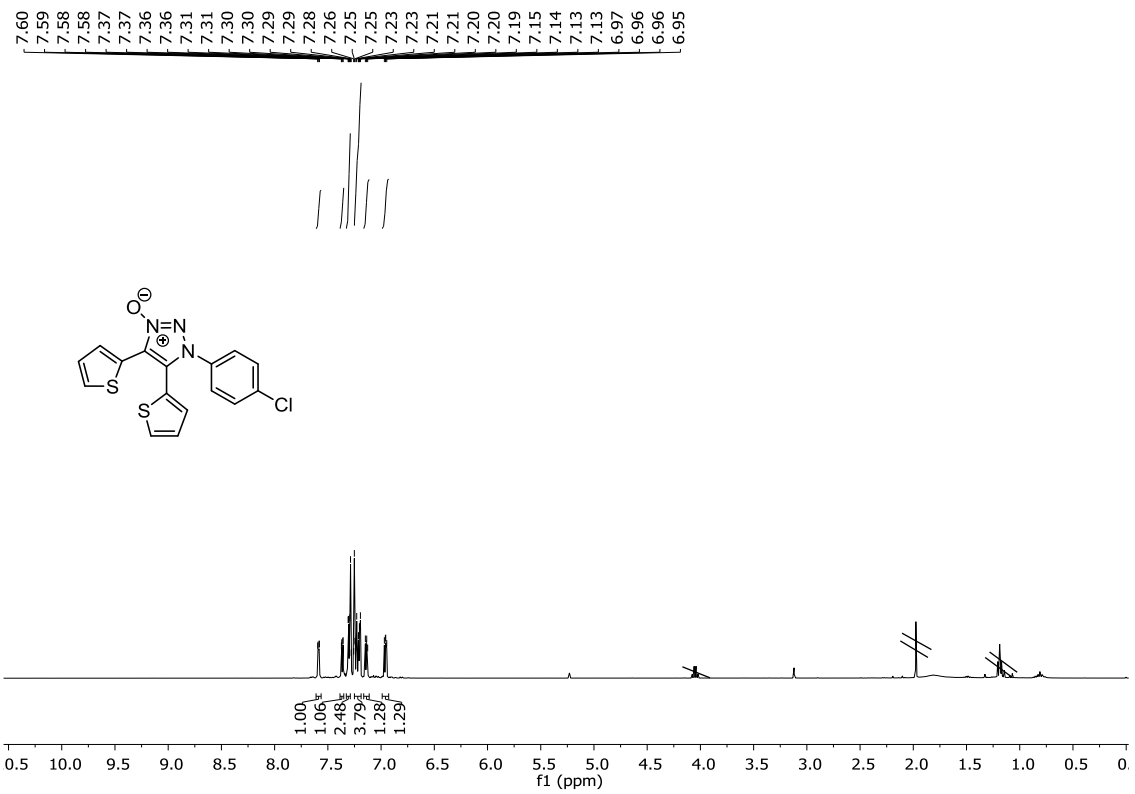
Spectrum 8.214. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26e**.



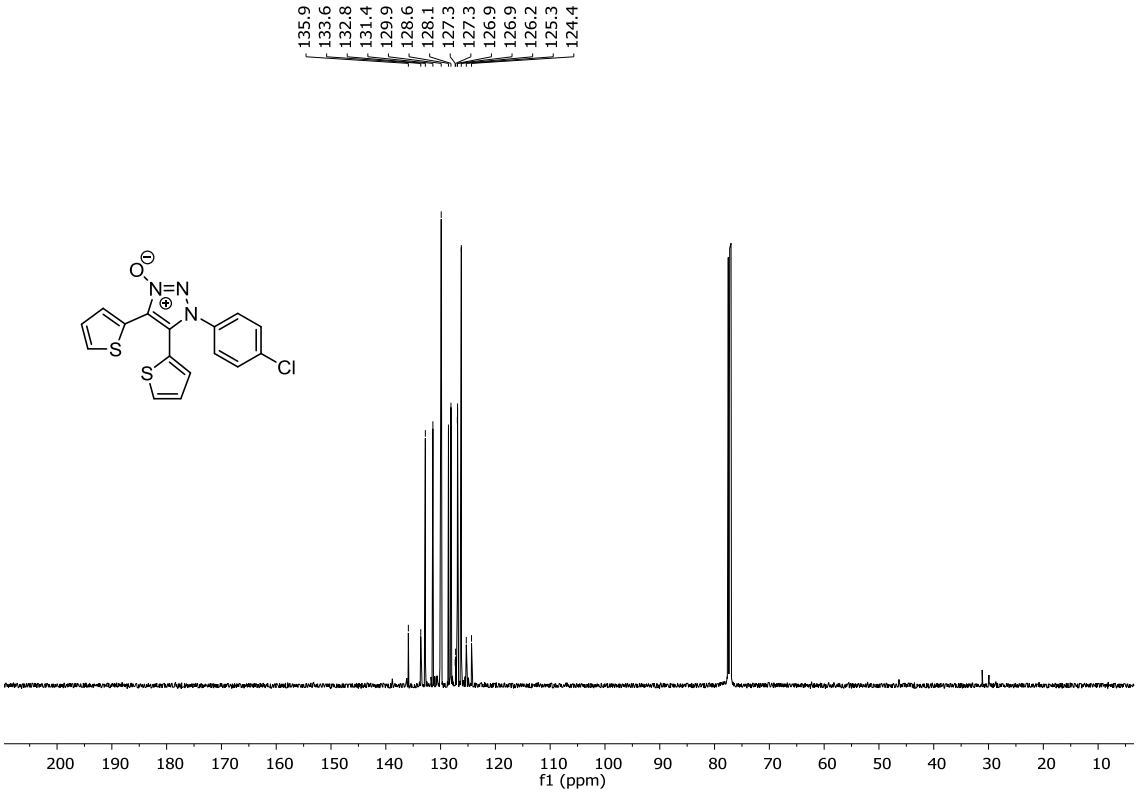
Spectrum 8.215. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26f**.



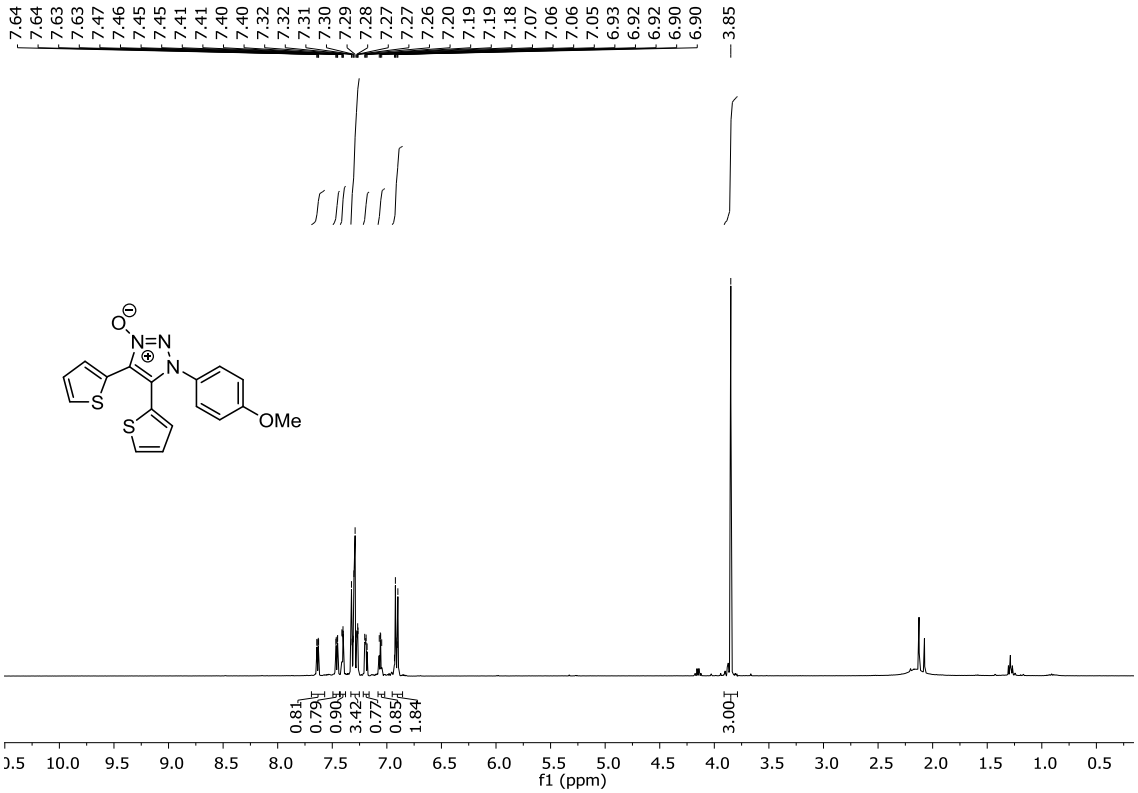
Spectrum 8.216. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26f**.



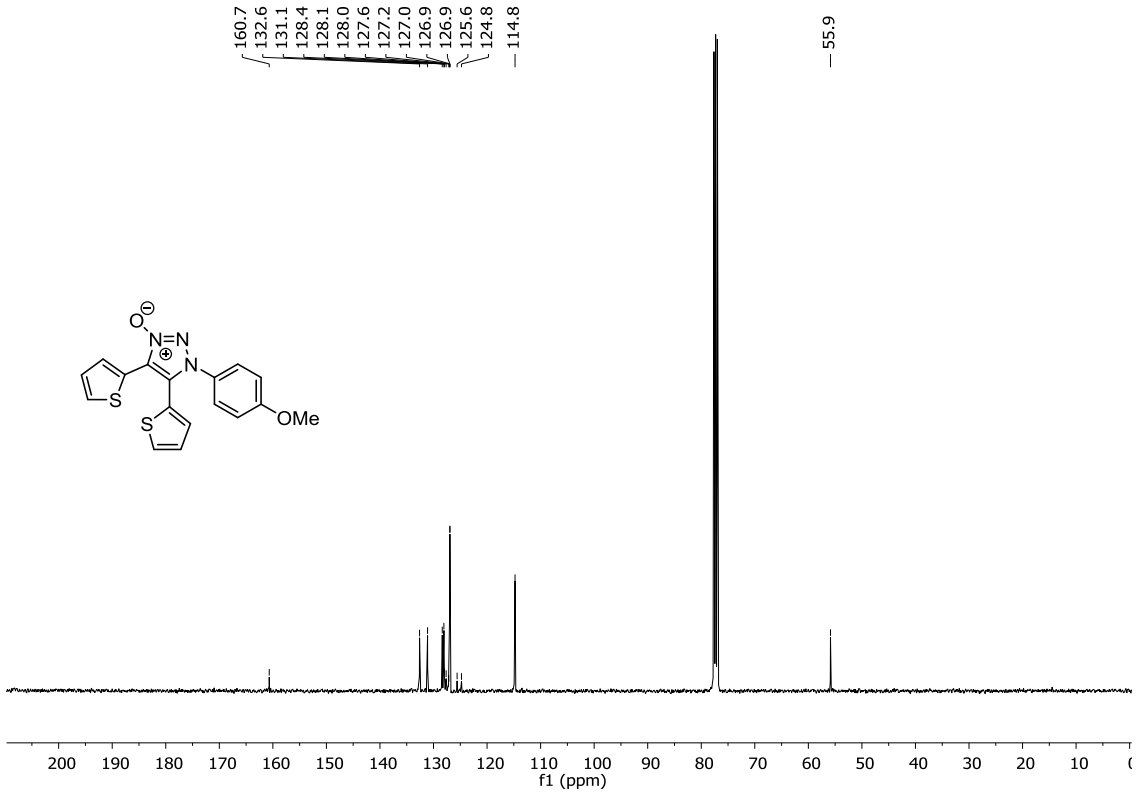
Spectrum 8.217. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26g**.



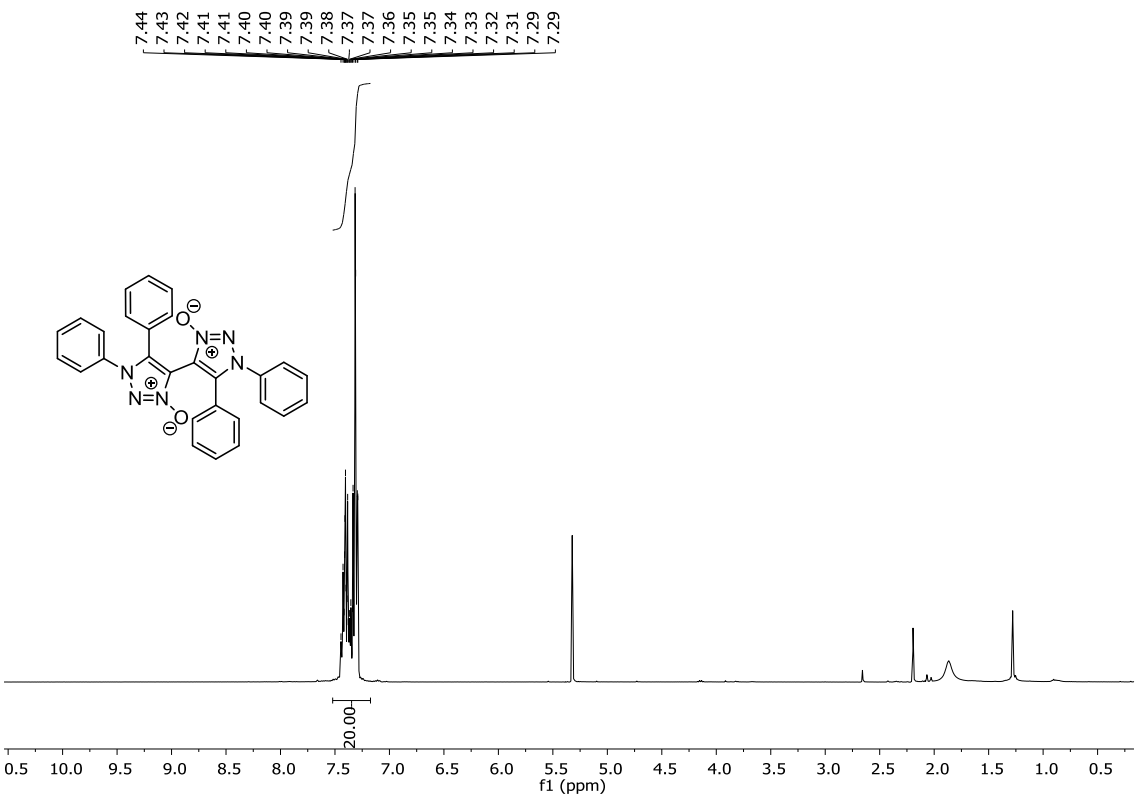
Spectrum 8.218. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26g**.



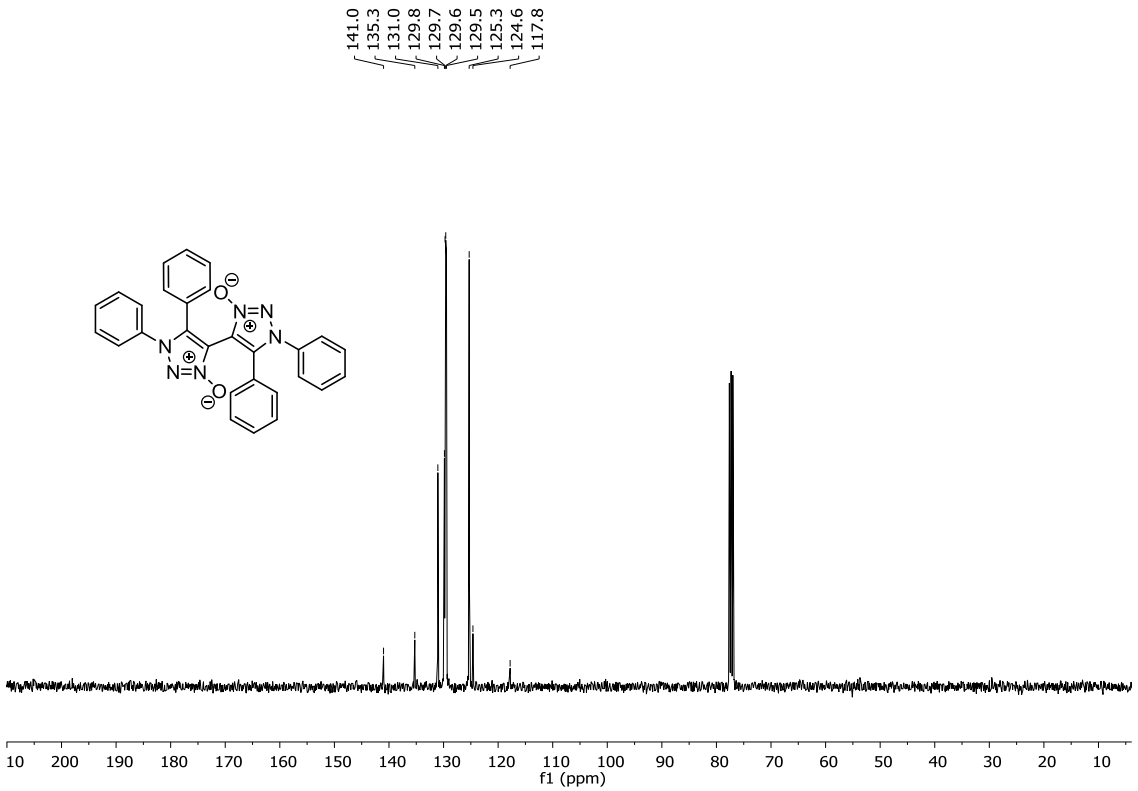
Spectrum 8.219. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **26h**.



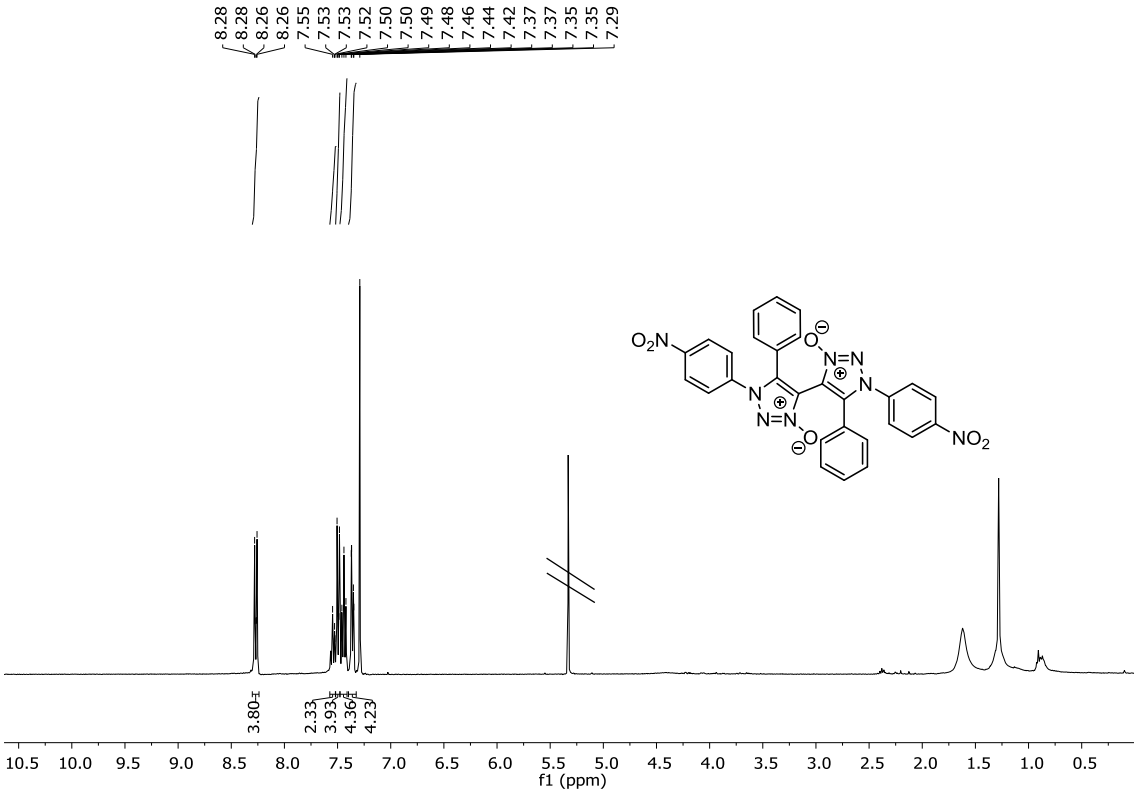
Spectrum 8.220. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **26h**.



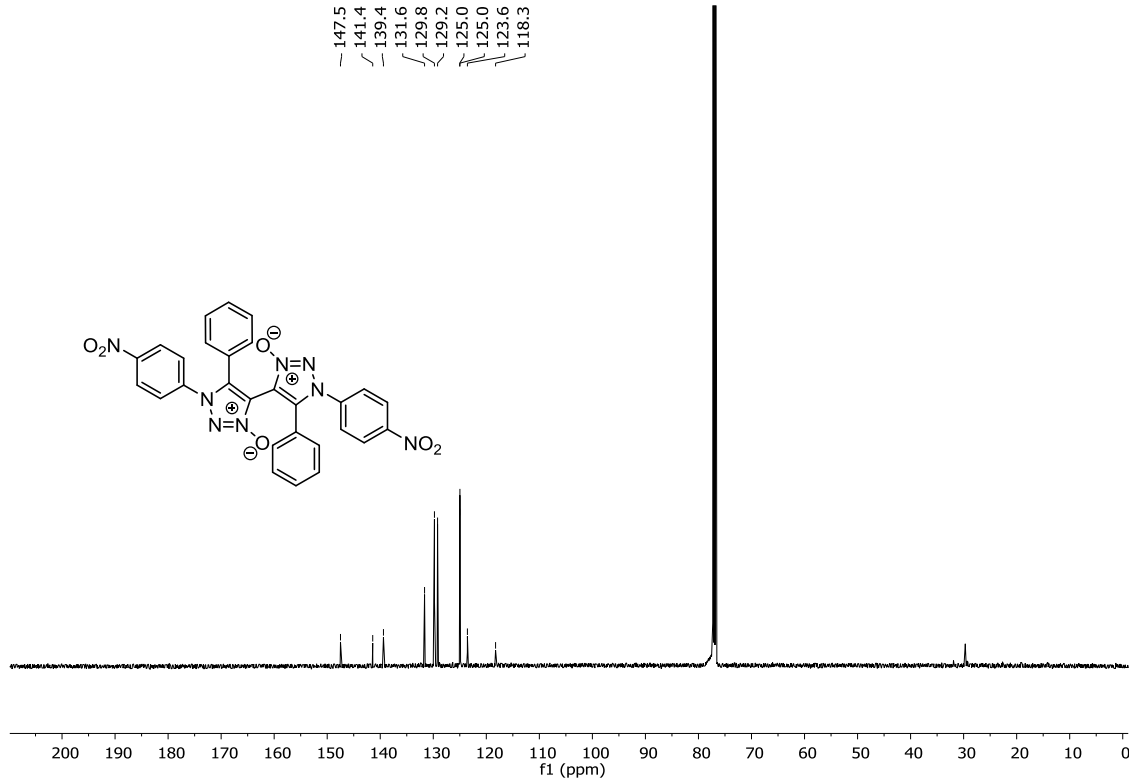
Spectrum 8.221. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28a**.



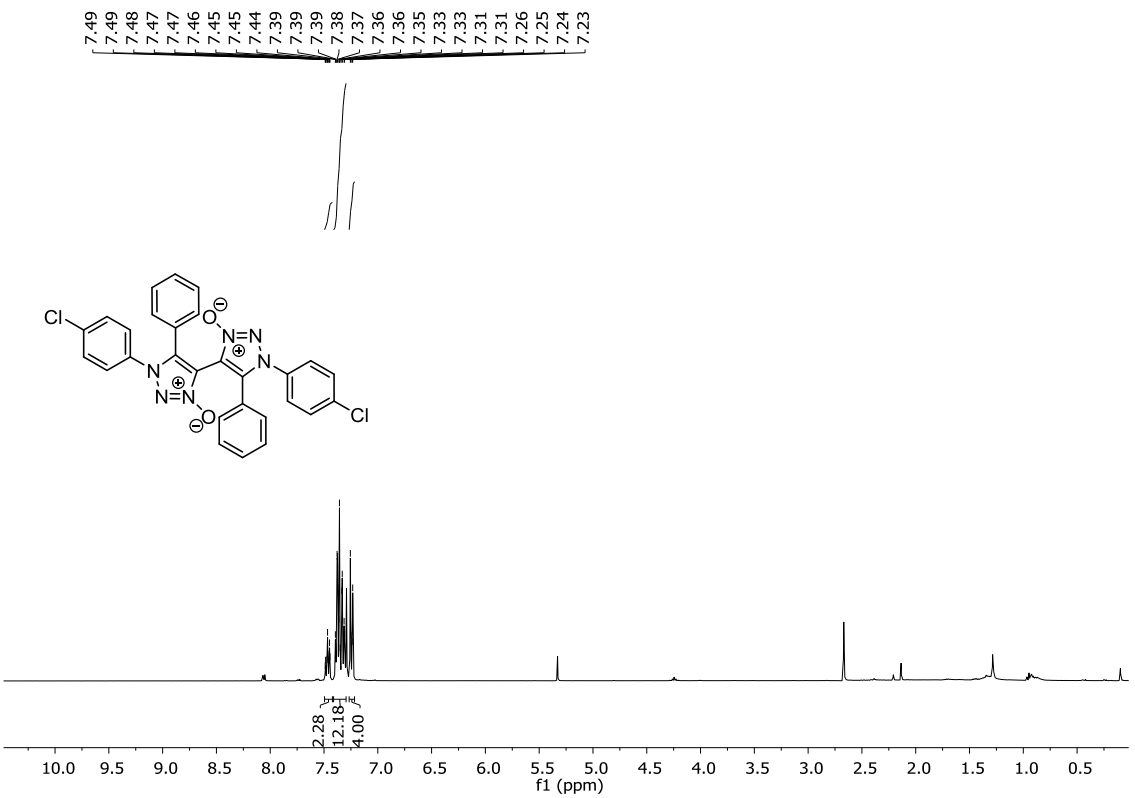
Spectrum 8.222. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28a**.



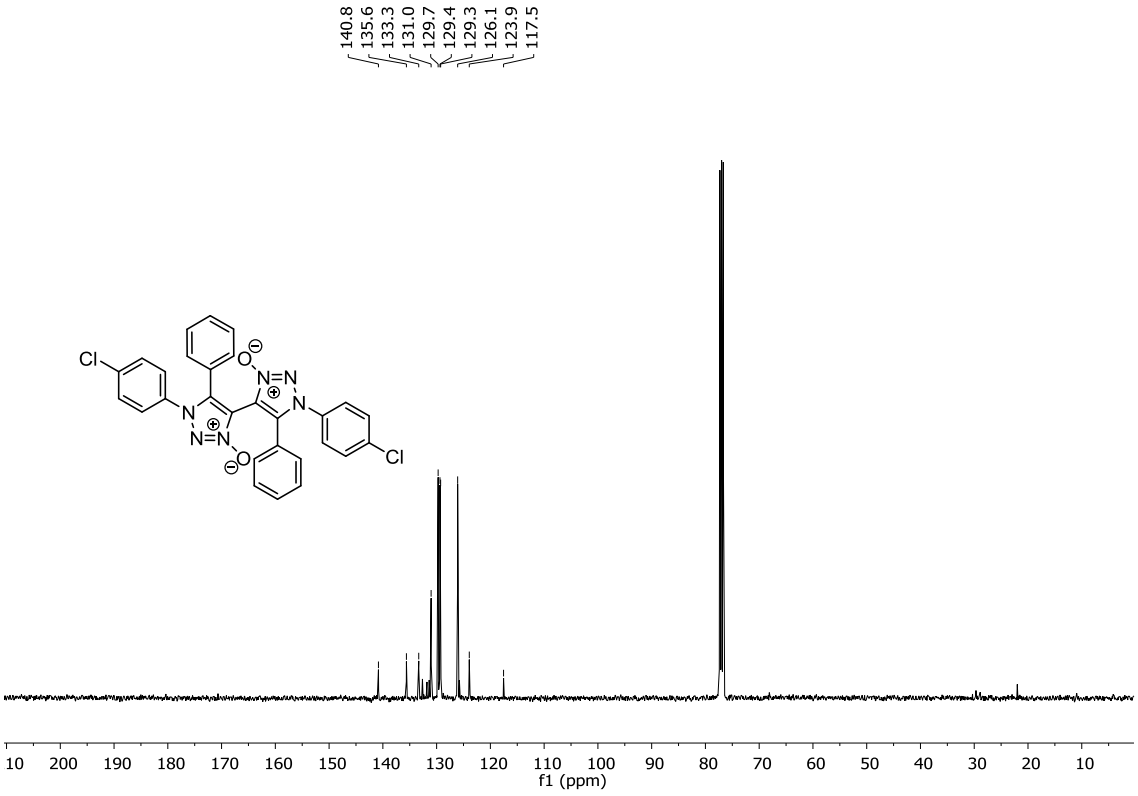
Spectrum 8.223. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28b**.



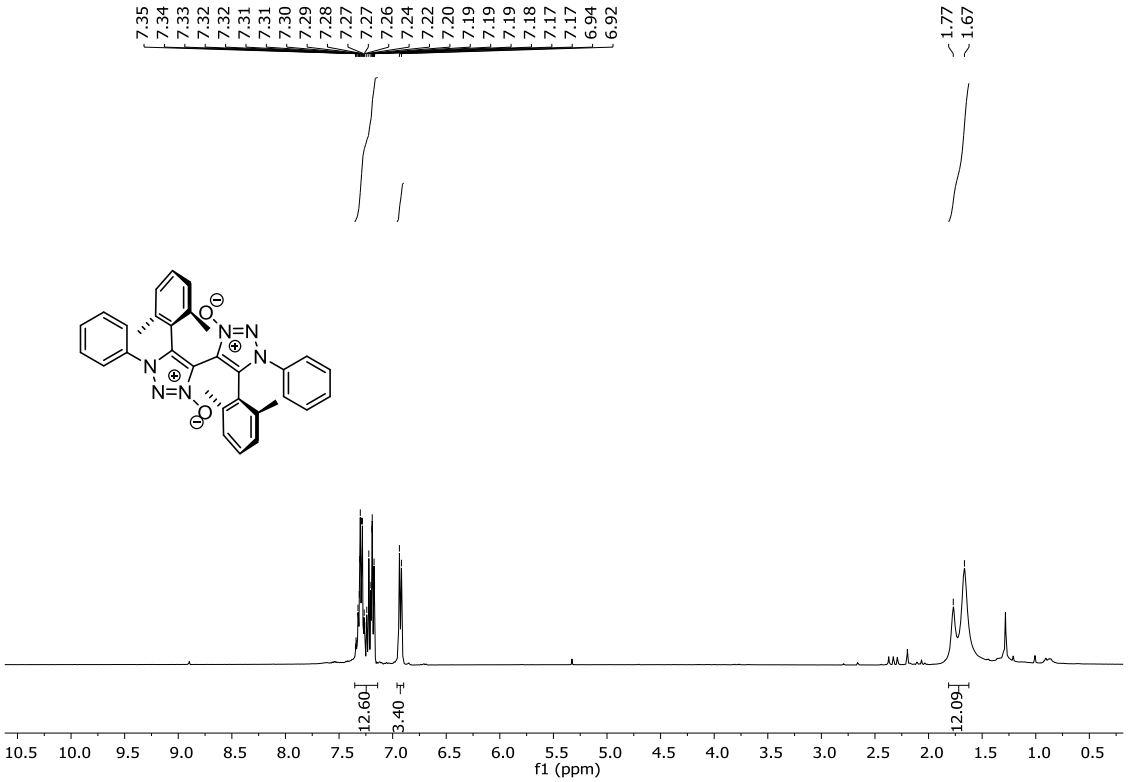
Spectrum 8.224. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28b**.



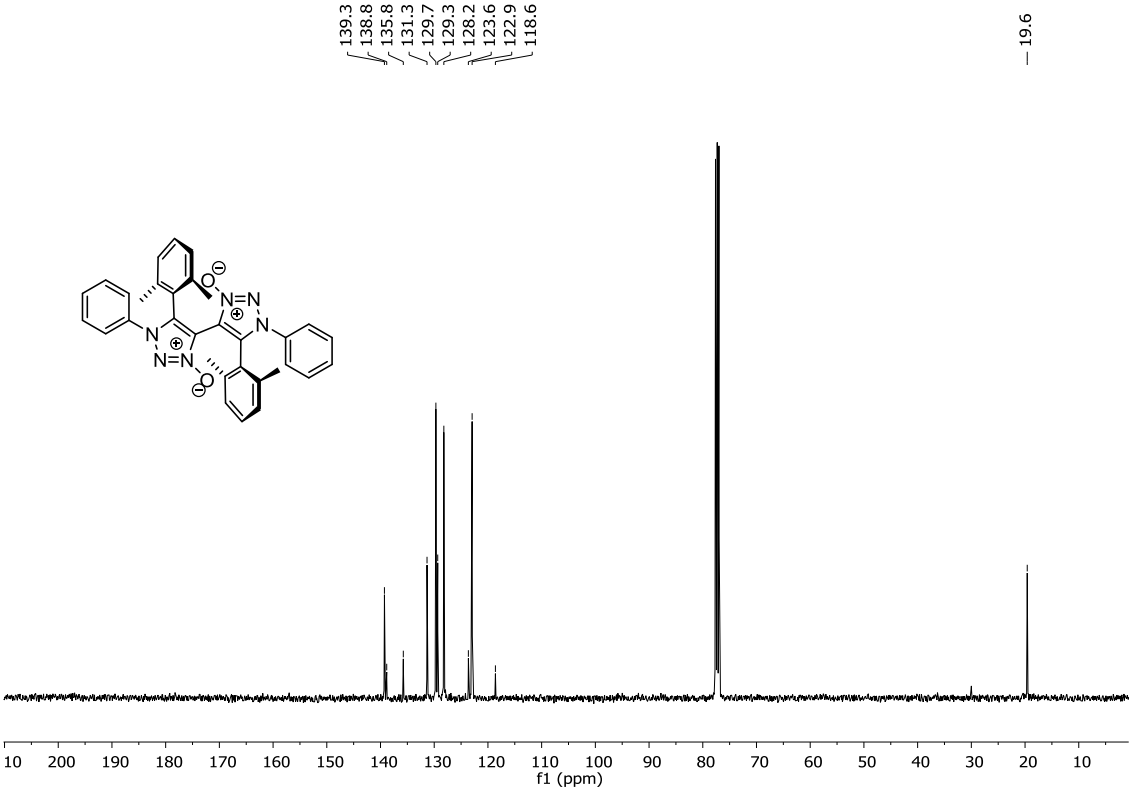
Spectrum 8.225. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28c**.



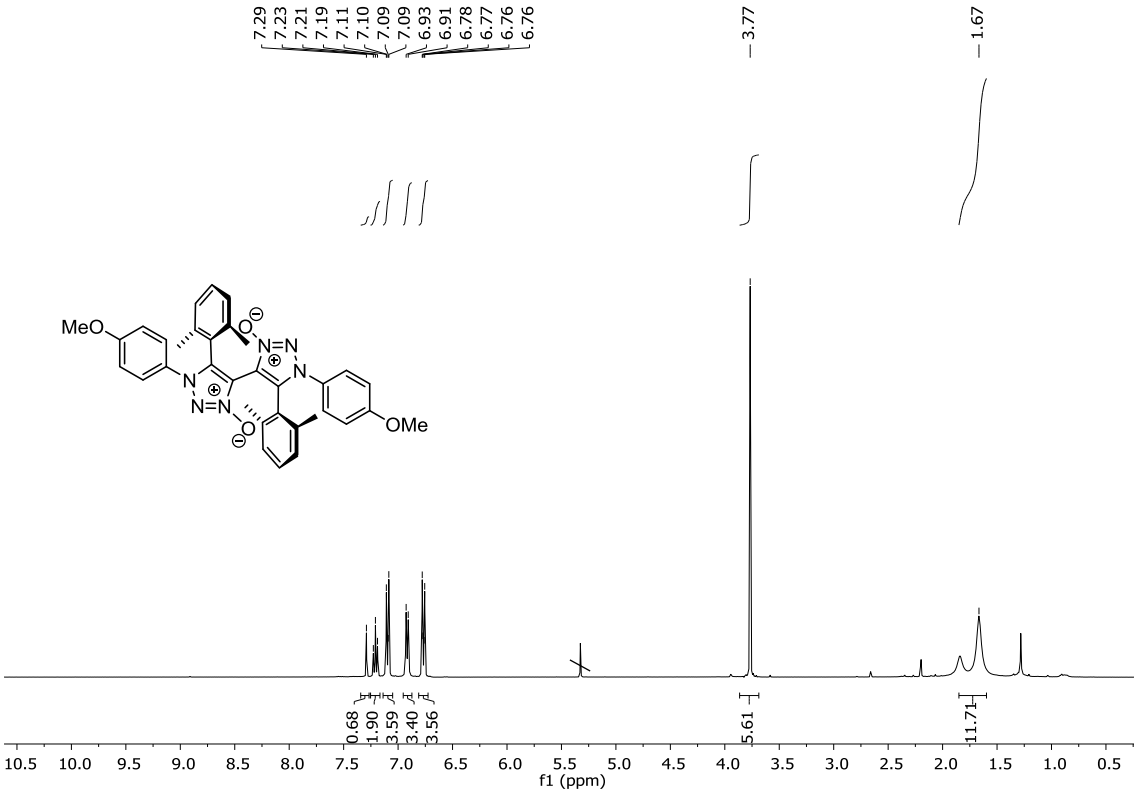
Spectrum 8.226. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28c**.



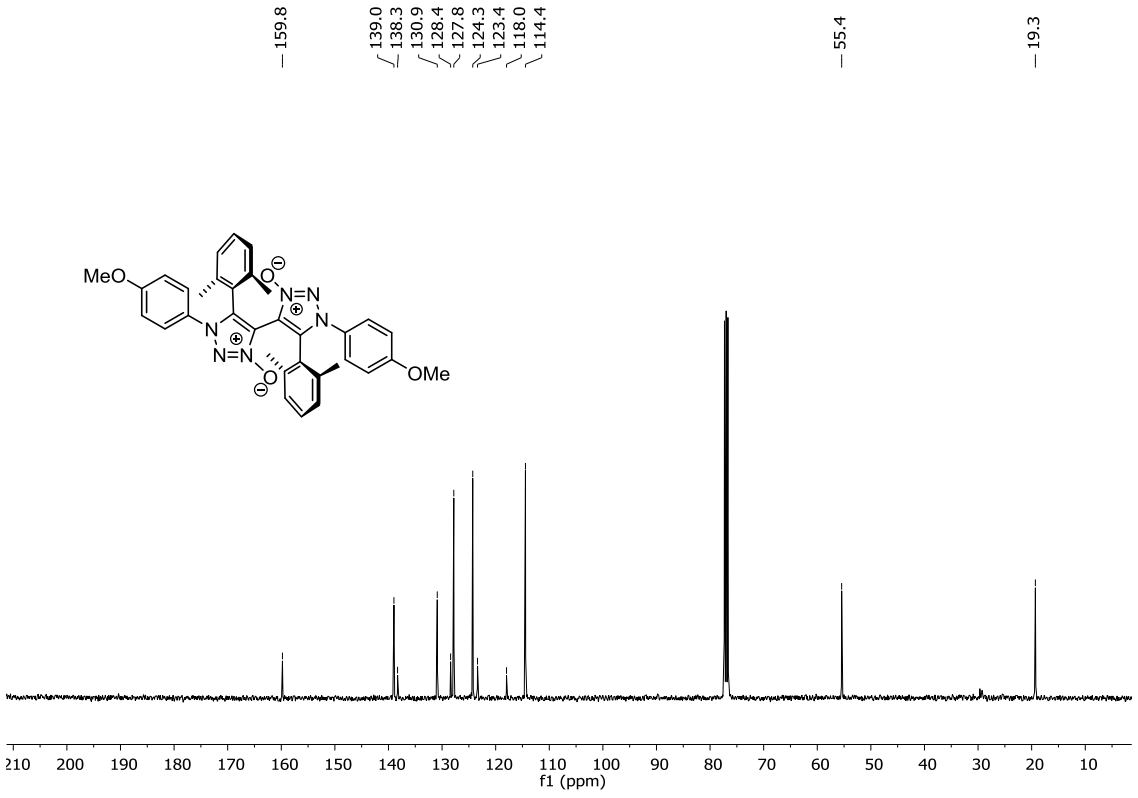
Spectrum 8.227. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28d**.



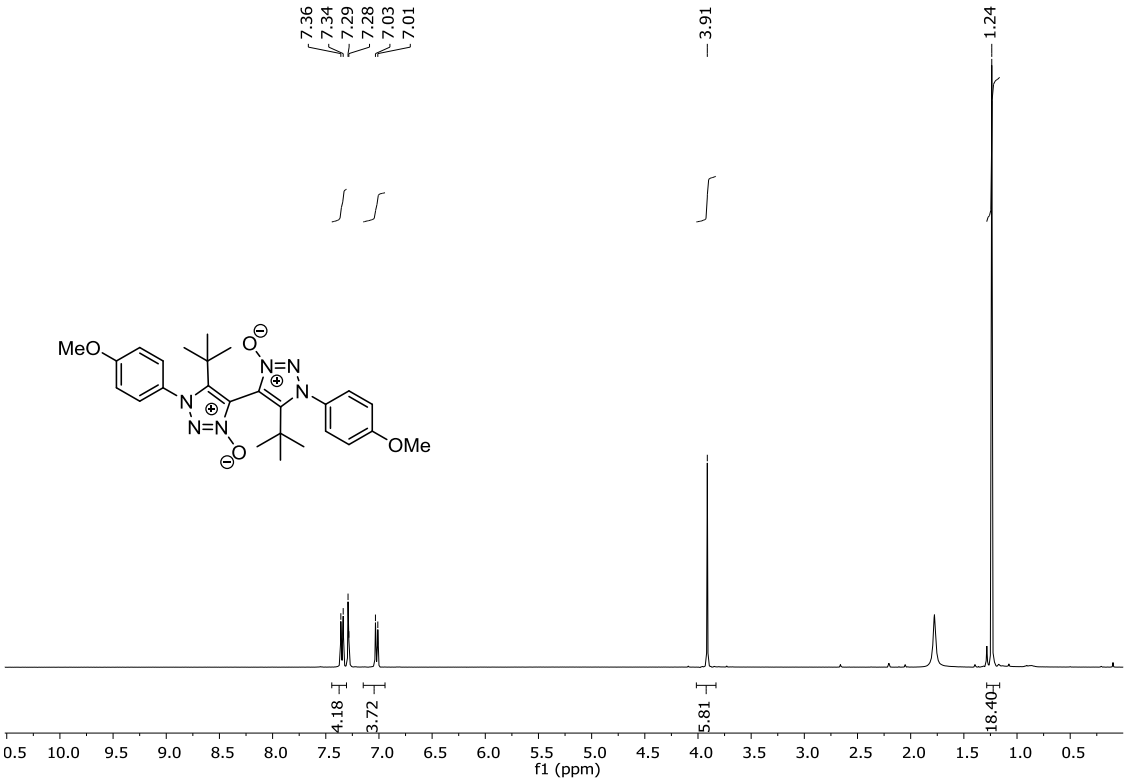
Spectrum 8.228. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28d**.



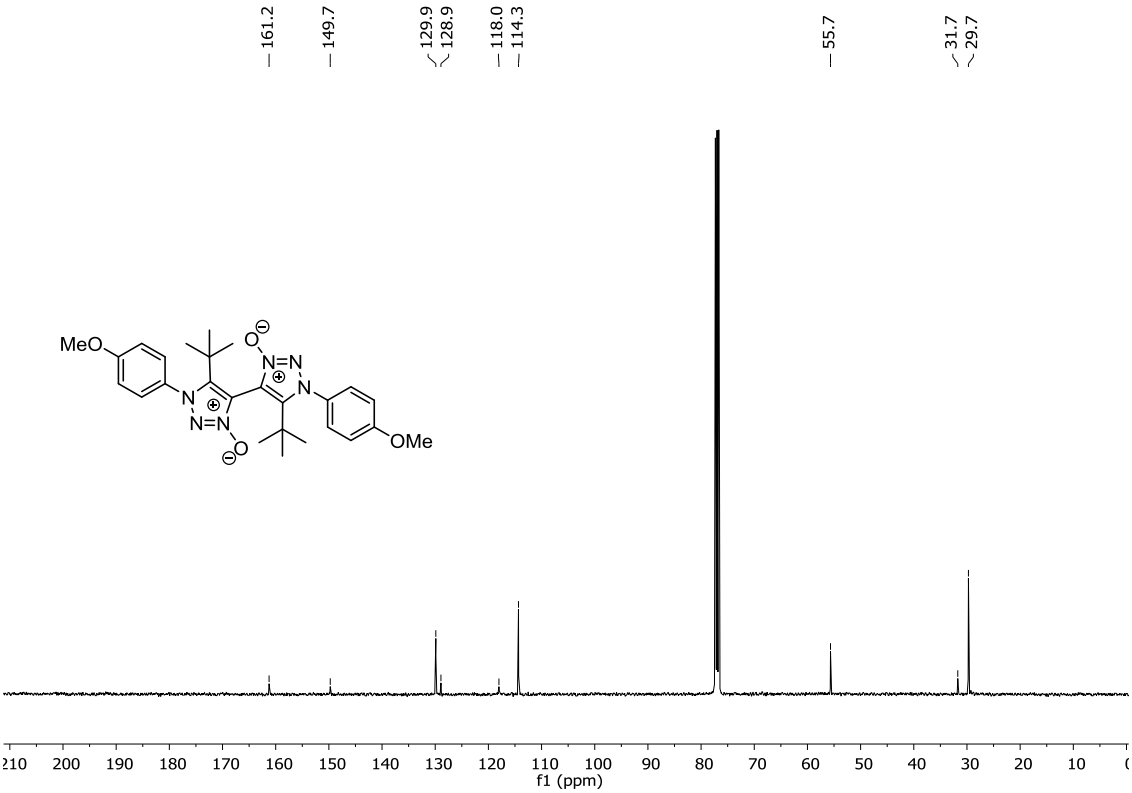
Spectrum 8.229. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28e**.



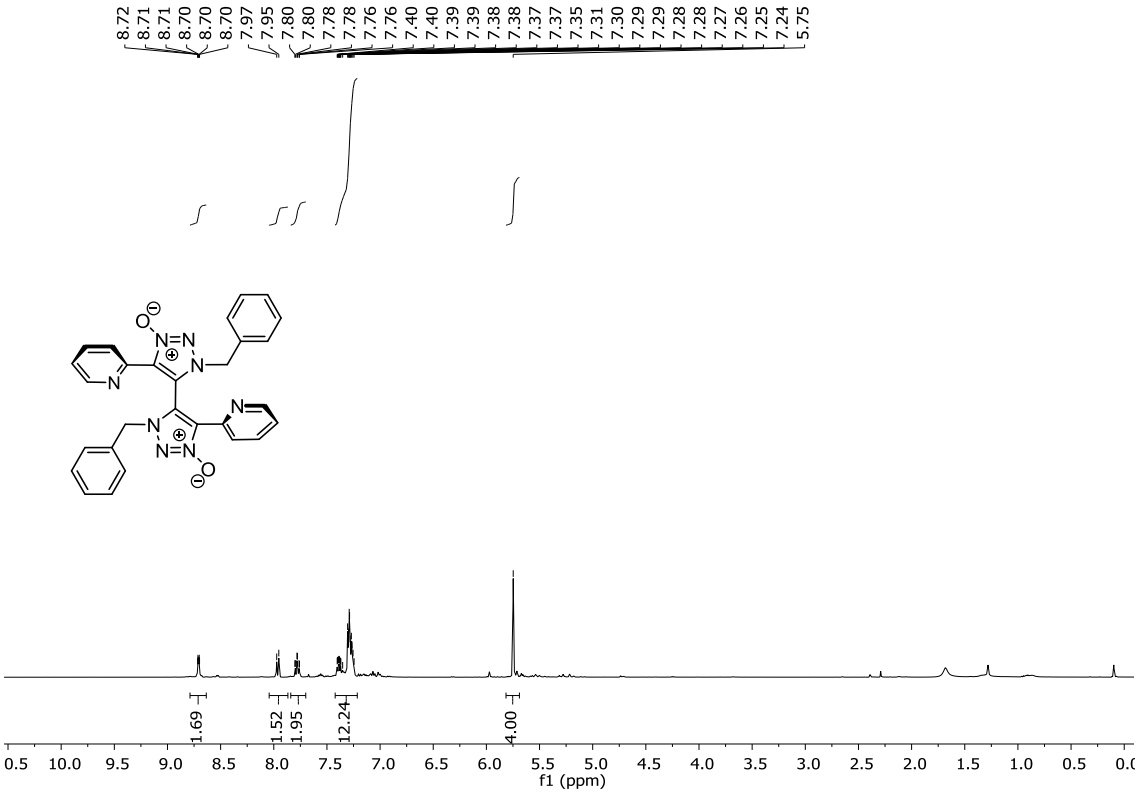
Spectrum 8.230. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28e**.



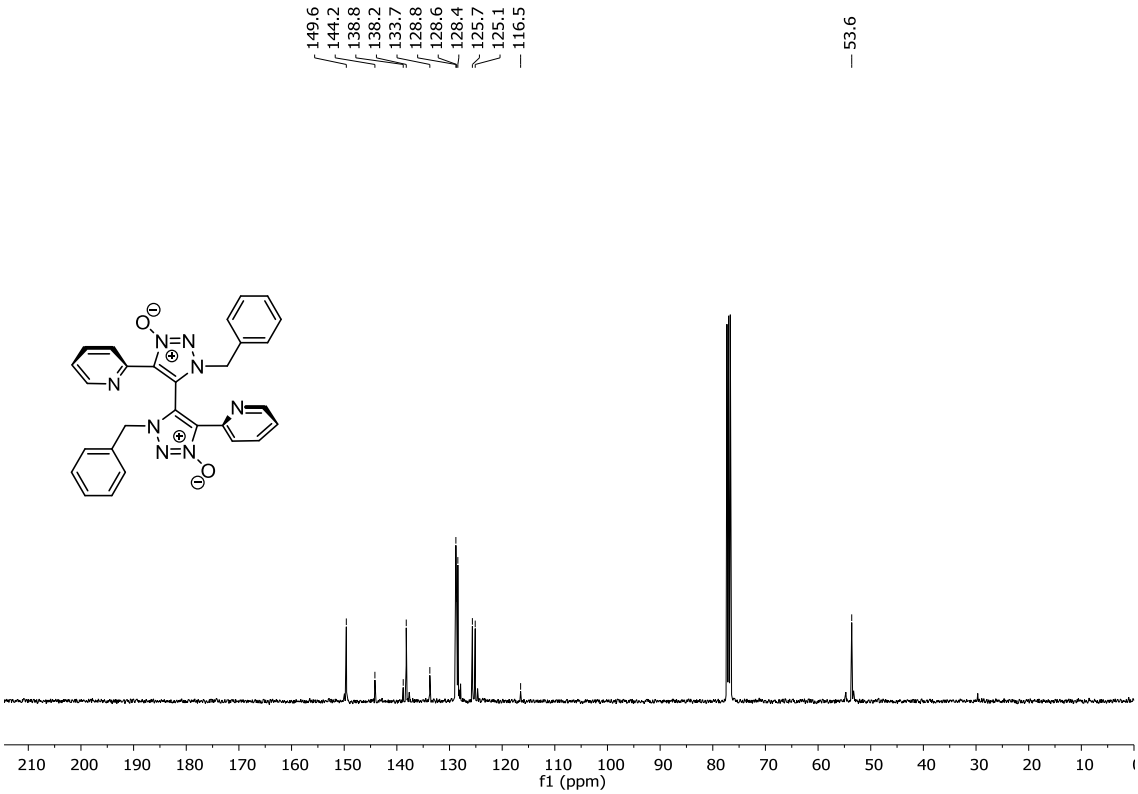
Spectrum 8.231. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **28f**.



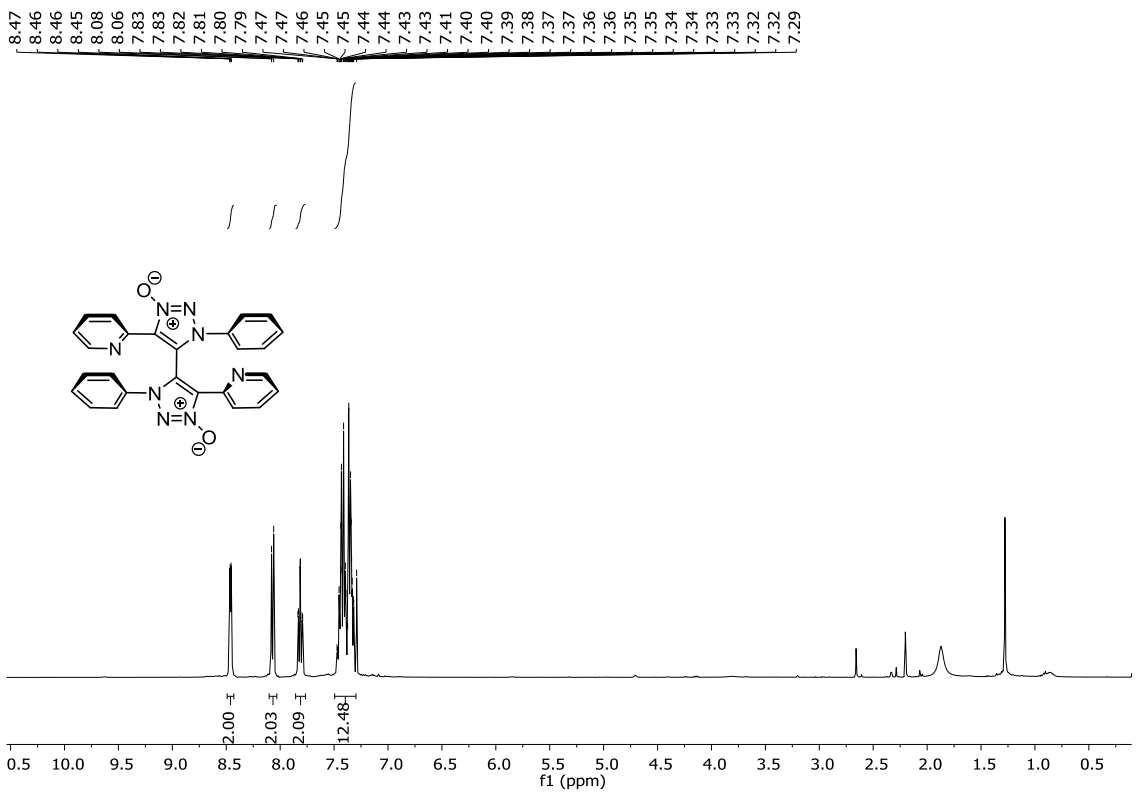
Spectrum 8.232. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **28f**.



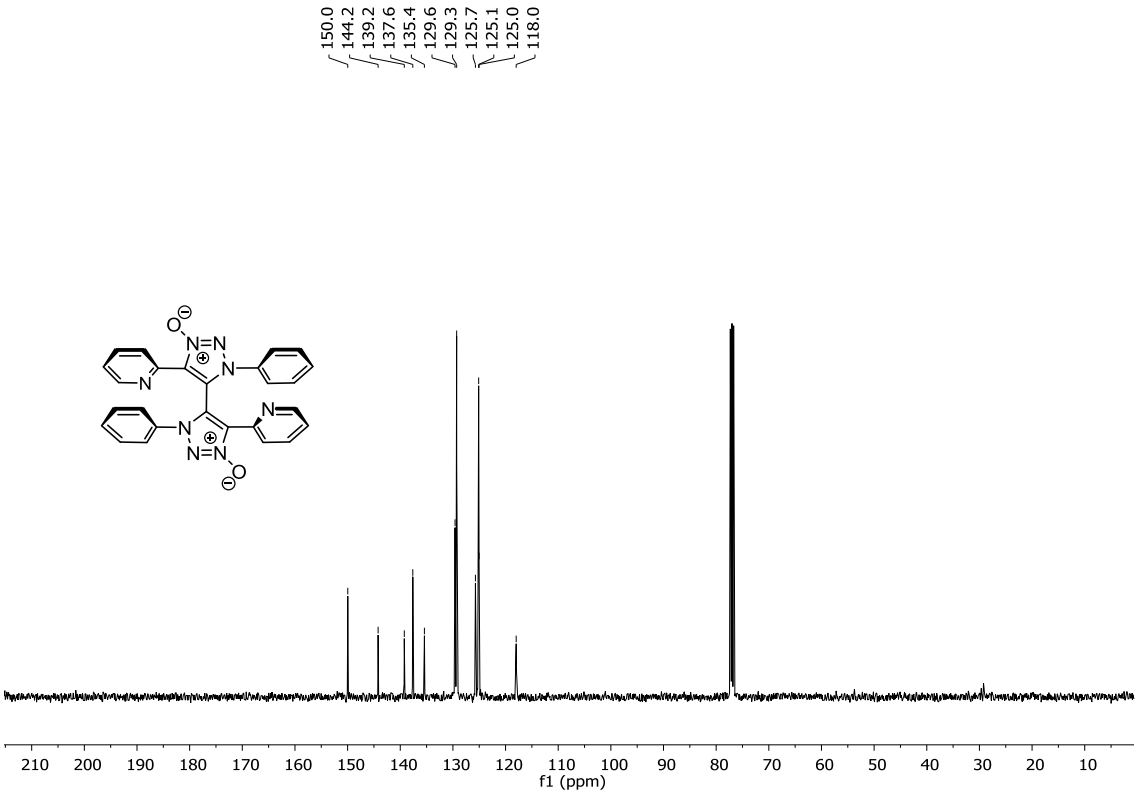
Spectrum 8.233. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **29a**.



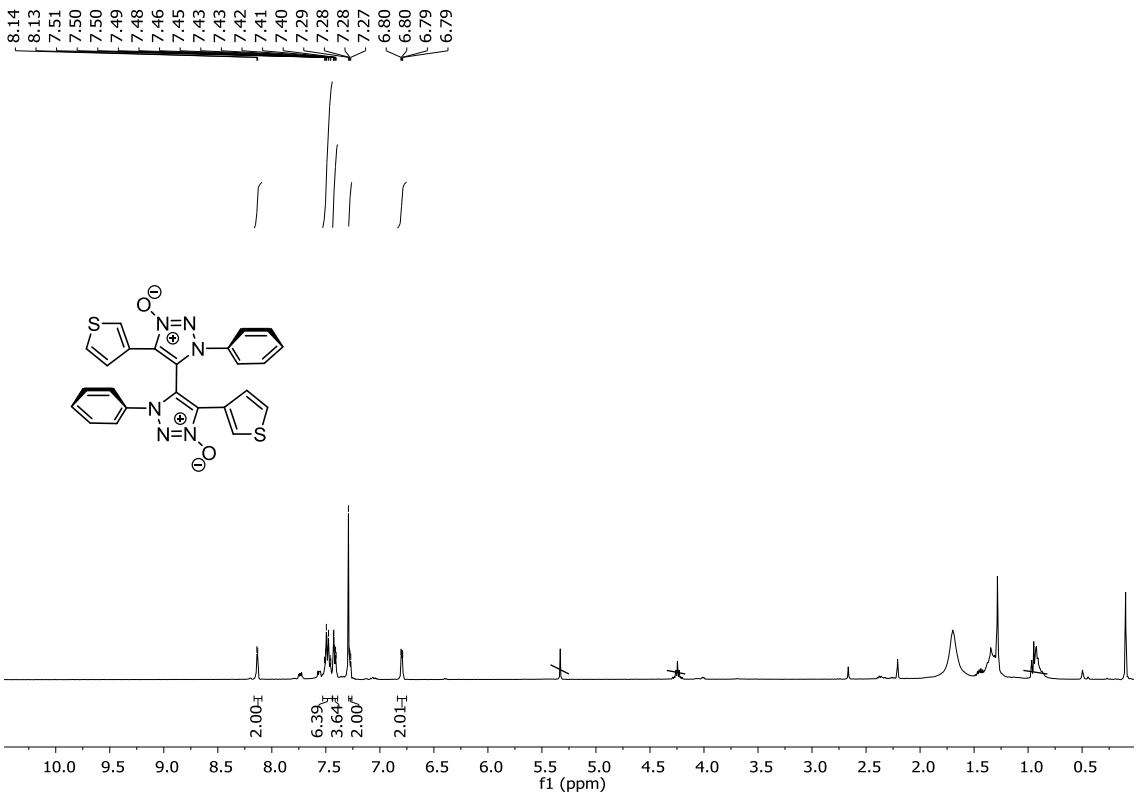
Spectrum 8.234. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **29a**.



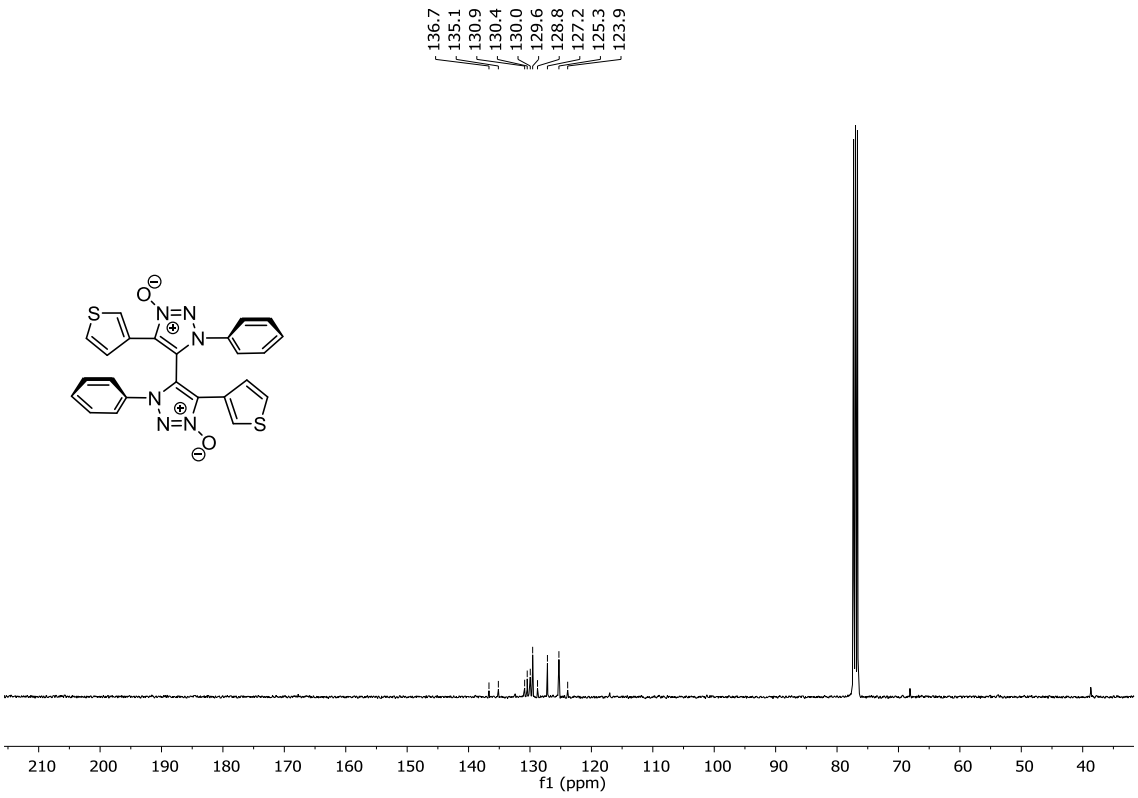
Spectrum 8.235. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **29b**.



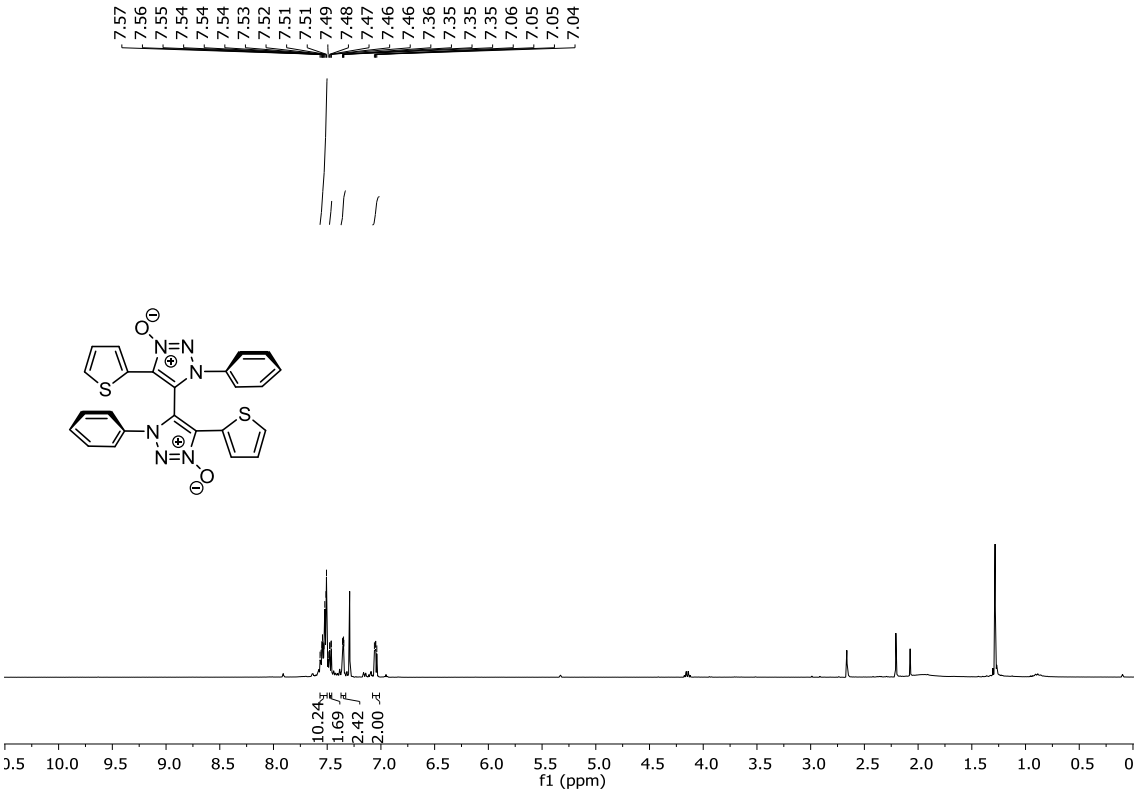
Spectrum 8.236. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **29b**.



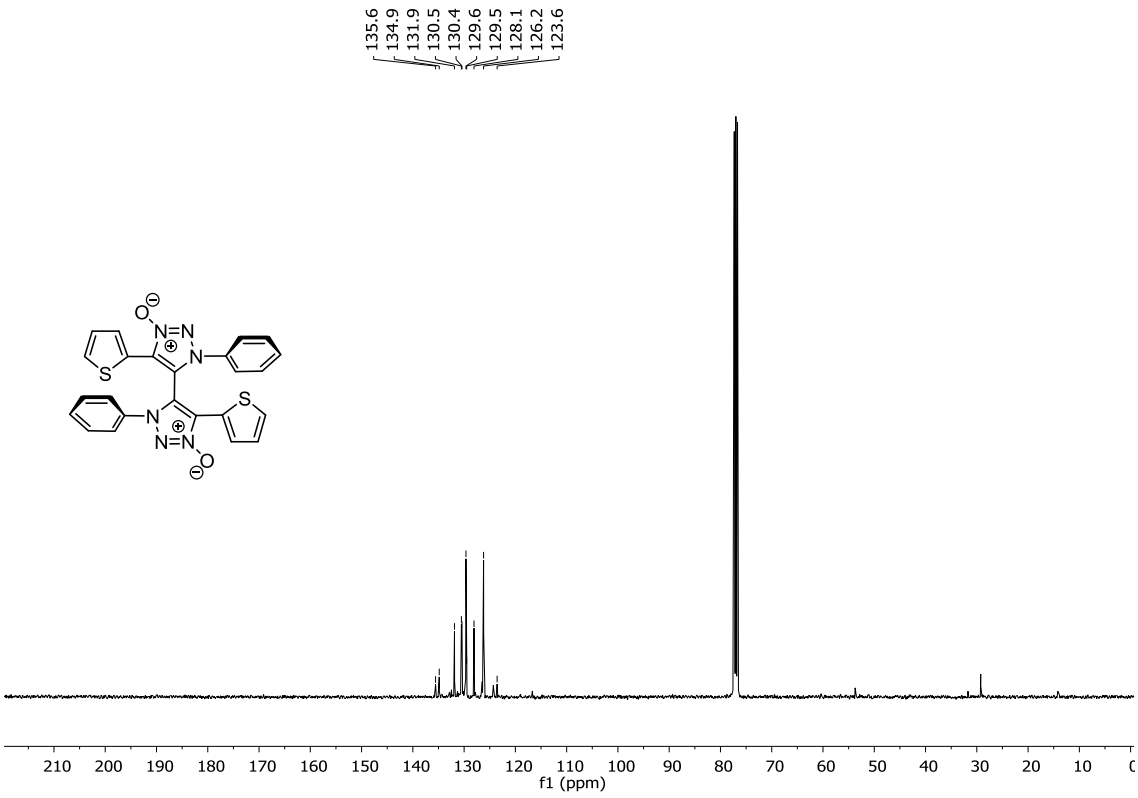
Spectrum 8.237. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **29c**.



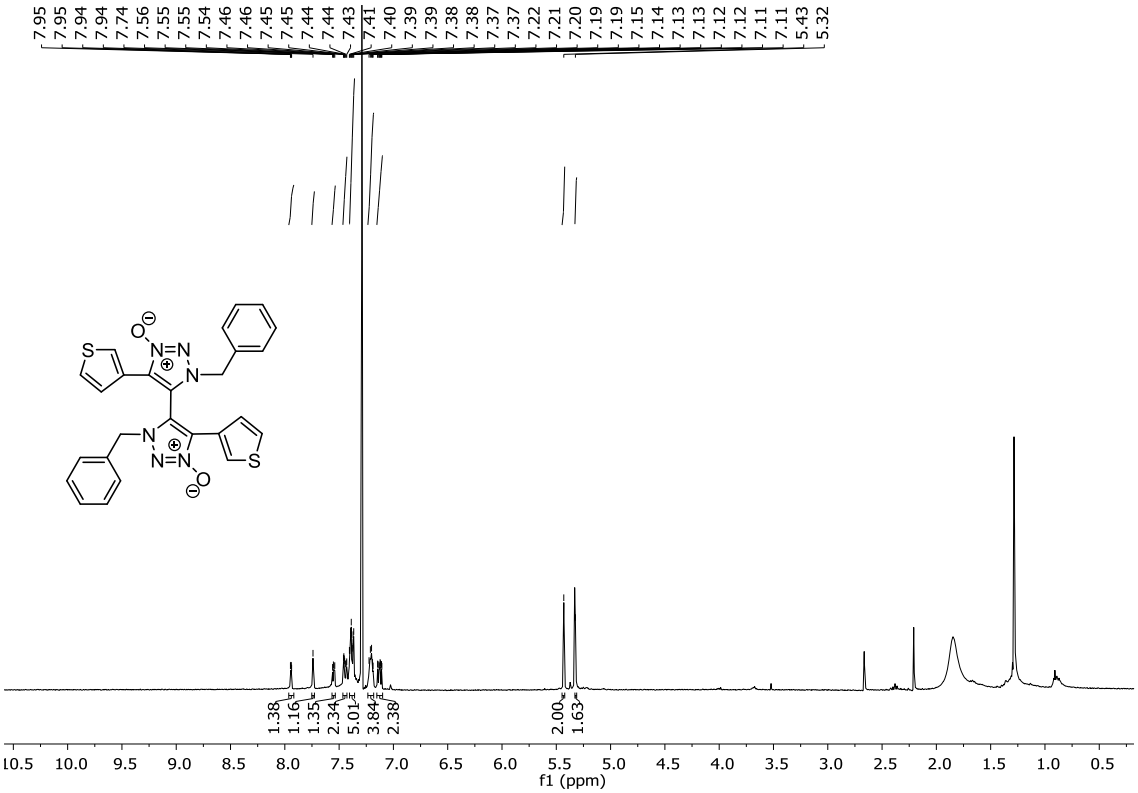
Spectrum 8.238. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **29c**.



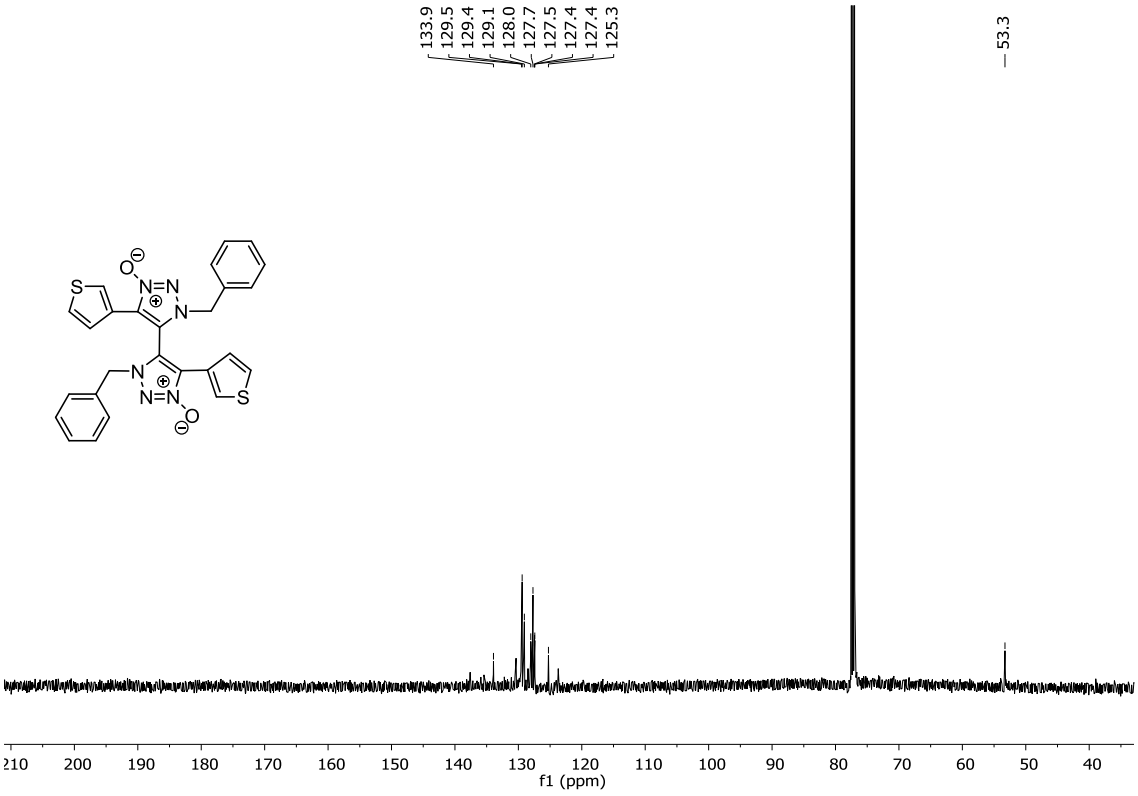
Spectrum 8.239. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **29d**.



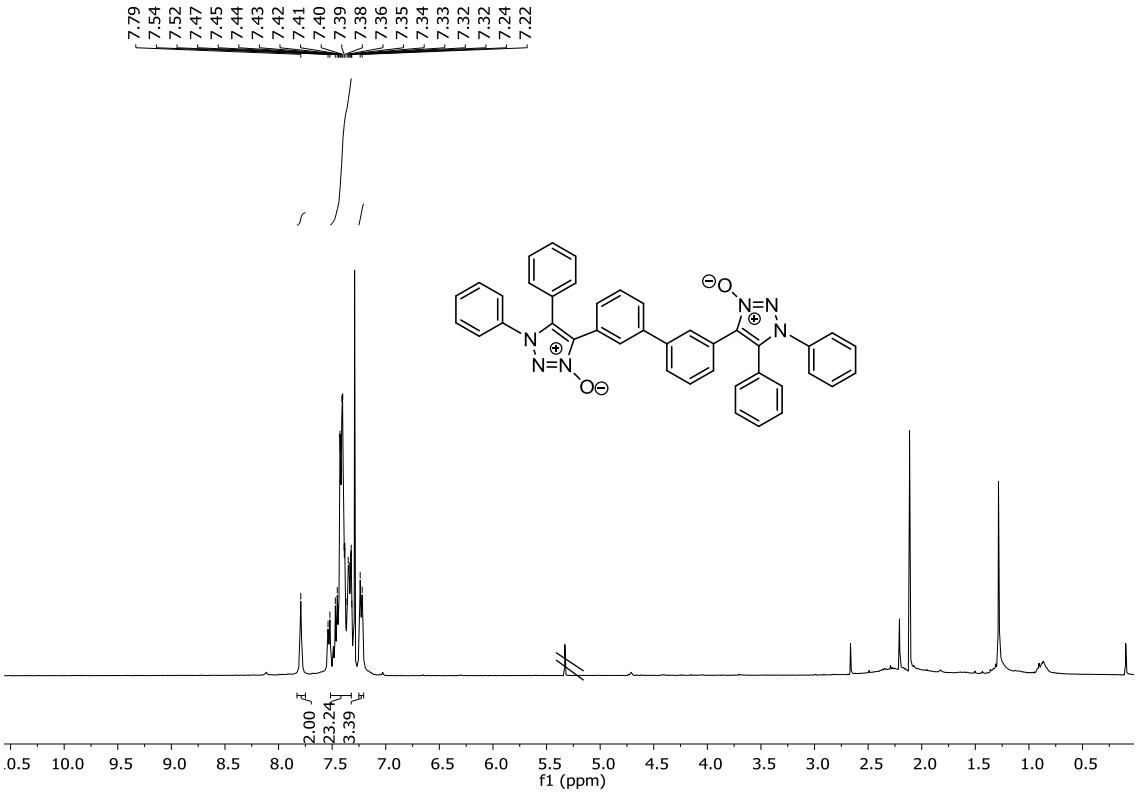
Spectrum 8.240. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **29d**.



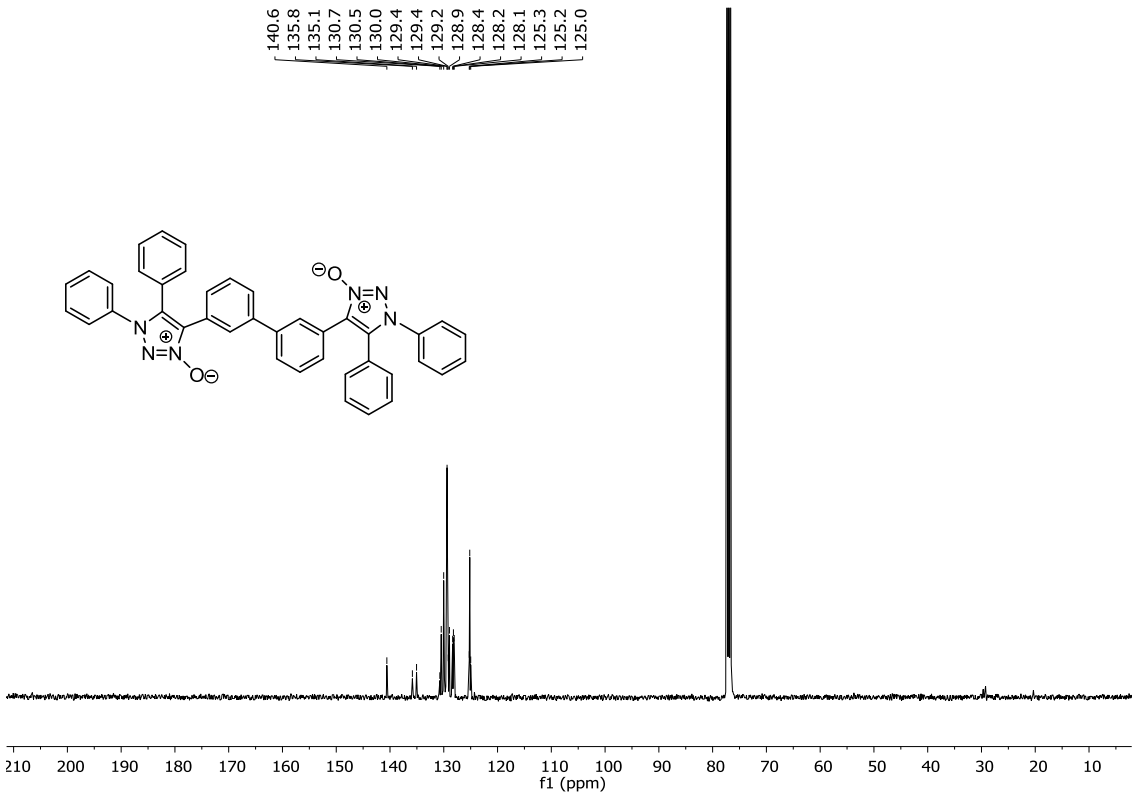
Spectrum 8.241. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **29e**.



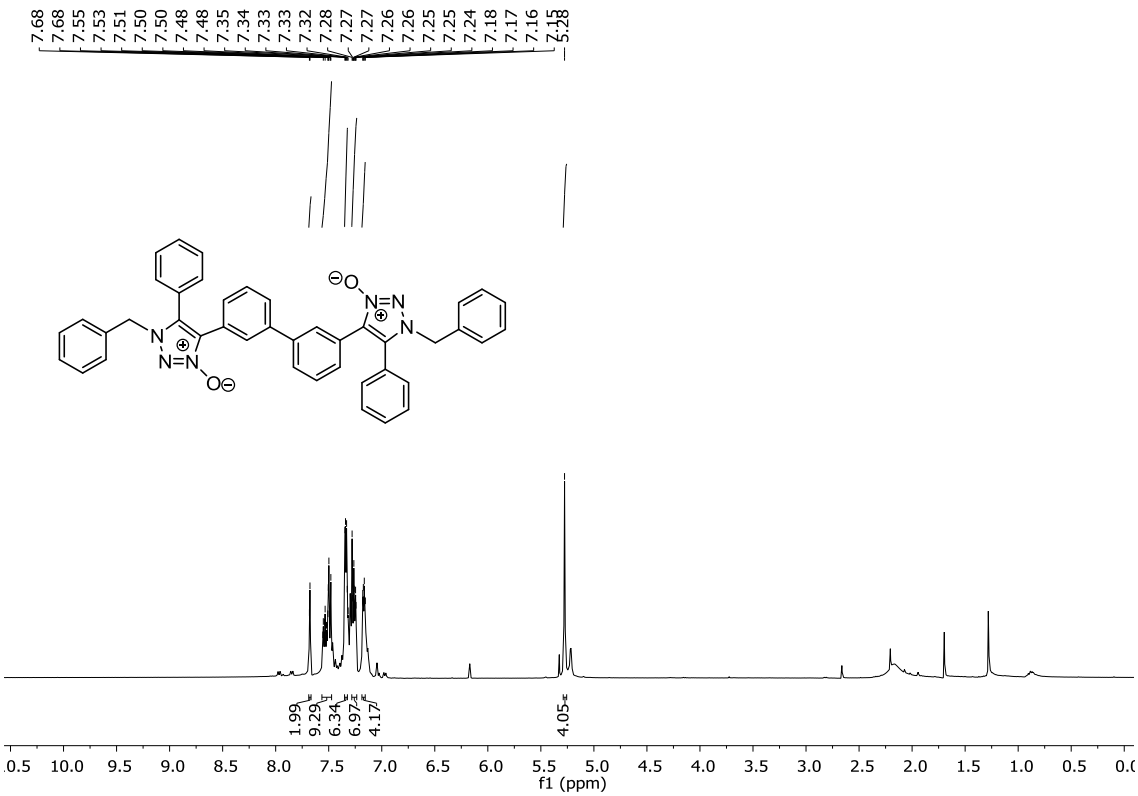
Spectrum 8.242. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **29e**.



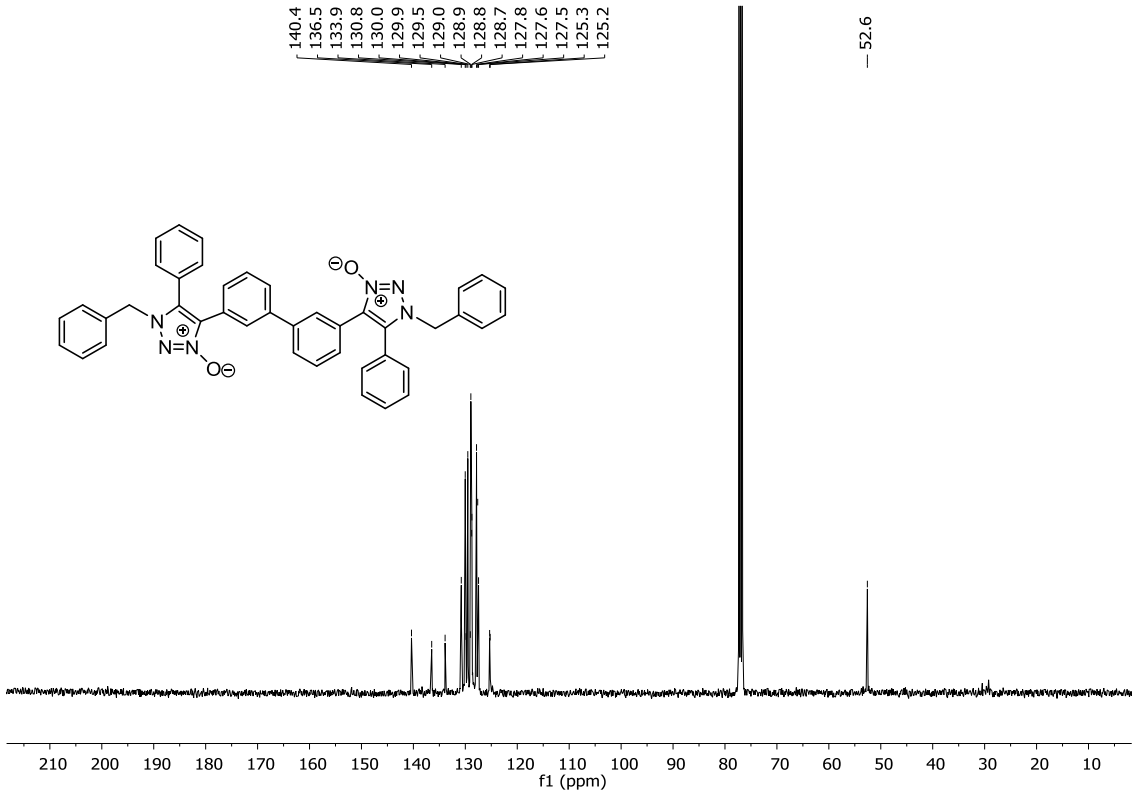
Spectrum 8.243. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32a**.



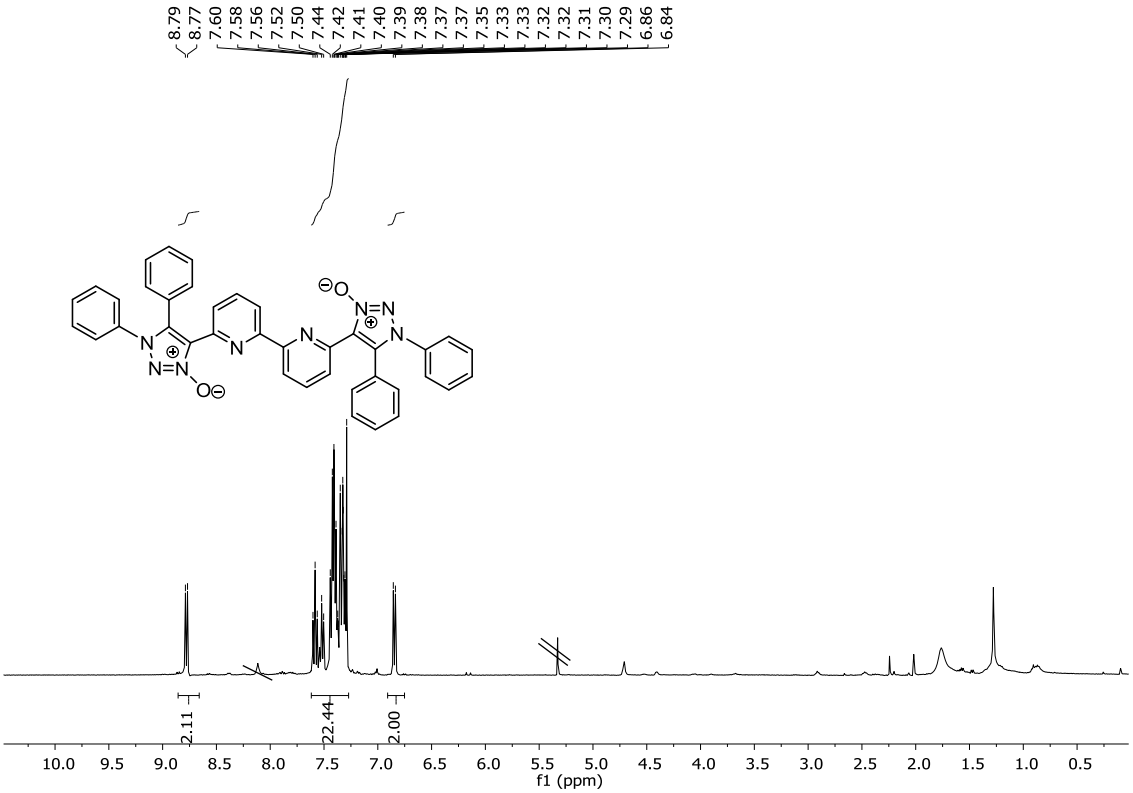
Spectrum 8.244. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32a**.



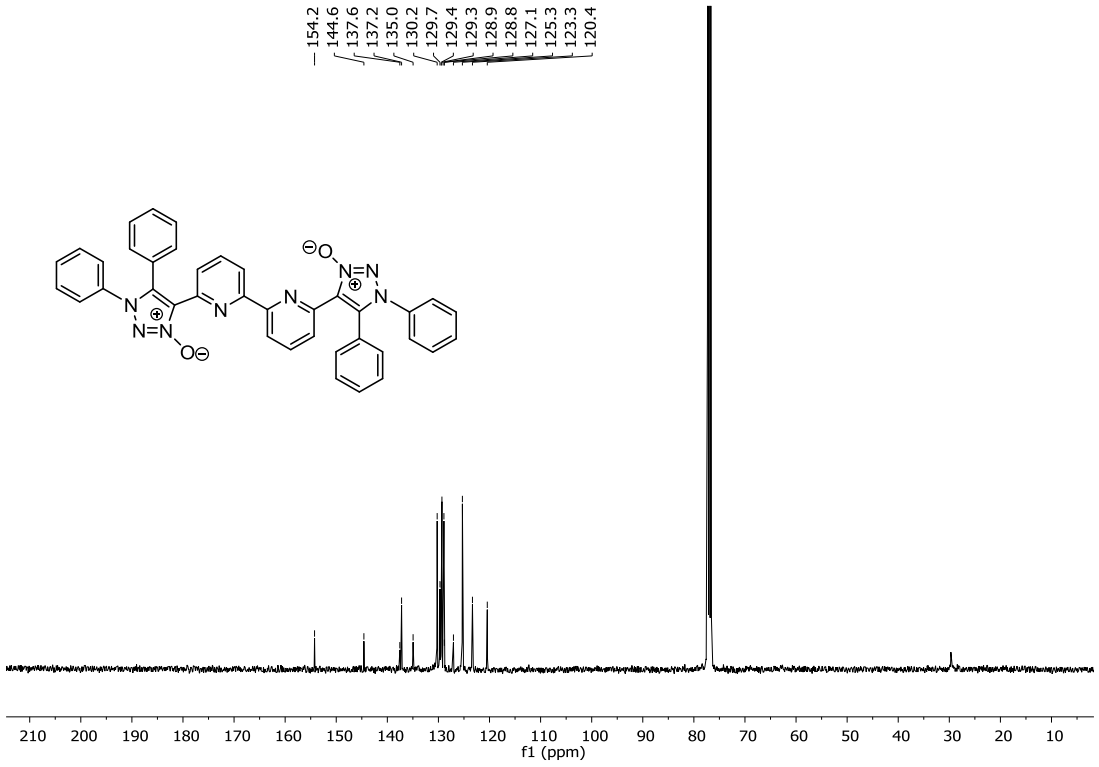
Spectrum 8.245. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32b**.



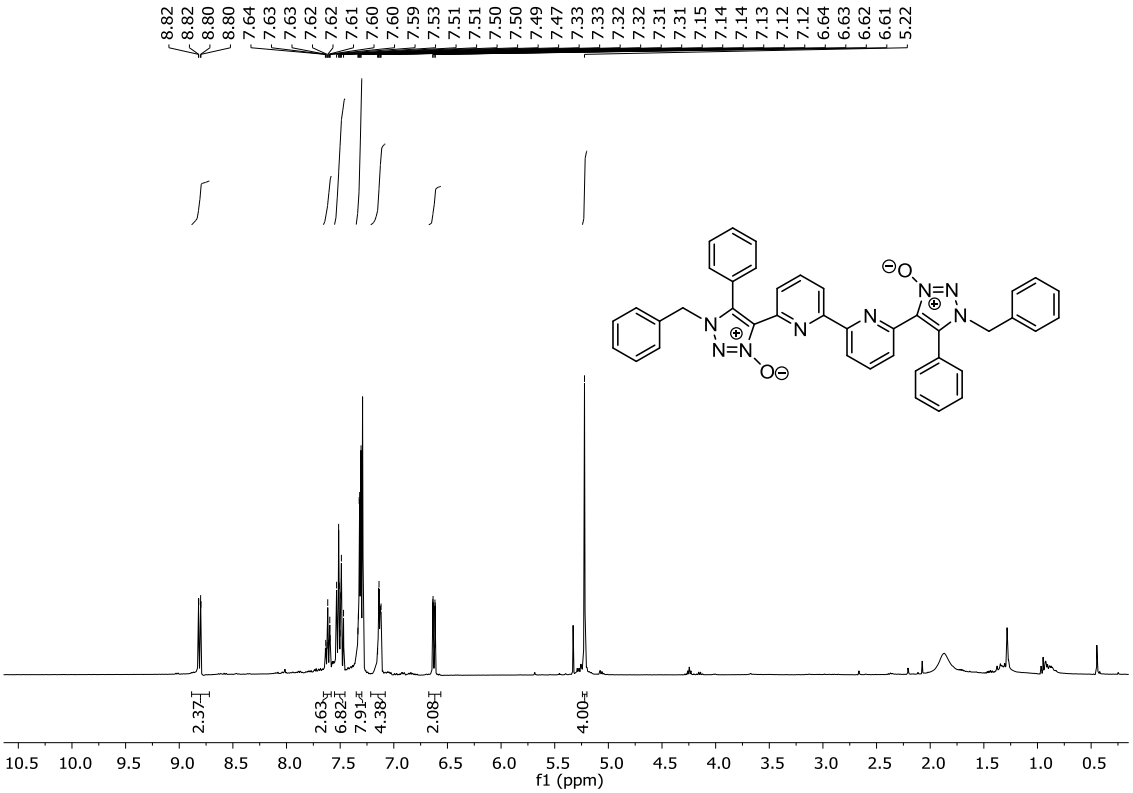
Spectrum 8.246. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32b**.



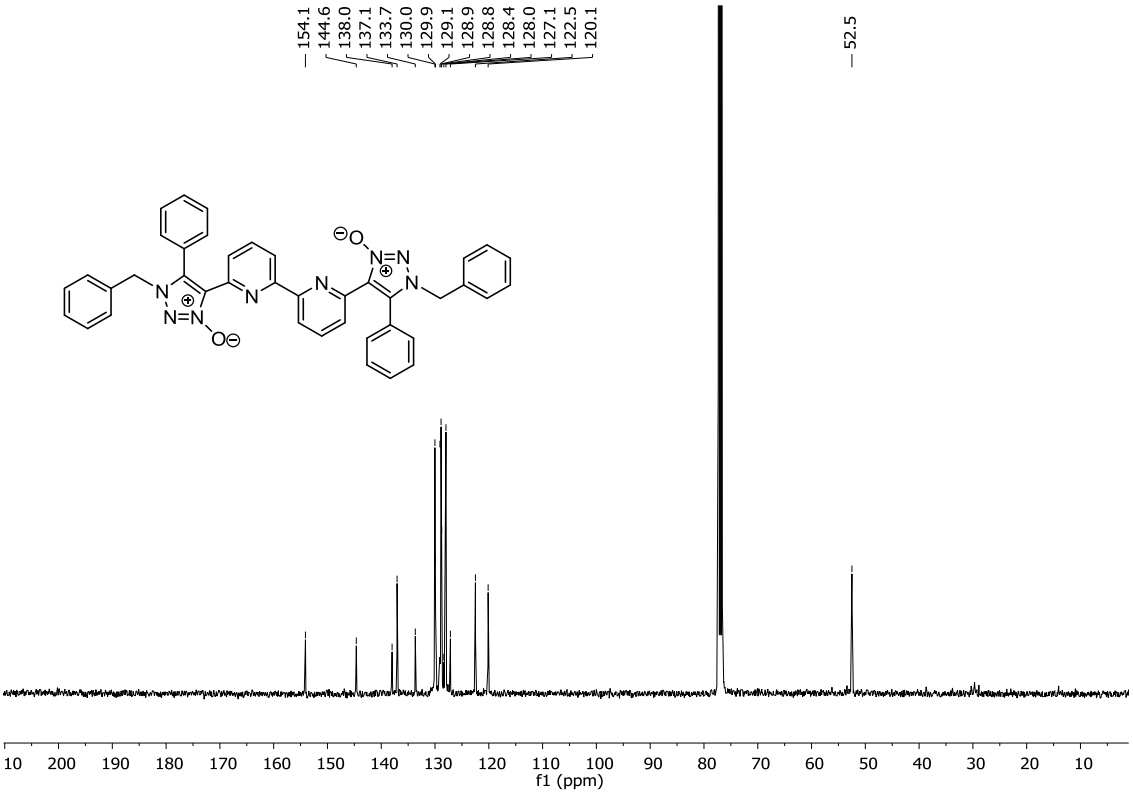
Spectrum 8.247. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32c**.



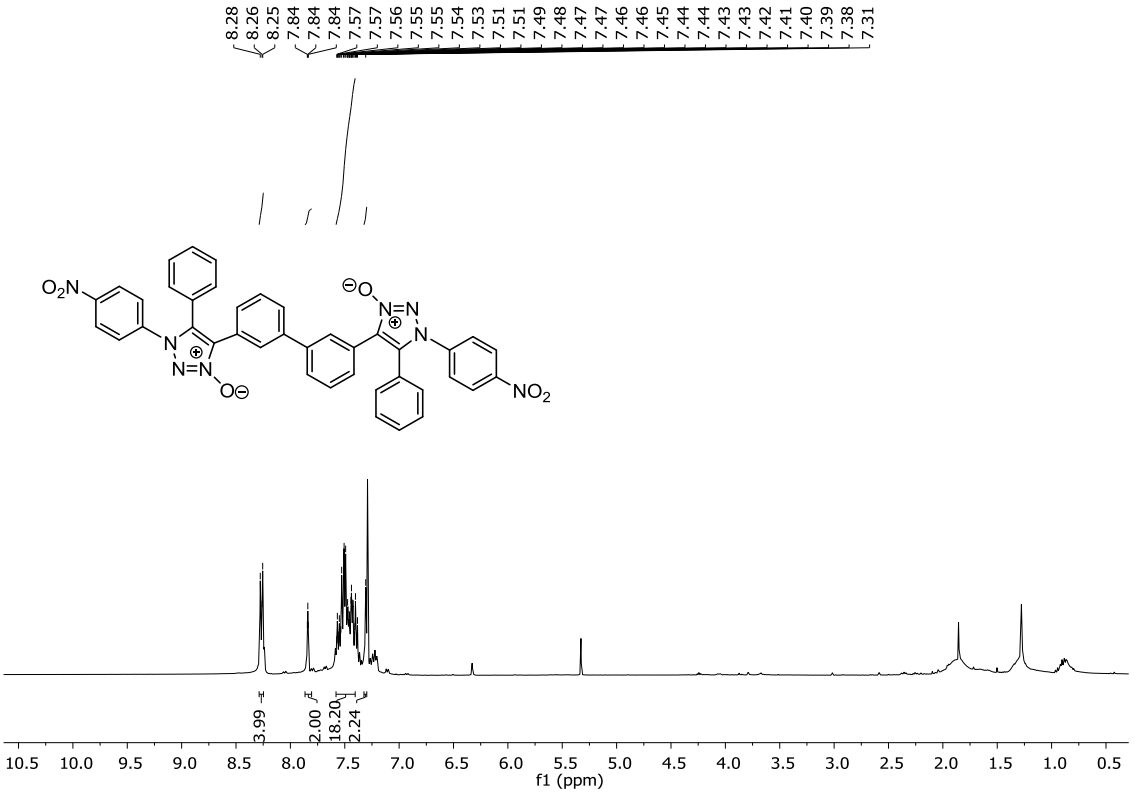
Spectrum 8.248. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32c**.



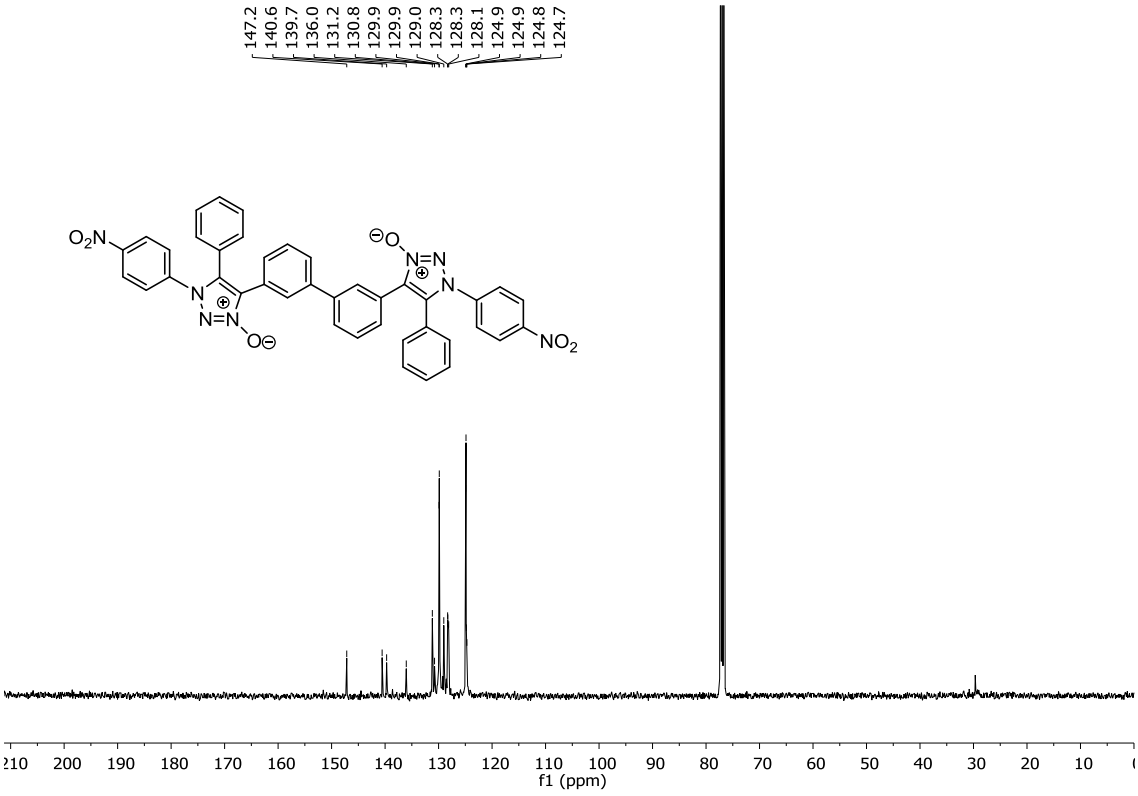
Spectrum 8.249. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32d**.



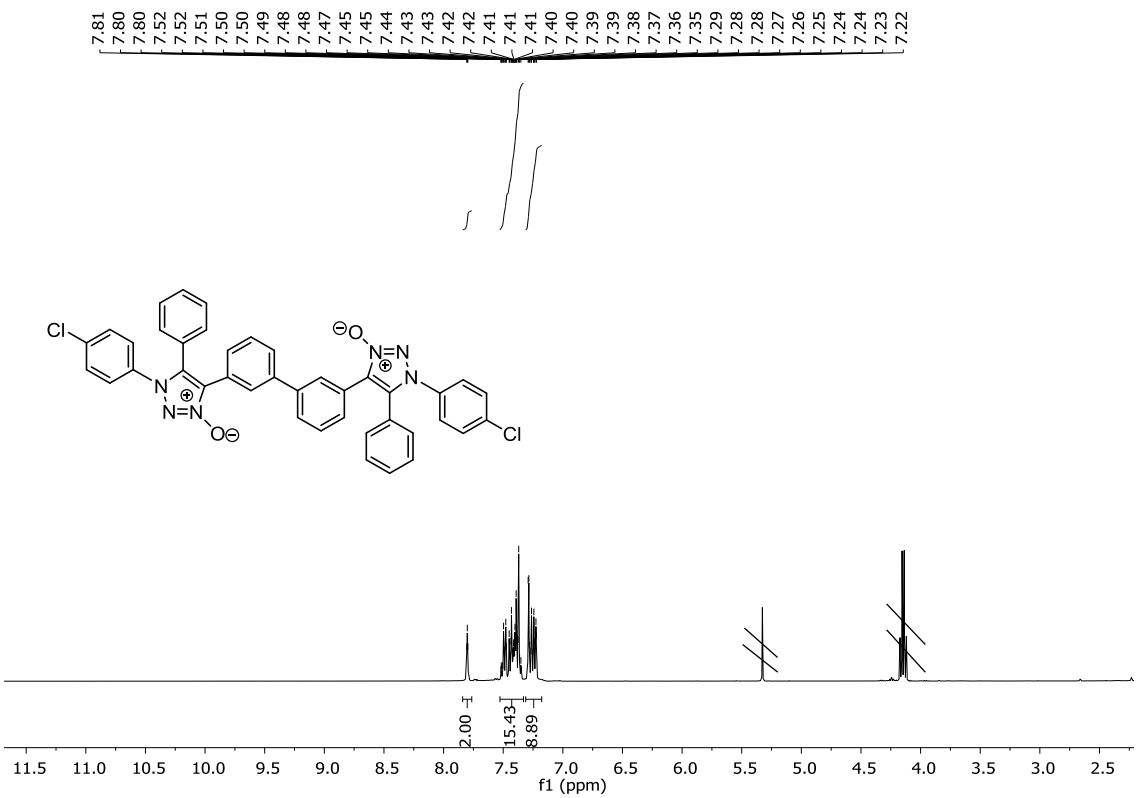
Spectrum 8.250. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32d**.



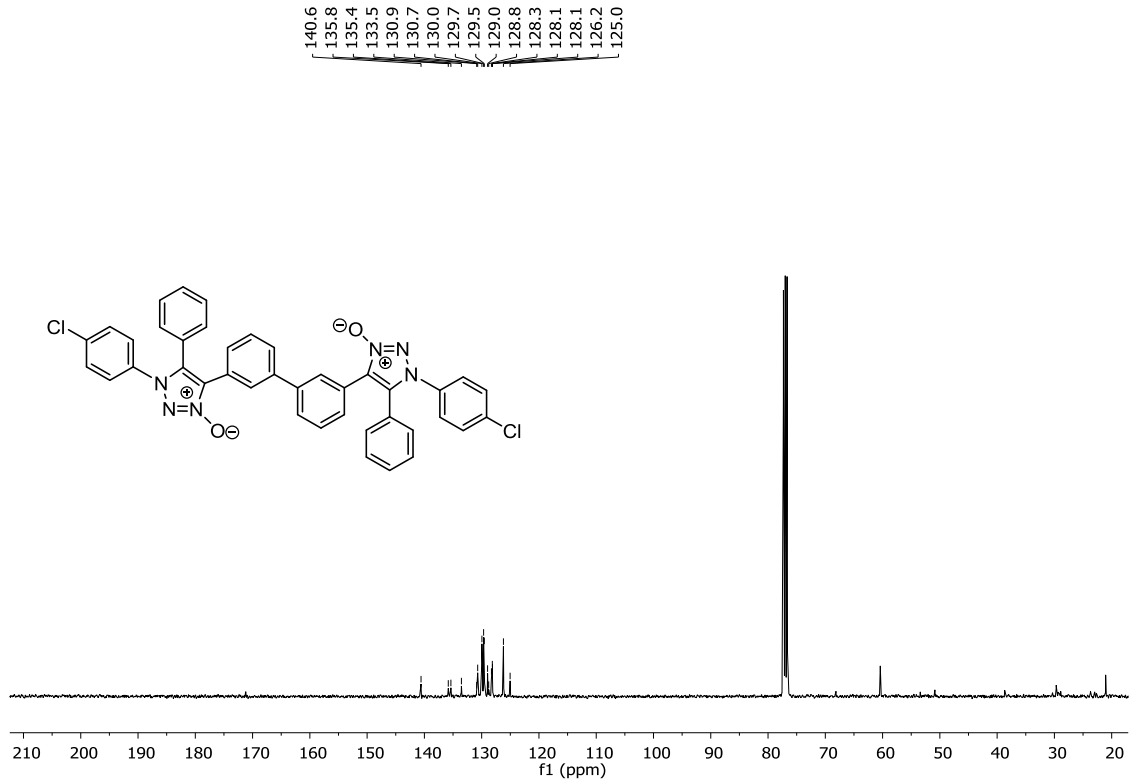
Spectrum 8.251. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32e**.



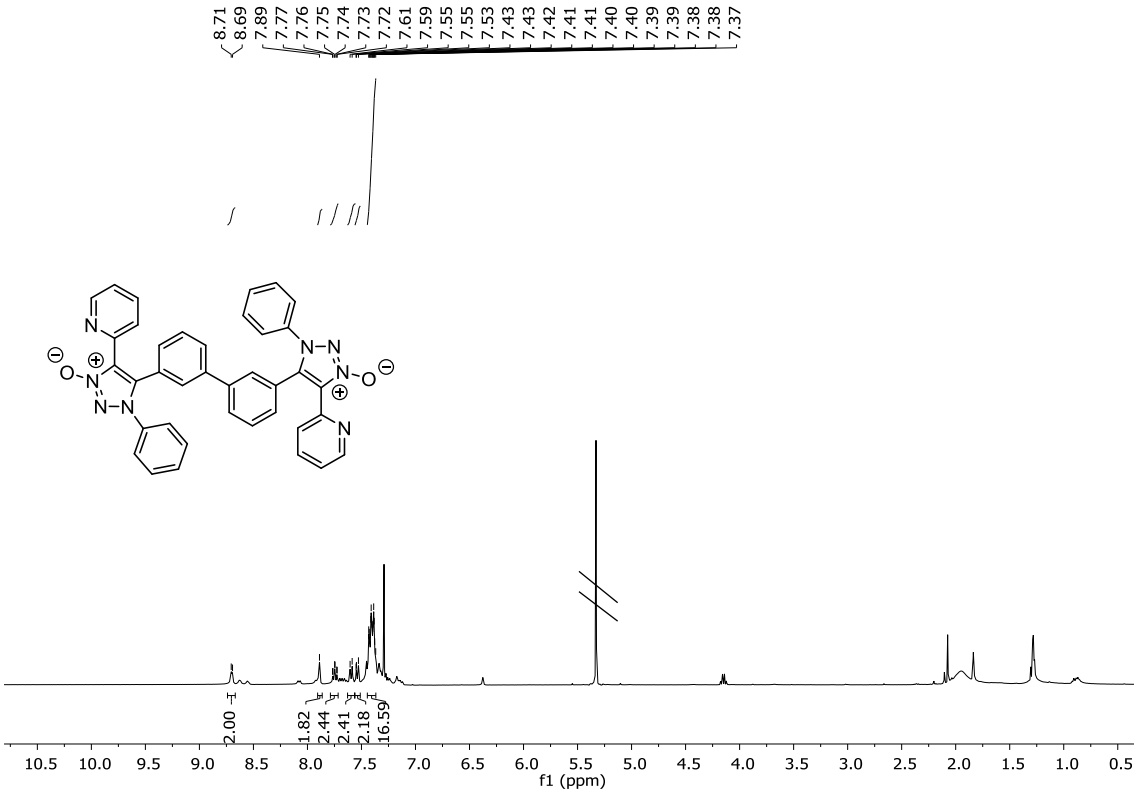
Spectrum 8.252. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32e**.



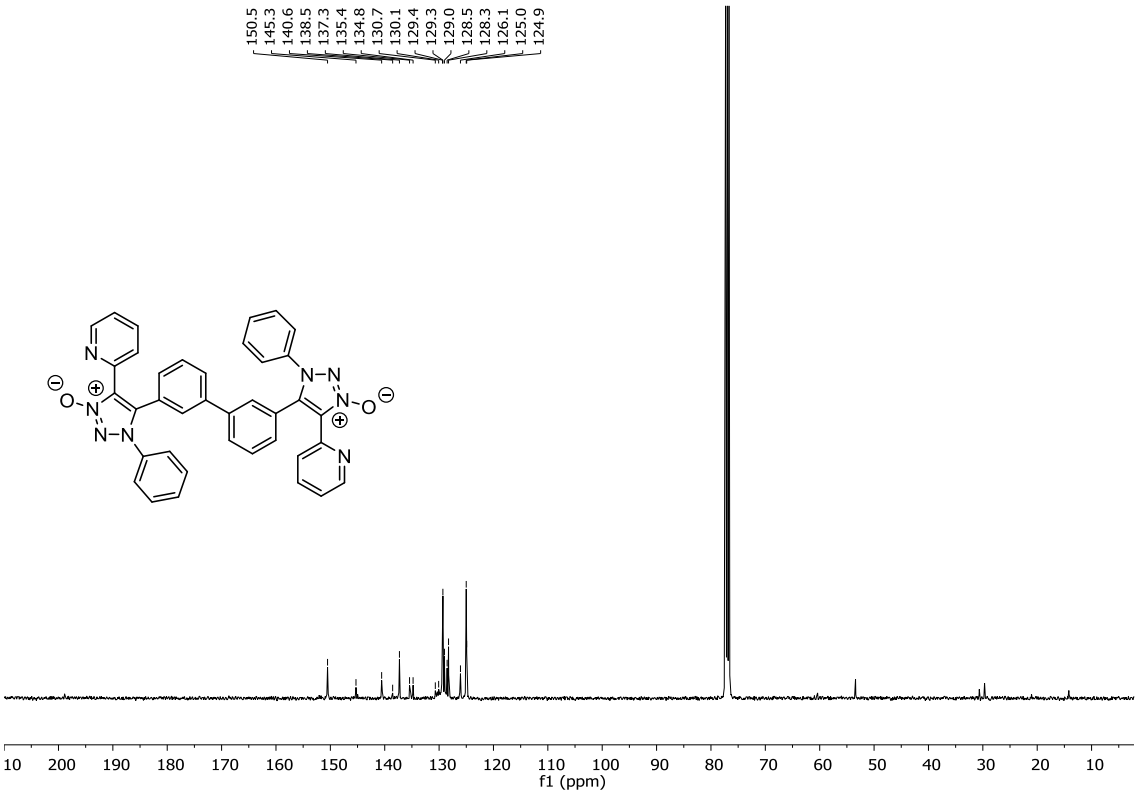
Spectrum 8.253. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32f**.



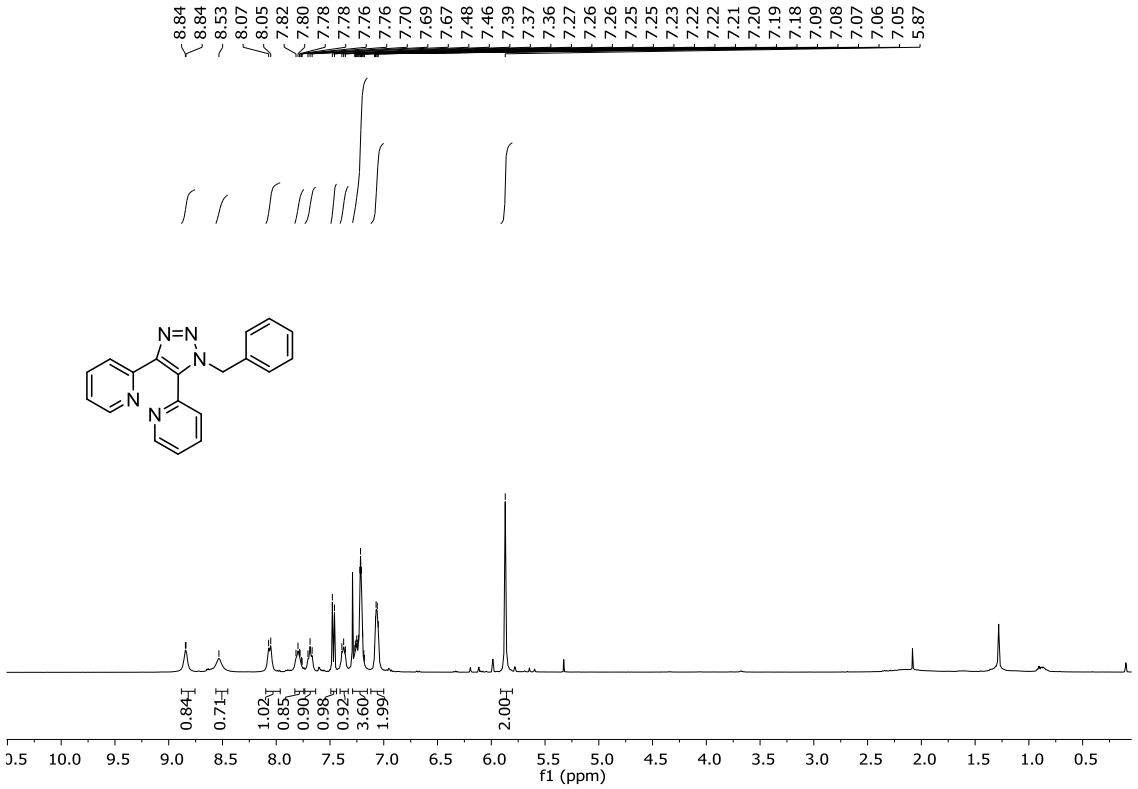
Spectrum 8.254. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32f**.



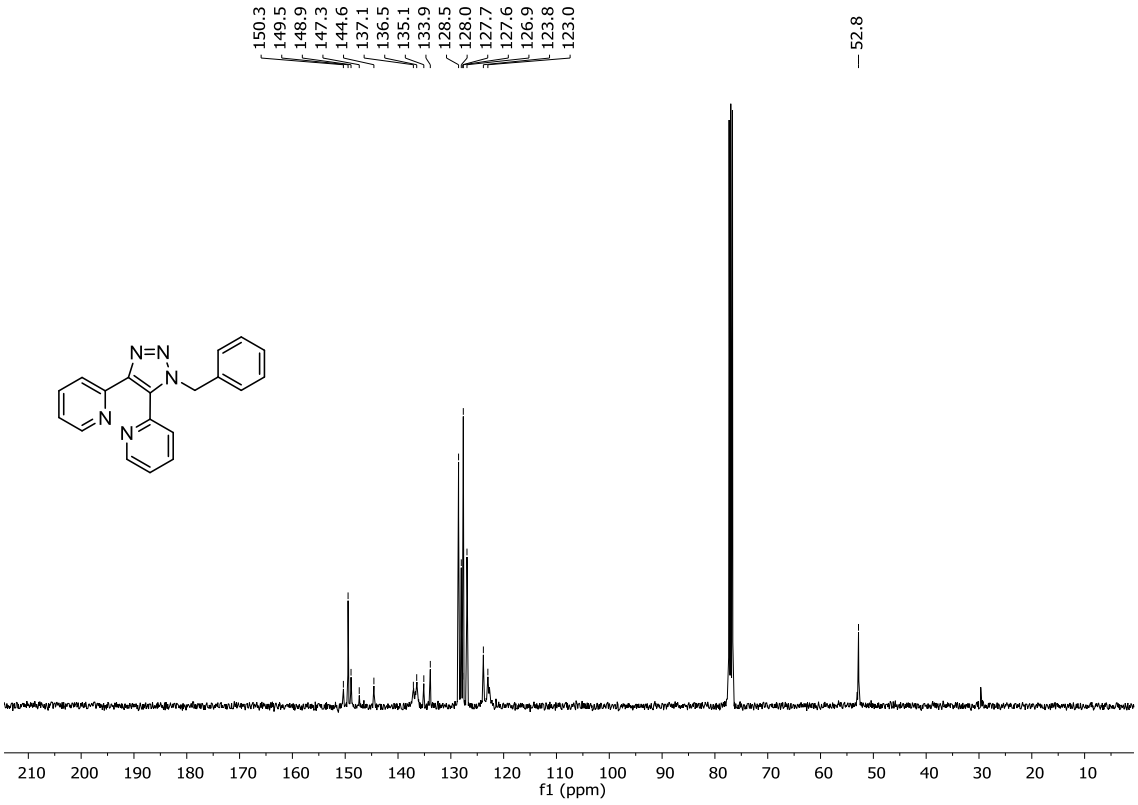
Spectrum 8.255. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **32g**.



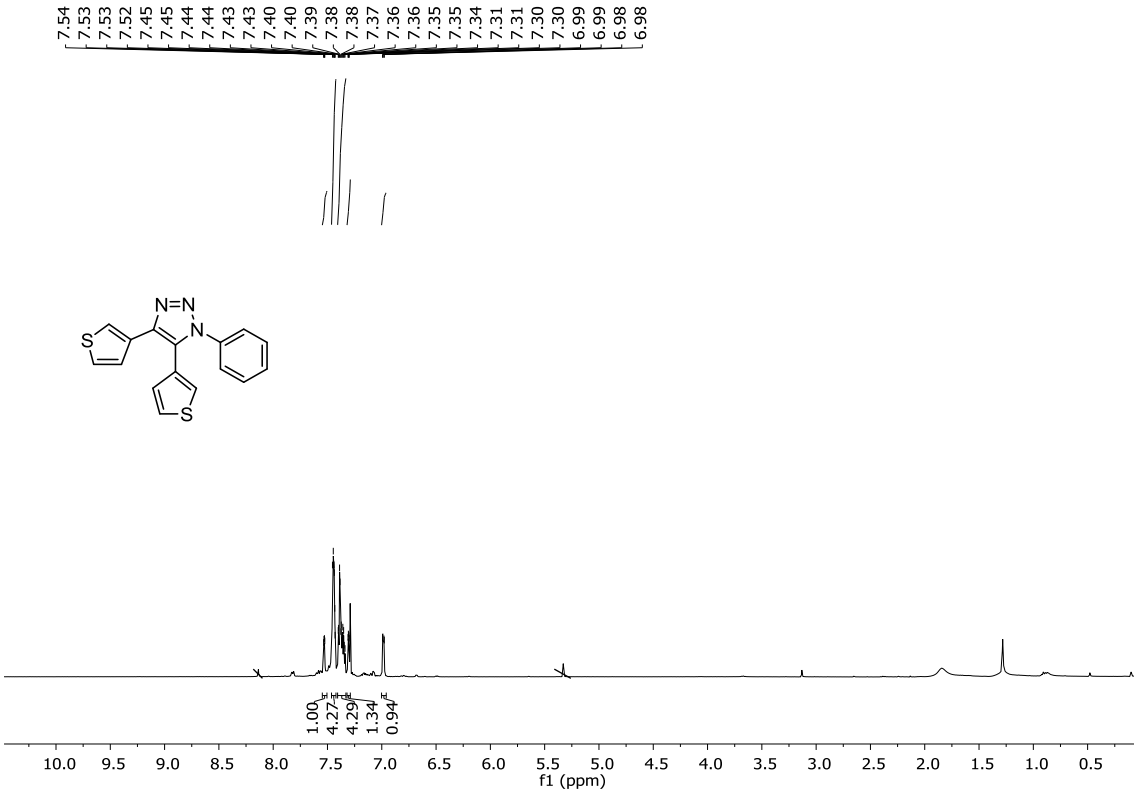
Spectrum 8.256. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **32g**.



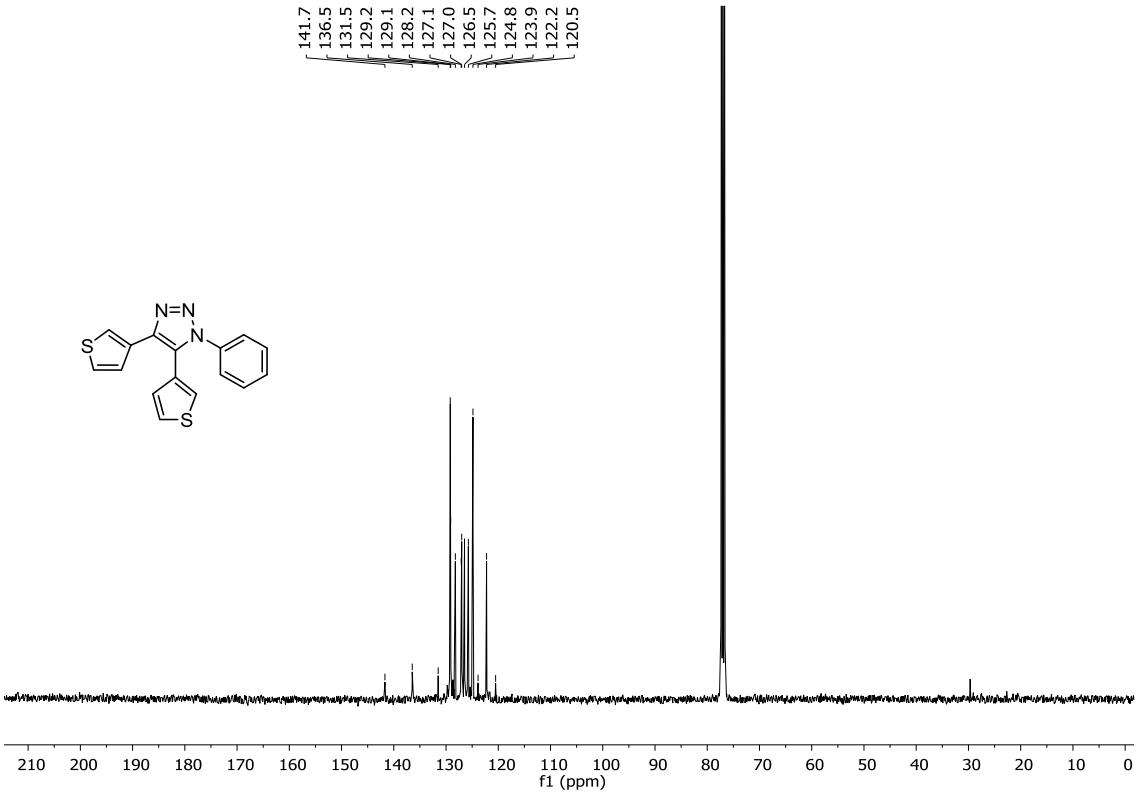
Spectrum 8.257. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **33b**.



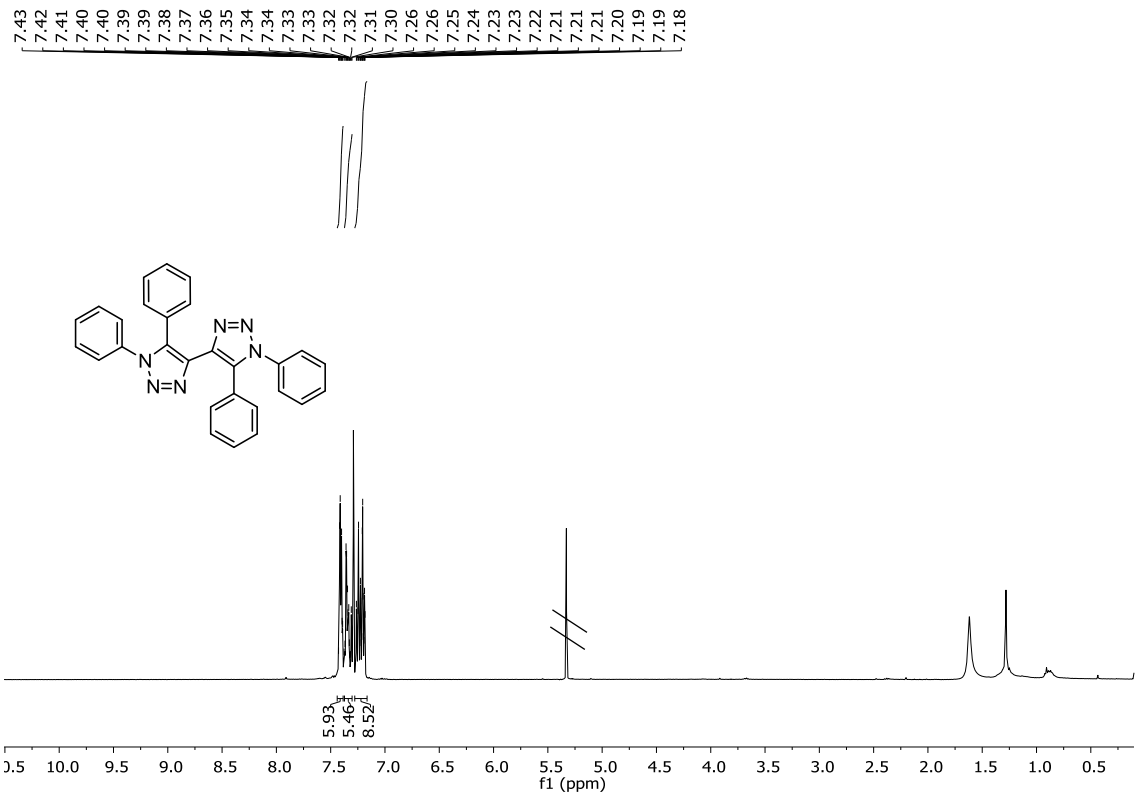
Spectrum 8.258. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **33b**.



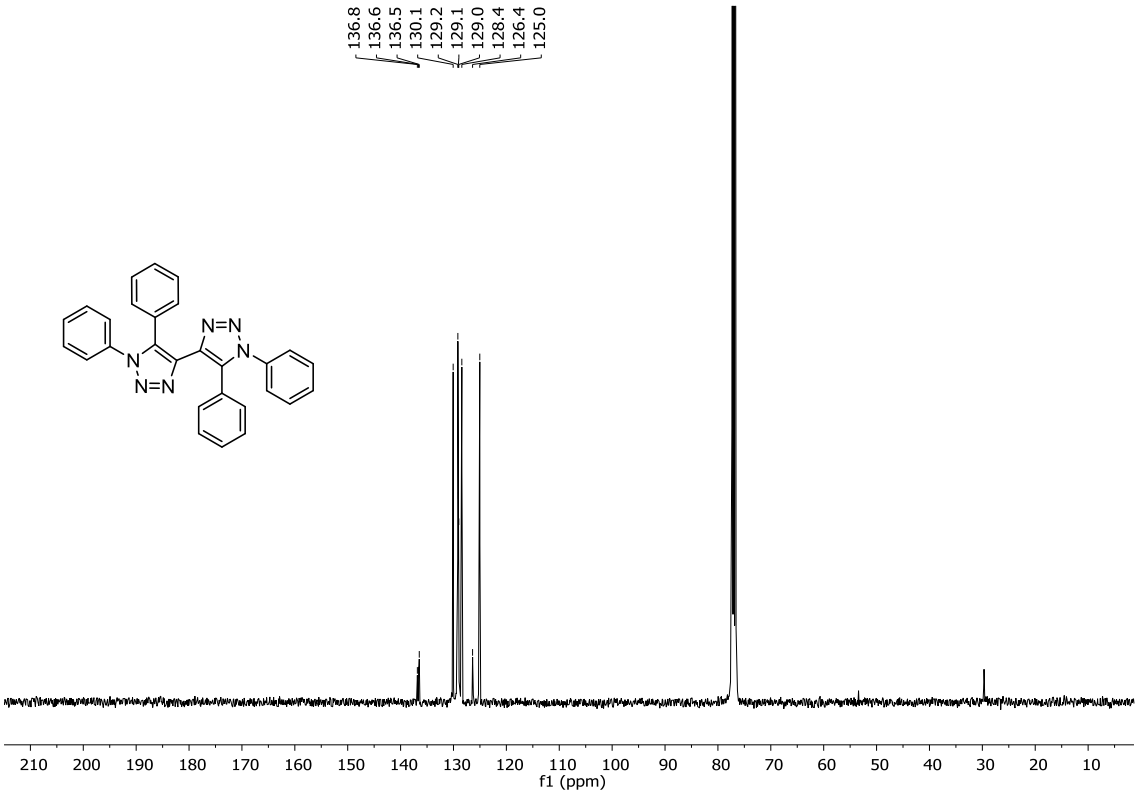
Spectrum 8.259. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **33c**.



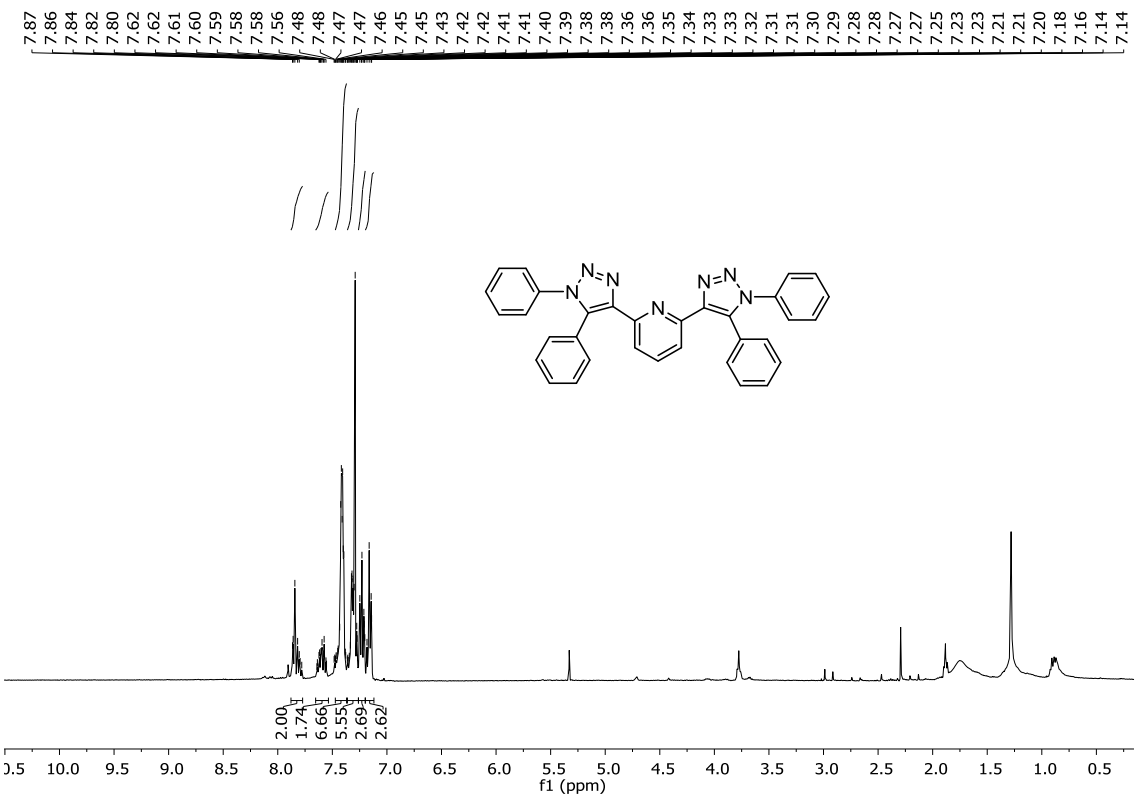
Spectrum 8.260. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **33c**.



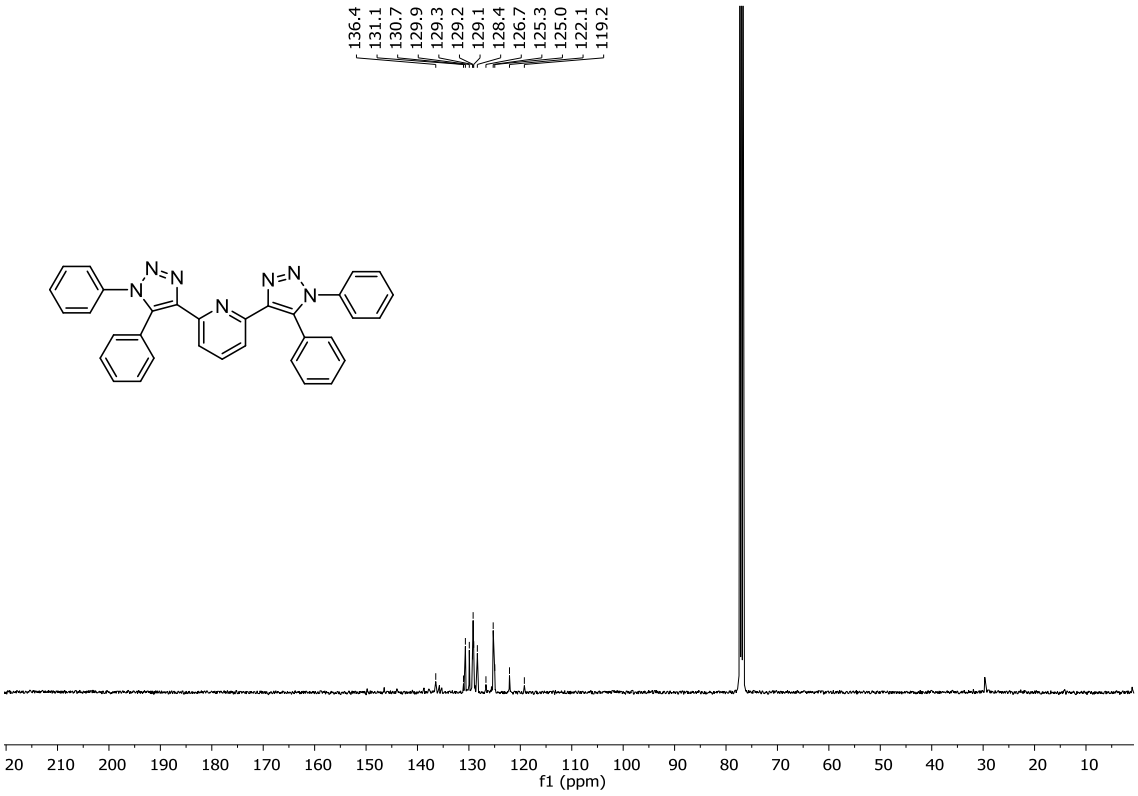
Spectrum 8.261. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **33d**.



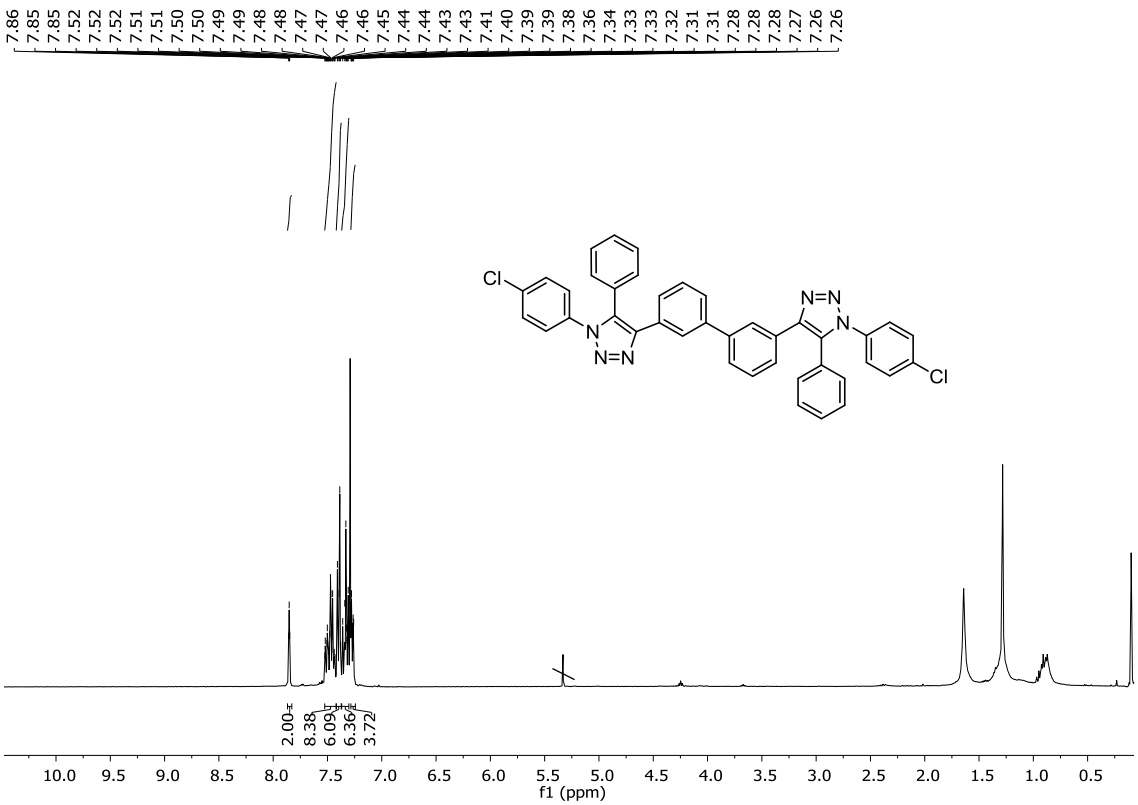
Spectrum 8.262. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **33d**.



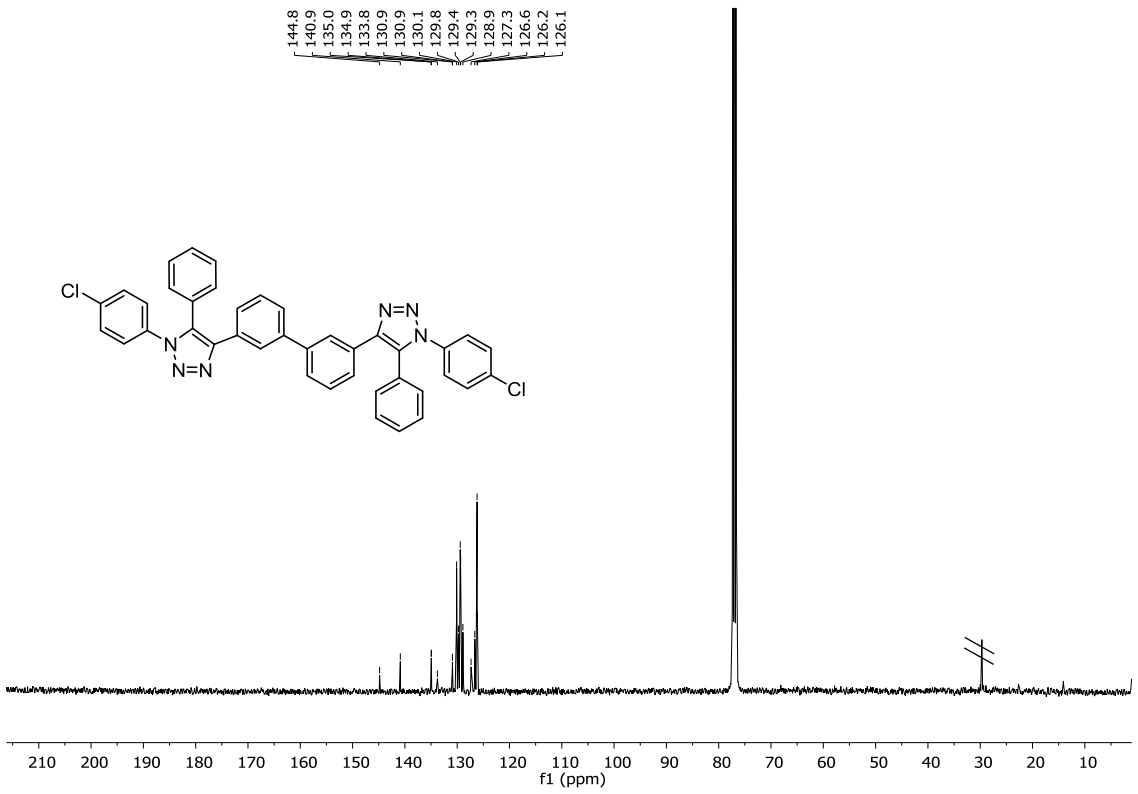
Spectrum 8.263. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **33e**.



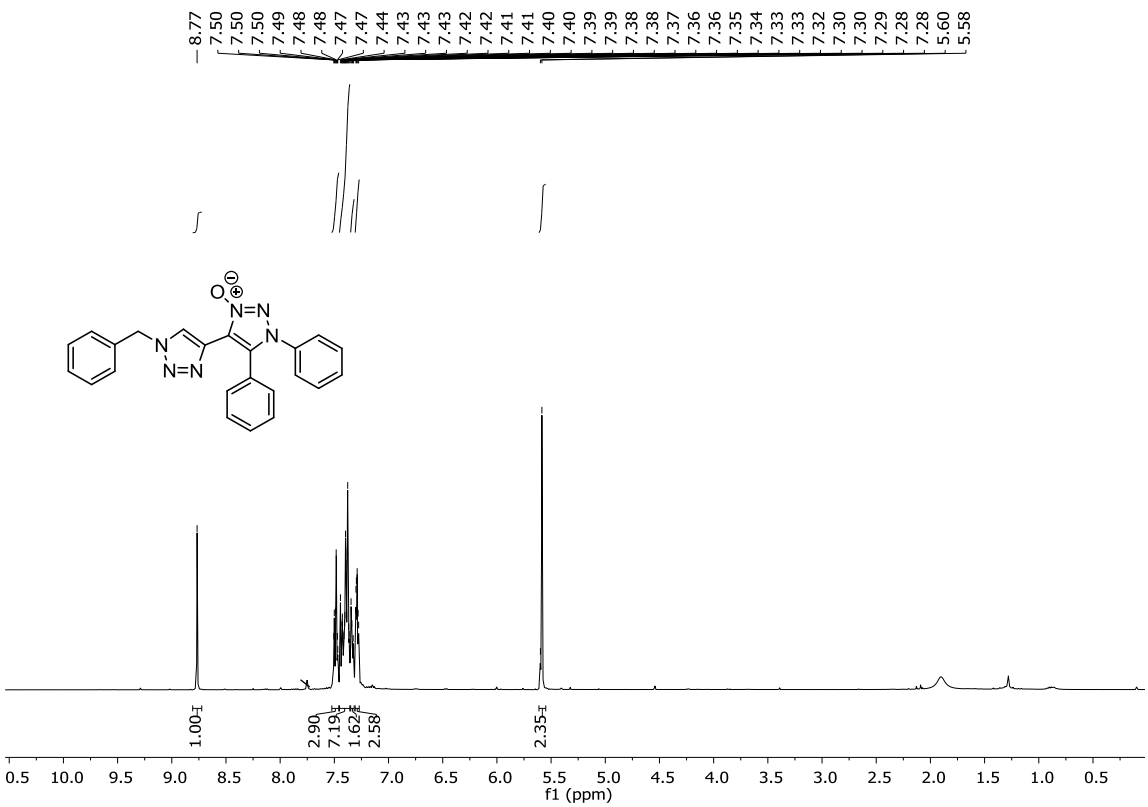
Spectrum 8.264. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **33e**.



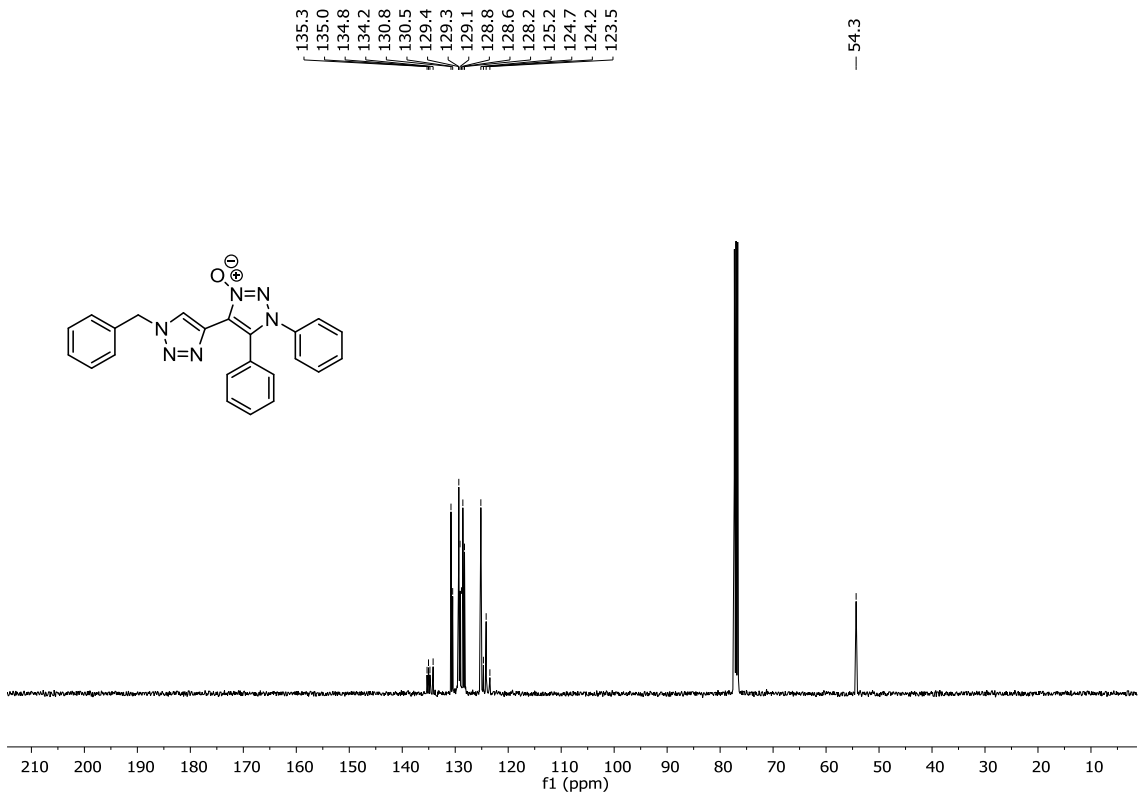
Spectrum 8.265. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **33f**.



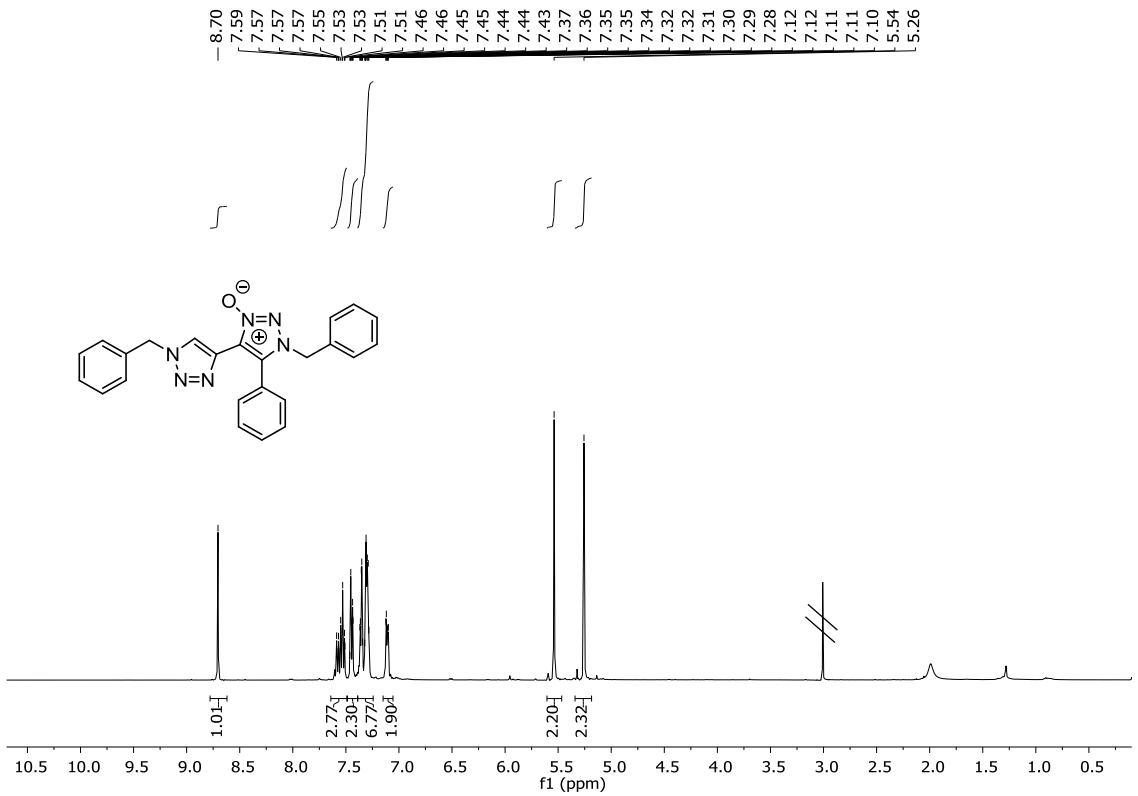
Spectrum 8.266. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **33f**.



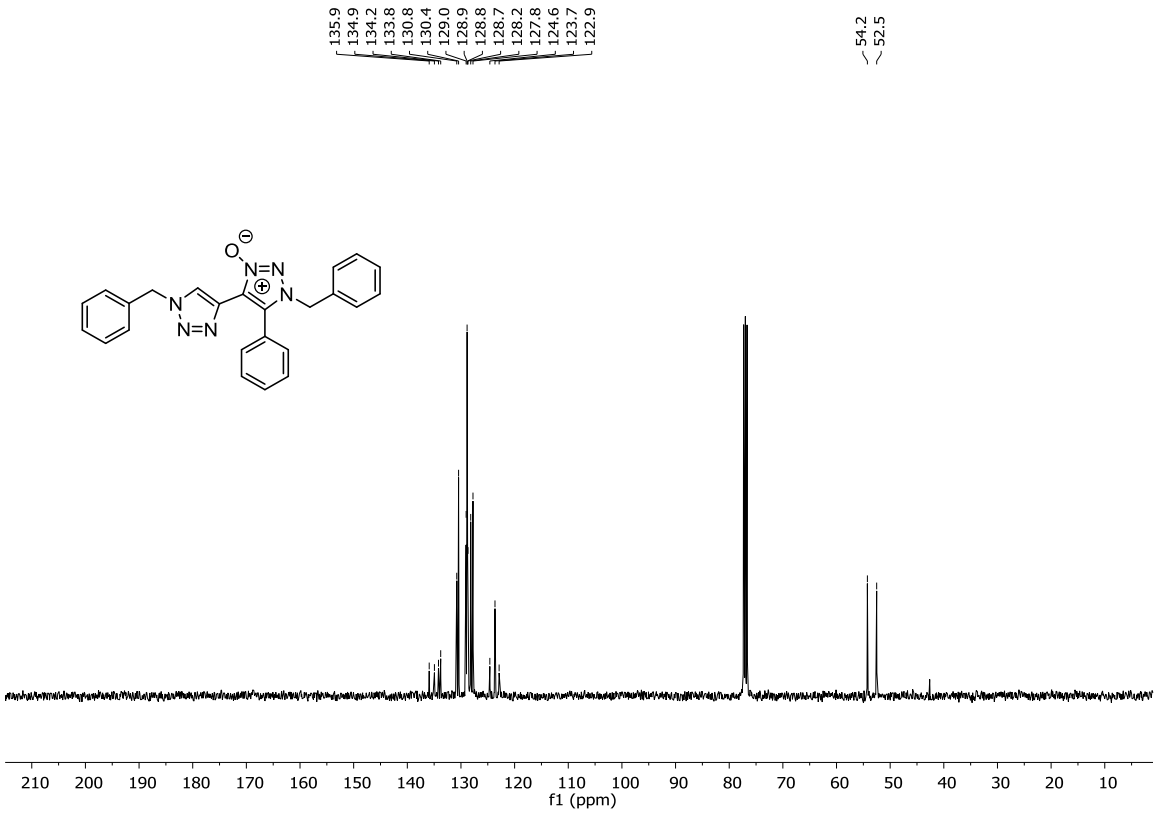
Spectrum 8.267. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34a**.



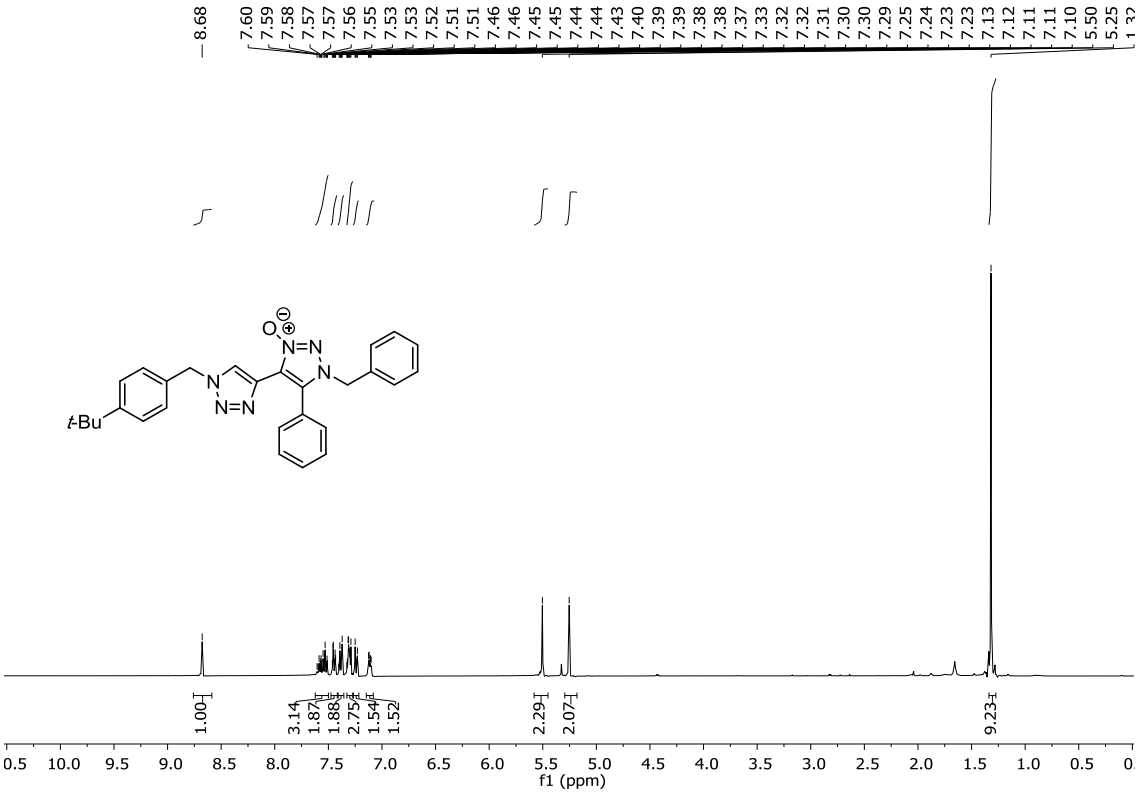
Spectrum 8.268. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34a**.



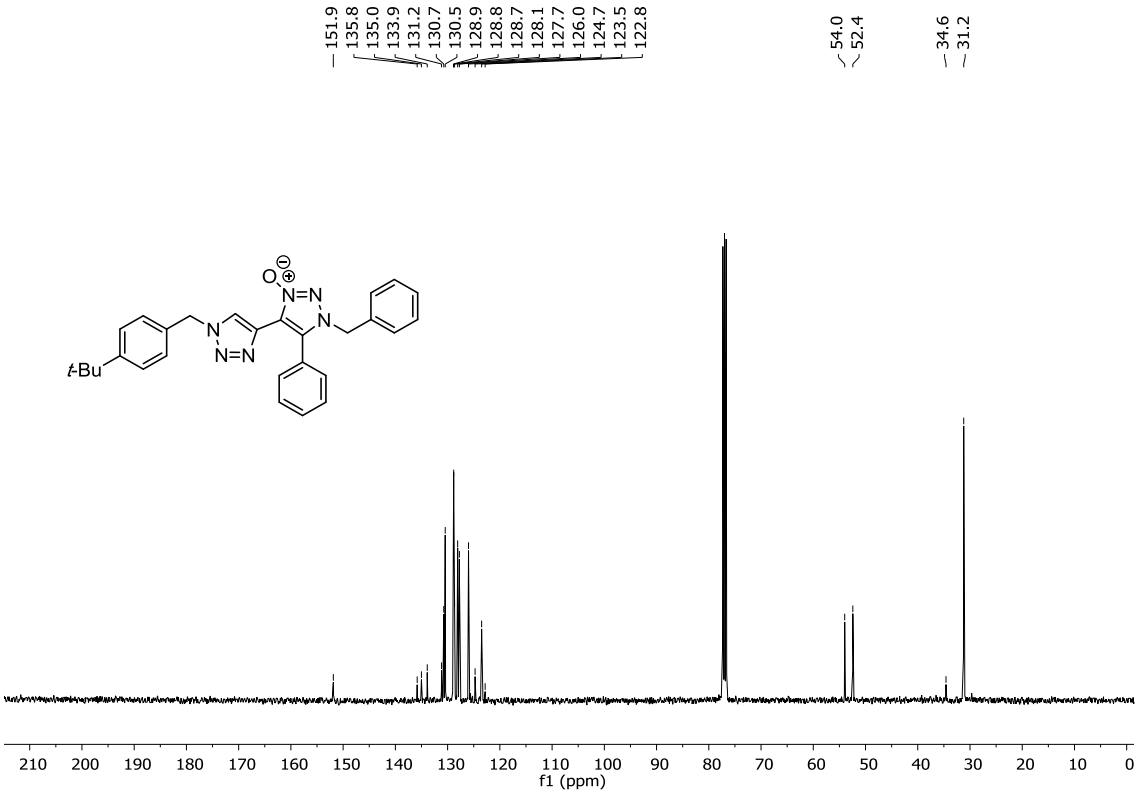
Spectrum 8.269. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34b**.



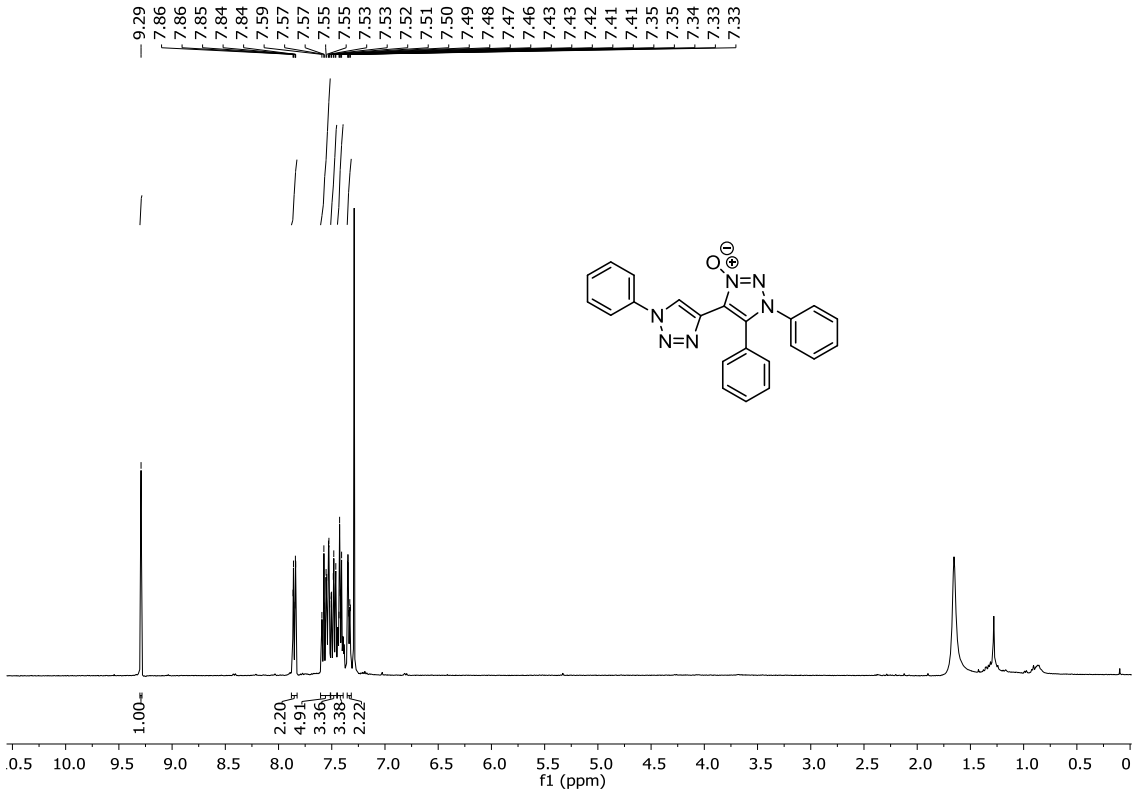
Spectrum 8.270. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34b**.



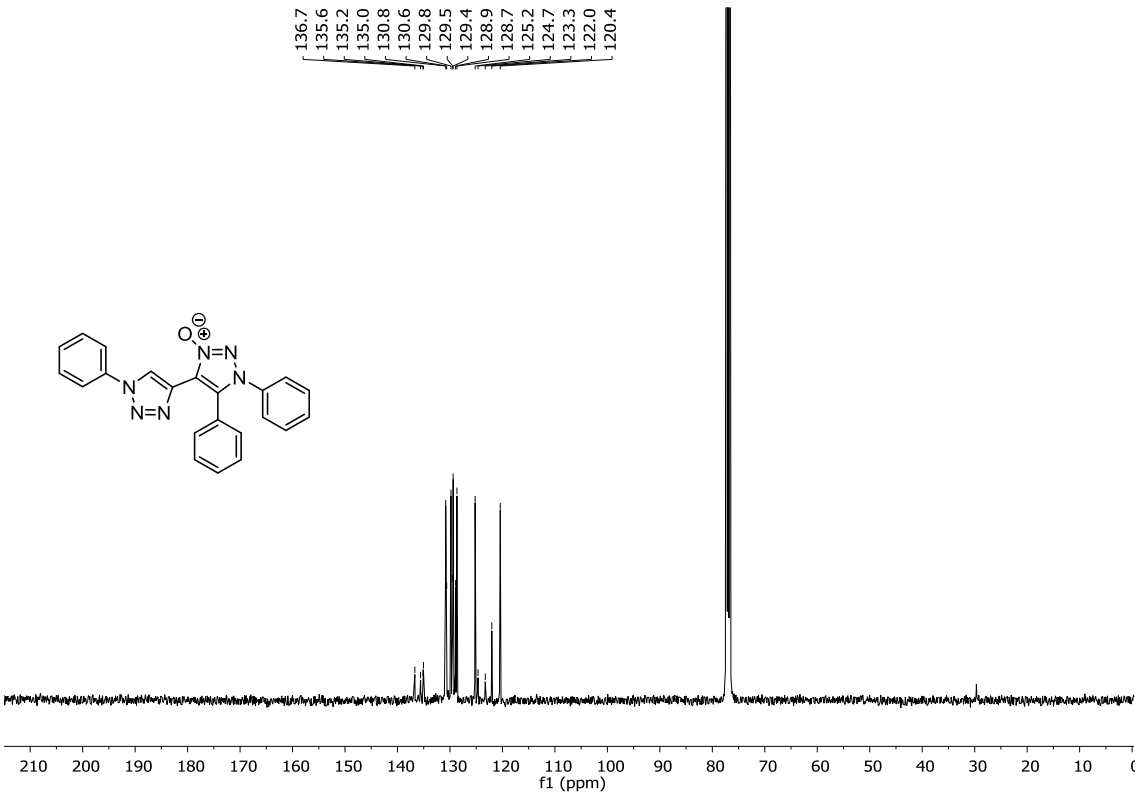
Spectrum 8.271. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34c**.



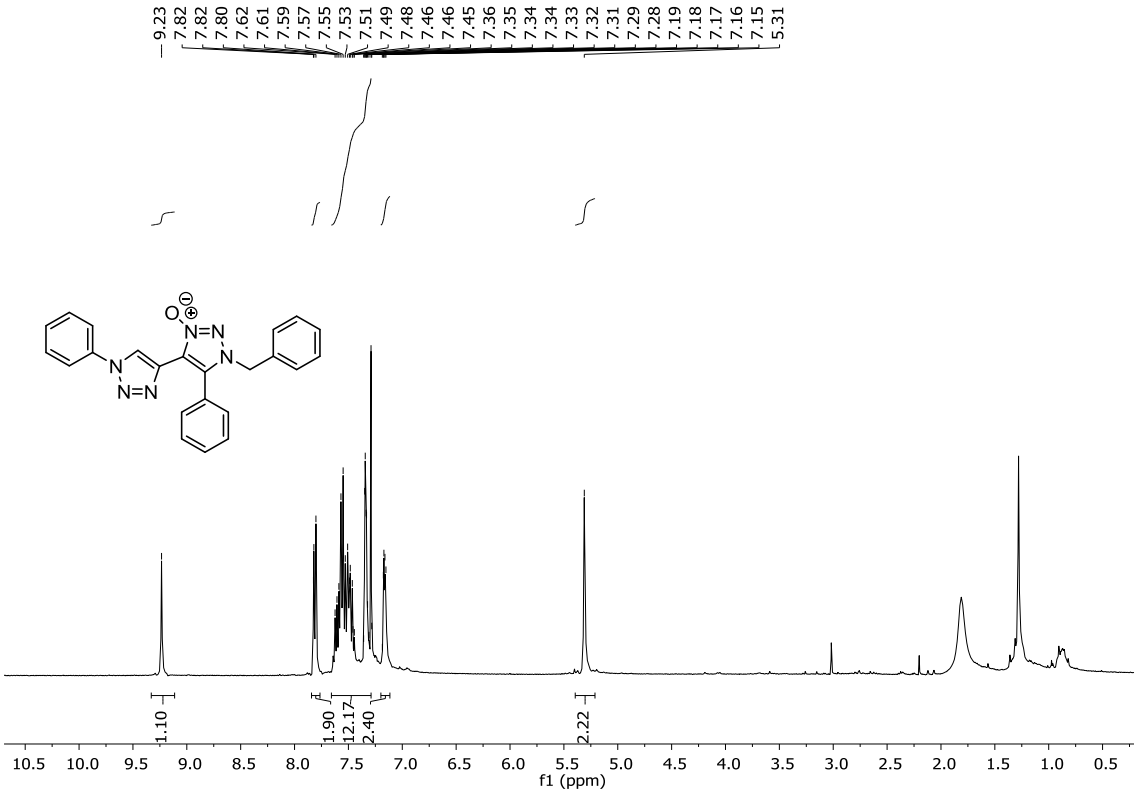
Spectrum 8.272. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34c**.



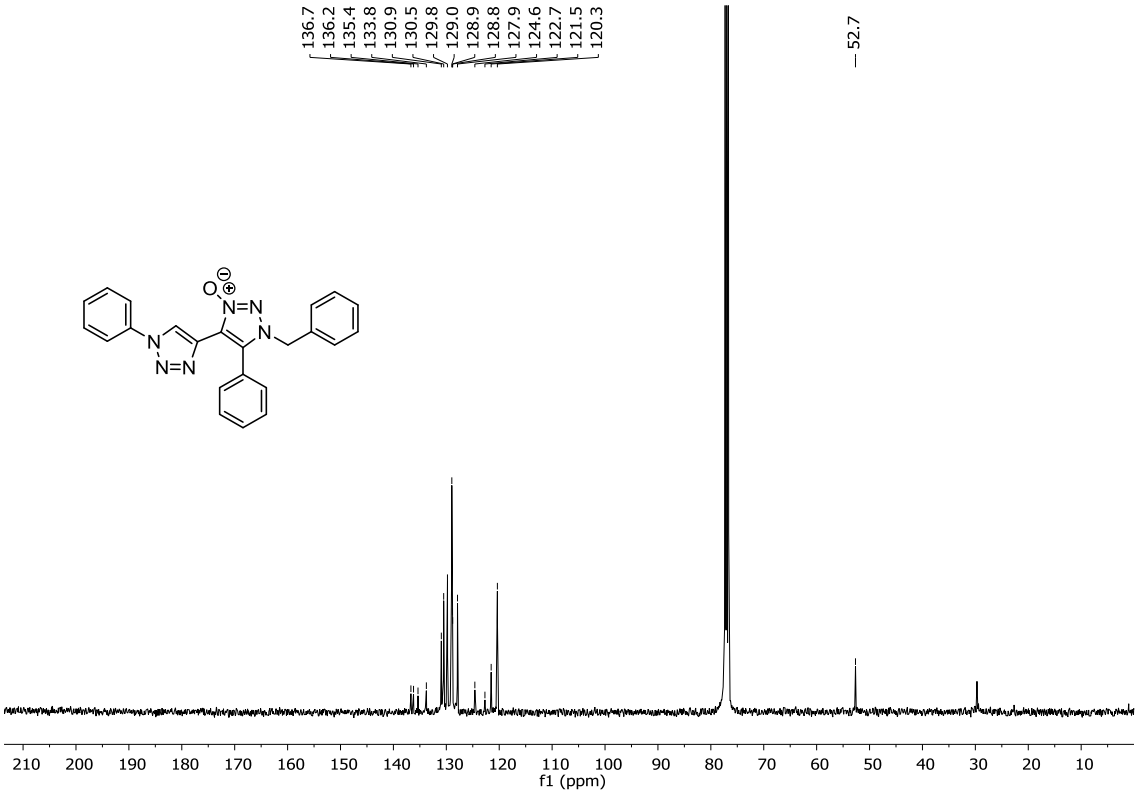
Spectrum 8.273. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34d**.



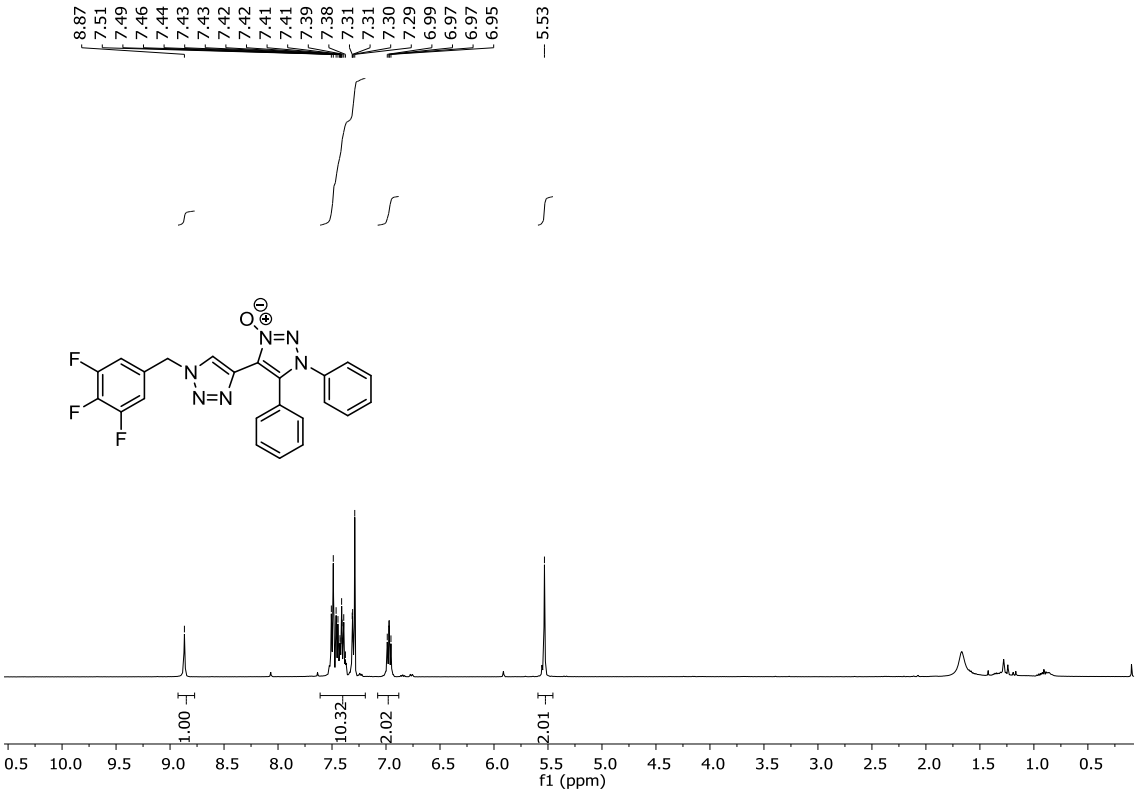
Spectrum 8.274. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34d**.



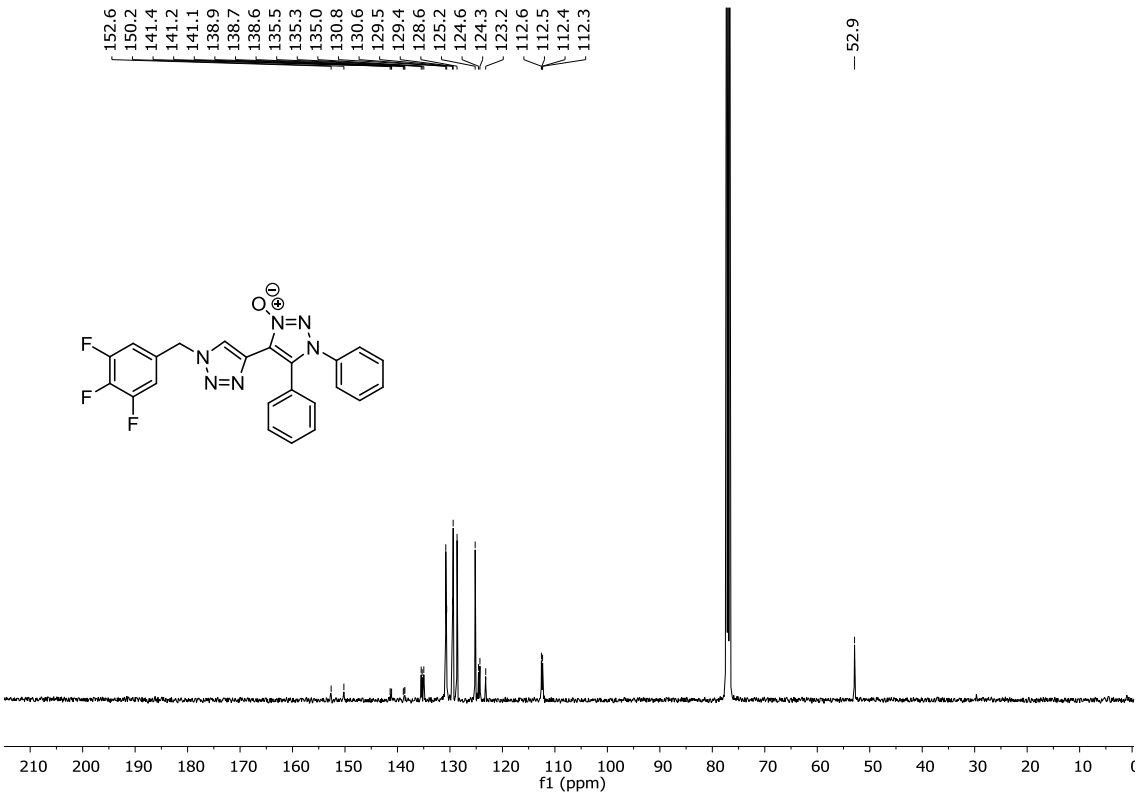
Spectrum 8.275. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34e**.



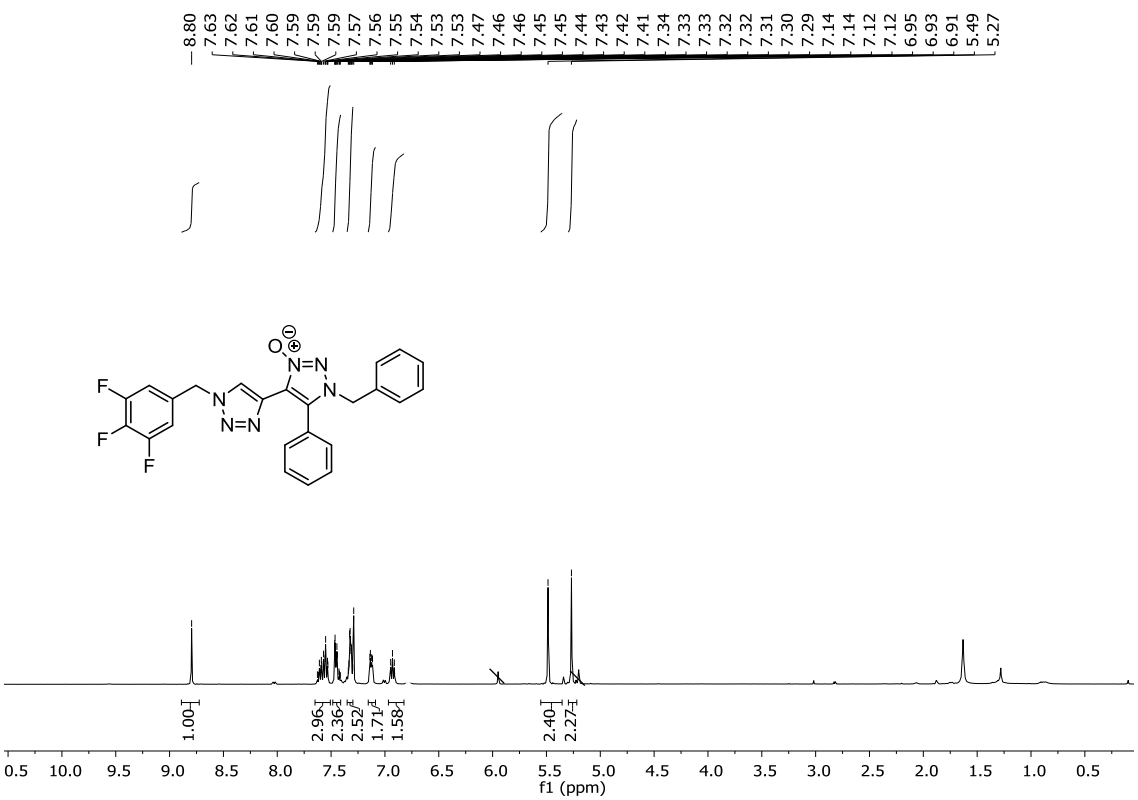
Spectrum 8.276. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34e**.



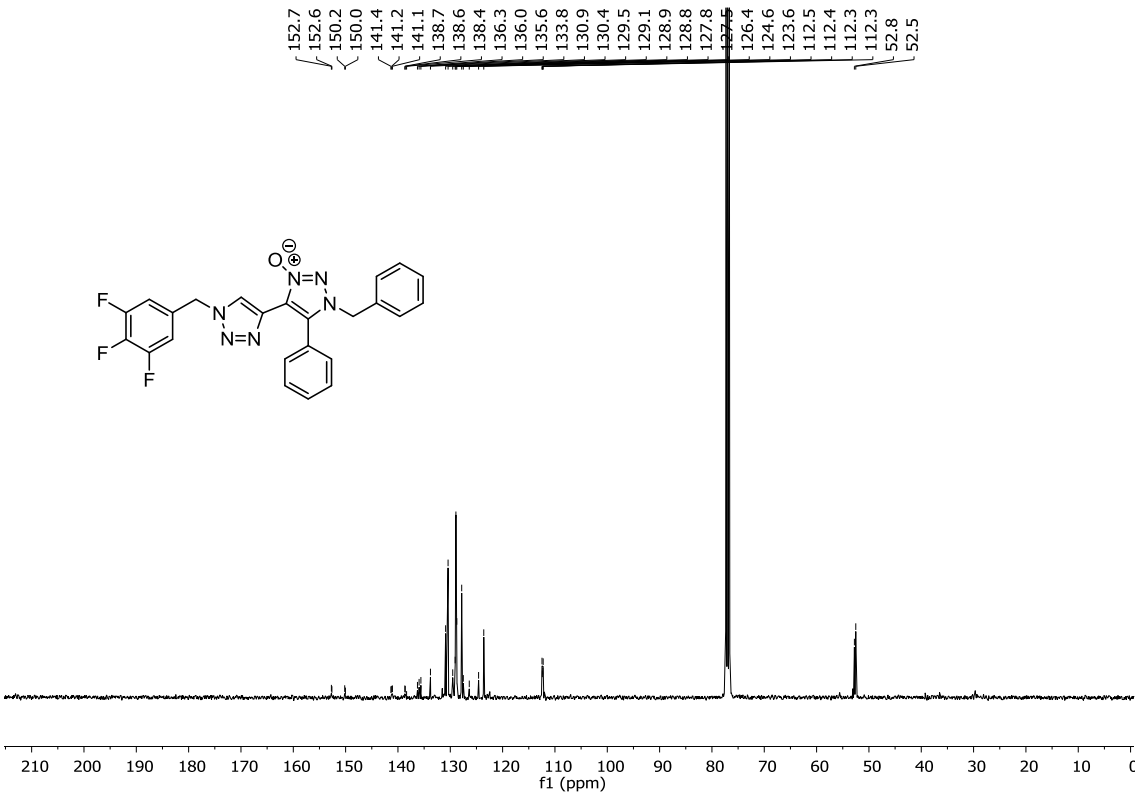
Spectrum 8.277. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34f**.



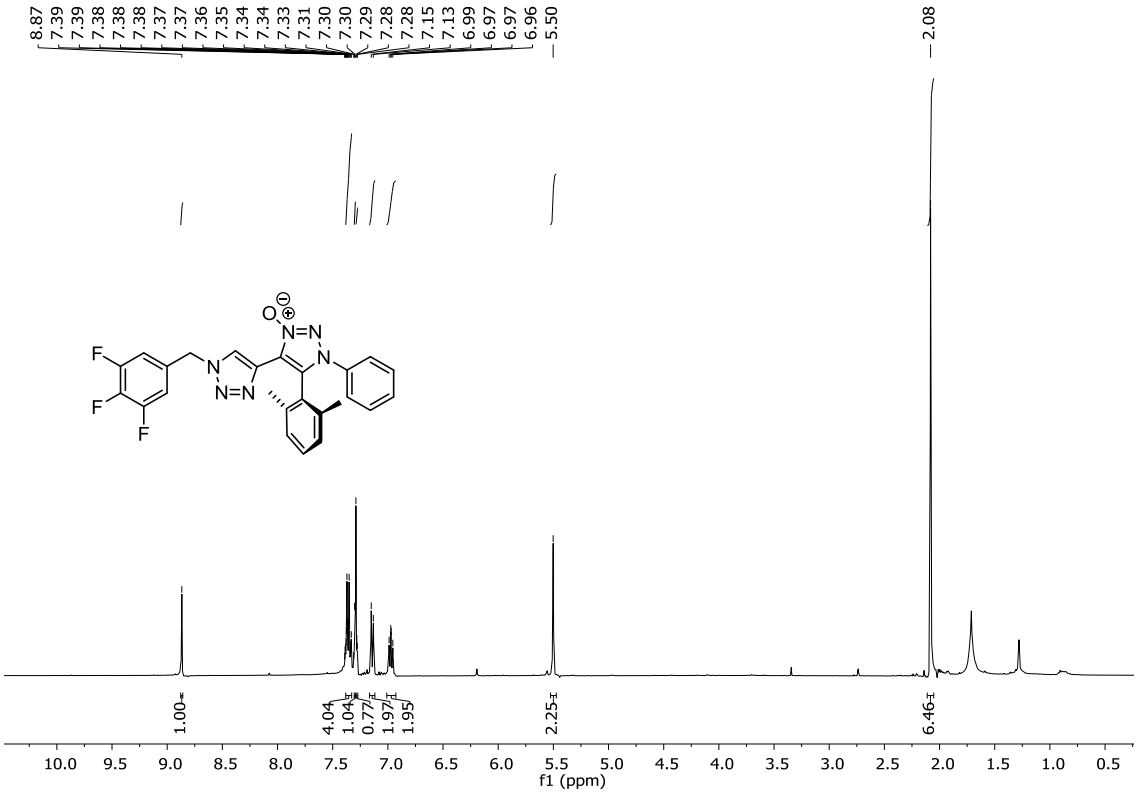
Spectrum 8.278. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34f**.



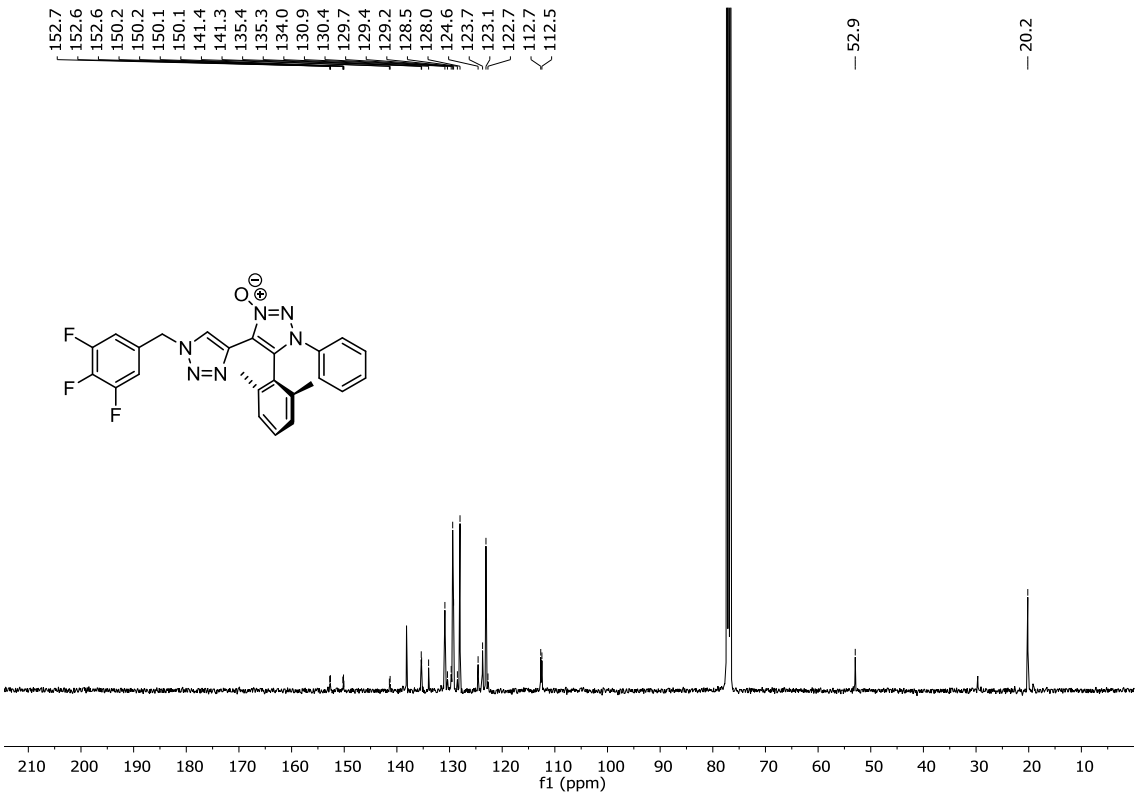
Spectrum 8.279. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34g**.



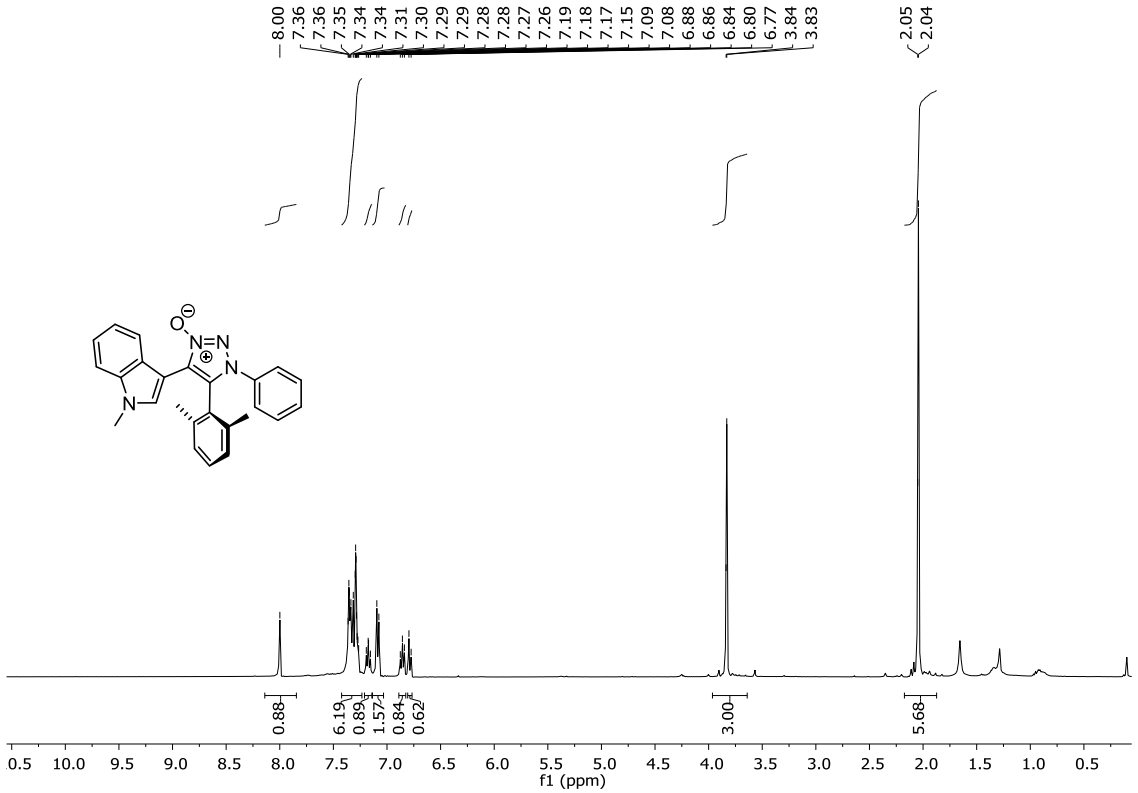
Spectrum 8.280. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34g**.



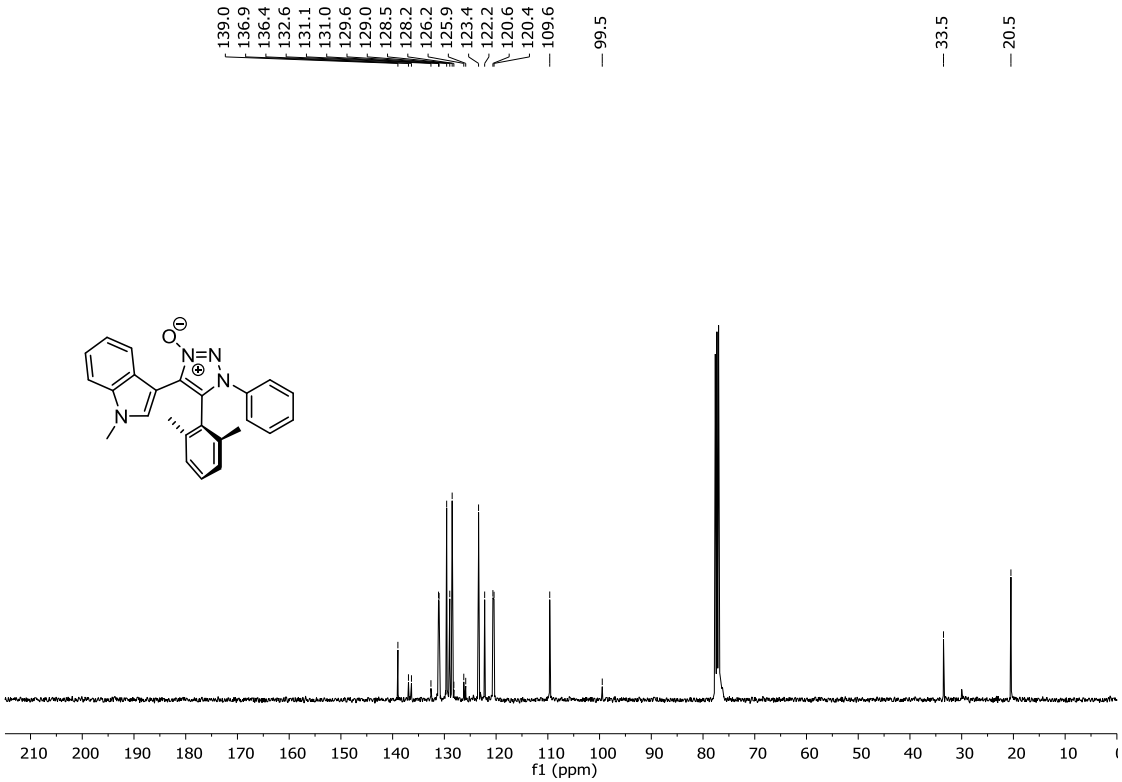
Spectrum 8.281. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **34h**.



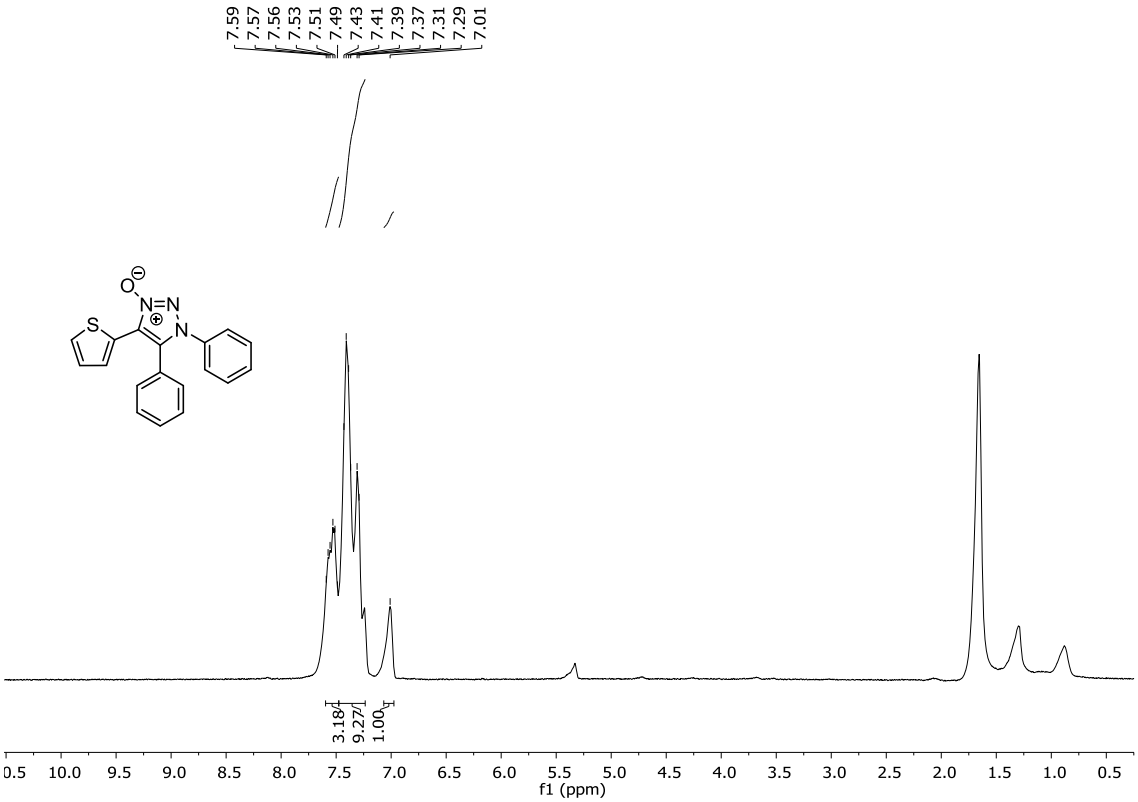
Spectrum 8.282. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **34h**.



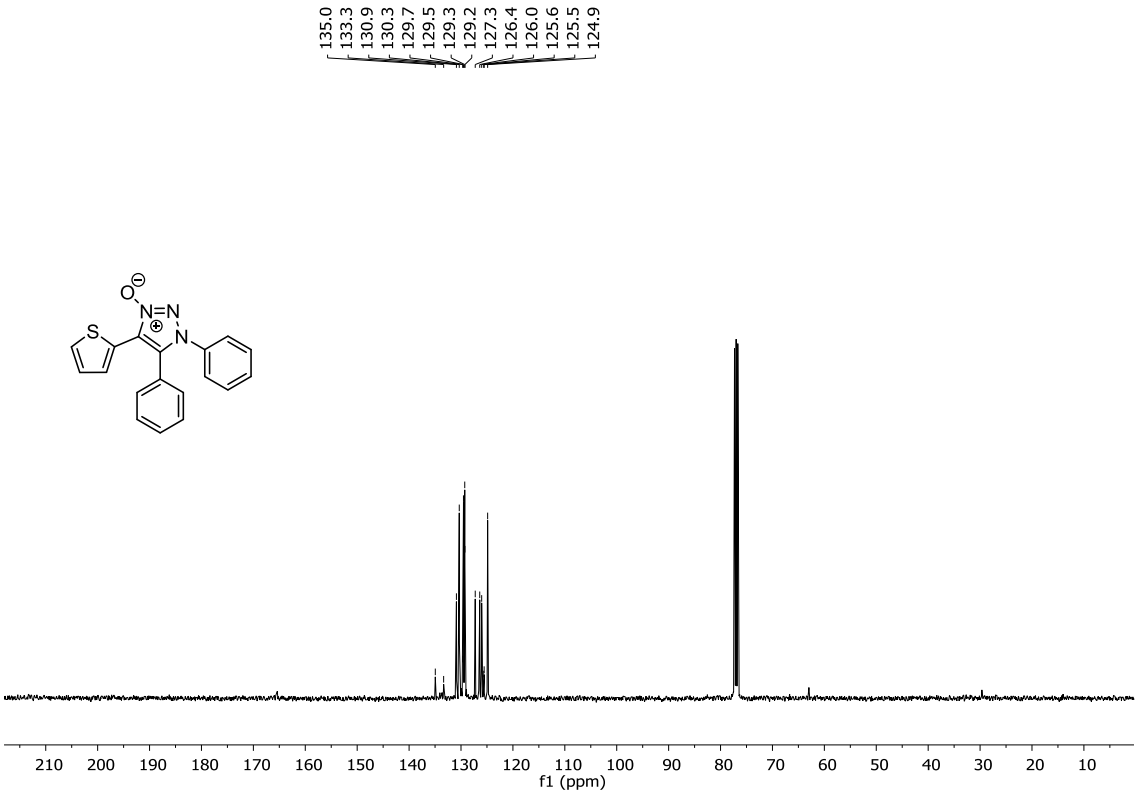
Spectrum 8.283. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36a**.



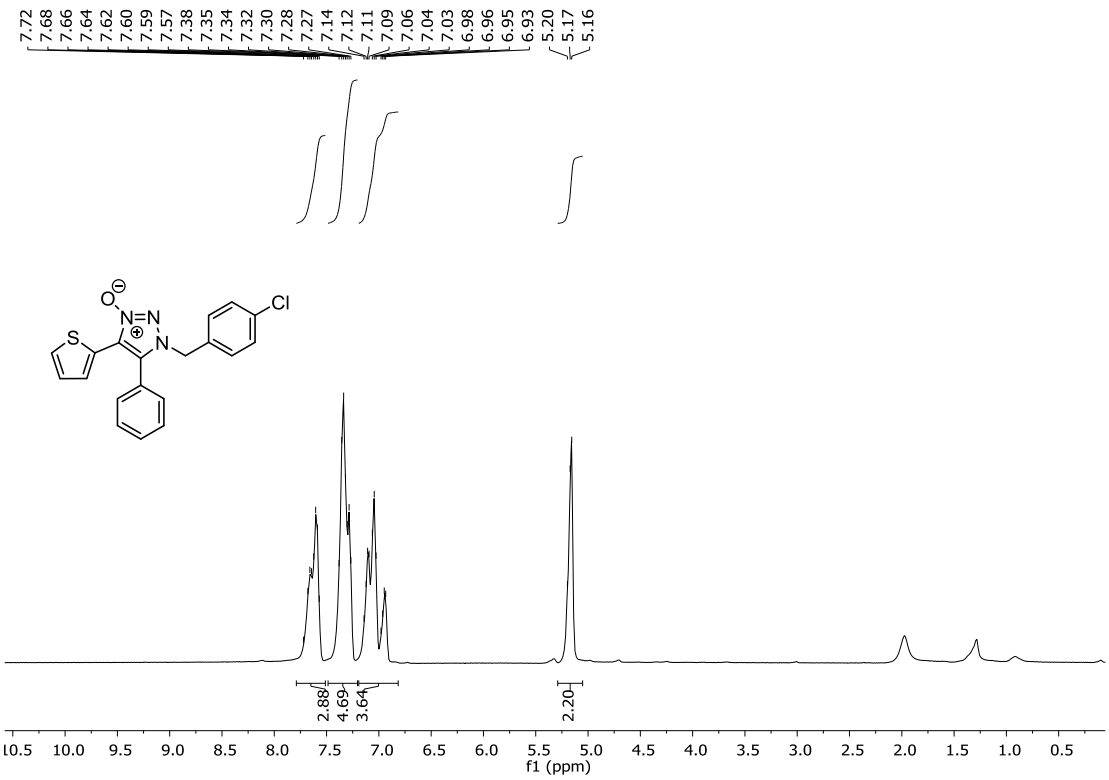
Spectrum 8.284. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36a**.



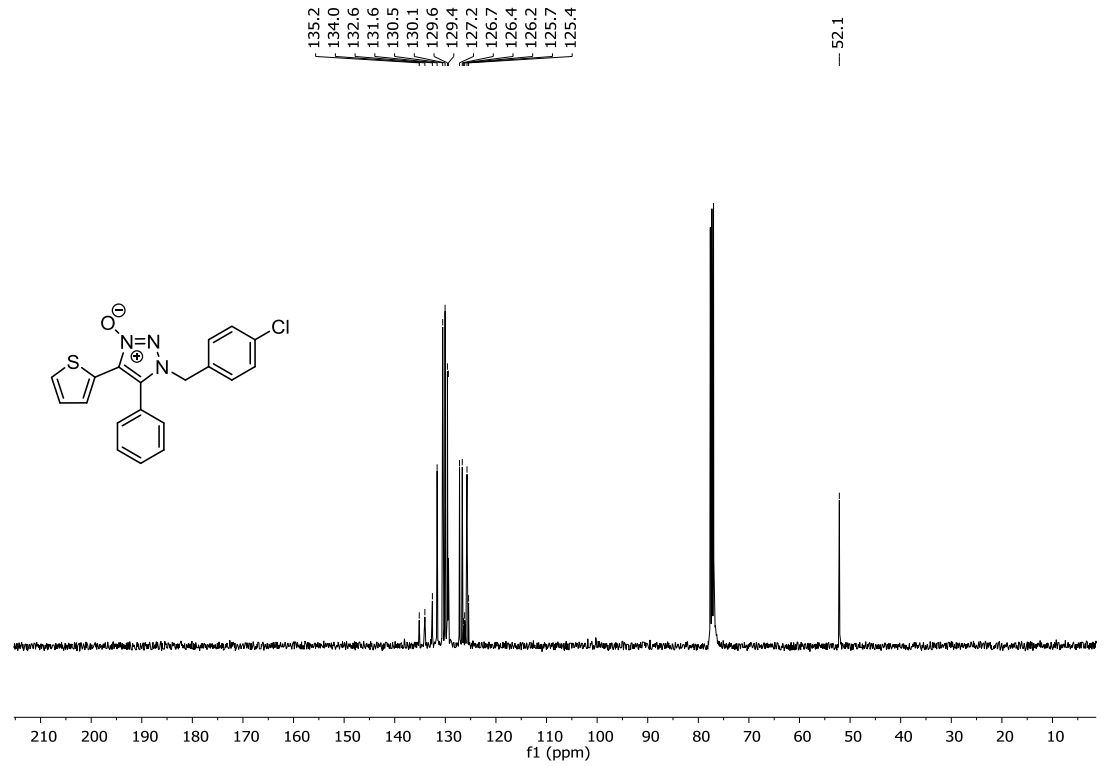
Spectrum 8.285. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36b**.



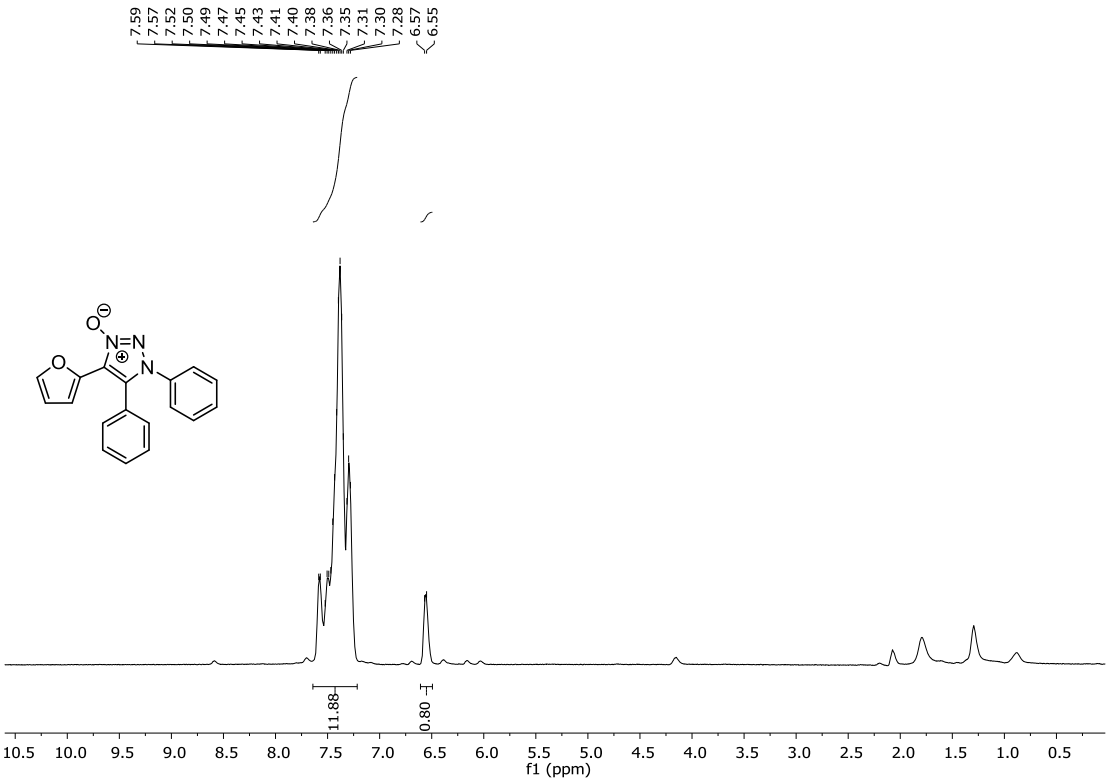
Spectrum 8.286. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36b**.



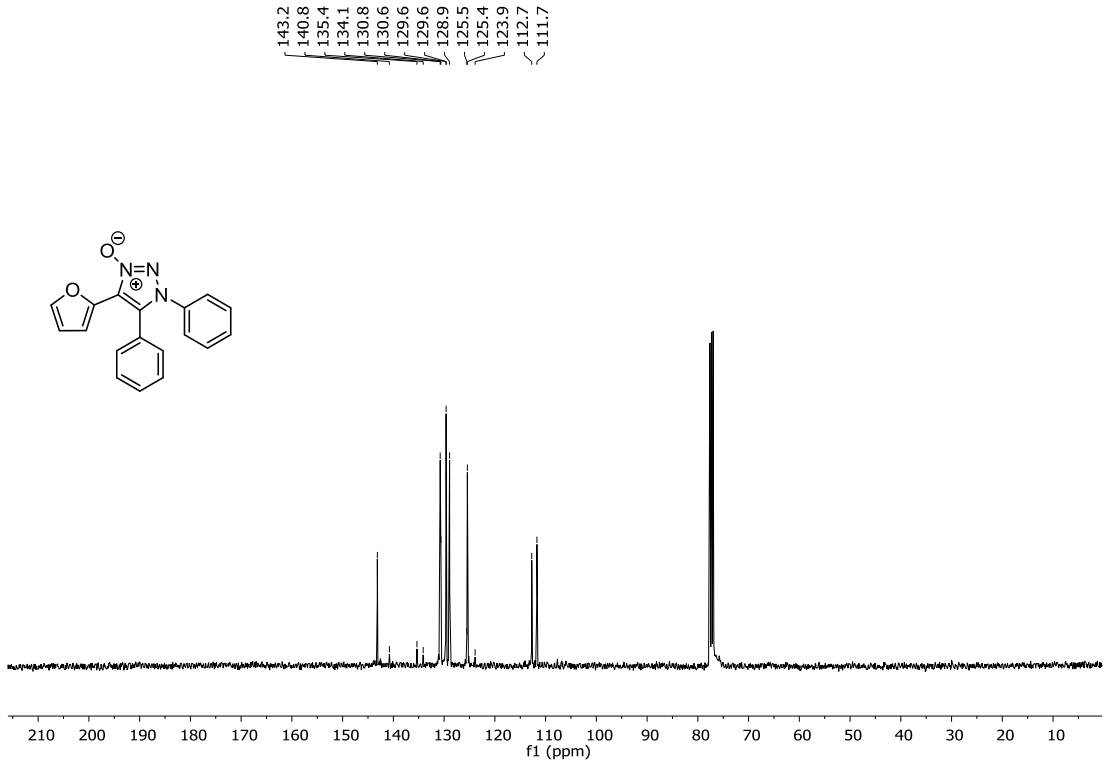
Spectrum 8.287. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36c**.



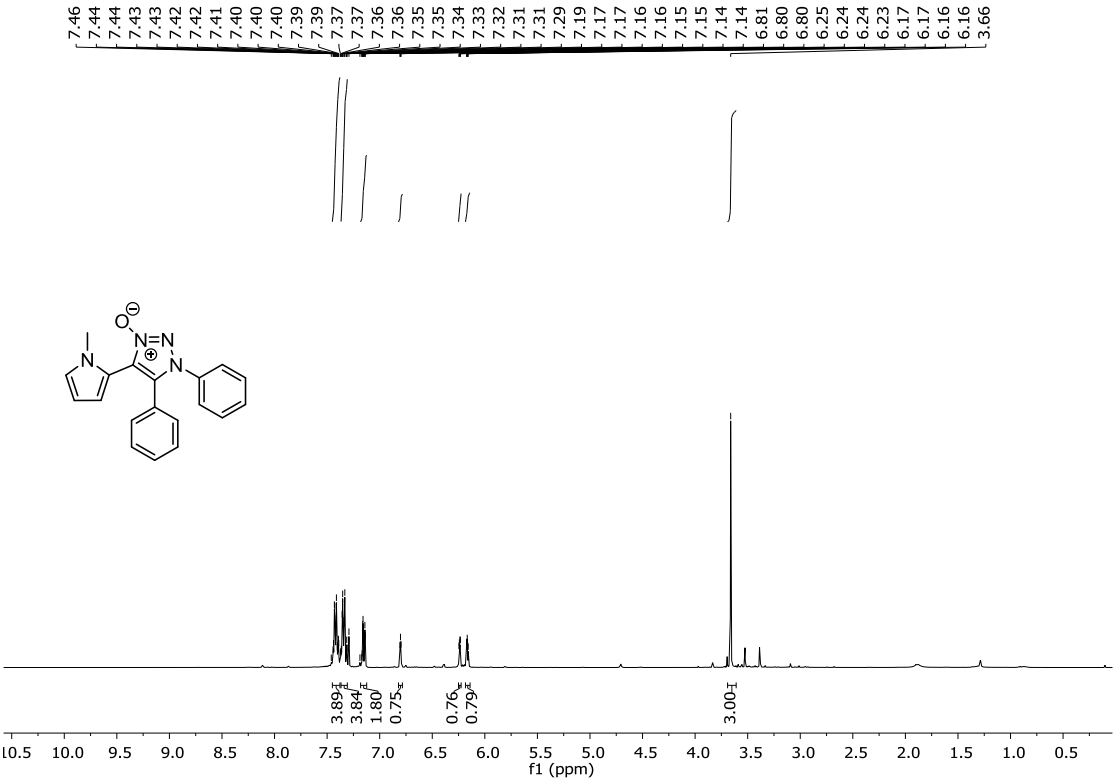
Spectrum 8.288. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36c**.



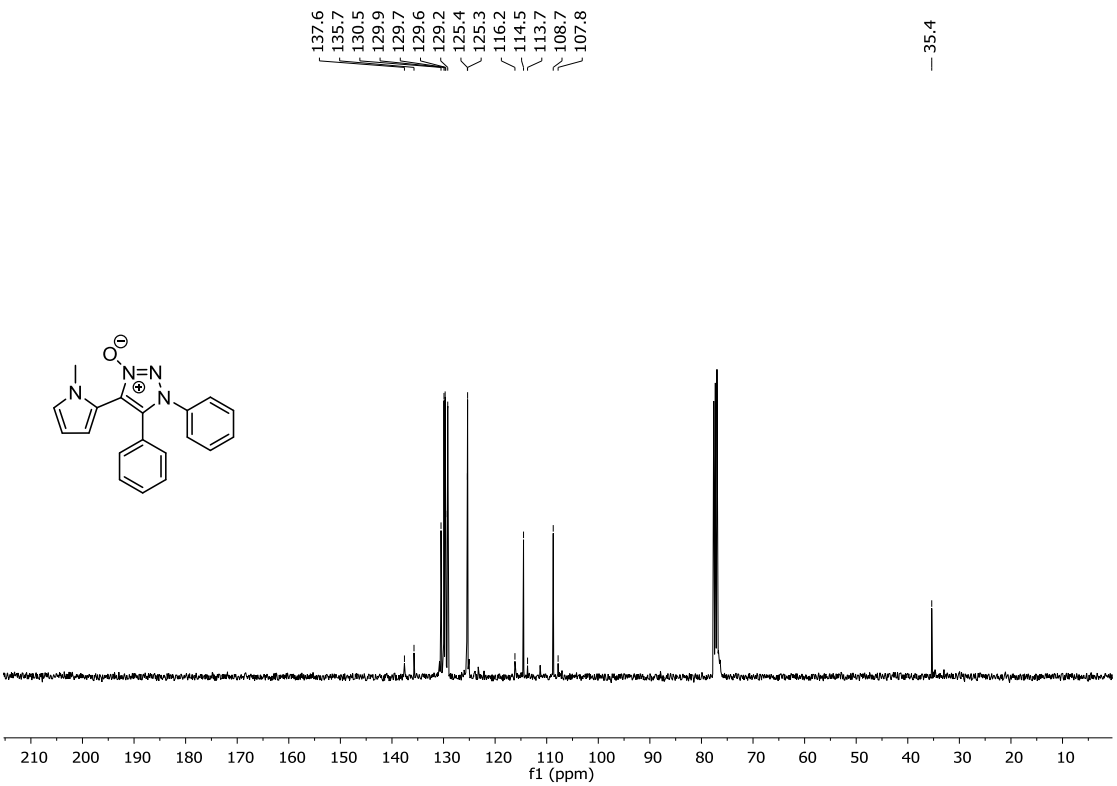
Spectrum 8.289. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36d**.



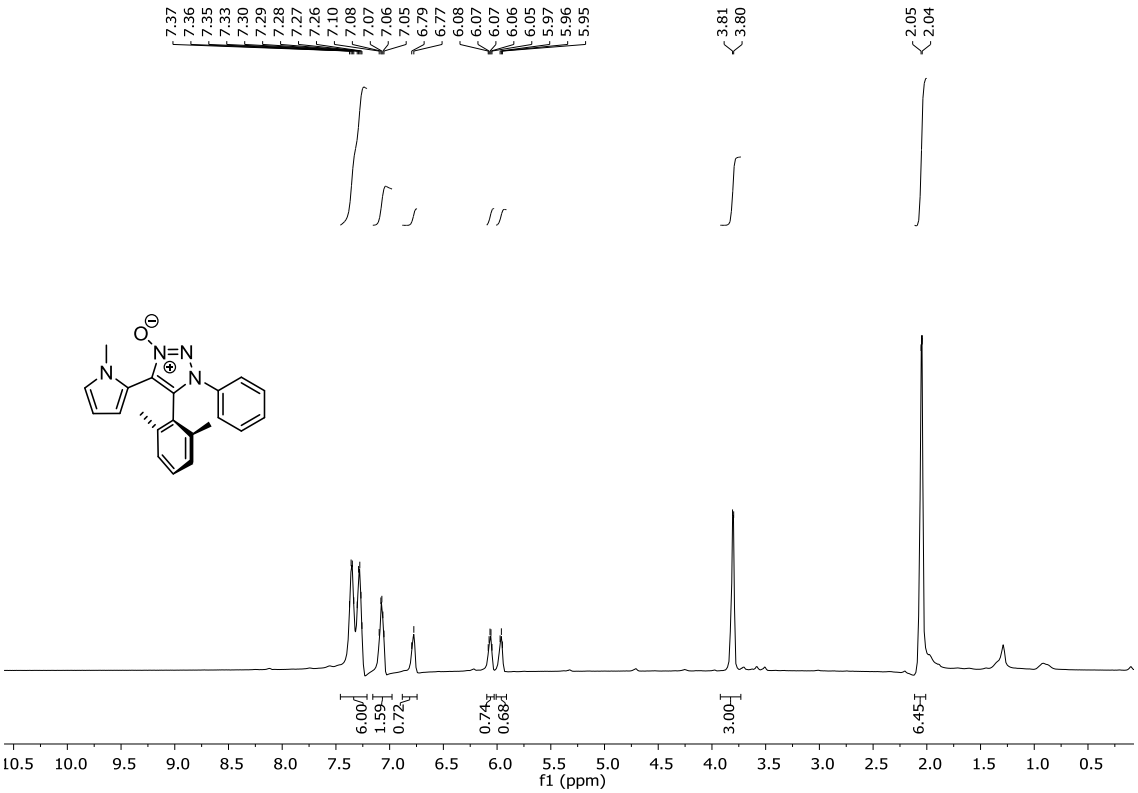
Spectrum 8.290. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36d**.



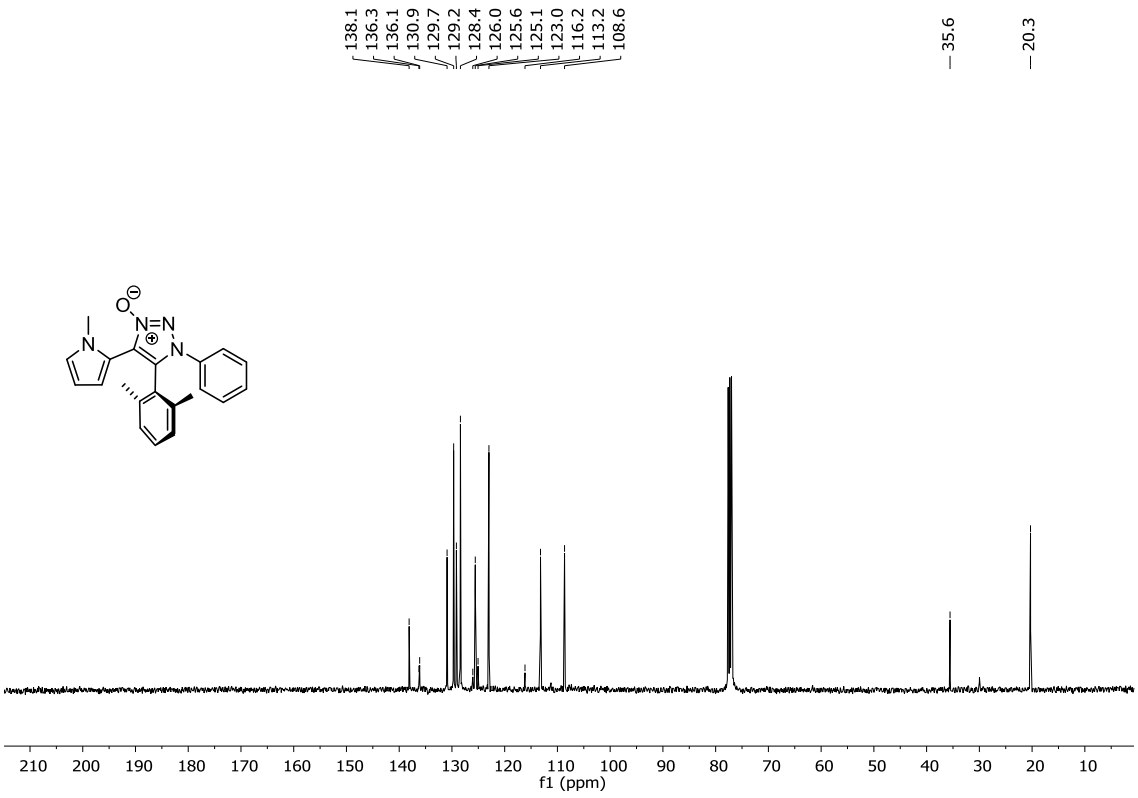
Spectrum 8.291. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36e**.



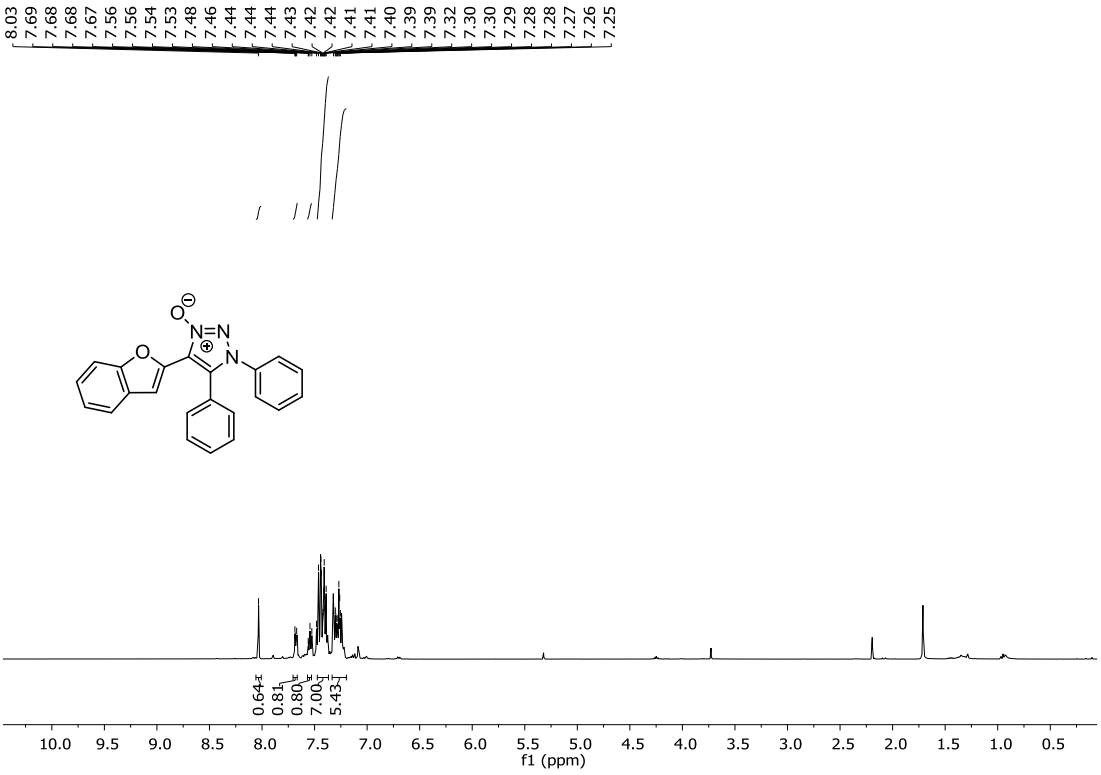
Spectrum 8.292. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36e**.



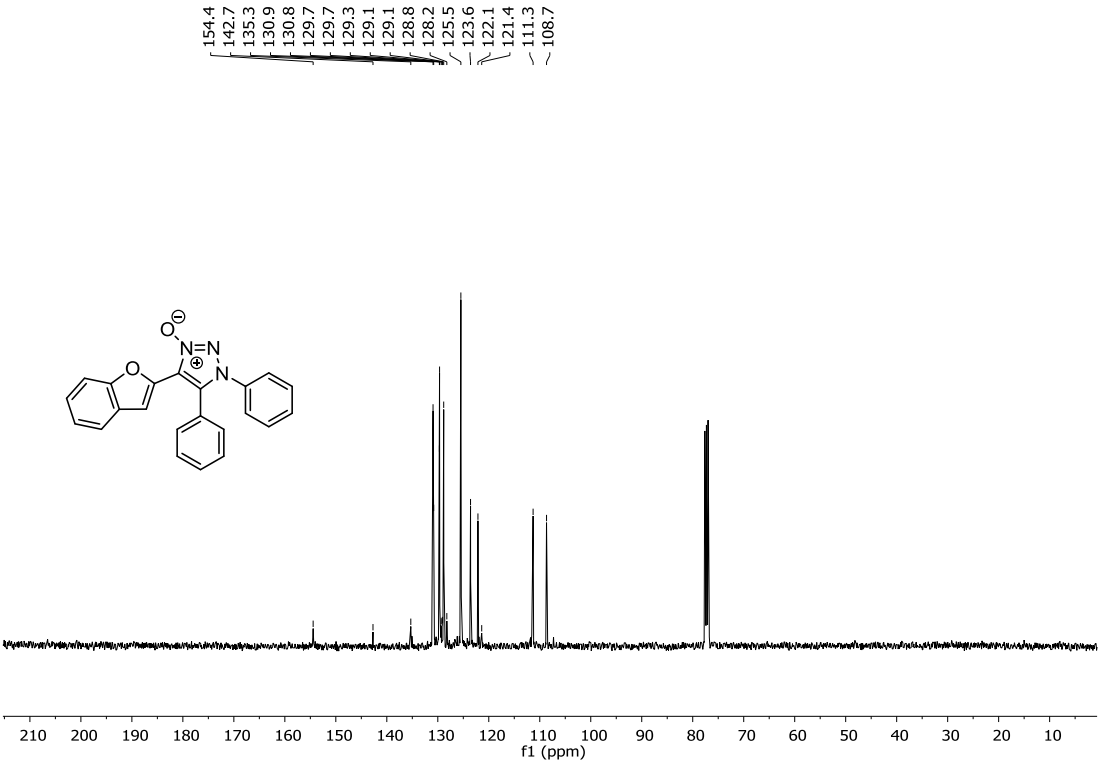
Spectrum 8.293. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36f**.



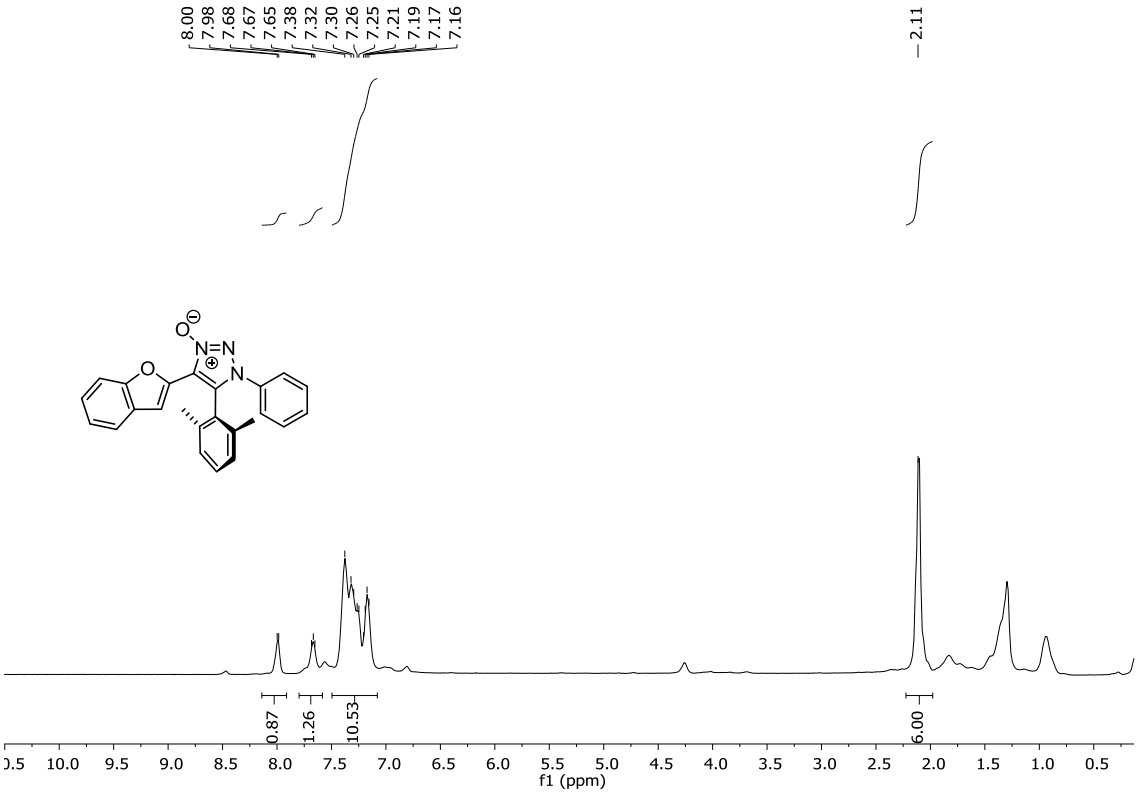
Spectrum 8.294. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36f**.



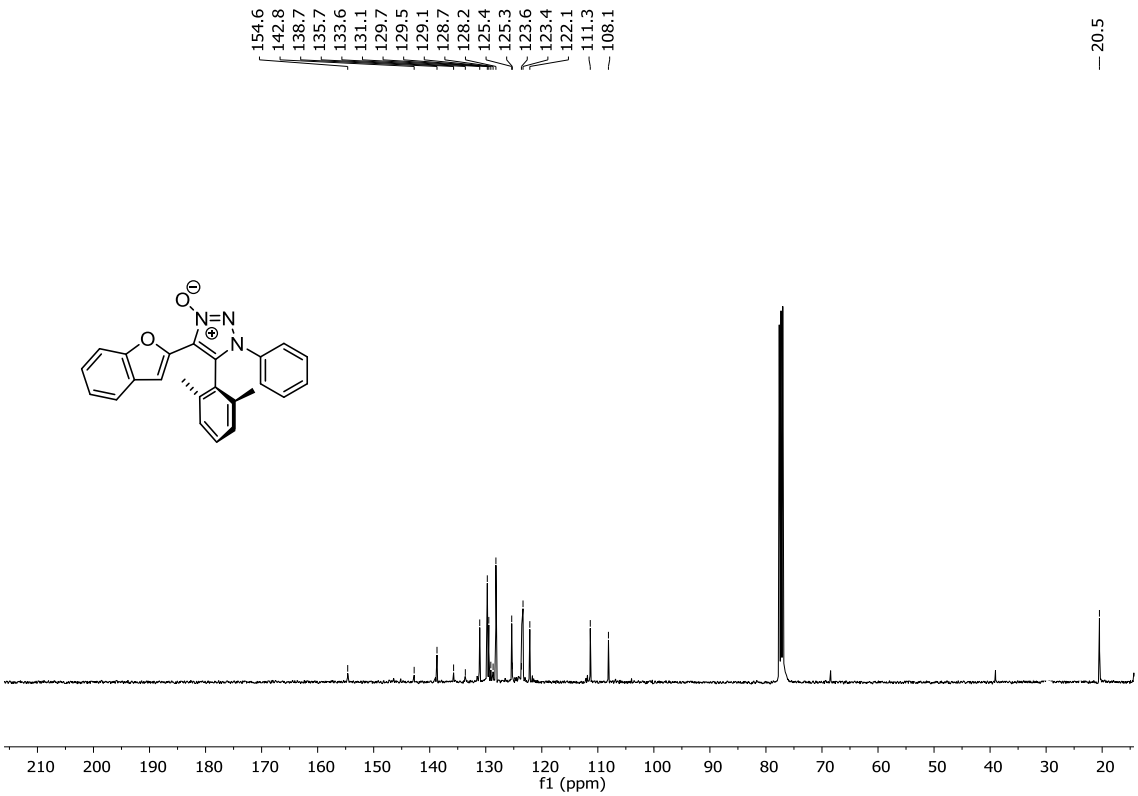
Spectrum 8.295. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36g**.



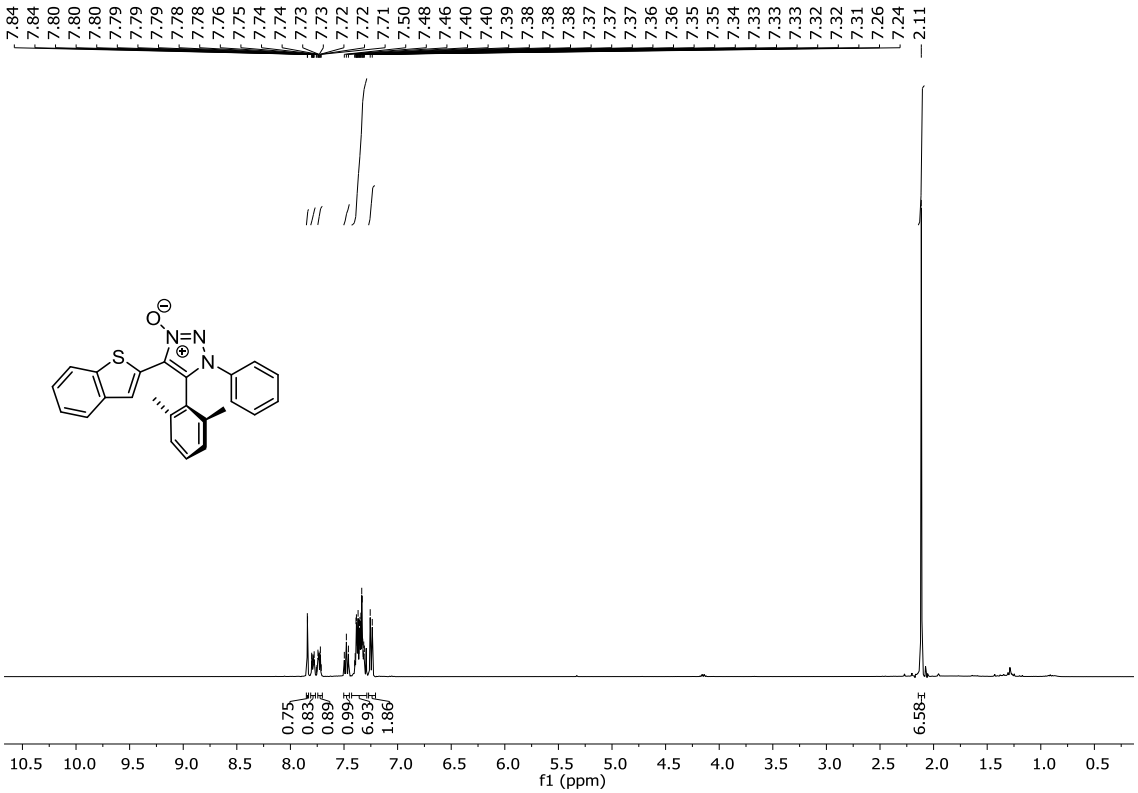
Spectrum 8.296. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36g**.



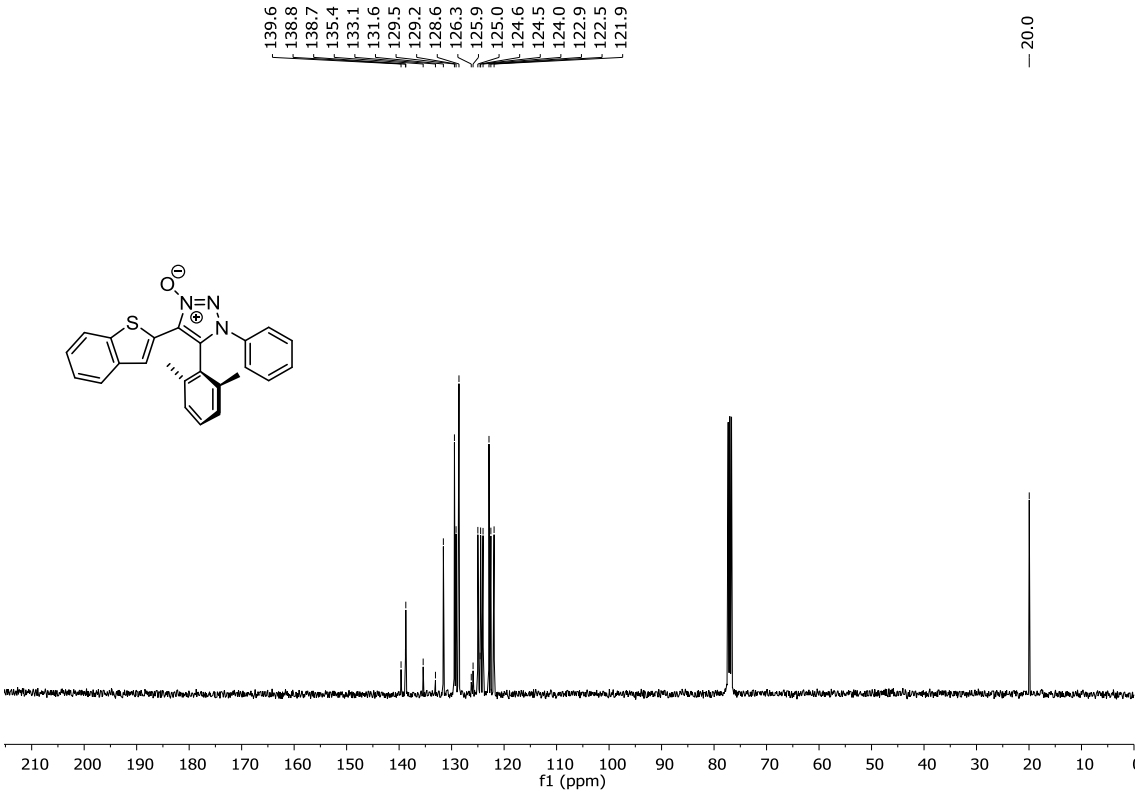
Spectrum 8.297. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36h**.



Spectrum 8.298. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36h**.

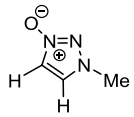


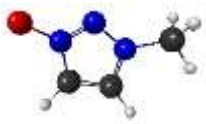
Spectrum 8.299. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **36i**.



Spectrum 8.300. ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **36i**.

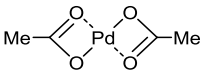
APPENDIX 2: Cartesian coordinates





E(RB3LYP) = -356.167176 Hartree

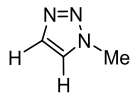
N	-7.482897	0.599300	0.044500
N	-8.093097	-0.331400	-0.325500
C	-7.279697	-1.329000	-0.534200
C	-6.057698	-0.875200	-0.235300
N	-6.279398	0.325200	0.112800
H	-5.080998	-1.367100	-0.264400
O	-9.396397	-0.375500	-0.506000
H	-7.563897	-2.328199	-0.884100
C	-5.175198	1.205400	0.530600
H	-5.354198	1.564399	1.569699
H	-4.184399	0.698500	0.507600
H	-5.125398	2.090599	-0.143500



E(RB3LYP) = -584.2881450 Hartree

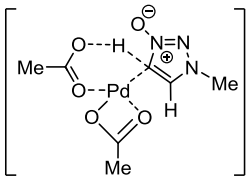
Pd	-5.84130	-0.58457	-0.31211
C	-7.35893	-0.81716	-2.20225
O	-6.91739	-1.82977	-1.56834
O	-6.95446	0.32194	-1.79998
O	-4.72339	-1.48648	1.17832
C	-4.33073	-0.34413	1.58249
O	-4.76952	0.66431	0.93950
C	-3.42846	-0.19335	2.76550
C	-8.32426	-0.95354	-3.33670

H	-4.04256	-0.17336	3.68116
H	-2.74460	-1.05105	2.83174
H	-2.86981	0.74996	2.69905
H	-9.34966	-0.96105	-2.93110
H	-8.22727	-0.09904	-4.02003
H	-8.15687	-1.90200	-3.86536



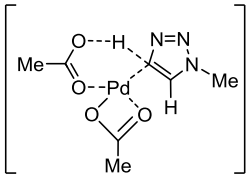
E(RB3LYP) = -281.1661152 Hartree

N	-7.46307	0.66609	0.11587
N	-8.15093	-0.35306	-0.30249
C	-7.30456	-1.38656	-0.56044
C	-6.01603	-0.97382	-0.28214
N	-6.16790	0.31066	0.13650
H	-5.04819	-1.46491	-0.34246
H	-7.66154	-2.34898	-0.92189
C	-5.16022	1.26764	0.55241
H	-5.41949	1.67285	1.54087
H	-4.18594	0.76458	0.60945
H	-5.09903	2.09802	-0.16748

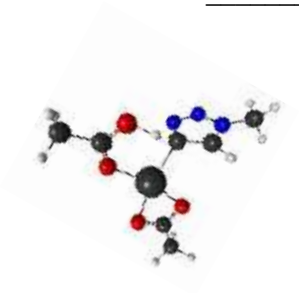


E(RB3LYP) = -940.520099 Hartree

N	-5.143411	2.123655	1.914741
N	-5.872836	1.687729	0.900101
C	-5.292764	0.530955	0.267970
C	-4.128571	0.330741	1.031036
N	-4.091244	1.269225	1.975178
H	-3.361497	-0.436017	0.939551
O	-6.912380	2.242706	0.547963
H	-5.281940	0.659528	-0.977065
O	-5.489077	0.874169	-2.324393
C	-6.560066	0.291394	-2.620060
O	-7.194366	-0.511367	-1.859980
C	-7.248114	-2.959335	1.441282
O	-6.361267	-2.096285	1.772643
Pd	-6.591138	-1.086783	-0.015034
O	-7.793079	-2.838232	0.306526
C	-3.112857	1.474139	3.026996
C	-7.189591	0.571662	-3.968159
C	-7.604175	-4.083290	2.369304
H	-3.611076	1.415421	4.006055
H	-2.344814	0.693960	2.953040
H	-2.651203	2.466587	2.918552
H	-7.808146	-0.273246	-4.298889
H	-7.836946	1.459329	-3.860645
H	-6.407946	0.804852	-4.704463
H	-7.127503	-5.010479	2.010656
H	-7.253908	-3.871041	3.388385
H	-8.691927	-4.242372	2.358606

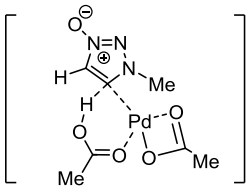


TS1



E(RB3LYP) = -865.432019 Hartree

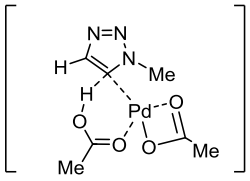
N	-5.143411	2.123655	1.914741
N	-5.872836	1.687729	0.900101
C	-5.292764	0.530955	0.267970
C	-4.128571	0.330741	1.031036
N	-4.091244	1.269225	1.975178
H	-3.361497	-0.436017	0.939551
H	-5.281940	0.659528	-0.977065
O	-5.489077	0.874169	-2.324393
C	-6.560066	0.291394	-2.620060
O	-7.194366	-0.511367	-1.859980
C	-7.248114	-2.959335	1.441282
O	-6.361267	-2.096285	1.772643
Pd	-6.591138	-1.086783	-0.015034
O	-7.793079	-2.838232	0.306526
C	-3.112857	1.474139	3.026996
C	-7.189591	0.571662	-3.968159
C	-7.604175	-4.083290	2.369304
H	-3.611076	1.415421	4.006055
H	-2.344814	0.693960	2.953040
H	-2.651203	2.466587	2.918552
H	-7.808146	-0.273246	-4.298889
H	-7.836946	1.459329	-3.860645
H	-6.407946	0.804852	-4.704463
H	-7.127503	-5.010479	2.010656
H	-7.253908	-3.871041	3.388385
H	-8.691927	-4.242372	2.358606



TS2

E(RB3LYP) = -940.295379 Hartree

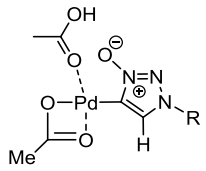
N	-5.263698	2.047999	2.167099
N	-6.141798	1.576699	1.030100
C	-5.353298	0.794800	-0.025200
C	-3.768599	0.826300	0.589500
N	-3.851599	1.592899	1.881299
H	-2.890199	0.385500	0.142900
H	-5.449998	1.246800	-1.233100
O	-5.432598	1.280500	-2.553299
C	-5.929898	0.076800	-3.009299
O	-5.588098	-1.095300	-2.362899
C	-6.658498	-2.994899	1.379500
O	-6.308398	-1.701399	1.598799
Pd	-6.059998	-1.144200	-0.374500
O	-6.572998	-3.200999	0.043700
C	-6.962898	0.054400	-4.119999
C	-7.757397	-3.651399	2.193799
H	-7.633697	-0.797700	-3.999299
H	-7.554297	0.970400	-4.104599
H	-6.454798	-0.025500	-5.080098
H	-7.564197	-4.723198	2.258299
H	-7.782097	-3.238199	3.205299
H	-8.726997	-3.489199	1.715999
C	-7.436497	1.759699	0.977900
H	-7.774097	2.463399	1.744199
H	-7.950097	0.807300	1.133700
H	-7.722197	2.163799	0.004100
O	-2.908299	1.816399	2.602599



TS2

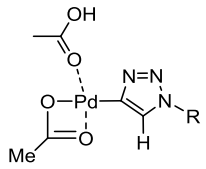
E(RB3LYP) = -865.432293 Hartree

N	-4.964898	1.780699	2.217799
N	-5.707798	1.664399	1.148200
C	-5.268198	0.644700	0.311500
C	-4.130999	0.189400	1.017900
N	-3.990099	0.883500	2.152899
H	-3.432199	-0.599100	0.733400
H	-5.311898	0.888900	-1.026600
O	-5.472398	1.142000	-2.385399
C	-6.393798	0.395300	-2.750199
O	-7.164597	-0.285700	-1.971599
C	-7.536197	-2.775799	1.247500
O	-6.752598	-1.881099	1.718999
Pd	-6.815598	-0.836900	-0.073700
O	-8.068197	-2.540099	0.118500
C	-6.683998	0.223500	-4.229798
C	-7.727297	-4.097499	1.927299
H	-7.063097	-0.791800	-4.424798
H	-7.450897	0.951900	-4.553098
H	-5.760398	0.411300	-4.797498
H	-7.077897	-4.820298	1.414299
H	-7.444397	-4.059999	2.984899
H	-8.755297	-4.444898	1.810399
C	-6.868098	2.515299	0.929100
H	-6.716098	3.461699	1.461399
H	-7.782197	2.021699	1.299900
H	-6.965498	2.694099	-0.151200



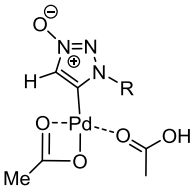
E(RB3LYP) = -940.541014 Hartree

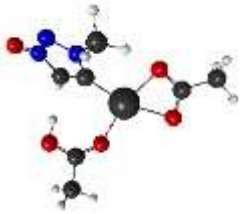
N	-4.5005480252	2.2679143525	1.0273228187
N	-5.3683245035	1.5698636539	0.3014001945
C	-5.5552993704	0.2759845918	0.8114951629
C	-4.7371060044	0.2364061424	1.9249350067
N	-4.1295426003	1.4437176396	2.0167662142
H	-4.5786398661	-0.5665850218	2.6408106352
H	-5.2464160980	-0.6727445485	-1.6217235588
O	-5.5058510598	-0.1905463845	-2.4360003828
C	-6.7513184650	0.2099457976	-2.3003114858
O	-7.4897668281	-0.1772672457	-1.3850066269
C	-7.2051498661	-3.2998340238	1.4920820465
O	-6.3513573200	-2.4059544182	1.8528306355
Pd	-6.7956445804	-1.1673081729	0.2824188187
O	-7.8690136603	-3.0956238959	0.4453083158
C	-3.1848609147	1.9167423782	3.0065619750
C	-7.2392556893	1.1249120617	-3.3728737080
C	-7.3810871954	-4.5294793950	2.3367566958
H	-3.5817019324	2.8100902177	3.5122018183
H	-3.0233849997	1.1205387740	3.7451335059
H	-2.2261244651	2.1744795883	2.5307881323
H	-8.3353110326	1.1406998471	-3.3872716809
H	-6.8612478169	2.1271210794	-3.1136803537
H	-6.8289422402	0.8357677663	-4.3501424776
H	-6.3993704196	-4.9728060634	2.5623918363
H	-7.8438554906	-4.2464964520	3.2960318320
H	-8.0217594041	-5.2569692310	1.8219387318
O	-5.9185201518	2.0736309621	-0.7123641013



E(RB3LYP) = -865.440600 Hartree

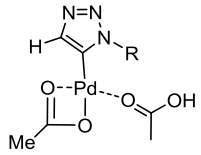
N	-5.133698	2.040099	2.058299
N	-5.862698	1.623199	1.094100
C	-5.276198	0.521300	0.476100
C	-4.076399	0.296600	1.169500
N	-4.024299	1.234300	2.124299
H	-3.299799	-0.453800	1.036600
H	-5.365098	0.623700	-1.093000
O	-5.504098	0.811000	-2.132099
C	-6.612798	0.300200	-2.424299
O	-7.289597	-0.450300	-1.649699
C	-7.196497	-3.030499	1.531499
O	-6.282598	-2.198499	1.862699
Pd	-6.596298	-1.091200	0.139000
O	-7.791197	-2.836599	0.430700
C	-3.032499	1.461899	3.158699
C	-7.229697	0.602400	-3.772799
C	-7.550697	-4.172999	2.435599
H	-3.310599	2.406699	3.654099
H	-3.049899	0.646400	3.897899
H	-2.027099	1.537699	2.719499
H	-7.812097	-0.256400	-4.131699
H	-7.916097	1.456799	-3.654399
H	-6.448398	0.879500	-4.492298
H	-6.634198	-4.665298	2.793299
H	-8.084097	-3.782599	3.317299
H	-8.194397	-4.890798	1.910699





E(RB3LYP) = -1116.59802509 Hartree

N	-4.612181	2.208473	1.646558
N	-5.597837	1.300455	1.438742
C	-5.298819	0.390863	0.474410
C	-4.029920	0.760712	0.040588
N	-3.647719	1.869152	0.805721
H	-3.308623	0.295429	-0.624680
H	-5.228596	1.298691	-1.551534
O	-5.504116	1.332954	-2.506594
C	-5.976899	0.177767	-2.900814
O	-6.192599	-0.781165	-2.151476
C	-7.831072	-2.717729	1.167256
O	-7.117985	-1.787662	1.705367
Pd	-6.473407	-1.085794	-0.106784
O	-7.855346	-2.795338	-0.087811
C	-6.258102	0.093125	-4.371393
C	-8.574657	-3.677121	2.049371
H	-6.520815	-0.933580	-4.649698
H	-7.094747	0.769355	-4.610916
H	-5.383295	0.443120	-4.938832
H	-7.857396	-4.392380	2.484015
H	-9.052784	-3.138956	2.880934
H	-9.320855	-4.228082	1.462459
C	-6.822390	1.451929	2.204264
H	-6.556962	1.806309	3.209560
H	-7.322631	0.478752	2.276841
H	-7.494126	2.189851	1.734652
O	-2.564262	2.472075	0.728096



E(RB3LYP) = -865.460151 Hartree

N	-4.869990	2.493626	1.118600
N	-5.908451	1.720857	0.725589
C	-5.536672	0.409620	0.604700
C	-4.185487	0.446947	0.949434
N	-3.832715	1.729154	1.251229
H	-3.476696	-0.375992	1.025207
H	-4.833060	0.348107	-1.310697
O	-5.023746	0.520210	-2.271737
C	-6.258053	0.204418	-2.567983
O	-7.041511	-0.359629	-1.793543
C	-7.337611	-3.089446	1.464758
O	-6.571673	-2.145865	1.881904
Pd	-6.700854	-1.114424	0.123005
O	-7.793860	-3.016025	0.292085
C	-6.698126	0.620136	-3.940439
C	-7.669037	-4.237858	2.374829
H	-7.450675	-0.080396	-4.323865
H	-7.165173	1.616755	-3.859890
H	-5.838799	0.698220	-4.619083
H	-7.398746	-5.183656	1.880600
H	-7.140625	-4.146483	3.332453
H	-8.756568	-4.258191	2.548392
C	-7.199569	2.336118	0.492319
H	-7.161868	3.347236	0.916372
H	-7.995823	1.756514	0.980255
H	-7.423252	2.409149	-0.584290