Doctoral Thesis

Site-Selective C–H Functionalization of Amino Acids and Peptides Upon Radical Chemistry

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Abbreviations and Acronyms

Ala = Alanine

Arg = Arginine

Asp = Aspartic Acid

AQ = 8-Aminoquinoline

Boc = *tert*-Butoxycarbonyl

BHT = Butylated Hydroxytoluene

BQ = 1,4-Benzoquinone

CAN = Ceric ammonium nitrate

CDC = Cross-Dehydrogenative Coupling

CFL = Compact fluorescent lamp

CHP = Cumene hydroperoxide

CSA = Camphorsulfonic acid

DABCO = 1,4-Diazabicyclo[2.2.2]octane

DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE = 1,2-Dichloroethane

DCM = Dichloromethane

DCP = Dicumyl peroxide

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DG =Directing Group

DHP = Dihydropyridine

DPPE = 1,2-Bis(diphenylphosphine)

DMBQ = 2,6-Dimethoxy-1,4-benzoquinone

DMA = Dimethylformamide

DTBP = Di-*tert*-butyl peroxide

Dtbpy = 4,4'-Di-*tert*-butyl-2,2'-dipyridyl

Gly = Glycine

HAT = Hydrogen Atom Transfer

HBpin = 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane

HFIP = Hexafluoroisopropanol

His = Histidine

HPLC = High Performance Liquid Chromatography

Ile = Isoleucine

LED = Light Emitting Diode

Leu = Leucine

Lys = Lysine

MeCN = Acetonitrile

Met = Methionine

MIA = 2-Methoxyiminoacetyl

MICA = 5-Methylisoxazole-3-carboxamide

MOCA = 2-Methyloxazole-4-carboxamide

Mp = Melting point

MS = Mass spectrometry

MTBE = Methyl *tert*-butyl ether

Mw = Microwave

NHPI = *N*-Hydroxyphthalimide

NHS = *N*-Hydroxysuccinimide

NMP = *N*-Methyl-2-pyrrolidone

PA = Picolinamide

Phe = Phenylalanine

PIDA = (Diacetoxyiodo)benzene

PINO = Phthalimide-*N*-oxyl

PIP = (Pyridine-2-yl)isopropyl amine

PMP = *p*-methoxyphenyl

Pybox = Pyridine Bis(oxazoline)

r.t = Room temperature

NMR = Nuclear Magnetic Resonance

Ser = Serine

SET = Single Electron Transfer

TBHP = *tert*-Butyl Hydroperoxide

$TBPA^{+\cdot}$ = Tris (4-bromophenyl)aminiun hexachloroantimonate

TBPB = *tert*-Butyl Peroxybenzoate

TEMPO = (2,2,6,6-Tetramethyl-1-piperidinyl)oxy

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic anhydride

TFE = Trifluoromethanol

THF = Tetrahydrofuran

TIPS = Triisopropylsilane

TMEDA = *N*,*N*,*N'*,*N*'-Tetramethylethylenediamine

Trp = Tryptophan

Tyr = Tyrosine

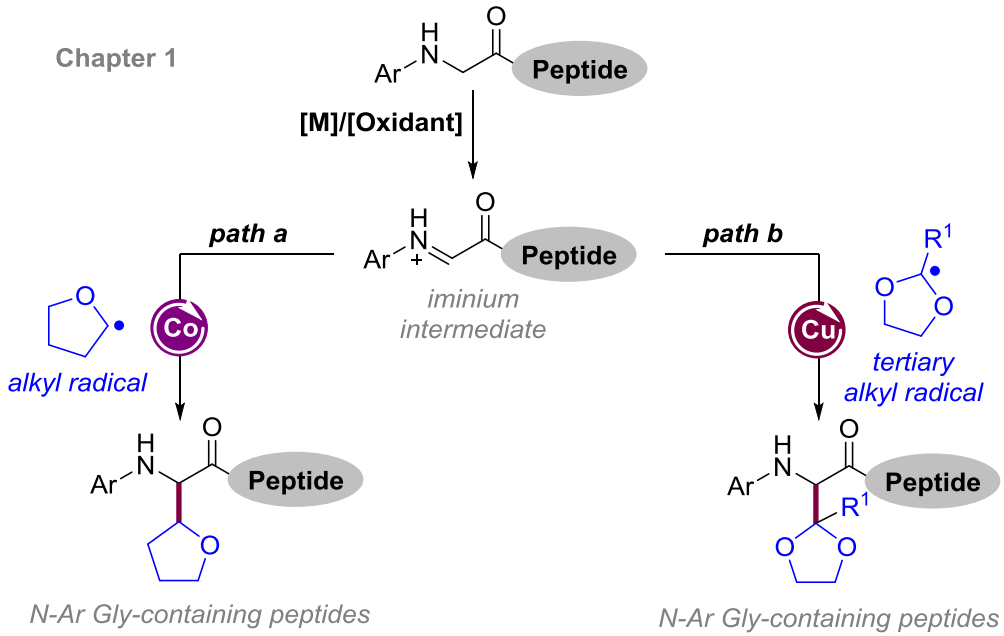
Val = Valine

Xphos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Abstract

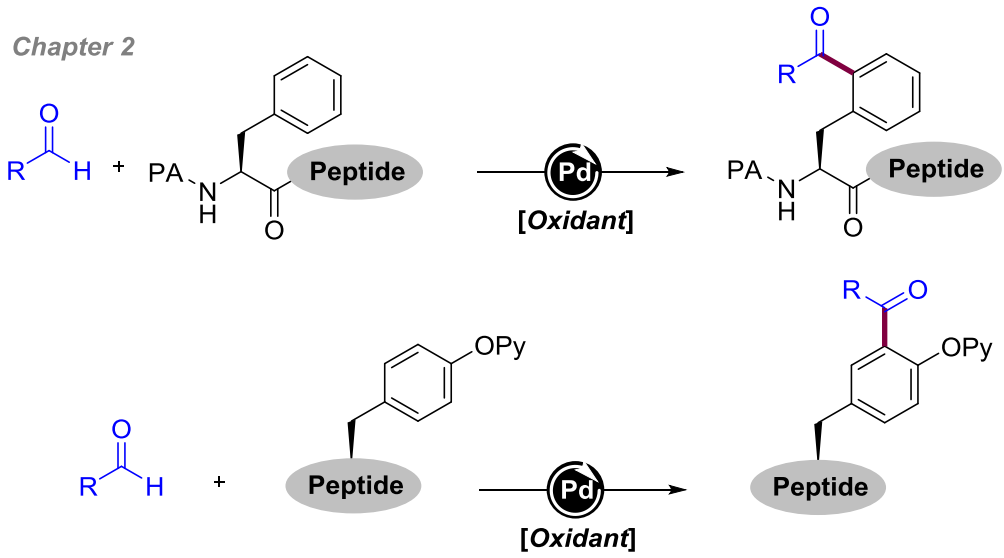
Amino acids are the building blocks of bioactive peptides and proteins. However, recently unnatural amino acids have attracted tremendous attention since they often improve the activity and pharmacokinetics of their parent natural derivatives. For this reason, new synthetic methods for the straightforward C–H modification of amino acids, peptide or proteins are of paramount importance. In this aspect, cross-dehydrogenative coupling (CDC) reactions have enabled the C–H functionalization of peptides' backbone with multiple types of nucleophiles an radicals, predominantly catalyzed by copper salts. In this doctoral thesis, we have studied use of alternative metals such as cobalt for the site-selective modification of amino acids and peptides employing ethers as coupling partners through CDC events. On the other hand, we have been focused on the site-selective C–H diversification of amino acids' and peptides' aromatic side-chains. In this regard, the introduction of exogenous directing groups was explored for the modification of Phe and Tyr residues within peptides through radical acylation reactions. This approach has been scarcely investigated in the field of bioconjugation and notably provide multiple advantages in comparison with more conventional chemistry such as cross-coupling reactions, where prefunctionalized reagents are required and the generation halogenated waste is unavoidable.

Concerning CDC-type reactions, the α-C(sp^2)–H bonds of *N*-aryl glycines are known to be activated under oxidative conditions in the presence of first-row transition metals to deliver the corresponding electrophilic intermediate, which can further react with nucleophilic species. Capitalizing on this, *in situ* generated alkyl radicals have been employed to react with the transient iminium intermediates. In this respect, two new methodologies have been developed based on this strategy. On the one hand, commonly employed solvents in organic chemistry such as THF and 1,3-dioxolane were used as coupling partners with *N*-aryl glycine derivatives, in the presence of cobalt catalysis (Scheme 1, path a). On the other hand, more complex 2-subtituted 1,3-dioxolanes were employed as versatile counterparts with *N*-aryl glycine derivatives, thereby forming new quaternary C-C bonds, upon copper catalysis (Scheme 1, *path b*).



Scheme 1. Cobalt- and copper-catalyzed selective alkylation of glycine derivatives with ethers.

Subsequently, we expanded our studies to the less explored C–H diversification of aromatic side-chains of Phe and Tyr units. This was achieved by the introduction of pyridine-type directing group in a strategic position within the Phe and Tyr residues, which enabled the desired site-selective radical acylation with catalytic amounts of Pd under oxidative conditions (Scheme 2).

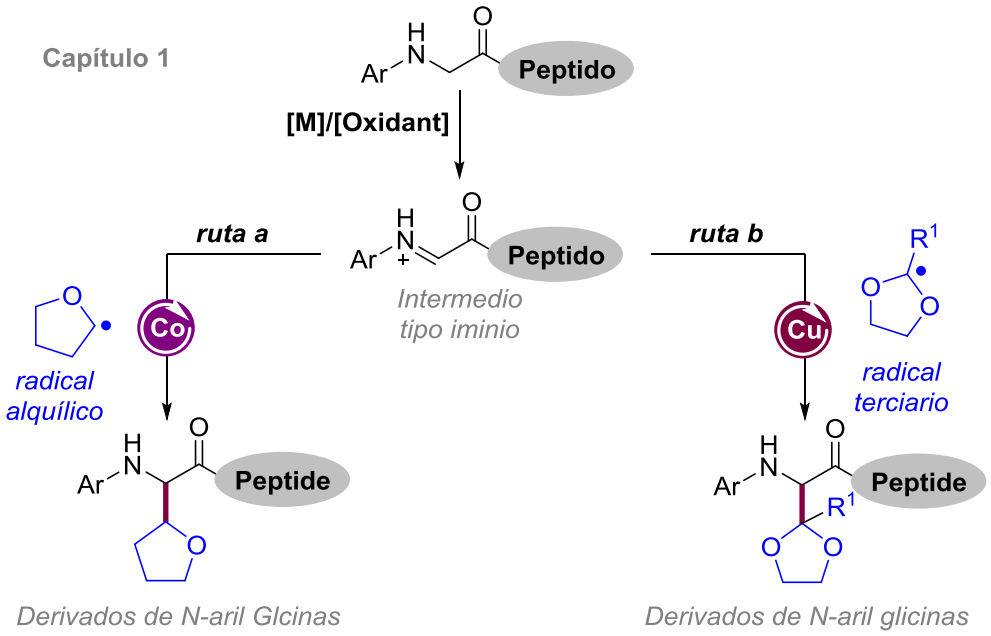


Scheme 2. Pd-Catalyzed site-selective C(sp^2)–H acylation of phenylalanine and tyrosine residues.

Resumen de Tesis Doctoral

Los aminoácidos son las materias primas de péptidos y proteínas con actividad biológica. Sin embargo, recientemente los aminoácidos no naturales han atraído mucha atención debido a que a menudo mejoran la actividad y farmacocinética respecto a sus análogos naturales. Por esta razón, el desarrollo de nuevos métodos sintéticos para la modificación directa de enlaces C–H de aminoácidos, péptidos y proteínas es de gran interés. En este aspecto, los procesos CDC (Cross-dehydrogenative coupling) han hecho posible la modificaciónde enlaces C– H de la estructura primaria de los péptidos, introduciendo una gran variedad de nucleófilos, predominantemente catalizados por sales de cobre. Nuestro objetivo en este campo ha sido estudiar metales alternativos como el cobalto para la modificación selectiva de aminoácidos y péptidos mediante procesos CDC. Por otra parte, también nos hemos interesado en la diversificación de enlace C– H de aminoácidos con ramificaciones aromáticas como la Phe y Tyr. Para ello se introdujeron grupos directores exógenos de tipo piridina en las estructuras peptídicas que permitieron llevar a cabo la acilación selectiva de enlaces C– H mediante procesos radicalarios. Esta aproximación sintética podría tener multiples ventajas frente a métodos más convencionales como los “cross-coupling” donde se requieren sustratos prefuncionalizados y la generación de residuos halogenados es inevitable.

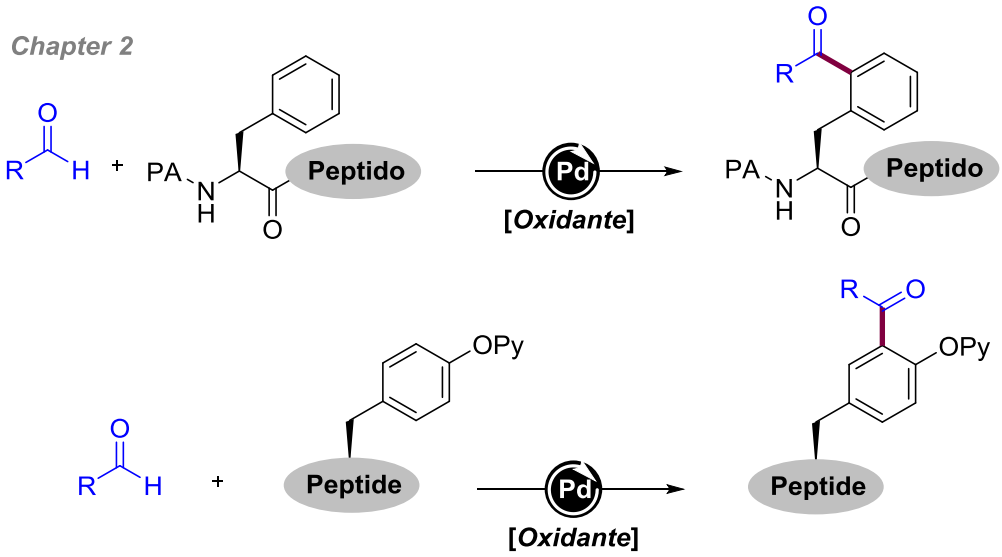
En cuanto las reacciones de tipo CDC, es sabido que las *N*-aril glicinas generan electrófilos de tipo iminio *in situ* en condiciones oxidantes y en presencia de metales de transición, los cuales pueden reaccionar con especies con carácter nucleófilo. En esta tesis doctoral, la generación *in situ* de radicales alquílicos fueron empleados para reaccionar como nucleófilos



Esquema 1. Alquilación selectiva de derivados de glicina empleando éteres mediante catálisis de cobalto y cobre.

con intermedios de tipo iminio. En base a esto, dos nuevas metodologías han sido desarrollados. Por una parte, los disolventes comunes como el THF y 1,3-dioxolane fueron empleados como fuente de radicales carbonados para reaccionar con derivados de *N*-aril glicinas en presencia de catalizadores de cobalto (Esquema 1, *ruta a*). Por otra parte, éteres más complejos como los 1,3-dioxolanes sustituidos en C2 también fueron empleados para la misma trasformación, creándose así un nuevo enlace cuaternario, en este caso utilizando catalizadores de cobre (Esquema 1, *ruta b*).

Posteriormente hemos extendimos nuestro estudio a la menos explorada funcionalización C-H de ramificaciones aromáticas de los aminoácidos Phe y Tyr. Esto fue conseguido tras la introducción de grupos directores de tipo piridina estratégicamente en la secuencia peptídica, el cual permitió llevar a cabo con éxito la acilación radicalaria de forma selectiva con cantidades catalíticas de Pd en condiciones oxidantes (Esquema 2).



Esquema 2. Acilación C(sp^2)–H de fenilalanina y tirosina mediante catálisis de Pd.

Chapter 1. Cobalt- and Copper-Catalyzed Selective Alkylation of Glycine Derivatives with Ethers

1.1. General Introduction

1.1.1. Importance of Amino Acids and Peptides

Amino acids are ubiquitous building blocks utilized by nature to synthesize bioactive peptides and proteins.[1] Moreover, their use as chiral catalysts,[2] chiral ligands[3] or in drug discovery has been extensively employed by scientists. Since the conformation of natural proteins and peptides are limited to a small number amino acids, the options that unnatural amino acids would provide to build up new structures with different properties are virtually unlimited. Nowadays, unnatural amino acids have become important candidates for drug discovery since they often show enhanced activities and improved pharmacokinetics than the parent natural derivatives.[4] Some examples of commercial drugs containing unnatural amino acids are shown in Figure 1.

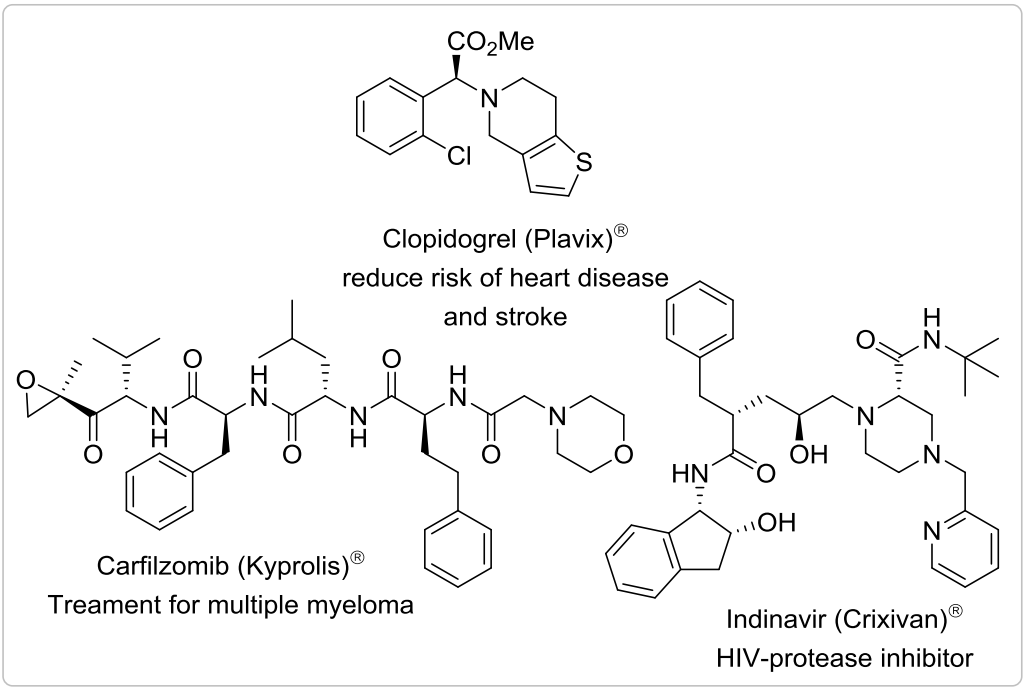


Figure 1. Examples of bioactive unnatural amino acids and small peptides.

[1] Torres, M. D. T.; De la Fuente-Nunez, C. *Chem*. *Commun*. **2019**, *55*, 15020.
[2] Yadav, G.; Deepa, Singh, S. *ChemistrySelect* **2019**, *4*, 5591.
[3] For the early observation of enantioselective functionalization using *mono-N*-protected amino acids as ligands, see: Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew*. *Chem*. *Int. Ed*. **2008**, *47*, 4882.
[4] a) Hallam, T. J.; Wold, E.; Wahl, A.; Smider, V. V. *Mol*. *Pharmaceutics* **2015**, *12*, 1848. b) Yu, Y.; Hu, C.; Xia, L.; Wang, J. *ACS Catal*. **2018**, *8*, 1851.

1.1.2. C–H Functionalization of Amino Acids and Peptides

Due to the increase interest for procedures to selectively modify natural amino acids or peptides in the past years, numerous strategies have been reported. In contrast to traditional methodologies,[5] direct C–H functionalization of amino acids and peptides represent many advantages. There is no requirement of prefunctionalization of the substrates to perform the reactions, the racemization of the chiral amino acids is avoided due to the mild reaction conditions and more recently, the development of chemo and site-selective approaches have been described that allow the late-stage functionalization of peptides of high structural complexity. These procedures can be differentiated according to the operative mechanism, and the position of the corresponding C–H bond within the peptide sequence. The α-C–H functionalization of peptide backbone and the modification of peptide's side-chain, which can be further classified into C(sp^2)– H or C(sp^3)– H functionalization of peptide (Figure 2).

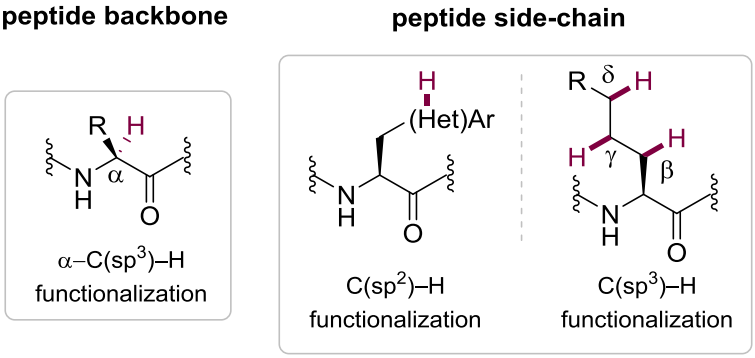


Figure 2. Sites for C–H functionalization of amino acids and peptides.

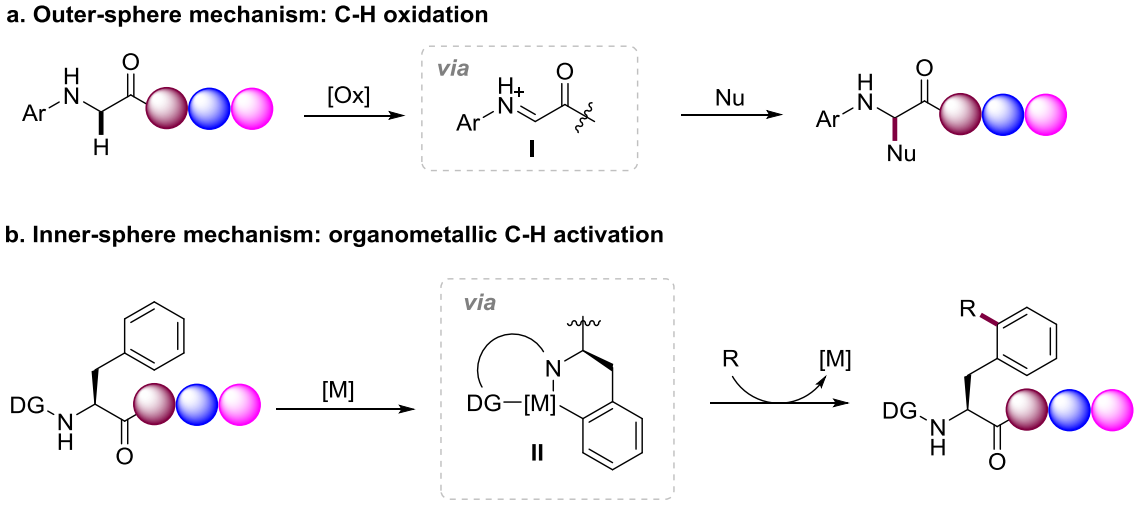
The α-C(sp^3)–H functionalization of the peptide backbone is typically catalyzed by a first-row transition metal,[6] although metal-free reactions are also known,[7] commonly stoichiometric amounts of an oxidant are used and an outer-sphere mechanism is proposed. In case of using glycine as the amino acid feedstock, it is commonly accepted that its oxidation would deliver the electrophilic cationic species **I**, that could further react with a nucleophilic counterpart (Scheme 3a). Conversely the inner-sphere mechanism is distinguished by the formation of a C–Metal intermediate **II** in the C–H activation step and often a directing group (DG) is used to

[5] a) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. b) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc. Chem. Commun*. **1977**, *19*, 683. c) Miyaura, N.; Yamada, K.; Suzui, A. *Tetrahedron Lett*. **1979**, *20*, 3437. d) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun*. **1979**, 866. e) Heck, R. F.; Nolley, J. P. *J. Org. Chem*. **1972**, *37*, 2320.

[6] a) San Segundo, M.; Correa, A. *Synthesis*. **2018**, *50*, 2853. b) Brandhofer, T.; Mancheño, O. G. *Eur. J. Org. Chem*. **2018**, 6059.

[7] a) Jia, X.; Wang, Y.; Peng, F.; Huo, C.; Yu, L.; Liu, J.; Wang, X. *Adv. Synth. Catal.* **2014**, *356*, 1210. b) Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Angew. Chem. Int. Ed*. **2014**, *53*, 13544.

selectively functionalize a particular C–H bond of the peptide or amino acid through the formation of a metallacycle (Scheme 3b).

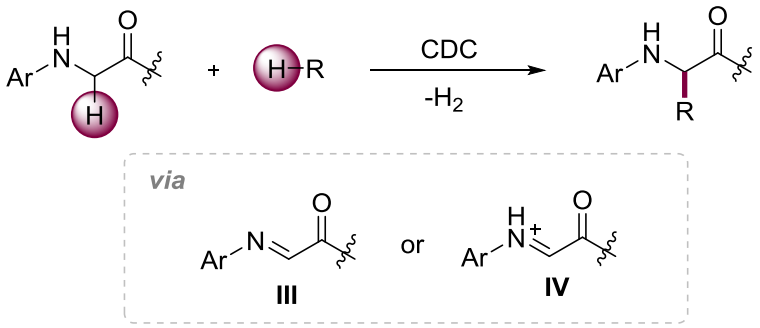


Scheme 3. Relevant mechanisms for the C–H functionalization of peptides.

1.1.3. Cross-Dehydrogenative-Coupling (CDC) of Glycine Derivatives

In this chapter we are going to focus on outer-sphere reactions, in particular in Cross-Dehydrogenative-Coupling (CDC) reactions for the site-selective functionalization of glycine derivatives or glycine-containing peptides. CDC reactions represent a new toolbox for the direct assembly of C–C bonds at expense of oxidation of two C–H bonds, in an efficient, atom-economical and in some cases, environmentally friendly conditions.[8] These reactions imply the activation of two C–H bonds and formally the release of H_2 during the process; however, it typically does not occur and the two hydrogen atoms are often abstracted by the oxidant. This approach opens the door for the straightforward construction of new α-substituted amino acids upon the modification of commercially available natural amino acids. The key step in these procedures constitutes the formation of an electrophilic α-aldimine **III** or α-aldiminium **IV** intermediate, through oxidation of the *N*-aryl α-amino carbonyl compound, which further reacts with the corresponding nucleophile, for the construction of new C–C or C–X bonds (Scheme 4). The presence of the *N*–aryl moiety is generally necessary as it facilitates the oxidation step and presumably stabilizes the transient electrophilic intermediates.[6]

[8] a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed*. **2014**, *53*, 74. b) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev*. **2017**, *117*, 9016. c) Huang, C.-Y.; Kang, H.; Li, J.; Li, C.-J. *J. Org. Chem*. **2019**, *84*, 12705.

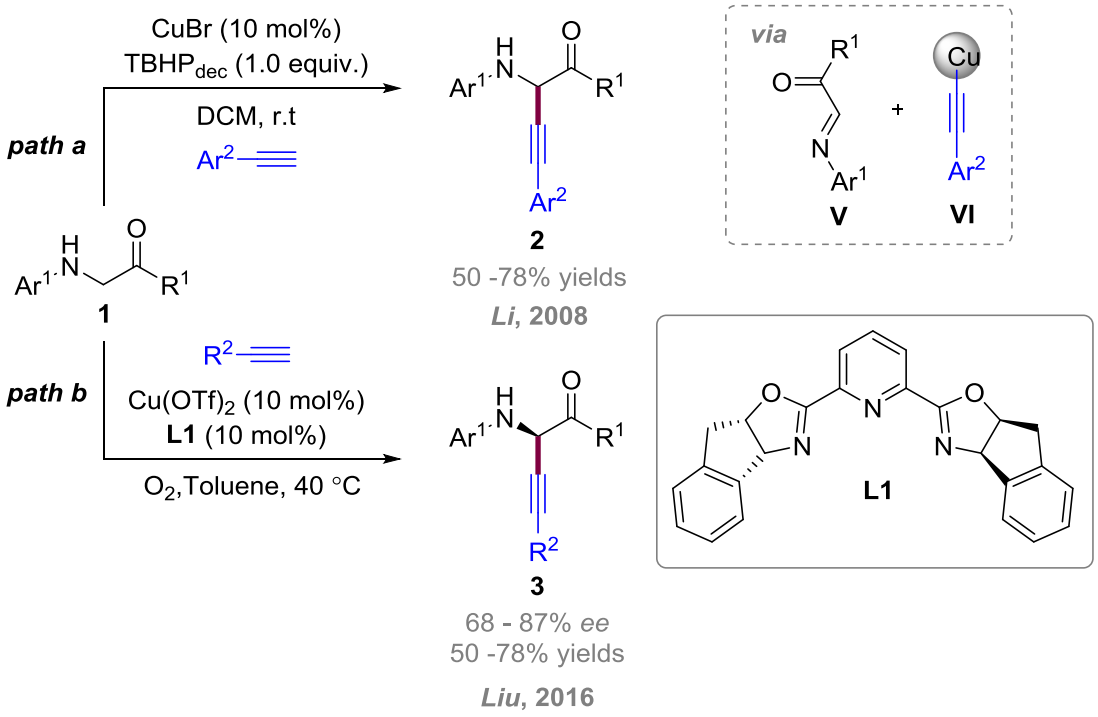


Scheme 4. CDCs of α-amino carbonyl compounds.

1.1.3.1. Reaction with Alkynes

In 2008, Li and co-workers reported the first procedure for the introduction of aromatic alkynes into glycine moieties, using a cross-dehydrogenative-coupling (CDC) event.[9] The reaction could be carried out at room temperature using a CuBr/$TBHP_{dec}$ system, where the reactivity of the substrate was attributed to the *para*-methoxyphenyl (PMP) protecting group (which lowered the oxidation potential of the amine). Thereby, a short family of aromatic alkynes where successfully introduced into glycine derivatives and short peptides under the optimized conditions. Concerning the proposed mechanism, in this seminal and early report the terminal alkyne would first form a copper acetylide **VI**, which would eventually undergo a nucleophilic addition to the *in situ* formed imine **V** species (Scheme 5, *path a*). In 2009, the same group elegantly extended the scope of the methodology to a vast array of peptide derivatives[10] and in 2016, a Cu-catalyzed aerobic enantioselective approach was described by Liu and co-workers with the use of a pybox type ligand (**L1**) (Scheme 5, *path b*).[11]

[9] Zhao, L.; Li, C.-J. *Angew*. *Chem*. *Int*. *Ed*. **2008**, *47*, 7075.
[10] Zhao, L.; Baslé, O. Li, C.-J. *Proc*. *Natl*. *Acad*. *Sci*. *USA* **2009**, *106*, 4106.
[11] Xie, Z.; Liu, X.; Liu, L. *Org*. *Lett*. **2016**, *18*, 2982.



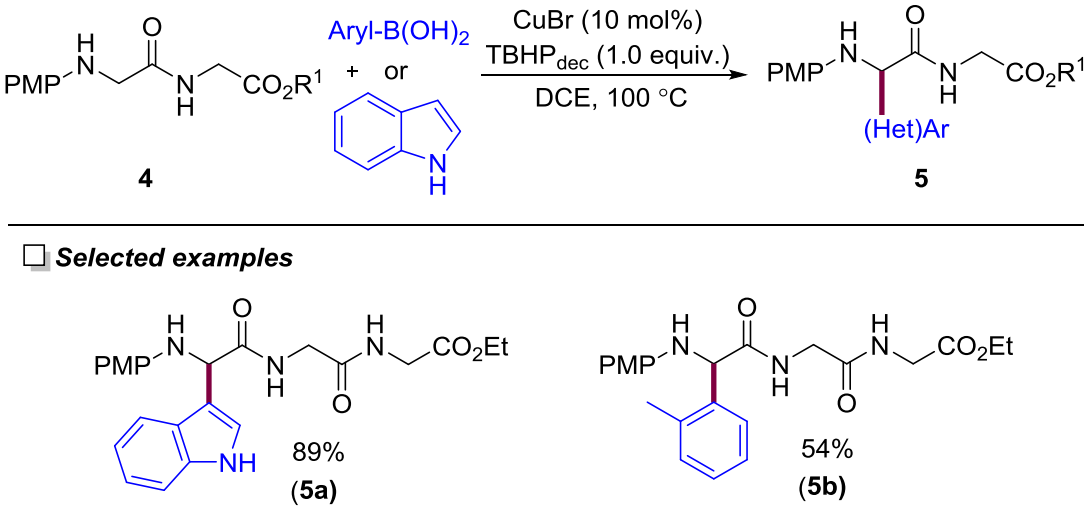
Scheme 5. Cu-catalyzed alkynylation of Gly derivatives.

1.1.3.2. Reaction with (Hetero)arenes

Aryl glycines are a class of nonproteinogenic amino acids of paramount importance. Since the discovery of the first glycopeptide with antibiotic activity named vancomycin,[12] which is a heptapeptide where three of the amino acids residues are aryl glycines, these types of structures have attracted more and more attention in the field of organic chemistry and medicine.[13] Although traditional methodologies such as the Streker synthesis,[14] the Ugi reaction[15] and Petasis reaction[16] are important tools for the construction of aryl glycines, the direct functionalization of glycine units represents a much more powerful approach. In this regard, Li and co-workers did an outstanding work in the field of CDCs achieving a site-selective α-C–H arylation of *N*-aryl glycines and short peptides at the *N*-aryl terminal Gly unit (Scheme 6).[10] Boronic acids and indoles were used as the nucleophilic aryl source and the CuBr/TBHP$_{dec}$ system was employed for the activation of the substrates. Under optimized conditions, several short peptides and glycine derivatives underwent selective (hetero)arylation to furnish the final products (**5**) with moderate to excellent yields. This work set the basis for the future advances in the field and a vast array of methodologies have been devised in the last years for the

[12] Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356.
[13] Okano, A.; Isley, N. A.; Boge, D. L. *Chem. Rev*. **2017**, *117*, 11952.
[14] a) Wang, J.; Liu, X.; Feng, X. *Chem Rev*. **2011**, *111*, 6947. b) Liu, Y.-L.; Zhau, J. *Synthesis* **2015**, *47*, 1210.
[15] Zhi, S.; Ma, X.; Zhang, W. *Org. Biomol. Chem*. **2019**, *17*, 7632.
[16] Wu, P.; Givskov, M.; Nielsen, T. E. *Chem*. *Rev*. **2019**, *119*, 11245.

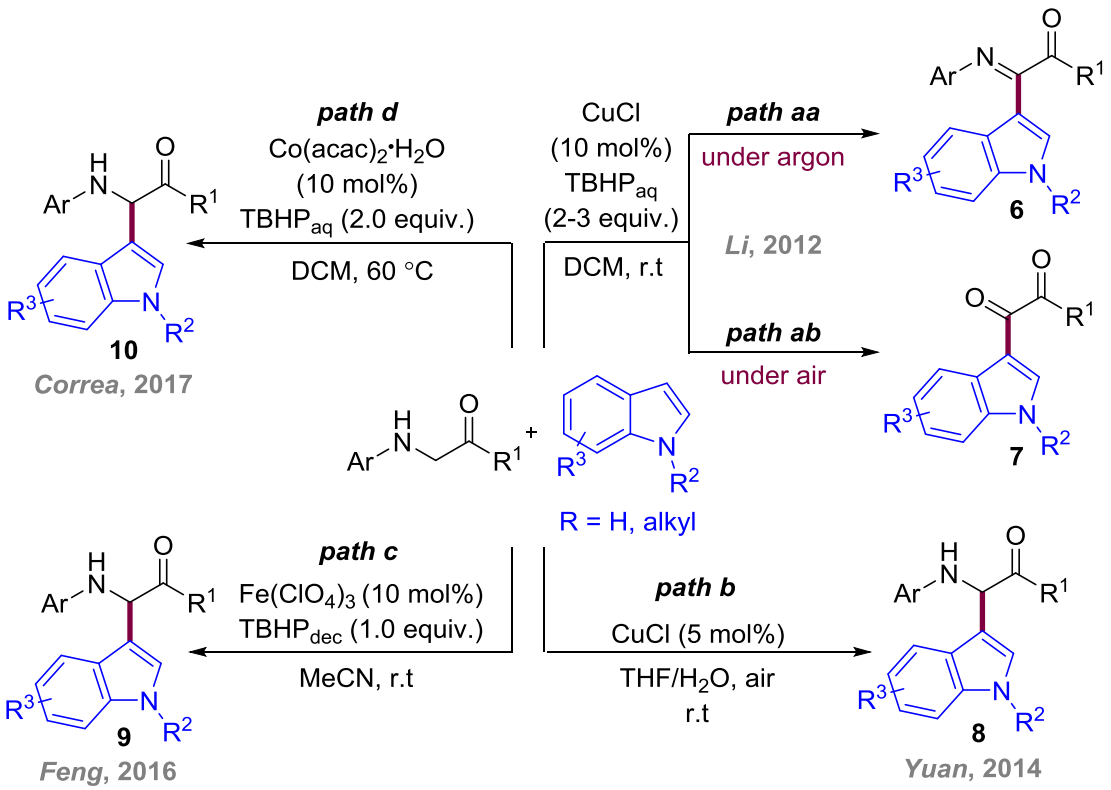
α-arylation of amino acid derivatives with (hetero)arenes. Despite the novelty and importance of the method, the mayor downside relied on the requirement of highly activated *p*-methoxyphenyl-Gly derivatives for the process to occur.



Scheme 6. Cu-catalyzed (hetero)arylation of short peptides.

Among all the heteroaromatic compounds, the indole moiety has been extensively explored in CDC reactions with glycine derivatives, probably due to its innate nucleophilic character at the C3-position and its prevalence in a wide range of natural products.[17] In 2012, the group of Li reported a Cu-catalyzed CDC reaction between *N*-aryl glycine esters and ketones (Scheme 7).[18] While the reaction delivered α-imino derivatives **6** under an argon atmosphere (Scheme 7, *path aa*), when an air atmosphere was used instead, α-oxo carbonyl compounds **7** were obtained (Scheme 7, *path ab*). Under exceptionally mild conditions, the group of Yuan was able to selectively heteroarylate glycine derivatives with indoles (Scheme 7, *path b*).[19] Afterwards, an alternative Fe-catalyzed protocol was established to couple indoles with α-amino ketones or α-amino esters (Scheme 7, *path c*).[20] Recently, our group has proved that the less explored cobalt salts can also assist this transformation; remarkably, this Co-catalyzed protocol enabled the late-stage-functionalization of peptides that had not been explored by the other methodologies (Scheme 7, *path d*). [21]

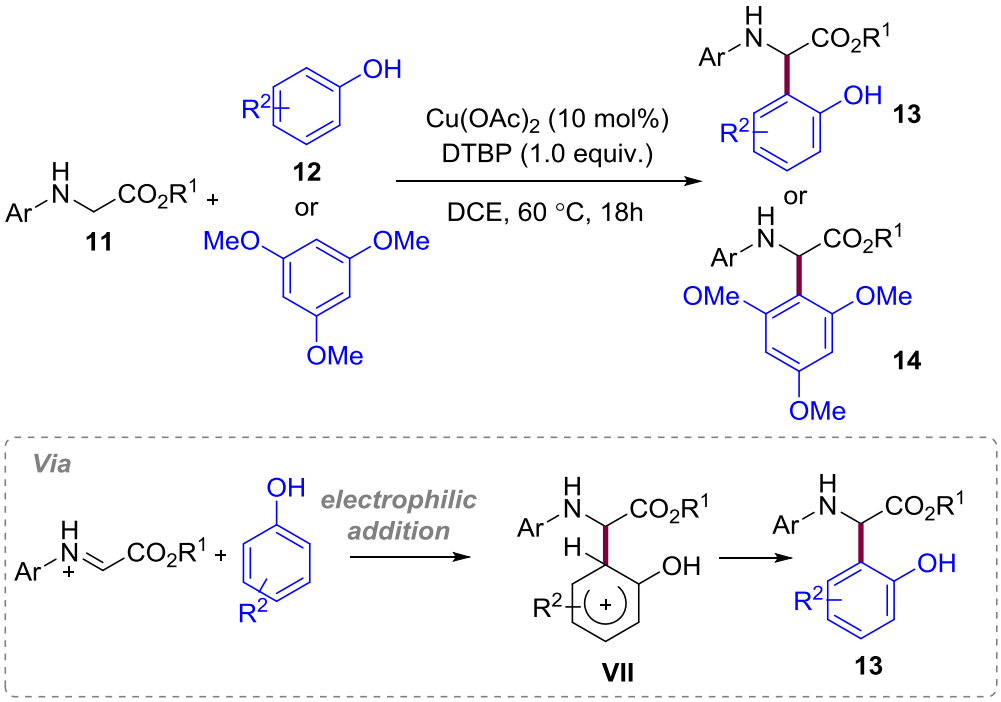
[17] Chadha, N.; Silakari, O. *J. Med. Chem*. **2017**, *134*, 159.
[18] Wu, J.-C.; Song, R.-J.; Wang, Z.-Q.; Huang, X.-C.; Xie, Y.-X.; Li, J.-H. *Angew. Chem. Int. Ed*. **2012**, *51*, 3453.
[19] Huo, C.; Wang, C.; Wu, M.; Jia, X.; Xie, H.; Yuan, Y. *Adv. Synth. Catal*. **2014**, *356*, 411.
[20] Zhang, Y.; Ni, M.; Feng, B. *Org. Biomol. Chem*. **2016**, *14*, 1550.
[21] San Segundo, M.; Guerrero, I.; Correa, A. *Org. Lett*. **2017**, *19*, 5288.



Scheme 7. CDC reaction of glycine derivatives with indoles.

In 2016, the introduction of phenols and related ethers into glycine derivatives was achieved by the group of Huang.[22] The reaction tolerated the use of different *N*-aryl glycine derivatives (**11**) with $Cu(OAc)_2$ as catalyst and di-*tert*-butyl peroxide (DTBP) as oxidant, which enabled the installation of a variety of substituted phenols or 1,3,5-trimethoxybenzene (Scheme 8). Interestingly, the CDC reaction was selective toward the *ortho*-coupling in the case of the phenol derivatives and *para*-coupling isomer was never detected. The mechanistic proposal by the authors suggested that phenol derivatives would undergo electrophilic addition with the *in situ* formed iminium ion to form σ-complex **VII**, which after the lost of a proton would deliver α-aryl glycine derivatives **13** and **14**.

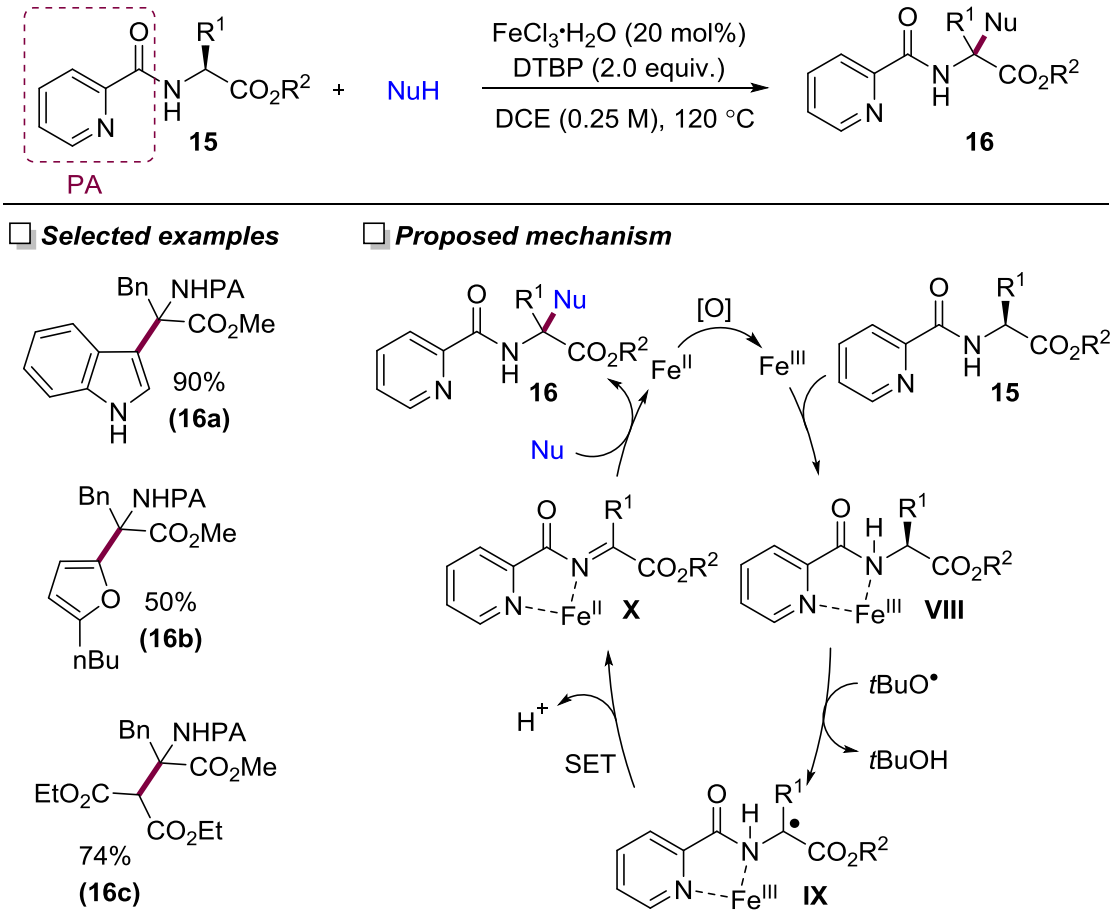
[22] Salman, M.; Zhu, Z.-Q.; Huang, Z.-Z. *Org*. *Lett*. **2016**, *18*, 1526.



Scheme 8. Cu-catalyzed selective arylation of Gly derivatves with phenols and 1,3,5-trimethoxybenzene.

A major breakthough in the field came with the first transition-metal-catalyzed oxidative cross-coupling reaction of α-tertiary α-amino acids to deliver α-quaternary derivatives.[23] The construction of α-quaternary α-amino acids through transition-metal catalysis had remained a challenging subject as it would involve the formation of a challenging ketimine intermediate. In general, the double bond within a ketimine is more difficult to form and less reactive than its parent aldimine. To overcome this issue, the authors envisioned that the use of a chelating directing group would promote the formation of the corresponding α-ketimine and would further activate the resulting intermediate for a further nucleophilic attack.[9] To test their hypothesis, a set of directing groups (DGs) were examined in the presence of $FeCl_3 \cdot 6H_2O$ and di-*tert*-butyl peroxide (DTBP) as the oxidant. It was found that a number of (*N*-heteroarene)-carbonyl groups were effective DGs to promote the oxidative coupling reaction, where 2-picolinamide (PA) gave the best result. Under optimized conditions, a variety of electron-rich heterocycles such as indole, furan and malonates were effectively coupled to give the desired α-quaternary amino acid derivatives **16** (Scheme 9).

[23] Li, K.; Tan, G.; Huang, J.; Song, F.; You, J. *Angew*. *Chem*. *Int*. *Ed*. **2013**, *52*, 12942.



Scheme 9. PA-directed formation of α-quaternary amino acids derivatives.

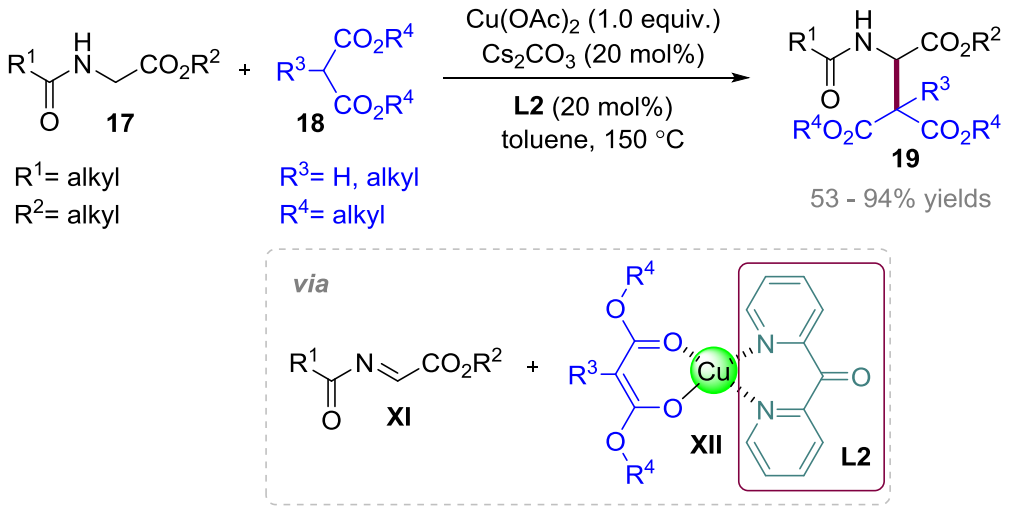
The plausible mechanism reported by the authors suggested that initial chelation of the substrate with the Fe^{III} catalyst would generate intermediate **VIII**. Afterwards, the latter would be oxidized by the *tert*-butoxyl radical ($tBuO^{\bullet}$) to form the radical intermediate **IX**, which would be further oxidized by Fe^{III} upon an intramolecular single-electron-transfer (SET) reaction to deliver the α-ketimine intermediate **X**. Finally, once the electrophilic α-ketimine **X** is formed, the corresponding nucleophilic addition would afford the desired α-quaternary α-amino acid ester **16** (Scheme 9). Accordingly, the so-called bidentate directing group[24] plays a crucial role to assist the oxidation of the α-C(sp^3)–H bond.

[24] Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev*. **2020**, *120*, 1788.

1.1.3.4. Reaction with Alkyl Reagents

In the past, synthetic methods for the α-alkylation of amino acids had relied mostly on enolate chemistry.[25] This approach has been successfully applied to generate enantio-enriched stereocenters with chiral catalysts derived from cinchona alkaloids. However, the latter suffered from many drawbacks; the requirement of pre-designed substrates, lack of applicability for the late-stage-functionalization of peptides and strong basic conditions were often used. In this regard, CDC reactions have surpassed many of these disadvantages for the direct coupling two C(sp^3)–H bonds in a more atom-economical fashion and less reaction steps.

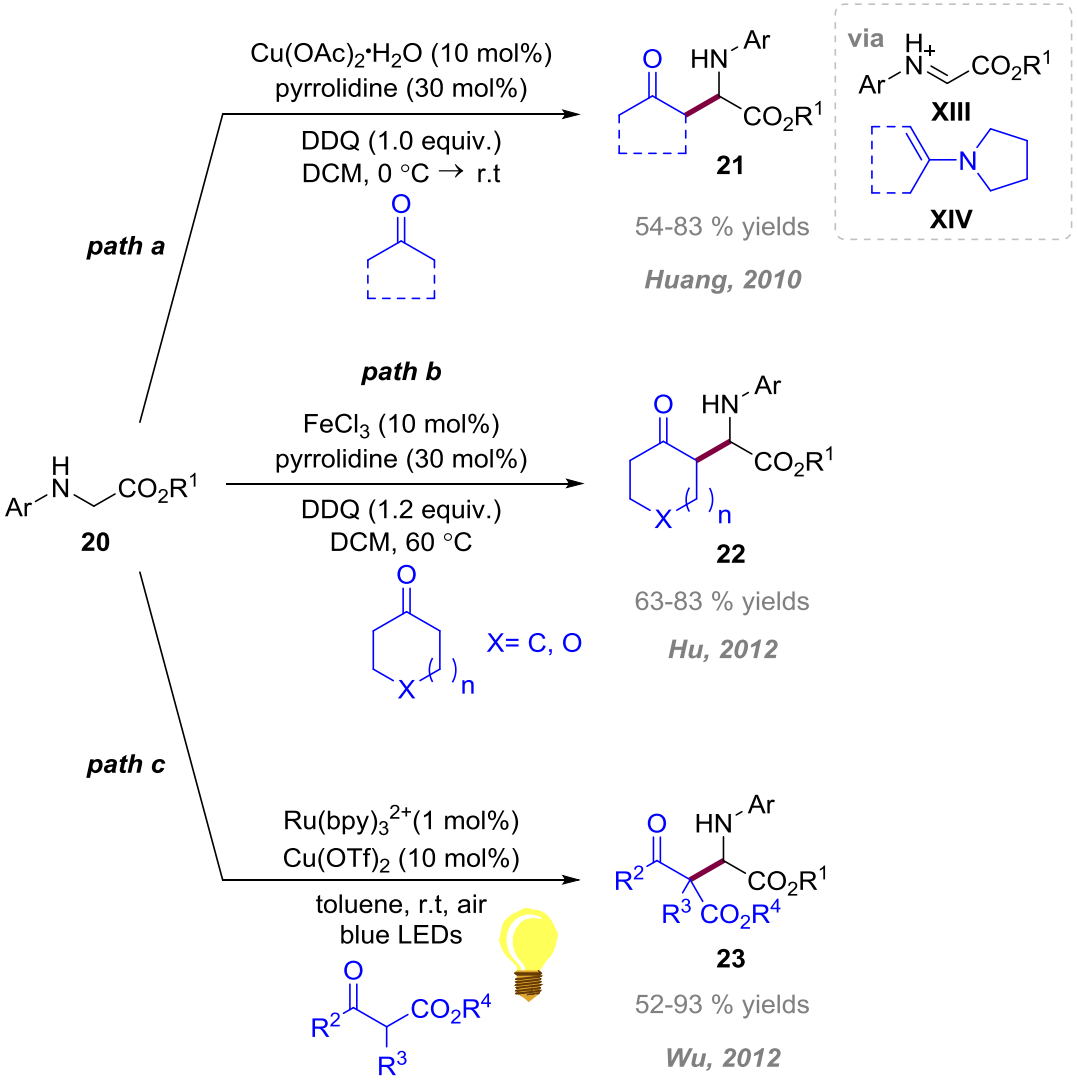
In 2008, the group of Li reported a novel method for the functionalization of *N*-acetyl glycine esters and malonates, to furnish a new C(sp^3)–C(sp^3) bond through a CDC process.[9] The reaction was proposed to occur *via* the formation of the imine **XI** and the nucleophilic enolate **XII** with the cooperation of the bidentate ligand **L2.** Herein, a short family of glycine esters **17** were successfully coupled with malonates (**18**), obtaining the final products **19** with moderate to excellent yields (Scheme 10). In addition, control experiments revealed that both the stoichiometric amounts of $Cu(OAc)_2$ and the ligand **L2** were essential for the success of the transformation, which demonstrated the challenge that represented the functionalization of such unactivated compound as *N*-acetyl glycine derivatives. In fact, this example still represents a rare example of modification of glycines derivatives devoid of an *N*-aryl group, and the harsh reaction conditions underpinned the difficulty of performing such a process.



Scheme 10. CDC reaction of malonates with *N*-acetyl glycine derivatives.

[25] Hashimoto, T.; Maruoka, K. *Chem*. *Rev*. **2007**, *107*, 5656.

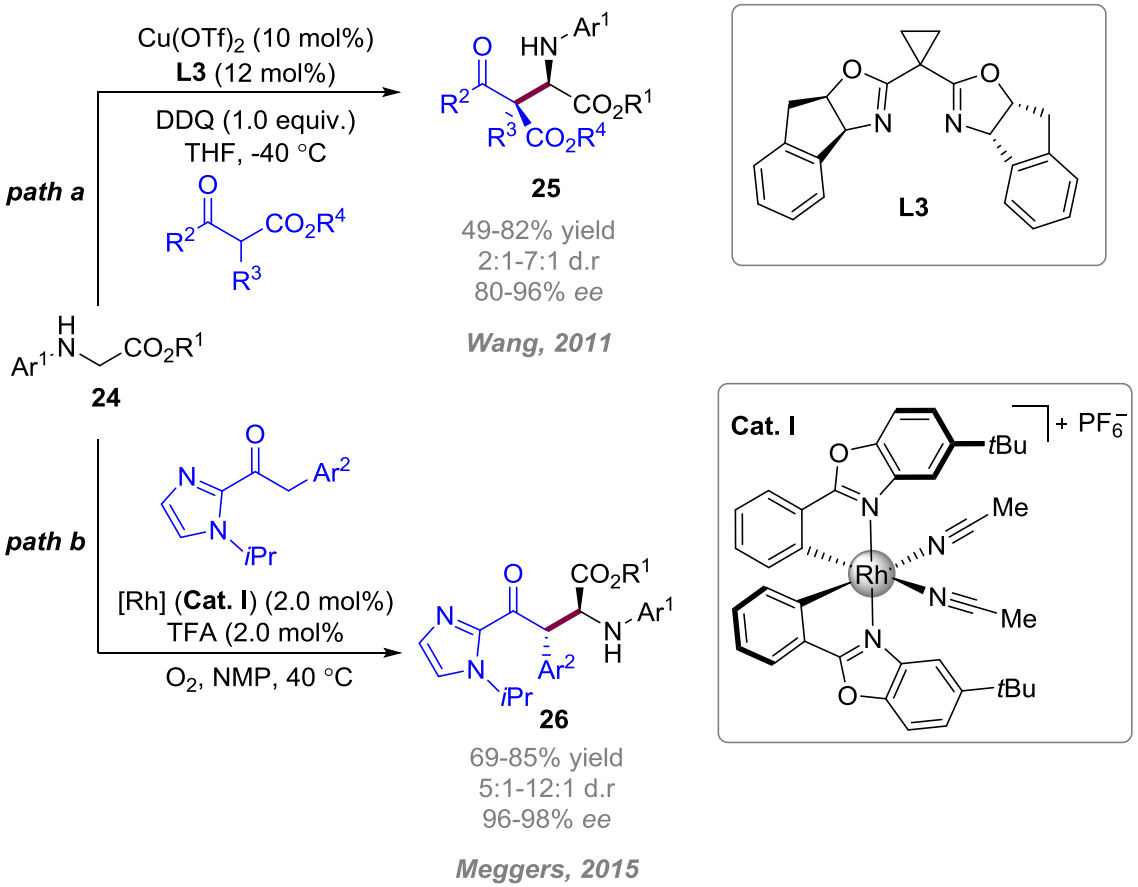
In 2010, Huang and co-workers developed a CDC reaction between *N*-aryl glycinates **20** with ketones, catalyzed by copper salts along with an organocatalyst.[26] This cooperative catalytic effect resulted from the *in situ* formation of the iminium ion **XIII** upon the oxidation of Cu/DDQ system, which then reacted with *in situ* formed enamine **XIV** derived from pyrrolidine and the corresponding ketone (Scheme 11, *path a*). Later on, Hu and co-workers reported the same transformation catalyzed by an environmentally friendly $FeCl_3$ catalyst (Scheme 11, *path b*)[27] and the group of Wu extended the procedure to the use of visible light with Ru and Cu catalysis for the coupling of *N*-aryl glycine derivatives with β-keto esters (Scheme 11, *path c*).[28]



Scheme 11. Alkylation of *N*-aryl glycine derivatives with enamines/enolates.

[26] Xie, J.; Huang, Z.-Z. *Angew*. *Chem*. *Int*. *Ed*. **2010**, *49*, 10181.
[27] Liu, P.; Wang, Z.; Lin, J.; Hu, X. *Eur. J. Org. Chem*. **2012**, 1583.
[28] Gao, X.-W.; Meng, Q.-Y.; Xiang, M.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Adv. Synth. Catal*. **2013**, *355*, 2158.

Despite the advances achieved in the alkylation of glycine moieties through CDC processes, the development of asymmetric procedures remained a challenging task of high importance. In 2011, the group of Wang reported the first Cu-catalyzed asymmetric alkylation protocol to alkylate *N*-aryl glycine derivatives with the use of a chiral bisoxazoline ligand (**L3**) (Scheme 12, *path a*).[29] Under optimized conditions, final products **25** were obtained with moderate diastereoselectivity (up to 7:1) and high enantioselectivity (up to 96%). These results set the stage for the discovery of further asymmetric procedures. Thereby, in 2015, the group of Meggers was able to introduce 2-acylimidazoles in a diastereo-/enantio-enriched fashion with the use of chiral Rh^{III} catalyst (**Cat. I**) under aerobic conditions (Scheme 12, *path b*).[30]

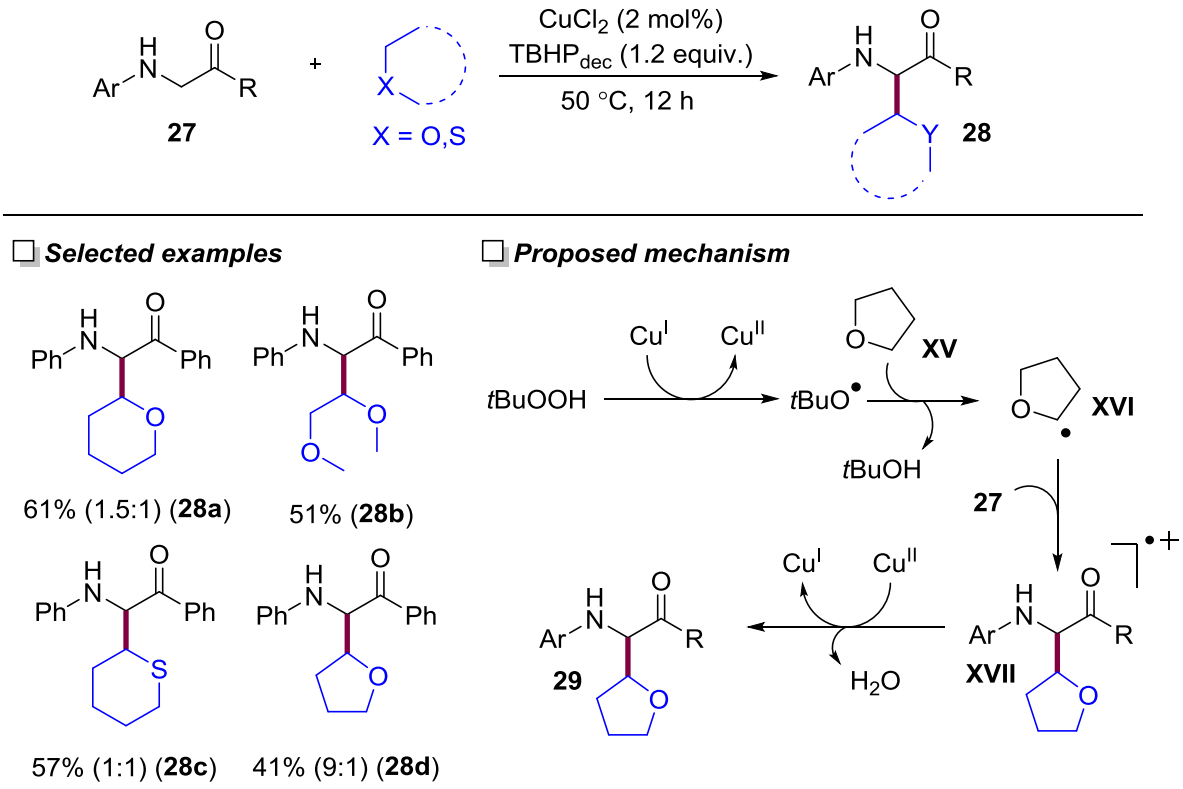


Scheme 12. Asymmetric alkylation of glycine derivatives.

In 2014, Li and co-workers reported the first example of a metal-catalyzed oxidative α-C–H alkylation of α-amino carbonyl compounds with cyclic ethers, such as THF and tetrahydropyran, acyclic ethers and

[29] Zhang, G.; Zhang, Y.; Wang, R. *Angew*. *Chem*. *Int*. *Ed*. **2011**, *50*, 10429.
[30] Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. *Angew*. *Chem*. *Int*. *Ed*. **2015**, *54*, 13045.

thioethers.[31] This dual C(sp^3)–H bond activation was achieved with catalytic amounts of $CuCl_2$ and $TBHP_{dec}$ as oxidant at 50 °C. The mechanistic proposal by the authors involved the formation of the alkyl radical **XVI** under oxidative conditions, which was added to the glycine derivative **27** to form the cationic intermediate **XVII**. Finally, the latter would be further oxidized by the copper catalyst to produce the final alkylated product **29** and regenerate the active catalyst (Scheme 13).

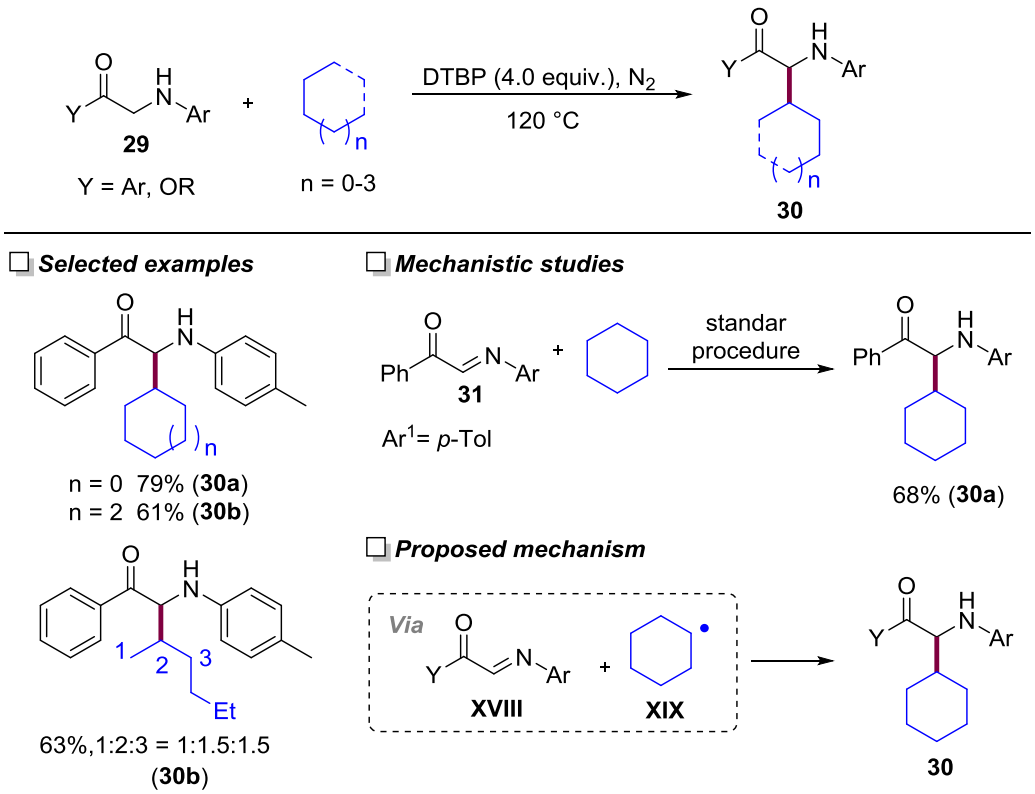


Scheme 13. Cu-catalyzed alkylation with ethers.

Subsequently, the group of Cheng was able to extend the methodology towards the activation of simple alkanes, which were also introduced into α-carbonyl compounds by oxidative C(sp^3)–H functionalization reactions.[32] In this case, DTBP was the oxidant of choice and no metal was employed as they did not exhibit any improvement in the outcome. Nevertheless, high temperatures (120 °C) were required for the optimal performance of the reaction. Thereby, several cyclic alkanes were effectively introduced into the glycine moiety (**30a**-**b**), whereas in the case of acyclic alkanes a mixture of isomers was obtained (**30c**). Mechanistic studies revealed that when alternative prepared imine **31** was employed instead of the starting glycine derivative, the reaction proceeded smoothly delivering the corresponding product **30a** in 68% yield, which

[31] Wei, W.-T.; Song, R.-J.; Li, J.-H. *Adv. Synth. Catal.* **2014**, *356*, 1703.
[32] Peng, H.; Yu, J.-T.; Jiang, Y.; Yang, H.; Cheng, J. *J. Org. Chem.* **2014**, *79*, 9847.

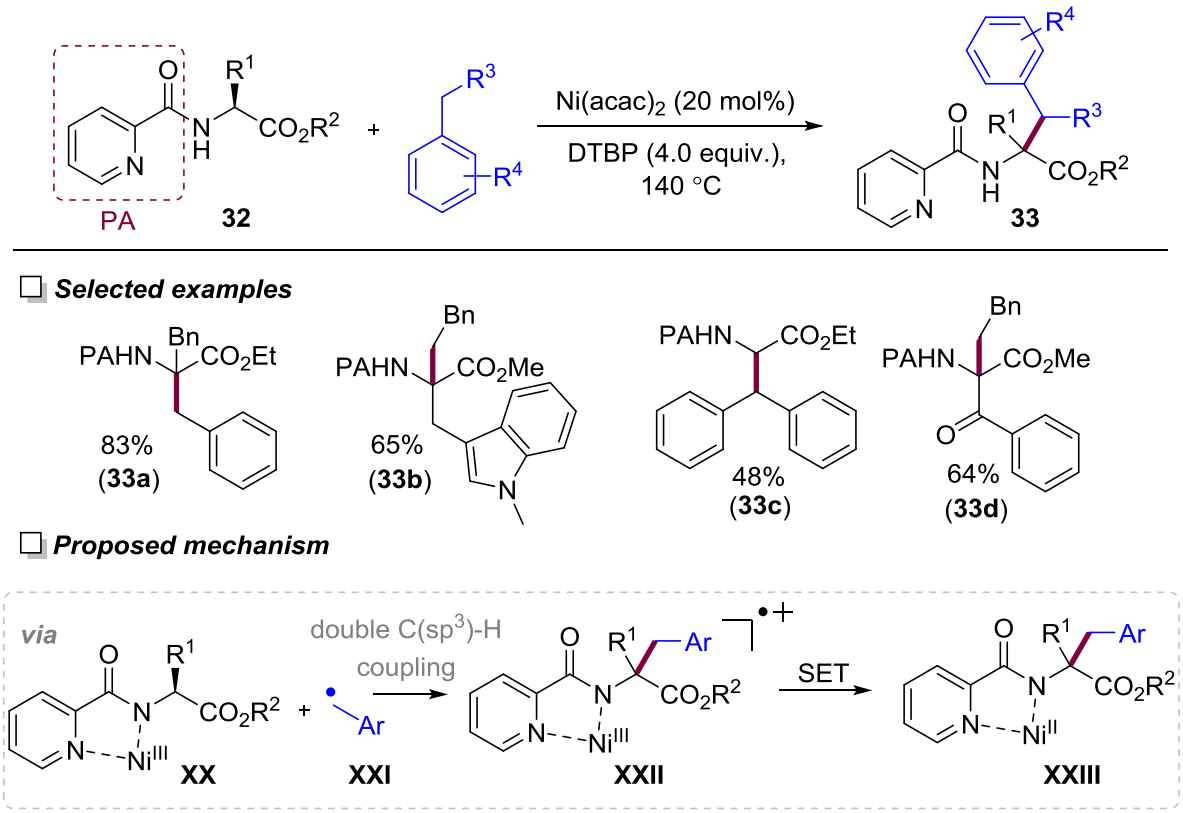
from author's point of view, evidenced its plausible role as a reaction intermediate to react with the transient alkyl radical **XIX** (Scheme 14).



Scheme 14. Metal-free alkylation with simple alkanes.

In connection with their previous findings in the synthesis of α-quaternary bonds,[23] You and co-workers reported a new protocol for the formation of new tertiary/quaternary carbon centers upon the radical activation of benzylic C(sp^3)–H bonds (Scheme 15).[33] The activation of the amino acids was enhanced using a chelating directing group, where once again, picolinamide (PA) provided the best results. Remarkably, nickel salts outperformed other metals salts such as iron, copper or ruthenium salts and DTBP exhibited the best result under high reaction temperatures. The protocol displayed a wide tolerance of amino acids as substrates (Gly, Ala, Val, Leu, Ile, Asp, Tyr, Trp, Met, Lys, and Ser, among others) for the oxidative coupling with a vast range of (hetero)arylmethanes. Based on control experiments, the authors proposed that the *in situ* formed benzyl radical **XXI** would add to the α-carbon of amino ester **32**. The resulting radical cation intermediate **XXII** then would undergo an intramolecular SET event by the electron deficient Ni^{III}, to finally release the final product **33** and the active Ni^{II} catalyst.

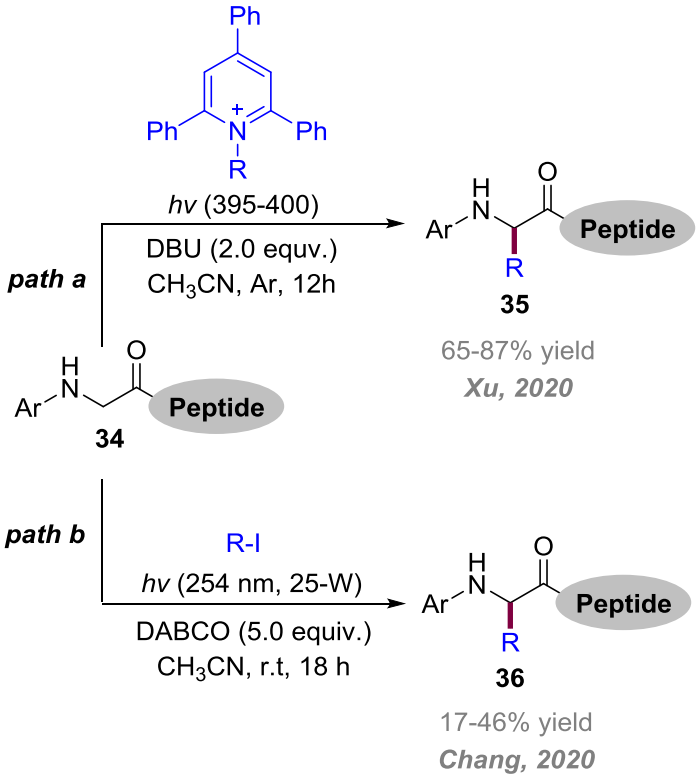
[33] Li, K.; Wu, Q.; You, J. *Nat. Commun*. **2015**, *6*, 8404.



Scheme 15. Assembly of β-aryl-α-amino esters.

Recently, Xu and co-workers have reported a visible-light-promoted alkylation of *N*-aryl glycines and peptides using Katritzky salts as alkylation reagents.[34] The transformation was carried out under simple conditions and exhibited excellent functional group tolerance (Scheme 16, *path a*). Similarly, employing widely available alkyl-iodides or alkyl-chlorides the group of Chang was able to perform the same transformation in low to moderate yields (Scheme 16, *path b*). Also recently, diacyl peroxides have been employed to alkylate *N*-aryl glycines under metal-free conditions by the group of Wang.[35]

[34] Wang, C.; Qi, R.; Xue, H.; Shen, Y.; Chang, M.; Chen, Y.; Wang, R.; Xu, Z. *Angew. Chem Int. Ed*. **2020**, *59*, 7461.
[35] Tian, H.; Xu, W.; Liu, Y. ; Wang, Q. *Org. Lett*. **2020**, *22*, 5005.



Scheme 16. Photo-induced C(sp^3)–H alkylation of *N*-aryl glycines and peptides.

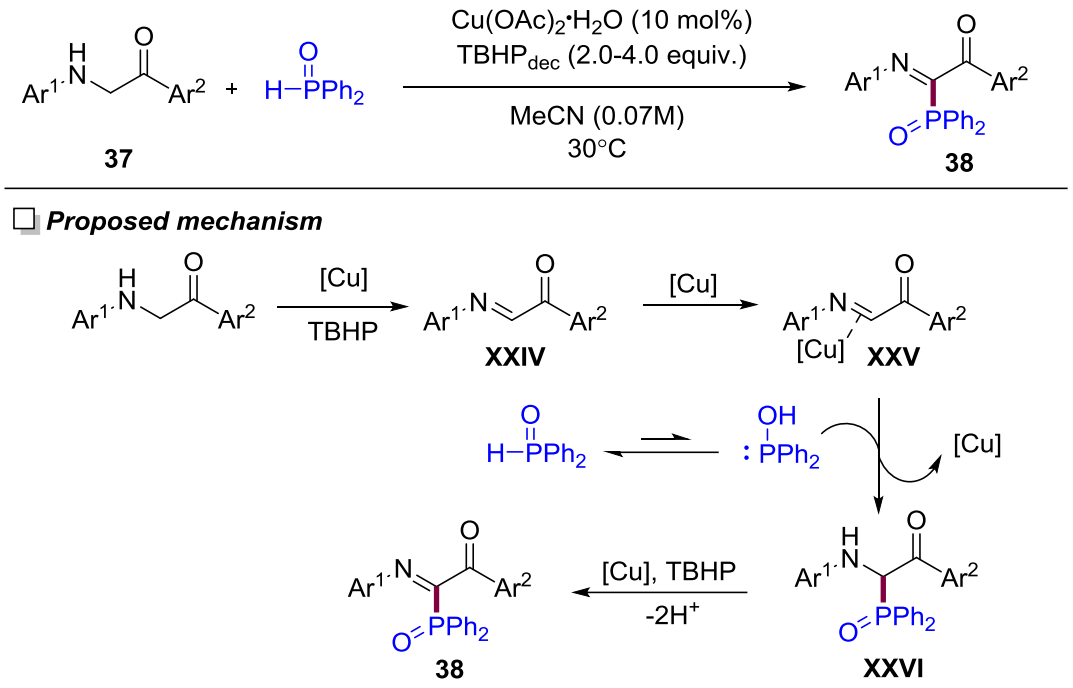
1.1.3.5. C–Heteroatom Bond-Forming Oxidative Couplings

1.1.3.5.1. C–P Bond Formation

Organic phosphorus compounds are widely present as building-blocks, pharmaceutical chemicals, and phosphine-containing ligands.[36] Therefore, the development of more precise and straightforward methods to build C–P bonds has gained a lot of interest in the field of organic chemistry. Recently, procedures to form new C–P bonds from simple C–H bonds catalyzed by first-row metals under oxidative conditions have opened the door to innovative bond disconnections.[37] The first example of a C–P bond formation with α-amino carbonyl compounds, was reported by Yang and co-workers.[38] This pioneering method enable the introduction of

[36] a) Van der Jeught, S.; Stevens, C. V. *Chem*. *Rev*. **2009**, *109*, 2672. b) Alexandre, F.-R.; Amador, A.; Bot, S.; Caillet, C.; Convard, T; Jakubik, J.; Musiu, C.; Poddesu, B.; Vargiu, L.; Liuzzi, M.; Roland, A.; Seifer, M.; Standring, D.; Storer, R.; Dousson, C. B. *J. Med*. *Chem*. **2011**, *54*, 392. c) Zhao, D.; Wang, R. *Chem*. *Soc*. *Rev*. **2012**, *41*, 2095.
[37] a) Han, W.; Ofial, A. R. *Chem*. *Commun*. **2009**, 6023. b) Ke, J.; Tang, Y.; Yi, H.; Li, Y.; Cheng, Y.; Liu, C.; Lei, A. *Angew*. *Chem*. *Int*. *Ed*. **2015**, *54*, 6604. c) Xu, P.; Wu, Z.; Zhou, N.; Zhu, C. *Org*. *Lett*. **2016**, *18*, 1143. d) Shen, J.; Xiao, B.; Hou, Y.; Wang, X.; Li, G.-Z.; Chen, J.-C.; Wang, W.-L.; Cheng, J.-B.; Yang, S.-D. *Adv*. *Synth Catal*. **2019**, *361*, 5198.
[38] Yang, B.; Yang, T.-T.; Li, X.-A.; Wang, J.-J.; Yang, S.-D. *Org*. *Lett*. **2013**, *15*, 5024.

diphenylphospine oxide into glycine derivatives with the Cu/$TBHP_{dec}$ system, to deliver imidoylphosphonate moieties **38** as the final products (Scheme 17).

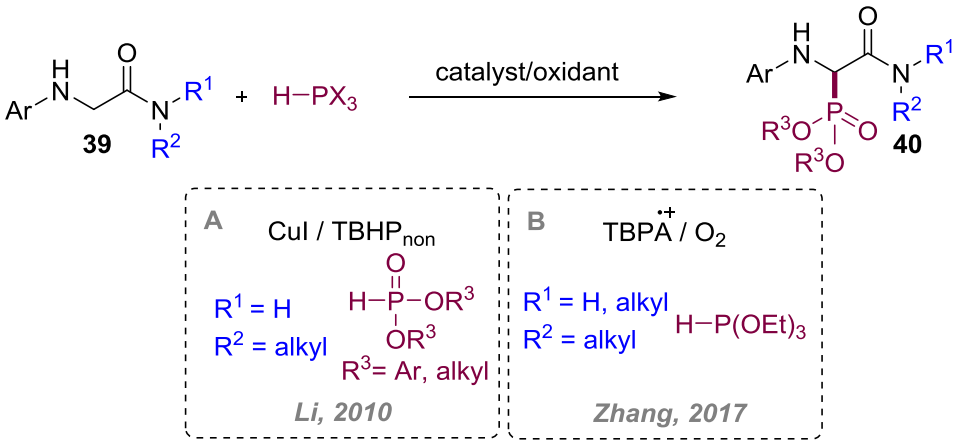


Scheme 17. Oxidative phosphonation of amino ketones.

The mechanistic proposal involved the formation of the corresponding imine (**XXIV**) with the Cu/$TBHP_{dec}$ system, where the coordination of the copper would enhance its electrophilic nature thus forming the intermediate **XXV**, which would react with diphenylphosphine oxide. Finally, the latter would suffer an oxidative deprotonation to produce the final product **38** (Scheme 17).

In 2016, the research group of Li developed a phosphorylation reaction of glycine amides **39**, using alkyl or aryl phosphites with catalytic amounts of a copper salt along with TBHP in nonane as oxidant (Scheme 18, A).[39] Subsequently, Zhang and co-workers reported an alternative procedure to phosphorylate glycine amides. In this case, catalytic amounts of $TBPA^{+\cdot}$ [tris (4-bromophenyl)aminiun hexachloroantimonate], was employed along with oxygen atmosphere as oxidant to phosphorylate a wide variety of tertiary and secondary glycine amides **39** (Scheme 18, B).[40]

[39] Zhi, H.; Ung, S. P.-M.; Liu, Y.; Zhao, L.; Li, C.-J. *Adv. Synth. Catal.* **2016**, *358*, 2553.
[40] Jia, X.; Liu, X.; Yuan, Y.; Yuan, Y.; Zhu, Y.; Hou, W.; Zhang, X. *Adv. Synth. Catal.* **2017**, *359*, 4399.

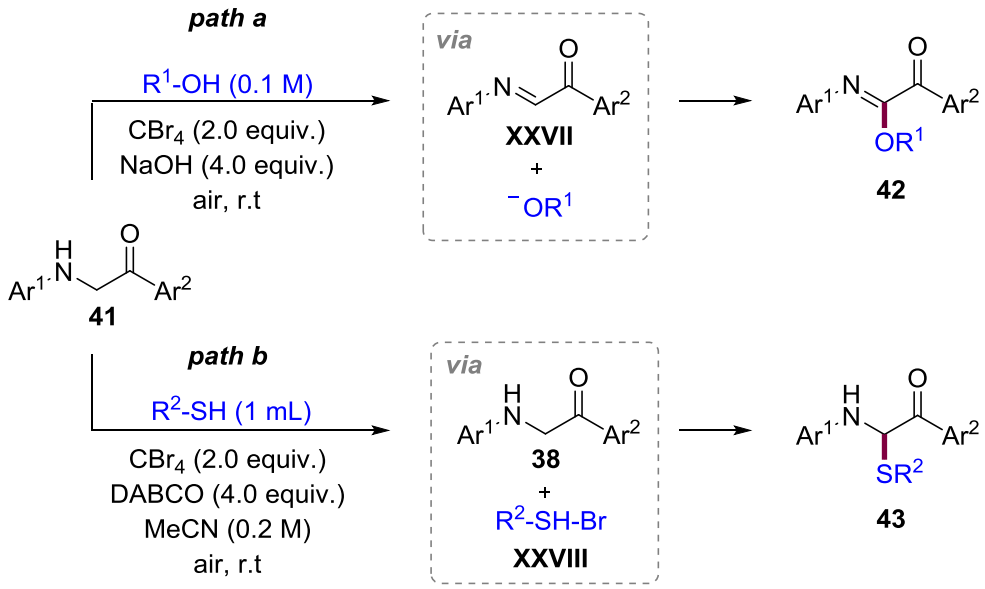


Scheme 18. Oxidative phosphorylation of α-amino amides.

1.1.3.5.2. C–O and C–S Bond Formation

With the aim of extending the known protocols to form other C–heteroatom bonds in α-amino carbonyl compounds, Huang and co-workers reported the first alkoxylation/thiolation of glycine derivatives with simple and widely available alcohols/thiols.[41] This metal-free reaction was performed with the use of CBr_4, under air and basic conditions, allowing the efficient coupling of vast array of alkyl alcohols and thiols. Unfortunately, the reaction was limited to alkyl nucleophiles, and phenols or thiophenols showed to be unreactive under the optimized conditions. The authors proposed two distinct mechanistic pathways depending on the nature of the nucleophile. While the alkoxylation was proposed to occur *via* the conventional accepted pathway, the coupling of imine **XXVII** and the alkoxylate (Scheme 19, *path a*), the thioalkoxylation was suggested to proceed via formation of the electrophilic **XXVIII** intermediate, which would be then *in situ* trapped by the α-C atom of the α-amino carbonyl compound **41** (Scheme 19, *path b*).

[41] Liu, X. ; Pu, J.; Luo, X.; Cui, X; Wu, Z.; Huang, G. *Org. Chem. Front*. **2018**, *5*, 361.



Scheme 19. CDCs with alcohols and thiols.

1.2. C–H Functionalization of Ethers

Due to their chemical inertness, the use of ethers such as tetrahydrofuran (THF) have been extensively employed as organic solvents in organic chemistry. However, in the last decade the activation of this type of compounds has been successfully achieved by CDC reactions and a plethora of procedures for the modification of inert ethers have been reported.[42] α-C–H Functionalization of such unactivated ethers is a challenging task of great significance, due to their presence in many of biologically active compounds (Figure 3).[43]

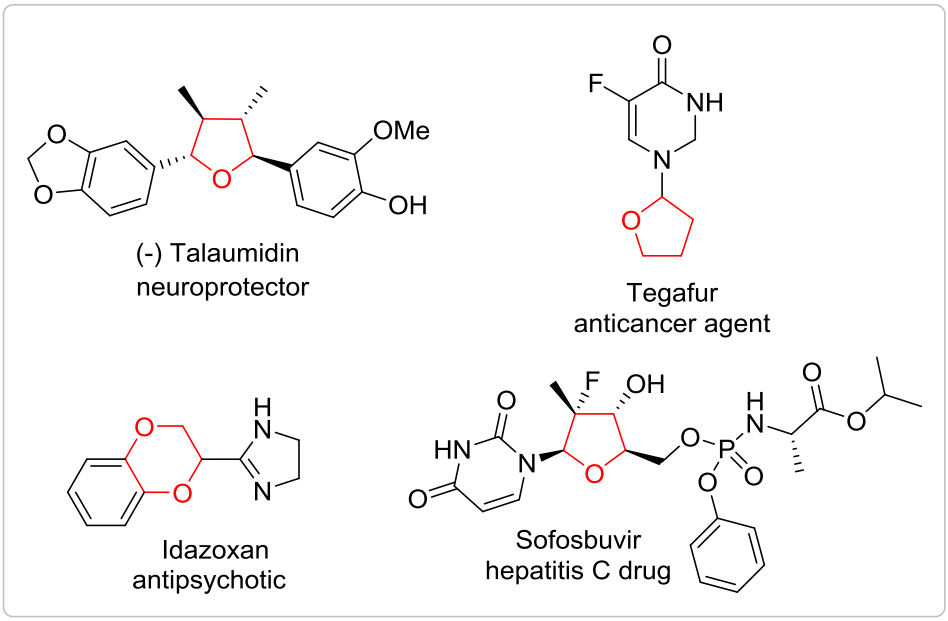


Figure 3. Selected biologically active ether-containing compounds.

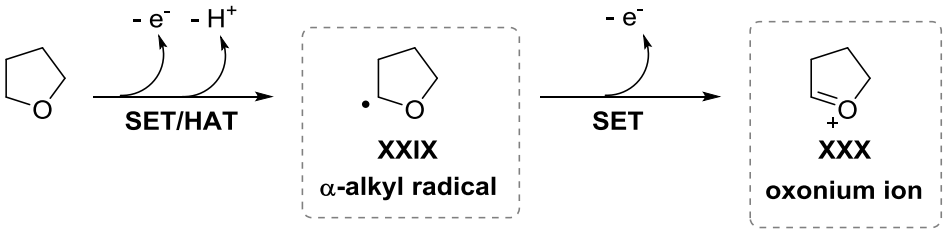
Commonly, the functionalization of C(sp^3)–H bonds in α-position to the oxygen atom of ethers is achieved by the use of stoichiometric amounts of an oxidant and it can be catalyzed by first-row transition metals through single electron transfer (SET) and hydrogen atom transfer (HAT) processes (Scheme 20).[44] The nucleophilic radical **XXIX** can serve as key intermediate in C–H functionalization, specially due to its reactivity

[42] a) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev*. **2011**, *40*, 1937. b) Guo, S.-R.; Santhosh k. P.; Yang, M. *Adv. Synth. Catal*. **2017**, *359*, 2. c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev*. **2017**, *117*, 9016. d) Lakshman, M. K.; Vuram, P. K. *Chem. Sci*. **2017**, *8*, 5845. e) Batra, A.; Singh, P.; Nain Singh, K. *Eur. J. Org. Chem*. **2017**, 3739.

[43] a) Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J. *J. Org. Chem*. **2004**, *69*, 6874. b) Nakata, T. *Chem. Rev*. **2005**, *105*, 4314. c) Roughley, S. D.; Jordan, A. M. *J. Med. Chem*. **2011**, *54*, 3451. d) Mammoli, V.; Bonifazi, A. ; Del Bello, F.; Diamanti, E.; Giannella, M.; Hudson, A. L.; Mattioli, L.; Perfumi, M.; Piergentili, A.; Quaglia, W.; Titomanlio, F.; Pigini, M. *Bioorg. Med. Chem*. **2012**, *20*, 2259.

[44] Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res*. **2014**, *47*, 3459.

with unsaturated bonds to form new C–C bonds. The radical **XXIX** can also undergo a further oxidation step and loose another electron to generate an electrophilic cationic intermediate (**XXX**), which could then react with another nucleophile.[45]

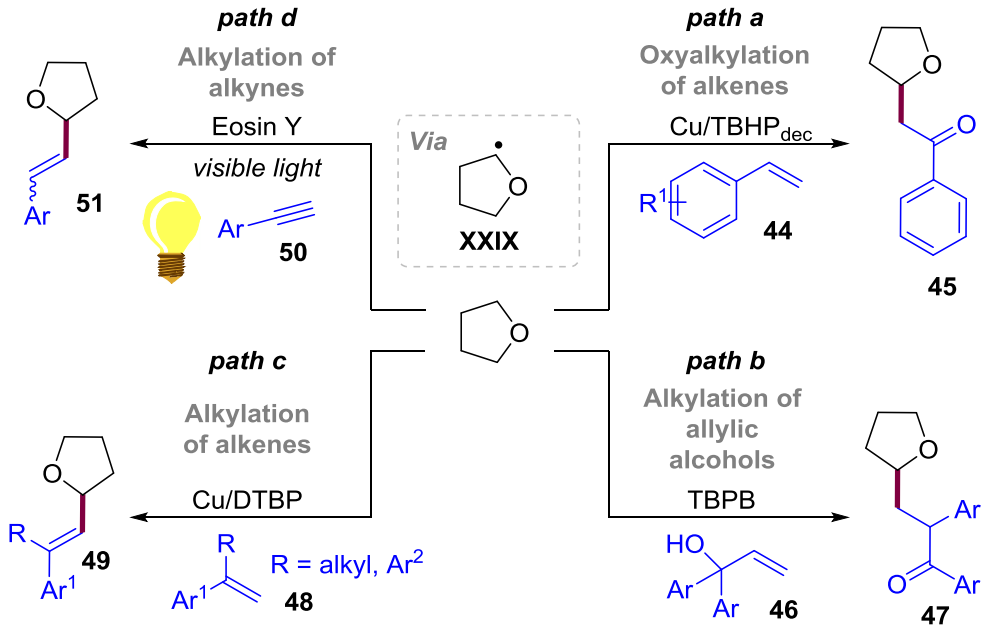


Scheme 20. C–H activation via SET/HAT processes.

1.2.1. Ethers as Alkyl Radicals Source

As summarized in Scheme 21, reactions of radicals derived from ethers such as THF are diverse. The difunctionalization of simple and widely available styrenes **44** by the Cu/$TBHP_{dec}$ system is one of the examples, in which the alkylation spontaneously occurred *via* Wacker oxidation[46] to deliver the final alkylated product as ketones **45** (Scheme 21, *path a*).[47] The functionalization of allylic alcohols **46** also has been described,[48] in this case the addition of the alkyl radical **XXIX** follows a 1,2-migration[49] to release the final ketone product **47** (Scheme 21, *path b*).[48] Moreover, the formation of allylic ethers from the coupling of radical **XXIX** with simple olefins **48** under the Cu/DTBP system has also been reported (Scheme 21, *path c)*,[50] along with a visible-light-promoted alkylation of aromatic alkynes **50** (Scheme 21, *path d*).[51]

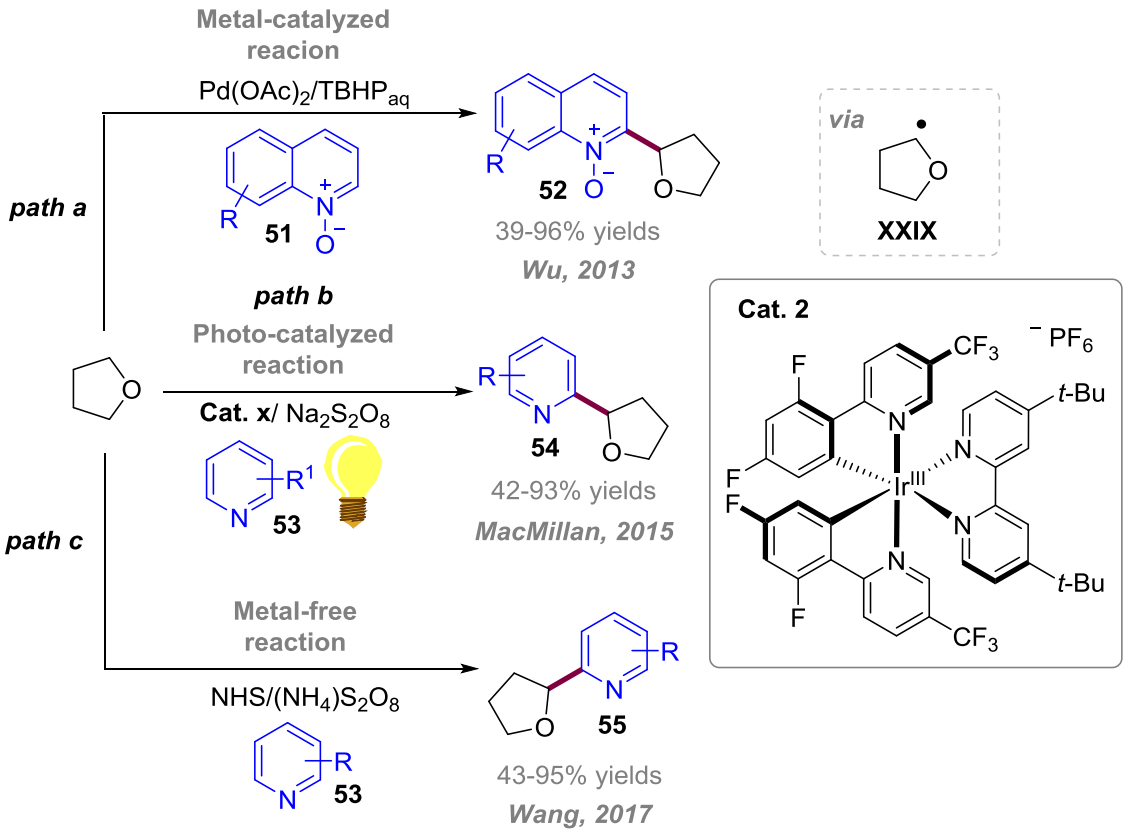
[45] a) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L. ; Lou, H. *J. Org. Chem*. **2013**, *78*, 3104. b) Muramatsu, W.; Nakano, K. *Org. Lett*. **2013**, *15*, 3659. c) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org*. *Lett*. **2010**, *12*, 1932. d) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem. Int. Ed*. **2013**, *52*, 4453. e) Correa, A.; Fisher, B.; Gomez-Bengoa, E. *Chem. Commun*. **2015**, *51*, 13365.
[46] Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev*. **2005**, *105*, 2329.
[47] Cheng, K.; Huang, L.; Zhang, Y. *Org. Lett*. **2009**, *11*, 2908.
[48] Chu, X.-Q.; Meng, H.; Zi, Y.; Xu, X.-P.; Ji, S.-J. *Chem*. *Commun*. **2014**, *50*, 9718.
[49] For reviews and recent examples see: a) Chen, Z.-M.; Bai, W.; Wang, S.-H.; Yang, B.-M.; Tu, Y.-Q.; Zhang, F.-M. *Angew. Chem. Int. Ed*. **2013**, *52*, 9781. b) Weng, W.-Z.; Zhang, B. *Chem. Eur. J.* **2018**, *24*, 10934. c) Sarkar, S.; Banerjee, A.; Yao, W.; Patterson, E. V.; Ngai, M.-Y. *ACS Catal*. **2019**, *9*, 10358.
[50] Liu, D.; Liu, C. ; Li, H.; Lei, A. *Chem. Commun*. **2014**, *50*, 3623.
[51] Li, J.; Zhang, J.; Tan, H.; Wang, D. Z. *Org*. *Lett*. **2015**, *17*, 2522.



Scheme 21. Alkylation of unsaturated bonds with cyclic ethers.

The straightforward formation of the alkyl radical **XXIX**, has allowed the use of ethers as alkyl feedstock for a plethora of Minisci-type reactions.[52] This radical alkylation of electron deficient heterocycles with ethers has been mostly applied to electron-poor pyridines or quinolone derivatives as it is summarized in Scheme 22. The group of Wu implemented a Pd-catalyzed C2-alkylation of quinoline *N*-oxides **51** with cyclic ethers (Scheme 22, *path a*).[53] In 2015, the group of MacMillan developed the first alkylation process for the ubiquitous pyridine or quinoline derivatives **53** in a photoredox manner and the activation of both cyclic and acyclic ethers was achieved (Scheme 22, *path b*).[54] In the same year, a metal-free protocol was described by the group of Singh,[55] for the alkylation of heteroarenes with ethers under stoichiometric amounts of $K_2S_2O_8$ as oxidant. Likewise, a related metal-free protocol featuring the use of NHS (*N*-hydroxysuccinimide) and $(NH_4)S_2O_8$ as oxidant was reported by Wang (Scheme 22, *path c*).[56]

[52] Proctor, R. S. J.; Phipps, R. J. *Angew. Chem. Int. Ed.* **2019**, *58*, 13666.
[53] Wu, Z.; Pi, C.; Cui, X.; Bai, J.; Wu, Y. *Adv. Synth. Catal.* **2013**, *355*, 1971.
[54] Jin, J.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1565.
[55] Ambala, S.; Thatikonda, T.; Sharma, S.; Munagala, G.; Yempalla, K. R.; Vishwakarma, R. A.; Singh, P. P. *Org. Biomol. Chem.* **2015**, *13*, 11341.
[56] Liu, S.; Liu, A.; Zhang, Y.; Wang, W. *Chem Sci.* **2017**, *8*, 4044.



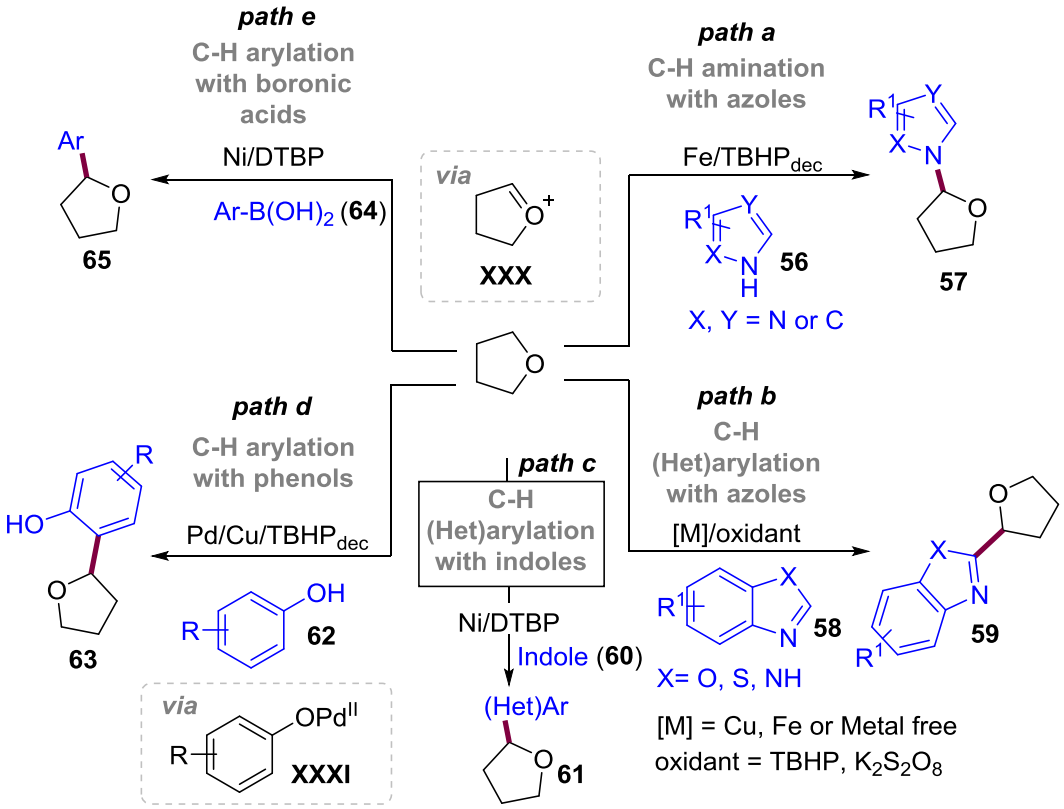
Scheme 22. Minisci-type reactions with cyclic ethers.

1.2.2. Ethers as Oxonium Ion Source

In sharp contrast, two consecutive SETs and a HAT process would deliver an electrophilic oxonium ion **XXX**, which in the last years has been widely used in the field of metal-catalyzed C–H functionalization as a powerful and versatile electrophilic carbon feedstock to react with multiple nucleophiles, as depicted in Scheme 23. In 2010, the iron-catalyzed *N*-alkylation of azoles (**56**) with ethers was reported by the group of Li (Scheme 23, *path a*).[45c] The selective C2-alkylation of azoles (**58**) has been extensively explored both under metal catalysis and under metal-free reaction conditions (Scheme 23, *path b*).[57,42e] The group of Cai reported the regioselective C2- or C3-alkylation of indole (**60**) with cyclic ethers controlled by additives. Upon the addition of catalytic amounts of $Zn(OT_F)_2$ to the $Ni(acac)_2$/DTBP system the C3-alkylated product was obtained, whereas the addition of catalytic amounts of PPh_3 to the NiF_2/DTBP system afforded the C2-alkylated product **63** (Scheme 23, *path c*).[58] The palladium-catalyzed alkylation of phenols (**62**) was reported by the group of

[57] a) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett*. **2011**, *13*, 5016. b) Xie, Z.; Cai, Y.; Hu, H.; Liu, C.; Jiang, J.; Chen, Z.; Wang, L.; Pan, Y. *Org. Lett*. **2013**, *15*, 4600.
[58] Jin, L.-K.; Wan, L.; Feng, J.; Cai, C. *Org. Lett*. **2015**, *17*, 4726.

Lee,[59] where formation of a Pd^{II} phenolate[60] **XXXI** was proposed to react with the oxonium ion **XXX** to form the new C–C bond (Scheme 23, *path d*). Of paramount importance was the work done by the group of Lei,[45d] where the Ni-catalyzed arylation of ethers was achieved with the use of boronic acids **64** (Scheme 23, *path e*).



Scheme 23. The use of the oxonium **XXX** as electrophile.

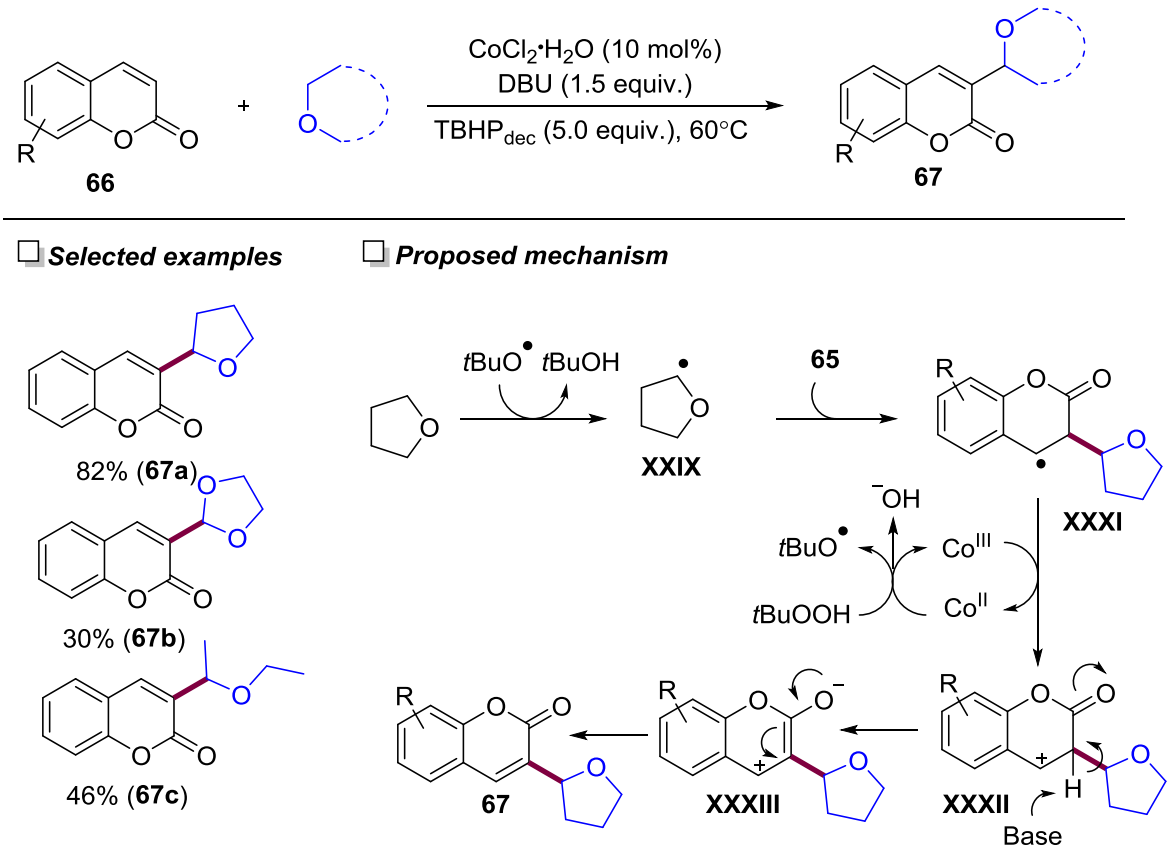
[59] Pandit, R. P.; Lee, Y. R. *Adv. Synth. Catal.* **2014**, *356*, 3171.
[60] Huang, Z.; Lumb, J.-P. *ACS Catal.* **2019**, *9*, 521.

1.3. Cobalt-Catalyzed Cross-Dehydrogenative Coupling Reaction with Cyclic Ethers

Cobalt is present in many biologically relevant compounds such as vitamin B12. Moreover, cobalt is considerably less expensive and less toxic than the noble metals, which constitutes an appealing alternative to perform cross-coupling reactions[61] and C–H functionalization.[62] Accordingly, cobalt has emerged as a new and advantageous first-row transition metal catalyst for cross-dehydrogenative-coupling reactions, although its applications remain scarcely explored.[63]

In 2016, a cobalt-catalyzed selective C3-alkylation of coumarins with ethers was described by the group of Du.[64] The optimized conditions relied on the use of $CoCl_2 \cdot 6H_2O$ as catalyst, $TBHP_{dec}$ as oxidant and DBU as base showed to improve the yield of the alkylated products. Under those conditions, cyclic ethers such as THF (**67a**) and 1,3-dioxolane (**67b**) or acyclic ethers (**67c**) were perfectly accommodated into coumarin motifs with moderate to goods yields (Scheme 24).

[61] Hamman, J. M.; Hofmayer, M. S.; Lutter, F. H. ; Thomas, L.; Knochel, P. *Synthesis* **2017**, *49*, 3887.
[62] a) Mei, R.; Dhawa, U.; Samanta, R. C.; Ma, W.; Delord, J. W.; Ackermann, L. *ChemSusChem.* **2020**, *13*, 3306. b) Pototschnig, G.; Maulide, N.; Schnürch, M. *Chem*. *Eur*. *J*. **2017**, *23*, 9206. c) Wang, S.; Chen, S.-Y.; Yu, X.-Q. *Chem*. *Commun*. **2017**, *53*, 3165.
[63] Phillips, A. M. F. Pombeiro, A. J. L. *ChemCatChem*. **2018**, *10*, 3354.
[64] Dian, L.; Zhao, H.; Zhang-Negrerie, D.; Su, Y. *Adv. Synth. Catal.* **2016**, *358*, 2422.

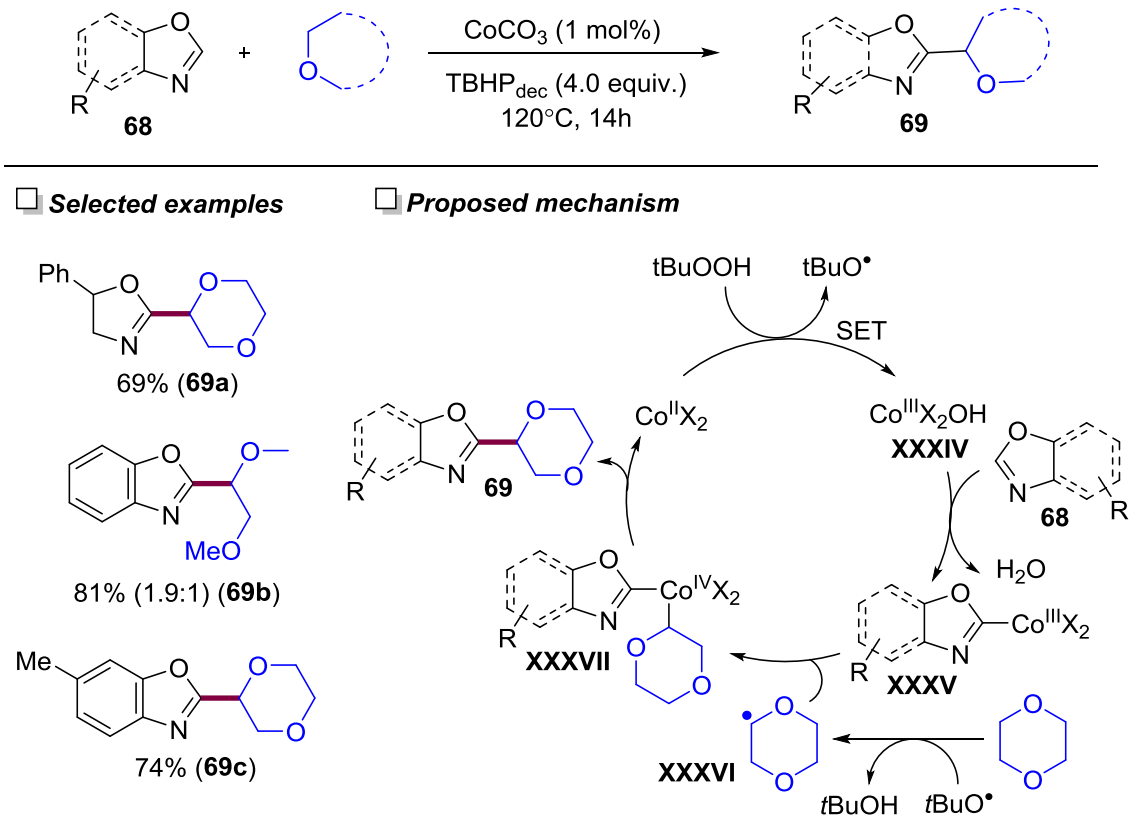


Scheme 24. Selective C3-alkylation of coumarins with ethers.

As depicted in Scheme 24, the proposed mechanism would start with the cobalt-promoted decomposition of $TBHP_{dec}$ to deliver the *tert*-butoxyl radical. Next, homolytic cleavage of the alkyl C–H bond induced by the *tert*-butoxyl radical would generate the radical **XXIX**, which would react with the coumarin moiety forming the intermediate **XXXI**. This intermediate **XXXI**, would be further oxidized by Co^{III} to form the cationic species **XXXII**, which after an isomerization process (**XXXIII**) would deliver the final product.

In the same year, a cobalt-catalyzed C2-alkylation of (benz)oxazoles with ethers was reported by the group of Lu.[65] The system consisted in $CoCO_3$ as catalyst and $TBHP_{dec}$ as oxidant, where just 1 mol% of the catalyst was required to perform the reaction. Several (benz)oxazoles were selectively alkylated with either cyclic ethers (**69a**, **69c**) or acyclic ethers (**69b**) as depicted in Scheme 25. The proposed mechanism consisted in the formation of the electrophilic organometallic intermediate **XXXV**, which would undergo an oxidative addition of the alkyl radical **XXXVI** to generate the Co^{IV} species **XXXVII**. Finally, the reductive elimination of Co^{IV} would deliver the desired product **69** and regenerate the active Co^{II} catalyst.

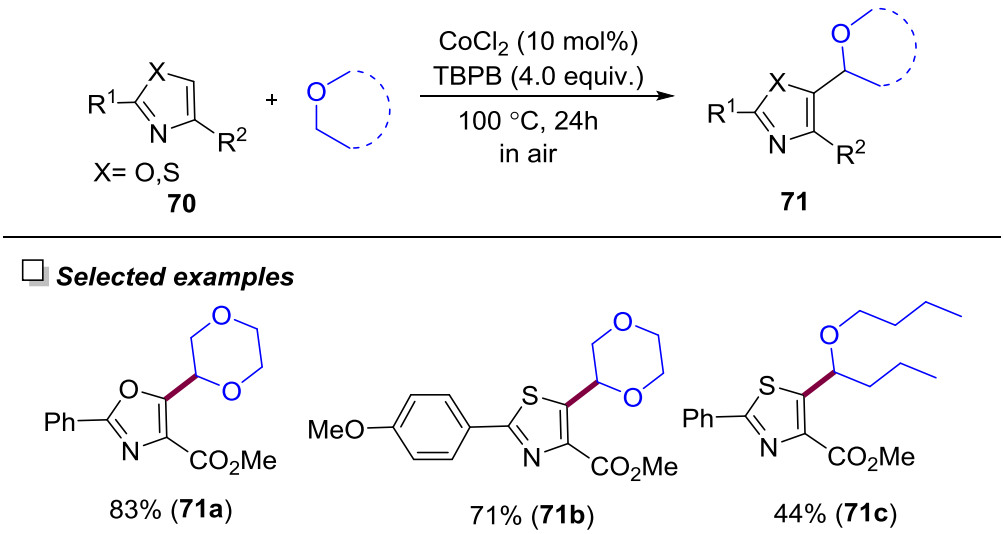
[65] Li, Y.; Wang, M.; Fan, W.; Qian, F.; Li, G.; Lu, H. *J. Org. Chem.* **2016**, *81*, 11743.



Scheme 25. Cobalt-catalyzed selective C2-alkylation of (benz)oxazoles with ethers.

Later on, the group of Li described a selective C5-alkylation of oxazoles and thiazoles with ethers.[66] In connection with the protocol described by the group of Lu (see Scheme 25), the optimized system was based in a cobalt salt and *tert*-butyl peroxybenzoate (TBPB) as oxidant, where in this case $CoCl_2$ exhibited the best catalytic activity. Regarding to the scope, a wide range of functional groups were well tolerated at C2-positions of the substrates, to couple with cyclic or acyclic ethers (Scheme 26).

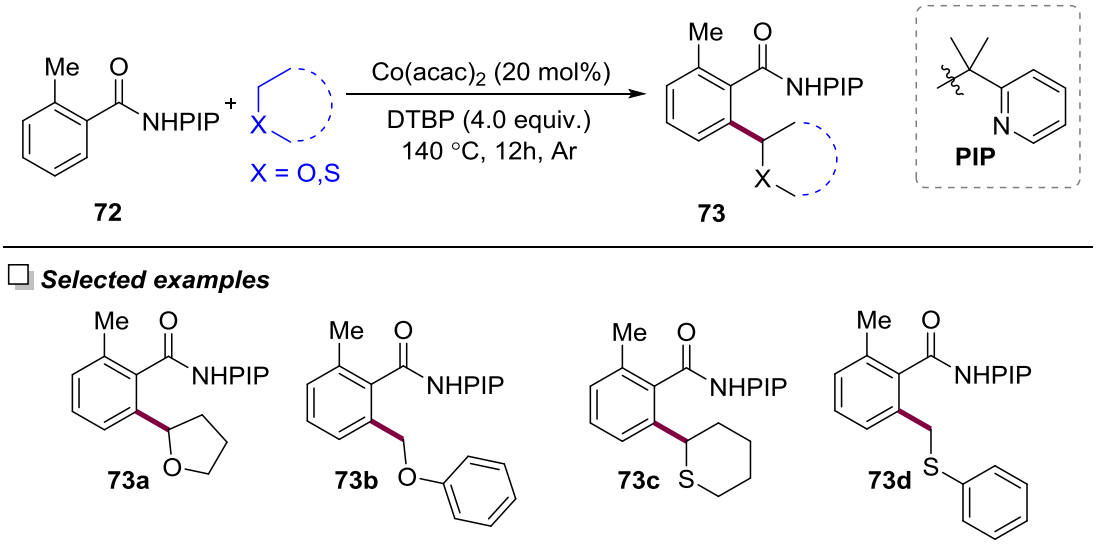
[66] Wang, X.; Lei, B.; Ma, L. ; Zhu, L.; Zhang, X.; Zuo, H.; Zhuang, D.; Li, Z. *Chem. Asian J.* **2017**, *12*, 2799.



Scheme 26. Cobalt-catalyzed selective C5-alkylation of oxazoles and thiazoles with ethers.

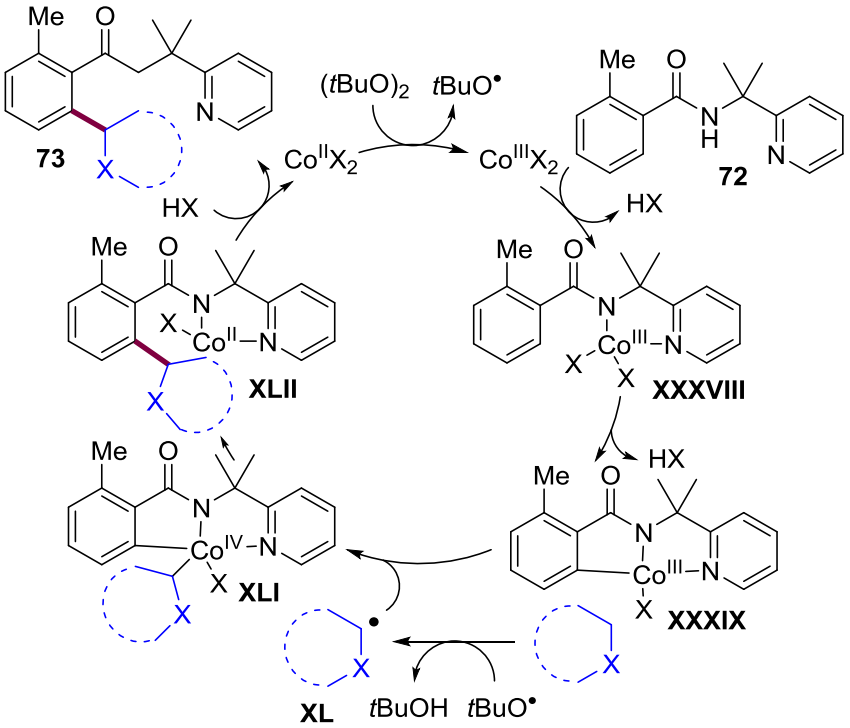
Unlike heterocycles, which have intrinsically reactive C–H bonds due to the presence of heteroatoms in their structures, simple phenyl groups are inert moieties that represent a mayor challenge to perform C–H functionalizations. To overcome this issue, one of the strategies is the use of a directing group.[67] The group of Li reported a cobalt-catalyzed alkylation of benzamides with ethers with the assistance of the bidentate directing group (pyridine-2-yl)isopropyl amine (PIP).[68] Among the cobalt salts tested in the screening process, only substoichiometric amounts of $Co(acac)_2$ exhibited a remarkable activity and the conditions were optimized with the use of DTBP as oxidant under high temperature (140 °C). Under these conditions, 2-methylbenzamide **72** was successfully alkylated with cyclic (thio)ethers (**73a**, **73b**), acyclic (thio)ethers and aromatic (thio)ethers (**73b**, **73c**) (Scheme 27). Even though the employment of 2-methylbenzamide **72** enabled the exclusive formation of *mono*-alkylated products **73**, it considerably limited the scope of the process.

[67] Sambiago, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-delord, J.; Besset, T.; Maes, B. V. W.; Schnürch, M. *Chem. Soc. Rev*. **2018**, *47*, 6603.
[68] Li, Q.; Hu, W.; Hu, R.; Lu, H.; Li, G. *Org. Lett*. **2017**, *19*, 4676.



Scheme 27. PIP-directed cobalt-catalyzed alkylation of benzamides with ethers.

On the basis of several control experiments and previous reports, a plausible catalytic cycle was proposed (Scheme 28). After the homolytic cleavage of the DTBP, the Co^{III} would be coordinated to the DG to form the intermediate **XXXVIII**. The latter would undergo a concerted metalation-deprotonation (CMD) to form **XXXIX** and the alkyl radical **XL** would react with organo-cobalt intermediate **XXXIX** to form the Co^{IV} intermediate **XLI**. Eventually, the reductive elimination of **XLI** would deliver the final alkylated products **73** and the Co^{II} which could continue the catalytic cycle.



Scheme 28. Proposed mechanism for the PIP-directed cobalt-catalyzed alkylation of benzamides with ethers.

1.4. Co-Catalyzed C(sp)^3–H Oxidative Coupling of Glycine and Peptide Derivatives

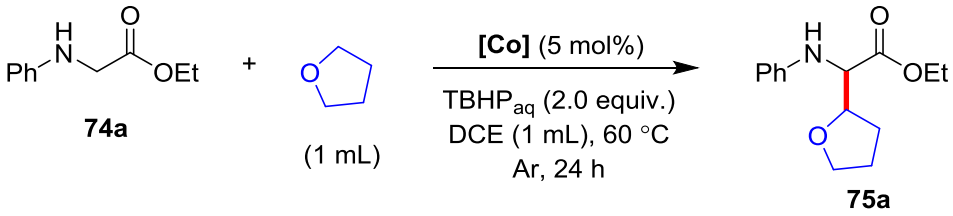
1.4.1. General Objectives

As we have mentioned before, straightforward alkylation of *N*-aryl glycine moieties with ethers represents a challenge of great scientific interest. Although there is no doubt that remarkable improvements have been achieved in this field, these types of reactions are mostly catalyzed by copper and iron salts. Hence, we envisioned that an alternative first-row transition metal such as cobalt, could be applied to perform these reactions and open up new horizons in organic chemistry, thereby broadening the scope of existing methodologies to enable the diversification of challenging short peptides. As a result, we established the following main objectives of this project:

- To explore the use of cobalt salts for the selective alkylation of *N*-aryl glycine moieties with ethers.
- To broad the scope of existing methodologies to short-to-medium peptides.
- To gain some insights into the reaction mechanism.

1.4.2. Optimization of the Reaction Conditions

We first evaluated the viability of using cobalt salts as catalysts for the alkylation of commercially available Ph-Gly-OEt (**74a**) with THF (Table 1). The oxidant of choice was the inexpensive aqueous solution of *tert*-butyl hydroperoxide ($TBHP_{aq}$), DCE as co-solvent at 60 °C under an argon atmosphere.



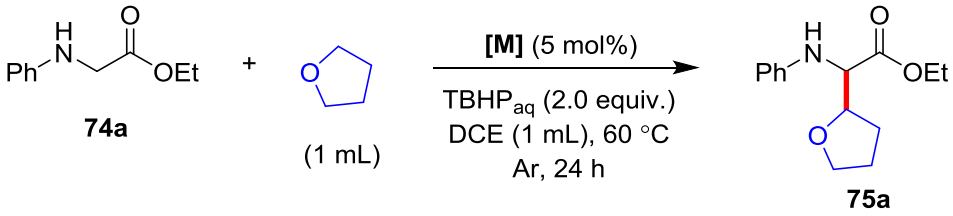
Entry	[Co]	Yield (%)
1	$Co(acac)_2{\cdot}H_2O$	78
2	$Co(acac)_3$	64
3	$CoCl_2$	71
4	CoF_2	0
5	CoF_3	0
6	$Co(NO_3)_2$	0
7	$Co(OAc)_2$	69
8	$CoBr_2$	77

Reaction conditions: **74a** (0.5 mmol), **THF** (1 mL), [Co] (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 1. Screening of cobalt salts.

Fortunately, under these reaction conditions, several cobalt salts showed great catalytic activity for this particular reaction (Table 1, entries 1-3; entries 7-8). Nonetheless, other cobalt salts did not afford the desired product (Table 1, entries 4-6), which could be due to solubility issues. Among the cobalt salts tested $Co(acac)_2{\cdot}H_2O$ exhibited the best activity, obtaining the desired alkylated product **75a** with a remarkable 78% yield (Table 1, entry 1).

Next, we performed some comparative studies with other conventional copper and iron salts (Table 2). To our delight, the cobalt catalyst outperformed the activity of other copper salts (Table 2, entries 6-7) and iron salts (Table 2, entries 2-4). Likewise, the more sustainable and earth-abundant manganese salt $Mn(OAc)_2$, produced product **75a** in only trace amounts (Table 2, entry 5).

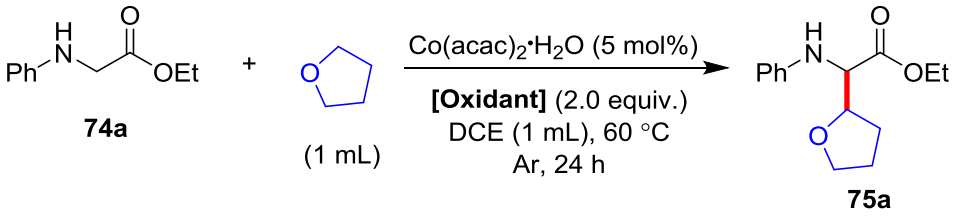


Entry	[Metal]	Yield (%)
1	$Co(acac)_2{\cdot}H_2O$	78
2	$FeCl_2$	62
3	$Fe(acac)_3$	0
4	$Fe(OAc)_2$	0
5	$Mn(OAc)_2$	traces
6	$CuCl_2$	30
7	$CuBr_2$	34

Reaction conditions: **74a** (0.5 mmol), **THF** (1 mL), [Co] (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 2. Screening of different metal salts.

Afterwards, we turned our attention to the effect of the oxidant on the reaction outcome. As shown in Table 3, the aqueous solution of TBHP gave better result than its analogue in decane (Table 3, entry 2), which represented an added-bonus from economical and sustainability standpoint. Other related oxidants were shown unreactive (Table 3, entries 3-6), or delivered **75a** in low yield (Table 3, entry 9). The use of highly oxidizing compounds such as PIDA and DDQ resulted in the degradation of the starting material (Table 3, entries 7-8). Unfortunately, the use of O_2 as a benign oxidant did not provide the desired product (Table 3, entry 10).

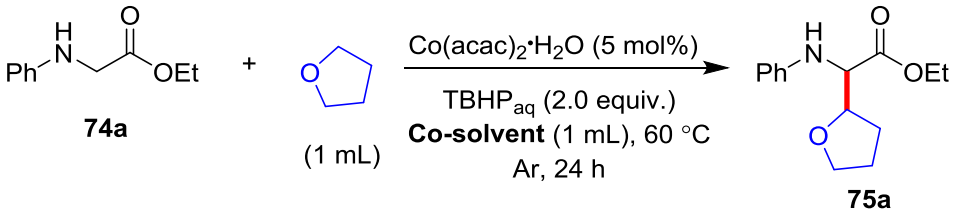


Entry	Oxidant	Yield (%)
1	$TBHP_{aq}$	78
2	$TBHP_{dec}$	48
3	DCP	0
4	DTBP	0
5	$K_2S_2O_8$	0
6	NHPI	0
7	PIDA	degradation
8	DDQ	degradation
9	CHP	37
10	O_2 (1 atm)	0

Reaction conditions: **74a** (0.5 mmol), **THF** (1 mL), $Co(acac)_2{\cdot}H_2O$ (5 mol%), [oxidant] (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O), TBHPdec = *tert*-butyl hydroperoxide (5.0-6.0 M in decane), DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide, CHP = cumene hydroperoxide.

Table 3. Screening of oxidants.

Despite its low-price, in order to decrease the amount of THF, we next investigated the influence of adding other co-solvents to the reaction. However, neither a polar solvent such as DMA or apolar solvents such as toluene resulted in better yields (Table 4, entries 1-3). Likewise, the performance of the reaction in neat THF provided lower yield of **75a**, thus reinforcing the key role of DCE in the reaction outcome (Table 4, entry 4).

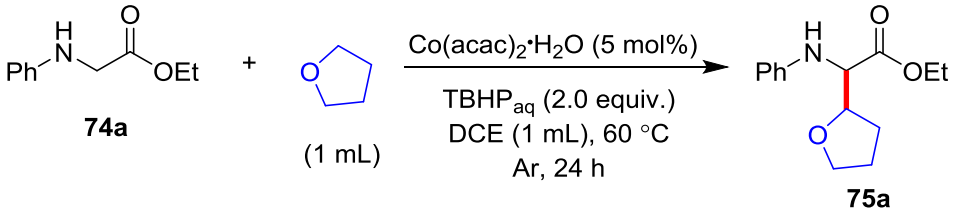


Entry	Co-solvent	Yield (%)
1	DCE	78
2	DMA	56
3	Toluene	36
4[a]	--	61

Reaction conditions: **74a** (0.5 mmol), **THF** (1 mL), $Co(acac)_2 \cdot H_2O$ (5 mol%), $TBHP_{aq}$ (2.0 equiv.), Co-solvent (1 mL), 60 °C, 24 h, under argon atmosphere. [a] 2 ml of THF. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 4. Screening of co-solvents.

Finally, some control experiments were performed with the aim of gaining more knowledge about the reaction insights. As expected, blank experiments in which Co catalyst or the oxidant were omitted resulted in no product formation (Table 5, entries 2-3). Lowering the catalyst loading decreased the yield of the product **74a** (Table 5, entry 4) and the performance of the reaction under an air atmosphere had also a negative effect (Table 5, entry 5).



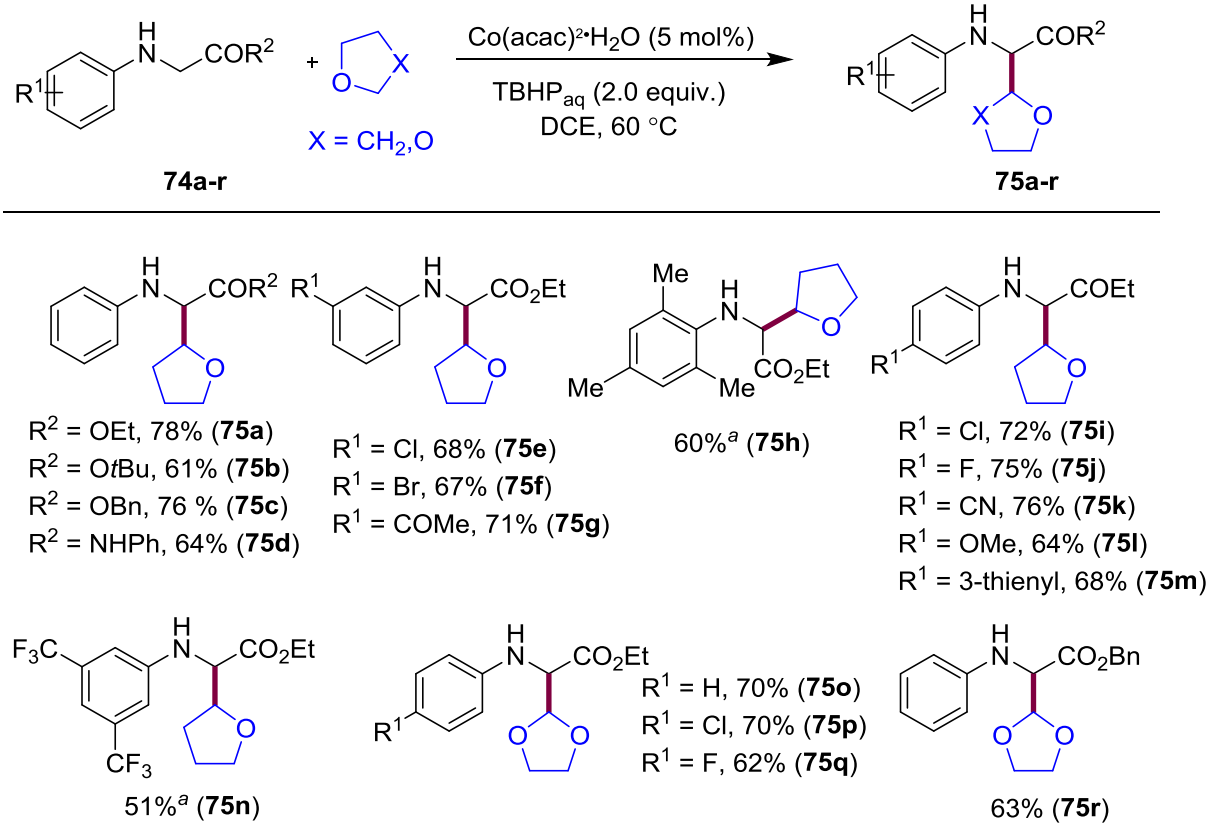
Entry	Metal	Oxidant	Co-solvent	Yield (%)
1	$Co(acac)_2 \cdot H_2O$	TBHPaq	DCE	78
2	--	TBHPaq	DCE	0
3	$Co(acac)_2 \cdot H_2O$	---	---	traces
4[b]	$Co(acac)_2 \cdot H_2O$	TBHPaq	DCE	49
5[c]	$Co(acac)_2 \cdot H_2O$	TBHPaq	DCE	54

Reaction conditions: **74a** (0.5 mmol), **THF** (1mL), $Co(acac)_2 \cdot H_2O$ (5mol%), $TBHP_{aq}$ (2.0 equiv.), Co-solvent (1mL), 60 °C, 24 h, under argon atmosphere. [b] 3 mol% of $Co(acac)_2 \cdot H_2O$. [c] under air. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 5. Control experiments.

1.4.3. Co-Catalyzed C–H Alkylation of *N*-Aryl Glycine Derivatives with Cyclic Ethers

With a robust system in hand, we next turned our attention to investigate the generality of our transformation with different *N*-aryl glycine derivatives with ethers as shown in Scheme 29. The required *N*-aryl glycine derivatives **74** were easily prepared following standard organic reactions.[10] A variety of *N*-aryl glycinates bearing alkyl (**74a**-**b**) or benzyl substituent (**74c**) were suitable for the reaction. Likewise, *N*-aryl glycine amide **74d** could be successfully utilized. Remarkably, the success of the process was not limited to the use of *N*-phenyl derivatives and a wide number of *N*-aryl glycine compounds housing a vast array of substituents smoothly underwent the target C–H alkylation. Substrates with *meta*-substituted aromatic rings bearing halogens (**74e-f**) or ketone (**74g**) delivered the target products (**75e**-**g**) in good yields. A similar trend was observed with *para*-substituted substrates having halogens (**74i**-**j**), cyano (**74k**), ethers (**74l**) or the heteroaromatic thienyl moiety (**74m**) furnished the products (**75i**-**m**) in good to high yields. In contrast, sterically hindered substrates afforded comparatively lower yields (**75h**, **75n**). Importantly, not only THF but also 1,3-dioxolane could be used as alkyl feedstock. In fact, it showed total selectivity towards the C2-position providing **75o-r**, which represented versatile masked aldehyde derivatives.



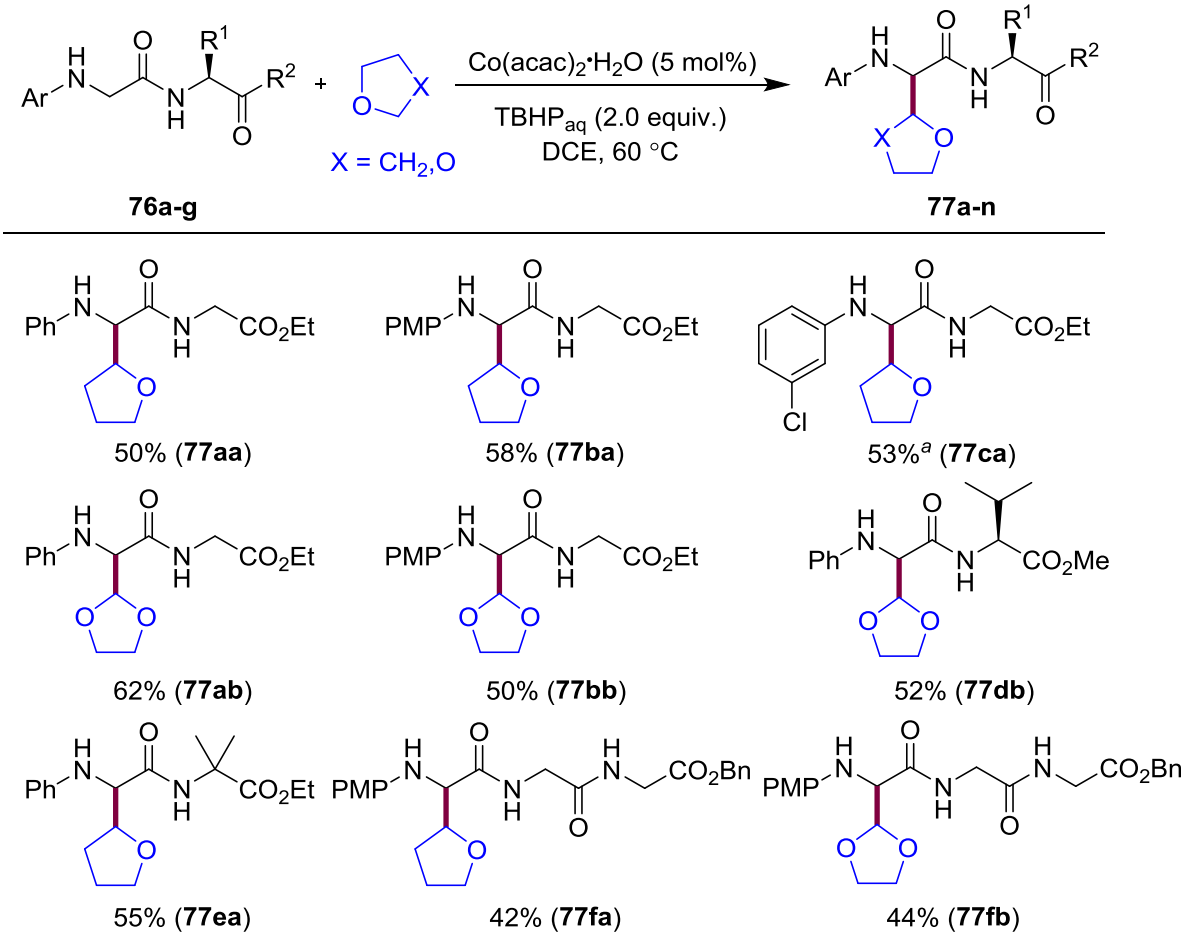
Reaction conditions: **74a-r** (0.5 mmol), **ether** (1 mL), $Co(acac)_2{\cdot}H_2O$ (5 mol%), $TBHP_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. Isolated yields, average of at least two independent runs. [a] 80 °C.

Scheme 29. Scope of *N*-aryl glycine derivatives with ethers.

Importantly, our method tolerated the same functional groups at the *N*-aryl moiety as Li's work (Scheme 13)[31] and in addition, groups such as nitrile (**75k**), ketone (**75g**), trifluromethyl (**75n**) or thiophene (**75 m**) were incorporated into glycine backbone. A remarkable feature of our Co-based method relies on the use of an aqueous solution of TBHP, whereas the protocol involving Cu-catalysis required the use of anhydrous TBHP.

1.4.4. Co-Catalyzed α-Functionalization of Peptides

Encouraged by these results, we turned our attention to the more challenging and less explored selective C–H functionalization of peptides (Scheme 30). Hence, the alkylation of several dipeptides and tripeptides selectively occurred at the terminal *N*-aryl Gly unit, obtaining the corresponding products **77a**-**m** with moderate to good yields. Importantly, the functional group tolerance in the aromatic ring of the substrate was not limited to the use of highly reactive *p*-OMe (**77b, 77e, 77l-m**) group, which has been proposed to stabilize the corresponding electrophilic intermediate,[10] as simple Ph (**77a**, **77d**, **77f-g**) or even the electron withdrawing *m*-Cl (**77c**) also delivered the target products.



Reaction conditions: **76a-g** (0.5 mmol), **ether** (1 mL), $Co(acac)_2.H_2O$ (5 mol%), $TBHP_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. Isolated yields, average of at least two independent runs. [a] 80 °C.

Scheme 30. Scope of *N*-aryl glycine containing peptides with ethers.

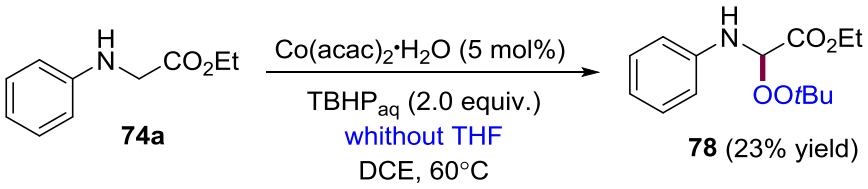
In the case of dipeptides housing two Gly residues, they were successfully alkylated with THF (**77aa**, **77ba** and **77ca**) or 1,3-dioxolane (**77db** and **77bb**) in moderate yield at the *N*-terminal Gly unit. Likewise, dipeptides containing a Val residue or a quaternary center also delivered the final products (**77eb** and **77fa**, respectively) in moderate yield in site-selective fashion. Unfortunately, the chiral peptide bearing the bulky Val residue (**77eb**) did not induce any diastereoselectivity (dr = 1:1). Furthermore, a more challenging tripeptide formed by three Gly residues (**76g**) which could inhibit the catalyst's performance through coordination with the additional amide groups,[6b] were also selectively alkylated with THF (**77ga**) and 1,3-dioxolane (**77gb**) in moderate yields. It is worth mentioning that despite the moderate yields obtained, the starting materials (**76a-g**) were always completely consumed and other byproducts were not found, which may suggest that some undesired degradative processes could simultaneously happen during the transformation. To our delight, 1,3-dioxolanes reacted exclusively at the C2-position and the competitive reaction at C3-position, which has been reported in other transformations,[50] was never observed. To the best

of our knowledge, this procedure represented the first example of site-selective alkylation of peptides with cyclic ethers as alkylating feedstock. Notably, the chiral integrity of dipeptide **77eb** was maintained along the oxidative process, which was verified by chiral HPLC analysis.

Contrary to Li's work (Scheme 13),[31] where their Cu-catalyzed alkylation of glycine derivatives with ethers was limited to glycine ketones, esters and amides, our Co-catalyzed protocol was not only successful with glycine esters or amides but also was extended to the functionalization of more challenging peptides, which represented a significant step forward in the field of CDC reactions.

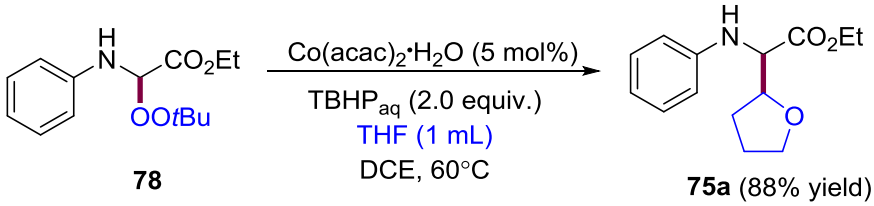
1.4.5. Mechanistic Experiments

In order to gain some insights into the reaction mechanism, we performed several experiments. On the one hand, when the reaction was set up in the presence of radical traps such as TEMPO or BHT, the reaction was totally inhibited, which may support a radical pathway. On the other hand, when the reaction was performed in the absence of THF, the peroxide **78** was isolated in 23% yield (Scheme 31). The latter was shown to be totally stable and its characterization was properly done.[69]



Scheme 31. Isolation of the peroxide 78.

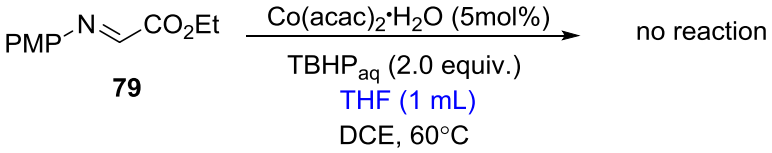
Interestingly when the peroxide **78** was submitted to the reaction conditions, it delivered the alkylated product **75a** with an outstanding 88% yield, which could indeed underpin its key intermediary along the reaction pathway (Scheme 32).



[69] Xia, Q.; Wang, Q.; Yan, C. ; Dong, J.; Song, H.; Li, L. ; Liu, Y.; Wang, Q. ; Liu, X.; Song, H. *Chem. Eur. J*. **2017**, *23*, 10871.

Scheme 32. Reaction of the peroxide **78** with THF.

The formation of an imine is often proposed in CDC with glycine derivatives.[6] In order to test this hypothesis, imine **79** was synthesized[70] and used as substrate under the standard reaction conditions with THF (Scheme 33). However, the imine **79** remained unreactive, which may indicate that imine species was not formed along our reaction or was not the reactive intermediate.

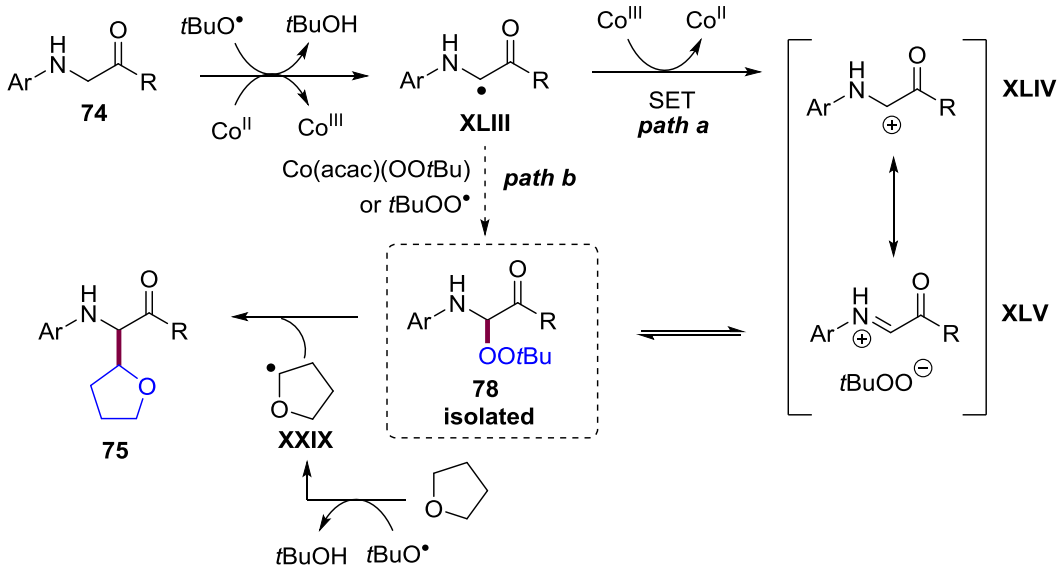


Scheme 33. Reaction of the imine 79 with THF.

1.4.6. Mechanistic Proposal

With the information revealed by the mechanistic experiments and based on previous literature reports,[6] a mechanistic proposal is described in Scheme 34. Firstly, the Co^{II} would promote the cleavage of TBHP to generate a highly oxidizing *tert*-butoxyl radical and a Co^{III} species. Then the *N*-aryl glycine would undergo a HAT event by *t*BuO$^{\bullet}$ to form the radical intermediate **XLIII**, which could be oxidized by a SET reaction assisted by Co^{III}, to form the electrophilic **XLIV**. The latter could be trapped by *t*BuOO^{-} to deliver peroxide **78**, which could finally react with the *in situ* formed radical **XXIX** to release the final product **75** (Scheme 34, *path a*). Another plausible scenario entail the direct formation of peroxide **78** upon a radical-radical coupling between the radical **XLIII** and *t*BuOO$^{\bullet}$ (Scheme 34, *path b*).[71] Thereafter, the reaction would evolve as mentioned above (*path a*), reacting with the *in situ* formed alkyl radical **XXIX** to furnish the final product **75**. Without any doubt, in-depth studies are required to clearly understand all the fundamental steps of the present process. In this regard, DFT studies performed in the group supported the key role of the *N*-aryl group within the formation of the electrophilic intermediate.[72]

[70] Ji, P.; Zhang, Y.; Wei, Y.; Huang, H.; Hu, W.; Mariano, P. A.; Wang, W. *Org. Lett*. **2019**, *21*, 3086.
[71] Ratnikov, M. D.; Doyle, M. P. *J. Am. Chem. Soc*. **2013**, *135*, 1549.
[72] Andrade-samedro, P.; Correa, A.; Matxain, J. M. *J. Org. Chem.* **2020**, *85*, 13133.



Scheme 34. Mechanistic proposal for the Co-catalyzed alkylation of glycine derivatives with ethers.

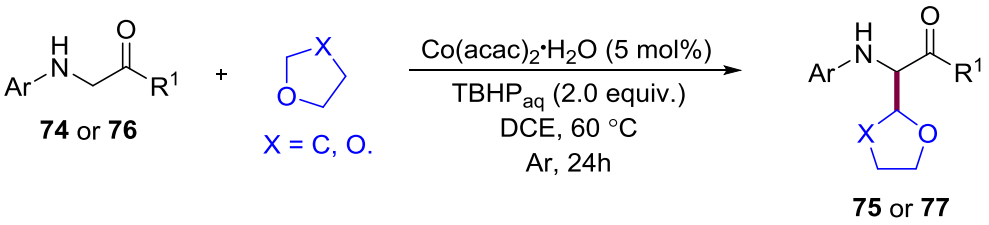
1.4.7. Conclusions

In summary, we have developed an unprecedented Co-catalyzed C(sp^3)–H functionalization reaction of *N*-aryl glycine derivatives and peptides with cyclic ethers.[21] The scope was successfully extended to short peptides, where total selectivity toward the terminal *N*-aryl glycine unit was achieved. Importantly, this protocol was mild enough so that the optical purity of the present stereogenic centers was maintained, which could set up the basis for future works in the field of late-stage-functionalization of peptides. Moreover, the method was found compatible with the use of an aqueous solution of TBHP, which represents an attractive feature with promising perspectives toward the modification of complex proteins.

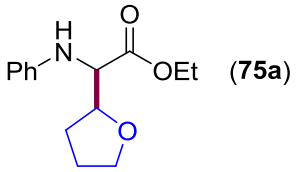
1.4.8. Experimental Procedures

In this section, some representative procedures as well as the characterization of selected illustrative compounds are provided. For a full detailed experimental description, please see the supporting information of the following article.[21]

1.4.8.1. Co-Catalyzed C–H Alkylation with Cyclic Ethers.

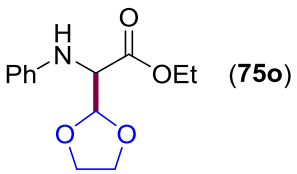


General Procedure: A reaction tube containing a stirring bar was charged with the corresponding α-amino carbonyl compound **74** or peptide **76** (if solid) (0.50 mmol, 1.00 equiv.) and $Co(acac)_2 \cdot H_2O$ (5 mol%). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). The corresponding α-amino carbonyl compound **74** or peptide **76** (if liquid) (0.50 mmol, 1.00 equiv.), an aqueous solution of TBHP (70 wt. % in H_2O) (2.00 equiv.), the corresponding ether (1 mL) and 1,2-dichloroethane (1 mL) were added under argon atmosphere. The reaction tube was next warmed up to 60°C and stirred for 24 hours. The mixture was then allowed to warm to room temperature, concentrated under reduced pressure and the corresponding product was purified by flash chromatography (hexane/EtOAc 8/2), unless otherwise indicated.



(**75a**)

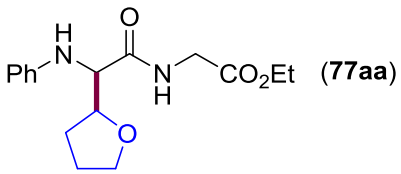
Ethyl 2-(phenylamino)-2-(tetrahydrofuran-2-yl)acetate (75a). Following the general procedure, using *N*-phenylglycine ethyl ester (**74a**) (0.50 mmol, 90 mg) provided 98 mg (79% yield) of **75a** as a white solid. Mp 77-78 °C. The spectroscopic data correspond to those previously reported in the literature.[31] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, J = 7.8 Hz, 2H), 6.85 – 6.61 (m, 3H), 4.52 (br s, 1H), 4.38 (td, J = 7.0, 3.3 Hz, 1H), 4.33 – 4.18 (m, 3H), 4.13 (dd, J = 9.6, 4.4 Hz, 1H), 3.99 – 3.88 (m, 1H), 3.85 – 3.76 (m, 1H), 2.09 –1.84 (m, 4H), 1.26 (td, J = 7.1, 1.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 172.1, 147.5, 147.0, 129.2, 129.2, 118.5, 118.4, 113.9, 113.6, 79.8, 79.3, 69.2, 68.7, 61.3, 61.17, 60.7, 59.8, 28.4, 28.0, 26.0, 25.6, 14.2, 14.2.



(**75o**)

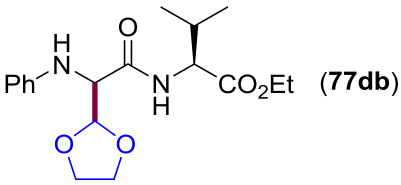
Ethyl 2-(1,3-dioxolan-2-yl)-2-(phenylamino)acetate (75o). Following the general procedure, using *N*-phenylglycine ethyl ester (**74a**) (0.50 mmol, 90 mg) and 1,3-dioxolane (1 mL) provided 87 mg (70% yield) of

75o as a yellowish solid. Mp 71-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, J = 8.5, 7.2 Hz, 2H), 6.85 – 6.68 (m, 3H), 5.41 (d, J = 2.2 Hz, 1H), 4.51 (br s, 1H), 4.35 (d, J = 2.4 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.16 – 4.07 (m, 1H), 4.06 – 3.89 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 146.8, 129.0, 118.4, 113.7, 103.3, 65.8, 65.4, 61.5, 60.1, 14.0. IR (neat, cm^{-1}): 3374, 1731, 1599, 741, 692. MS (ESI$^+$) *m/z* (%) 252 (M+H). HRMS *calcd.* for ($C_{13}H_{18}NO_4$): 252.1236, *found* 252.1258.



(**77aa**)

Ethyl 2-[(phenylamino)-2-(tetrahydrofuran-2-yl)acetyl]glycinate (77aa). Following the general procedure, using peptide **76a** (0.50 mmol, 118 mg) provided 76 mg (50% yield) of **77aa** as a brown oil (dr = 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 5.7 Hz, 1H), 7.26 – 7.11 (m, 2H), 6.78 (t, J = 7.3 Hz, 1H), 6.71 – 6.58 (m, 2H), 4.59 (d, J = 4.4 Hz, 0.5H), 4.43 (d, J = 3.9 Hz, 0.5H), 4.36 – 4.23 (m, 1H), 4.20 – 4.09 (m, 2H), 4.04 – 3.75 (m, 5H), 2.09 – 1.86 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.7, 169.6, 169.5, 147.2, 147.0, 129.5, 129.4, 119.2, 114.0, 113.9, 79.5, 79.0, 68.9, 68.8, 61.8, 61.8, 61.5, 41.3, 41.2, 28.4, 27.2, 25.8, 25.7, 14.2. IR (neat, cm^{-1}): 3360, 2978, 2873, 1744, 1659, 1602, 1504, 1198, 1065, 1026, 751, 693. MS (ESI$^+$) m/z (%) 307 (M+H). HRMS *calcd.* for ($C_{16}H_{23}N_2O_4$): 307.1658, *found* 307.1682.

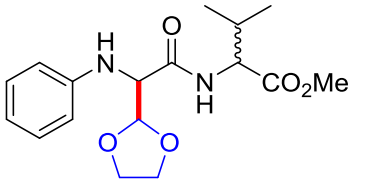


(**77db**)

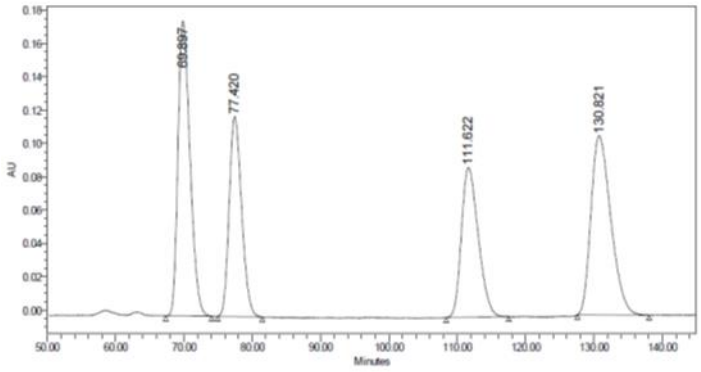
Methyl [2-(1,3-dioxolan-2-yl)-2-(phenylamino)acetyl]-*L*-valinate (77eb). Following the general procedure, using peptide **76d** (0.50 mmol, 132 mg) and 1,3-dioxolane (1 mL) provided 87 mg (52% yield) of **77db** as a white solid. Mp = 78-79 °C (dr = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 9.2 Hz, 1H), 7.23 (t, J = 9.2 Hz, 2H), 6.83 (t, J = 7.3 Hz, 1H), 6.75 – 6.67 (m, 2H), 5.35 (dd, J = 5.6, 2.2 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.23 – 3.92 (m, 6H), 3.75 (s, 1.5H), 3.68 (s, 1.5H), 2.26 – 2.11 (m, 1H), 0.96 (d, J = 6.9 Hz, 2H), 0.90 (dd, J = 10.7, 6.9 Hz, 4H), 0.79 (d, J = 6.9 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.0, 169.5, 147.1, 146.9, 129.5, 129.5, 119.5, 119.5, 114.5, 114.2, 102.9, 102.8, 65.7, 65.6, 65.5, 65.4, 60.9, 57.3, 57.1, 52.3, 52.2, 19.1, 17.8, 17.7. IR (neat, cm^{-1}): 3362, 2961, 1738, 1666, 1603, 1507, 1149, 751. MS (ESI$^+$) m/z (%) 337 (M+H). HRMS *calcd.* for

($C_{17}H_{25}N_2O_5$): 337.1763, *found* 337.1773. HPLC for the compounds with (D, L) and (L, L) configurations (Chiralpak IC; 97:3 Hexane: isopropanol; 1 mL/min, λ = 210 nm). t_R = 69, 2 min, t_R = 76.6 min.

1.4.8.2. HPLC chromatograms

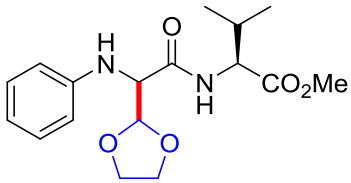


rac-(77db)

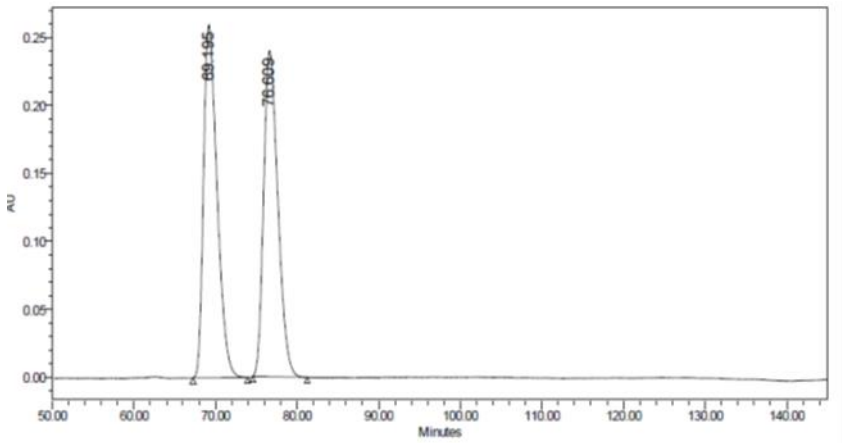


	RT	Area	% Area	Height
1	69.897	21589329	29.20	176780
2	77.420	15189427	20.54	120047
3	111.622	15401816	20.83	89753
4	130.821	21752387	29.42	107622

(Chiralpak IC; 97:3 Hexane: isopropanol; 1 mL/min, λ = 210 nm)

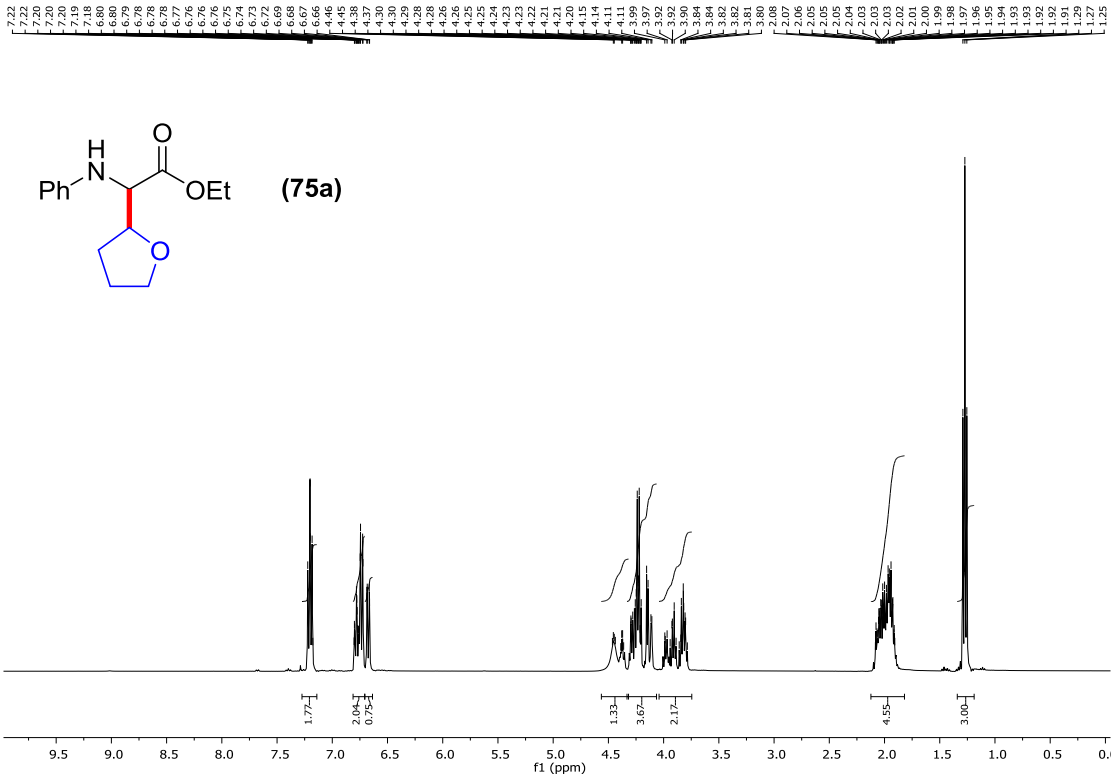


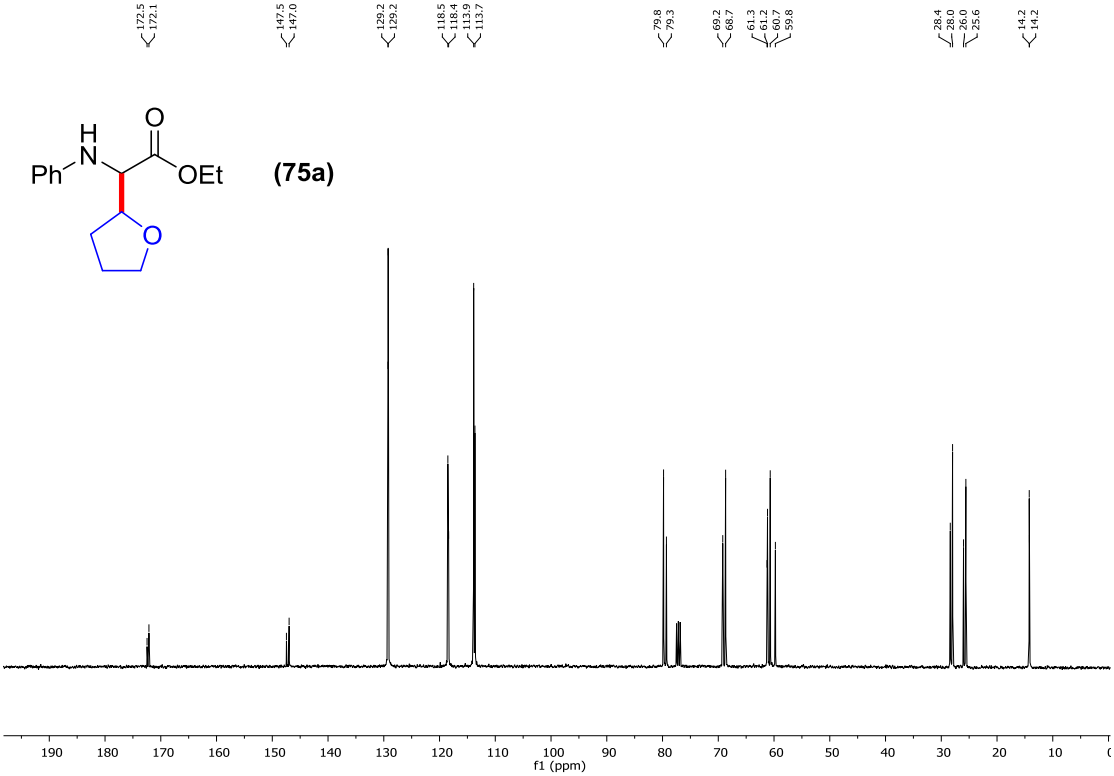
(77db)

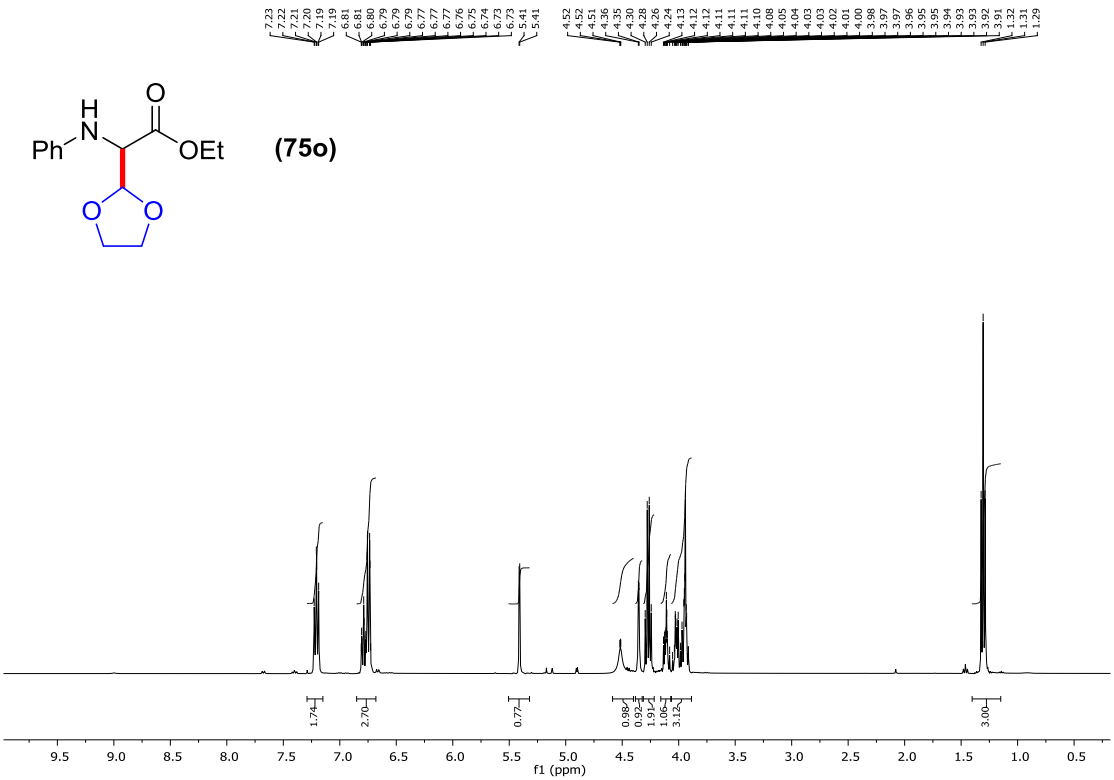


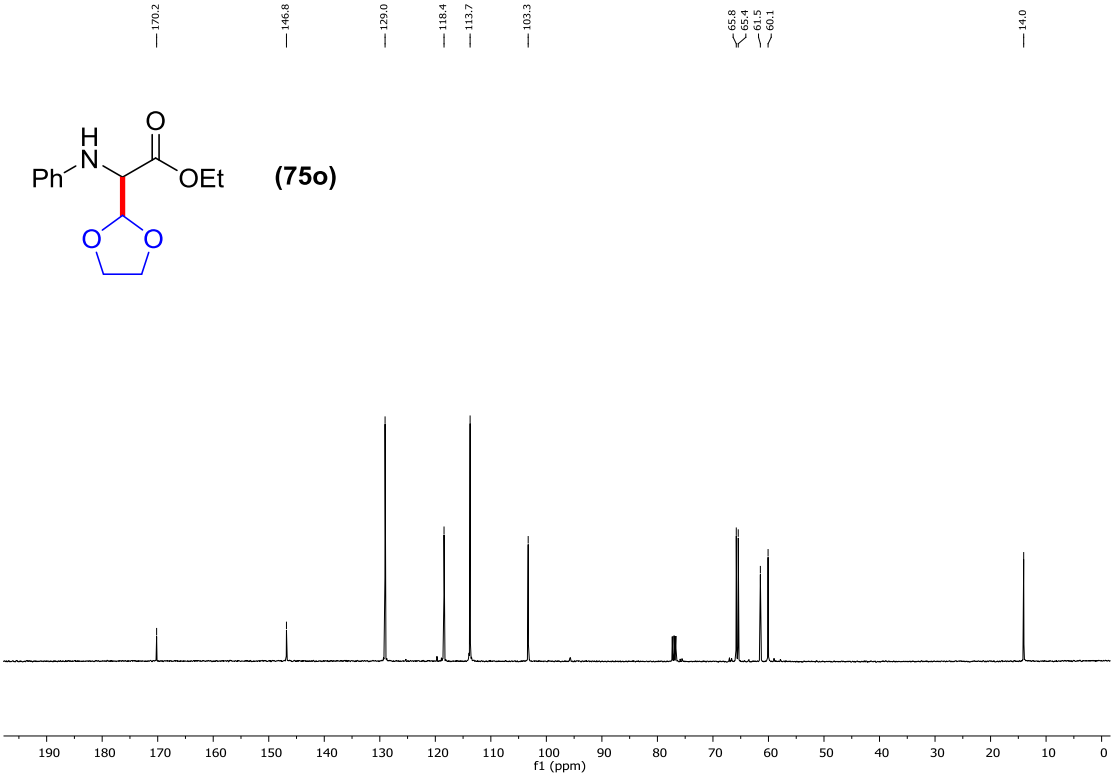
	RT	Area	% Area	Height
1	69.195	29854091	50.70	259466
2	76.609	29032117	49.30	239523

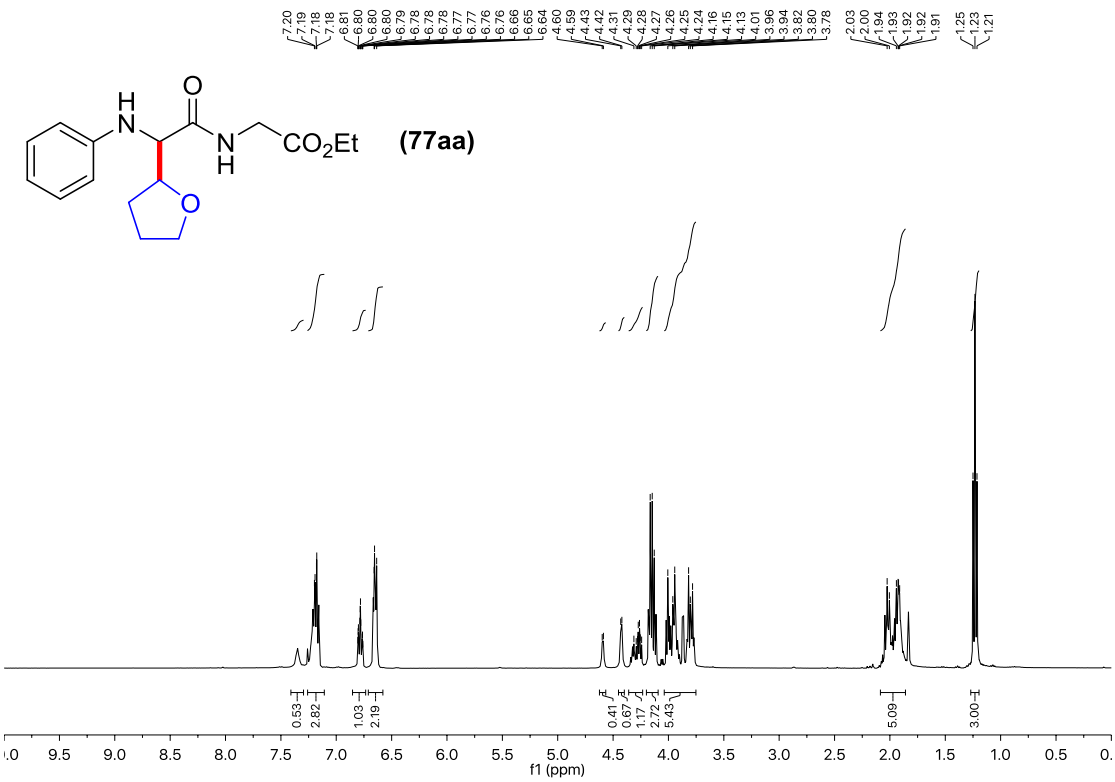
1.4.8.3. ^{1}H RMN and ^{13}C RMN Spectra

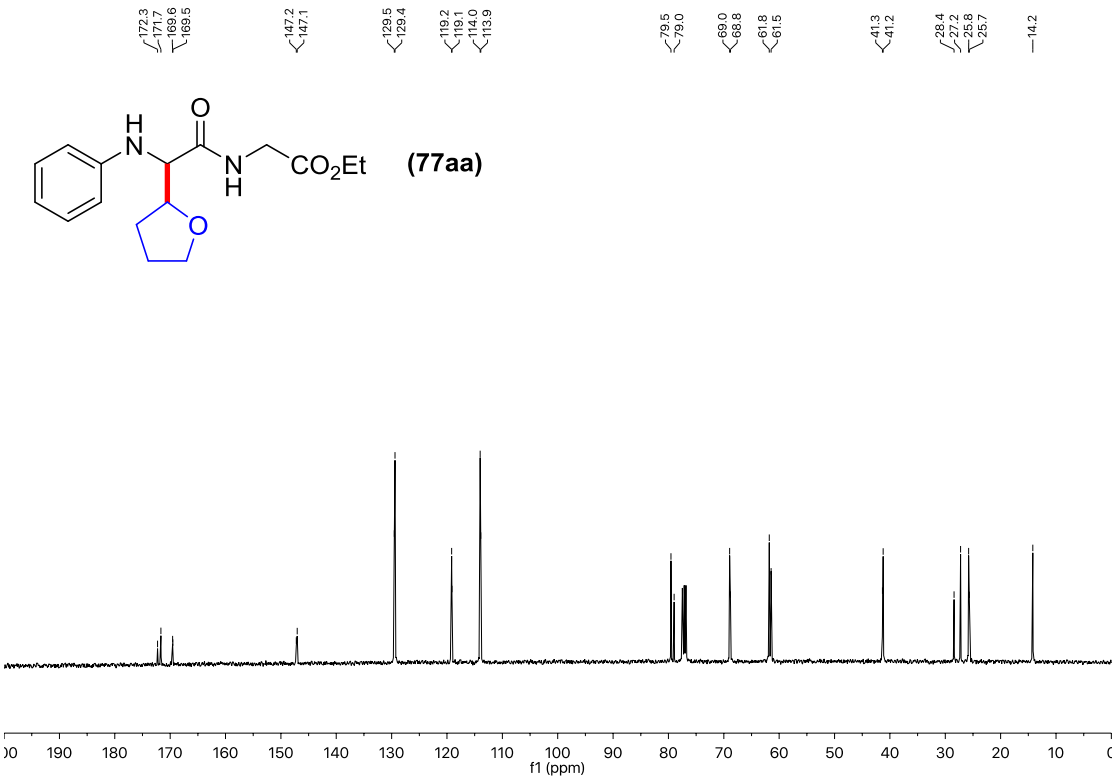


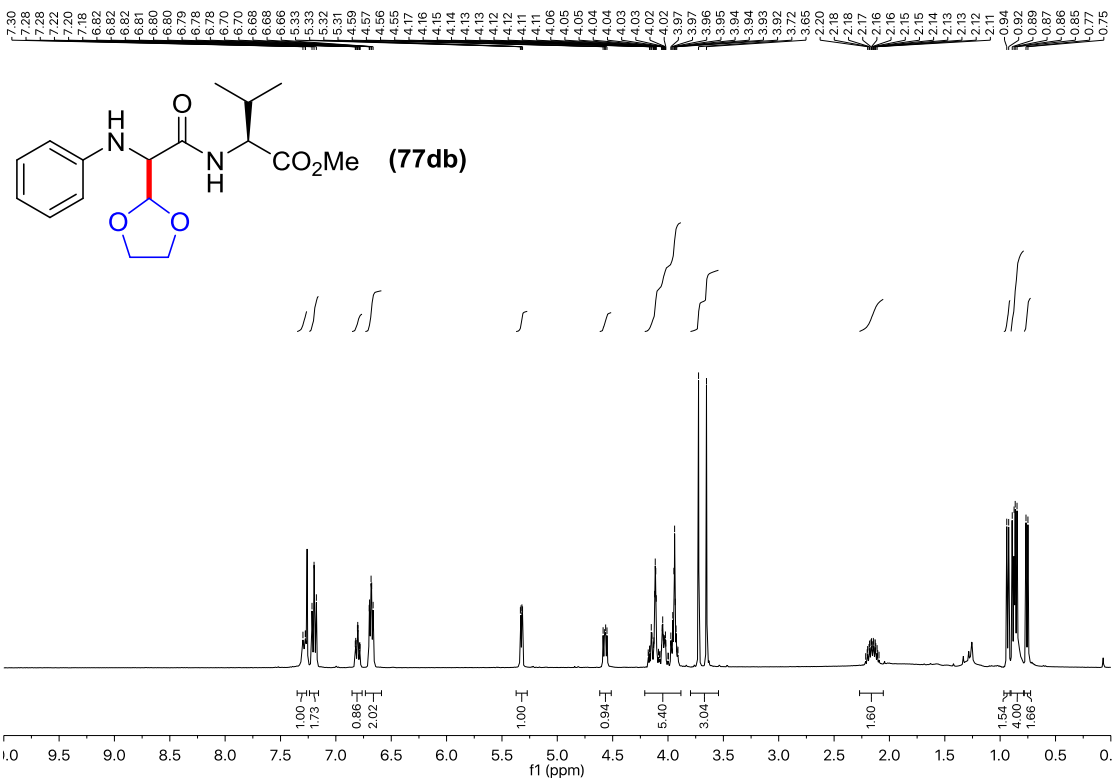


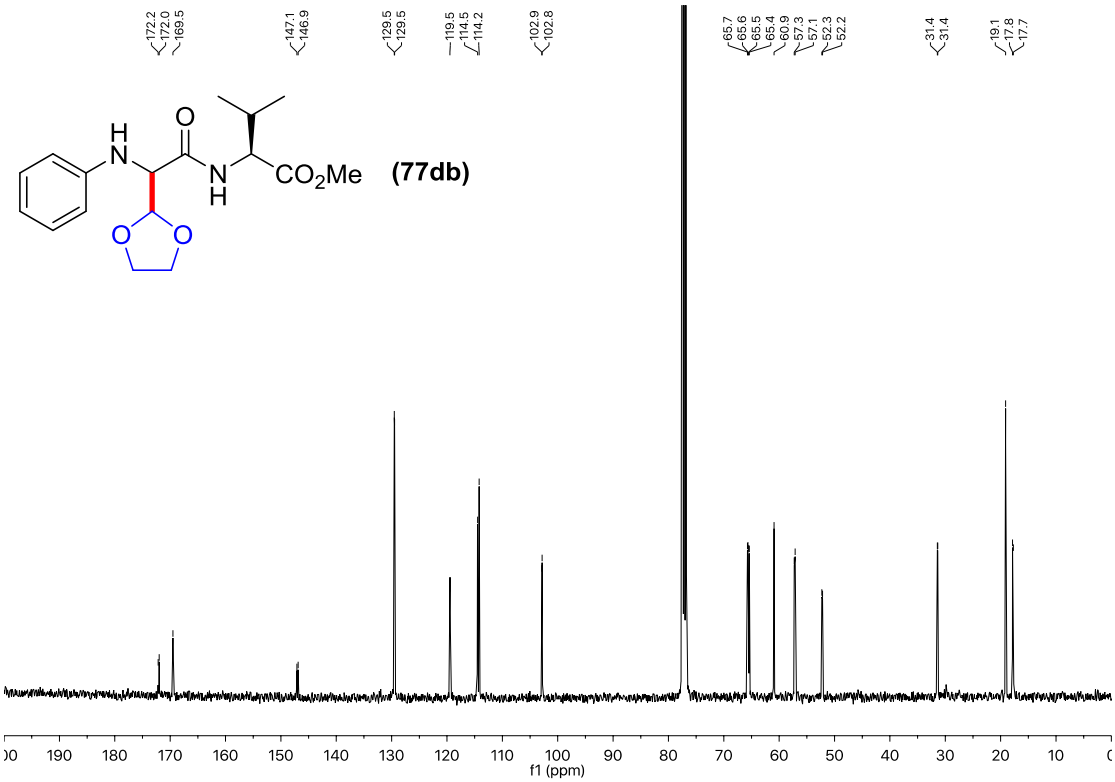

7.23 7.22 7.21 7.20 7.19 6.81 6.80 6.79 6.79 6.79 6.77 6.77 6.76 6.75 6.74 6.73 6.73 5.41 5.41
4.52 4.52 4.51 4.36 4.35 4.28 4.26 4.24 4.13 4.12 4.12 4.11 4.11 4.11 4.10 4.08 4.05 4.04 4.03 4.03 4.02 4.01 4.00 3.98 3.97 3.97 3.96 3.95 3.95 3.94 3.93 3.93 3.92 3.91 1.32 1.31 1.29
H
N
Ph
O
OEt
O
O
(75o)
1.74
2.70
0.77
0.98
0.92
1.91
1.06
3.12
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


170.2
146.8
129.0
118.4
113.7
103.3
65.8
65.4
61.5
60.1
14.0
H
N
Ph
O
OEt
O
O
(75o)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.20
7.19
7.18
7.18
6.81
6.80
6.80
6.80
6.79
6.78
6.78
6.78
6.77
6.77
6.76
6.76
6.66
6.65
6.64
4.60
4.59
4.43
4.42
4.31
4.29
4.28
4.27
4.26
4.25
4.24
4.16
4.15
4.13
4.01
3.96
3.94
3.82
3.80
3.78
2.03
2.00
1.94
1.93
1.92
1.92
1.91
1.25
1.23
1.21
H
N
O
N
H
CO2Et
(77aa)
0.53
2.82
1.03
2.19
0.41
0.67
1.17
2.72
5.43
5.09
3.00
f1 (ppm)


172.3
171.7
169.6
169.5
147.2
147.1
129.5
129.4
119.2
119.1
114.0
113.9
79.5
79.0
69.0
68.8
61.8
61.5
41.3
41.2
28.4
27.2
25.8
25.7
14.2
H
N
O
N
H
CO2Et
(77aa)
f1 (ppm)

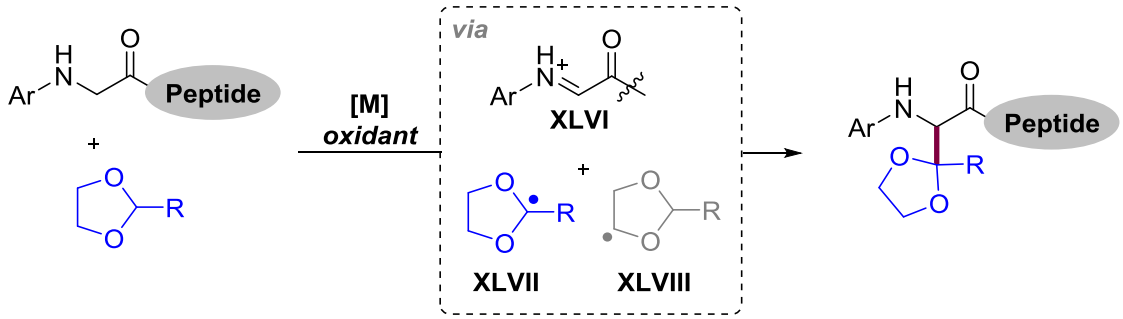

(77db)
f1 (ppm)


(77db)
f1 (ppm)

1.5. Site-Selective Cu-Catalyzed Alkylation of α-Amino Acids and Peptides Toward the Assembly of Quaternary Centers

1.5.1. General Objectives

Encouraged by the successful use of 1,3-dioxolane in the site-selective alkylation of *N*-aryl glycine compounds, we sought to exploit this simple and straightforward platform for creating molecular diversity. Given that the existing procedures were mostly restricted to the use of simple ethers such as THF or 1,3-dioxolane, we envisioned the use of 2-substituted 1,3-dioxolanes as novel coupling partners, thereby resulting in the assembly of new quaternary centers within the alkylation reaction. Although simple at first sight, regioselectivity issues may come into play given the presence of two oxidizable C–H bonds at C2 and C4 site of the dioxolane. If the reaction is governed by electronic factors, the formation of the more stable tertiary alkyl radical should be formed. Conversely, steric issues could result in the formation of the less hindered radical, hence resulting in functionalization at C4 site. Based on the literature, the formation of the alkyl radical in the C2 of the 2-substituted 1,3-dioxolanes (**XLVII**) should be favorable than its radical counterpart (**XLVIII**) in the C4-position (Scheme 35).[73]



Scheme 35. General approach for the assembly of quaternary centers with the use of 2-substituted 1,3-dioxolanes as alkyl reagents.

If successful, the use of 2-substituted 1,3-dioxolanes would constitute a new avenue to form an unprecedented quaternary carbon center within a peptide framework. In addition, it could allow for the installation of additional functional groups tethered to the 1,3-dioxolane, which would represent a big

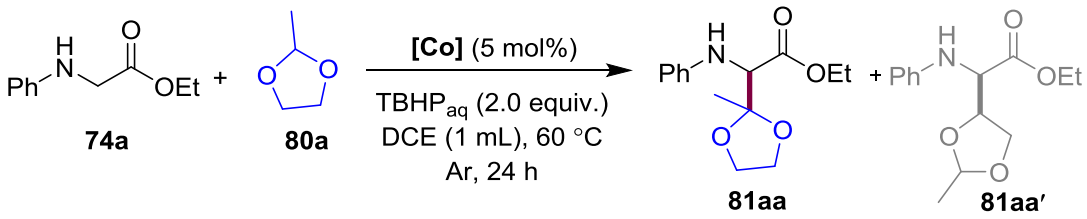
[73] a) Rarelli, D.; Albini, A.; Fagnoni, M. *Chem. Eur. J.* **2011**, *17*, 572. b) Du, P.; Li, H.; Wang, Y.; Cheng, J.; Wan, X. *Org. Lett.* **2014**, *16*, 6350. c) Sølvøj, A.; Ahlburg, A.; Madsen, R. *Chem. Eur. J.* **2015**, *21*, 16272. d) Lan, Y.; Liu, X.-W.; Meng, F.-F.; Ahmad, T.; Xu, Y.-H. Loh, T.-P. *Chem. Commun.* **2017**, *53*, 12353.

improvement in the field of C–H functionalization of peptides. Thus, we established the following objectives for this project:

- To assemble quaternary centers with the use of 2-substituted 1,3-dioxolanes.
- To achieve a chemo- and regioselective alkylation.
- To explore the late-stage-functionalization of peptides of highly structural complexity.

1.5.2. Optimization Process

The reaction between amino ester **74a** and the commercially available 2-methly-1,3-dioxolane was selected as the model reaction. In our initial attempts, we decided to keep all the parameters utilized on the previous work[21] and performed an exploratory screening of the metal catalyst. Fortunately, few of the cobalt salts were shown active to furnish the desired alkylated product **81aa** (entries 1-3), while the undesired alkylated product **81'aa** was not detected. Among the active cobalt salts, $CoBr_2$ gave us the best result, with a promising 67% yield. Nonetheless, other cobalt salts tested did not deliver the product **81aa** (Table 6, 5-8) or only traces were detected (Table 6, entry 4). The exclusive formation of **81aa** verified that the C–H oxidation of the dioxolane at C2 was more favored, and accordingly electronic factors seem to play a dominant role within the reaction pathway.

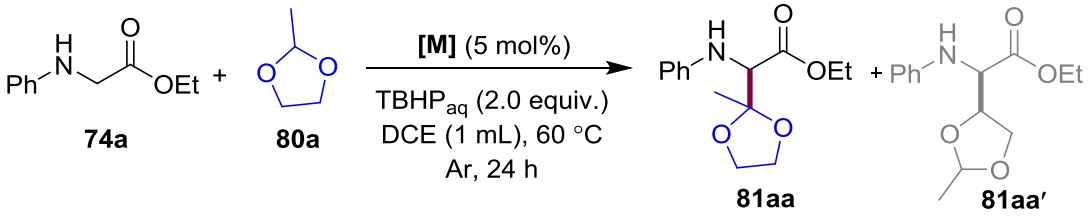


Entry	[Co]	Yield 81aa (%)
1	$CoBr_2$	67
2	$Co(acac)_2{\cdot}H_2O$	60
3	$CoCl_2$	41
4	$Co(acac)_3$	traces
5	CoF_2	0
6	CoF_3	0
7	$Co(OAc)_2$	0
8	$Co(OH)_2$	0

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (0.5 mL), [Co] (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O)

Table 6. Screening of cobalt salts.

Then we decided to evaluate the activity of other first-row metal salts that have been widely applied to perform this type of radical reactions. To our delight, Cu(OAc) and $Cu(OAc)_2$ salts delivered the same outcome with a remarkable 79% yield of the product **81aa**, which notably improved the 67% yield obtained was $Co(acac)_2{\cdot}H_2O$ (Table 7, entries 1-2). Other copper salts such us CuCl gave **81aa** with 44% yield, while other salts only delivered traces amounts of **81aa** (Table 7, entries 4-6) or degradation was observed (Table 7, entry 7). It is worth mentioning, that in none of the reactions **81'aa** was observed, meaning that the formation of the tertiary carbon radical at C2 was favored over its parent radical at C4. For atom economic reasons, the use of Cu(OAc) as catalyst was considered more convenient than its $Cu(OAc)_2$ counterpart.

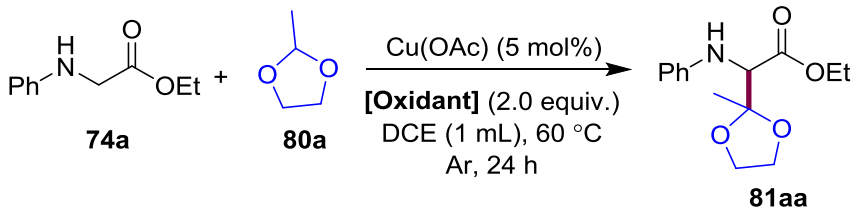


Entry	Metal	Yield 81aa (%)
1	Cu(OAc)	79
2	$Cu(OAc)_2$	79
3	CuCl	44
4	$Cu(Cl)_2$	traces
5	CuBr	traces
6	$CuBr_2$	traces
7	$Cu(OTf)_2$	degradation
8	$Co(acac)_2{\cdot}H_2O$	67
9	$Fe(OAc)_2$	0
10	$Mn(OAc)_2$	0
11	$Mn(OAc)_3$	0

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (0.5 mL), [M] (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O)

Table 7. Screening of metal salts.

Once Cu(OAc) was established as the catalyst of choice to perform this challenging reaction, we next decided to evaluate different types of oxidants with the aim of further improve the yield of **81aa**. Surprisingly, only TBHP-based solutions delivered the desired product **81aa** in a measurable manner, where aqueous solution outperformed its analogue in decane solution (Table 8, entries 1-2). Other oxidants only delivered traces amount of **81aa** (Table 8, entries 3-5). Unfortunately, cheap and environmentally friendly oxidants such as oxygen peroxide or oxygen did not deliver the final product and the starting material remained intact (Table 8, entries 6-7).

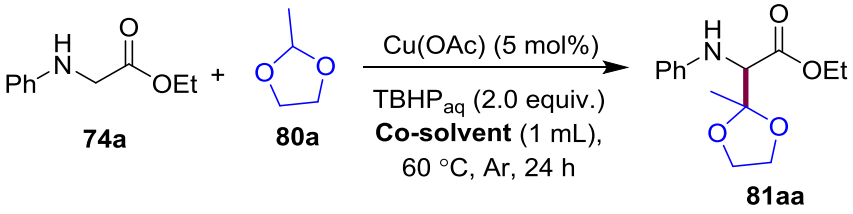


Entry	Oxidant	Yield 81aa (%)
1	$TBHP_{aq}$	79
2	$TBHP_{Dec}$	65
3	DTBP	traces
4	DDQ	traces
5	PIDA	traces
6	H_2O_2	0
7	O_2	0
8	$K_2S_2O_8$	0
9	NHPI	0

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (1 mL), Cu(OAc) (5 mol%), [Oxidant] (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 8. Screening of oxidants.

Thereafter, we tested some common solvents used in organic synthesis, but none of them was able to improve the 79% yield obtained with DCE, as it is illustrated in Table 9. The removal of DCE as co-solvent dropped the yield of **81aa** considerably (Table 9, entry 2) and other organic solvents delivered **81aa** in comparatively lower yield (Table 9, entries 3-5). Notably, the amount of dioxolane could be reduced from 1 mL to 0.5 mL without affecting the efficiency of the process.

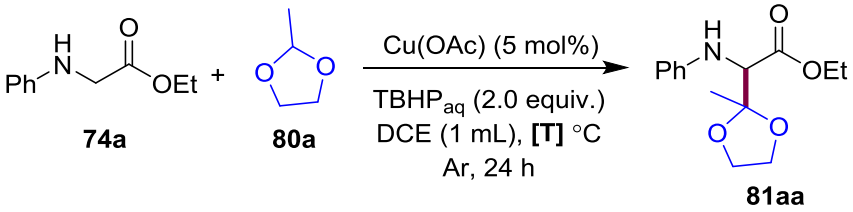


Entry	Co-solvent	Yield (%)
1	DCE	79
2[a]	--	65
3	EtOAc	54
4	MeCN	44
5	toluene	57

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), Solvent (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).[a] 1.0 mL of 2-methyl-1,3-dioxolane.

Table 9. Solvent screening.

As depicted in Table 10, the temperature played a crucial role in this reaction and 60 °C seemed to be the sweet spot for the course of this transformation, as higher or lower temperatures drastically dropped the yield of the alkylated product **81aa** (Table 10, entries 2-3).

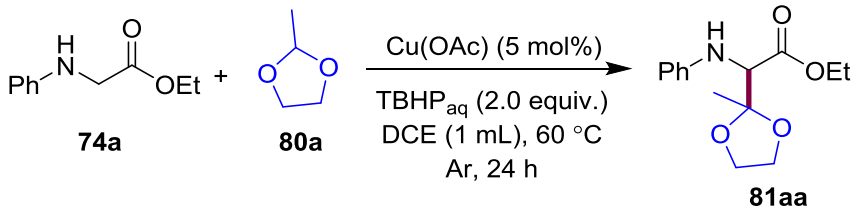


Entry	T (°C)	Yield (%)
1	60	79
2	70	43
3	40	46

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), Solvent (1 mL), [T] °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).

Table 10. Screening of temperature.

Finally, some control experiments were carried out (Table 11). As expected, copper salt and the oxidant were essential for the success of the transformation (Table 11, entries 3-4). Lowering the catalyst loading to 3 mol% of Cu(OAc) had almost no influence in the outcome, evidencing the robustness of the catalyst system (Table 11, entry 4). An aerobic atmosphere influenced negatively the formation of **81aa** (Table 11, entry 5). Importantly, reducing the amount of 2-methyl-1,3-dioxolane (**80a**) to just five equivalents or the oxidant to one equivalent gave the product **81aa** with still synthetically yields (Table 11, entries 6-7).



Entry	Variation from standard	Yield (%)
1	none	79
2	without Cu(OAc)	0
3	without TBHP$_{aq}$	0
4[a]	3 mol% of Cu(OAc) instead of 5 mol%	75
5[b]	under air instead of under argon	68
6[c]	5 equiv. of **80a** instead of 0.5 mL	60
7[d]	1.0 equiv. of TBHP$_{aq}$ instead of 2.0 eq.	67

Reaction conditions: **74a** (0.5 mmol), 2-methyl-1,3-dioxolane (0.5 mL), Cu(OAc) (5mol%), TBHP$_{aq}$ (2.0 equiv.), Solvent (1mL), [T] °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O).[a]

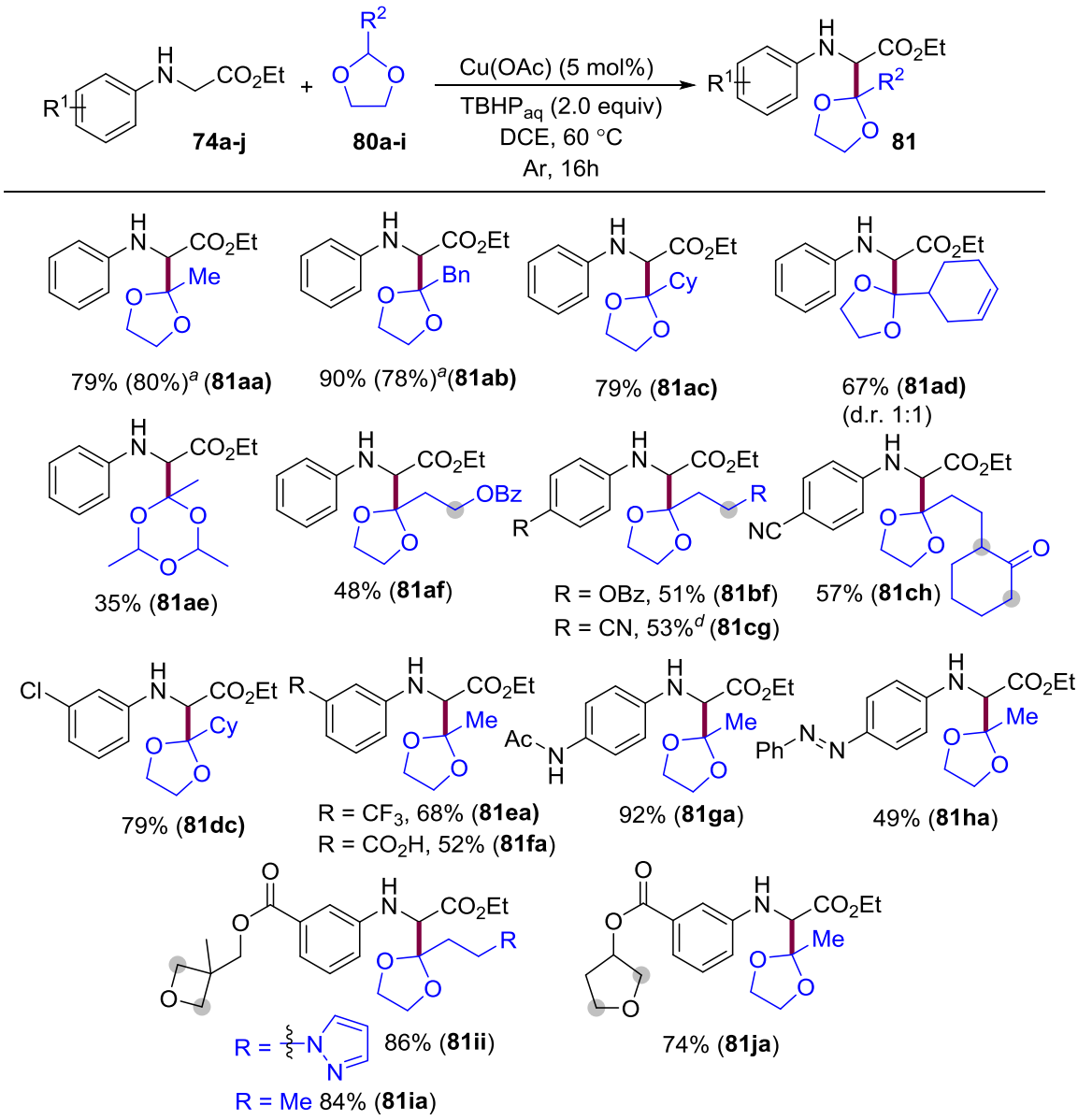
Table 11. Control experiments.

1.5.3. Scope of α-Amino Carbonyl Compounds

Having optimized all the parameters of the reaction, we next evaluated the generality of the process with a vast array of tertiary ethers and *N*-aryl glycine derivatives as depicted in Scheme 36. When the corresponding 1,3-dioxolane was not commercially available, they were prepared directly from the corresponding aldehyde and 1,2-ethanediol, or through S_N2 reactions.[74] However, many of them were

[74] Modify from: a) Domracheva, N.; Pyataev, A.; Manapou, R.; Gruzdev, M.; Chervonova, U.; Kolker, A. *Eur. J. Inorg. Chem.* **2011**, 1219. b) Alonso, J. A.; Andrés, M.; Bravo, M.; Buil, M. A.; Calbet, M.; Castro, J.; Eastwood, P. R.; Esteve, C.; Ferrer, M.; Forns, P.; Gómez, E.; González, J.; Lozoya, E.; Mir, M.; Moreno, I.; Petit, S.; Roberts, R. S.; Sevilla, S.; Vidal, B.; Vidal, L.; Vilaseca, P. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5127.

prepared from natural compounds or drugs having a carboxylic acid functional group upon a 3-step sequence; reduction of the carboxylic acid to aldehyde with $LiAlH_4$,[75] oxidation of the alcohol to the corresponding aldehyde[76] and final protection of the aldehyde to obtain the desired 1,3-dioxolane. To our delight, all types of 2-alkyl 1,3-dioxolanes were perfectly accommodated into the *N*-aryl glycinates, obtaining the alkylated products **81** with moderate to excellent yieds (Scheme 36). Importantly, the ethers showed total chemo



Reaction conditions: **74a-j** (0.5 mmol), **80** (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O). Yield of isolated product after column chromatography, average of at least two independent runs. [a] Reaction performed at gram-scale.

Scheme 36. Cu-catalyzed selective alkylation of α-amino esters.

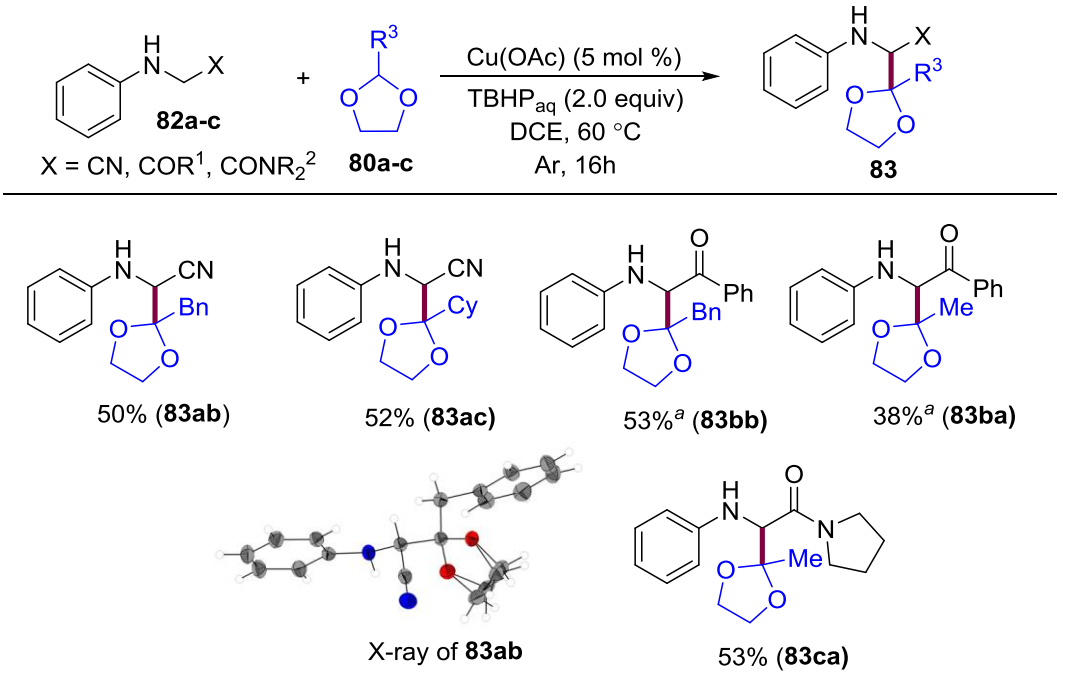
[75] West, T. H.; Walden, D. M.; Taylor, J. E.; Brueckner, A. C.; Johnston, R. C.; Cheong, P. H.-Y.; Lloyd-Jones, G. C.; Smith, A. D. *J. Am. Chem. Soc*. **2017**, *129*, 4366.
[76] Blake, M. E.; Bartlett, K. L.; Jones, M. *J. Am. Chem. Soc*. **2003**, *125*, 6485.

selectivity toward the tertiary C2 site as the possible competitive alkylation at the C4 position was never detected. Remarkably, apart from simple alkyl dioxolanes (**80a**, **80c**, **80e**), dioxolanes bearing alkenes (**80d**), benzyl groups (**80b**), ketones (**80g**), esters (**80f**), nitriles (**80h**), or pyrazole (**80o**) delivered the desired alkylated products, proving the robustness of the process. Notably, dioxolanes bearing oxidizable C(sp^3)–H bonds in adjacent position to a phenyl group (**80b**), ketone (**80h**), ester (**80f**) or nitrile (**80g**)[77] showed total chemoselectivity toward the C2 site of the dioxolane. Remarkably, the alkene within the compound **81ad**, which are prone to react with radical species,[78] remained unreactive. On the other hand, several substitution patterns were well tolerated in the *N*-aryl glycine motif such as halides (**74d**-**e**), carboxylic acids (**74f**), esters (**74i**-**j**), ethers (**74i**-**j**), amides (**74g**), and even sensitive azobenzenes (**74h**). Notably, substrates bearing other cyclic ethers (**74i**-**j**), highly prone to the formation of alkyl radical species, did not deliver any competitive alkylated products.

1.5.4. Scope of α-Carbonyl Derivatives

After great preliminary results, we then focused on the functionalization of a variety of glycine derivatives apart from glycine esters. α-Amino ketones (**82b**) or α-amino amide (**82c**) could be successfully alkylated under our optimized conditions in moderate yields. Furthermore, alkylation of *N*-phenyl glycinonitrile was achieved by this method, which to the best of our knowledge, represented the first example of a CDC reaction using this type of glycine derivative. In this regard, the alkylation of α-amino nitrile compounds delivered highly versatile motifs (**81ab-c**), and the structure of **81ab** was unambiguously assigned by X-ray analysis (Scheme 37).

[77] Chu, X.-Q.; Ge, D.; Shen, Z.-L.; Loh, T.-P. *ACS Catal.* **2018**, *8*, 258.
[78] Lan, X.–W.; Wang, N.-X.; Xing, Y. *Eur. J. Org. Chem*. **2017**, 5821.



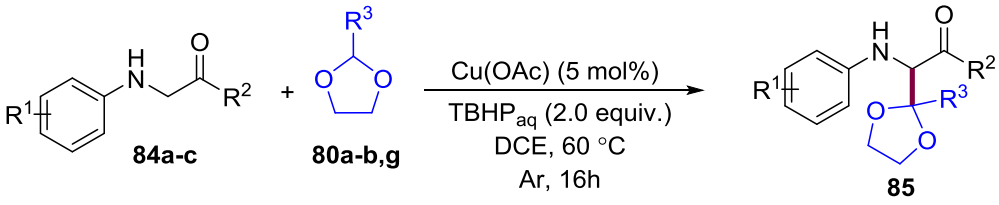
Reaction conditions: **82a-c** (0.5 mmol), **80a-c** (0.5 mL), Cu(OAc) (5 mol%), $TBHP_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O). Yield of isolated product after column chromatography, average of at least two independent runs. [a] Reaction performed with CuCl.

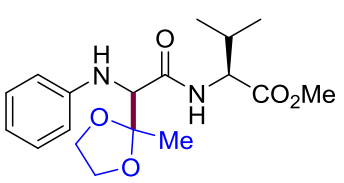
Scheme 37. Cu-catalyzed selective alkylation of α-amino carbonyl derivatives.

1.5.5. Scope of Short Peptides

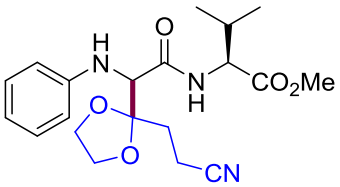
We next examined the use of this protocol for a more challenging selective alkylation of short-to-medium size peptides, which are more difficult to manipulate under oxidative conditions.[79] First, we easily prepared a short family of dipeptides containing a variety of amino acid residues such as valine (**84a**), alanine (**84b**), leucine (**84c**) or glycine (**84d**), which successfully furnished the alkylated products **85** at the terminal glycine unit with good to high yields (Scheme 38). On the other hand, alkyl (**80a**), benzylic (**80b**) or nitrile (**80g**) containing dioxolanes were efficiently introduced into peptide motifs to produce substituted dipeptides as diastereomeric mixture, but the optical purity of preexisting chiral centers remained intact as verified by chiral HPLC analysis. As expected, when a dipeptide housing two distinct glycine residues (**84d**) was employed, the alkylation occurred exclusively at the *N*-aryl glycine moiety (**85da**). Moreover, this particular example where the two glycine units are attached to an aryl ring reinforced the reactivity profile wherein the alkylation selectively occurred at the *N*-aryl Gly residue, regardless of its position along the sequence.

[79] Dean, R. T.; Fu, S; Stoker, R.; Davies, M. J. *Biochem. J*. **1997**, *324*, 1.

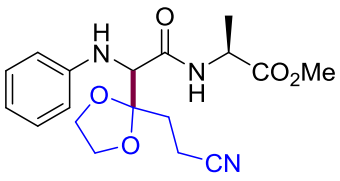




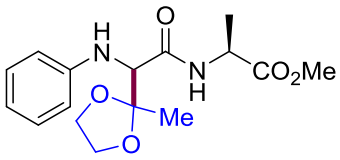
85% (d.r. 1:1)^{a,b} (**85aa**)
from Ph-Gly-Val-OMe



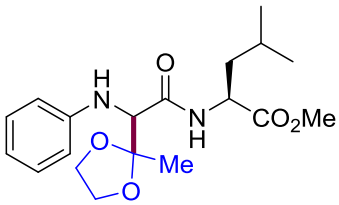
72% (d.r. 1:1)^{b} (**85ag**)
from Ph-Gly-Val-OMe



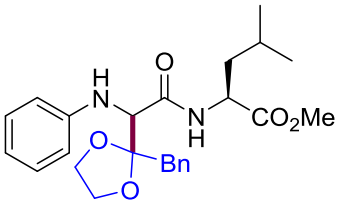
72% (d.r. 1:1)^{a,b} (**85bg**)
from Ph-Gly-Ala-OMe



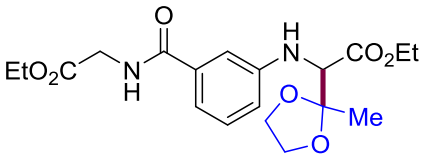
84% (d.r. 1:1)^{a,b} (**85ba**)
from Ph-Gly-Ala-OMe



71% (d.r. 1:1)^{b} (**85ca**)
from Ph-Gly-Leu-OMe



68% (d.r. 1:1)^{b} (**85cb**)
from Ph-Gly-Leu-OMe



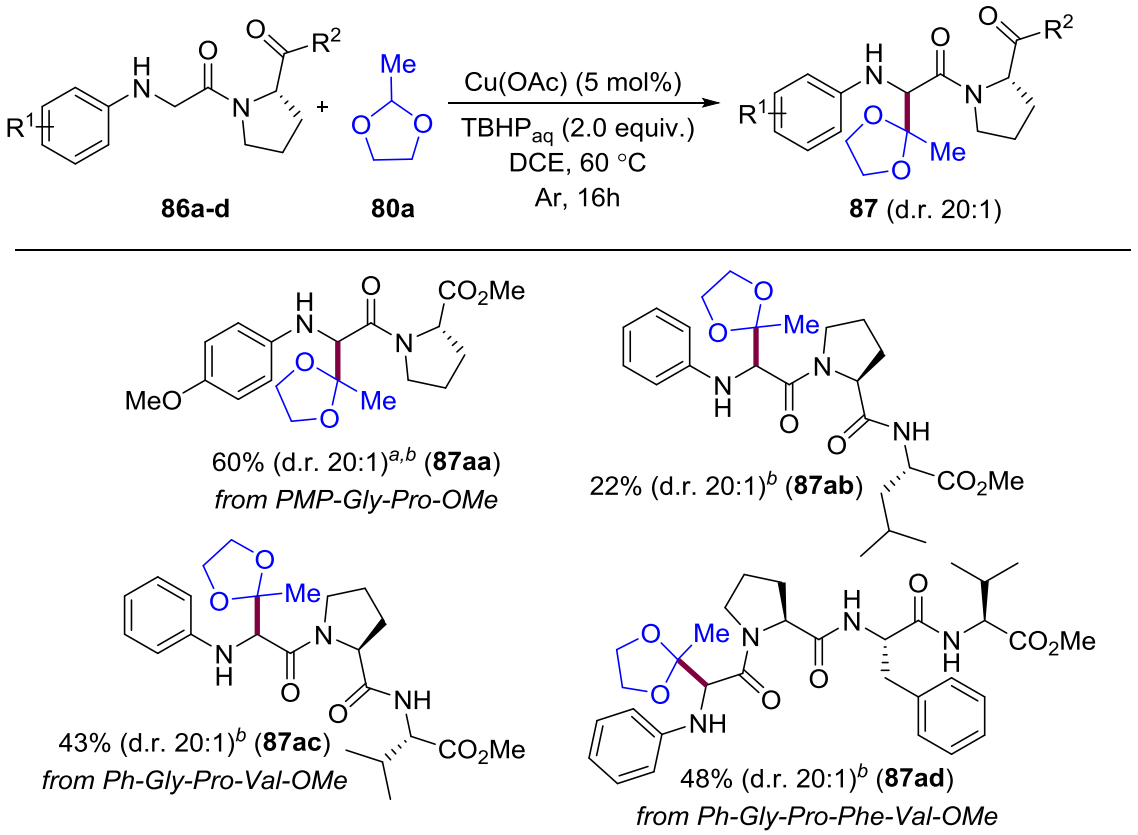
75% (**85da**)
from EtO-Gly-Ph-Gly-OEt

Reaction conditions: **84a-c** (0.5 mmol), **80a-b, g** (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O). Yield of isolated product after column chromatography, average of at least two independent runs. [a] HPLC analysis verified the retention of native chirality of the substrate. [b] d.r value calculated by ^{1}HRMN spectroscopy.

Scheme 38. Cu-catalyzed selective alkylation of dipeptides.

1.5.6. Proline-Directed Diastereo-Selective Alkylation of Peptides

A mayor breakthrough of this work came with the use of proline-containing peptides, as we came across that the presence of this particular amino acid delivered the alkylated products (**87a-d**) in a stereo-enriched fashion (Scheme 39). To test the generality of this asymmetric process, dipeptide (**86a**), tripeptides (**86b-c**) or even tretrapeptide (**86d**) were selectively alkylated with 2-methyl-1,3-dioxolane, affording the corresponding products in a remarkable diastereo selective manner (*dr* 20:1), which was verified through chiral HPLC analysis and NMR spectroscopy.



Reaction conditions: **86a-d** (0.5 mmol), **80a** (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O). Yield of isolated product after column chromatography, average of at least two independent runs. [a] HPLC analysis verified the retention of native chirality of the substrate. [b] d.r value calculated by ^{1}HRMN spectroscopy.

Scheme 39. Cu-catalyzed diastereo selective alkylation of proline-containing peptides.

According to the experimental results, we speculated that due to the rigidity of the proline backbone, once the electrophilic intermediate is formed, the alkyl radical would presumably attack from its less sterically hindered face, thus providing sterically enriched derivatives (Figure 4).

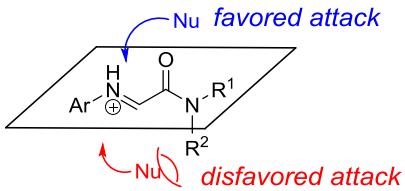
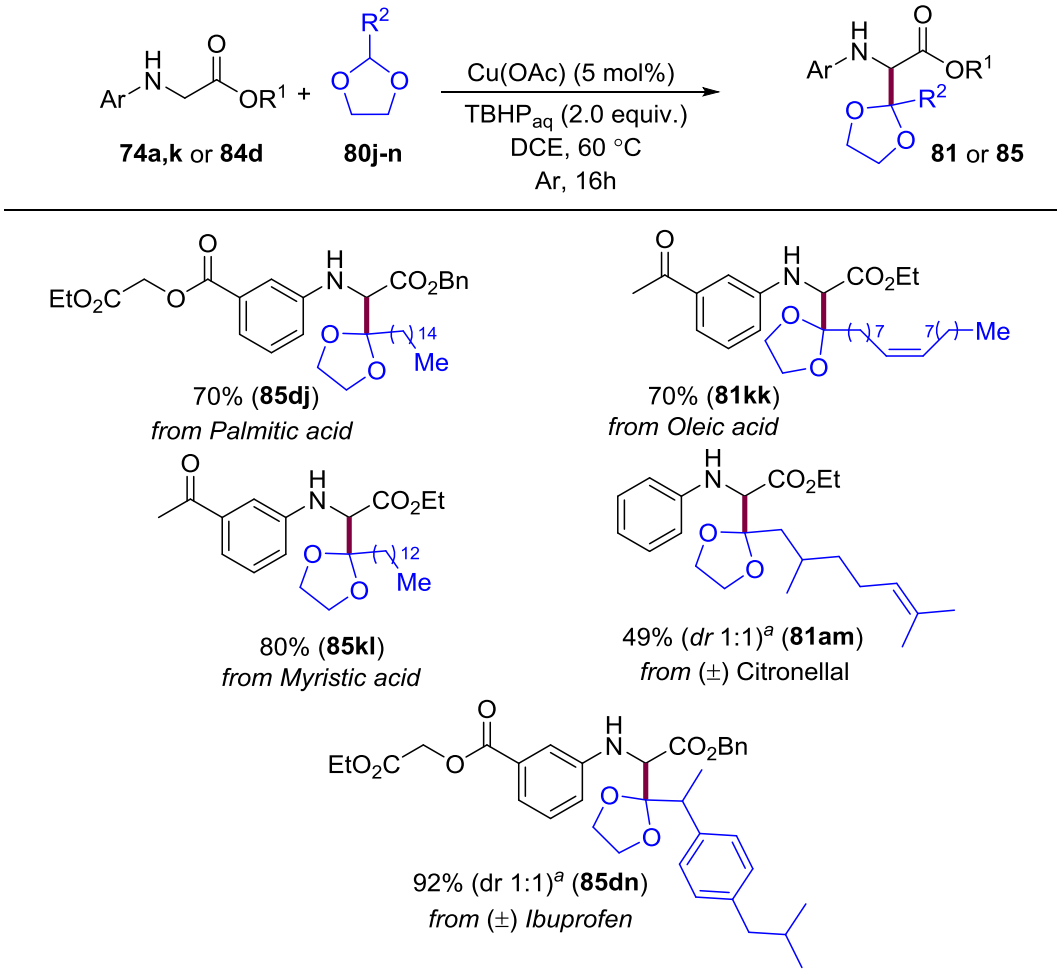


Figure 4. Proposal for stereo-control.

In the absence of any crystalized product **87**, we could not assign the absolute configuration of the new chiral center, but we hope this preliminary work could set the basis for future discoveries in the field of asymmetric functionalization of peptides.

1.5.7. Alkylation of *N*-Aryl Glycine Esters with Dioxolanes Derived From Natural Products and Drugs

With the aim of installing biologically relevant frameworks such us natural products and drugs into glycine derivatives, we prepared some dioxolanes derived from fatty acids (palmitic, oleic and myristic), ibuprofen and citronellal, a key component in perfums with lemon scent. Under optimized conditions, these

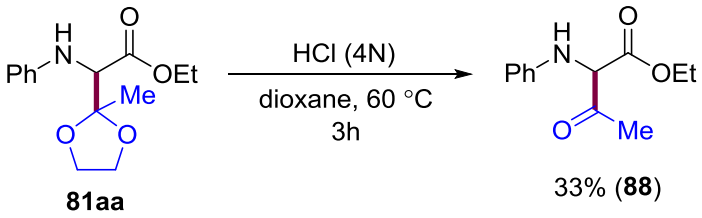


Reaction conditions: **74a,k** or **84d** (0.5 mmol), **80j-n** (0.5 mL), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE (1 mL), 60 °C, 24 h, under argon atmosphere. TBHPaq = *tert*-butyl hydroperoxide (70 wt. % in H_2O). Yield of isolated product after column chromatography, average of at least two independent runs. [a] d.r value calculated by ^{1}H RMN spectroscopy.

Scheme 40. Alkylation of α-amino esters with dioxolanes derived from natural products and drugs.

easily prepared dioxolanes derived from natural products and drugs behaved as selective alkylating reagents to produce **81** or **85** with moderate to excellent yields (Scheme 40), thus introducing added-value compounds into α-amino carbonyl derivatives in a simple and late-stage manner.

Although several procedures were tested for the cleavage of the dioxolane in compound **81aa**,[80] in most cases the starting material remained unreactive or degradation was observed, which we tentatively attributed to the low stability of the final product **88**. Finally, the deprotection was accomplished upon treatment with HCl in dioxane (Scheme 41), although product **88** was obtained in low yield.



Scheme 41. Cleavage of the dioxolane moiety.

1.5.8. Unsuccessful Reactions

1.5.8.1. Unsuccessful Dioxolanes

During the study of the generality of our protocol, we found out that several dioxolanes were not suitable coupling partners under the optimized reaction conditions (Figure 5). Even though the reaction tolerated a wide variety of alkyl dioxolanes, some of them resulted to be unreactive, including dioxolanes containing a chloride atom (**80ñ**), 2-methoxy-1,3-dioxolane (**80o**) or the dioxolane derived from cholesterol (**80r**), among others. Similarly, the thioacetal **80q** or the glucose derivative **80p** were also found unreactive. Unfortunately, the very accessible from commercially available benzaldehydes (**80s-u**) did not deliver the final alkylated product under standard conditions, which could be reasonably attributed to the formation of comparatively less stable aryl dioxolanes radical species. Even if the reaction tolerated dioxolanes bearing

[80] a) Baltork-Mohammadpoor, I.; Amini, M. K.; Farshidipoor, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2775. b) Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446. c) Bailey, A. D.; Cherney, S. M.; Anzalone, P. W.; Anderson, E. D.; Ernat, J. J.; Mohan, R. S. *Synlett* **2006**, 215. d) Khurana, J. M.; Dawra, K.; Sharma, P. *RSC Adv*. **2015**, *5*, 12048.

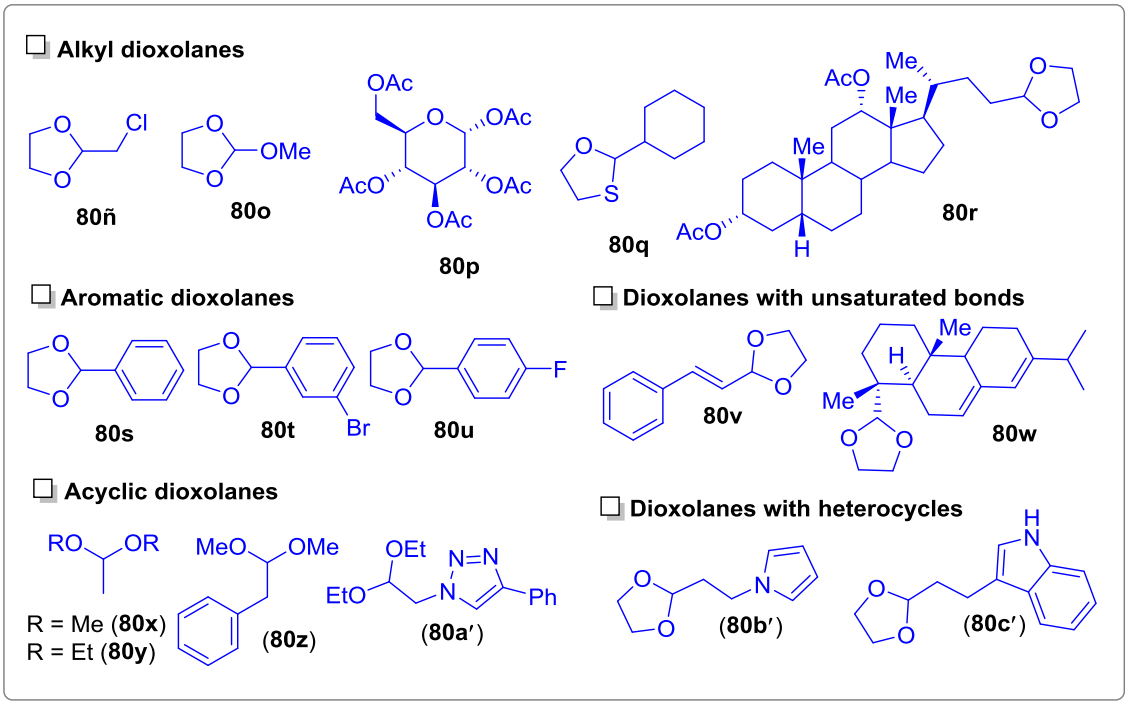


Figure 5. Unsuccessful dioxolanes.

alkenes (**81ad**, **81kk**, **81am**), conjugated alkenes (**80v-w**) could not be applied as alkylating reagents, although in the case of **80w** steric issues may also come into play. While 5-membered-cyclic dioxolanes exhibited high reactivity along with high site-selectivity, in the case of acyclic acetals such as **80x** or **80y**, low yields were obtained and with lack of site-selectivity as competitive C4-alkylation was also observed. Moreover, acyclic dioxolanes containing inert moieties such as phenyl (**80z**) or a triazole (**80a'**) were totally unreactive. Although the presence of pyrazole was perfectly accommodated in compound **81ii** (Scheme 36), dioxolanes bearing other heteroclycles such as pyrrole (**80b'**) or indole (**80c'**) did not deliver the desired products.

1.5.8.2. Unsuccessful Substrates

Regarding to the generality of the reaction concerning the glycine core, it tolerated a vast array of substrates, and only few of them were not suitable as depicted in Figure 6. Whereas the N-heteroaryl glycinate bearing an indole ring (**73l**) was degradated, in the case of naphthalene (**73m**) only starting material was recovered. As shown in Scheme 36, a variety of substitution patterns in the phenyl group were well tolerated and hence the result with **73m** was totally unexpected. The α-amino acid **73n** did not behave as its parent α-amino ester, and no product was observed, which could be attributed to solubility issues or even competitive chelation of the copper catalysts with the carboxylic acid group, thereby resulting in the inhibition of the process.

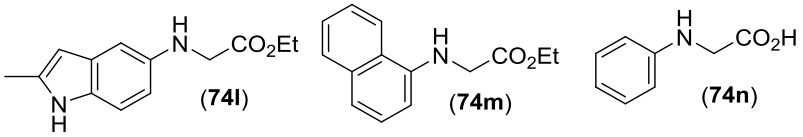
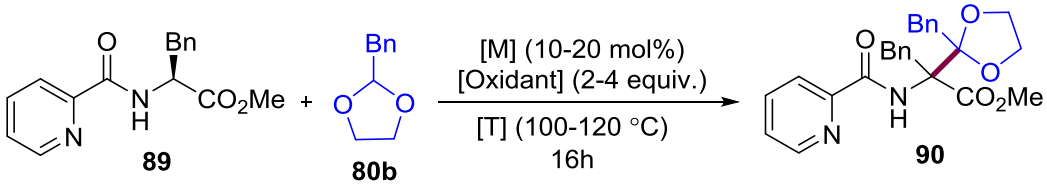


Figure 6. Unsuccessful substrates.

1.5.8.3. Alkylation of Tertiary α-Amino Acids

In order to expand the scope of our alkylation protocol, we decided to explore the formation of more challenging α-quaternary centers. Inspired by the group of You[23,33] (See Schemes 7 and 13), where picolinamide (PA) was introduced in the substrates to enable the formation of the corresponding electrophilic α-ketimide intermediate, we decided to use the same approach to activate the phenyl alanine derivative **87**. Iron, nickel and copper salts were explored as catalysts along with $TBHP_{aq}$ or DTBP as oxidants, but unfortunately in all of our attempts the starting material was recovered (Table 12, entries 1-6).



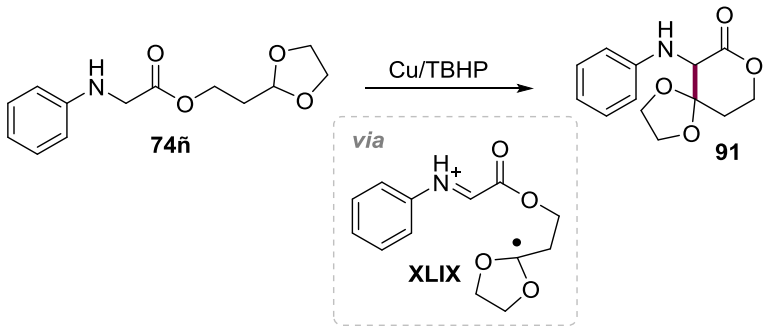
Entry	Metal	Oxidant	Co-solvent	T (º C)	Yield (%)
1	$FeCl_3$	TBHPaq	DCE	120	0
2	$FeCl_3$	DTBP	DCE	120	0
3[a]	$Ni(acac)_2$	DTBP	--	120	0
4[b]	Cu(OAc)	TBHPaq	--	100	0
5[c]	Cu(OAc)	TBHPaq	--	120	0
6[c]	Cu(OAc)	DTBP	--	120	0

Reaction conditions: **89** (0.25 mmol), 2-benzyl-1,3-dioxolane (1 mL), Metal (10 mol %), Oxidant (2.0 equiv.), DCE as co-solvent and 120 °C. [a] 20 mol % of metal and 4.0 equivalents of oxidant. [b] 100 °C. [c] 4.0 equivalents of oxidant.

Table 12. Alkylation of α-tertiary amino acids.

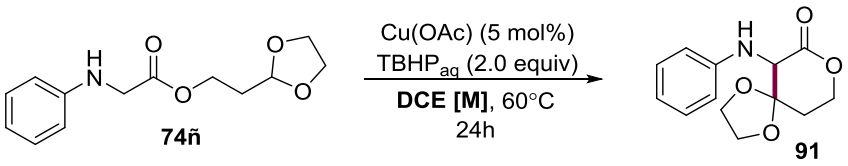
1.5.8.4. Intramolecular Approach

With the aim to create molecular diversity within a peptide framework, we decided to explore the more challenging intramolecular version of our protocol. Hereby, we designed the substrate **74ñ** with the tethered 1,3-dioxolane and the *N*-aryl glycine. Theoretically, this substrate could *in situ* generate the electrophilic iminium species along with the alkyl radical and hence enable an intra-molecular reaction, which would deliver the unprecedented cyclic product **91** (Scheme 42).



Scheme 42. Intramolecular approach.

With the idea that concentration could play a crucial role in this case, we performed the target reaction at different concentration values (Table 13, entries 1-3). Unfortunately, regardless of the dilution, only degradation was observed.



Entry	Oxidant	DCE (M)	Yield (%)
1	TBHP$_{aq}$	0.25	degradation
2	TBHP$_{aq}$	0.15	degradation
3	TBHP$_{aq}$	0.1	degradation

Reaction conditions: **74** (0.25 mmol), Cu(OAc) (5 mol%), TBHP$_{aq}$ (2.0 equiv.), DCE as solvent [M] and 60 °C.

Table 13. Concentration screening for the intramolecular approach.

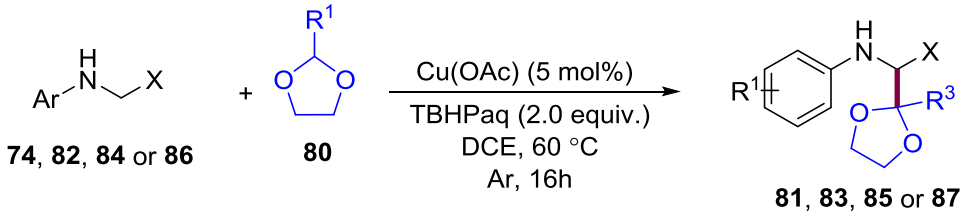
1.5.9. Conclusions

In summary, we have developed an unprecedented alkylation of glycine derivatives with the use 2-substituted 1,3-dioxolanes.[81] The methodology was applied for the late-stage-functionalization of peptides, where total selectivity was observed toward the terminal *N*-aryl glycine residue. The reaction tolerated several functional groups tethered to the dioxolane moiety, which overcome previous works in this field, where only simple ethers were utilized as alkyl reagents.[82] In addition, we have described a powerful, yet promising asymmetric protocol directed by the proline-containing peptide backbone, which furnished the alkylated peptides in a diastereo-enriched manner. Finally, the total selectivity toward the C2 in the 2-substituted 1,3-dioxolanes delivered the final products as masked ketones which represented a highly versatile functional group that could be further manipulated to create molecular diversity.

1.5.10. Experimental Procedure

In this section, some representative procedures as well as the characterization of a selection of illustrative compounds are provided. For a full detailed experimental description, please see the supporting information of the following article.[81]

1.5.10.1. Cu-Catalyzed C(sp^3)–H Alkylation of α-Amino Carbonyl Compounds

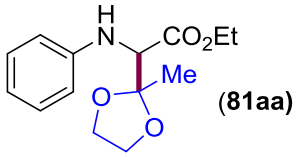


74, **82**, **84** or **86** + **80** → **81**, **83**, **85** or **87**

General Procedure: A reaction tube containing a stirring bar was charged with the corresponding α-amino carbonyl compound (if solid) (0.50 mmol, 1.00 equiv.) and Cu(OAc) (5 mol%). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). The corresponding α-amino carbonyl compound (if liquid) (0.50 mmol, 1.00 equiv.), an aqueous solution of TBHP (70 wt. % in H_2O) (2.00 equiv.), the corresponding 2-substituted-1,3-dioxolane (0.5 mL) and 1,2-dichloroethane

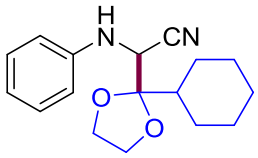
[81] San Segundo, M.; Correa, A. *ChemSusChem*, **2018**, *11*, 3893.
[82] For selective examples, see: a) Cheng, K.; Huang, L.; Zhang, Y. *Org. Lett*. **2009**, *11*, 2908. b) Du, P.; Li, H.; Wang, Y.; Cheng, J.; Wang, X. *Org. Lett*. **2014**, *16*, 6350. c) Su, R.; Li, Y.; Min, M.-Y.; Ouyang, X.-H.; Song, R.-J. ; Li, J.-H. *Chem. Commun*. **2018**, *54*, 13511.

(1.0 mL) were then added under argon atmosphere. The reaction tube was next warmed up to 60 ºC and stirred for 16-24 hours. The mixture was then allowed to warm to room temperature, concentrated under reduced pressure and the corresponding product was purified by flash chromatography.



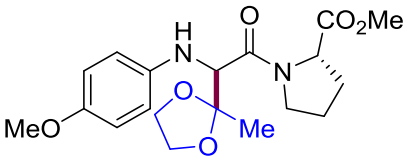
(**81aa**)

Ethyl 2-(2-methyl-1,3-dioxolan-2-yl)-2-(phenylamino)acetate (81aa). Following the general procedure, using commercially available *N*-phenylglycine ethyl ester (**74a**) (0.50 mmol, 90 mg) and 0.5 mL of commercially available 2-methyl-1,3-dioxolane (**80a**), provided 105 mg (79% yield) of **81aa** as a yellowish solid. Mp 40-41 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 2H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.32 – 4.16 (m, 3H), 4.10 – 3.97 (m, 4H), 1.53 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 147.1, 129.5, 118.8, 114.1, 109.5, 66.0, 65.7, 63.8, 61.5, 23.5, 14.5. IR (cm^{-1}): 3387, 2982, 2892, 1732, 1602, 1504, 1191, 1140, 1041, 749. HRMS *calcd.* for ($C_{14}H_{19}NO_4$): 265.1314, *found* 265.1310. *This reaction was also performed in a higher scale: the use of **74a** (5.59 mmol, 1.00 g), **80a** (4.0 mL), $TBHP_{aq}$ (1.55 mL) in DCE (8 mL) provided 1.18 g (80% yield) of **81aa** as a yellowish solid.*



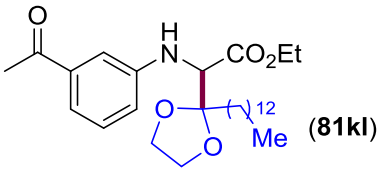
(**83ac**)

2-(2-Cyclohexyl-1,3-dioxolan-2-yl)-2-(phenylamino)acetonitrile (83ac). Following the general procedure, using commercially available *N*-phenylglycinonitrile (**82a**) (0.50 mmol, 66 mg), 10 mol% of Cu(OAc) and 0.5 mL of 2-cyclohexyl-1,3-dioxolane (**80c**), provided 75 mg (52% yield) of **83ac** as a white solid. Mp 124-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.50 – 4.35 (m, 2H), 4.19 – 4.06 (m, 3H), 2.00 (tt, *J* = 11.7, 3.1 Hz, 1H), 1.88 – 1.73 (m, 3H), 1.71 – 1.56 (m, 2H), 1.33 – 1.06 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 129.7, 120.3, 118.9, 114.4, 112.6, 67.6, 67.2, 51.2, 43.3, 27.4, 26.2, 26.1, 26.1, 26.0. IR (cm^{-1}): 3363, 2929, 2853, 1603, 1503, 1206, 1130, 751, 670. HRMS *calcd.* for ($C_{17}H_{22}N_2O_2$): 286.1681, *found* 286.1681.



(87aa)

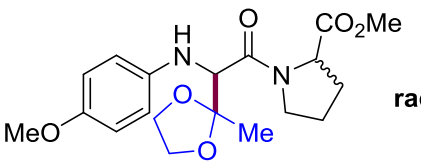
Methyl [2-((4-methoxyphenyl)amino)-2-(2-methyl-1,3-dioxolan-2-yl)acetyl]-*L*prolinate (87aa). Following the general procedure, using PMP-Gly-Pro-OMe (**86a**) (0.50 mmol, 146 mg) and 1.0 mL of 2-methyl-1,3-dioxolane (**80a**), provided 113 mg (60% yield) of **87aa** as a brownish oil. Diastereomeric ratio 20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.46 (dd, *J* = 8.7, 4.4 Hz, 1H), 4.16 (s, 1H), 4.05 – 3.80 (m, 5H), 3.73 (s, 4H), 3.56 (s, 3H), 2.26 – 1.86 (m, 4H), 1.49 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 170.0, 152.9, 141.4, 116.0, 115.4, 114.8, 110.6, 65.5, 65.4, 63.0, 59.5, 55.8, 52.1, 47.4, 29.2, 25.0, 22.8. IR (cm^{-1}): 3355, 2951, 2888, 1738, 1639, 1510, 1431, 1232, 1038. HRMS *calcd.* for ($C_{19}H_{26}N_2O_6$): 378.1791, *found* 378.1795. HPLC for the compounds with (D, L) and (L, L) configurations (Chiralpak IA; 90:10 Hexane: isopropanol; 1 mL/min, λ = 210 nm). t_R (major isomer) = 26.2 min, t_R (minor isomer) = 37.6 min.



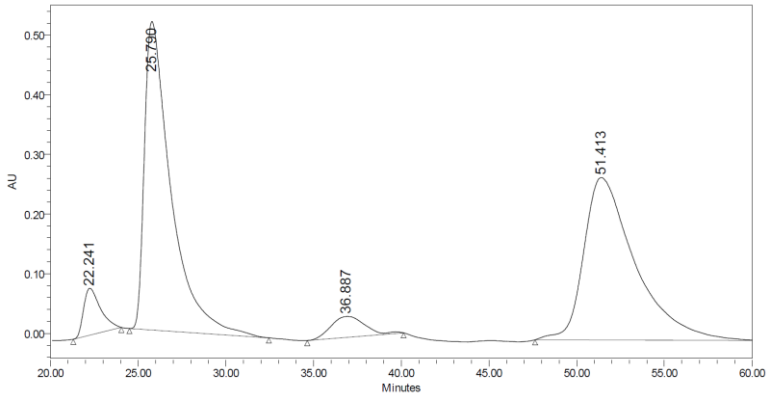
(81kl)

Ethyl 2-[(3-acetylphenyl)amino]-2-(2-tridecyl-1,3-dioxolan-2-yl)acetate (81kl). Following the general procedure, using ethyl (3-acetylphenyl)glycinate (**74k**) (0.25 mmol, 55 mg), 10 mol % of Cu(OAc), 0.5 mL of 2-tridecyl-1,3-dioxolane (**80l**) and 16 hours, provided 95 mg (80% yield) of **81kl** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.21 (m, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 4.31 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.13 – 3.99 (m, 4H), 2.58 (s, 3H), 1.84 (t, *J* = 8.2 Hz, 2H), 1.55 – 1.39 (m, 2H), 1.28 (s, 25H), 0.98 – 0.82 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 171.5, 147.2, 138.3, 129.5, 118.9, 118.5, 112.9, 111.2, 66.5, 66.1, 62.3, 61.5, 37.0, 32.1, 29.8, 29.8, 29.8, 29.7, 29.5, 26.8, 23.2, 22.8, 14.3, 14.2. IR (cm^{-1}): 3388, 2922, 2852, 1736, 1683, 1586, 1323, 1266, 1232, 1190, 1147, 993. HRMS *calcd.* for ($C_{28}H_{45}NO_5$): 475.3298, *found* 475.3302.

1.5.10.2. HPLC Chromatograms

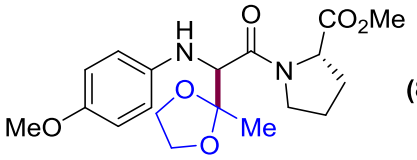


rac-(87aa)

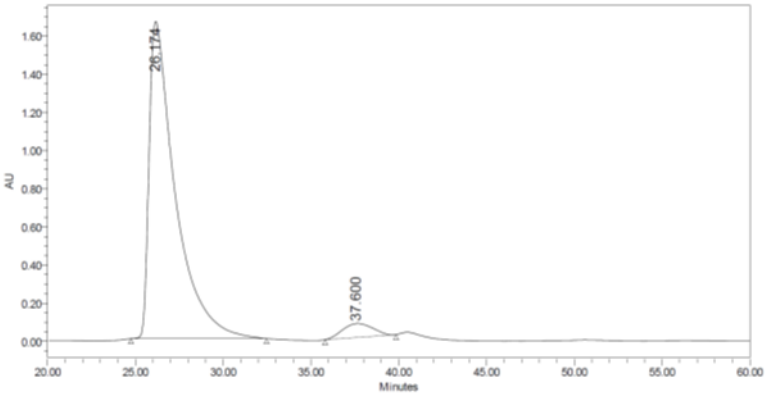


	RT	Area	% Area	Height
1	22.241	5284690	4.42	78735
2	25.790	54260092	45.35	516990
3	36.887	4693141	3.92	35271
4	51.413	55414008	46.31	272109

Chiralpak IA; 90:10 Hexane: isopropanol; 1 mL/min, λ = 210 nm.

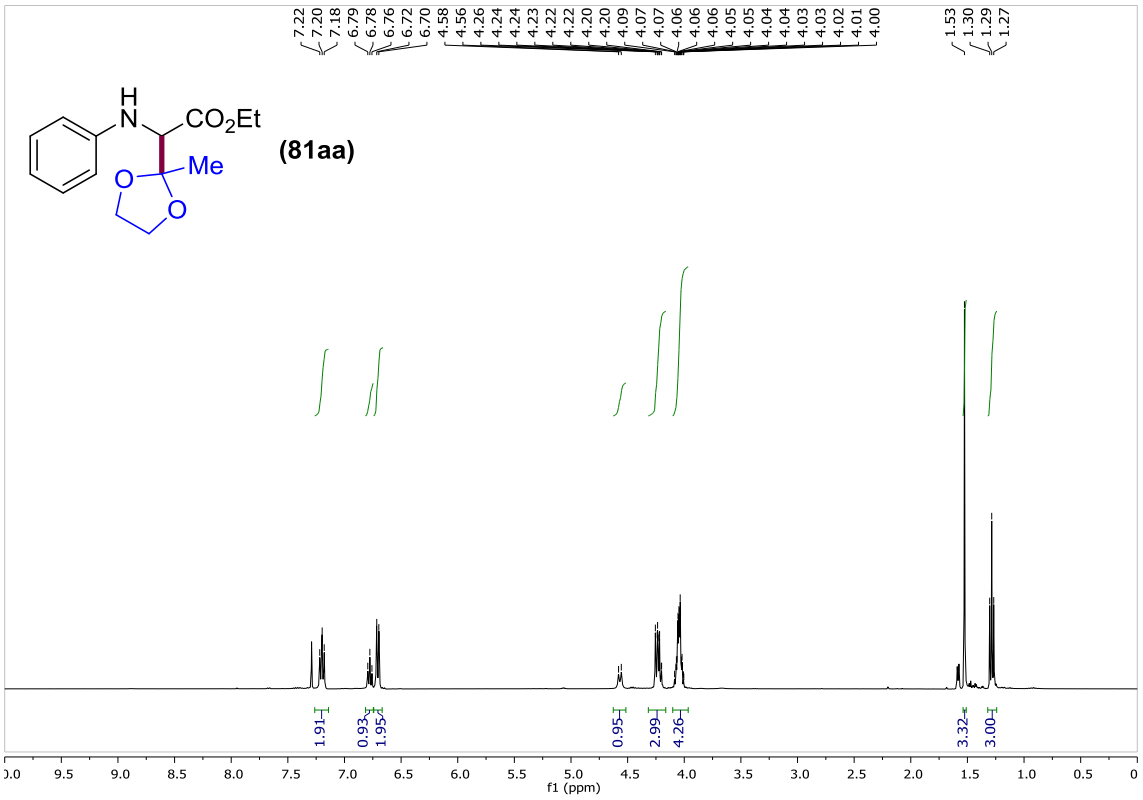


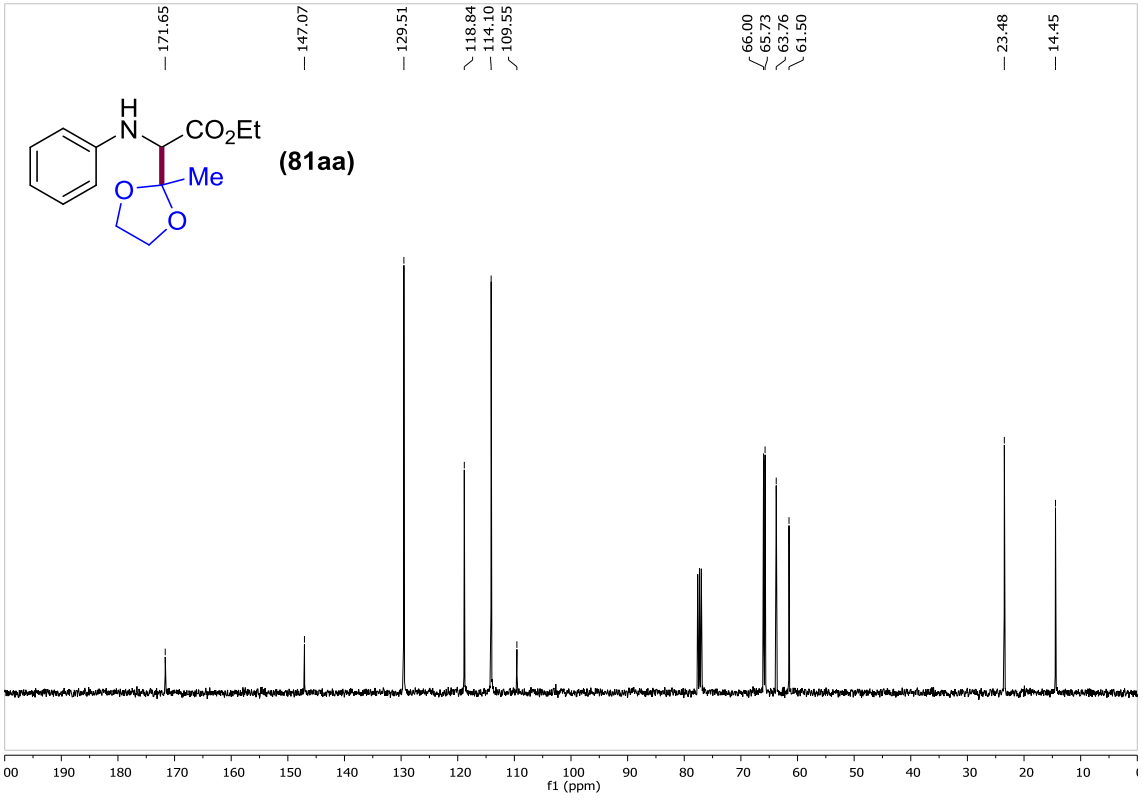
(87aa) *dr* 20:1

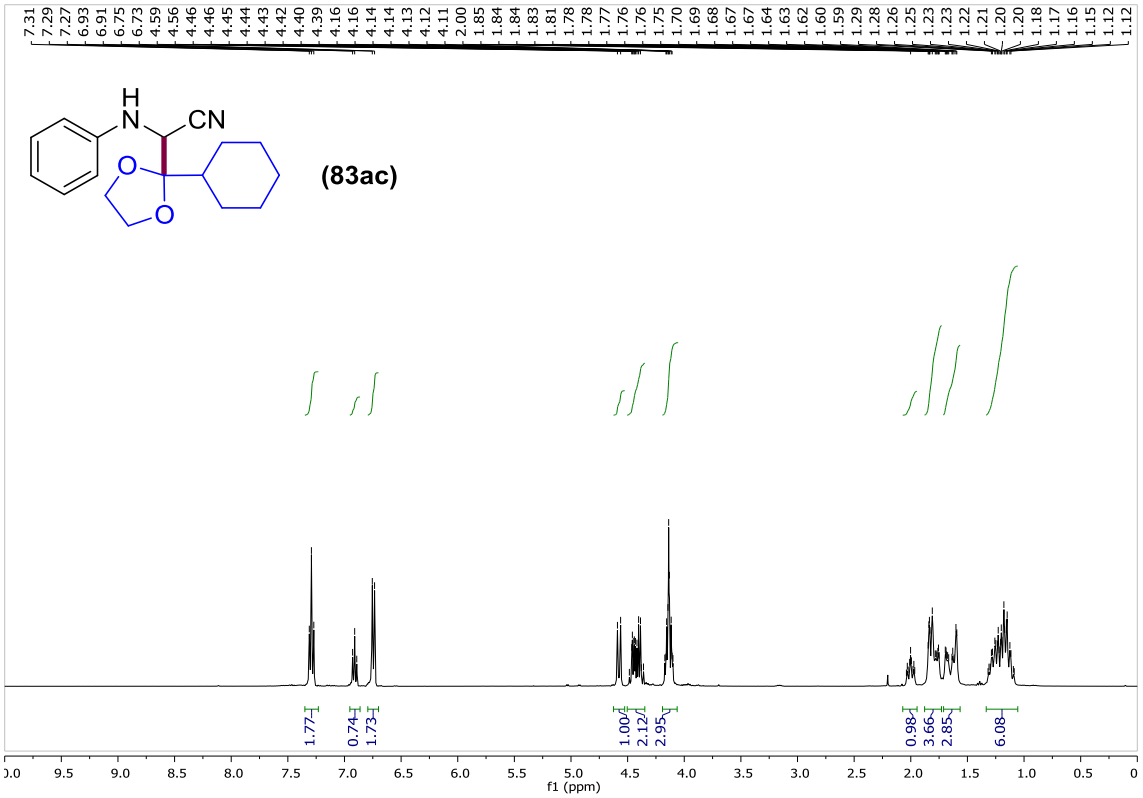


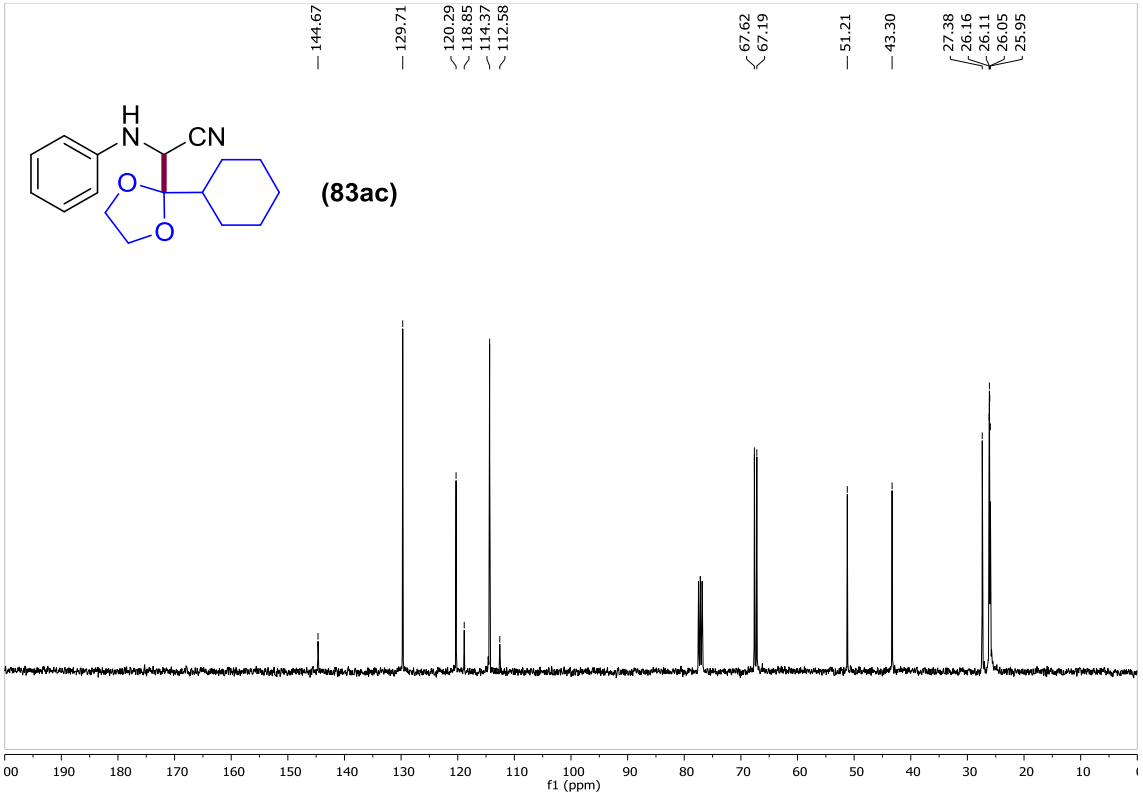
	RT	Area	% Area	Height
1	26.174	171926539	95.23	1662876
2	37.600	8607787	4.77	72962

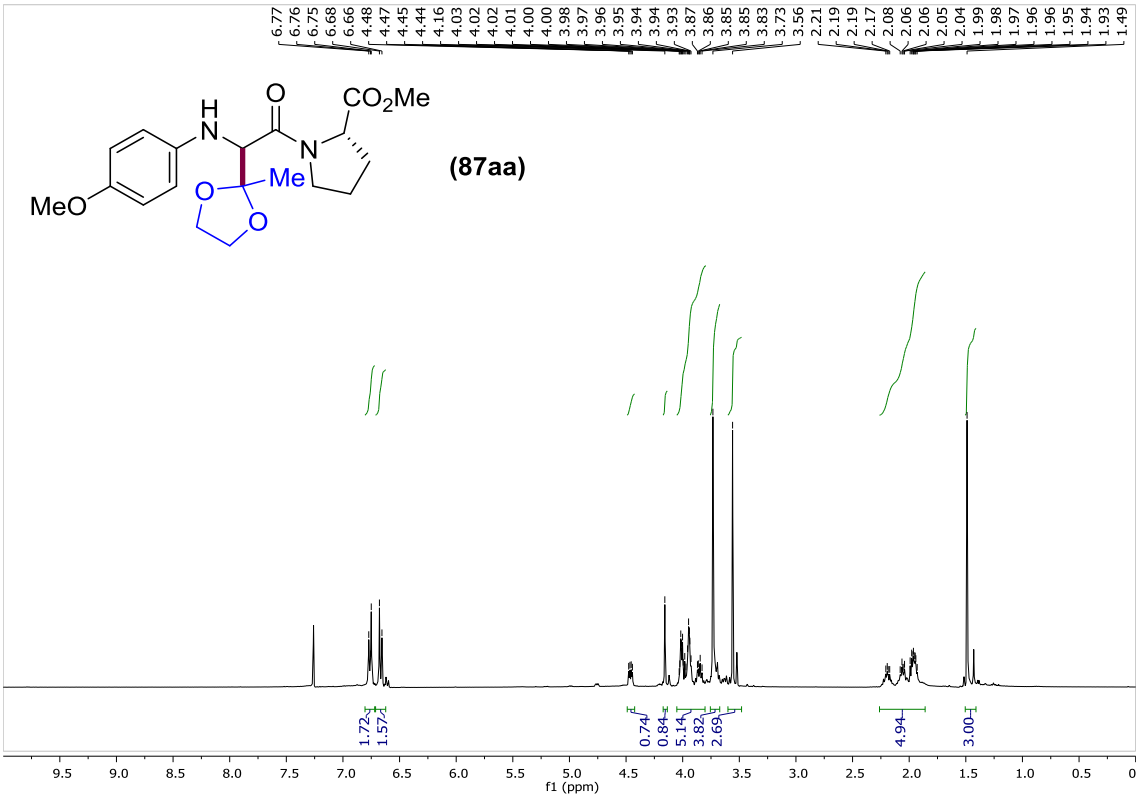
1.5.10.3. ^{1}H NMR and ^{13}C NMR Spectra

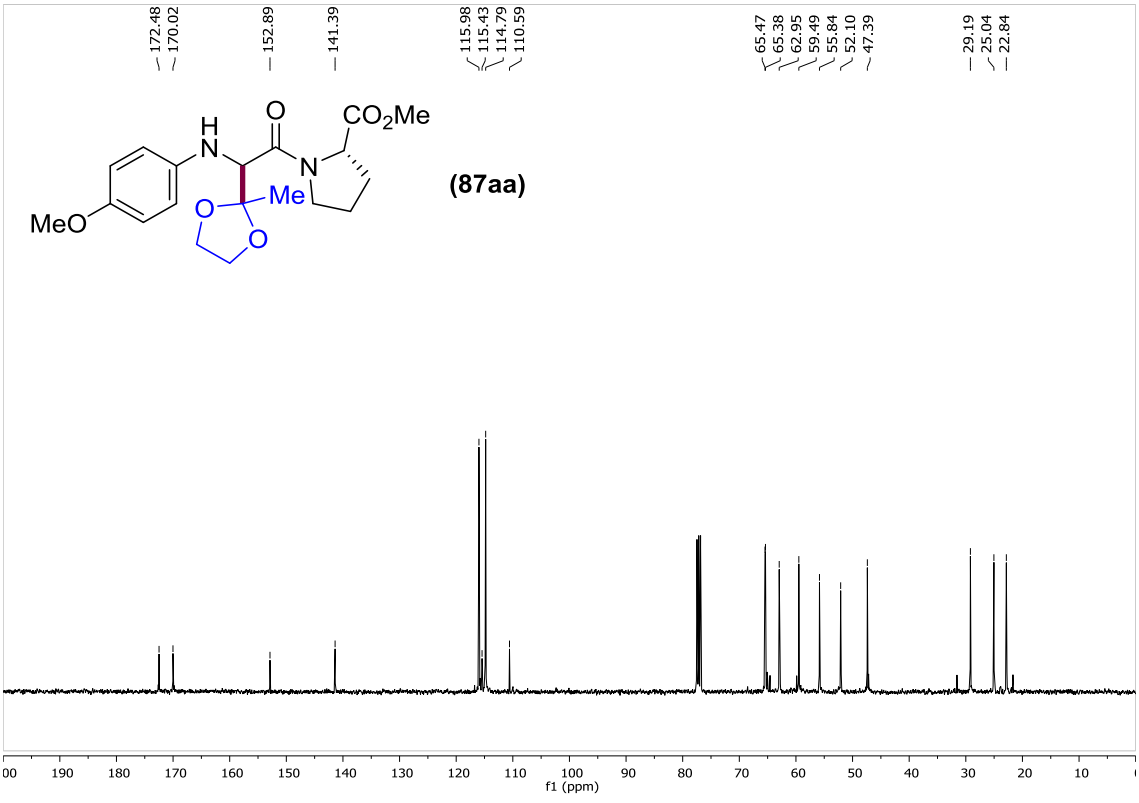


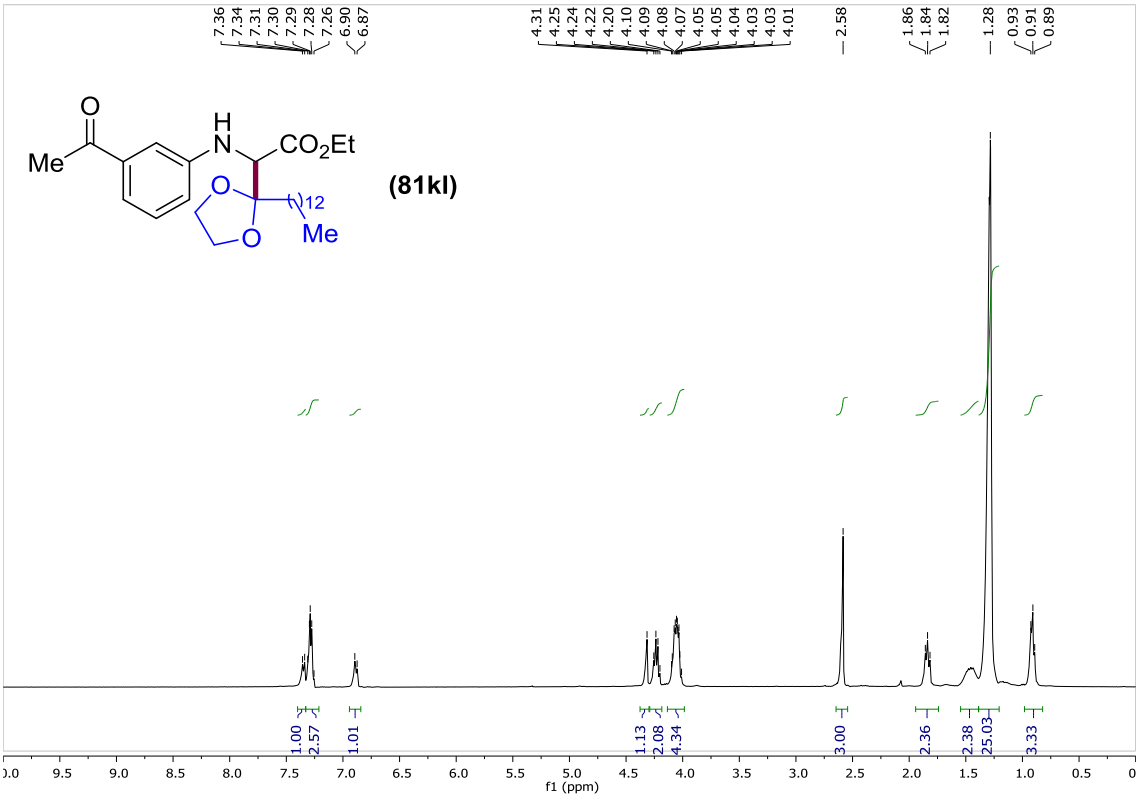



(83ac)
f1 (ppm)


(83ac)
f1 (ppm)


(87aa)
MeO
Me
CO2Me
f1 (ppm)


(87aa)
MeO
Me
CO2Me
f1 (ppm)


7.36
7.34
7.31
7.30
7.29
7.28
7.26
6.90
6.87
4.31
4.25
4.24
4.22
4.20
4.10
4.09
4.08
4.07
4.05
4.05
4.04
4.03
4.03
4.01
2.58
1.86
1.84
1.82
1.28
0.93
0.91
0.89
O
Me
H
N
CO2Et
O
12
Me
O
(81kl)
1.00
2.57
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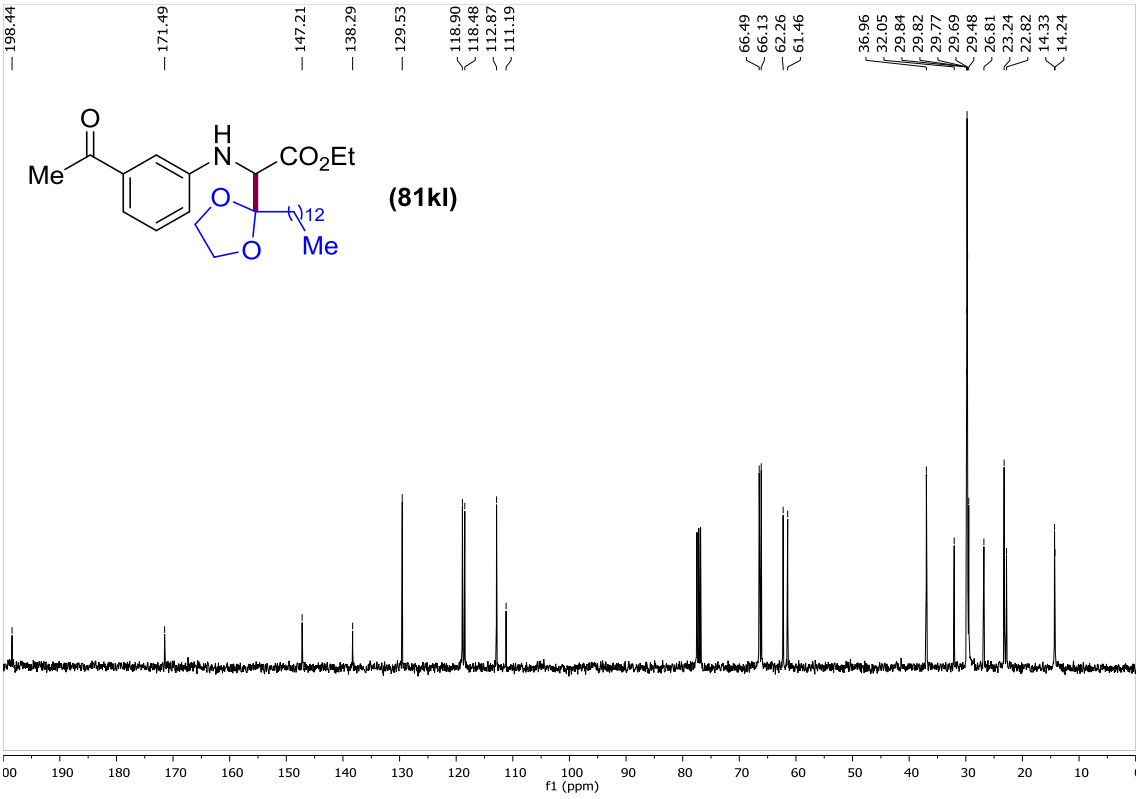
198.44
171.49
147.21
138.29
129.53
118.90
118.48
112.87
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62.26
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32.05
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29.82
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29.69
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O
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O
(81kl)
f1 (ppm)

Chapter 2. Pd-Catalyzed Site-Selective C(sp^2)–H Acylation of Phenylalanine and Tyrosine Residues

2.1. Side-Chains C–H Functionalization of α-Amino Acids and Peptides

2.1.1. Side-Chain C(sp^2) H–Functionalization of Aromatic α-Amino Acids and Peptides

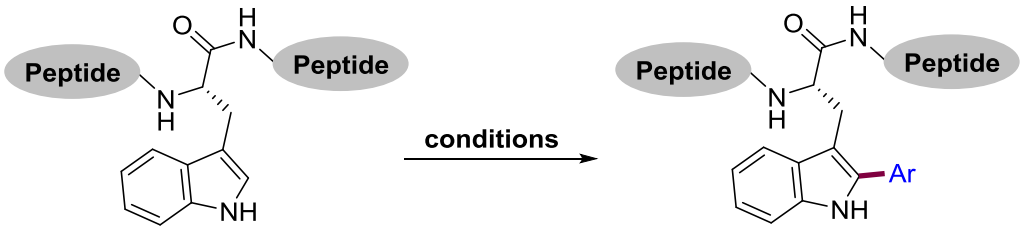
α-Amino acids with an aromatic side-chain such as tryptophan, phenylalanine, tyrosine or histidine, like other proteinogenic amino acids are the building blocks of proteins. In animal and humans, aromatic amino acids are precursors for bioactive compounds and neurotransmitters. For example, tyrosine is the initial precursor for the biosynthesis of dopamine or melanin, whereas tryptophan is the initial precursor for the biosynthesis of serotonin and melatonin, among others. For this reason, these compounds have attracted tremendous interest in the field of medicinal chemistry. In this regard, C(sp^2)–H functionalization processes have enabled the straightforward diversification of aromatic α-amino acids for a plethora of transformations, including the late-stage functionalization of complex peptides and proteins. In this section, some of the main transformations made for each aromatic amino acid are disclosed.

2.1.1.1. C–H Functionalization of Tryptophan Residues at C2-Position

Probably the most exploited amino acid in C–H functionalization processes has been the indole moiety of the tryptophan.[83] While traditional chemistry was mostly limited to *O*- and *N*-arylation reactions of tyrosine and tryptophan residues,[84] respectively, the metal-catalyzed C–H activation has overcome these limitations achieving the C2-arylation of the indole ring. Thereby, several site-selective arylation protocols have been described over the last decade, in which the use of palladium acetate has overshadowed the use of other transition metals (Table 14).

The remarkable work of Albericio, Lavilla and co-workers, achieved the first site-selective C2-arylation of tryptophan-containing peptides.[85] This was accomplished with catalytic amounts of $Pd(OAc)_2$ along with $AgBF_4$ as oxidant and an excess of the corresponding iodoarene, where the exposure of microwave irradiation was found to accelerate the reaction time to just 10 minutes (Entry 1).

[83] Gruß, H.; Sewald. N. *Chem. Eur. J.* **2020**, *26*, 5328.
[84] Chapman, C. J.; Matsuno, A.; Frost, C. G.; Willis, M. C. *Chem. Commun.* **2007**, 3903.
[85] Ruiz-Rodriguez, J.; Albericio, F.; Lavilla, R. *Chem. Eur. J.* **2010**, *16*, 1124.



Entry	Catalyst (mol%)	Oxidant (equiv.)	Reagent (equiv.)	Conditions/ Additives (equiv.)	Yield (%)
1[85]	$Pd(OAc)_2$ (5)	$AgBF_4$ (1)	Ar-I (4.0)	K_3PO_4 buffer, 80 °C, MW/ 2-NO_2Bz (1.5)	23-92
2[86,87]	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (2) or $Cu(OAc)_2$ (0.1)/air	$PhB(OH)_2$ (2.0-5.0)	AcOH, 40 °C	8-95
3[88]	$Pd(OAc)_2$ (5)	-	Ar-N_2BF_4 (1.0)	EtOAc, r.t	45-100
4[89]	$Pd(OAc)_2$ (5)	Ar_2IOTs (1.5)		AcOH or H_2O, r.t	41-98

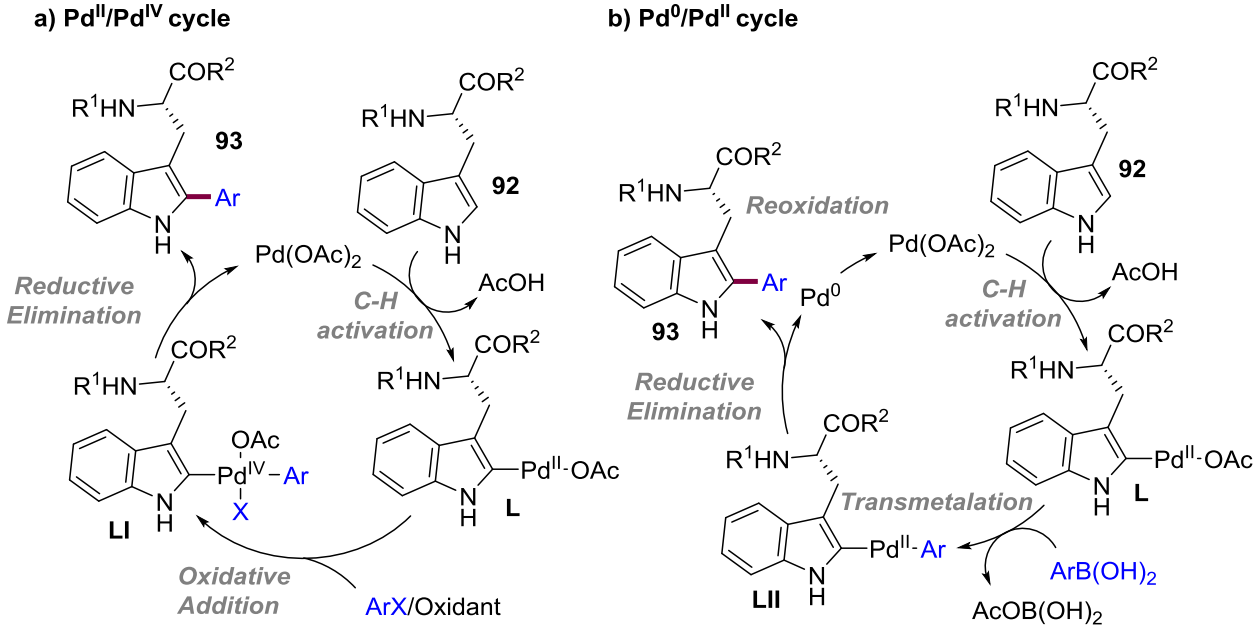
Table 14. Different procedures for the selective C2-arylation of tryptophan derivatives.

Afterwards, the group of Fairlamb alternately employed boronic acids as the aryl source to perform an oxidative Suzuki coupling reaction with the tryptophan moiety.[86,87] The transformation was achieved under low temperature (40 °C), acetic acid as solvent and either catalytic amounts of $Cu(OAc)_2$ or stoichiometric amounts of $PhI(OAc)_2$ as oxidant (entry 2). Recently, the same group has improved the reaction conditions toward more environmentally friendly, yet atom-economical conditions with the use of diazonium salts at room temperature (entry 3).[88] Meanwhile, the group of Ackermann had also achieved the late-stage arylation of tryptophan containing peptides, in this case with the use of diarylidonium salts, which acted as both oxidant and aryl source. Furthermore, the reaction was performed at room temperature and acetic acid or even water could be employed as solvent (entry 4).[89]

Commonly, there are two proposed mechanisms for the C(sp^2)–H arylation of tryptophan derivatives (Scheme 43).[90] One involves a Pd^{II}/Pd^{IV} cycle, which would begin with the C–H activation step to form the organometallic species **L**. Afterwards, the oxidative addition of either the iodoarene or aryl iodonium salt would generate the high valent Pd^{IV} intermediate **LI**, which upon reductive elimination would yield the arylated

[86] Reay, A. J.; Williams, T. J.; Fairlamb, I. J. S. *Org. Biomol. Chem.* **2015**, *13*, 8298.
[87] Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014**, *50*, 3052.
[88] Reay, A. J.; Hammarback, L. A.; Bray, J. T. W.; Sheridan, T.; Turnbull, D.; Whitwood, A. C.; Fairlamb, I. J. S. *ACS Catal.* **2017**, *7*, 5174.
[89] Zhu, Y.; Bauer, M.; Ackermann, L. *Chem. Eur. J.* **2015**, *21*, 9980.
[90] Sandtorv, A. H. *Adv. Synth. Catal.* **2015**, *357*, 2403.

product **93** and regenerate the active Pd^{II} catalyst (Scheme 43a). However, when boronic acids are employed, a Pd^0/Pd^{II} regime is proposed to occur. Hence, the intermediate **L** would undergo a transmetalation step, to form the arylpalladium **LII**, which would eventually deliver the final product **93** and Pd^0 through reductive elimination. Finally, the Pd^0 could be reoxidized under oxidative conditions to regenerate the active Pd^{II} catalyst (Scheme 43b).



Scheme 43. Mechanisms proposed for the palladium-catalyzed C–H arylation of tryptophan derivatives.

Cyclic peptides have shown to improve the peptide properties (cell penetration, stability, selectivity and so on) in comparison to their acyclic analogues, thereby enhancing the potential of these structures as therapeutics and bioprobes. Therefore, new protocols for the direct assembly of complex macrocyclic peptides is a subject of paramount interest.[91] This type of peptides were previously synthesized through ring-closing metathesis reaction,[92] amide coupling, or through "click reactions" with azide-alkyne cycloadditions.[93]

Related with their previous work, Lavilla, Albericio and co-workers, developed an elegant intramolecular C–H arylation with peptides containing a Trp residue and an iodinated Phe or Tyr unit for the formation of stapled peptides.[94] Preliminary studies revealed that the most suitable position of the iodo-substituent in Phe and Tyr moieties was the *meta*-position. Regarding to the preferential distance between Trp and Phe(Tyr)

[91] Rivera, D. G.; Ojeda-Carralero, G. M.; Reguera, L.; Van der Eycken, E. W. *Chem. Soc. Rev*. **2020**, 2039.
[92] Blackwell, H. E.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1998**, *37*, 3281.
[93] Dharanipragada, R. *Future Med. Chem.* **2013**, *5*, 831.
[94] Mendive-Tapia, L.; Preciado, S.; García, J.; Ramón, R.; Kielland, N.; Albericio, F.; Lavilla, R. *Nat. Commun*. **2015**, *6*, 7160.

residues, it ranged from one to three amino acids in a series of linear *N*-Acetyl peptides (**94**). This palladium-catalyzed intramolecular arylation reaction furnished the desired stapled peptides **95**, with moderate to excellent conversions (Table 15). Furthermore, the procedure tolerated peptides housing challenging amino acids compatible with C–H activation reactions such us asparagine, arginine or serine residues.

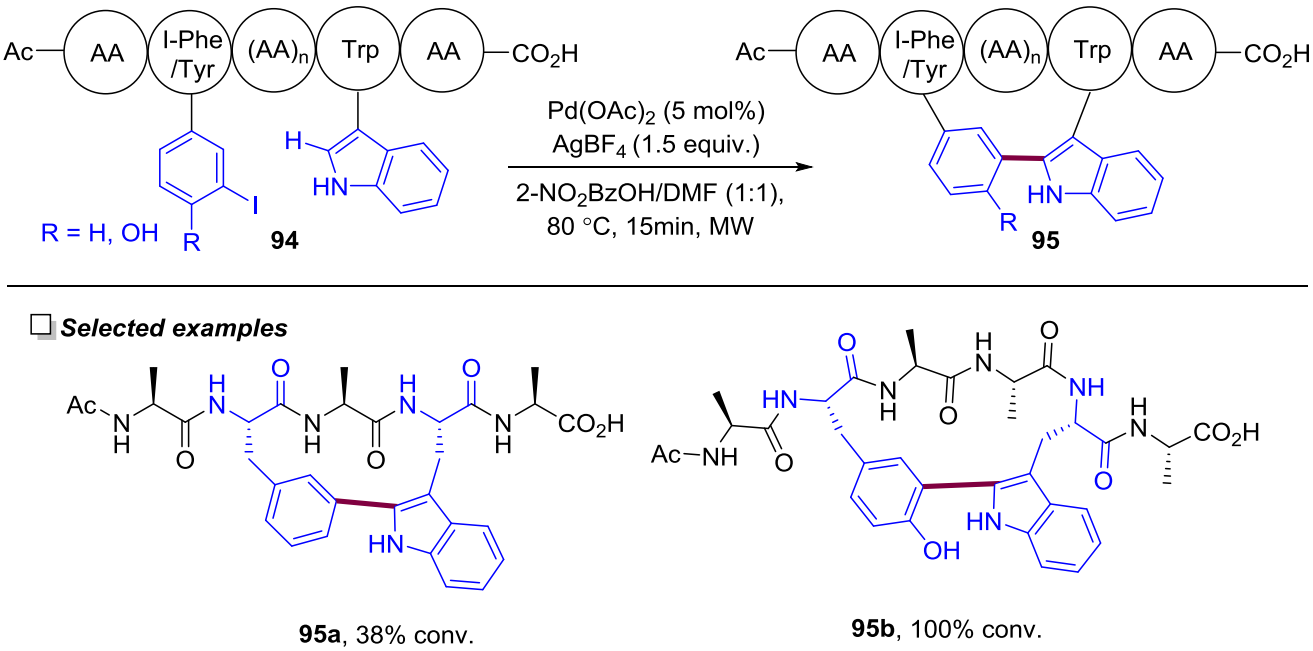
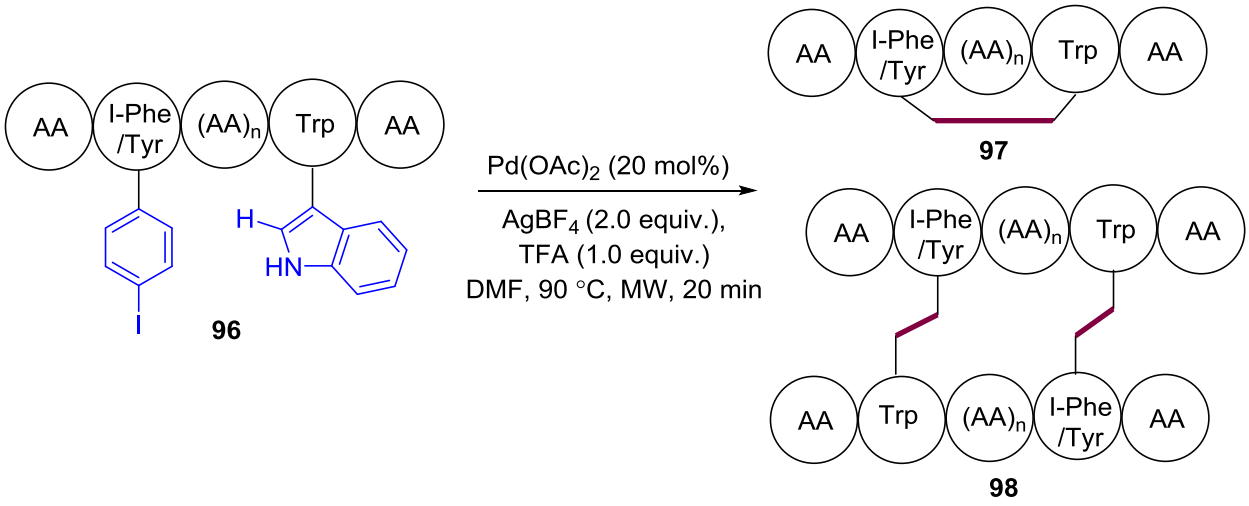


Table 15. Synthesis of stapled peptides by C–H arylation.

This intramolecular C–H arylation reaction was further studied by the group of Lavilla, Albericio and co-workers with the aim of evaluate the selectivity factors controlling the fate of this chemical transformation.[95] When *ortho*-I-Phe residues were employed to react with the Trp residue, the formation of the corresponding cyclic peptide was not observed which was attributed to the high strain that would be generated upon cycliczation. on the other hand, when *para*-I-Phe residues were employed, the final outcome was totally dependant on the number of residues between the I-Phe and the Trp residues (Table 16). When Phe and Tyr

[95] Mendive-Tapia, L.; Bertran, A.; García, J.; Acosta, G.; Albericio, F.; Lavilla, R. *Chem. Eur. J.* **2016**, *22*, 13114.



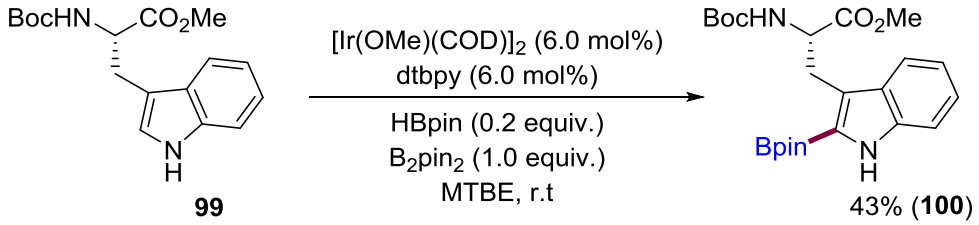
Entry	Peptide sequence	Cyclodimeric peptide	Cyclopeptide
1	Ala-**(*p*-I)Phe**-**Trp**-Ala	(**98a**) (60%)	(**97a**) n.d.
2	**(*p*-I)Phe**-Ala-**Trp**-Lys	(**98b**) (54%)	(**97b**) n.d.
3	Ala-**(*p*-I)Phe**-Lys-Gly-**Trp**-Ala	(**98c**) (23%)	(**97c**) (51%)
4	Ala-**(*p*-I)Phe**-Arg-Lys-Gly-**Trp**-Ala	(**98d**) n.d	(**97d**) (81%)

Table 16. Cyclodimerization versus cyclization.

residues were in adjacent position within the peptide sequence, only formation of the cyclodimeric **98a** was observed (Table 16, entry 1). Introducing one amino acid residue between Phe and Trp moieties did not change this tendency, and the cyclodimer **98b** was selectively formed (Table 16, entry 2). Things changed when a two amino acid sequence was introduced between the active residues, where a mixture of cyclodimeric **98c** (23% yield) and the intramolecular reaction product, the cyclopeptide **97c** (51% yield) were detected (Table 16, entry 3). Importantly, the introduction of three amino acids between the active Phe and Trp residues, exclusively delivered the cyclopeptide product **97d** (Table 16, entry 4).

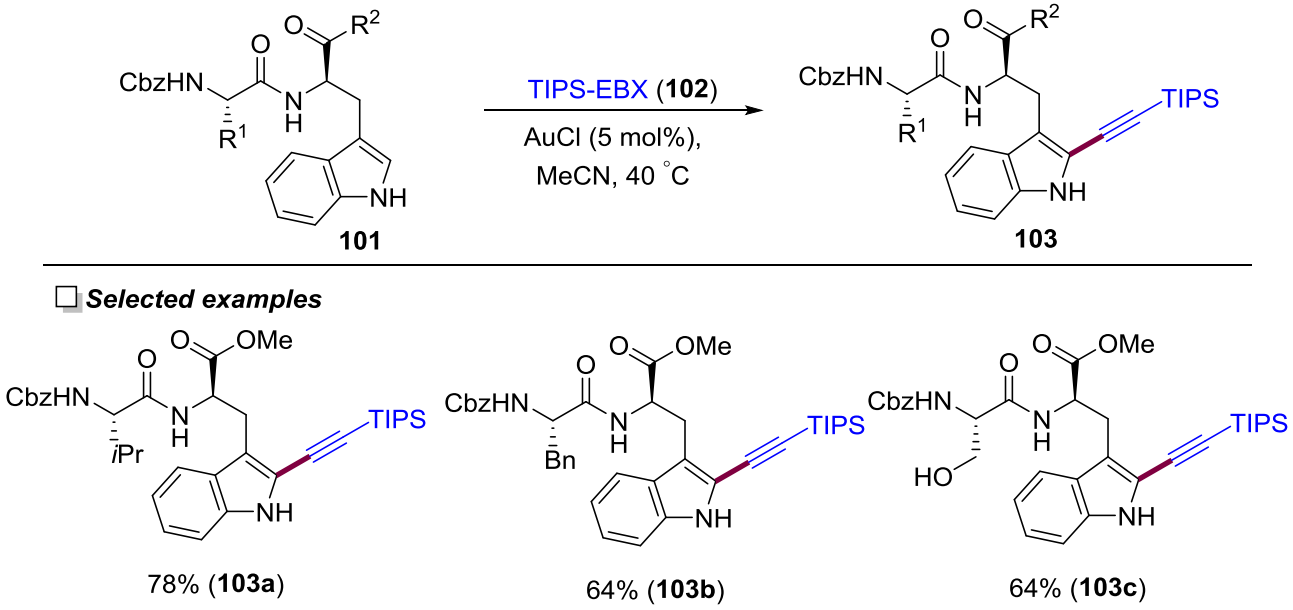
Organoboron compounds are considered highly versatile scaffolds, especially as intermediates for Suzuki-Miyaura cross-coupling[96] reactions and in consequence, C–H borylation reactions have attracted great attention.[97] Hereby, the group of Smith developed an iridium-catalyzed borylation of heterocycles, where the tryptophan unit **99** was selectively borylated at the C2-position (Scheme 44).[98] Under remarkably mild conditions, using $[Ir(OMe)(COD)]_2$ as the catalyst and B_2pin_2 as the boron source, borylated product **100** was obtained in moderate yield.

[96] Beletskaya, I. P.; Alonso, F.; Tyurin, V. *Coord. Chem. Rev*. **2019**, *385*, 137.
[97] Li, Y.; Wu, X.-F. *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 1770.
[98] Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka Jr, R. E.; Smith III, M. R. *J. Org. Chem.* **2009**, *74*, 9199.



Scheme 44. Iridium-catalyzed C–H borylation of tryptophan derivative.

Direct C–H alkynylation reactions also represent an important tool in organic chemistry, since it allows further manipulation such us alkyne-azide "click reaction", Glaser-Hay[99] or Sonogashira reactions.[100] In this context, a selective C2-alkynylation of tryptophan-containing peptides **101** was accomplished by the group of Waser (Scheme 45).[101] This reaction was achieved with catalytic amount of AuCl and 1.2 equivalents of TIPS-

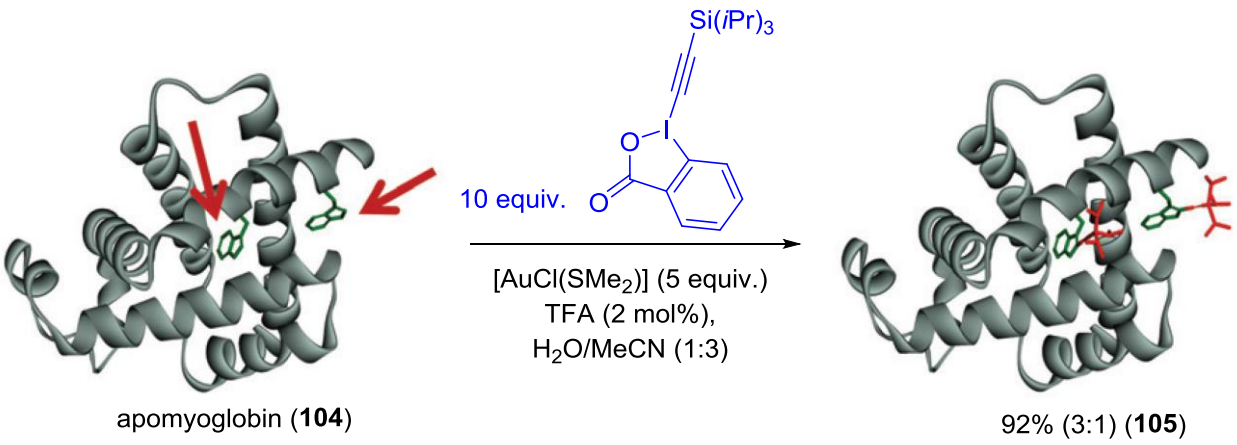


Scheme 45. Gold-catalyzed C–H alkynylation of tryptophan-containing small peptides.

EBX as the ethynyl source under the low temperature of 40 °C. Under these conditions, a small family of dipeptides (**101a**-**b**) or tripeptide (**101c**) were successfully alkynylated in moderate to good yields. Subsequently, the group of Hoeg-jensen performed an elegant, yet impressive alkynylation in biologically

[99] Su, L.; Dong, J.; Liu, L.; Sun, M.; Qui, R.; Zhou, Y.; Yin, S.-F. *J. Am. Chem. Soc.* **2016**, *138*, 12348.
[100] Thomas, A. M.; Sujatha, A.; Anilkumar, G. *RSC Adv.* **2014**, *4*, 21688.
[101] Tolnai, G. L.; Brand, J. P. ; Waser, J. *Beilstein J. Org. Chem.* **2016**, *12*, 745.

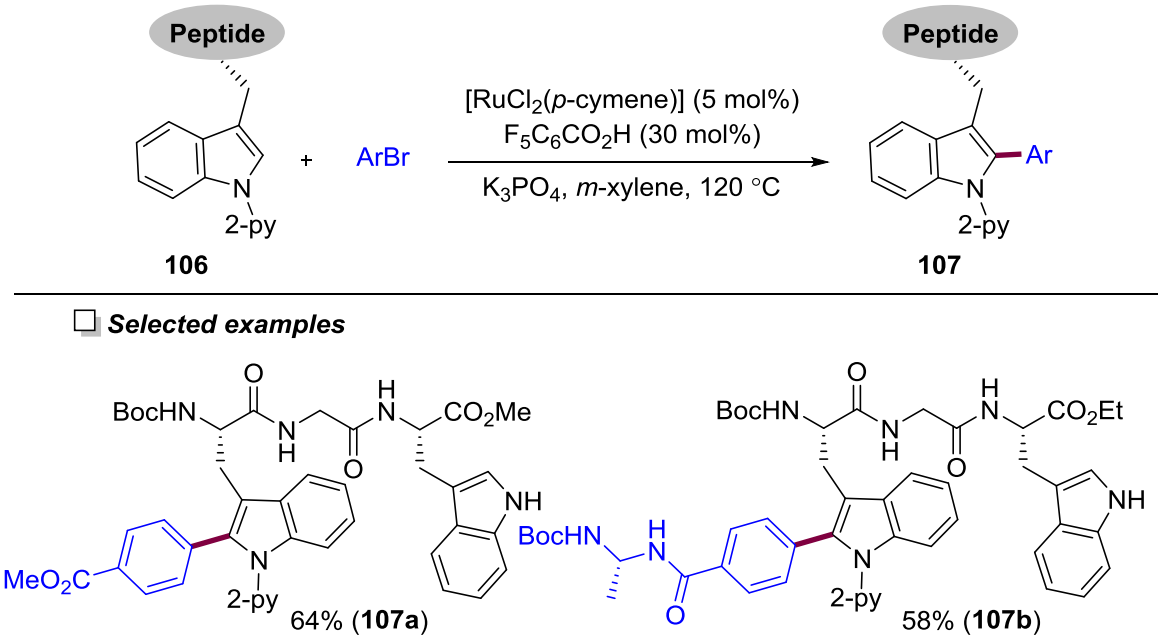
relevant biomolecules such as the protein apomyoglobin **104** bearing two Trp units (Scheme 46).[102] Obtaining the desired The final product **105** with an outstanding 92% yield and 3:1 *mono*:*di* alkynylation ratio, which was determined by MS-MS analysis.



Scheme 46. Direct modification of apomyoglobin protein **104**.

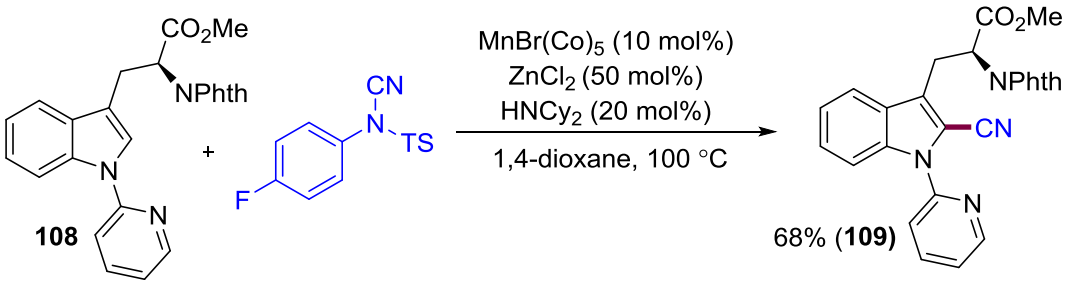
On the other hand, Ackermann and co-workers disclosed an unprecedented *N*-pyridyl-directed C–H arylation of tryptophan-containing peptides with aryl bromides.[103] Optimization studies revealed that the user-friendly [$RuCl_2$(*p*-cymene)]$_2$ as catalyst, K_3PO_4 as mild base in conjunction with $F_5C_6CO_2H$ exhibited the best results. Under these conditions, peptides **106** were effectively arylated in overall good yields with a wide range of aryl bromides having electron donating or withdrawing group (**107a**) and even with a peptide chains tethered to the aryl bromide scaffold (**107b**). In addition, a bioortogonal diversification of peptides was accomplished (**107a**), in which only the tryptophan having the *N*-pyridyl moiety was functionalized through coordination with the ruthenium catalyst (Scheme 47).

[102] Hansen, M. B.; Hubálek, F.; Skrydstrup, T.; Hoeg-Jensen, T. *Chem. Eur. J.* **2016**, *22*, 1572.
[103] Schischko, A.; Ren, H.; Kaplaneris, N.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 1576.



Scheme 47. Ruthenium-catalyzed arylation of tryptophan derivatives.

Ackermann and co-workers further exploited this approach for the Mn-catalyzed cyanation of tryptophan unit **108**.[104] Using Beller´s cyanation reagent in the presence of [$MnBr(Co)_5$] as the catalyst, $ZnCl_2$ as additive and $HNCy_2$ as base. These conditions afforded the desired cyanated tryptophan **109** in 68% yield under racemization-free conditions (Scheme 48). Unfortunately, this transformation was not extended to the late-stage-functionalization of peptides.

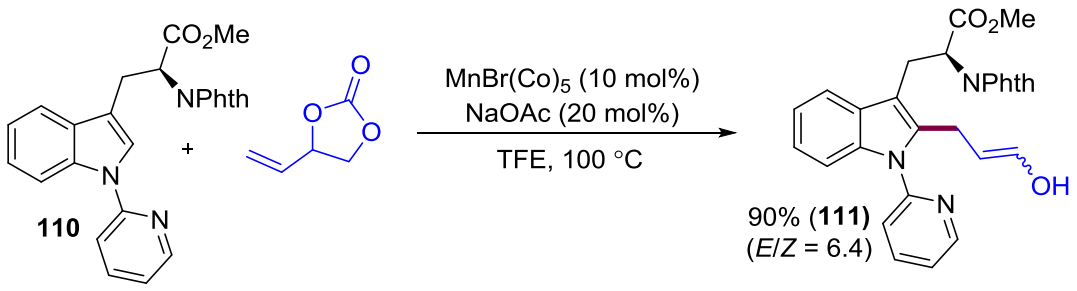


Scheme 48. Manganese-catalyzed C–H cyanation of tryptophan derivative.

Continuing with this approach, Ackermann and co-workers also developed a Mn-catalyzed allylation of tryptophan derivatives (**110**) through decarboxylative C–H/C–O sequence.[105] The catalytic system consisted in

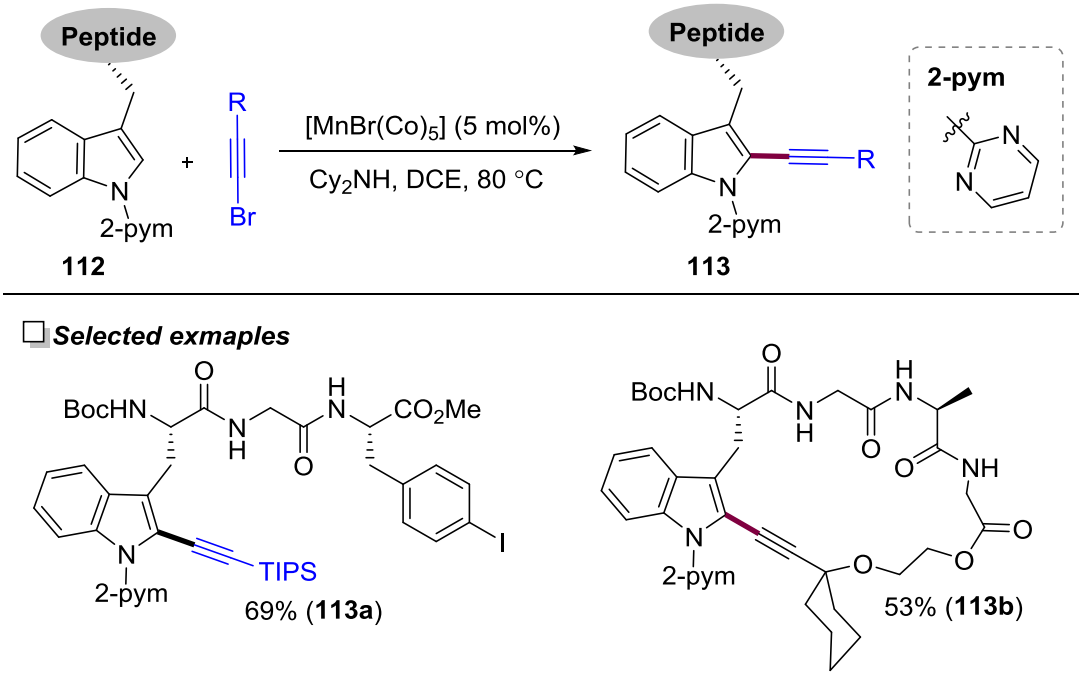
[104] Liu, W.; Richter, S. C.; Mei, R.; Feldt, M.; Ackermann, L. *Chem. Eur. J.* **2016**, *22*, 17958.
[105] Wang, H.; Lorion, M. M.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 6339.

the use of $MnBr(Co)_5$ as catalyst along with substoichiometric amounts of NaOAc as base, which delivered the product **111** with excellent yields in a stereo-enriched and racemization-free manner (Scheme 49).



Scheme 49. Manganese-catalyzed allylation of tryptophan derivatives.

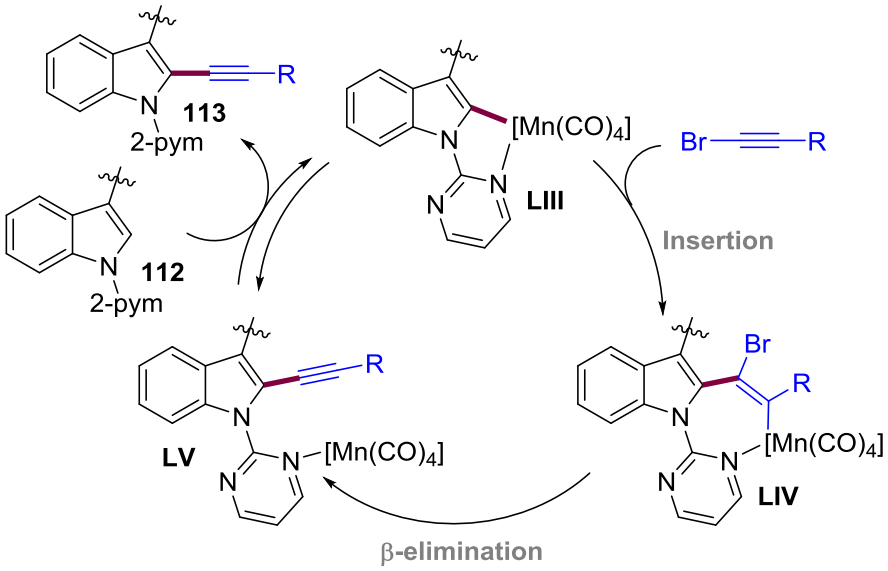
Furthermore, the same group also developed a manganese-catalyzed alkynylation of the tryptophan and tryptophan-containing peptides with alkynyl bromides.[106] Among a variety of bases and solvents, $HNCy_2$ and DCE, respectively, afforded optimal results along with catalytic amounts of [MnBr(Co)] as catalyst. Thus, the alkynylation of densely decorated peptides **112** was accomplished with overall high yields and total selectivity toward the *N*-pyrimidine-containing tryptophan residue (Scheme 50). Remarkably, by slight changes in reaction conditions, an intramolecular reaction was achieved for the assembly of cyclic peptide **113b**, which proved the robustness of this transformation.



[106] Ruan, Z.; Sauermann, N.; Manoni, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 3172.

Scheme 50. Mn-catalyzed alkynylation of tryptophan-containing peptides.

Concerning the mechanism, the authors proposed a C–H activation step to initiate the catalytic cycle. Subsequently, a migratory insertion would occur to form a seven-membered metallacycle **LIV**, which would deliver the final product **113** through a β-elimination (Scheme 51). However, a mechanism *via* conventional oxidative addition and reductive elimination was not ruled out.



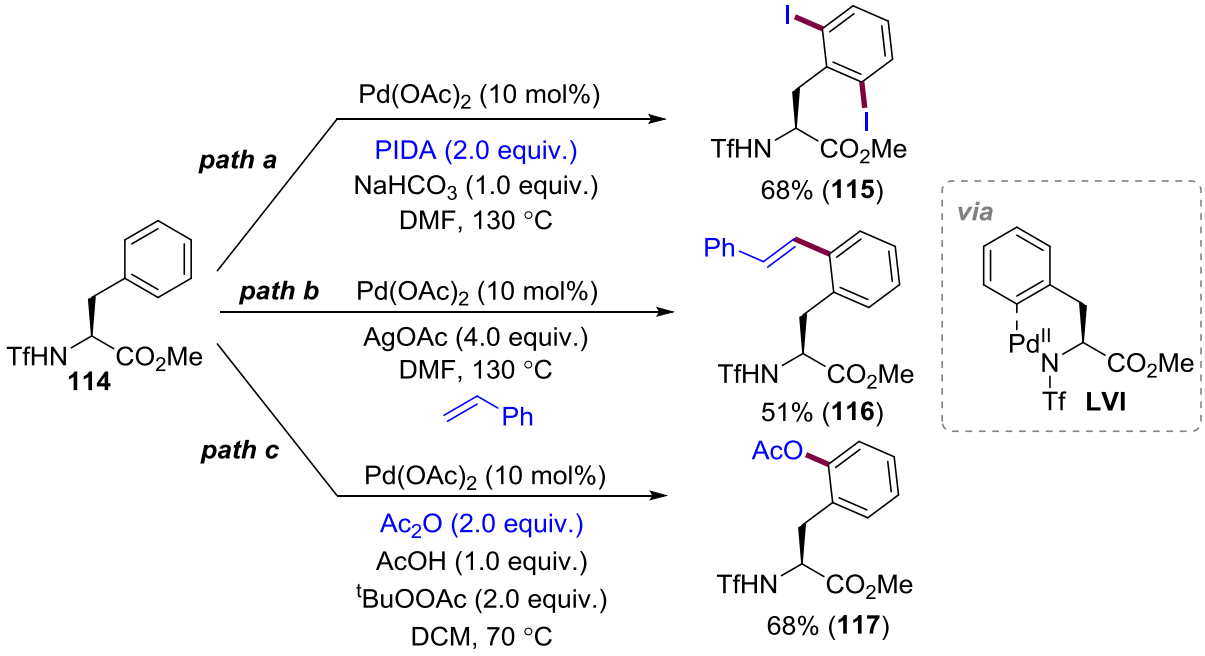
Scheme 51. Proposed mechanism for the Mn-catalyzed alkynylation of tryptophan-containing peptides.

2.1.1.2. Functionalization of Phenylalanine Residues

Regarding to the C(sp²)–H functionalization of phenylalanine, the group of Yu developed a new strategy for the straightforward C–H functionalization of the triflamide-protected Phe **112**. The authors envisioned that the electron poor character of the *N*-triflamide moiety could generate the stable 6-membered palladacycle **LVI**, thus maintaining sufficient electrophilicity of the Pd^{II} intermediate **LVI** for further manipulations. Employing this strategy, a iodination reaction was performed with the use of catalytic amounts of $Pd(OAc)_2$ and PIDA, where the *N*-triflamide group directed the iodination reaction toward the *ortho*-position of the phenyl ring, providing the *bis*-iodinated product **115** with 59% of yield (Scheme 52, *path a*).[107] The oxidative Heck reaction of **114** was also reported by the group of Yu.[107] In this case, $Pd(OAc)_2$ was also employed as catalyst with stoichiometric amounts of AgOAc as oxidant, which delivered the *mono*-alkenylated

[107] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452.

phenylalanine **116** with 51 % of yield (Scheme 52, *path b*). Later on, the same group further demonstrated the versatility of this system when a selective C(sp^2)–H acetoxylation of **114** was accomplished. This Pd-catalyzed reaction was performed with Ac_2O as the acetoxy source and produced the final *mono*-acetoxylated product **117** with 71% yield (Scheme 52, *path c*).[108]

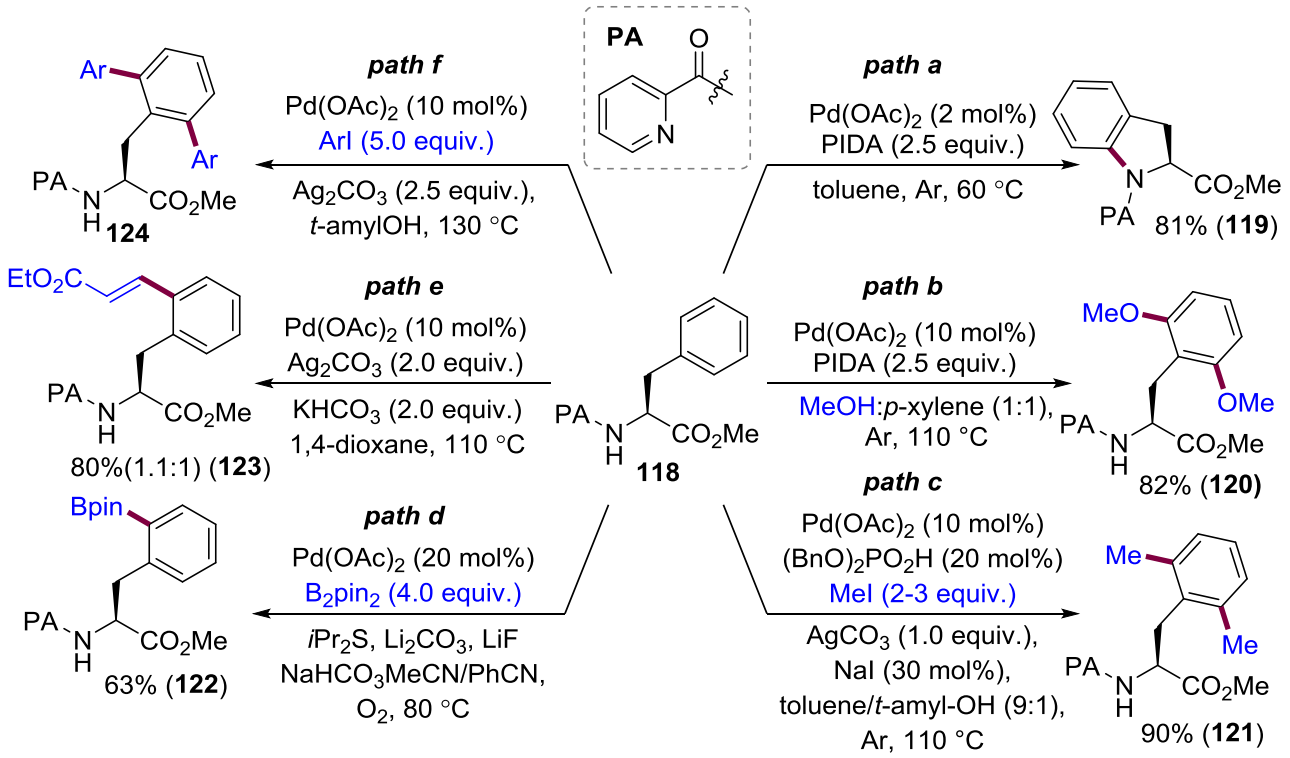


Scheme 52. Straightforward C–H functionalization of the phenylalanine triflate **114**.

The use of picolinamide (PA) as a bidentate directing group for the direct *ortho* C(sp^2)– H functionalization of the phenylalalnine **116**, has been very effective for several transformations (Scheme 53). This approach was firstly disclosed by the group of Chen, when an intramolecular amination or alkoxylation of the phenylalanine **118** was achieved. These Pd-catalyzed reactions employed stoichiometric amount of PIDA as oxidant, which delivered the final indoline derivative **119** (Scheme 53, *path a*)[109] or in case of adding methanol as nucleophile, the *bis*-methoxylated phenylalanine **120** in high yields (Scheme 53, *path b*).[110] Using methyl iodide, the same group was able to obtain the *di*-alkylated phenylalanine **121** with excellent yield (Scheme 53, *path c*).[111] In this case, the authors proposed that the use of Ag_2CO_3 could act as an oxidant and might improve the catalytic turnover due to its ability to scavenge iodide anions.[112] Afterwards, the group of Shi disclosed a Pd-catalyzed borylation of **118** with the use of B_2pin_2.[113] This is a challenging transformation,

[108] Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511.
[109] He, G.; Zho, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.
[110] Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313.
[111] Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chen. Soc.* **2013**, *135*, 2124.
[112] Bay, K. L.; Yang, Y -F.; Houk, K. N. *J. Org. Chem*. **2018**, *83*, 6776.
[113] Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899.

as the oxidant serves to complete the catalytic cycle, but it must be mild enough to avoid the oxidation of the so-formed C–B bond. Furthermore, an alkaline environment was required to ensure the stability of the C–B bond under reaction conditions. After exhaustive screenings, this was accomplished with the use of stoichiometric amounts of iPr$_2$S, Li$_2$CO$_3$, LiF and NaHCO$_3$ at 80 °C, which delivered *mono*-borylated phenylalanine **122** with 63% yield (Scheme 53, *path d*). Thereafter, the group of Chen reported a PA-directed Heck reaction, which outperformed the previous work done by Yu's group (See Scheme 52, *path b*) extending the substrate scope and the synthetic utility of the methodology.[114] Under Pd(OAc)$_2$ and Ag$_2$CO$_3$ system, the desired alkenylated phenylalanine **1223** (Scheme 53, *path e*) and its derivatives were obtained with moderate to excellent yields. Recently, Jiang and co-workers have reported a selective arylation of phenyalanine **118** with a short family of aryl iodides, in which under Pd(OAc)$_2$/Ag$_2$CO$_3$ system, *bis*-arylated phenylalanine **123** were obtained in low to high yields (Scheme 53, *path f*).[115]

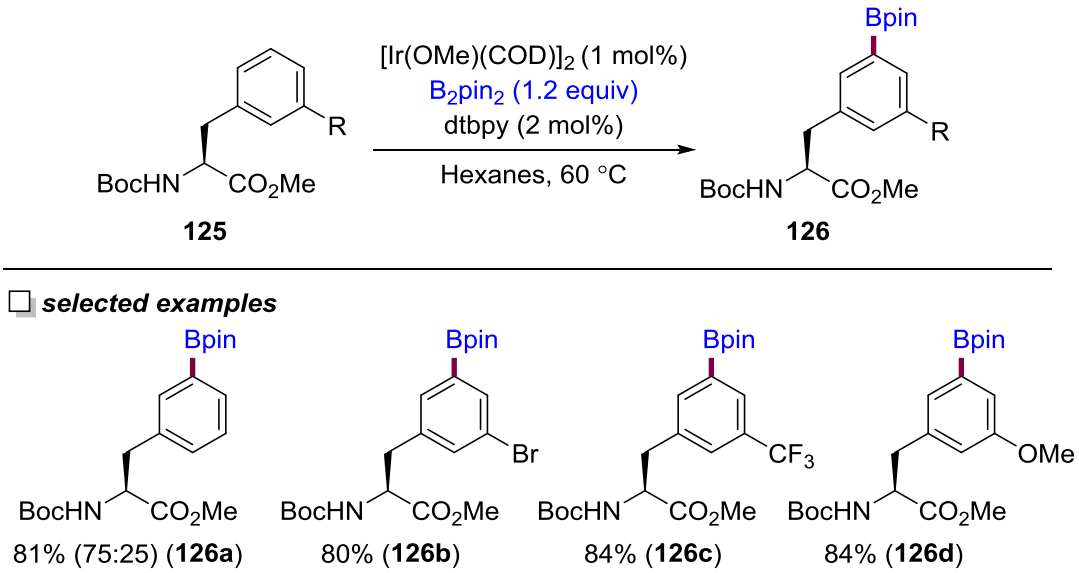


Scheme 53. PA-directed C–H diversification of phenylalanine derivatives.

On the other hand, James and co-workers tackled the challenging task of *meta* C–H functionalization of readily available *meta*-substituted *N*-Boc-phenylalanine methyl esters **125** (Scheme 54).[116] These substrates

[114] Zhao, F.; Jia, X. ; Zhao, J.; Fei, C.; Liu, L.; Liu, G.; Wang, D.; Chen, F. *RSC Adv.* **2017**, *7*, 25031.
[115] Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. *Org. Biomol. Chem.* **2018**, *16*, 598.
[116] Meyer, F.-M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.* **2010**, *12*, 3870.

were treated with B_2pin_2, $[Ir(OMe)(COD)]_2$ and dtbpy to obtain the borytaled products in high yield (**126a**-**d**). Given that regiochemistry is highly affected by steric hindrance in Ir-catalyzed borylation reactions,[117] the products were predominantly or exclusively *meta*-borylated, thus being the 3,5-isomer mostly formed over the 3,4-isomer. In addition, functional groups with electron withdrawing (**126b**-**c**) or electron donating (**126d**) properties were perfectly tolerated.

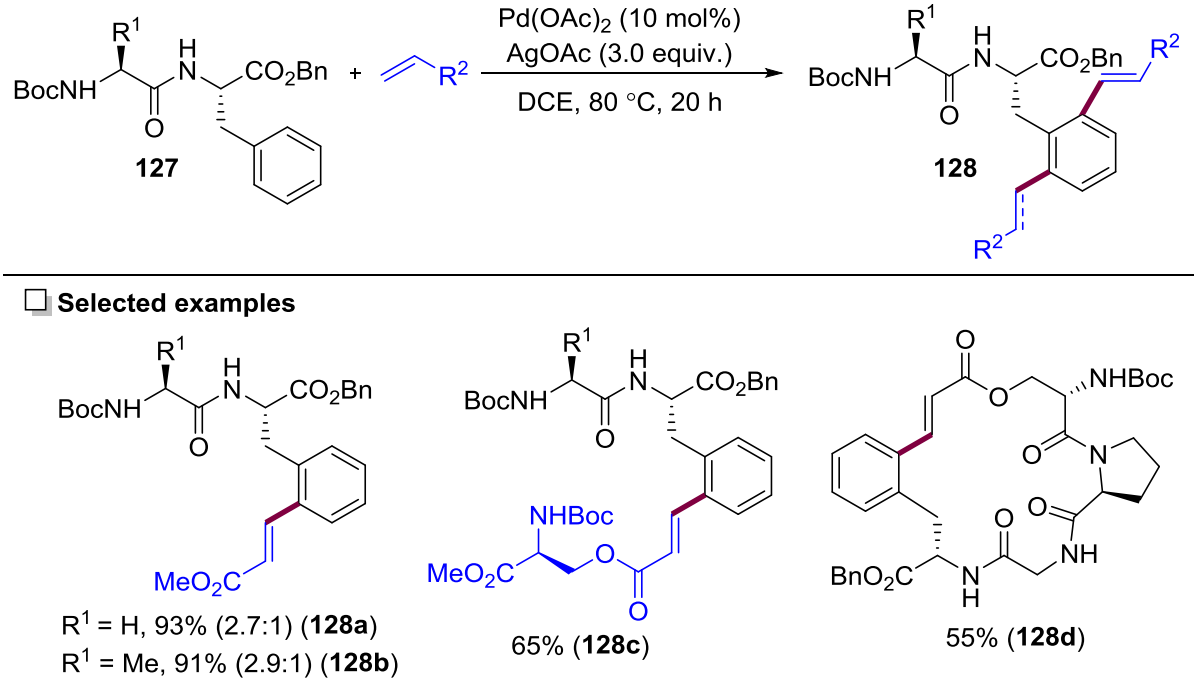


Scheme 54. Iridium-catalyzed *meta* C–H borylation of phenylalanine derivatives.

Recently, some peptide-backbone-directed δ-(sp^2)–H olefination of Phe residues have been reported. These protocols utilized the peptide backbone as the efficient directing group, thus achieving a straightforward C–H olefination of the Phe residue in native peptides. However, the Phe residue must be appropriately placed in the amino chain sequence in order to achieve the transformation. The first peptide-backbone-directed olefination of Phe was reported by the group of Wang.[118] Under optimized conditions, which consisted in the $Pd(OAc)_2/Ag(OAc)_2$ system, a small family of dipeptides **127** smoothly reacted with alkenes bearing alkyl, ester (**128b**), amide or aromatic groups, delivering a mixture of *mono*- and *di*-olefinated peptides **128a**-**b** in high yields (Scheme 55). Additionally, alkene-modified serine was succesfully employed as reagent to deliver the tripeptde **128c**, demostrating the potential of this protocol to assemble complex peptides. Encouraged by these results, the authors explored the intramolecular olefination between alkene-modified Ser and Phe residues to generate cyclic peptides with unique aryl-alkene cross-links. Under standard conditions, highly decorated peptides with 3-6 amino acids length furnished the desired cyclic peptides (**128d)** in moderate yield.

[117] a) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924. b) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103.
[118] Bai, Z.; Cai, C.; Yu, Z,; Wang, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 13912.

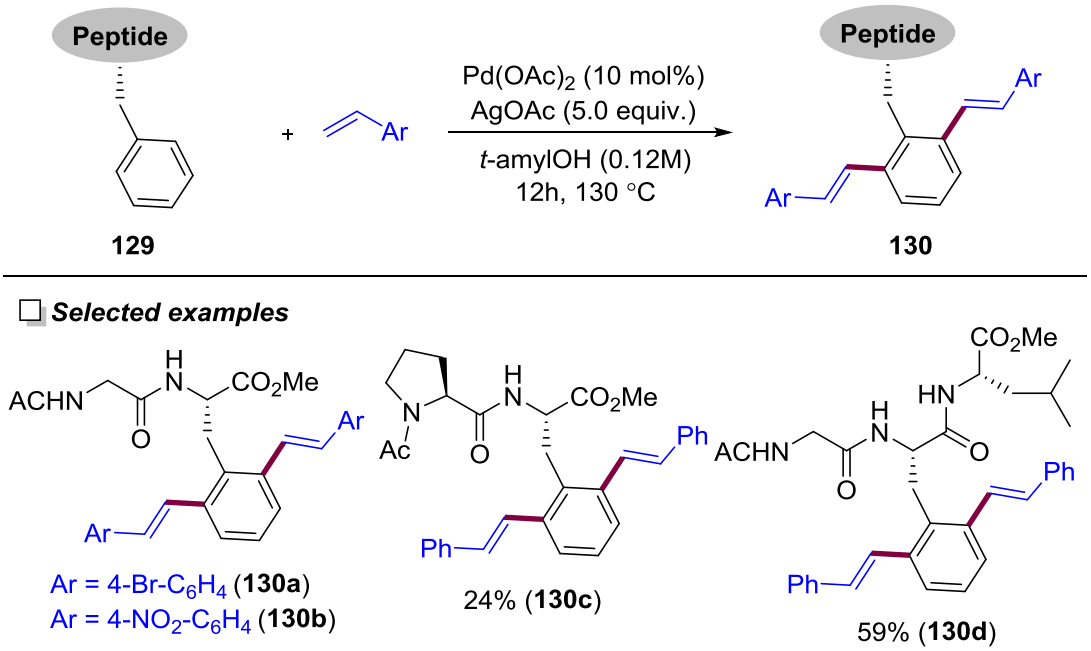
Furthermore, *O*-methyl tyrosine residue could be employed as Phe surrogate, proving the versatility of the method.



Scheme 55. Peptide-backbone-directed δ-C(sp²)–H olefination of Phe residues.

Subsequently, the group of Cross employed the same strategy for the peptide-backbone-directed *di*-olefination of Phe residues.[119] In this case, styrenes were exclusively employed as the alkene source, along with catalytic amounts of $Pd(OAc)_2$ and high excess of AgOAc (5.0 equiv.) were required for optimal results. Under optimal conditions, styrenes bearing halogen, alkyl, methoxy, nitro and nitrile groups smoothly reacted with dipeptide **129a** to give *di*-alkenylated products **130a-b** in low to high yield. Moreover, peptides decorated with aliphatic amino residues such as Ala, Leu, ILeu and Val were compatible with the reaction, as well as methionine (Met), which possesses a thioether side-chain. On the other hand, when Pro was introduced within the peptide-backbone (**129c**), the yield dropped significantly, probably due to the tertiary amide group of proline, which may show lower binding ability with the metal catalyst. Longer peptides, up to four amino residues having the Phe residues in either terminal or internal (**130d**) position were also *di*-alkenylated with styrene, which delivered the products **130d** in low to good yield without racemization of the existing chiral centers (Scheme 56).

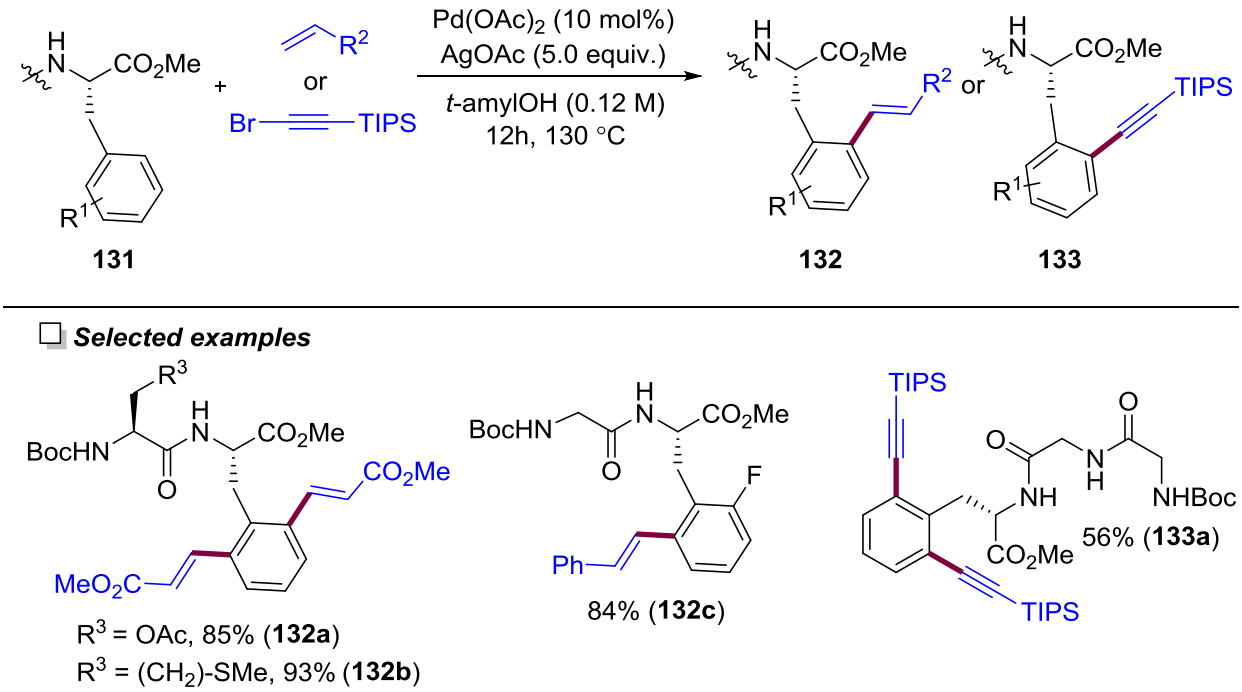
[119] Terrey, M. J.; Perry, C. C.; Cross, W. B. *Org. Lett.* **2019**, *21*, 104.



Scheme 56. Peptide-backbone-directed *di*-alkenylation of Phe residues.

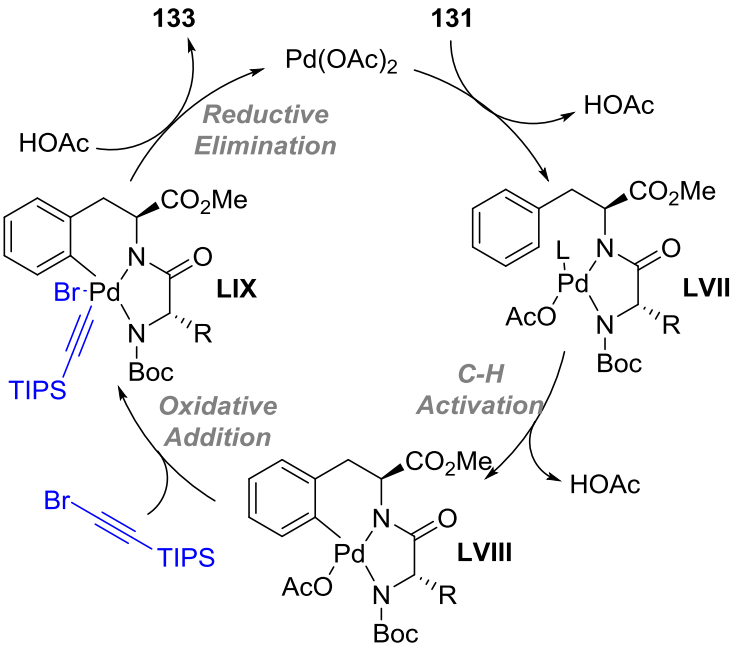
The group of Song further exploited the Pd-catalyzed site-selective C(sp^2)–H olefination and in addition, the unprecedented alkynylation of phenylalanine residues in peptides.[120] Under $Pd(OAc)_2$/AgOAc system, several di- and tripeptides were coupled with acrylate or styrene derivatives, which gave overall high yields of the product **132** as *mono*- and *di*-alkenylated mixture. Interestingly, peptides bearing *O*-acetylated serine and methionine, selectively furnished the *di*-alkenylated product (**132a** and **132b**, respectively), presumably due to the ability of methylthio and acetoxyl groups to act as efficient directing groups, thus accelerating the C–H olefination process. Substituted Phe residues with Cl, F (**131c**), and NO_2 gave the target products and Trp residue also could be olefinated under the standard conditions. The optimized conditions for the alkynylation reaction consisted in the use of $Pd(OAc)_2$ as catalyst, K_2CO_3 as base and PivOH as additive, in which (bromoethynyl)triisopropylsilane was employed as the alkynyl source. Hereby, several di- and tripeptides containing Phe residues furnished the target products **133** in overall high yields as *mono*- and *di*-alkynylated mixture (Scheme 57).

[120] Zheng, Y.; Song, W. *Org. Lett.* **2019**, *21*, 3257.



Scheme 57. Peptide-backbone-directed alkenylation and alkynylation of Phe residues.

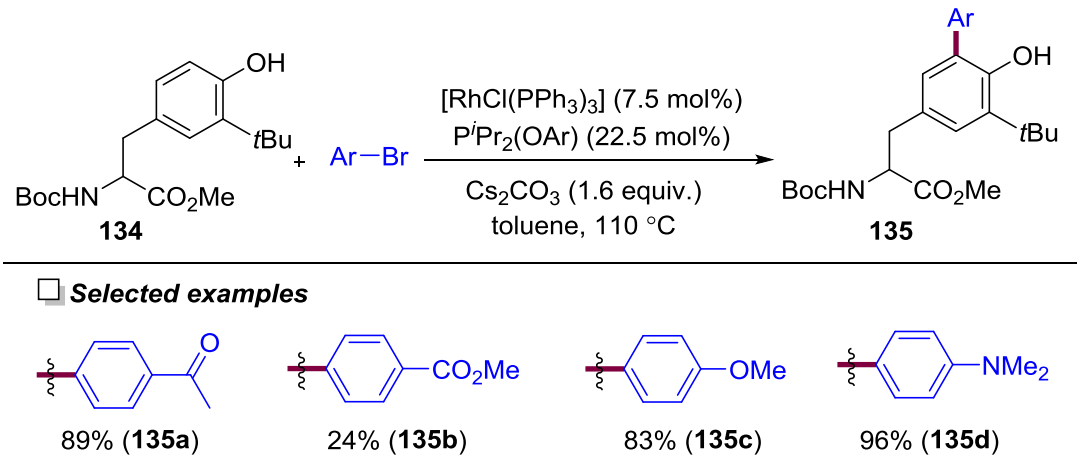
The plausible mechanism for this peptide-backbone-directed C–H alkynylation is depicted in the Scheme 58. Firtsly, the peptide would be coordinated with $Pd(OAc)_2$ to form the palladium complex **LVII**. The latter then would undergo a C–H activation to deliver the intermediate **LVIII**. Afterwards, the oxidative addition of TIPS-acetylene bromide would afford the Pd^{IV} intermediate **LIX**, which after a reductive elimination would yield the alkynylated product **133** and the active Pd^{II} catalyst.



Scheme 58. Proposed mechanism for the peptide-backbone directed C–H alkynylation of Phe residues.

2.1.1.3. Functionalization of Tyrosine and Histidine Residues

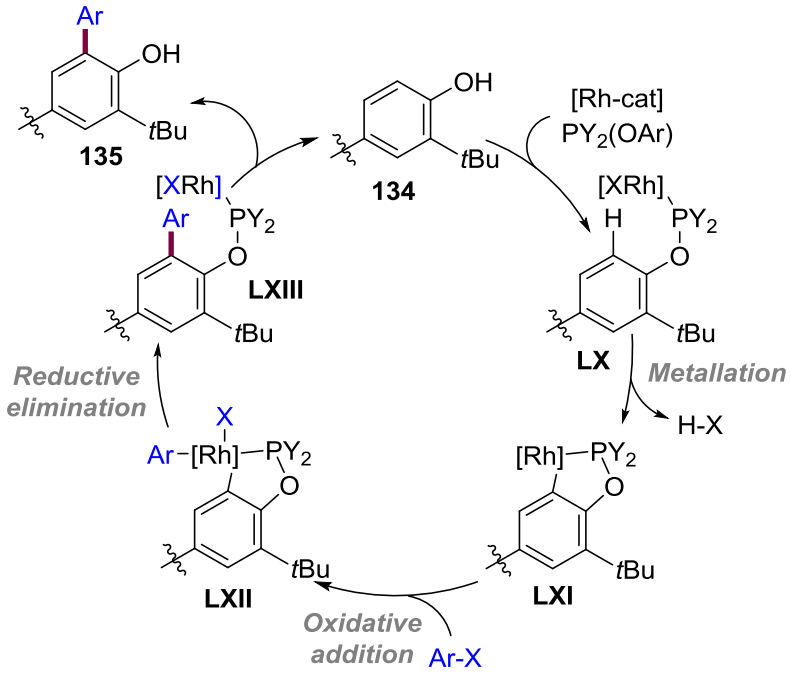
While procedures for the C(sp^2)–H diversification of tryptophan and phenylalanine residues have been extensively explored, procedures for the C(sp^2)–H functionalization of tyrosine or histidine are less abundant. Bedford and co-workers reported a Rh-catalyzed C(sp^2)–H arylation of 2-substituted tyrosine derivatives **134** with bromoarenes.[121] The best results to achieve this transformation were obtained with Wilkinson´s catalyst, along with P^{i}Pr$_2$(OAr) as ligand and Cs_2CO_3 as base. Under these conditions, final products **135** were obtained with low to excellent yields and both, electron withdrawing (**135a**-**b**) or donating (**135c**-**d**) functional groups within the aryl bromides were well tolerated (Scheme 59). Nevertheless, the requirement of 2-subtituted tyrosine instead of the natural tyrosine moiety represents a significant drawback in terms of the applicability of the process.



Scheme 59. Rh-catalyzed *ortho*-arylation of tyrosine derivatives.

The mechanistic proposal is disclosed in Scheme 60, in which the key step was the formation of the rhodacyclic intermediate **LXI** with the cooperation of the phospinite ligand. The rhodacycle **LXI** then would undergo an oxidative addition with the aryl bromide forming species **LXII** and subsequent reductive elimination of **LXII** would form the arylated tyrosine **LXIII**. Finally, a transesterification of **LXIII** with the starting phenol **134** would deliver the desired product **135**.

[121] Bedford, R. B.; Haddow, M. F.; Webster, R. C.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3119.



Scheme 60. Mechanistic proposal for the Rh-catalyzed *ortho*-arylation of tyrosine derivatives**.**

Arylomycin A (Figure 7) and its derivatives, are biaryl-bridged cyclic peptides that exhibit good antibacterial and antifugal properties. However, the preparation of the arylomycin cyclic core **136** had remained challenging in the field of drug discovery.[122]

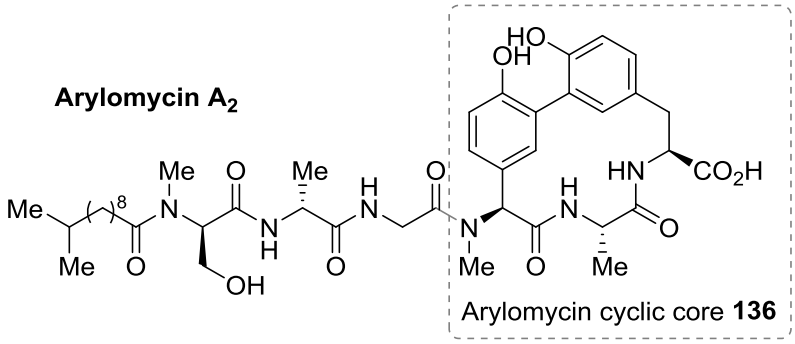
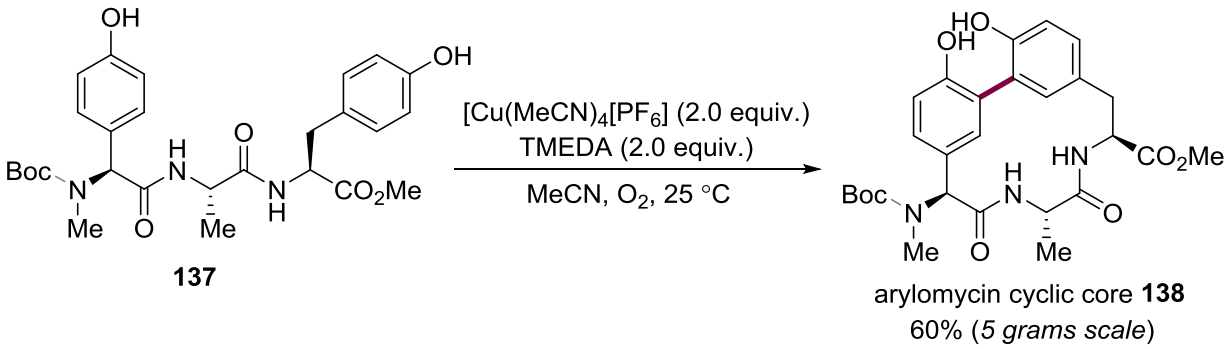


Figure 7. Structure of Arylomycin A_2.

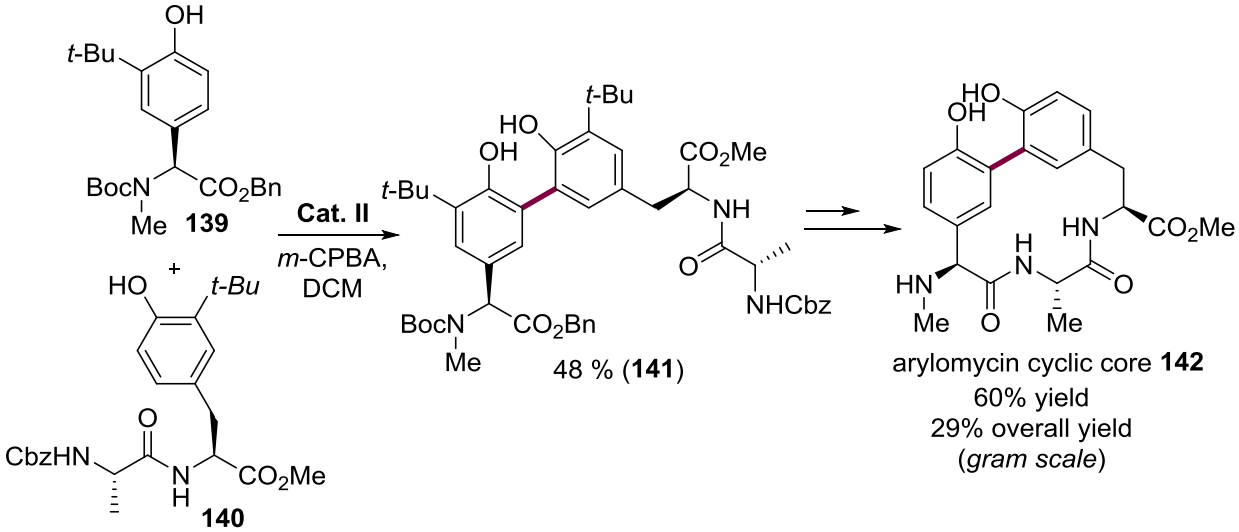
[122] a) Zorzi, A.; Deyle, K.; Heinis, C. *Curr. Opin. Chem. Biol.* **2017**, *38*, 24. b) Smith, P. A.; Koehler, M .F .T.; Girgis, H. S.; Yan, D.; Chen, Y.; Chen, Y.; Crawford, J. J.; Durk, M. R.; Higuchi, R. I.; Kang, J.; Murray, J.; Paraselli, P.; Park, S.; Phung, W.; Quin, J. G.; Roberts, T. C.; Rouge, L.; Scharz, J. B.; Ekippington, E.; Wai, J.; Xu, M.; Yu, Z.; Zhang, H.; Tan, M.-W.; Heise, C. E. *Nature* **2018**, *561*, 189.

Baran, Romesberg and co-workers reported a rapid and efficient assembly of arylomycin cyclic core **138** from its linear peptide analogue **137**.[123] This was accomplished with the use of stoichiometric amounts of $[Cu(MeCN)_4[PF_6]$, TMEDA and oxygen atmosphere as oxidant, which delivered the cyclic core **138** with a remarkable 60% yield at 5 grams scale (Scheme 61).



Scheme 61. Synthesis of the Arylomycin cyclic core **138** *via* oxidative macrocyclization.

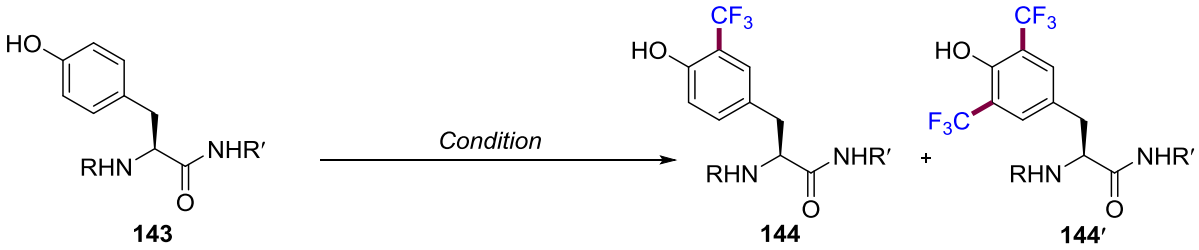
Just recently, the group of Pappo has described a chemoselective cross-coupling between two phenols-based amino acids (**139** and **140**), followed by a cyclization reaction, which delivered the arylomycin cyclic core **142**.[124] The formation of the key intermediate, the biaryl-bridged linear peptide **141**, was achieved with 1 mol % of Fe[TPP]Cl (**Cat. II**) and stoichiometric amounts of *m*CPBA, which delivered **141** with 48% yield at multigram scale. After the cyclization of the linear peptide **141** and removal of *tert*-butyl and Boc groups, the desired cyclic core **142** was obtained in 60% yield (29% overall) at gram scale (Scheme 62).



[123] Peters, D. S.; Romesberg, F. E.; Baran, P. S. *J. Am. Chem. Soc.* **2018**, *140*, 2072.
[124] Ben-Lulu, M.; Gaster, E.; Libman, A.; Pappo, D. *Angew. Chem. Int. Ed.* **2020**, *59*, 4835.

Scheme 62. Synthesis of arylomycin cyclic core **141** with oxidative coupling approach.

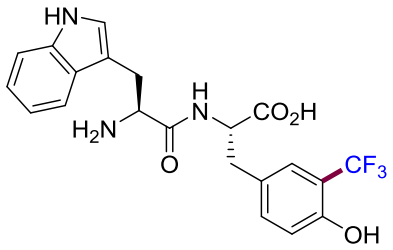
Procedures for the selective fluorination of peptides and proteins are of great interest as enables ^{19}F-observed bio-NMR spectroscopy.[125] In this regard, the group of krska developed a trifluoromethylation protocol of tyrosine-containing peptides in ausence of protecting groups.[126] For this, two reaction conditions were disclosed, one employing $Zn(SO_2CF_3)_2$/$TBHP_{aq}$ system in aqueous solvent, and the other utilizing Ir[dFCF$_3$ppy] as photocatalyst and $NaSO_2CF_3$ as CF_3 source under mixed organic/aqueous solvent (Scheme 63).



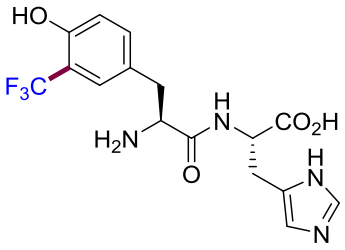
Condition A: $Zn(SO_2CF_3)_2$ (3.0 equiv.), $TBHP_{aq}$ (5.0 equiv.) in AcOH (aq) (0.03-0.1 M), 37 °C, 16h

Condition B: Ir[dFCF$_3$ppy] (15 mol%), $NaSO_2CF_3$ (20 equiv.) in CH_3CN: 10% AcOH (aq) (1:1, 0.03 M), 26 °C, 20 h

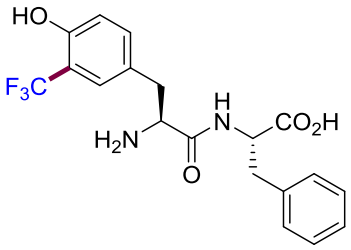
❑ ***Selected examples***



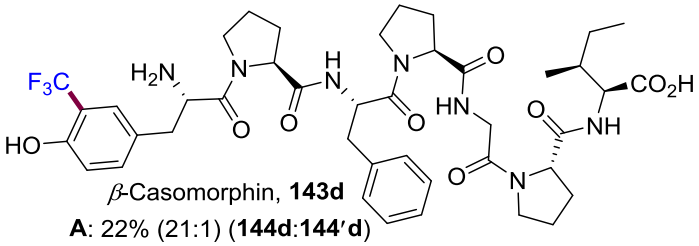
A: 45% (1:3.5) (**144a**:**145**, 2-CF_3 Trp)
B: 29% (8:3:18) (**144a**:**144′a**:**145**)



A: 31% (9.3:1) (**144b**:**144′b**)
B: 31% (**144b** only)



A: 17% (**144c** only)
B: 12% (5:1)(**144c**:**144′c**)



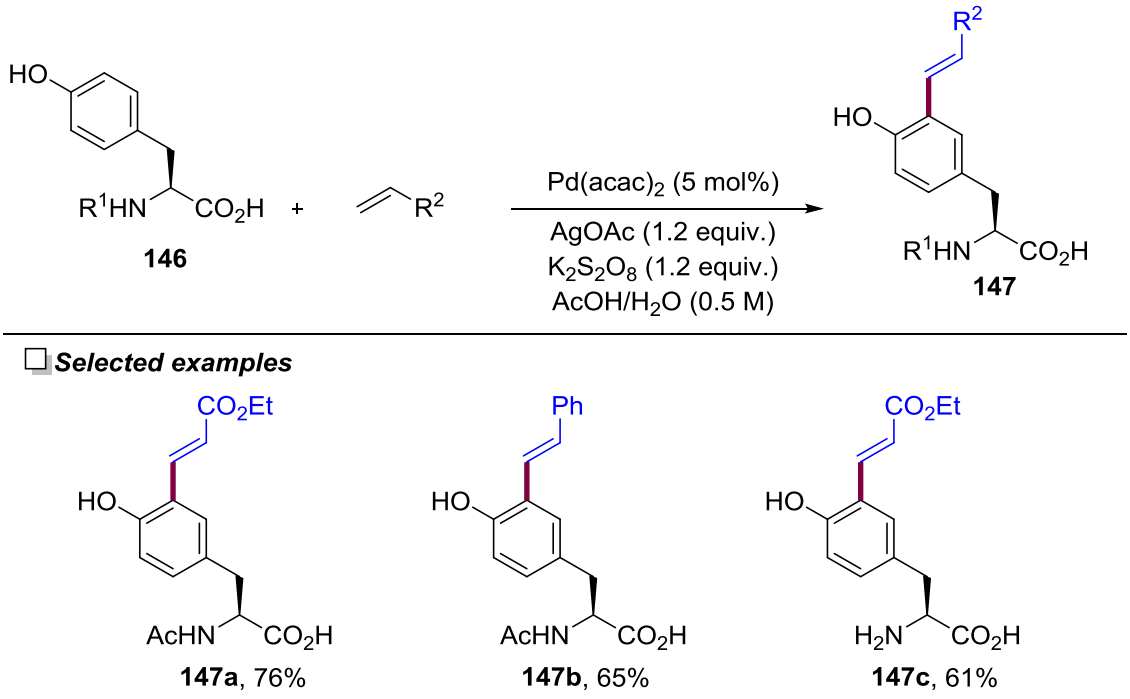
β-Casomorphin, **143d**
A: 22% (21:1) (**144d**:**144′d**)
B: 55% (6:1) (**144d**:**144′d**)

[125] a) Dalvit, C.; Vulpetti, A. *ChemMedChem*, **2011**, *6*, 104. b) Arntson, K. E; Pomerantz, W. C. K. *J. Med. Chem*. **2016**, *59*, 5158.
[126] Ichiishi, N.; Caldwell, J. P.; Liu, M.; Zhong, W.; Zhu, X.; Streckfuss, E.; Kim, H.-Y.; Parish, C. A.; Krska, S. W. *Chem. Sci*. **2018**, *9*, 4168.

Scheme 63. C–H Trifluoromethylation of tyrosine-containing peptides.

In the case of the Trp-Tyr peptide **143a**, in addition to the expected trifluoromethylation of the tyr residue (**144a**), the Trp residue was more susceptible to react at the C2-position under both conditions (procedure A and B), thus delivering the undesired side-product **145**. However, Tyr showed superior reactivity over His and Phe in each respective dipeptide (**144b** and **144c**). Moreover, longer peptides such as *β-Casomorphin* **143d** were selectively trifluoromethylated at the Tyr residue, regardless of whether the Tyr residue was placed at the peptide *N*-terminus or at an internal position. Just recently, a novel ^{18}F-trifluoromethylation of tyrosine-containing peptides was disclosed by the group of gouverneur.[127] These ^{18}F-radiolabeled peptides can serve to measure the distribution and can be used as biomarkers for therapy.[128]

The hydroxyl group of the tyrosine was explored as native directing group for the selective *ortho*-alkenylation of tyrosine derivatives by the group of Zhu.[129] After extensive optimizations, the combination of



[127] Kee, C. W.; Tack, O.; Guibbal, F.; Wilson, T. C.; Isenegger, P. G.; Imiolek, M.; Verhoog, S.; Tolby, M.; Boscutti, G.; Ashworth, S.; Chupin, J.; Kashani, R.; Poh, A. W. J.; Sosabowski, J. K.; Macholl, S.; Plisson, C.; Cornelissen, B.; Willis, M. C.; Passchier, J.; Davis, B. G.; Gouverneur, V. *J. Am. Chem. Soc*. **2020**, *142*, 1180.

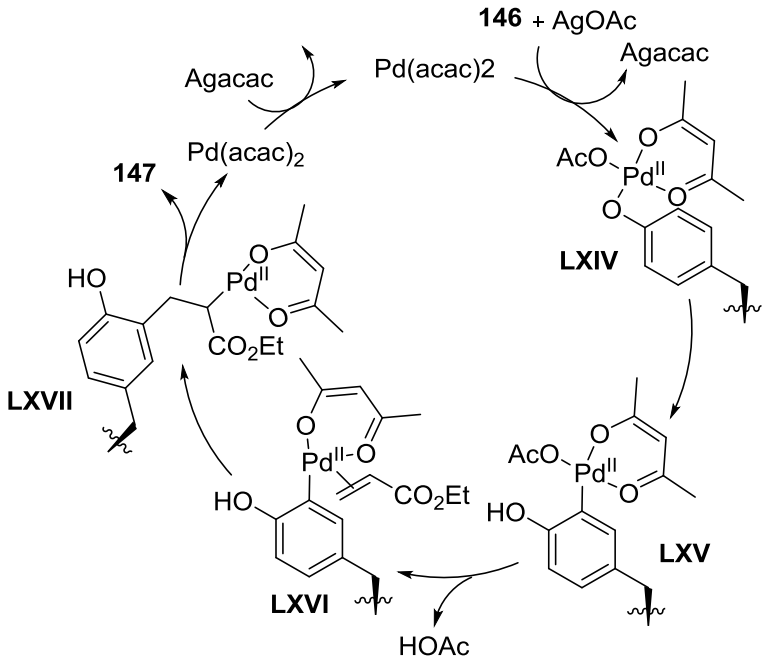
[128] a) Richter, S.; Wuest, F. ^{18}F-Labeled peptides: the future is bright. Molecules. **2014**, *19*, 20536. b) Sah, B. R.; Burger, I. A.; Schibli, R.; Friebe, M.; Dinkelborg, L.; Graham, K.; Borkowski, S.; Bacher-Stier, C.; Valencia, R.; Srinivasan, A.; Hany, T. F.; Mu, L.; Wild, P. J.; Schaefer, N. G. Dosimetry and First Clinical Evaluation of the New ^{18}F-Radiolabeled Bombesin Analogue BAY 864367 in Patients with Prostate Cancer. *J. Nucl. Med*. **2015**, *56*, 372.

[129] Dou, Y.; Kenry.; Liu, J.; Jiang, J.; Zhu, Q. *Chem. Eur. J*. **2019**, *25*, 6896.

Scheme 64. Pd-catalyzed C–H alkenylation of tyrosine derivatives.

$Pd(acac)_2$ and ester acrylates along with stoichiometric amounts of AgOAc and $K_2S_2O_8$ as oxidants, delivered satisfactory yields. Herein, ester acrylates or styrene were coupled with *N*-acetyl tyrosines (**147a-b**), tyrosine esters or more importantly, with the free tyrosine **147C** in good to high yields (Scheme 64).

Based on the above results and the bibliography,[130] the authors proposed the reaction mechanism depicted in the Scheme 65. Firstly, the palladium catalyst would coordinate to the hydroxy group to form the intermediate **LXIV**. Then, 1,3-migration of the palladium through **LXIV** species would generate the *ortho*-metalated intermediate **LXV**. Finally, the oxidative heck-type reaction would deliver the alkenylated tyrosine product **147** and regenerated the active Pd^{II} catalyst. Continuing with traditional reactions, the group of Barluenga described a practical Suzuki-Miyaura-type reaction of unprotected iodinated Tyrosine-containing peptides under aqueous conditions.[131]

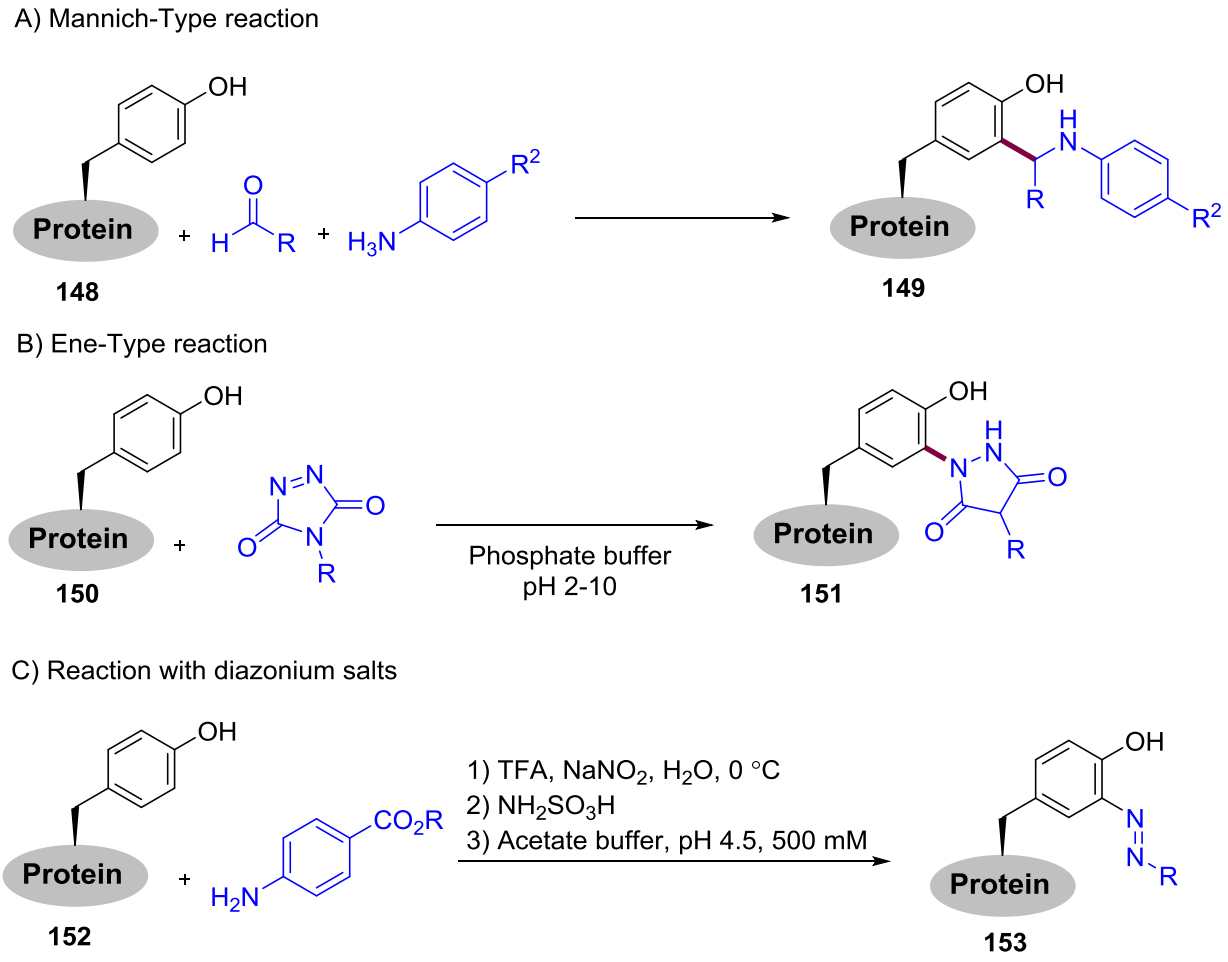


Scheme 65. Proposed catalytic mechanism for the Pd-catalyzed C–H alkenylation of tyrosine derivatives.

Nonetheless, some metal-free approaches have also been explored for the site-selective C– H functionalization of tyrosine-containing peptides or proteins. For example the group of Francis described a

[130] Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K.; *Angew. Chem. Int. Ed*. **2013**, *52*, 4607.
[131] Vilaró, M.; Arsequell, G.; Valencia, G.; Ballesteros, A.; Barluenga, J. *Org. Lett*. **2008**, *10*, 3243.

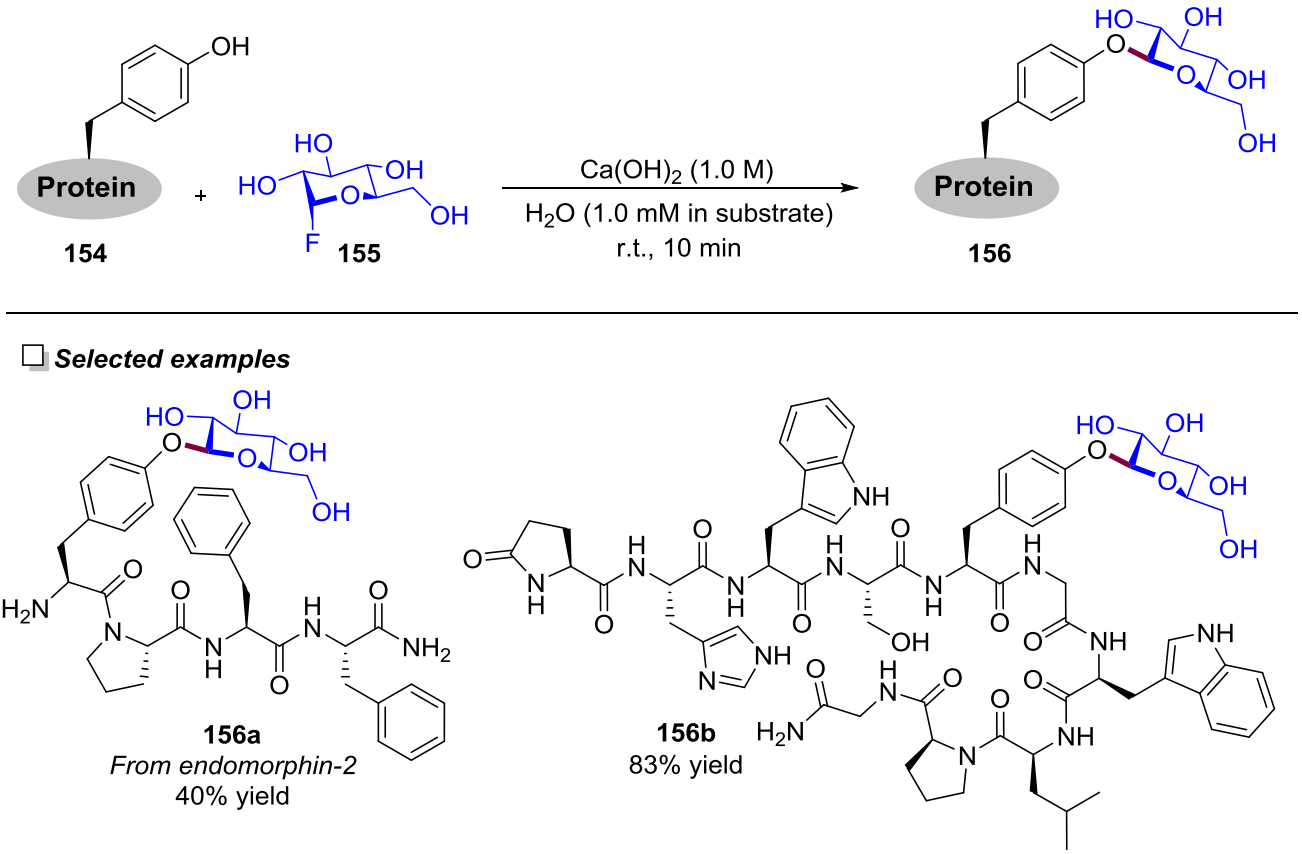
Mannich-type reaction for the modification of tyrosine-containing proteins **148** using imines formed *in situ* from aldehydes and electron-rich anilines under mild conditions (Scheme 66, A).[132] Later on, a reaction between cyclic diazodicarboxamides and tyrosine residues **149** through ene-like reaction was described (Scheme 66, B).[133] This transformation worked in aqueous solution over a broad range of pHs and allowed the modification of small molecules, peptides and proteins. On the other hand, the group of haddleton utilized *in situ* formed diazonium salts to react with tyrosine-containing peptides or proteins **152** to obtain the products **153** with the azobenzene linker (Scheme 66, C).[134] In this case, the key for the Tyr-selectivity was the pH of the solution,[135] which was established at 4.5 for optimal results.



Scheme 66. Metal-free selective C–H functionalization of tyrosine-containing proteins.

[132] Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc*. **2004**, *126*, 15943.
[133] Ban, H.; Gavrilyuk, J.; Barbas, C. F. *J. Am. Chem. Soc*. **2010**, *132*, 1523.
[134] Jones, M. W.; Mantovani, G.; Blindauer, C. A.; Ryan, S. M.; Wang, X.; Brayden, D. J.; Haddleton, D. M. *J. Am. Chem. Soc*. **2012**, *134*, 7406.
[135] Curreli, N.; Oliva, S.; Rescigno, A.; Rinaldi, A. C.; Sollai, F.; Sanjust, E. *J. Appl. Polym. Sci*. **1997**, *66*, 1433.

Capitalizing on the electron-rich phenol group of the tyrosine, several *O*-modification have been described, including arylation,[136] alkylation[137] and glycosylation reactions. The latter was accomplished by the group of Miller employing glycosyl fluorine donor **155** and fully unprotected Tyr-containing peptides in water (Scheme 67).[138] Biologically active peptides **154** were selectively *O*-glycosylated in moderate to high yields, with predictable stereochemistry due to SN_2 nature of the transformation and all amino residues were tolerated with the singular exception of the Cysteine residue.

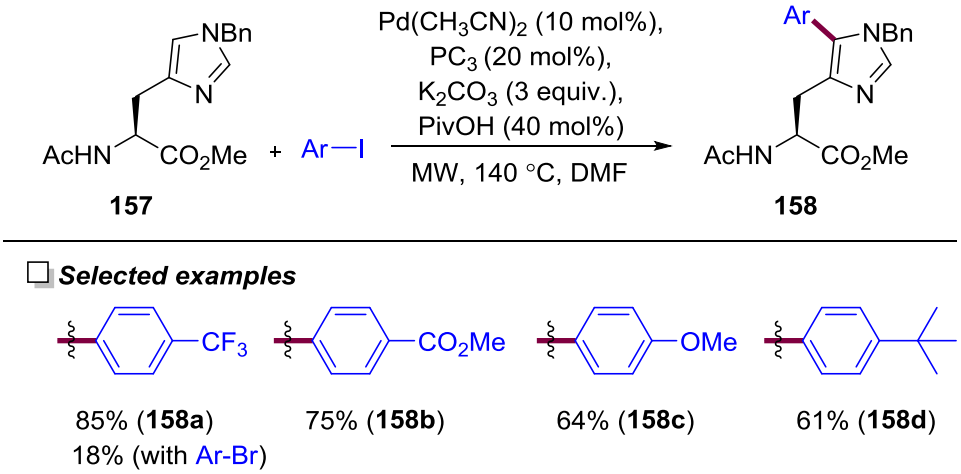


Scheme 67. Selective *O*-glycosilation of Tyr-containing peptides.

Concerning the His residue, Jain and coworkers developed a selective Pd-catalyzed arylation of the *N*-benzyl histidine **157** under microwave condition.[139] The optimized conditions consisted in the use of $Pd(CH_3CN)_2$ as catalyst along with the ligand PCy_3, which significantly improved the yield in screening reactions. Thereby, the histidine unit **157** was selectively arylated at the most nucleophilic C5-position of the pyrazole

[136] Seim, K. L.; Obermeyer, A. C.; Francis, M. B. *J. Am. Chem. Soc.* **2011**, *133*, 16970.
[137] Tilley, S. D.; Francis, M. B. *J. Am. Chem. Soc*. **2006**, *128*, 1080.
[138] Wadzinski, T. J.; Steinaver, A.; Hie, L.; Pelletier, G.; Schepartz, A.; Miller, S. J. *Nat. Chem*. **2018**, *10*, 644.
[139] Mahindra, A.; Bagra, N.; Jain, R. *J. Org. Chem.* **2013**, *78*, 10954.

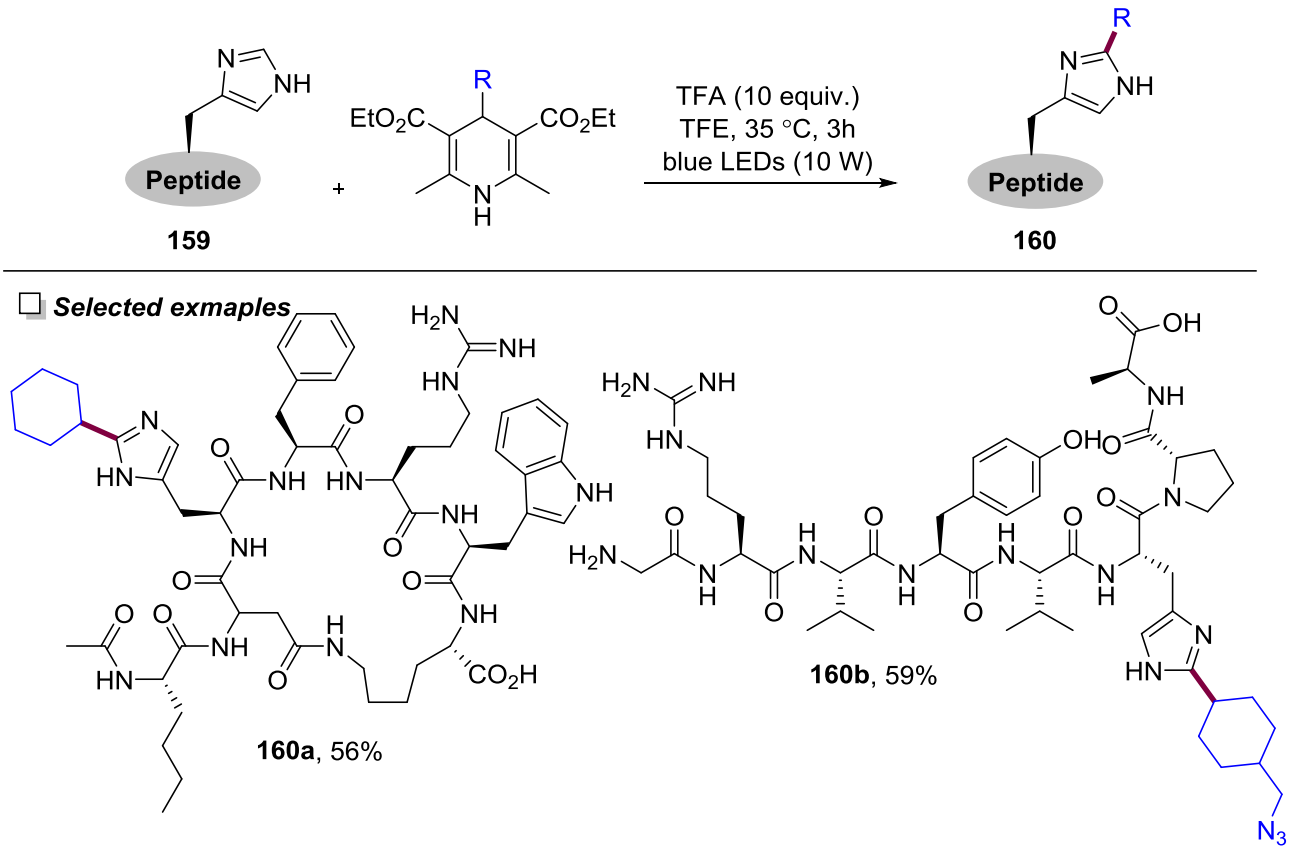
ring. Iodoarenes with different electronic properties or hindrance furnished the products **158** in high yields, whereas bromoarenes delivered the final product in low yields (Scheme 68).



Scheme 68. C-5 arylation of *N*-benzyl histidine **157**.

In contrast, taking advantage of the electrophilic character of the C2-position of the histidine, the group of Wang performed a Minisci-type radical-mediated C–H alkylation of histidine-containing peptides through a photoredox approach (Scheme 69).[140] Under optimized conditions, His-containing peptides **159** were effectively alkylated with C_4-alkyl-1,4-dihydropyridine (DHP) reagents. This method exhibited an exceptionally broad scope for both peptides and DHP alkylation reagents. Furthermore, its utility was demonstrated in a series of important peptide drugs, complex natural products, and small proteins.

[140] Chen, X.; Ye, F.; Luo, X.; Liu, X.; Zhao, J.; Wang, S.; Zhou, Q.; Chen, G.; Wang, P. *J. Am. Chem. Soc*. **2019**, *141*, 18230.



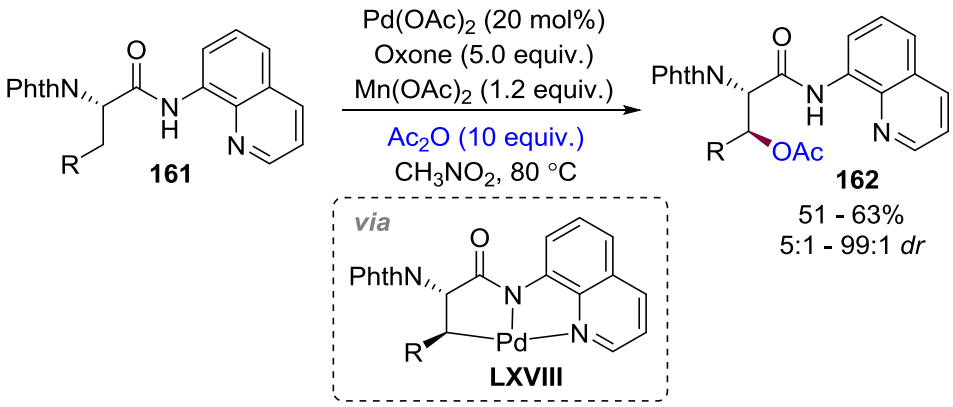
Scheme 69. Visible-light-promoted C–H alkylation of histidine-containing peptides.

2.1.2. Side-Chain C(sp^3)-H Functionalization of α-Amino Acids and Peptides

The activation of side-chain C(sp^3)–H bonds of proteinogenic α-amino acids or peptides has witnessed a significant progress in the last decade. Despite the inertness of these C(sp^3)–H bonds and the challenge that represents the activation of a single C–H bond among many others present in α-amino acids or proteins, many procedures for the site-selective C(sp^3)–H diversification have been reported. In this section, the variety of transformations achieved at different positions are disclosed.

2.1.2.1. Functionalization at the β-Position

The use of a directing group has facilitated the transition-metal-catalyzed functionalization of a vast array amino acid's aliphatic side chain positions.[141] These reactions usually proceed through the formation of a metallacycle intermediate, consequently the selectivity of the reactions can be easily predicted. In 2006, the group of Corey disclosed the first 8-aminoquinoline (AQ) directed C(sp^3)–H alkoxylation of amino acids residues **161** at the β-position (Scheme 70).[142] The authors obtained the final alkoxylated products **161** in a diastereo-enriched fashion, which was explained by the formation of the sterically more favored 5-membered *trans*-palladacylce **LXVIII**, where the protected amino group (NPhth) and R residues would adopt a *trans*-orientation.

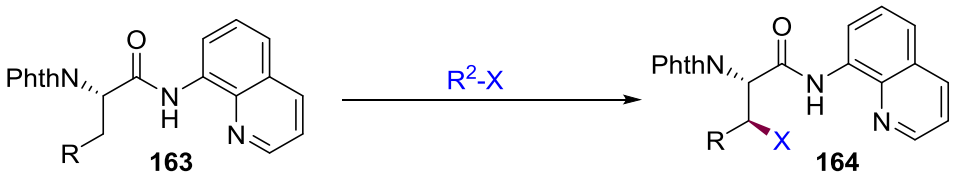


Scheme 70. AQ-directed C–H alkoxylation.

This pioneering work stablished the bases for future works, in which 8-aminoquinoline directed transformations have attracted great attention in the field of C– H activation. The most relevant transformations are shown in the Table 17. Along with the alkoxylation reaction (Scheme 70), Corey and co-

[141] a) Mondal, S.; Chowdhury, S. *Adv. Catal.* **2018**, *360*, 1884. b) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 14700. c) Brandhofer, T.; Mancheño, O. G. *Eur. J. Org. Chem.* **2018**, 6050.
[142] Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

workers also reported an unprecedented arylation reaction (Table 17, Entry 1).[142] Alkyl β-position of amino acids **161** were successfully arylated with iodoarenes, $Pd(OAc)_2$ as catalyst and AgOAc as oxidant. Remarkably, in the case of tertiary residues such us valine or isoleucine, γ-arylated products were obtained instead. Few years later, the group of Chen reported a Pd-catalyzed *mono*-arylation or -heteroarylation of the alanine unit **163**, where *di*-arylation of the substrate was avoided with the use of AgTFA (Table 17, Entry 2).[143] Additionally, some β-alkylation procedures also were described.[144] For example, the group of Shi reported an alkylation protocol, where both, alkyl iodides and bromides could be applied as alkyl reagents (Table 17, Entry 3).[144a] The same group also described a stereoselective C–H silylation of primary and secondary C–H bonds (Table 17, Entry 4).[145] Hexamethyldisilane was employed as reagent to obtained the silylated amino acids with high diastereoselectivities by employing $Pd(OAc)_2$ as catalyst along with Ag_2CO_3 and DMBQ. On the other hand, a stereoretentive C–H olefination was reported by the group of Chen.[146] In this case a wide variety of vinyl



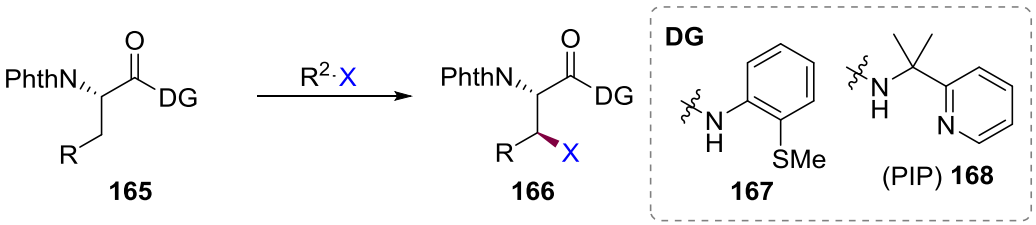
Entry	Catalyst (mol%)	Oxidant (equiv.)	Reagent (equiv.)	Conditions/ additives (equiv.)	Yield (%)
1[142]	$Pd(OAc)_2$ (20)	AgOAc (1.5)	Ar-I (4)	110 °C	79-93
2[143]	$Pd(OAc)_2$ (5-11)	AgTFA (2.0)	Ar-I (3)	TCE/H_2O (1:1), r.t.	68-92
3[144a]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.8)	Alkyl-I (1.5) or Alkyl-Br (3.0)	DCE/*t*BuOH (1:1), 50 or 90 °C $(BnO)_2PO_2H$ (0.3)	16-91
4[145]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (0.5), DMBQ (1.5)	$(Me_3Si)_2$ (5)	1,4-dioxane, 125 °C	36-81
5[146]	$Pd(OAc)_2$ (10)	AgOAc (3.0), TFA (2.0)	Alkenyl-I (2)	1,4-dioxane, r.t.	30-90
6[147]	$Pd(TFA)_2$ (10)	AgOAc (1.5), TfOH (1.0)	$P(O)R_2CH_2I$	DCE, 60 °C	47-99
7[148]	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.0), I_2 (1.0)	RO_2C-Cl	Toluene, 120 °C	45-95

[143] Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952.
[144] a) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. b) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. c) Chen, K.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 11950.
[145] Liu, Y.-J.; Liu, Y.-H.; Zhang, Z.-Z.; Yan, S.-Y.; Chen, K.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2016**, *55*, 13859.
[146] Wang, B.; Lu, Z.; Zhang, S.-Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 6260.

Table 17. Selected AQ-directed β-diversification of amino acids residues.

Iodides were successfully introduced in the alanine unit by employing the $Pd(OAc)_2$/AgOAc system at room temperature (Table 17, Entry 5). In addition, phosphate-containing alkyl iodides were effectively introduced into multiple amino acids residues by the group of Yang.[147] The reaction produced the final phosphonated product in overall high yields and in a diastereoselective fashion with the $Pd(TFA)_2$/ AgOAc system (Table 17, Entry 6). Finally chloroformates were employed as alkoxycarbonylation reagents by the group of Shi.[148] This reaction was accomplished with the use of $Pd(OAc)_2/Ag_2CO_3$ system and iodine as additive, which delivered the desired product in moderate to excellent yields (Table 17 ,Entry 7). Noteworthly, when amino residues such us valine or isoleucine were employed, the reactions ocurred at the γ-position, although in lower yields.

Besides 8-aminoquinoline (AQ), other bidentate directing groups have also been used to perform β-functionalization on amino acid residues (Table 18). For example, Dougalis an coworkers reported an arylation reaction of the alanine unit **165** with the use of 2-thiomethylaniline **167** and iodoarenes (Table 18, Entry 1).[149] Interestingly, this Pd-catalyzed reaction delivered **166** exclusively as *mono*-arylated, in contrast, when AQ was employed, *di*-arylated products were obtained. However, the thioether functionality might not be the most



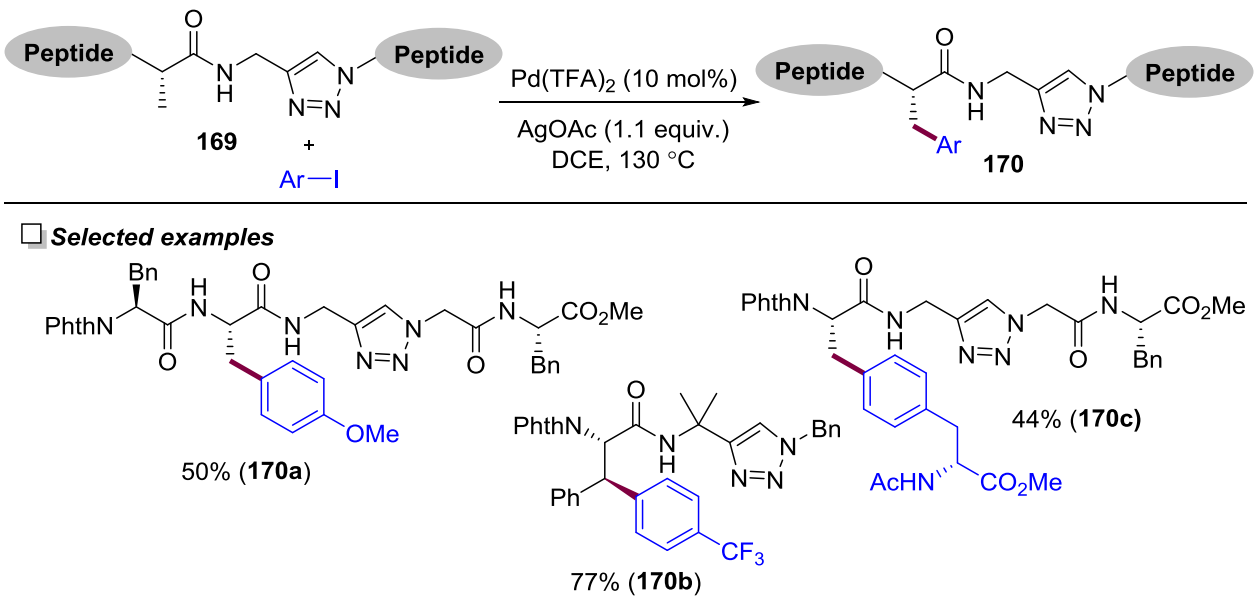
Entry 1	DG	Catalyst (mol%)	Oxidant (equiv.)	Reagent (equiv.)	Conditions/ Additives (equiv.)	Yield (%)
1[149]	**167**	$Pd(OAc)_2$ (5)	AgOAc (2)	Ar-I (4)	Toluene, 60 °C	60-81
2[150]	**168**	$Pd(OAc)_2$ (10)	CuF (1.5)	Ar-I (1.5)	DMPU (5), acetone, 100 °C	35-89
3[150]	**168**	$Pd(OAc)_2$ (10)	$NaIO_4$ (2) AC_2O (10)	--	MeCN, 70 °C	46-86
4[151]	**168**	$Pd(OAc)_2$ (6)	Selectfluor (1)		DCM/*i*PrCN (30:1) 80 °C	31-73

[147] Yang, Q.; Yang, S.-D. *ACS Catal* **2017**, *7*, 5220.
[148] Liao, G.; Yin, X.-S.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Nat. Commun.* **2016**, *7*, 12901.
[149] Tran, L. T.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 188.

Table 18. β-Functionalization with bidentate directing groups.

suitable one under oxidative conditions. In this aspect, the group of Shi came out with a *mono*-arylation of alanine unit employind the 2-(pyridin-2-yl)isopropyl (PIP) **168**, a more convenient directing group.[150] The scope was broadened to the use of iodoheteroarenes and high yields were obtained in most of the cases by employing $Pd(OAc)_2$ as catalyst and CuF_2 as additive (Table 18, Entry 2). In addition, by changing the reaction conditions, an intramolecular amidation could be achieved to furnished the product **166** as β-lactams in high diastereoselectivities (Table 18, Entry 3). Finally, a PIP (**168**) directed fluorination of several amino acids residues **165** was described by the group of Shi.[151] Multiple F^+ reagents were tested, in which selectfluor exhibited the best result along with catalytic amount of $Pd(OAc)_2$. Remarkably, the final products **166** were obtained with total diastereoselectivity and either, aliphatic or benzylic β-positions were fluorinated in moderate to high yields (Table 18 ,Entry 4).

Recently, the group of Ackermann have developed an 1,2,3-triazole-directed C(sp³)–H arylation of amino acids and peptide derivatives **169**.[152] This easily accesible triazole moieties are also present in various bioactive peptidomimetics[153] and allowed the β-C–H arylation at either internal (**170a**) or terminal positions (**170b-c**). Furthermore, the late-stage-functionalization of a broad range of peptides **169** was accomplished, which

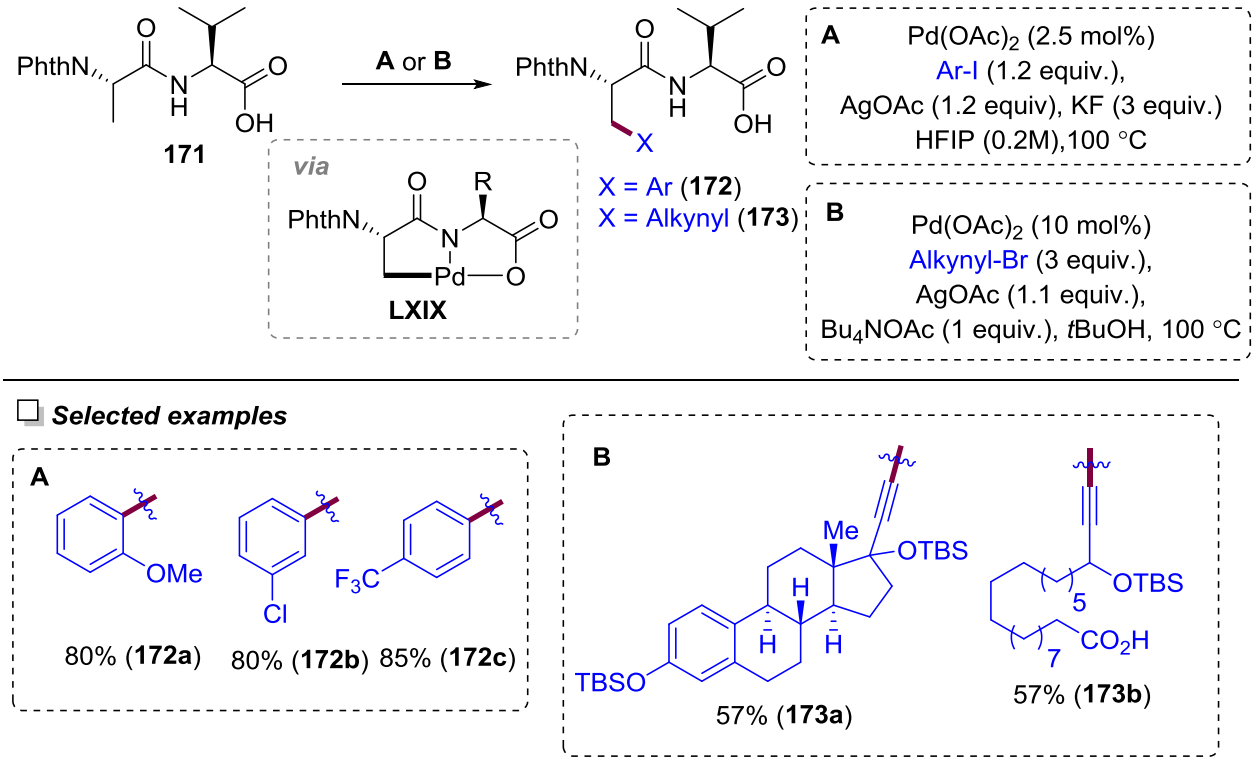


[150] Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2013**, *52*, 13588.
[151] Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219.
[152] Bauer, M.; Wang, W.; Lorion, M. M.; Dong, C.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 203.
[153] a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. b) Piñeda-Castañeda, H. M.; Bonilla-Velásquez, L. D.; Leal-Castro, A. L.; Fierro-Medina, R.; García-Castañeda, J. E.; Rivera-Monroy, Z. J. *ChemistrySelect* **2020**, *5*, 1655.

Scheme 71. 1,2,3-triazole-directed directed β-C–H arylation.

proceeded with excellent diastereoselectivities (of >20:1) and moderate to high yields. In addition, a variety of iodoarenes bearing electron-donating (**170a**) or electron withdrawing (**170b**) proved to be viable reagents under the $Pd(TFA)_2$/AgOAc system (Scheme 71).

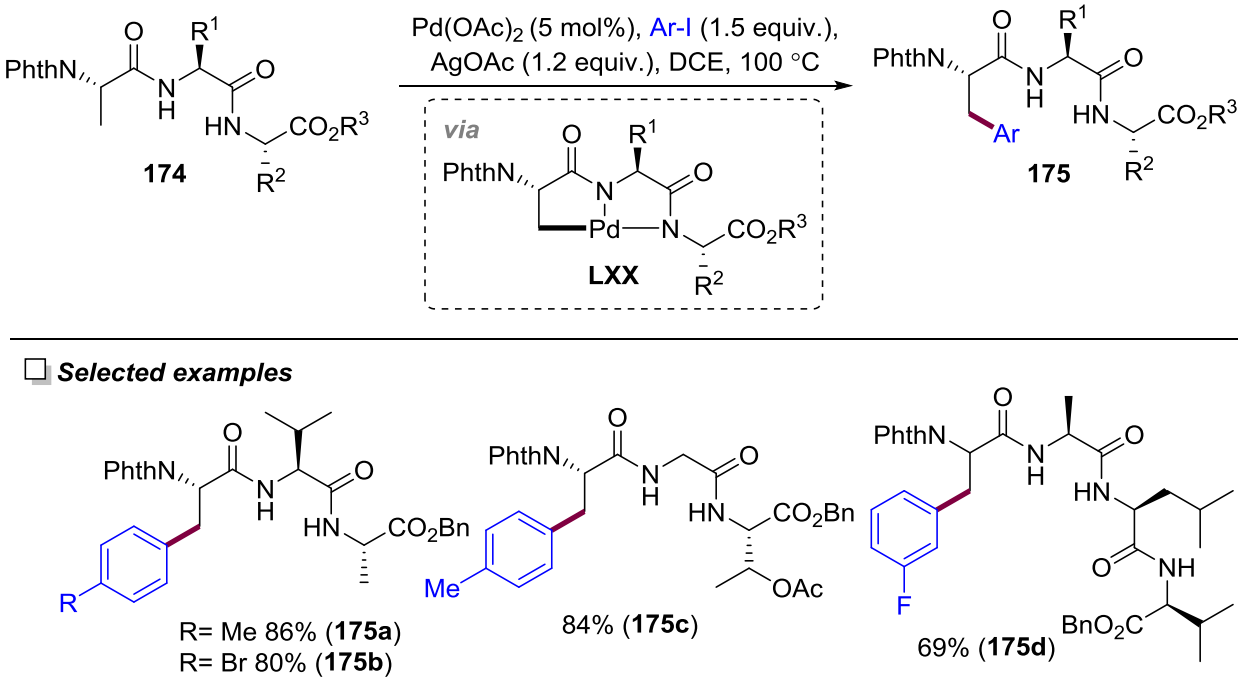
The group of Yu demonstrated that the peptide backbone itself could direct a C–H functionalization at β-position of the adjacent amino acid unit. This represents a big advantage over the introduction of an exogenous DG, as it allows the straightforward functionalization of native peptides. Firstly, an arylation of dipeptides **171** was reported by Yu, which delivered the phenylalanine derivatives **172** in high yields under the conditions disclosed in the Scheme 72, A.[154] Both electron-donating (**172a**) and electron-withdrawing (**172b-c**) groups at different positions (*ortho*, *meta* or *para*) were tolerated, whereas the reaction with heteroarenes was unsuccessful. Additionally, the important role of the terminal carboxylic acid group was demonstrated by switching it with an ester group, which lacked in reactivity. Later on, by slight changes in the reaction conditions (Scheme 72, B), the group of Yu reported an alkynylation reaction of dipeptides **171**.[155] There, several alkynyl moieties were introduced selectively into alanine residues in high yields, even bearing pharmaceutically relevant structures such as estradiol (**173a**) or fatty acid **173b**.



[154] Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940.
[155] Liu, T.; Qiao, J. X.; Poss.; M. A.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 10924.

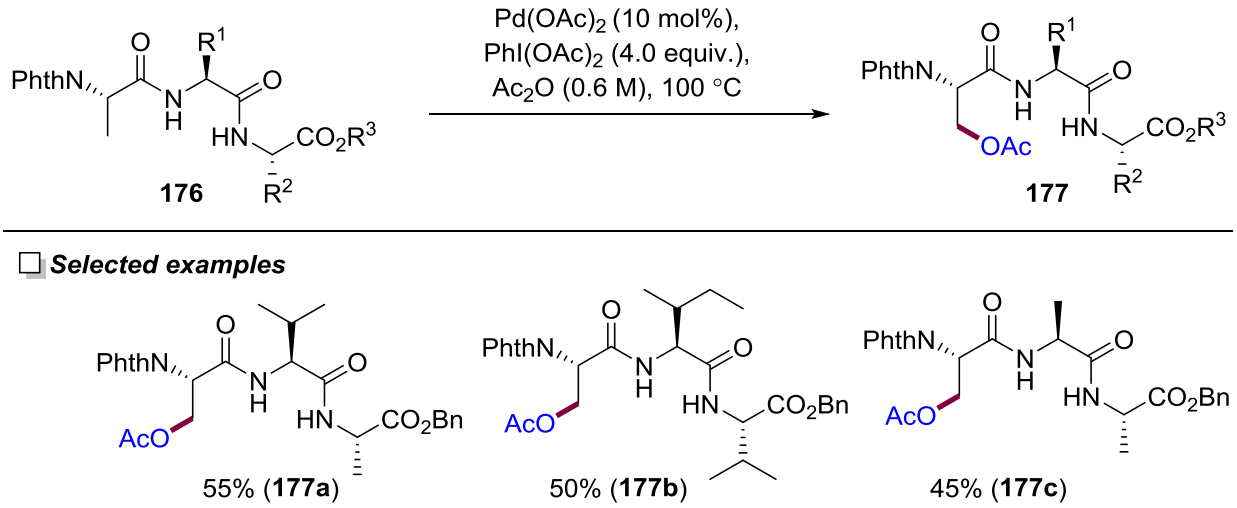
Scheme 72. Backbone-directed arylation and alkynylation of dipeptides.

In the case of the arylation process, the transformation was further extended to the late-stage-functionalization of alanine residue in tri- and tetrapeptides.[154] This time, the authors proposed that the reaction would occur *via* the formation of the *N,N*-biscoordinated palladacycle **LXX**, structurally analogue to the *N,O*-Pd complex **LXIX** of the Scheme 72. Herein, a wide range of amino acid residues embedded in tri- and tetrapeptides (**174**) reacted with a variety of electronically distinct iodoarenes to furnished final arylated peptides **175** in moderate to high yields (Scheme 73).



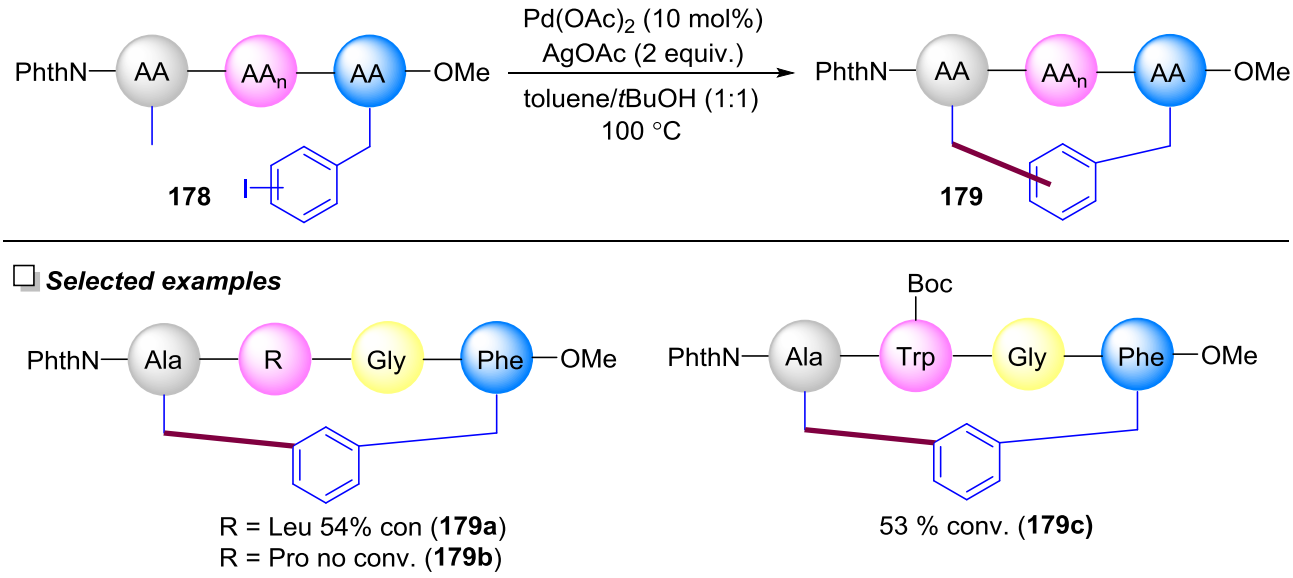
Scheme 73. Backbone-directed arylation of tri- and tetrapeptides.

The *N,N*-biscoordinated strategy was also applied for the selective acetoxylation of tripeptides **176** by the group of Yu.[154] This Pd-catalyzed reaction was achieved with stoichiometric amounts of PIDA as oxidant and Ac_2O as solvent, which delivered the selective acetoxylation of terminal alanine residues (**177**) with moderate yields (Scheme 74).



Scheme 74. Peptide backbone-directed acetoxylation of tripeptides.

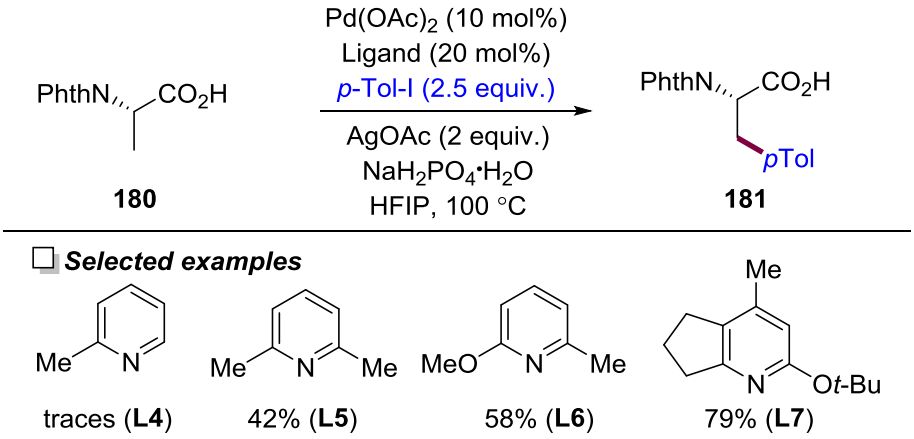
Afterwards, a much more challenging peptide-backboned-directed intramolecular cyclization was developed by the group of Albericio.[156] The cyclization occurred between the alanine residue and the *meta*- or *para*-iodophenylalanine moiety, under the simple conditions of $Pd(OAc)_2$ as catalyst and AgOAc as oxidant (Scheme 75). The optimal distance between the active moieties were 2-3 amino acid residues, which delivered the complex cyclic peptides **179** in low to excellent yields. Peptides with residues such us Pro (**179b**), His and Cys prevented de formation of the new C–C bond and the activation of secondary β-C(sp^3)–H bond also failed. Nonetheless, the peptide containing the sensitive Trp(Boc) residue successfully underwent intramolecular cyclization to afford **179c** in 53% conversion.



[156] Noisier, A. F. M.; García, J.; Ionut, I. A.; Albericio, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 314.

Scheme 75. Peptide-backbone-directed intramolecular cyclization.

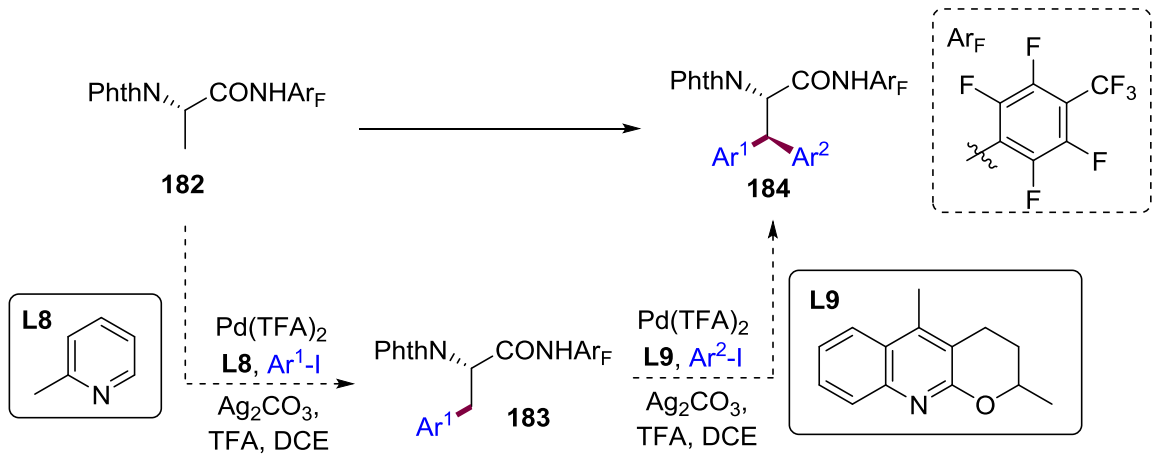
The installation and removal of exogenous DG is a big drawback that hampers many applications of C-H activation methodologies. In this regard, the group of Yu came out with an auxiliary-free direct arylation of the *N*-protected alanine unit **180** avoiding the previous disadvantages.[157] Given the weakly nature of carboxylic acids as directing groups, the authors envisioned that a ligand could be essential to accelerate the desired transformation. Thereby, several pyridine- and quinolone-based ligands **L4**-**7** were tested, from which **L7** exhibited the best performance along with $Pd(TFA)_2$ as catalyst and AgOAc as oxidant, under basic conditions (Scheme 76). Importantly, a control experiment showed that the reaction did not proceed without ligand. Thus, various iodoarenes underwent the target arylation reaction in moderate to high yields, whereas secondary C(sp³)–H bonds were not reactive or delivered the product in poor yields.



Scheme 76. Ligand-enabled β-C–H arylation of *N*-protected alanine **180**.

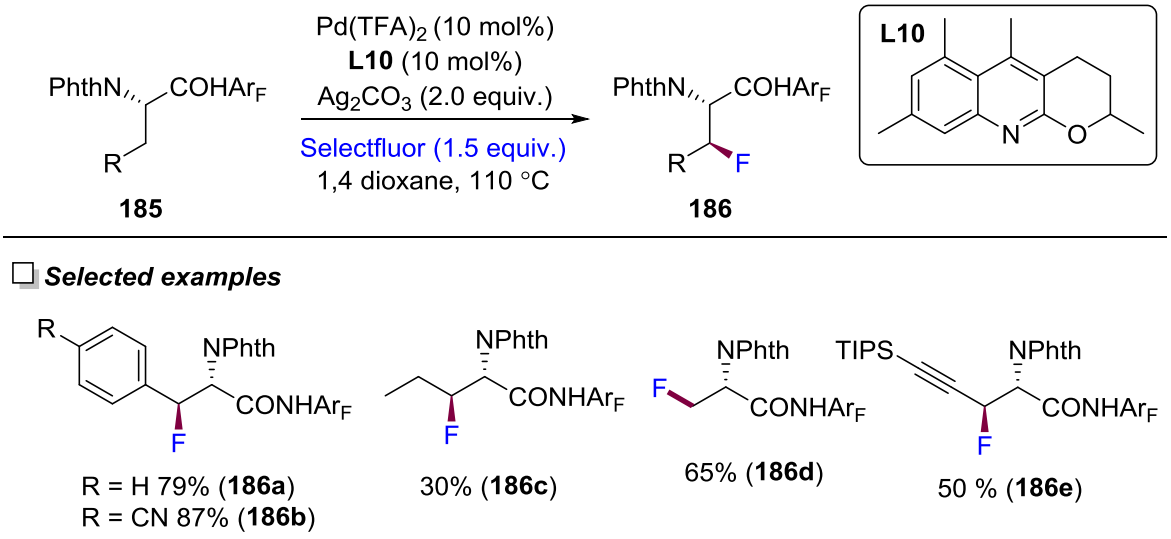
An outstanding work was presented by Yu and co-workers when a ligand-enabled synthesis of β-Ar-β-Ar´-α-amino acids from simple alanine amides **182** was achieved.[158] The weakly coordinating 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline along with **L8** enabled the selective *mono*-arylation of alanine **183** in excellent yields, whereas **L9** promoted the diastereoselective arylation of phenylalanine derivatives **184** in high yields. Remarkably, the combination of **L8** and **L9** not only allowed the sequential one-pot introduction of two distinct aryl groups into β-postion of alanine **184**, but they were also obtained with good yields and excellent diastereoselectivity (Scheme 77).

[157] Chen, G.; Zhuang, Z.; Li, G.-C.; Saint-Denis, T. G.; Hsiao, Y.; Joe, C. L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 1506.
[158] He, J.; Li, S.; Deng, H.; Fu, H.; Laforteza, B. N.; Spanger, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216.



Scheme 77. Ligand-enabled synthesis of *di*-aryl alanine derivatives.

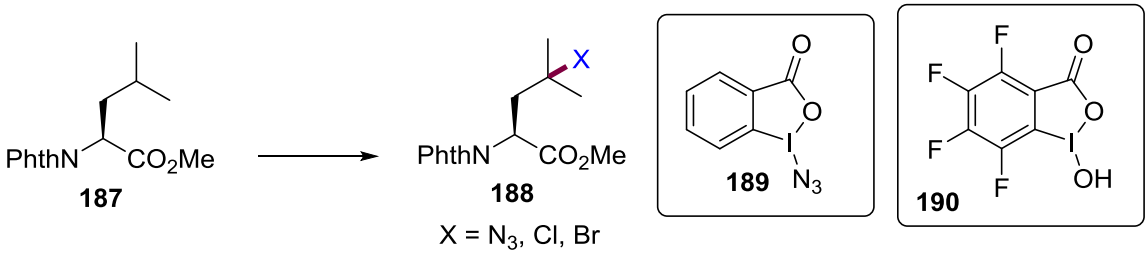
In a similar manner, the group of Yu reported a β-fluorization of both primary and secondary C(sp^3)–H bonds of **185**.[159] The established conditions consisted in the use of selectfluor as fluorine source, along with Pd(TFA)$_2$/Ag$_2$CO$_3$ system (Scheme 78). Under these conditions, benzylic positions were fluorinated in high yields (**186a**-**b**), whereas more challenging aliphatic positions delivered the final product in lower yields (**186c**-**e**). Moreover, secondary C(sp^3)–H bonds were fluorinated in highly diastereo-enriched manner (**186a**-**c, e**).



Scheme 78. Ligand-enabled β-fluorination of amino acid residues.

[159] Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067.

Interestingly, tertiary C(sp³)–H bonds of leucine derivatives were selectively functionalized by the group of Chen with light mediated processes.[160] Under visible light and a photosensitizer Ru-catalyst, the hypervalent iodine **189** was employed as oxidant and azidation reagent to obtain azidated products **188** in low to high yields (Table 19, entry 1). In a similar manner, by adding LiCl or *n*Bu$_4$NBr to the reaction mixture, chlorination or bromination reactions were accomplished (Table 19, entry 2 and entry 3, respectively). Whereas the hypervalent iodine **190** under CFL (23W) afforded the hydroxylated products **188** (Table 19, entry 4).[161]

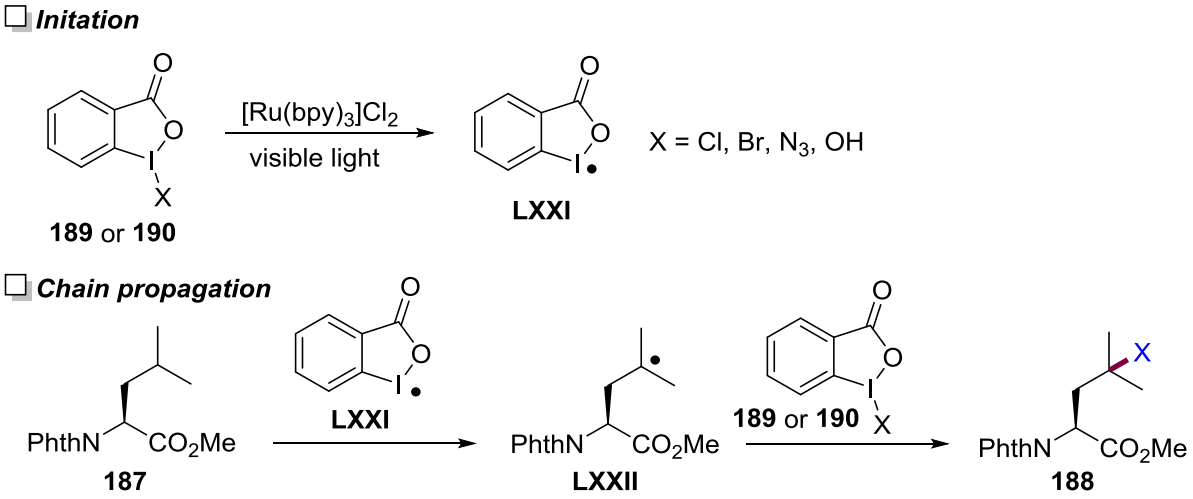


Entry	[Ru(bpy)$_3$]Cl$_2$ (mol%)	Oxidant	Reagent (equiv.)	conditions	Yields (%)
1	0.1 mol%	**189**		Visible light, HFIP, Ar, rt	30-85
2	0.1 mol%	**189**	LiCl (4)	Visible light, HFIP, Ar, rt	45-93
3	2.0 mol%	**189**	*n*Bu$_4$NBr (2)	Visible light, HFIP, Ar, rt	62-71
4	2.5 mol%	**190**		CFL (23 W), HFIP/H$_2$O (26/1), Ar, 30 °C	29-81

Table 19. Light-mediated tertiary C(sp³)–H bond diversification of leucine and derivatives.

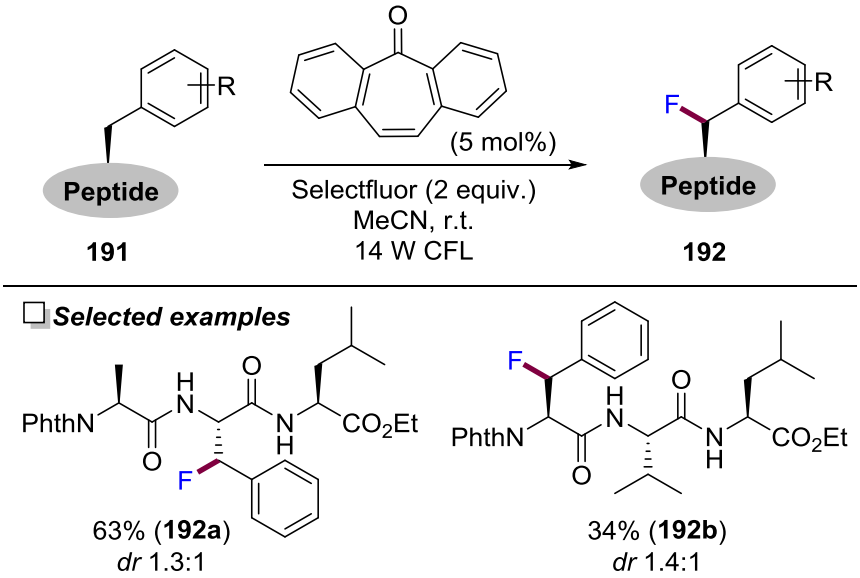
The mechanistic proposal involves the formation the iodanyl radical **LXXI** by the action photo activated ruthenium catalyst. Subsequently, this radical **LXXI** would oxidize the tertiary C(sp³)–H of the substrate **187**, forming the radical species **LXXII**. Finally, the intermediate **LXXII** would react with **189** or **190** to form the desired product **188** and regenerate the radical **LXXI** which would propagate the radical chain reaction (Scheme 79).

[160] Wang, Y.; Li, G.-X.; Yang, G.; He, G.; Chen, G. *Chem. Sci.* **2016**, *7*, 2679.
[161] Li, G.-X.; Morales-Rivera, C. A.; Gao, F.; Wang, Y.; He, G.; Liu, P.; Chen, G. *Chem. Sci.* **2017**, *8*, 7180.



Scheme 79. Mechanistic proposal for the light-mediated tertiary C–H bond diversification.

Alternately, Lectka and co-workers developed a photochemical fluorination of benzylic position of phenylalanine-containing peptides.[162] In this case, catalytic amounts of dibenzosuberenone were employed as photosensitizer, selectfluor as fluorine source and visible light (14 Walt CFT). Remarkably, this reaction exhibited total chemoselectivity toward benzylic positions even in presence of tertiary C–H bonds in the substrate (**191**), obtaining the final products **192** as diastereomeric mixtures in moderate to high yields (Scheme 80).

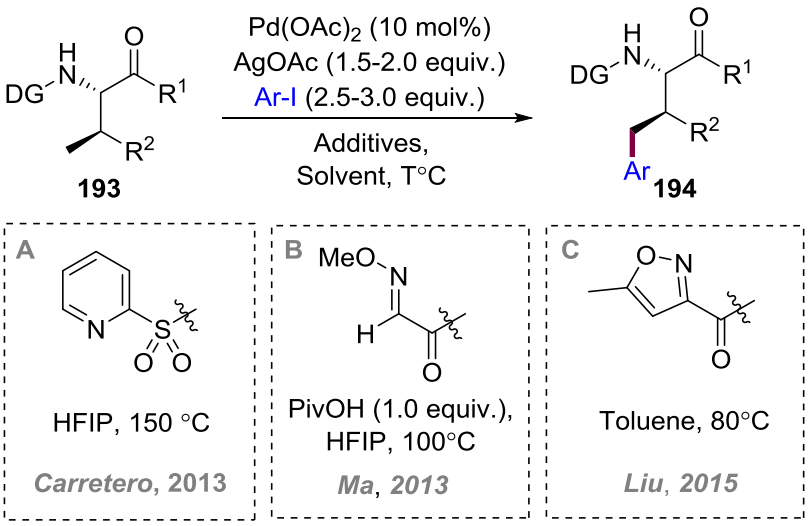


Scheme 80. Light-mediated benzylic C–H fluorination of phenylalanine derivatives.

[162] Bume, D. D.; Pitts, C. R.; Jokhai, R. T.; Lectka, T. *Tetrahedron.* **2016**, *72*, 6031.

2.1.2.2. Functionalization at the γ-Position

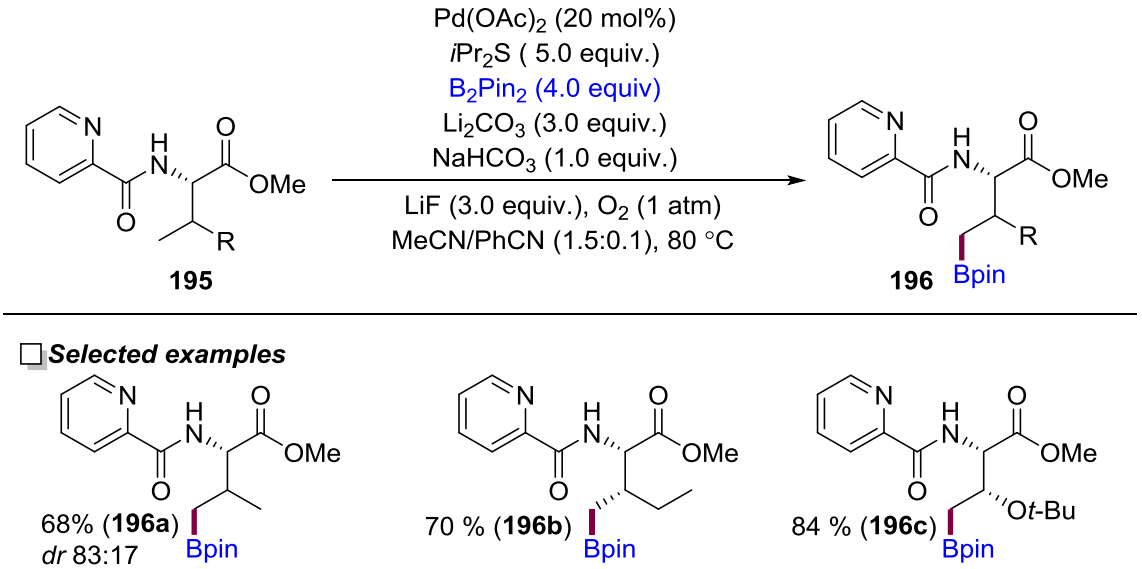
Despite that some examples of γ-arylation of natural amino acids side-chain were described by Corey,[142] there was plenty of room for further improvement of γ-C(sp^3)–H diversification processes. Taking advantage of this, Carretero and co-workers reported a *N*-(2pyridyl)sulfonamide-directed γ-arylation of amino acid residues **193**.[163] With the $Pd(OAc)_2$/AgOAc system and the employment of iodoarene reagents, the reaction took place exclusively at γ-methyl group leaving the analogue γ-position intact. Thereby, amino acid residues such as *allo*-isoleucine, protected threonine or valine were arylated with electron donating or withdrawing iodoarenes. (Scheme 81, A). With a similar approach, the group Ma reported 2-methoxyiminoacteyl (MIA)-directed γ-arylation of amino acids **193**.[164] This protocol was suitable for the introduction of a wide range of iodoarenes with the $Pd(OAC)_2$/AgOAc system, which delivered the arylated product **194** in moderate to high yields. Furthermore, MIA moiety could be easily hydrolyzed or hydrogenated to obtain homophenylalanine derivatives (Scheme 36, B). The isoxazole moiety was also employed for the γ-arylation of amino acids **193** by the group of Liu.[165] In this case, the solvent had a big impact in the final outcome, where toluene exhibited the best result with the $Pd(OAc)_2$/AgOAC system (Scheme 36, C). It is notewhorty that when a new chiral center was formed (when R^2 = Me), regardless of the DG, a single diastereomer was isolated, due to the formation of the less sterically hindered *trans*-palladacycle intermediate.



Scheme 81. *N*-directed γ-C–H arylation of aliphatic side-chains.

[163] Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibañez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175.
[164] Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152.
[165] Pasunooti, K. K.; Banerjee, B.; Yap, T.; Yaojia, J.; Liu, C.-F. *Org. Lett.* **2015**, *17*, 6094.

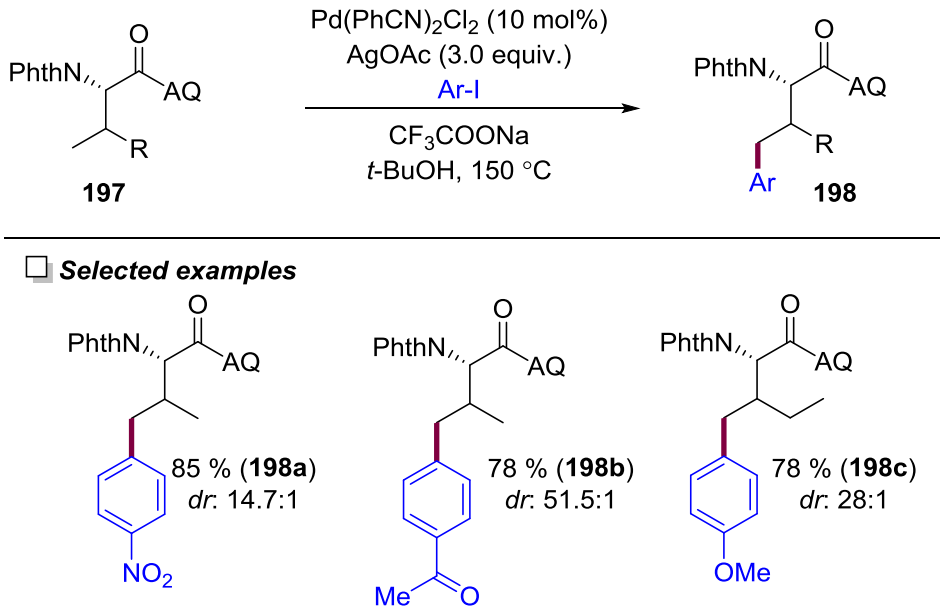
Afterwards, a PA-directed γ-borylation of C(sp^3)–H bonds was disclosed by the group of Shi.[113] To accomplish this reaction, a complex system was utilized, consisted in catalytic amounts of $Pd(OAc)_2$, excess of iPr_2S as ligand, B_2pin_2 as boron source, alkaline environment and oxygen as terminal oxidant (Scheme 82). With these conditions in hand, natural amino acid residues such us valine (**195a**), isoleucine (**195b**) or *O*-protected threonine (**195c**) were successfully *mono*-borylated at γ-positions in good yields. Notably, in the case of the valine residue, the reaction proceeded in a stereo-controled fashion delivering **196a** with 83:17 diastereomeric ratio.



Scheme 82. PA-directed γ-borylation.

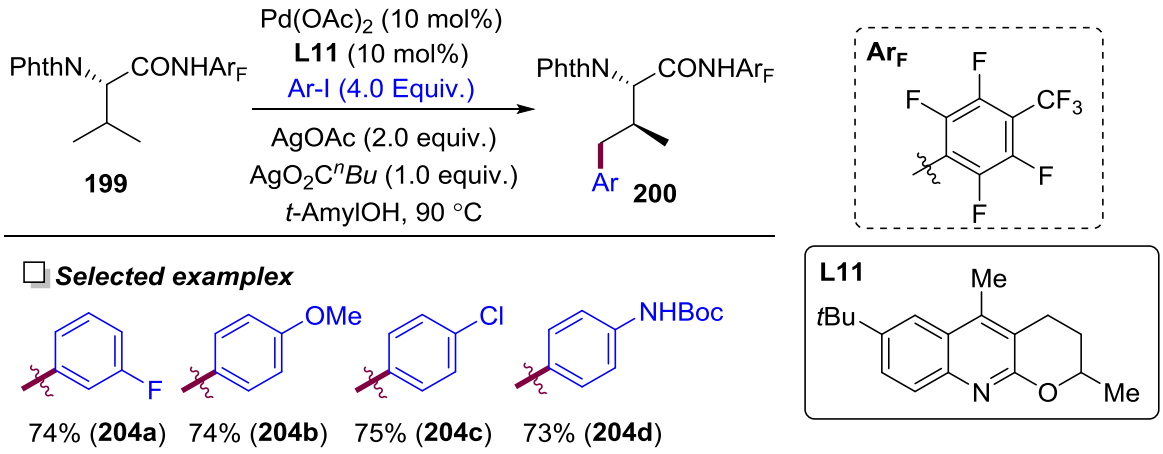
Commonly utilized 8-aminoquinoline (AQ) also was employed for the selective *mono*-arylation of valine and leucine units at γ-position.[166] In addition to $Pd(PhCN)_2Cl_2$/AgOAc system, the use of sodium trifluoroacetate and the bulky polar solvent *t*-BuOH improved the final outcome. As expected, diastereo-enriched products **198** were obtained and different functional groups such as nitro (**198a**), ketone (**198b**) or methoxy (**198c**) were tolerated at *para*-position of iodoarenes (Scheme 83). However, excess of amino acid residues **197** were employed to perform the target reaction, which represented a relevant drawback from the point of view of cost and atom-economy.

[166] Dey, C.; Pimparkar, S.; Deb, A.; Guin, S.; Maiti, D. *Adv. Synth. Catal.* **2017**, *359*, 1301.



Scheme 83. AQ-directed γ-arylation.

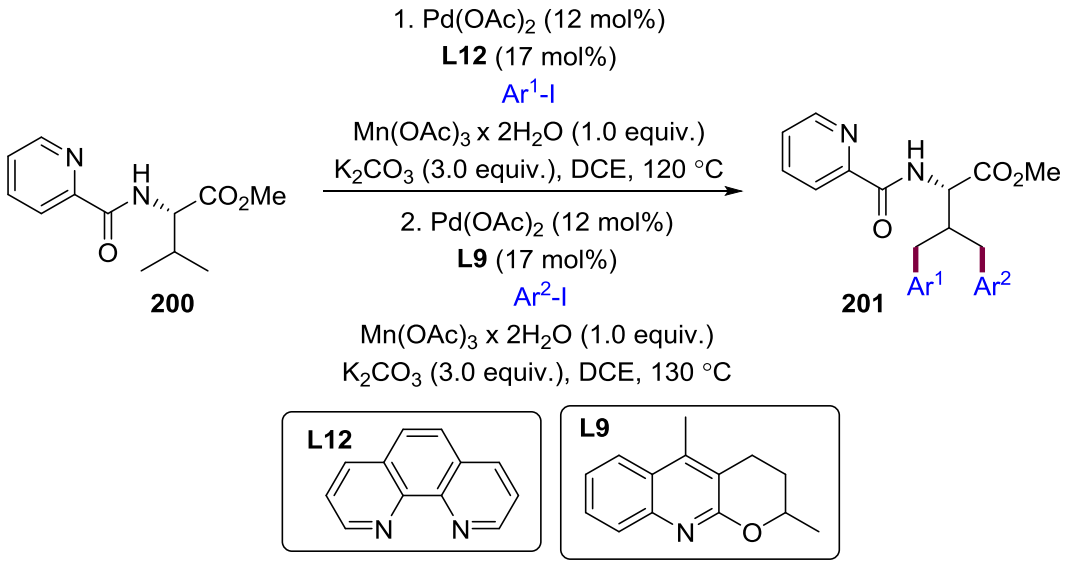
Related with their previously reported ligand enabled β-arylation of amino acids,[158] Yu and co-workers also developed a procedure for the γ-arylation of the valine moiety.[167] In this case, the combination of the weak coordinating directing group [2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl] with the ligang **L11** enabled the γ-arylation of valine to yield a vast array of *mono*-arylated valines **200** with good to excellent yields. Various substituted iodoarenes were compatible with this reaction and in all cases the final products **200** were obtained with high diastereoselectivities (Scheme 84).



Scheme 84. Ligand enabled γ-arylation.

[167] Li, S.; Zhu, R.-Y.; Xiao, K.-J.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 4317.

Furthermore, Jana and co-workers reported a ligand-enabled unsymmetrical *di*-arylation of valine moiety.[168] The first **L12**-enabled arylation proceed in overall good yields and in some cases, with high diastereoselectivities. Taking advantage of this, the authors performed a subsequent **L9**-enabled γ-arylation to deliver unsymmetrical *di*-arylated products **201** in moderate yields (Scheme 85).



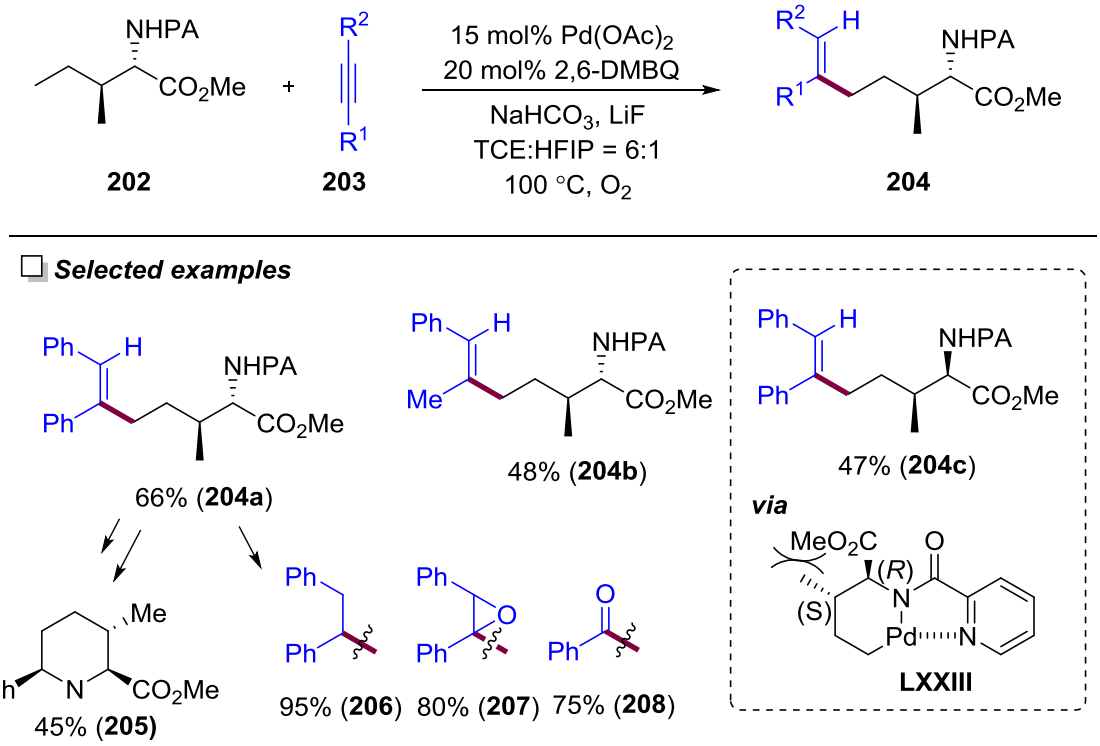
Scheme 85. Unsymmetrical γ-*di*-arylation of valine moiety.

2.1.2.3. Functionalization at the δ-Position

Regarding to δ-C(sp^3)–H functionalization, only a couple of examples have been described, which clearly reflects the challenge that represents the transformations at this distant position. The group of Shi disclosed the first example of δ-C(sp^3)–H functionalization of aliphatic amino acids residues, in which an alkenylation reaction was achieved with the use of alkynes though Pd-catalysis.[169] This picolinamide (PA)-directed transformation apart from catalytic amounts of $Pd(OAc)_2$, required substoichoimetric amounts of 2,6-dimethylbenzoquinone and basic conditions, where either symmetric or unsymmetrical alkynes **203** were employed (Scheme 86). Under optimized conditions, isoleucine moiety was selectively alkenylated in moderate to good yields, while functionalization of the *allo*-isoleucine (**204c**) resulted more challenging due to unfavorable steric hindrance of the intermediate **LXXIII**. To highlight the synthetic utility of this reaction, several transformations of the product **204a** were performed; for example, it was converted into the

[168] Das, S.; Bairy, G.; Jana, R. *Org. Lett.* **2018**, *20*, 2667.
[169] Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750.

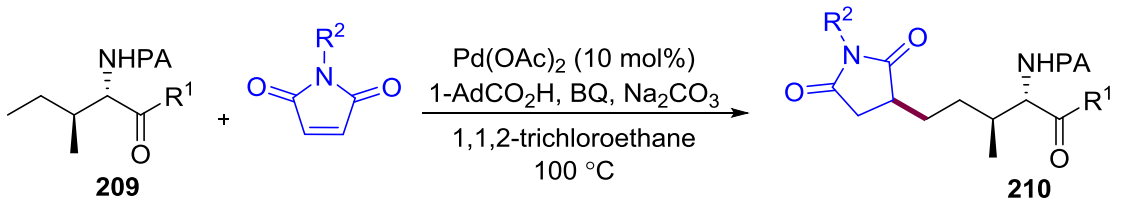
corresponding chiral piperidine **205** through several synthetic steps. By employing conventional approaches, **204a** was also hydrogenated (**206**), epoxidated (**207**) or oxidated to the corresponding ketone derivative (**208**).



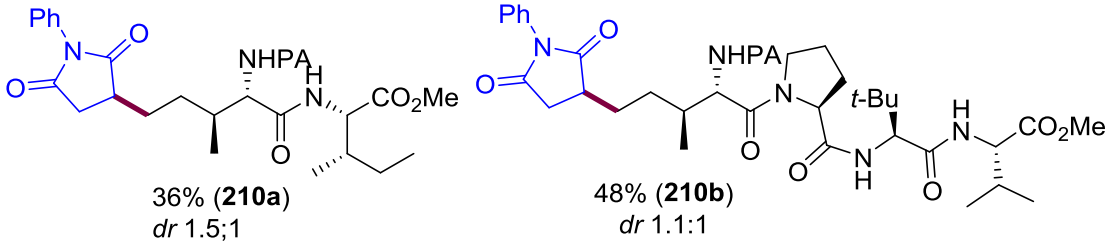
Scheme 86. PA-directed δ-C–H alkenylation.

Moreover, the same group was able to extend this strategy to achieve a site-selecive δ-alkylation of the isoleucine moiety with the use of maleimides.[170] Unlike in the previous work (Scheme 86), this time the scope of the reaction was broadened to the late-stage-functionalization of di-(**209a**), tri- and tetrapeptides (**209c**), delivering the final peptide **210** in moderate yields and as diastereomeric mixtures (Scheme 87). Nonetheless, only simple aliphatic amino residues were incorporated into the peptide **209** chain.

[170] Zhan, B.-B.; Li, Ya.; Xu, J.-W.; Nie, X.-L.; Fan, J.; Jin, L.; Shi, B.-F. *Angew. Chen. Int. Ed.* **2018**, *57*, 5858.



❑ ***Selected examples***

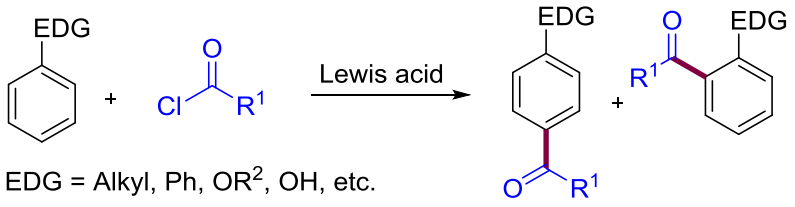


Scheme 87. PA-directed δ-alkylation of isoleucine derivatives.

2.2. Heterocycle-Directed C–H Acylation of Arenes

2.2.1. Introduction

Aryl ketones are important building blocks present in many biologically active natural products, pharmaceuticals and agrochemicals.[171] Therefore, the synthesis of aryl ketones from simple arenes in a regioselective manner is extremely valuable in organic synthesis. Traditionally, routes to synthesize aryl ketones from arenes relied on the Friedel-Craft reaction in the presence of $AlCl_3$ as Lewis acid and a highly activated acyl source, which usually gave poor *ortho*/*para* selectivity (Scheme 88). In addition, the required work-up to hydrolyze the formed complex between the ketone product and $AlCl_3$, generates substantial amount of waste in the process.



Scheme 88. Classical Friedel-Craft acylation reaction.

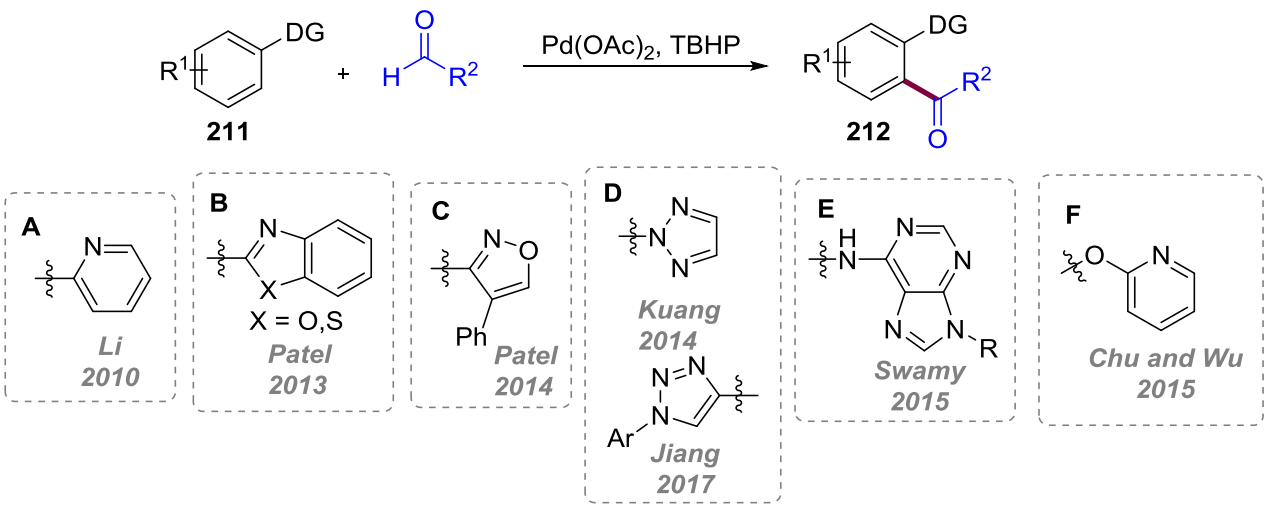
With the aim to overcome these issues, in the last decade we have witnessed tremendous advances on transition-metal-catalyzed C–H acylations of arenes or heteroarenes with heterocycles as practical directing groups. For these transformations a wide variety of acyl sources have been employed and the main results will be detailed along the next section.

2.2.2. C–H Acylation with Aldehydes

In 2010, the group of Li disclosed a straightforward acylation of arenes with the use of the pyridyl moiety as directing group and aldehydes as acyl source (Scheme 89, A).[172] The common system of $Pd(OAc)_2$/$TBHP_{dec}$ allowed the activation of aromatic and aliphatic aldehydes, including the activation of the low-boiling point acetaldehyde. Furthermore, mechanistic studies evidenced a Pd^{II}/Pd^{IV} catalytic cycle, and the alternative

[171] a) Deng, Yo.; Chai, H.; Keller, W. J.; Kinghorn, A. D. *J. Nat. Prod*. **2007**, *70*, 2049. b) Romines, K. R.; Freeman, G. A.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Tidwell, J. H.; Andrews, C. W.; Stammers, D. K.; Hazen, R. J.; Ferris, R. G.; Short, S. A.; Chan, J. H.; Boone, L. R. *J. Med. Chem*. **2006**, *49*, 727.
[172] Baslé, O.; Bidange, J.; Sherai, Q.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1145.

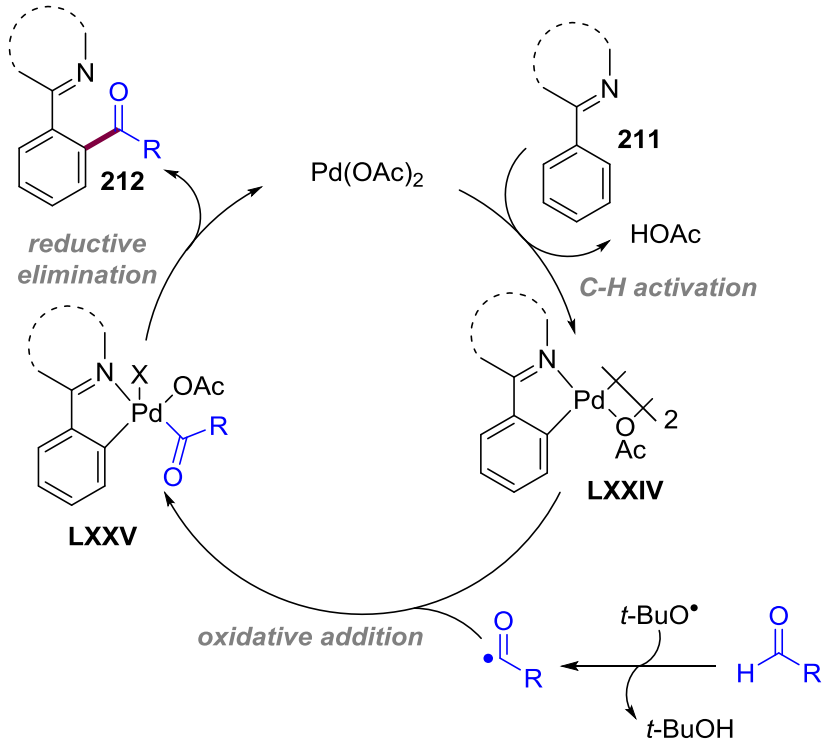
Pd^0/Pd^{II} catalytic cycle was ruled out by the authors. Afterwards, the important scaffolds of benzo(thia)zoles (Scheme 87, B)[173] and 3,5-diarylisoxazoles (Scheme 89, C)[174] were employed for the acylation of arenes by the group of Patel. A wide range of (hetero)aromatic aldehydes were successfully introduced into the arene moiety under the $Pd(OAc)_2$/TBHP system, whereas aliphatic aldehydes poorly reacted. Nonetheless, high yields of the *mono*-acylated products **212** were obtained. On the other hand, the group of Kuang[175] and Jiang,[176] employed the important 1,2,3-triazoles as auxiliaries for the Pd-catalyzed C–H acylation. Several 2-aryl-1,2,3-triazoles smoothly reacted with substituted aryl aldehydes which gave **212** in moderate to good yields. In addition, aliphatic aldehydes and even α,β-unsaturated aldehydes were also suitable for this reaction (Scheme 89, D). One of the DNA building blocks, the purine, was also employed as directing group for the *ortho*-acylation of arenes by the group of Swamy.[177] As in previous works, the combination of $Pd(OAc)_2$ with TBHP enabled the selective acylation of 6-anilinopurine derivatives with alkyl aldehydes or α-oxocarboxylic acids as acyl feedstock (Scheme 89, E). Interestingly, the protocol could be extended to 6-anilinopurine nucleosides. Finally, the *O*-pyridyl moiety was utilized as directing group by Chu, Wu and co-workers (Scheme 89, F).[178] This directing group along with $Pd(OAc)_2$ and TBHP, allowed the introduction of a vast array of electronically and sterically divergent aryl aldehydes in low to excellent yields. Unlike in other cases, the final products **212** often were obtained as a mixture of *mono*- and *di*-acylation products. Furthermore, the C–O bond cleavage of the directing group offered an easy access to 2-acylated phenols.



Scheme 89. Heteroclycle-directed *ortho*-acylation of arenes with aldehydes.

[173] Banerjee, A.; Santra, S. K.; Guin, S.; Rout, S. K.; Patel, B. K. *Eur. J. Org. Chem.* **2013**, 1367.
[174] Banerjee, A.; Bera, A.; Santra, S. K.; Guan, S.; Patel, B. K. *RSC Adv.* **2014**, *4*, 8558.
[175] Wang, Z.; Tian, Q.; Yu, X.; Kuang, C. *Adv. Synth. Catal.* **2014**, *356*, 961.
[176] Jiang, Y.; Ma, X.; Zhao, F.; Han, C. *Synlett*, **2017**, *28*, 713.
[177] Allu, S.; Swamy, K. C. K. *RSC Adv.* **2015**, *5*, 92045.
[178] Chu, J.-C.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. *Organometallics*. **2015**, *34*, 953.

The generally proposed mechanism would start with the C–H activation step to form palladacycle **LXXVI**, which was isolated by several reports with different *N*-heterocycles as DG.[179] The acyl radical formed through oxidation with TBHP, would react with the palladaclycle intermediate **LXXIV** to form a dimeric Pd^{III} or Pd^{IV} **LXXVI**.[180] Finally, the high valent intermediate **LXXVII** would undergo reductive elimination to generate the acylated product **211** and regenerate the active Pd^{II} catalyst (Scheme 90). Despite the initial palladacycle **LXXVI** has been well documented, in-depth studies are clearly required to elucidate the fundamental oxidative addition of the acyl radical and the actual nature of this putative intermediates.



Scheme 90. Proposed mechanism for the heterocycle-directed C–H acylation of arenes.

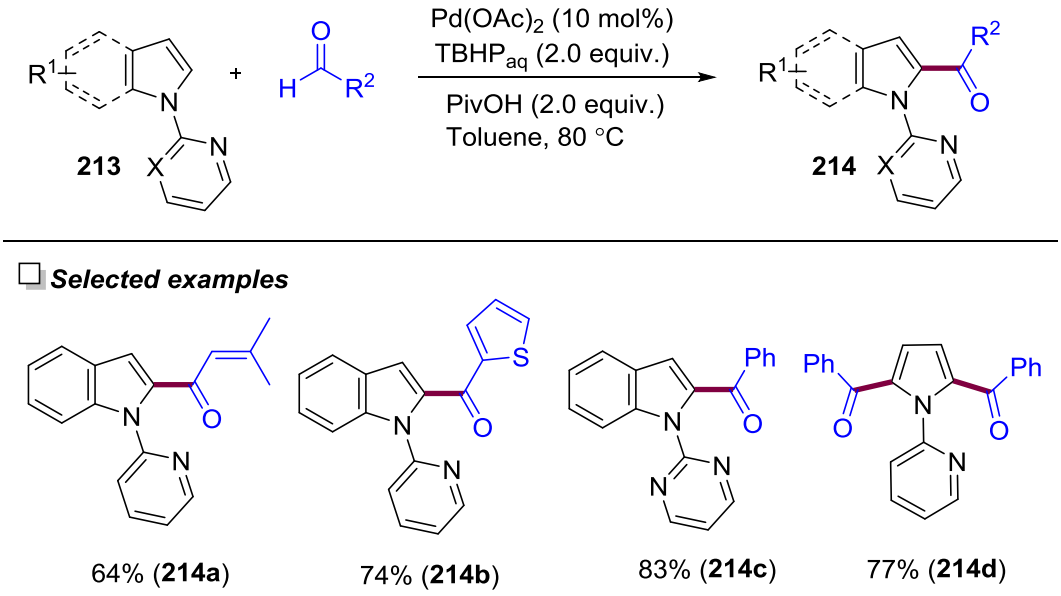
On the other hand, the introduction of heterocycles such us pyridine or pyrimidine in the nitrogen of the indole or analogues, has enabled the regioselective acylation of these moieties. In this context, Liu and co-workers reported a Pd-catalyzed selective C2-acylation of pyri(mi)dyl-protected indoles and related.[181] This

[179] a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. b) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120.

[180] a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050. b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. c) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. c) Zhang, L.-L.; Zhang, L.; Li, S.-J.; Fang, D.-C. *Dalton Trans.* **2018**, 47, 6102.

[181] Yan, X.-B.; Shen, Y.-W.; Chen, D.-Q.; Gao, P.; Li, Y.-X.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Tetrahedron* **2014**, *70*, 7490.

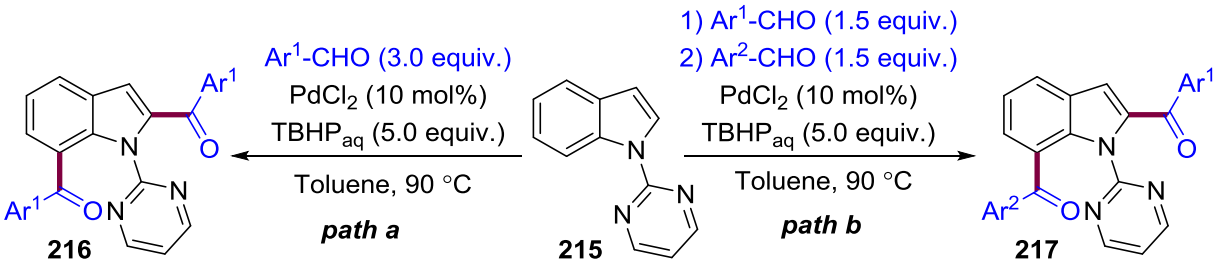
efficient protocol allowed the introduction of aldehydes including aromatic (**214c**-**d**), heteroaromatic (**214b**), aliphatic, and even conjugated aldehydes (**214a**) as acyl feedstock, utilizing $TBHP_{aq}$ as oxidant and PivOH as additive (Scheme 91). Substituted indoles efficiently underwent the target reaction, the use of pyrimidine also afforded the final acylated product **214c** and when pyrrole was employed as substrate, the *di*-acylated product **214d** was obtained. Importantly, the removal of the pyridine motif in the final products **214** was easily achieved by treament of MeOTf (Methyl trifluoromethanesulfonate) in dichloromethane and sodium hydroxide in methanol.



Scheme 91. Heterocycles-directed C2-acylation of indoles.

Using this approach and pyrimidine as directing group, the group of Sekar extended the methodology toward C2- and C7-*di*-acylation of indoles.[182] Using excess of aldehyde (3.0 equiv.), symmetrical C2,C7-*di*-acylated products **216** were obtained in good yields (Scheme 92, path a), whereas employing two distinct aldehydes (1.5 equiv. each) in a subsequent manner, delivered the unsymmetrical C2,C7-*di*-acylated product **217** (Scheme 92, path b).

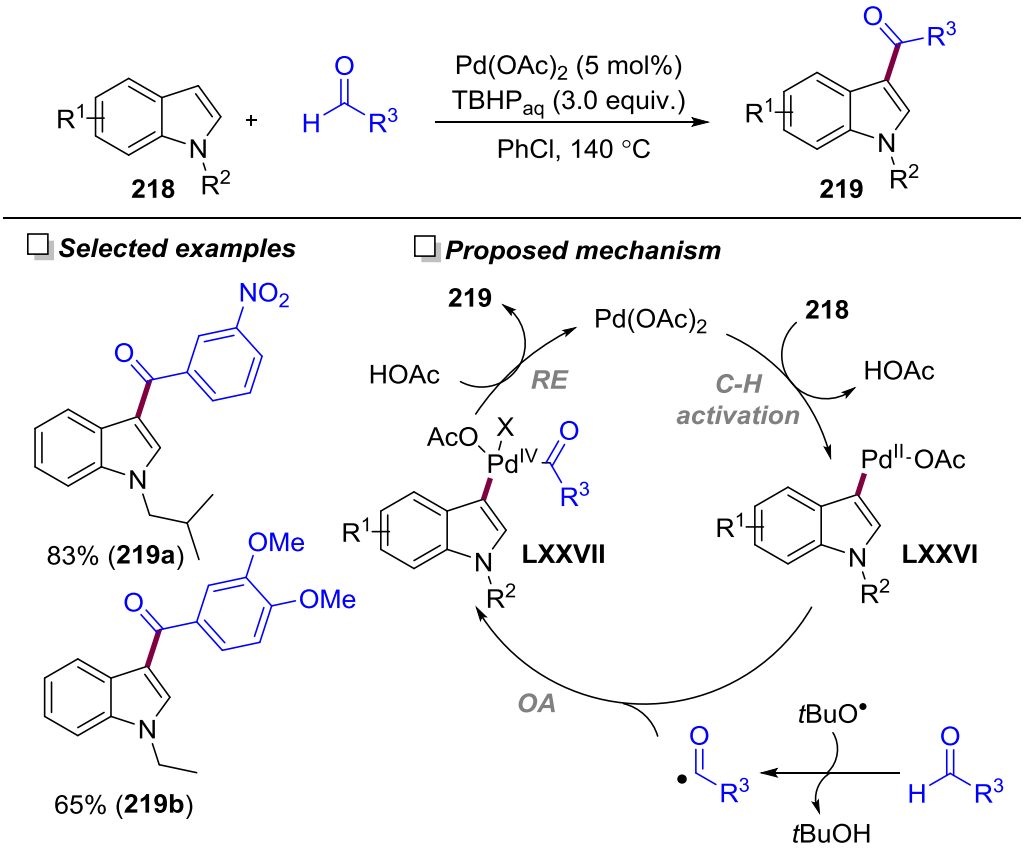
[182] Kumar, G.; Sekar, G. *RSC Adv.* **2015**, *5*, 28292.



Scheme 92. Pyrimidine-directed *di*-acylation of indoles.

In contrast, *N*-alkyl indoles **218** reacted with aldehydes in the presence of $TBHP_{aq}$ and $Pd(OAc)_2$ to deliver 3-acylindoles **219**.[183] Whereas aromatic aldehydes containing electron-withdrawing groups gave the acylated products **219** in good yields, aldehydes containing electron-donating groups furnished the final products **219** with slightly lower yields. Regarding to the mechanism, the authors proposed the metalation of the indole moiety at C3-position to form the intermediate **LXXVI**. Then the acyl radical derived from the oxidation of the aldehyde would react with the intermediate **LXXVI** to form the Pd^{IV} intermediate **LXXVII**, which would eventually undergo a reductive elimination to deliver the desired product **219** and recycle the active Pd^{II} species (Scheme 93).

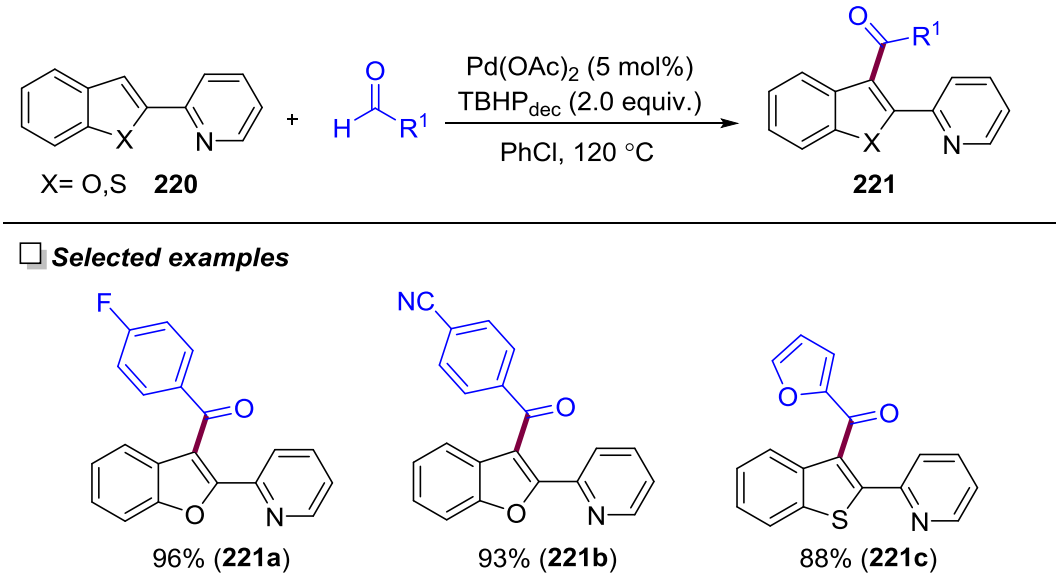
[183] Kianmehr, E.; Kazemi, S.; Foroaunadi, A. *Tetrahedron* **2014**, *70*, 349.



Scheme 93. Pd-catalyzed C3-acylation of *N*-alkyl indoles.

Alternatively, the group of Pan and Han described a Pd-catalyzed C3-acylation of benzofuranes and benzothiophenes with aldehydes.[184] In this case, pyridine-containing substrates **220** allowed the introduction of a vast array of heteroaromatic aldehydes with remarkable high yields (Scheme 94). However, aliphatic aldehydes did not undergo the target reaction and the removal of the pyridine as directing group was uncuccessful, which limited the applicability of the process.

[184] Zhao, J.; Fan, H.; Xie, C.; Han, J.; Li, G.; Pan, Y. *Asian J. Org. Chem.* **2013**, *2*, 1044.

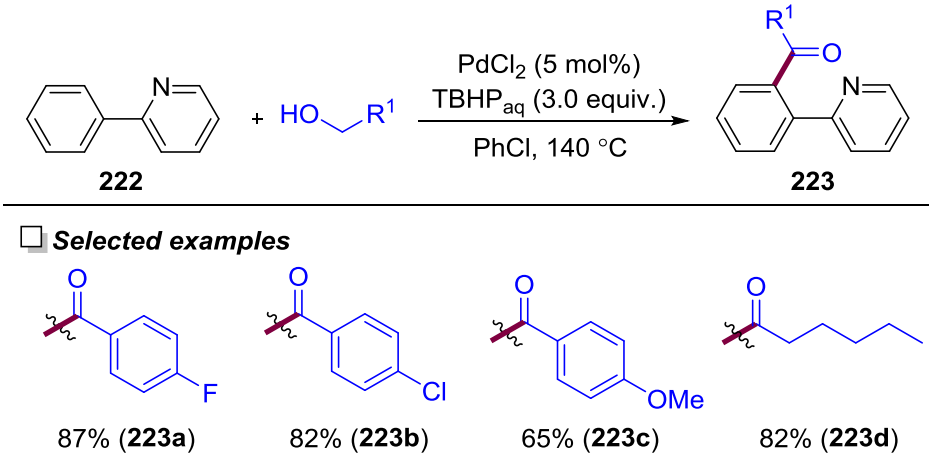


Scheme 94. Pyridine-directed C3-acylation of bezofuranes and benzothiophenes.

2.2.3. C–H Acylation with Alcoholes

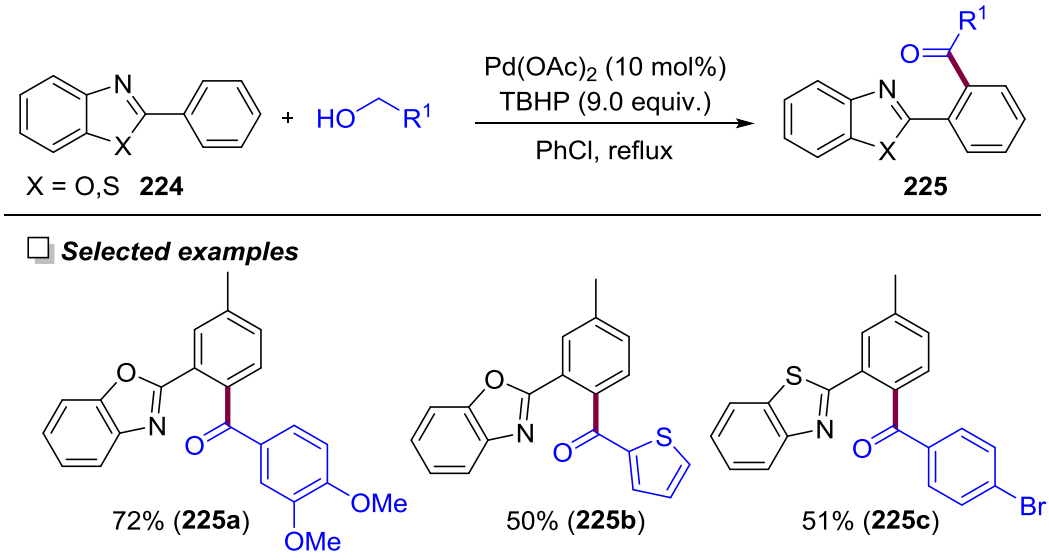
The easy oxidation of alcohols to the corresponding aldehyde *in situ*, has enabled the use of alcohols as acylation reagents for multiple heterocycle-directed C(sp^2)– H acylation processes.[185] Furthermore, the abundance of alcohols, which are widely available and easy to handle, makes them very convenient to use as powerful acyl feedstock. In this regard, Li, Deng and co-workers reported a Pd-catalyzed C(sp^2)–H acylation of 2-arylpyridines with alcohols.[186] The reactions conditions were similar to the ones employed for the activation of aldehydes (Scheme 89), which consisted in the use of catalytic amounts of $PdCl_2$ in the presence of $TBHP_{aq}$ (Scheme 95). This system allowed the activation of benzylic alcohols bearing electron-withdrawing (**223a**) or –donating (**223b**) groups in good yields and alcohols such us 1-hexanol (**223d**) were also reactive.

[185] Wu, X.-F. *Chem. Eur. J.* **2015**, *21*, 12252.
[186] Xiao, F.; Shuai, Q.; Zhao, F.; Baslé, O.; Deng, G.; Li, C.-J. *Org. Lett.* **2011**, *13*, 1614.



Scheme 95. Pyridine-directed acylation of arenes with alcohols.

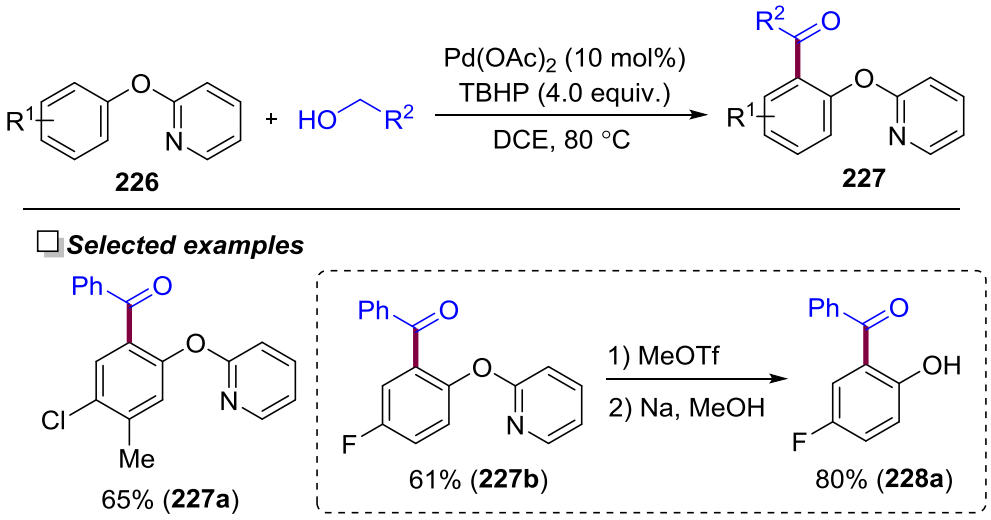
In a similar fashion, 2-arylbenzoxazoles and 2-arylbenzothiazoles were effectively acylated with benzylic alcohols by Wu, Yang and co-workers.[187] In this case, the reaction required a very high excess of TBHP (9.0 equiv.) in order to achieve high yields along with catalytic amounts of $Pd(OAc)_2$, which allowed the formation of *mono*-acylated derivatives **225**. In general, electronic effects had significant impact on the final outcome, being electron-rich alcohols more reactive than their electron-deficient analogues. Moreover, alcohols bearing heterocycles such as thiophene delivered the target product **225c** in moderate yield (Scheme 96). Independently, the group of Peng and Ding improved the yields of the same transformation by adding 1,4-benzoquinone (BQ, 10 mol%) as a key additive.[188]



[187] Zhang, Q.; Yang, F.; Wu, Y. *Tetrahedron* **2013**, *69*, 4908.
[188] Ding, Q.; Ji, H.; Ye, C.; Wang, J.; Wang, J.; Zhou, L.; Peng, Y. *Tetrahedron* **2013**, *69*, 8661.

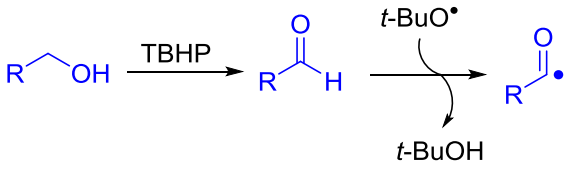
Scheme 96. Benzo(thia)zole-directed acylation of arenes with alcohols.

Finally, Kim and co-workers described a Pd-catalyzed acylation of 2-phenoxypyridines with alcohols as acyl surrogates.[189] Under optimized conditions, substituted arenes were coupled with aromatic and aliphatic alcohols to give **227** in good to excellent yields (Scheme 97). In addition, the removal of the pyridine gave access to *ortho*-acylphenols **228a** in excellent yields.



Scheme 97. Acylation of 2-phenoxypyridines with alcohols.

The key step in these transformation is the formation of the reactive acyl radical through consecutive oxidation steps of the starting alcohol (Scheme 98).

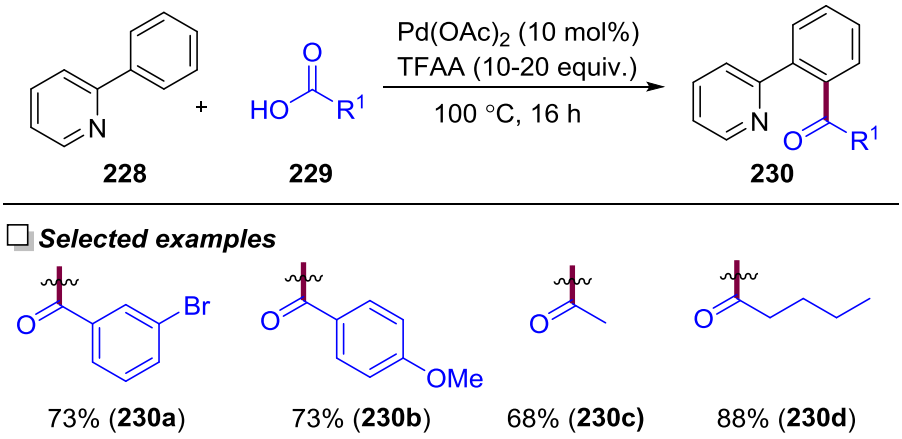


Scheme 98. Oxidative activation of alcohols.

[189] Kim, M.; Sharma, S.; Park, J.; Kim, M.; Choi, Y.; Jeon, Y.; Kwak, J. H.; Kim, I. S. *Tetrahedron* **2013**, *69*, 6552.

2.2.4. C–H Acylation with Carboxilyc Acids

The use of readily available carboxylic acids as acyl feedstock for the *ortho*-acylation of 2-arylpyridines was disclosed by the group of Fu.[190] The reaction was catalyzed by $Pd(OAc)_2$ and required excess of carboxylic acids for optimal yields, along with high excess of TFAA (trifluoroacetic anhydride) as activating agent. Under

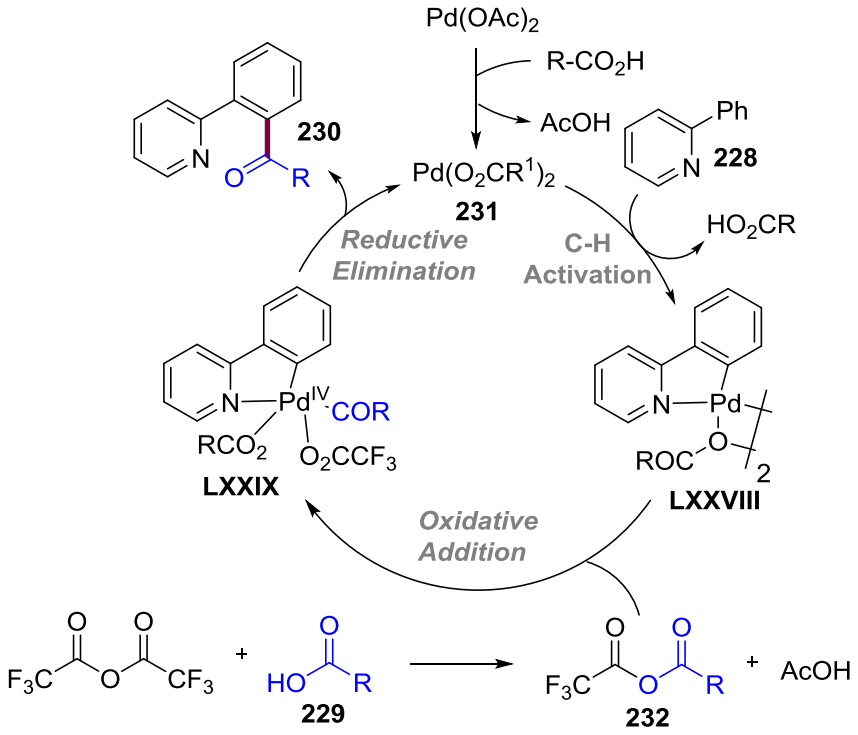


Scheme 99. Acylation of 2-arylpyridines with carboxylic acids.

optimized conditions, aromatic carboxylic acids **229** bearing alkyl, halogen, ether or nitro group gave the *mono*-acylated products **230** in moderate to excellent yield. The protocol was not limited to the use of aromatic carboxylic acids as aliphatic counterparts also exhibited great reactivity, delivering the *ortho*-acylated products **230** in overall high yields (Scheme 99).

According to the results above, the authors proposed a plausible mechanism (Scheme 100). The excess of carboxylic acid (**228**) with $Pd(OAc)_2$ would provide the catalyst **231** and the reaction of TFAA with **229** would give the anhydride **232**. The C–H activation of **232** with 2-phenylpyridine (**228**) would afford the intermediate **LXXVIII**. Then the intermediate **LXXVIII** would undergo an oxidative addition with the anhydride **232** to yield the complex **LXXIX**. Finally, reductive elimination of complex **LXXIX** would provide the target product **230**, regenerating the active Pd^{II} catalyst.

[190] Lu, J.; Zhang, H.; Chen, X.; Liu, H.; Jiang, Y.; Fu, H. *Adv. Synth. Catal.* **2013**, *355*, 529.



Scheme 100. Proposed mechanism for the acylation of 2-arylpyridines with carboxylic acids.

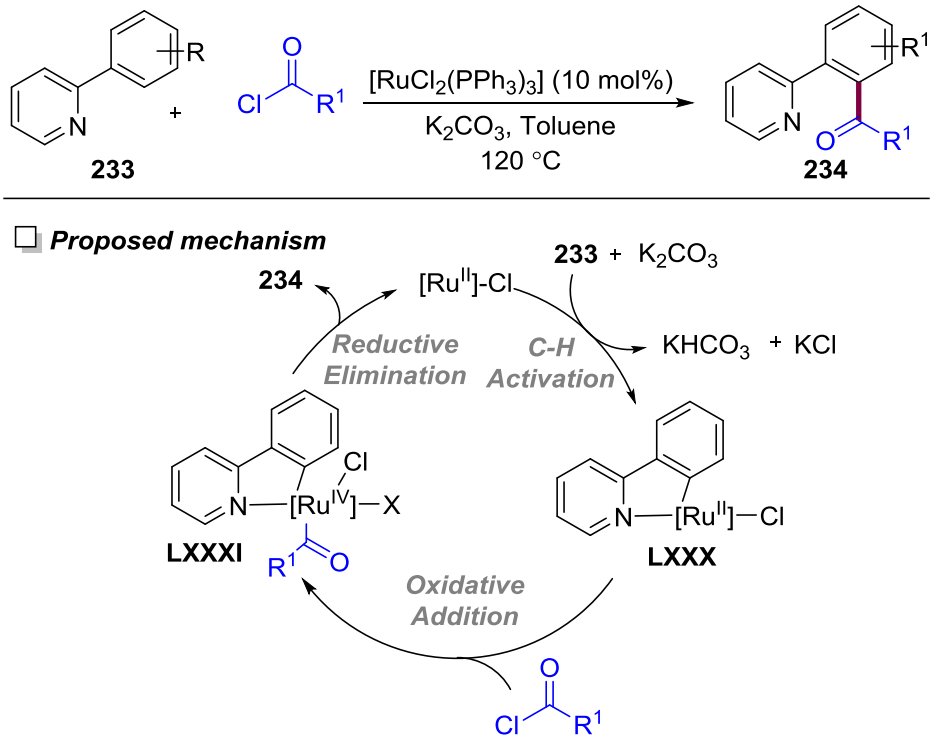
2.2.5. C–H Acylation with Acyl Chlorides

The group of Fumitoshi reported a novel ruthenium-catalyzed *ortho*-acylation of arylpyridines with acyl chlorides as acyl source.[191] Even though acyl chlorides are pre-activated reagents that generate halogenated waste, the use of ruthenium catalyst instead of the commonly utilized expensive palladium catalyst represented an important advantage. The optimal conditions were stablished with $[RuCl_2(PPh_3)_2]$ as catalyst and basic environment by adding excess of K_2CO_3. Under these conditions, substituted 2-arylpyridines were compatible with a vast array of benzoyl chlorides bearing electron-donating and withdrawing groups and α,b-unsaturated acyl chlorides which afforded the target acylated products **234** in low to excellent yields (Scheme 101). The use of $[RuCl_2(p\text{-cymene})]_2$ as catalyst also allowed the selective *mono*-acylation of 1-arylpyrazoles with both aromatic and aliphatic acyl chlorides as coupling partners.[192]

The mechanistic proposal involved the coordination of the Ru^{II} species to give the five-membered ruthenacycle **LXXX**. Then, the acyl chloride could undergo oxidative addition to **LXXX**, forming Ru^{IV} species

[191] Kochi, T.; Tazawa, A.; Honda, K.; Kakiuchi, F. *Chem. Lett.* **2011**, *40*, 1018.
[192] Liu, P. M.; Frost, C. G. *Org. Lett*. **2013**, *15*, 5862.

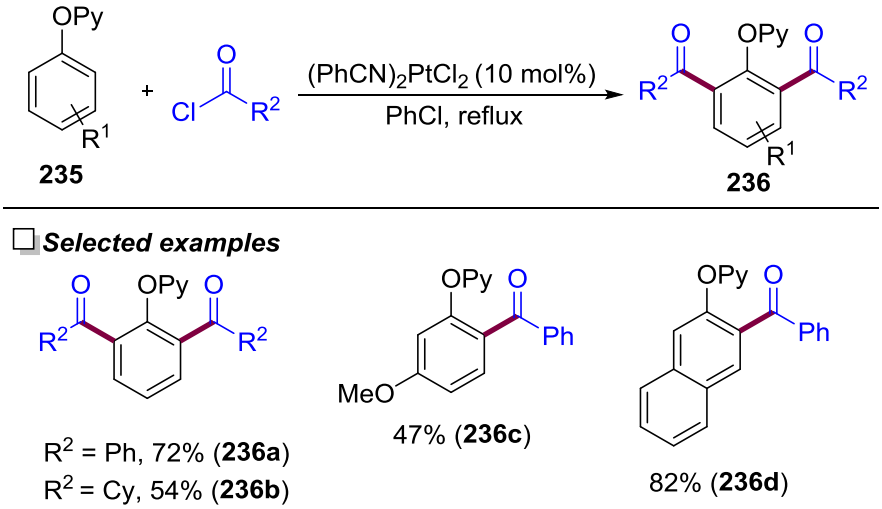
LXXXI. Finally, the reductive elimination of **LXXXI** would deliver the desired product **234** and the active Ru^{II} catalyst (Scheme 101).



Scheme 101. Ru-catalyzed C–H acylation of 2-arylpyridines with acyl chlorides.

Later on, the group of Huo employed acyl chlorides for the selective *di*-acylation of 2-aryloxypyridines catalyzed by $(PhCN)_2PtCl_2$.[193] This Pt-catalyzed *di*-acylation protocol was suitable for all types of acyl chlorides: aromatic (**235a**, **235c**-**d**), aliphatic (**235b**), heteroaromatic, and α,β-unsaturated acyl chlorides, which delivered the products **236** in moderate to excellent yields (Scheme 102). Interestingly, when the *meta*-position of the 2-phenoxypyridine was occupied, only *mono*-acylation occurred at the less congested *ortho*-position (**236c**) and in the case of 2-(2-naphthalenoxy)pyridine the acylation occurred exclusively at the 3-position (**236d**).

[193] McAteer, D. C.; Javed, E.; Huo, L.; Huo, S. *Org. Lett.* **2017**, *19*, 1606.

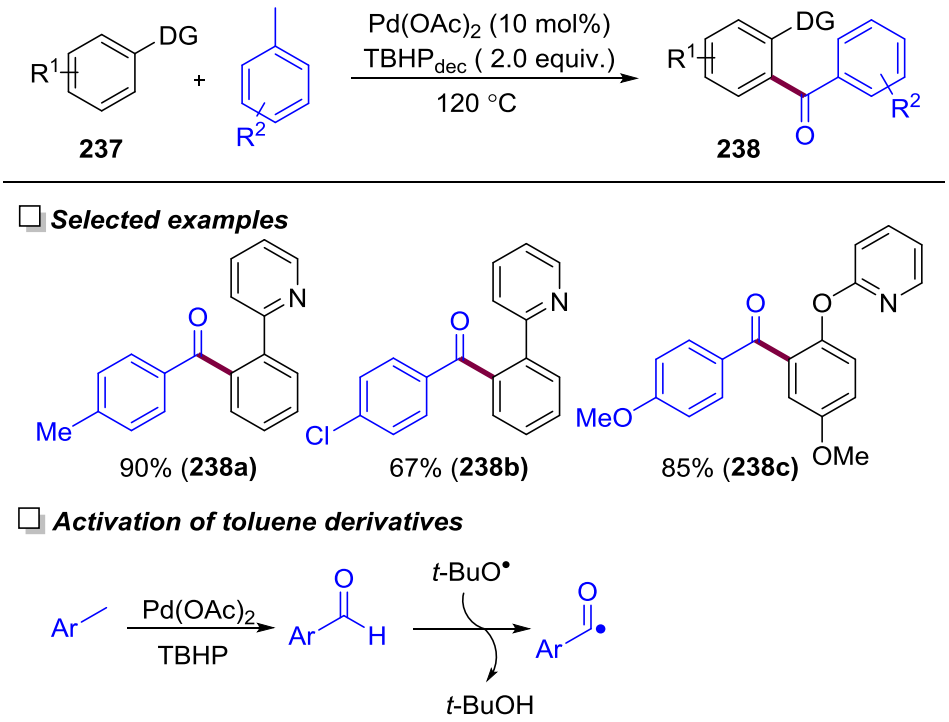


Scheme 102. Pt-catalyzed C–H acylation of 2-aryloxypyridines with acyl chlorides.

2.2.6. C–H Acylation with Toluenes

The use of toluene derivatives as acyl surrogates in C– H activation processes is a cost-efficient alternative and a direct route. The employment of toluene derivatives for direct C– H acylation through heterocycle-directed reactions was firstly described by Patel and co-workers.[194] The use of $Pd(OAc)_2$ as catalyst along with $TBHP_{dec}$ as oxidant, allowed the activation of xylenes, *p*-methoxy toluene and *p*-chloro toluene, which delivered exclusively *mono*-acylated products **238** in high yields. On the other hand, substrates such as in 2-arylpyridine (**238a-b**) and 2-aryloxypyridine derivatives (**238c**), had a similar trend in reactivity and selectivity (Scheme 103). Afterwards, the group of Xuan[195] and Chakraborti[196] extended the methodology employing a wide variety of *N*-Conatining heterocycles as directing groups. Regarding the activation of toluene derivatives, the authors proposed the *in situ* oxidation of toluene to the corresponding aldehyde which would be oxidate again to form the reactive acyl radical.

[194] Guin, S.; Rout, S. K.; Banerjee, A.; Nandi, S.; Patel, B. K. *Org. Lett*. **2012**, *14*, 5294.
[195] Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Zhang, S.-W.; Xuan, L.-J. *Tetrahedron* **2015**, *71*, 1574.
[196] Pipaliya, B. V.; Chakraborti, A. K. *J. Org. Chem.* **2017**, *82*, 3767.

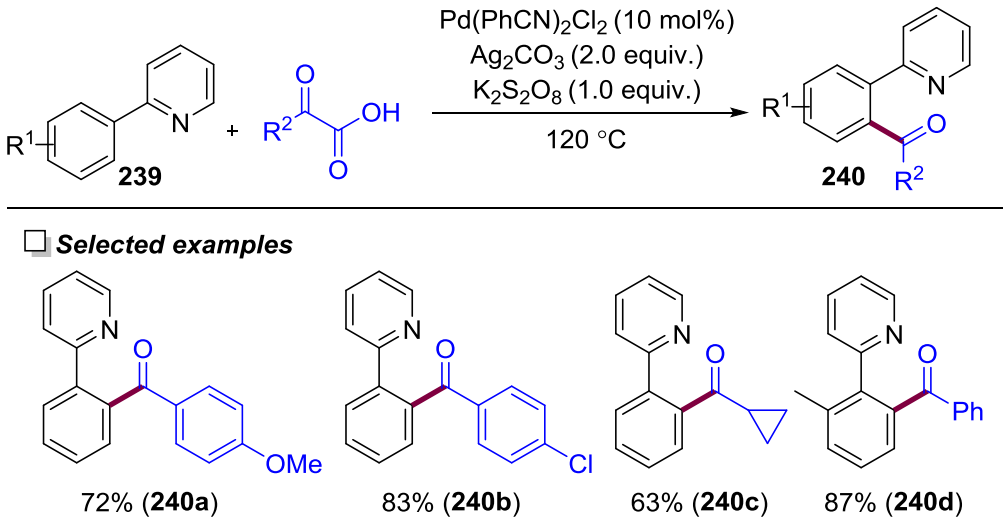


Scheme 103. Acylation of 2-arylpyridines and 2-aryloxypyridines with toluenes.

2.2.7. C–H Acylation with α-Oxocarboxylic Acids

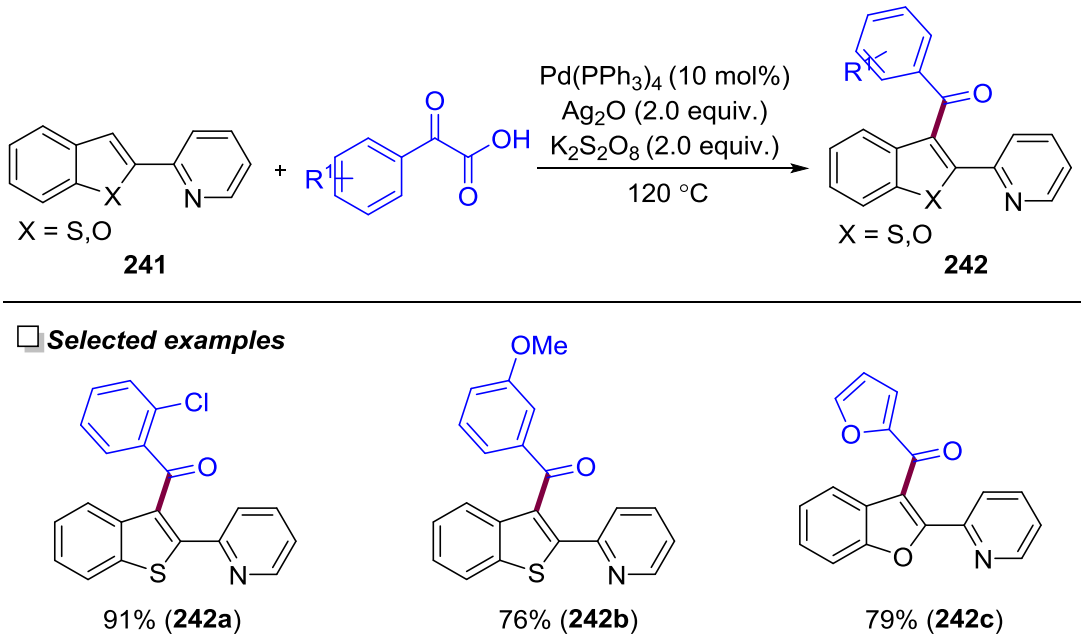
α-Oxocarboxylic acids compounds are less atom-economical and less abundant acyl sources than their parent aldehydes. However, the easy activation and high reactivity of these reagents have outweighed their drawbacks, making them usual reagents in the field of C– H activation. The first heterocycle-directed decarboxylative acylation of arenes was described by Ge and co-workers.[197] There, 2-arylpyridines were employed for the target acylation reaction with the use of α-oxocarboxylic acids which was accomplished with stoichiometric amounts of Ag_2O and $K_2S_2O_8$ along with $Pd(PhCN)_2Cl_2$ as catalyst. Besides the palladium catalyst, the use of Ag_2O was essential, probably due its role in the decarboxylation step, while the use of $K_2S_2O_2$ significantly improved the yield in the optimization reactions. With optimized conditions in hand, aromatic α-oxocarboxylic acids bearing electron-donating (**240a**) or withdrawing (**240b**) groups were effectively accommodated, while steric hindrance had a negative effect in the reaction outcome. In addition, aliphatic α-oxocarboxilic acids were also suitable (**240c**) as well as a short family of substituted 2-phenylpyridines (Scheme 104).

[197] Li, M.; Ge, H. *Org. Lett.* **2010**, *12*, 3464.



Scheme 104. Decarboxylative acylation of 2-arylpyridines.

Later on, the group of Lang reported a Pd-catalyzed C3-acylation of benzofurans and benzothiophenes with α-oxocarboxylic acids.[198] The installation of the pyridine moiety at C2-position of the substrates **241** acted as directing group enabling the acylation at the C3-position. As in the previous case (Scheme 104), the reaction required stoichiometric amounts of Ag_2O and $K_2S_2O_8$ with $Pd(PPh_3)_4$ as catalyst. A short variety of σ-keto acids

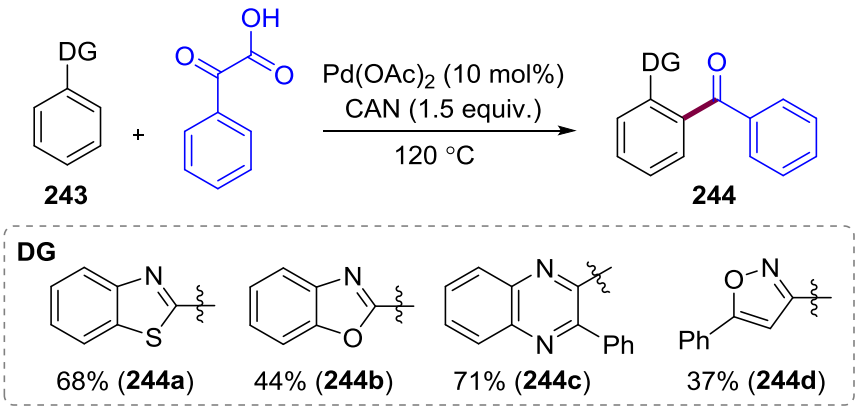


[198] Gong, W.-J.; Liu, D.-X.; Li, F.-L.; Gao, J.; Li, H.-X-: Lang, J.-P. *Tetrahedron*. **2015**, *71*, 1269.

Scheme 105. Pyridine-directed C3-acylation of benzofurans and benzothiophenes with α-oxocarboxylic acids.

were utilized to furnish the target compounds in high yields regardless of their electronic nature. It is noteworthy that heteroaromatic α-keto acids also provided the desired products (**242c**) in moderate yield (Scheme 105).

Alternatively, the employment of ceric ammonium nitrate (CAN) and palladium catalysis afforded the decarboxylative acylation of arenes with several *N*-containing heterocycles.[199] Interestingly, benzothiazole and 2,3-diphenylquinoxaline heterocycles delivered the corresponding products (**244a** and **244c**, respectively) in high yields, whereas heterocycles containing *N*- and *O*-chelating atoms such as benzoxazole or 3,5-diphenylisoxazole provided the expected *ortho*-acylated products (**244b** and **244d**, respectively) in comparatively lower yields (Scheme 106). The authors justified this distinct reactivity profile due to the affinity of the cerium atom with the oxygen of the directing group which could inhibit the oxidative ability of CAN.

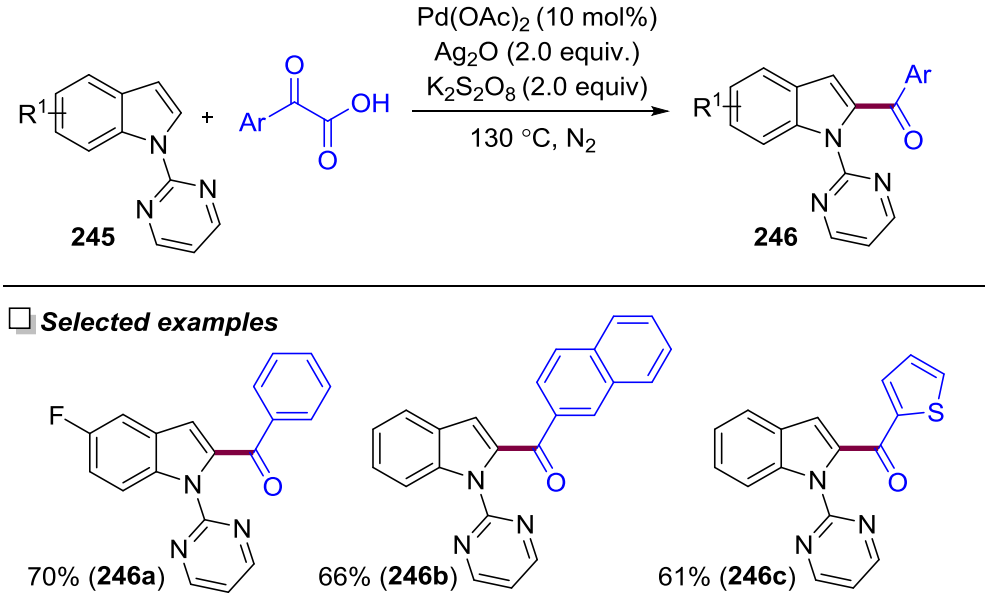


Scheme 106. Heterocycle-directed *ortho*-acylation of arenes with α-phenylglyoxylic acid.

The group of Zhu also exploited the use of α-oxocarboxylic acids for the selective C2-acylation of indoles directed by pyrimidine.[200] The C2-selectivity was achieved through the previously well-stablished coordination of Pd^{II} with *N*-pyrimidine moiety, while stoichiometric amounts of Ag_2O and $K_2S_2O_8$ enabled the activation of α-keto acids. Thereby, aromatic α-oxocarboxylic acids containing alkyl, halogen, naphthalene or heteroaromatic thiophene and furane proceed smoothly to furnish the final ketone products **246** in moderate

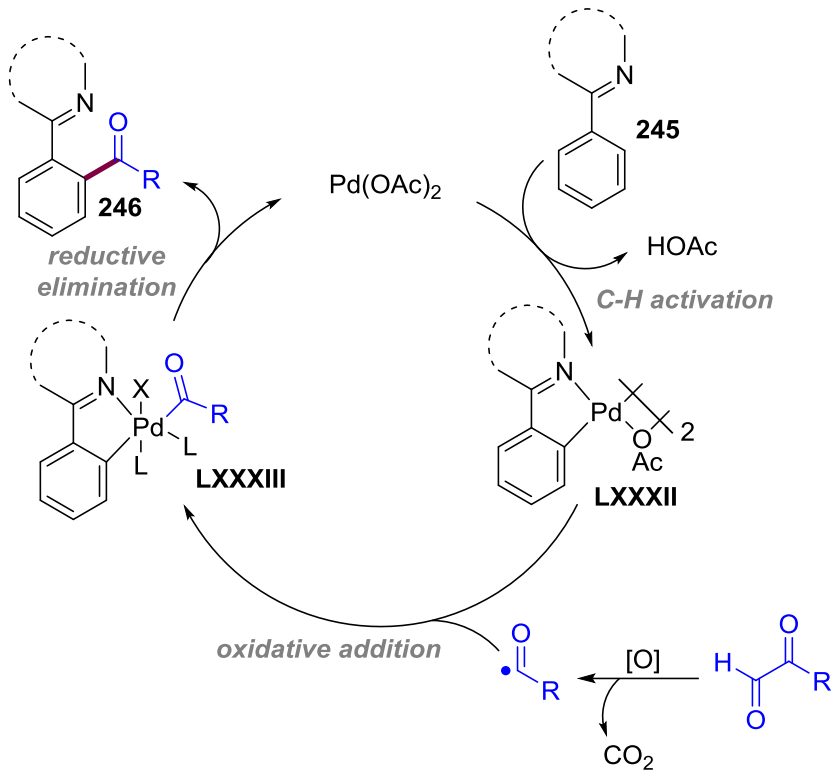
[199] Santra, S. K.; Banerjee, A.; Khatun, N.; Patel, B. K. *Eur. J. Org. Chem.* **2015**, 350.
[200] Pan, C.; Jin, H.; Liu, X.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 2933.

to good yields (Scheme 107). Regarding the substrate scope, indoles possessing electron-donating groups reacted more efficiently than those with electron-withdrawing groups.



Scheme 107. Pyrimidine-directed C2-acylation of indoles with α-oxocarboxylic acids.

The general mechanistic proposal for the Pd-catalyzed *ortho*-acylation of arenes with α-oxocarboxylic acids is described in the Scheme 108. Initially, heterocycle-directed C–H activation would occur to form palladacycle **LXXXII**. Thereafter, the palladacycle **LXXXII** would experience an oxidative addition by the acyl radical, which would be formed *in situ* through oxidative decarboxylation of the α-oxocarboxylic acid. Finally, reductive elimination from the putative Pd^{III} or Pd^{IV} intermediate **LXXXIII**[180] would afford the desired ketone product **156** and regenerate the active Pd^{II} catalyst.

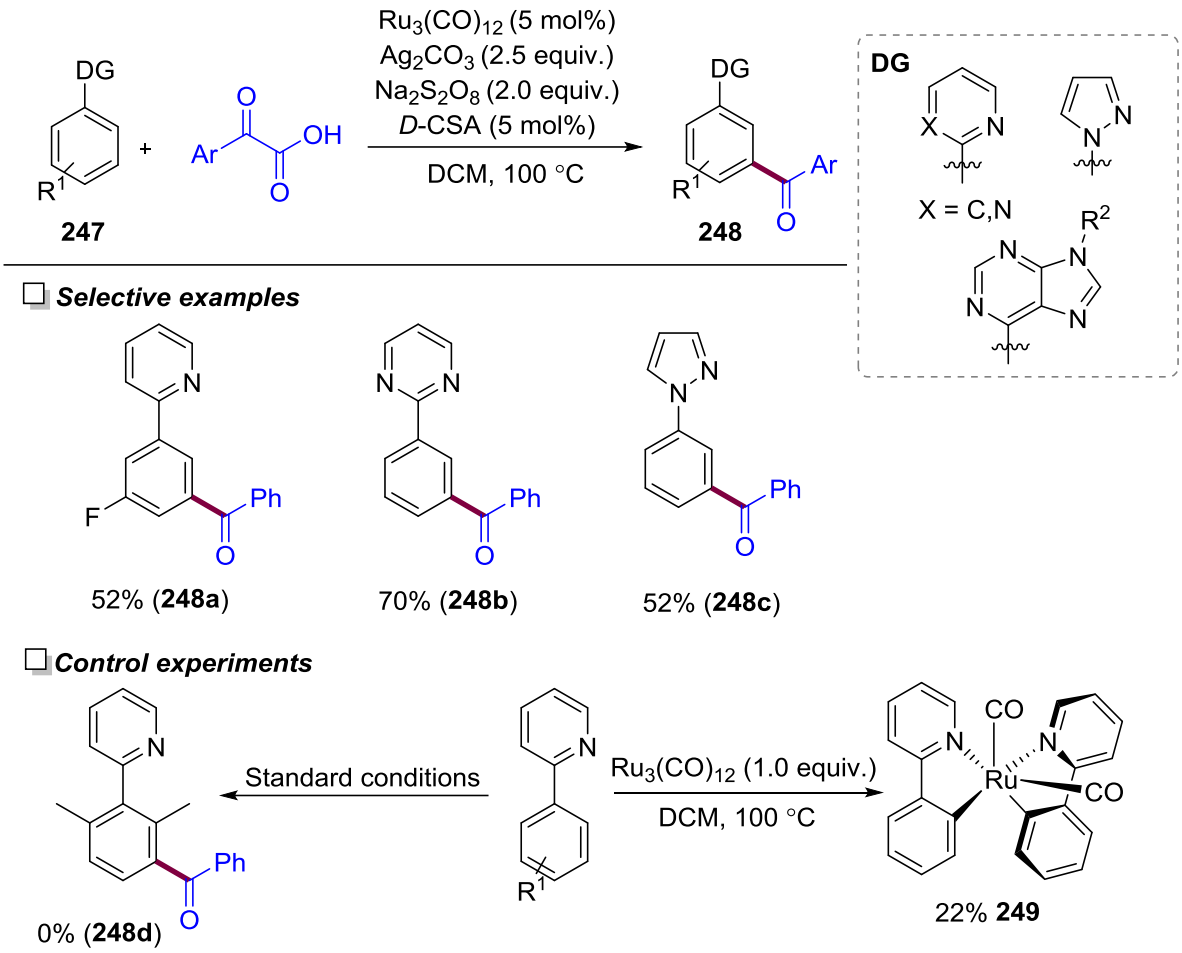


Scheme 108. Mechanism for the Pd-catalyzed *ortho*-acylation of arenes with α-oxocarboxylic acids.

Of paramount importance was the step forward achieved by the group of Wang featuring a Ru-catalyzed decarboxylative *meta*-acylation of 2-arylpyridines.[201] Among the tested Ruthenium catalysts, only $Ru_3(CO)_{12}$ along with Ag_2CO_3 delivered the desired *meta*-acylated product **248**. When the oxidant $Na_2S_2O_8$ was added in conjunction with camphorsulfonic acid (D-CSA) as additive the yield was increased and the optimal conditions were stablished with dichloromethane as solvent. Thereafter, the authors proceeded to evaluate the scope and functional group tolerance with respect to the 2-arylheterocycles. The *ortho-*, *meta-* and *para*-substituted 2-phenylpyridines were well-tolerated regardless of the electronic character of functional groups, where in some cases a mixture of *mono-* and *di*-acylated products **248** were obtained. Not only pyridine could be employed as the directing group, but also pyrimidine, pyrazole or even purine derivatives were suitable to promote the *meta*-acylation in moderate to good yields. On the other hand α-phenylcarboxylic acids bearing alkyl, (thio)ether, halogen, or nitrile afforded *meta*-acylated products **248** in moderate to good yields. Some control experiments were performed to gain some reaction insights, the substrate bearing two *ortho*-methyl groups failed to give product **248d** under standard conditions, which revealed the importance of the *ortho*-metallation step in the *meta*-acylation process. Complex **249** was isolated through stoichiometric amounts of

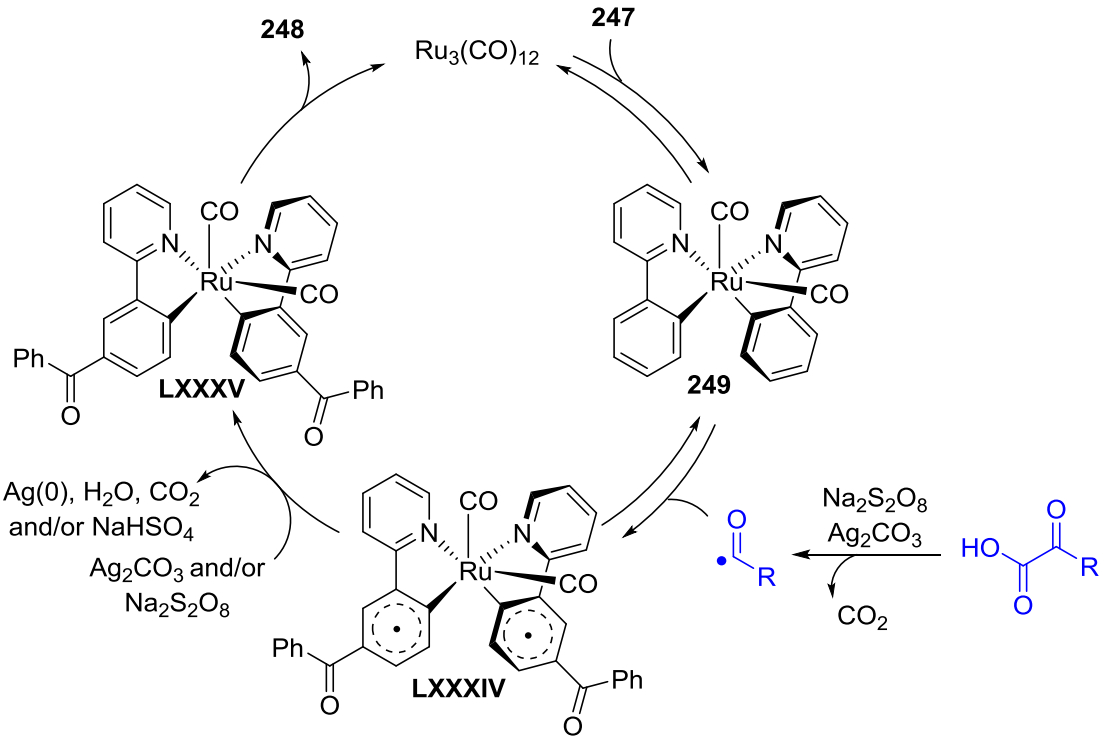
[201] Jing, K.; Li, Z.-Y.; Wang, G.-W. *ACS Catal.* **2018**, *8*, 11875.

ruthenium and catalytic experiments utilizing the latter gave the target product in good yield, indicating that **249** might be a competent intermediate in this reaction (Scheme 109).



Scheme 109. Ru-catalyzed meta-acylation of arenes with α-oxocarboxylic acids.

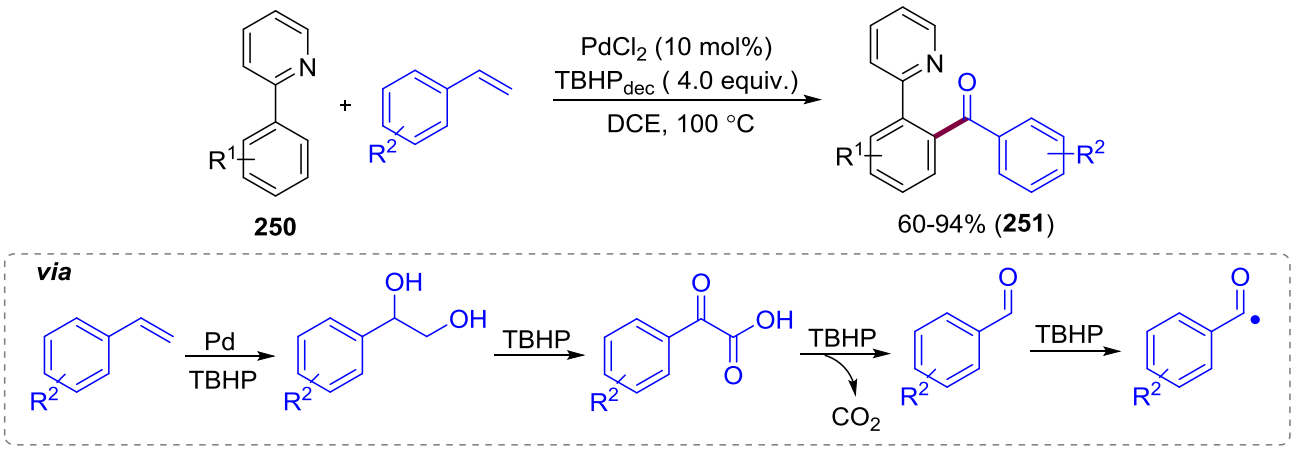
On the basis of mechanistic experiments and previous literature, a plausible mechanism was described (Scheme 109). At first, ruthenium intermediate **XCIII** would be formed through reversible C–H activation. A continuation, **XCIII** would undergo electrophilic attack by the acyl radical at *para*-position of the Ru–C, leading intermediate **XCIV**, which would be oxidized by Ag_2CO_3 and/or $Na_2S_2O_8$ furnishing the intermediate **XCV.** Finally, the desired *meta*-acylation product **158** would be released through protonation and ligand exchange of **XCV** with **157**, completing the catalytic cycle with the regeneration of intermediate **XCIII**.



Scheme 109. Mechanism for Ru-catalyzed *meta*-acylation of arenes with α-oxocarboxylic acids.

2.2.8. C–H Acylation With Styrenes

The use widely available styrenes as acyl surrogates was disclosed by the group of Bhanage for the *ortho*-acylation of 2-arylpyridines through palladium catalysis.[202] The optimal conditions were stablished with catalytic amounts of $PdCl_2$ and two equivalents of $TBHP_{dec}$ as oxidant. The key step in this reaction was the

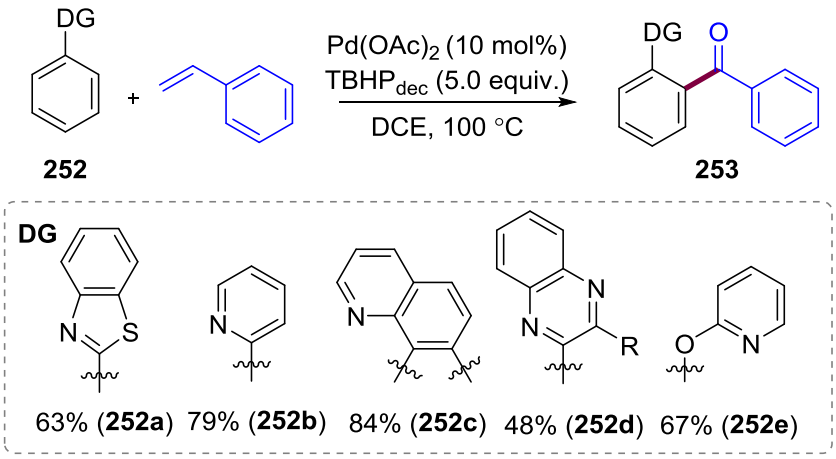


[202] Khemnar, A. B.; Bhanage, B. M. *Eur. J. Org. Chem.* **2014**, 6746.

Scheme 110. Pd-catalyzed *ortho*-acylation of 2-arylpyridines with styrenes.

activation of the styrenes through sequential oxidations with TBHP to form the acyl radical *in situ* (Scheme 110). Thereby, styrenes containing donating or withdrawing functional groups afforded the *mono*-acylated produts **251** in good to excellent yields. Additionally, the use of pyrazole as directing group also produced the desired produts, although, in lower yield.

Using the same approach, styrenes were employed as acyl source with a variety of *N*-containing heterocycles by the group of Patel.[203] As shown in the Scheme 111, heterocycles such us benzothiazole (**252a**), pyridine (**252b**), quinolone (**252c**), quinoxaline (**252d**), oxypyridine (**252e**) reacted with styrene to deliver final ketone **253** in moderate to high yields. Apart from simple styrene, other aromatic alkenes bearing electron-donating or withdrawing groups at *meta*- or *para*-position were suitable for this transformation. However, when alkynes were used as alkene surrogates, the yield drastically dropped.



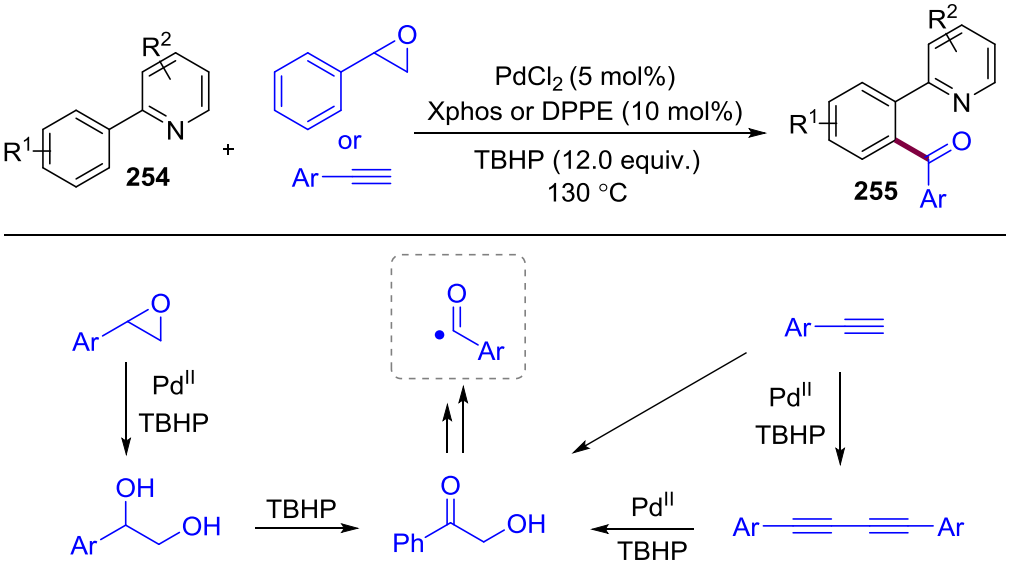
Scheme 111. Heteroclycle-directed *ortho*-acylation of arenes with styrenes.

2.2.9. C–H Acylation with Phenylacetylenes or Styrene Epoxides

The efficient implement of phenylacetylenes or styrene epoxide as acyl source for *ortho*-acylation of 2-arylpyridines was reported by the group of Li.[204] Optimized conditions were established with catalytic amounts of $Pd(OAc)_2$, Xphos or DPPE as ligand and high excess of TBHP (9-12 equiv.) which probably were required for the oxidation of styrene epoxide or phenylacetylenes into the corresponding acyl radical *in situ* (Scheme 112).

[203] Khatun, N.; Banerjee, A.; Santra, S. K.; Behera, A.; Patel, B. K. *RSC Adv.* **2014**, *4*, 54532.
[204] Zhang, Q.; Wang, Y.; Yang, T.; Li, L.; Li, D. *Tetrahedron*. **2016**, 57, 90.

Some substituents such as Me, OMe, F, Cl or Br were well-accomodated on both the 2-arylpyridines and aryl acetylenes, which afforded the final products **255** in moderate to good yields.



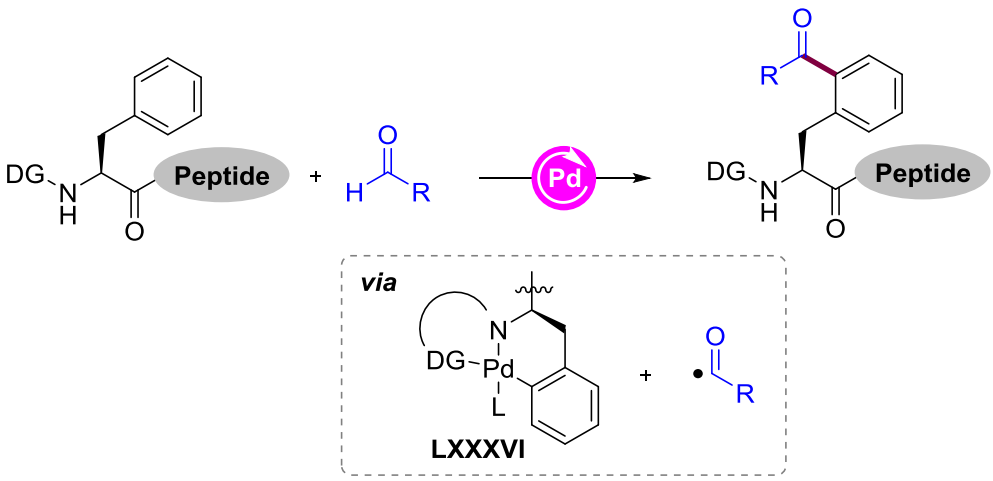
Scheme 112. Acylation of 2-arylpyridines with aryl acetylenes or styrene epoxide.

Despite all the reagents disclosed in this section to for the C(sp^2)– H radical acylation, the use of aldehydes represents the most straightforward and atom-economical manner to perform these transformation. Although most of the radical acylation procedures rely on the expensive and toxic palladium salts. In this aspect, an alternative transition metal would be highly desirable to achieve cheaper and sustainable radical acylations. Other acyl surrogates such as toluene or styrene represents a cheap and available option. However the scope is more limited than in the case of aldehydes, and the multiple oxidation step to form the corresponding acyl radical consumes bigger amount of oxidant and can generated undesired side-reactions. Finally, acyl chlorides are versatile reagent that compatible with multiple metals but the functional groups tolerance is lower and halogenated waste is generated during the transformation.

2.3. Pd-Catalyzed Site-Selective C(sp^2)– H Radical Acylation of Phenylalanine Containing Peptides with Aldehydes

As described along the introduction section, transition-metal-catalyzed C– H functionalization of peptides side-chains has gained tremendous interest in the last decade. The strategical introduction of *N*-containing heterocycles as directing groups has allowed the functionalization of aliphatic amino residues at β-, γ- or δ-position and the C(sp^2)–H diversification of the tryptophan moiety at the C2-position. However, this strategy has been scarcely explored for other aromatic residues such as phenylalanine, tyrosine or histidine. In the case of phenylalanine, few examples for the modification of simple Phe unit were known, and just recently, oxidative Heck reactions have been applied to phenylalanine-containing peptides and cyclopeptides by Wang[118] and Cross,[119] respectively. Inspired by the emerging trends in radical chemistry, we envisioned that the use of cheap and widely available aldehydes in combination with palladium catalysis could enable the selective, yet unprecedented, C(sp^2)–H acylation of Phe unit and Phe-containing peptides.

We anticipated that that this approach would require a directing group (DG) to reach the target C–H bond upon the formation of 6-membered palladacycle **LXXXVI**, which could further react with the corresponding *in situ* formed acyl radical species (Scheme 113).



Scheme 113. General strategy for the site-selective Pd-catalyzed C(sp^2)–H acylation of Phe-containing peptides.

If successful, this reaction would represent the first example of late-stage acylation of peptides and would conceptually differ from previously described methods as this acylation would occur through a radical

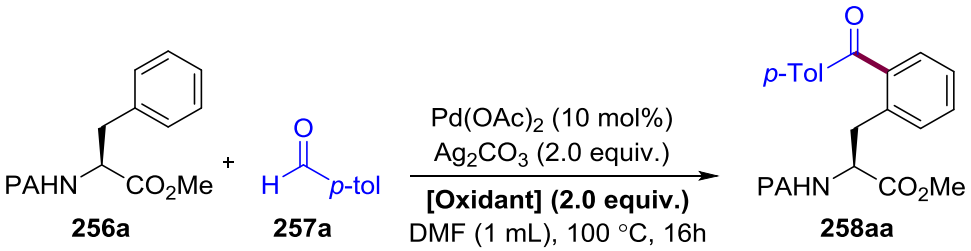
pathway, whereas most existing methodologies relied on traditional approaches such as cross-coupling reactions with aryl halides, boranes, alkenes, etc. Thus, for the present project we established the following objectives:

- To report the first late-stage peptide acylation process.
- To explore the use of aryl, heteroaryl and alkyl aldehydes as acyl source.
- To stablish a racemization-free and scalable transformation.
- To achieve high chemo- and site-selective acylations.

2.3.1. Optimization Process

A simple system was chosen to evaluate the feasibility of our synthetic protocol, in which picolinamide (PA) protected L-Phe-OMe (**256a**) was selected as substrate to react with *p*-tolyl aldehyde (**257a**) as the model reaction. This auxiliary has shown great abilities as directing group (DG) with palladium catalysts for C–H diversification of peptides and pyridine or relative heterocycles have enabled C–H acylation reactions with aldehydes, so we envisioned that PA could be a suitable DG for this specific transformation. On the other hand, commonly utilized $Pd(OAc)_2$ was selected as preliminary catalyst along with two equivalents of Ag_2CO_3 as additive which could help to enhance the concerted-metallation-deprotonaton (CMD) step and also could act as oxidant in the Pd^{II}/Pd^{III} or Pd^{II}/Pd^{IV} catalytic cycle.[205] Regarding to the other parameters, DMA was establish as the solvent, 110 °C of temperature and argon atmosphere were employed. Under these conditions, several oxidants were tested (Table 20, entries 1-9) as is shown in the Table 20. The role of the oxidant is undoubtedly important in C–H acylation reactions with aldehydes, as it oxidizes the aldehyde to form the corresponding active acyl radical and can also act as terminal oxidant within the catalytic cycle. With the use of inorganic oxidants, the target product **258aa** was not observed (Table 20, entries 1-3), while all the organic peroxides delivered the final product **258aa** in good to high yields and good *mono*/*di*-acylation ratio (Table 20, Entries 4-7). The TBHP in aqueous solution and DTBP produced similar outcomes with respect to yield and *mono*-selectivity (Table 20, Entries 4 and 6). Switching the TBHP aqueous to TBHP in decane solution had a positive effect and the yield was slightly improved (Table 20, entry 5). However, the best result was obtained with the use of DCP, which delivered the product **258aa** with a remarkable 78% yield and moderate *mono*-selectivity (6:4) (Table 20, entry 7). Unfortunately, with more sustainable and cheap oxidants such as H_2O_2 and oxygen, the starting material remained intact (Table 20, entries 8-9).

[205] Mudarra, A. L.; Martínez de salines, S.; Pérez-temprano, M. H. *Org. Biomol. Chem*. **2019**, *17*, 1655.

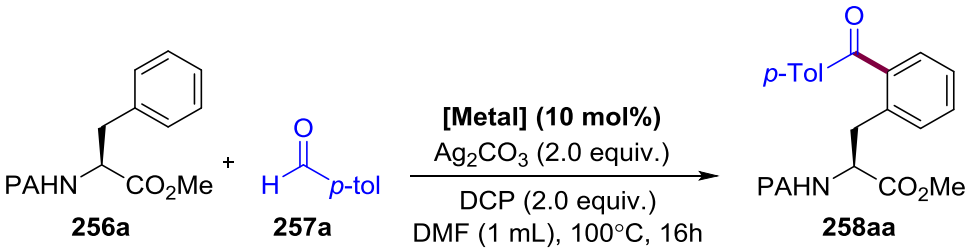


Entry	Oxidant	Yield (%)[b,c]
1	$(NH_4)_2S_2O_8$	0
2	$K_2S_2O_8$	0
3	Oxone	0
4	$TBHP_{aq}$	63 (72:28)
5	$TBHP_{Dec}$	72 (69:31)
6	DTBP	64 (8:2)
7	DCP	88 (6:4)[d]
8	H_2O_2	0
9	O_2 (1 atm)	0

[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), dry DMF (1ml), Ar, 16h at 100 °C. [b] Conversion determined by ^1H NMR analysis. [c] Ratio of mono- and diacylated product **258aa**:**258'aa**.[d] Yield of isolated product after column chromatography.

Table 20. Screening of oxidants.

In order to evaluate the sustainability of the process, we next explored the acylation of PA-Phe-OMe In the presence of other cost-efficient catalysts (Table 21, Entries 1-7). Among the first-row metals, sustainable $Mn(OAc)_2$ or cheaper alternatives to $Pd(OAc)_2$ such as $Ni(acac)_2$ or $Co(acac)_2$ were shown unreactive and the starting material was recovered (Table 21, Entries 2-4). Unlike Ru catalysts have proven efficient in C–H of simple arenes;[201] unfortunately, the tested Ru sources were not efficient to perform the parent acylation in a more complex Phe unit and the starting material was recovered instead (Table 21, Entries 5-7).

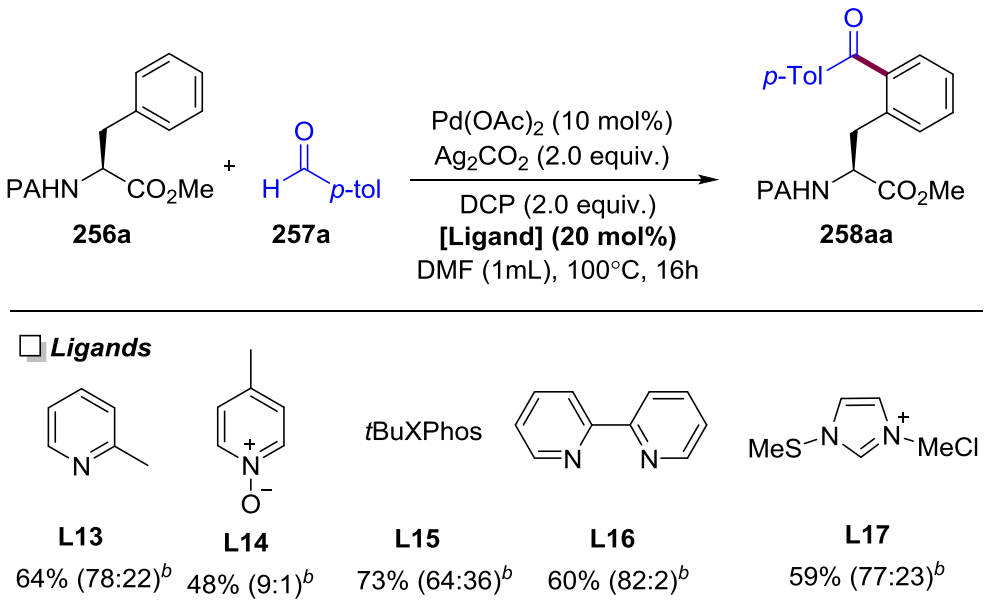


Entry	Oxidant	Yield (%)[b]
1	$Pd(OAc)_2$	88 (6:4)
2	$Mn(OAc)_2$	0
3	$Ni(acac)_2$	0
4	$Co(acac)_2$	0
5	$Ru_3(CO)_9$	0
6	$RuCl_3$	0
7	$[RuCl(p\text{-cymene})]_2$	0

[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.5 mmol), [M] (10 mol %), Ag_2CO_3 (2.0 equiv.), dry DMF (1 mL), Ar, 16h at 110 °C. Yield of isolated product after column chromatography. [b]Ratio of mono- and diacylated product **258aa:258aa'**.

Table 21. Screening of metals.

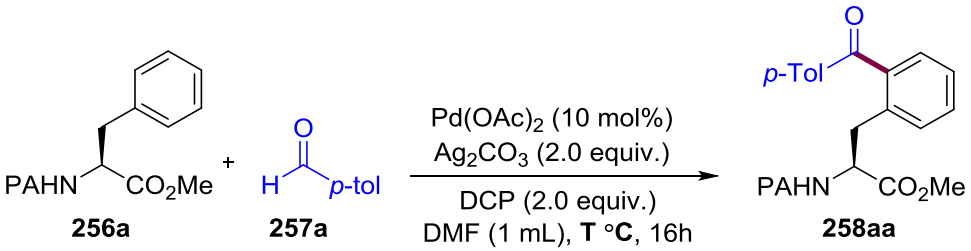
With the aim of improve the *mono*-selectivity, some common ligands in related Pd-catalyzed C–H functionalization were tested as is depicted in Scheme 114. Pyridine-type ligands 2-picoline (**L13**) and 2,2´-bipyridine (**L16**) improved the *mono*-selectivity but at significant cost on the yield. With the use of 4-picoline *N*-oxide (**L14**) as ligand, the reaction exhibited great selectivity but the yield dropped from 78% to 48%. Finally, phosphine-type ligand *t*BuXPhos (**L15**) delivered the product **167aa** in high yield along with good selectivity and the imidazolium-type ligand **L17** delivered **258aa** in moderate yield and high selectivity. Careful analysis of these results evidenced that high selectivity toward the targeted *mono*-acylation product was achieved at expense of lower conversion, that is, the higher yield the lower the selectivity. Accordingly, we continued our screening studies without an external ligand because in its absence a good balance between yield and *mono*-selectivity was achieved (88 % yield, 6:4 ratio, table 8, entry 1).



[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), [Ligand] (20 mol%), dry DMF (1ml), Ar, 16h at 100 °C. Conversion determined by ^1H NMR analysis. [b]Ratio of mono- and diacylated product **258aa**:**258aa'**.

Scheme 114. Screening of ligands.

Next, we decided to evaluate the effect of the temperature, so the model reaction was set up at different temperatures (Table 22). The screening clearly revealed that the sweet spot was at 100 °C, which furnished the product **258aa** in high yield (79%) along with some *mono*-selectivity (6:4) (Table 22, entry 2). At 90 °C some starting material remained unreactive (Table 22, entry 1) and at higher temperatures (110-130°C) some degradation was observed, which resulted in lower yields (Table 22, entries 3-5).

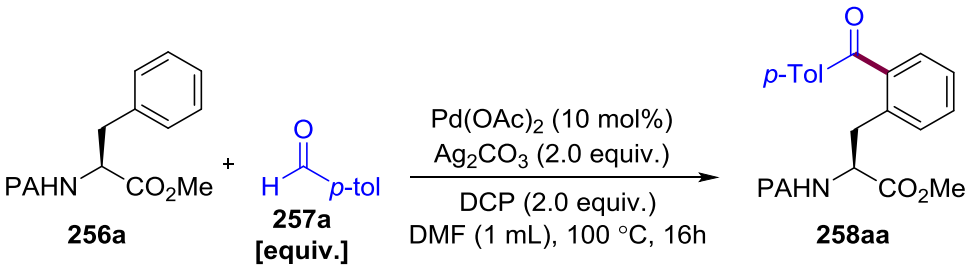


Entry	T(°C)	Yield (%)[b,c]
1	90	54 (85:15)
2	100	88 (6:4)[d]
3	110	66 (83:17)
4	120	63 (78:22)
5	130	61 (75:25)

[a]Reaction conditions: **256a** (0.25mmol), **257a** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), [T] (°C), dry DMF (1 ml), Ar, 16h at 110 °C. [b] conversion determined by ^1H NMR analysis. [c]Ratio of mono- and diacylated product **258aa**:**258aa'**.[d] Yield of isolated product after column chromatography.

Table 22. Screening of temperature.

In order to adjust the aldehyde equivalents to improve the *mono*-selectivity of product **258aa**, a small screening was set up using 4-6 equivalents of aldehyde **258a** (Table 23). As expected, by reducing the aldehyde equivalents the selectivity improved but the yield was slightly lower. However, when using 5.0 equivalents of aldehyde the yield was maintained considerably high (79%) and the *mono*-selectivity was improved from 6:4 obtained with 6.0 equivalents to 7:3 (Table 23, entry 2).

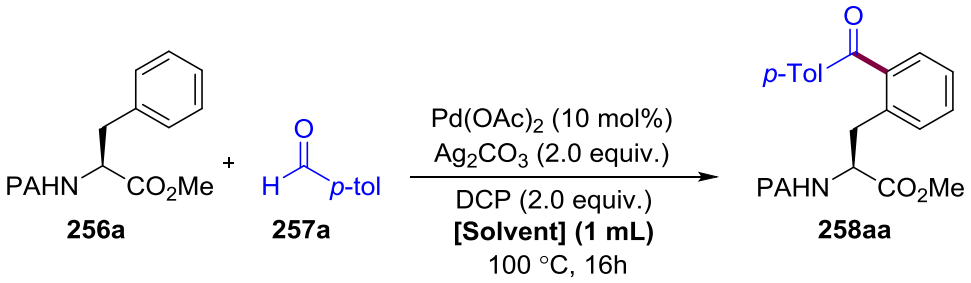


Entry	Equiv. of **166a**	Yield (%)[b,c]
1	4	73 (75:25)
2	5	79 (7:3)[d]
3	6	88 (6:4)

[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.0-1.5 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), dry DMF (1 ml), Ar, 16h at 100 °C. [b] conversion determined by ^1H NMR analysis. [c]Ratio of mono- and diacylated product **258aa**:**258aa'**.[d] Yield of isolated product after column chromatography.

Table 23. Screening of aldehyde equivalents.

Afterwards, the effects of commonly utilized organic solvents was explored (Table 24). Interestingly, regardless the polarity of the solvent the final product was obtained in high yields (Table 24, entries 1-5). For example, DCE slightly improved the yield (Table 24, entry 2) and toluene gave exactly the same yields (Table 24, entry 3). Whereas other solvents delivered *mono*- and *di*- product in equal ratios (Table 24, entries 3-5) and in the case of DCE, it preferentially gave the *di*-acylated product **258aa'** (Table 24, entry 2). The yield was slightly reduced with solvents such as PhCl or dioxane (Table 24, entries 4-5). However, the main difference was in the department of *mono*-selectivity, in which DMF clearly outperformed the other solvent tested obtaining product **258aa** with a 7:3 *mono*:*di* ratio (Table 24, entry 1).



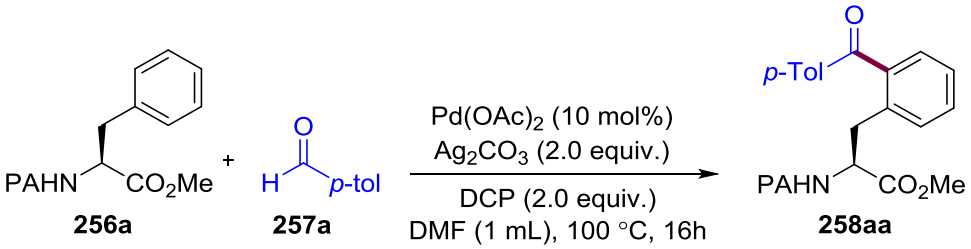
Entry	Solvent	Yield (%)[b,c]
1	DMF	79 (7:3)[d]
2	DCE	84 (38:62)
3	Toluene	79 (54:46)
4	PhCl	75 (48:54)
5	Dioxane	75 (55:48)

[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), dry solvent (1 ml), Ar, 16h at 110 °C. [b] conversion determined by ^1H NMR analysis. [c]Ratio of mono- and diacylated product **258aa**:**258aa'**.[d] Yield of isolated product after column chromatography.

Table 24. Screening of solvents.

Once we stablished the optimal conditions, some control experiments were performed (Table 25). As expected, the role of both $Pd(OAc)_2$ as catalyst and DCP as oxidant were crucial for the success of the transformation as not even traces of **258aa** were observed in their absence (Table 25, entries 2 and 3, respectively). As highlighted before, the synergy between palladium and silver salts its well-known in the field of C–H functionalization. In this case, the addition of different amounts of Ag_2CO_3 enhanced the production of **258aa** (Table 25, entry 1, entries 5-6), where the best result was obtained with 2.0 equivalents of Ag_2CO_3 (Table

25, entry 1). Importantly, undesirable reaction such as the functionalization of α- and β-C(sp^3)–H bond of the Phe backbone or the possible decarbonyltive alkylation were not observed.



Entry	$Pd(OAc)_2$	DCP	Ag_2CO_3	Yield of 3a (%)[b,c]
1	Yes	Yes	Yes (2.0 eq.)	79 (7:3)[d]
2	No	Yes	No	0
3	Yes	No	Yes	0
4	Yes	Yes	No	56 (82:18)
5	Yes	Yes	Yes (0.5 eq.)	65 (7:3)
6	Yes	Yes	Yes (1.0 eq)	71 (7:3)

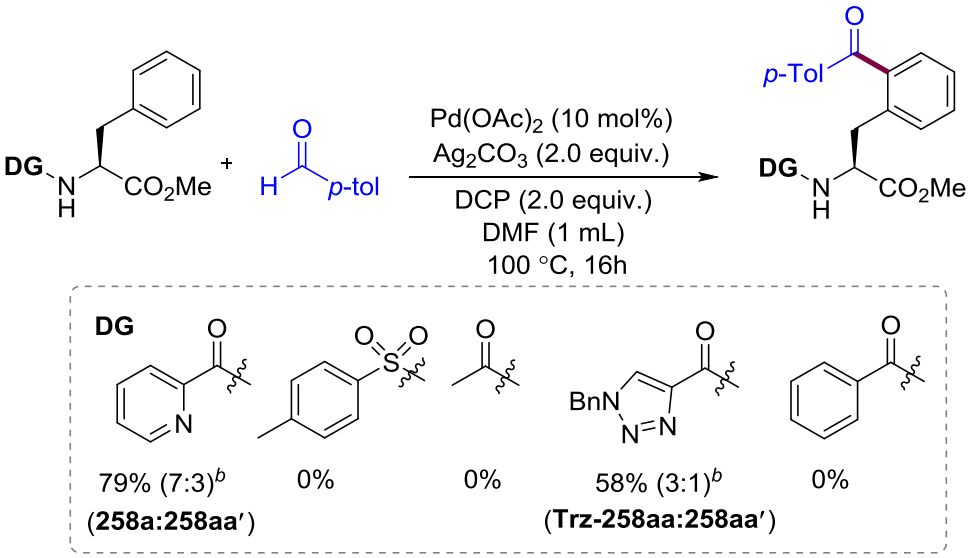
[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), dry DMF (1 ml), Ar, 16h at 100 °C. [b] conversion determined by ^{1}H NMR analysis. [c]Ratio of mono- and diacylated product **258aa**:**258aa'**.[d] Yield of isolated product after column chromatography.

Table 25. Control experiments.

Finally, aside from picolinamide, other directing groups were tested (

Scheme **115**). The role of the *N*-chelating heterocycle was essential as benzoyl-, tosyl- or acetyl-protected substrates remained unreactive. Importantly, medicinally relevant 1,2,3-triazole[206] was proven an efficient DG within the process, albeit the product was obtained in lower yields.

[206] Guerrero, I.; Correa, A.; *Eur. J. Org. Chem*. **2018**, 6034.



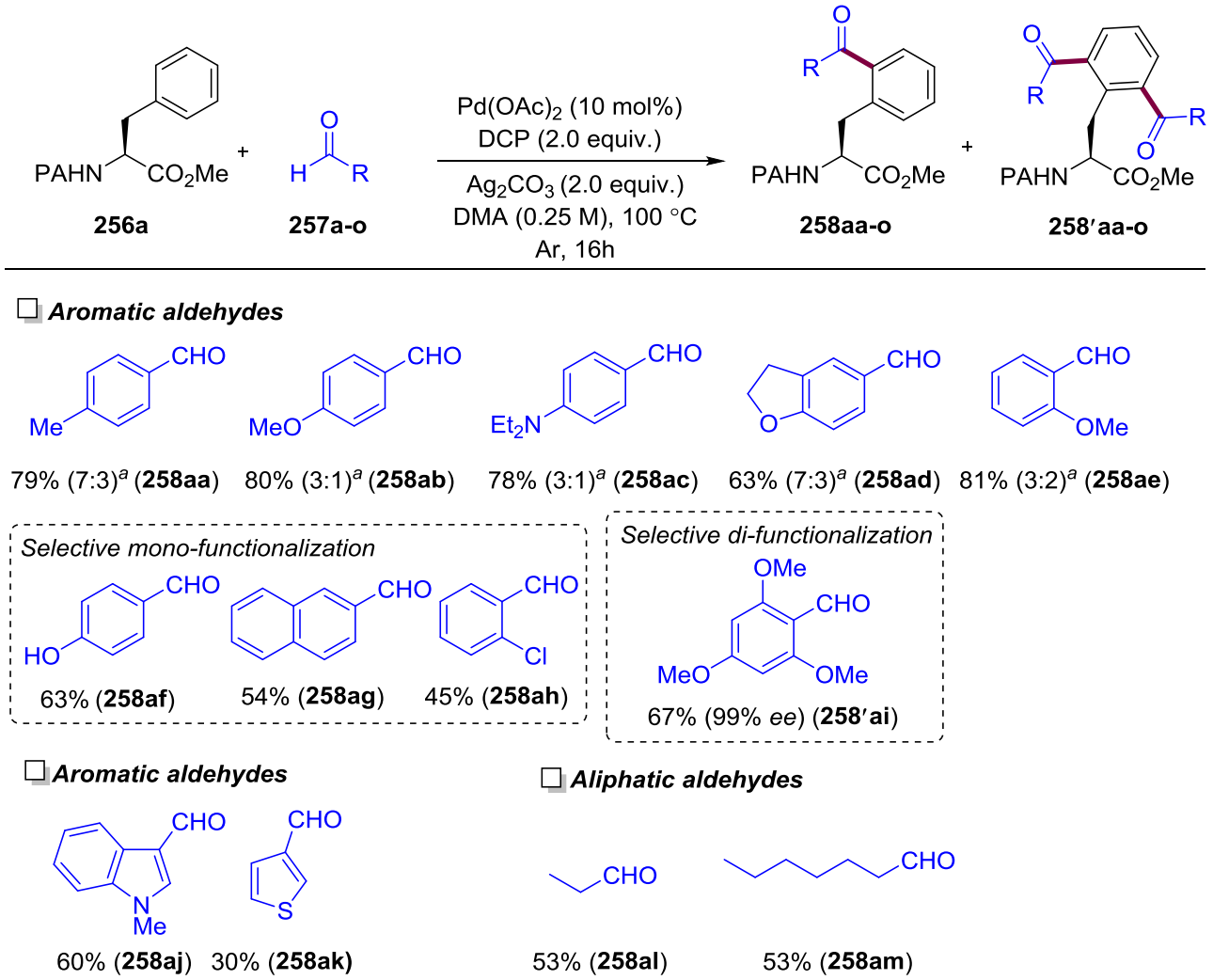
[a]Reaction conditions: **256a** (0.25 mmol), **257a** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), dry DMF (1 ml), Ar, 16h at 100 °C. Yield of isolated product after column chromatography. [B]Ratio of mono- and diacylated product **258aa**:**258aa'**.

Scheme 115. Screening of directing groups.

2.3.2. Scope of Aldehydes

With the optimized conditions in hand, the robustness of the process was explored with the reaction between Phe derivative **256a** and a wide variety of aldehydes. As shown in Scheme 116, different types of aldehydes reacted smoothly to furnish the target products **258aa-o** in moderate to excellent yields. Aromatic aldehydes including OMe (**257b** and **257e**), Et_2N (**257c**) and 2,3-dihydrofuryl (**257d**) delivered the corresponding products **258ab**-**d** in high yields with the preferential formation of the *mono*-acetylated product, which could be easily purified through column chromatography. However, the highly electron-rich 2,4,6-trimethoxybenzaldehyde **257i** exhibited a major reactivity, which resulted in the exclusive formation of the *di*-acetylated product **258'ai** in 67% yield. The latter compound could be crystallized and its absolute configuration was confirmed by X-ray analysis. Contrary to other electron-rich aldehydes, the *p*-hydroxybenzaldehyde **257f** afforded only the *mono*-acylated product **258af**, which could be attributed to the inhibitory effect of the hydroxy group within the catalytic cycle. Consequently, the lower reactivity of electron-poor aldehydes resulted in total selectivity toward the *mono*-acylated products and **258ag**-**h** were obtained in moderate yields. To our delight, aliphatic aldehydes also resulted in efficient acylation reactions, which gave selectively the corresponding *mono*-acylated products **258am-n** in moderate yields. Remarkably, biologically relevant *N*-methylindolyl (**258aj**) and 2-thienyl carboxaldehyde (**258ak**) also could be accommodated, furnishing the corresponding *mono*-acylated products **258aj**-**k**. It is worth mentioning that the activation of aldehydes was preferential over susceptible

C(sp³)–H bonds adjacent to nitrogen or oxygen atoms, whereas aldehydes bearing alkenes or ferrocene motif were not compatible with this transformation.



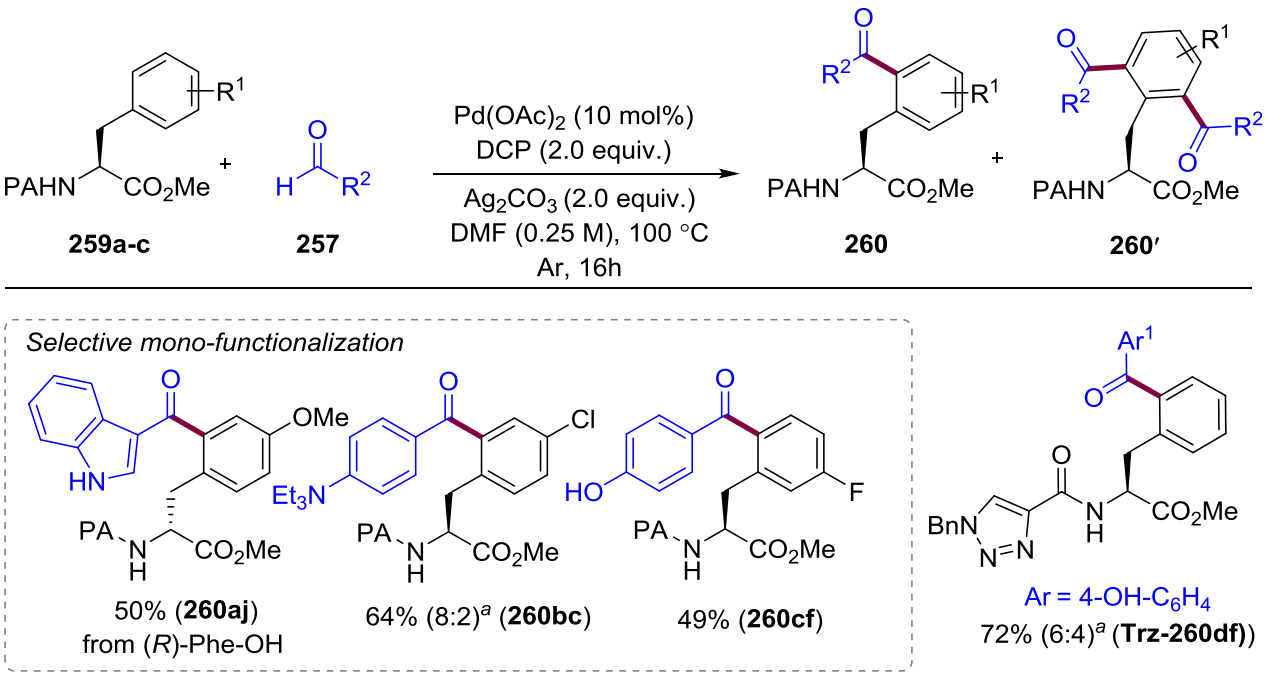
Reaction conditions: **256a** (0.25 mmol), **257a** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), DMF (1 ml), Ar, 16h at 100 °C. Yield of the isolated product after column chromatography. [a] Ratio of *mono*- and *di*-acylated product **258aa**:**258aa**'.

Scheme 116. Pd-catalyzed δ-C(sp²)–H acylation of Phe unit with aldehydes.

2.3.3. Scope of Phe Derivatives

Next, some substituted Phe were tested as substrates for this site-selective C–H acylation process (Scheme 117). In the case of *p*-OMe and *p*-Cl substituted Phe, they had similar trend in reactivity and selectivity as the unsubstituted Phe, obtaining the target products **260** in good yield and total or high *mono*-selectivity. Interestingly, when *m*-F substituted Phe was employed, only *mono*-acetylated product **260cf** was isolated, in

which the less sterically hindered *ortho*-position was exclusively functionalized. As observed before, not only PA could be employed as directing group, but also the 1,2,3-triazole moiety enabled the target C–H acylation reaction (**Trz-260df**) in high yield and moderate selectivity.

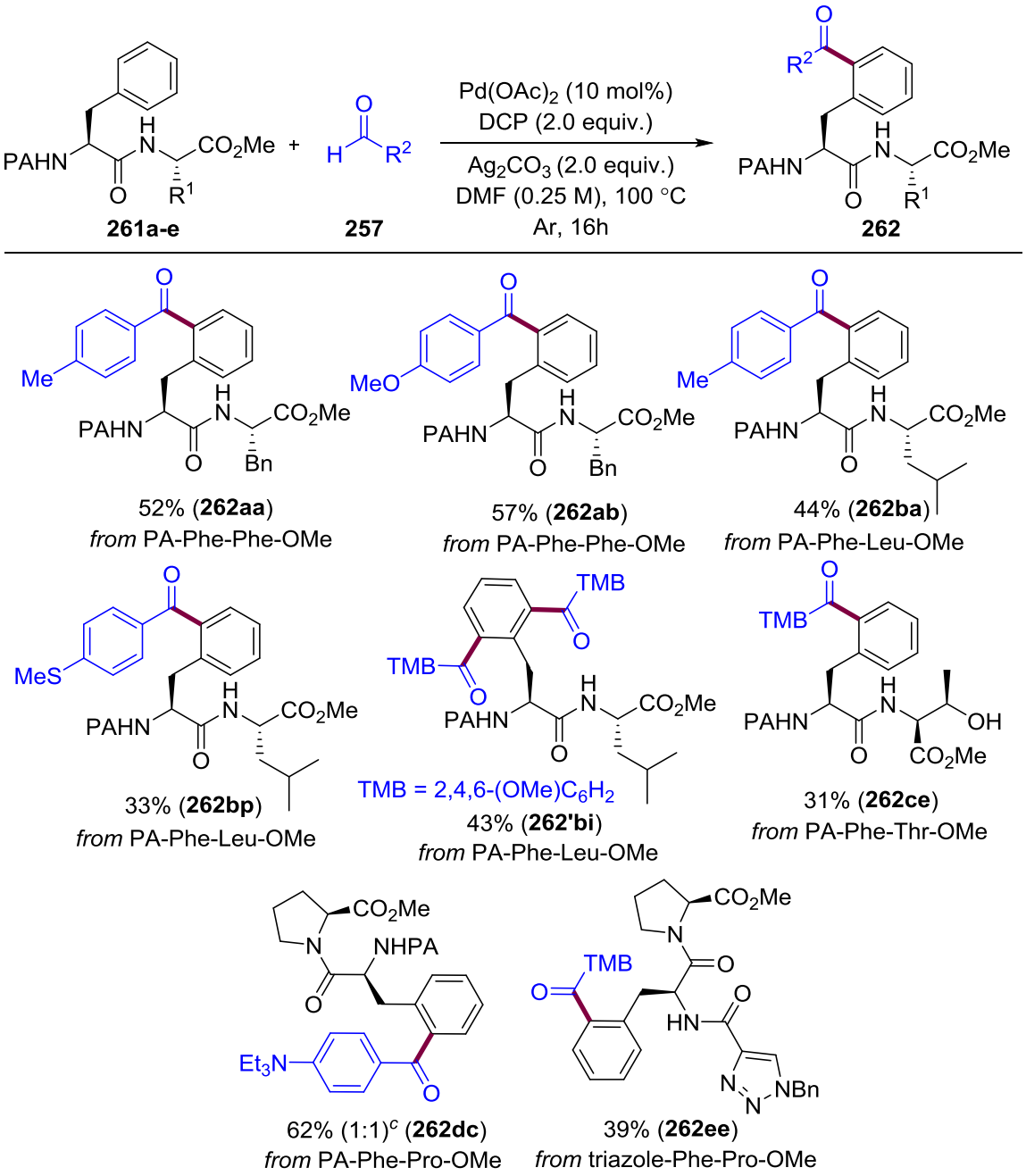


Reaction conditions: **259** (0.25 mmol), **257** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), DMF (1 ml), Ar, 16h at 100 °C. Yield of the isolated product after column chromatography. [a] Ratio of *mono*- and *di*-acylated product **260**:**260′**.

Scheme 117. Pd-catalyzed δ-C(sp^2)–H acylation of Phe unit derivatives with aldehydes.

2.3.4. Scope of Phe-Containing Dipeptides

Encouraged by these results, we turned our attention to the more challenging late-stage-functionalization of peptides. We first prepared by conventional peptide chemistry a short family of PA-Phe-containing peptides and further evaluated their reactivity within our radical acylation technique. Herein, dipeptides containing Phe (**261a**), Leu (**261b**) and Pro (**261d-e**) residues successfully underwent the target PA-directed acylation reaction with benzaldehydes on the terminal Phe unit (Scheme 118). Remarkably, the hydroxyl group of the Thr residue of dipeptide **262ce** remained intact after the oxidative transformation. Furthermore, the use of 1,2,3-triazole moiety as directing group also afforded the desired product **262ee** in modest yield. Importantly, the absence of a racemization process was verified by NMR analysis, wherein a single diastereoisomer was observed in all cases.



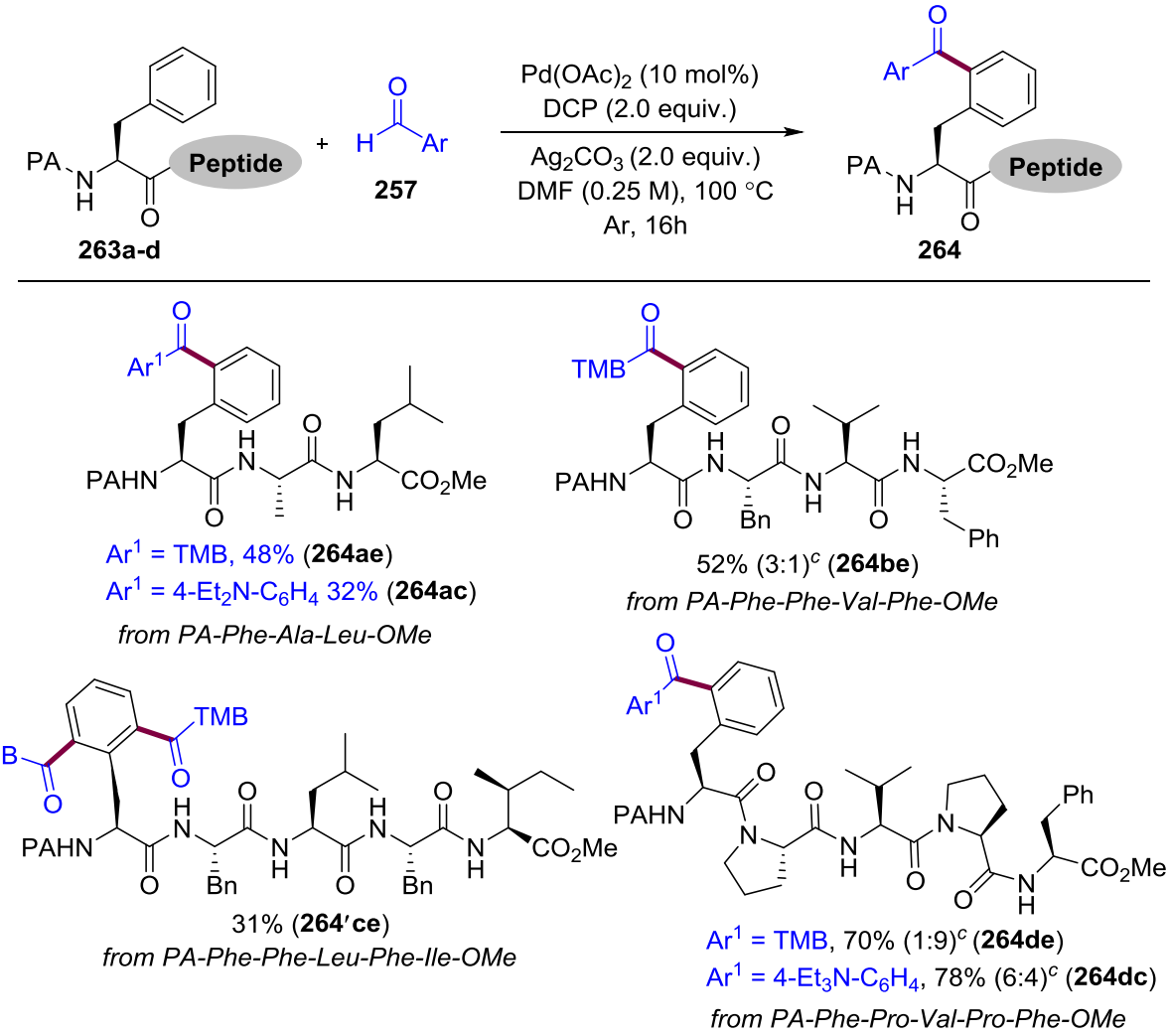
Reaction conditions: **261** (0.25 mmol), **257** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), DMF (1 ml), Ar, 16h at 100 °C. Yield of the isolated product after column chromatography. [a] Ratio of *mono*- and *di*-acylated product **262**:**262'**.

Scheme 118. Pd-catalyzed δ-C-(sp²)–H acylation of Phe-containing dipeptides with aldehydes.

2.3.5. Late-Stage Acylation of Phe-Containing Peptides

Encouraged by these results, we further evaluated the feasibility of tagging more complex peptide settings and collection of more complex oligopeptides was synthesized following traditional peptide

chemistry. The robustness of our protocol was further proven when the site-selective C–H acylation of tri- (**264ae** and **264ac**), tetra- (**264be**) and even pentapeptides (**264'ce**, **264de** and **264dc**) was accomplished in moderate to high yields (Scheme 119). As expected, the additional amide groups of the peptide chain had an inhibitory effect through *N,N*-chelation with the catalyst. In this light, with the use of peptides having Pro residues this issue was avoided and the products **264de** and **264dc** were obtained in comparatively much higher yields.

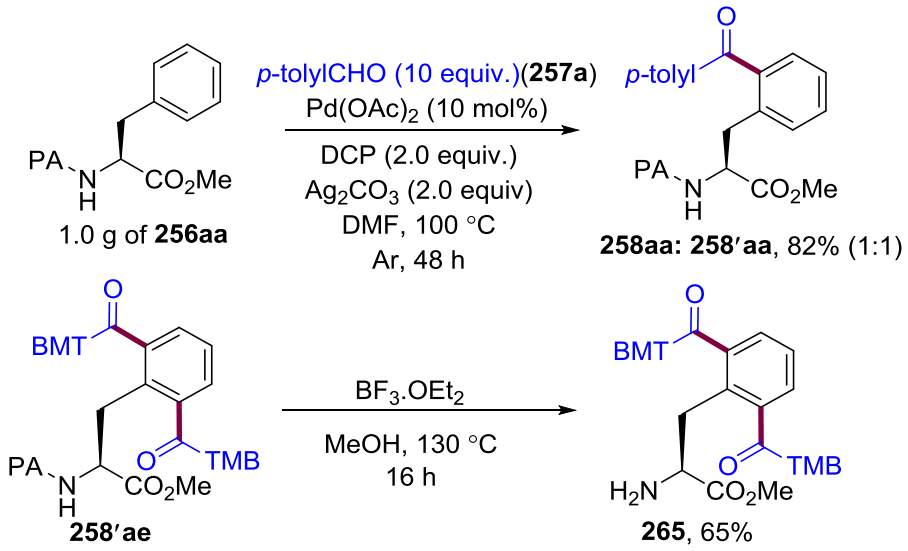


Reaction conditions: **263** (0.25 mmol), **257** (1.25 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv.), DMF (1 ml), Ar, 16h at 100 °C. Yield of the isolated product after column chromatography. [a] Ratio of *mono*- and *di*-acylated product **264**:**264'**.

Scheme 119. Pd-catalyzed late-stage δ-C(sp^2)–H acylation of Phe-containing peptides with aldehydes.

2.3.6. Big Scale and Deprotection Experiments

As shown in Scheme 120, the reaction could be scaled up to gram scale, adding more excess of aldehyde **257a** and additional time than in the standard conditions, the product **258aa** was obtained with 82% yield and 1:1 selectivity. Importantly, the removal of the PA-directing group to deliver the versatile free-amino group (**173**) showcased the applicability of the reported transformation.

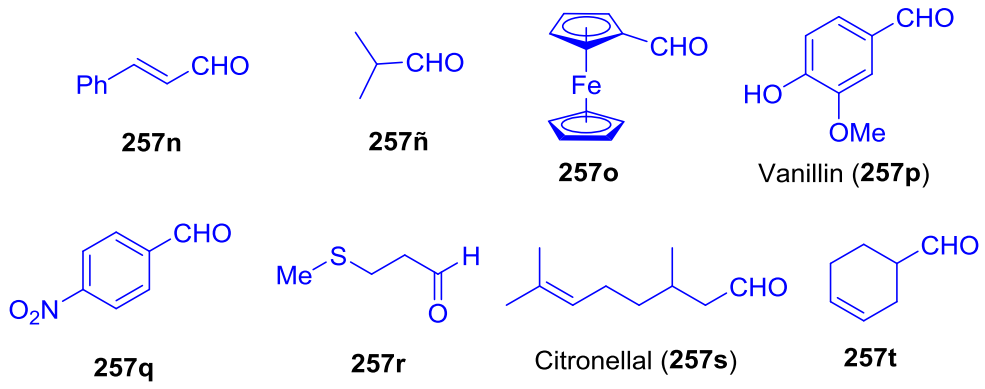


Scheme 120. Cleavage of the DG and gram scale synthesis.

2.3.7. Unsuccessful Reactions

2.3.7.1. Unsuccessful Aldehydes

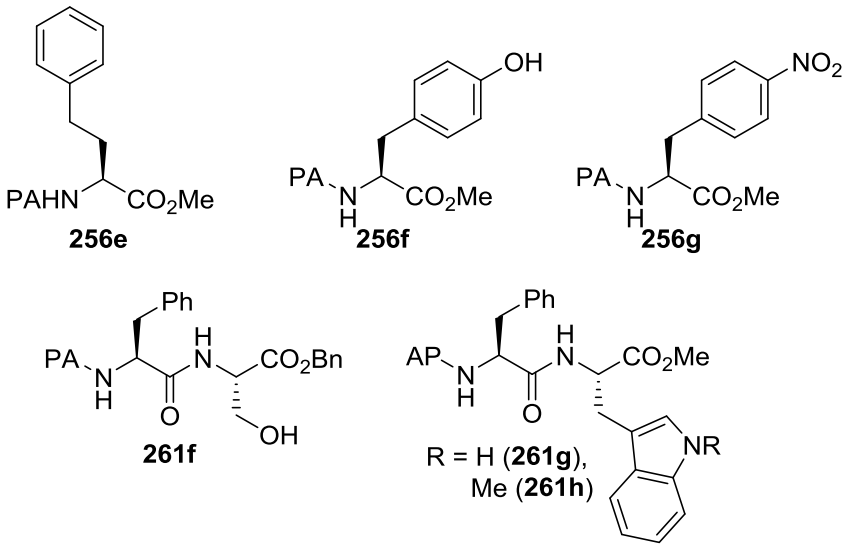
Unfortunately regarding the aldehyde scope, not all type of aldehyde were tolerated and when aldehydes described in the Scheme 121 were employed, the desired acetylated products were not observed. For example, α,β-unsaturated aldehyde **257n** and aldehydes bearing simple alkene groups (**257s** and **257t**) were not suitable for this transformation, which could be explained by the affinity of acyl radicals to react with unsaturated bonds, even though no side product was isolated. Other structures such us ferrocene (**166o**), vanillin (**257p**), or the aldehyde containing the thioether group (**257r**) were not reactive and 4-Nitrobenzaldehyde (**257q**) formed an undetermined side-product.



Scheme 121. Unsuccesful aldehydes.

2.3.7.2. Unsuccessful Substrates

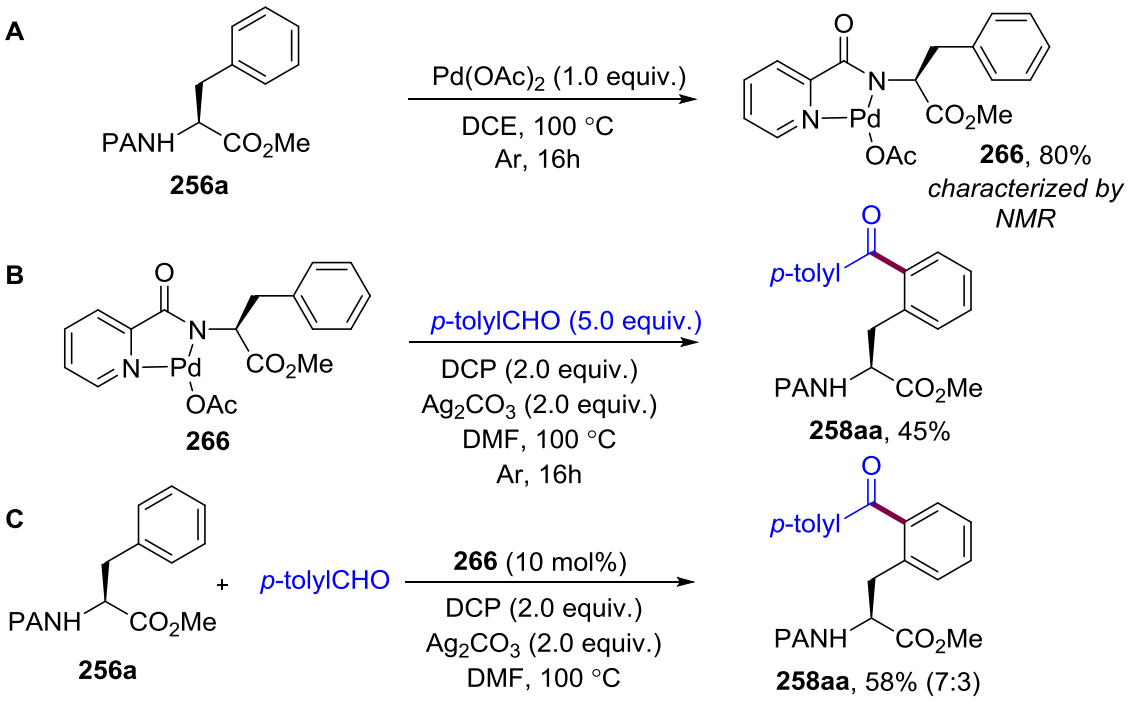
On the other hand, some Phe derivatives and dipeptides were not suitable for this procedure. For example, Homophenylalanine **256e** where the corresponding acylation would occur through the formation of the less stable 7-membered palladacycle was not reactive, either was the tyrosine unit **256f** and in the case of 4-Nitrophenyalanine **256g** it delivered an undetermined side-product. Similar scenario occurred with the dipeptides containing serine residue (**260f**) or Tryptophan residues (**260g-h**) in which only substrate was recovered after the reaction time. In these cases, it was postulated that the polar groups of Ser and Trp could inhibited the palladium catalyst through chelation.



Scheme 122. Unsuccessful substrates.

2.3.8. Mechanistic Experiments

Some mechanistic experiments were carried out in order to gain some mechanistic insights (Scheme 123). In the presence of radical traps such as TEMPO, BHT and diphenylethylene, the reaction was totally inhibited which suggested that a radical pathway may be operative. Interestingly, the reaction with stoichiometric amounts of $Pd(OAc)_2$ in the absence of aldehyde afforded complex **174** in 80% yield, which could be characterized by NMR spectroscopy (Scheme 123, A). All of our attempts to obtain crystals were unsuccessful. When the latter was employed as substrate under the standard conditions *mono*-acetylated product **167aa** was isolated in 45% (Scheme 123, B). Furthermore, complex **174** also catalyzed the model reaction delivering the product **167aa** in 58% isolated yield (Scheme 123, C), which clearly indicates its key role as an active intermediate.

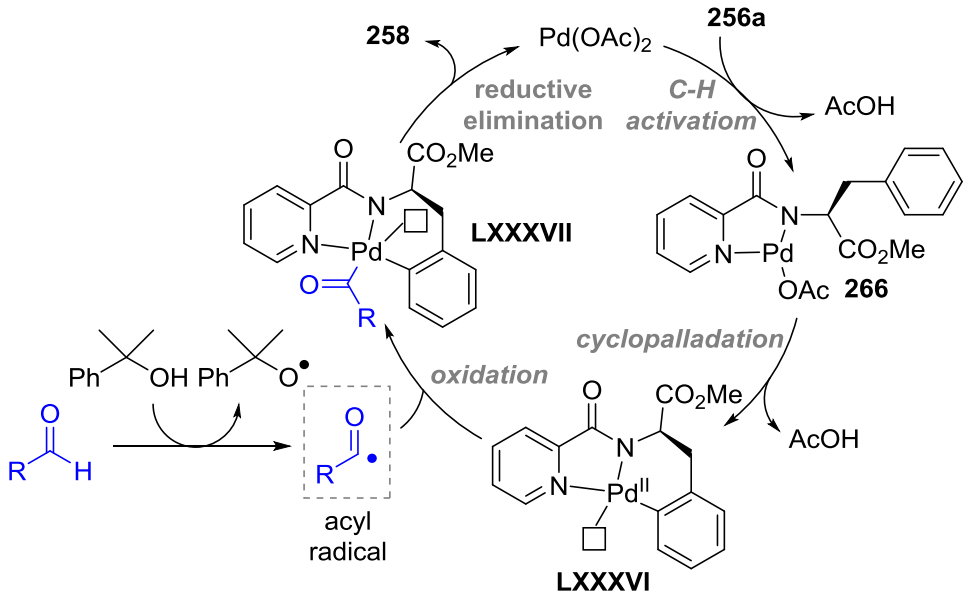


Scheme 123. Control experiments.

2.3.9. Mechanistic Proposal

On the basis of our experiments and previous literature,[185] a plausible mechanism was proposed (Scheme 124). Initially, intermediate **266** would be formed by coordination of the substrate with the $Pd(OAc)_2$, which subsequently would undergo a concerted-deprotonation-metallation (CMD) step at *ortho*-position to provide the six-membered palladacycle **LXXXVI**. On the other hand, the *in-situ* generated acyl radical would then react

with palladacycle **LXXXVI** to generate either Pd^{IV} or the dimeric Pd^{III} intermediate **LXXXVII**.[180] Finally, the desired ketone product **258** would be furnished through reductive elimination of intermediate **LXXXVII**, thus regenerating the active Pd^{II} catalyst. It is convenient to mention that whereas the C–H activation step to provide the corresponding palladacycle has been well-documented with a number of DG, the underlying fundamental steps of the subsequent addition of the transient acyl radical species still requires in-depth studies to fully understand the nature of the corresponding intermediates. In this context, DFT studies may be useful tool to support the intermediary of either Pd^{IV} or Pd^{III} dimers, which would be formed after oxidation of the putative Pd^{III} complex.



Scheme 124. Proposed mechanism for the PA-directed C–H acylation of Phe derivatives.

2.3.10. Conclusions

In summary, we have described an unprecedented late-stage C(sp^2)–H acylation of Phe-containing peptides with efficient yields.[207] A plethora of aldehydes were compatible for the transformation, including aromatic, aliphatic and heteroaromatic aldehydes. Under optimized conditions, the formation of *mono*-acylated product was favored and the optical purity of the amino residues was maintained during the transformation. Additionally, a practical and sustainable C(sp^2)–H *di*-halogenation protocol was also described.

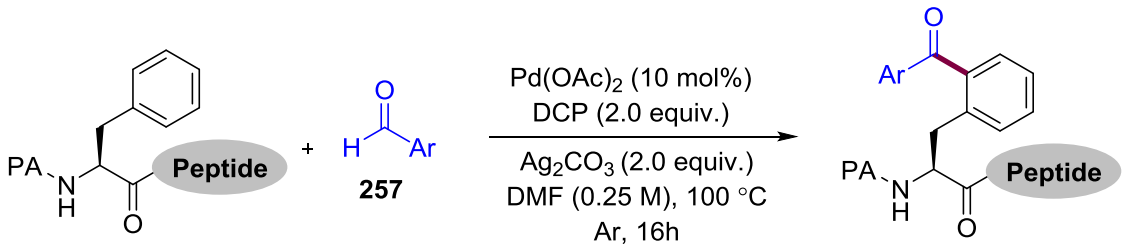
[207] San Segundo, M. and Correa, A.; *Chem. Sci*. **2019**, *10*, 8872.

Importantly, the reaction could be carried up at gram scale and the directing group was easily removed, which delivered the modified Phe derivative with a versatile free amine.

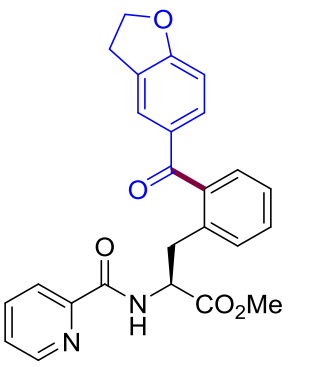
2.3.11. Experimental Procedure

In this section, some representative procedures as well as the characterization of illustrative compounds are provided. For a full detailed experimental description, please see the supporting information of the following article.[207]

2.3.11.1. Pd-Catalyzed δ-C(sp²)–H Acylation of Phe Derivatives

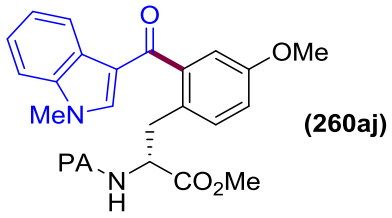


General Procedure: A reaction tube containing a stirring bar was charged with the corresponding Phe derivative (0.25 mmol, 1.00 equiv.), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.50 mmol, 2.00 equiv.), DCP (0.50 mmol, 2.00 equiv.) and the corresponding aldehyde **257** (if solid) (1.25 mmol, 5.00 equiv.). The reaction tube was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). The corresponding aldehyde **257** (if liquid) (1.25 mmol, 5.00 equiv.) and DMF (1 mL) were added under argon atmosphere. The reaction tube was next warmed up to 100 °C and stirred for 16 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and evaporated. The resulting crude was then purified by column chromatography to afford the corresponding product.



(258ad)

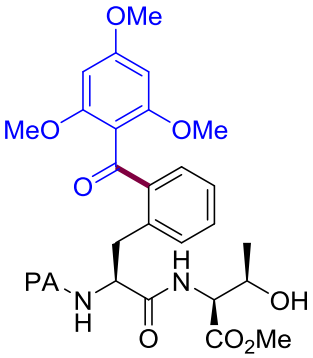
Methyl (*S*)-3-[2-(2,3-dihydrobenzofuran-5-carbonyl)phenyl]-2-(picolinamido)propanoate (258ad). Following the general procedure, using commercially available 2,3-dihydrobenzofuran-5-carboxyaldehyde **257d** (1.25 mmol, 157 µL) and **256a** (0.25 mmol, 71 mg) provided 73 mg (63% yield) (7:3 ratio) of **258ad** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 4.7 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.72 (s, 1H), 7.60 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.34 (m, 1H), 7.33 – 7.23 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.08 – 4.90 (m, 1H), 4.65 (t, *J* = 9.4 Hz, 2H), 3.69 (s, 3H), 3.47 – 3.30 (m, 2H), 3.26 – 3.11 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 172.0, 164.7, 164.5, 149.4, 148.3, 139.4, 137.0, 136.0, 133.2, 131.0, 130.8, 130.4, 129.2, 127.8, 127.6, 126.2, 126.1, 122.2, 108.9, 72.4, 54.3, 52.5, 34.6, 29.0. IR (cm^{-1}): 3379, 2952, 1742, 1675, 1649, 1602, 1513, 1435, 1294, 1270, 1214, 1086, 939. HRMS *caldc* for ($C_{25}H_{22}N_2O_5$): 430.1529, *found* 430.1522.



(260aj)

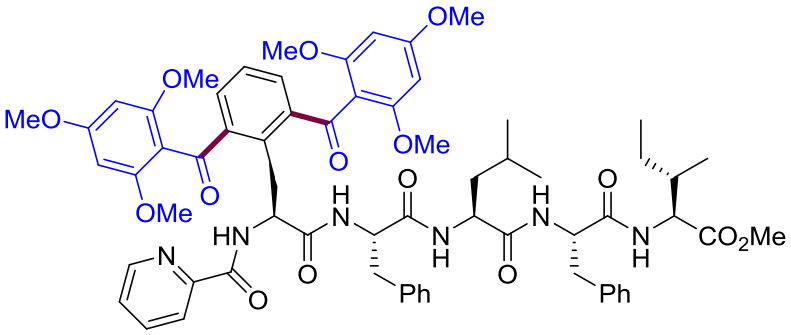
Methyl (*D*)-3-[4-methoxy-2-(1-methyl-1*H*-indole-3-carbonyl)phenyl]-2-(picolinamido)propanoate (260aj). Following the general procedure, using commercially available 1-methylindole-3-carboxyaldehyde **257j** (1.25 mmol, 199 mg) and **256c**[208] (0.25 mmol, 79.0 mg) provided 59 mg (50% yield) of **260aj** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 7.9 Hz, 1H), 8.49 – 8.40 (m, 1H), 8.33 (d, *J* = 4.5 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 – 7.26 (m, 6H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.95 (dd, *J* = 8.5, 2.8 Hz, 1H), 5.02 – 4.86 (m, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.48 – 3.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 172.1, 164.6, 157.6, 149.4, 148.1, 142.2, 139.2, 137.6, 136.8, 132.1, 127.3, 126.9, 125.9, 123.7, 122.9, 122.0, 116.9, 115.2, 114.6, 109.7, 55.5, 54.6, 52.4, 33.7, 33.6. IR (cm^{-1}): 3424, 2950, 1741, 1672, 1604, 1519, 1464, 1367, 1217, 731. HRMS *caldc* for ($C_{27}H_{25}N_3O_5$): 471.1794, *found* 471. 1806.

[208] Kluge, A.; Lagu, B.; Maiti, P.; Panigrahi, S. K. PCT Int. Appl. (**2018**), WO 2018213150 A1.



(**262ce**)

Methyl [(*S*)-2-(picolinamido)-3-(2-(2,4,6-trimethoxybenzoyl)phenyl)propanoyl]-*L*-threoninate (262ce). Following the general procedure, using commercially available 2,4,6-trimethoxybenzaldehyde **257e** (1.25 mmol, 245.0 mg) and PA-Phe-Thr-OMe (**261c**) (0.25 mmol, 96.3 mg) provided 46 mg (31% yield) of **262ce** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 7.6 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.38 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.21 – 7.13 (m, 1H), 6.14 (s, 2H), 5.07 – 4.96 (m, 1H), 4.59 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.35 – 4.21 (m, 1H), 3.85 (s, 3H), 3.81 – 3.72 (m, 1H), 3.70 (s, 3H), 3.68 (s, 6H), 3.43 (dd, *J* = 13.4, 9.7 Hz, 1H), 2.63 (brs, 1H), 1.20 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 172.2, 171.1, 165.0, 162.8, 159.1, 149.6, 148.4, 138.8, 138.1, 137.2, 132.0, 131.9, 131.9, 126.9, 126.3, 122.3, 112.7, 90.9, 68.6, 57.9, 56.1, 55.6, 55.54, 52.6, 36.6, 20.1. IR (cm^{-1}): 3349, 2945, 1742, 1663,1604, 1589,1516, 1227, 1205, 1127. HRMS *caldc* for ($C_{30}H_{33}N_3O_9$): 579.2217, *found* 579.2213.

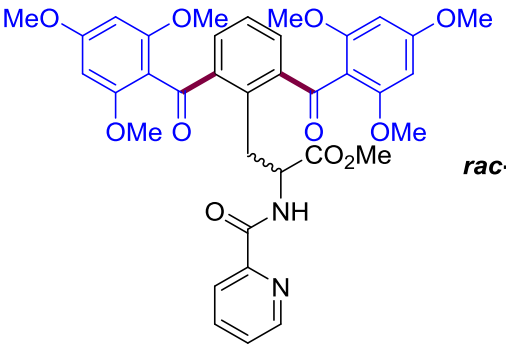


(**264′ce**)

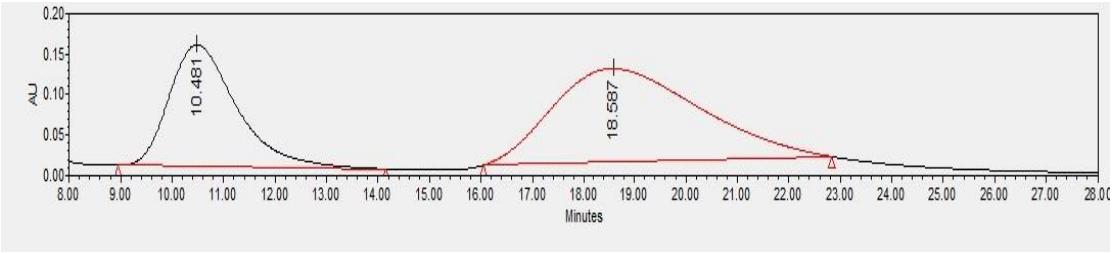
Methyl [(*S*)-3-(2,6-bis(2,4,6-trimethoxybenzoyl)phenyl)-2-(picolinamido) propanoyl]-*L*-phenylalanyl-*L*-leucyl-*L*-phenylalanyl-*L*-isoleucinate (264'ce). Following the general procedure, using commercially available 2,4,6-trimethoxybenzaldehyde **257e** (0.75 mmol, 147.0 mg) and PA-Phe-Phe-Leu-Phe-Ile-OMe (**263c**) (0.15 mmol, 121.0 mg) provided 50.0 mg (31% yield) of **172'ce** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (d, *J* = 4.7 Hz, 1H), 8.66 (d, *J* = 4.5 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.47 – 7.44 (m, 1H), 7.43 (d, *J* = 4.0 Hz, 2H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.21 – 7.14 (m, 4H), 7.14 – 7.04 (m, 3H), 7.03 – 6.93 (m, 4H), 6.83 – 6.71 (m, 3H), 6.01 (s, 4H), 4.95 – 4.85 (m, 1H), 4.70 – 4.61 (m, 1H), 4.54 – 4.37 (m, 2H), 4.30 – 4.19 (m, 1H), 3.79 (s, 6H), 3.71

(s, 3H), 3.56 (s, 12H), 3.47 (dd, *J* = 13.8, 11.8 Hz, 2H), 3.32 (ddd, *J* = 17.1, 12.5, 4.9 Hz, 2H), 3.03 – 2.93 (m, 1H), 2.90 – 2.79 (m, 1H), 2.03 – 1.90 (m, 1H), 1.62 – 1.50 (m, 1H), 1.43 – 1.14 (m, 4H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.79 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 173.4, 172.5, 172.1, 171.4, 171.3, 166.5, 163.3, 159.6, 149.4, 148.8, 142.2, 138.4, 136.9, 136.2, 135.6, 132.3, 129.6, 129.2, 128.5, 128.0, 126.8, 126.4, 126.1, 125.7, 122.2, 112.4, 91.0, 57.2, 57.0, 56.0, 55.6, 55.6, 55.2, 53.1, 52.0, 39.4, 37.8, 37.6, 36.0, 28.9, 25.3, 24.3, 23.4, 21.0, 15.5, 11.8. IR (cm^{-1}): 3289, 2956, 1739, 1661, 1603, 1520, 1455, 1365, 1227, 1217, 1205, 1127. HRMS *caldc* for ($C_{66}H_{76}N_6O_{15}$): 1192.5369, *found* 1192.5391.

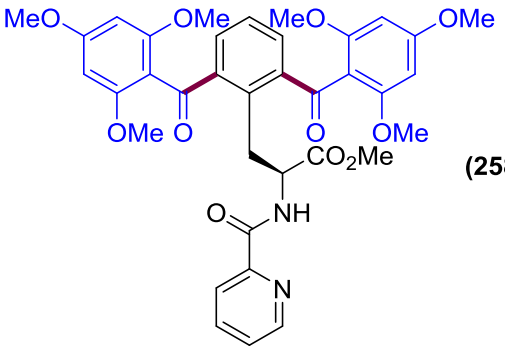
2.3.11.2. Determination of *ee* by HPLC Analysis



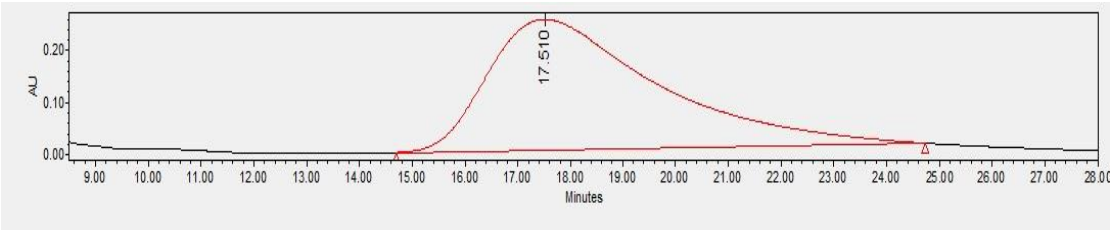
***rac*-(258ai')**



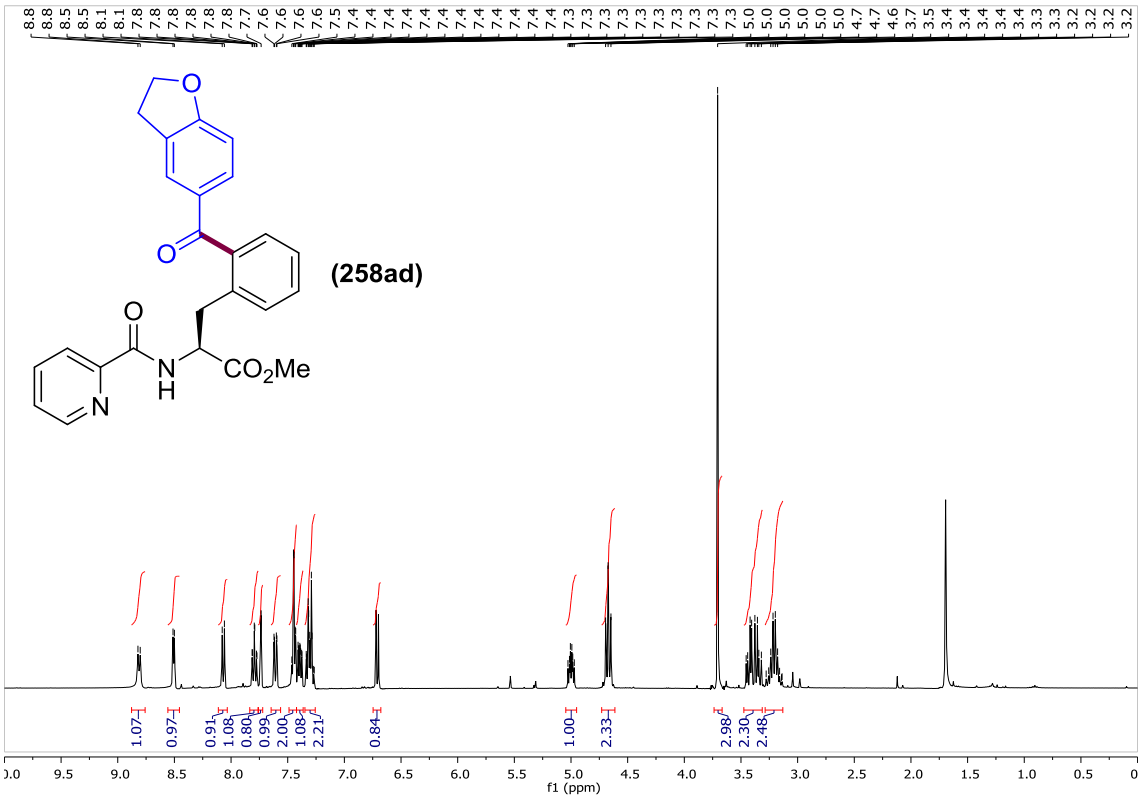
Chiralpak IA; 20:80 Hexane: isopropanol; 1 mL/min, λ = 245 nm

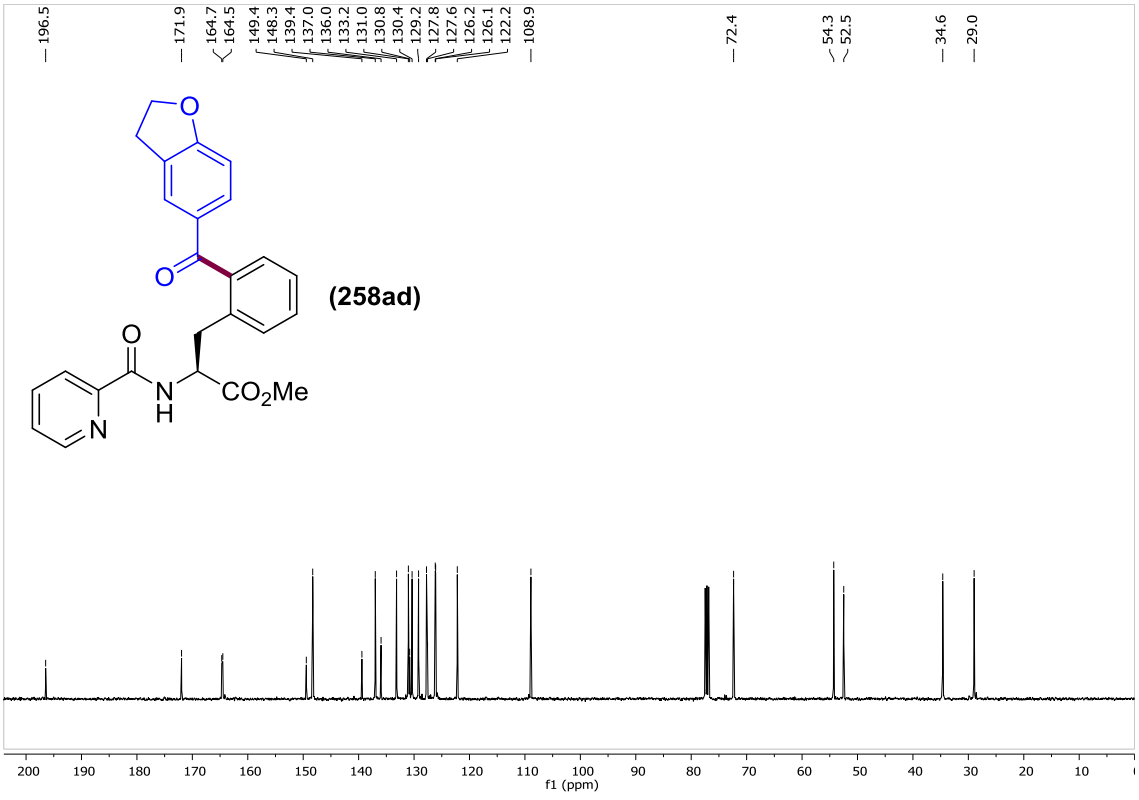


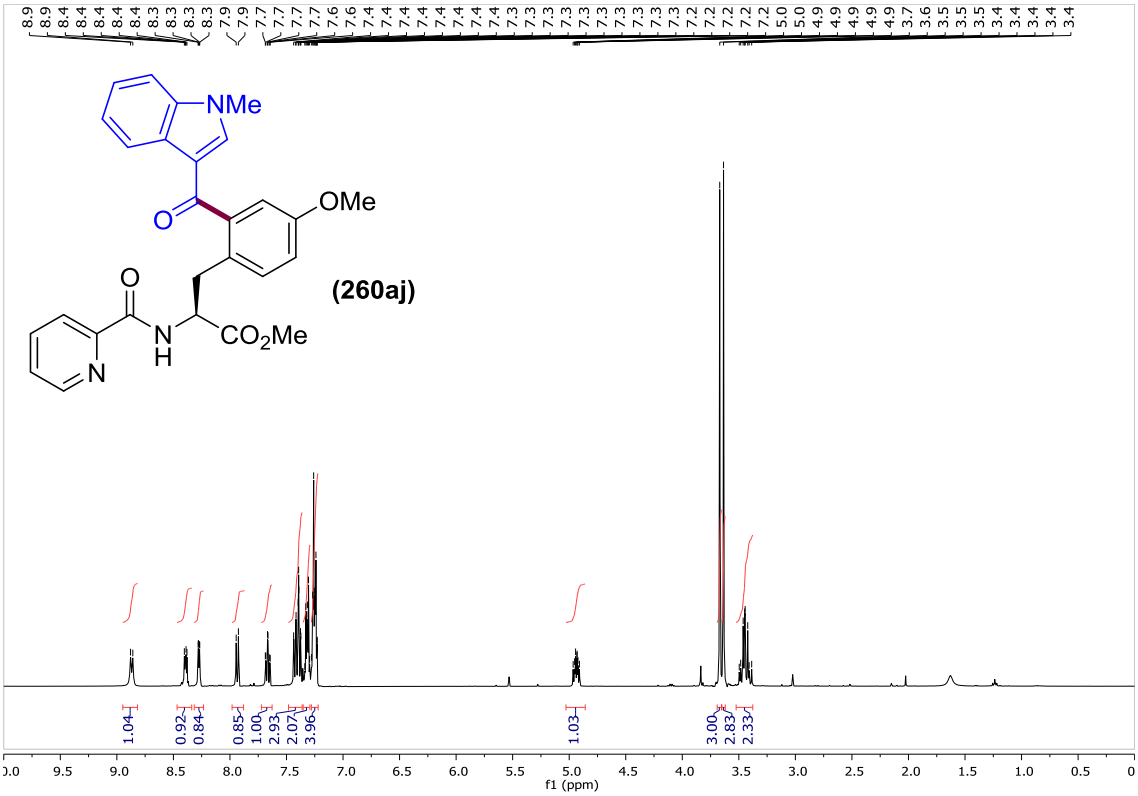
(258′ai) 99% *ee*

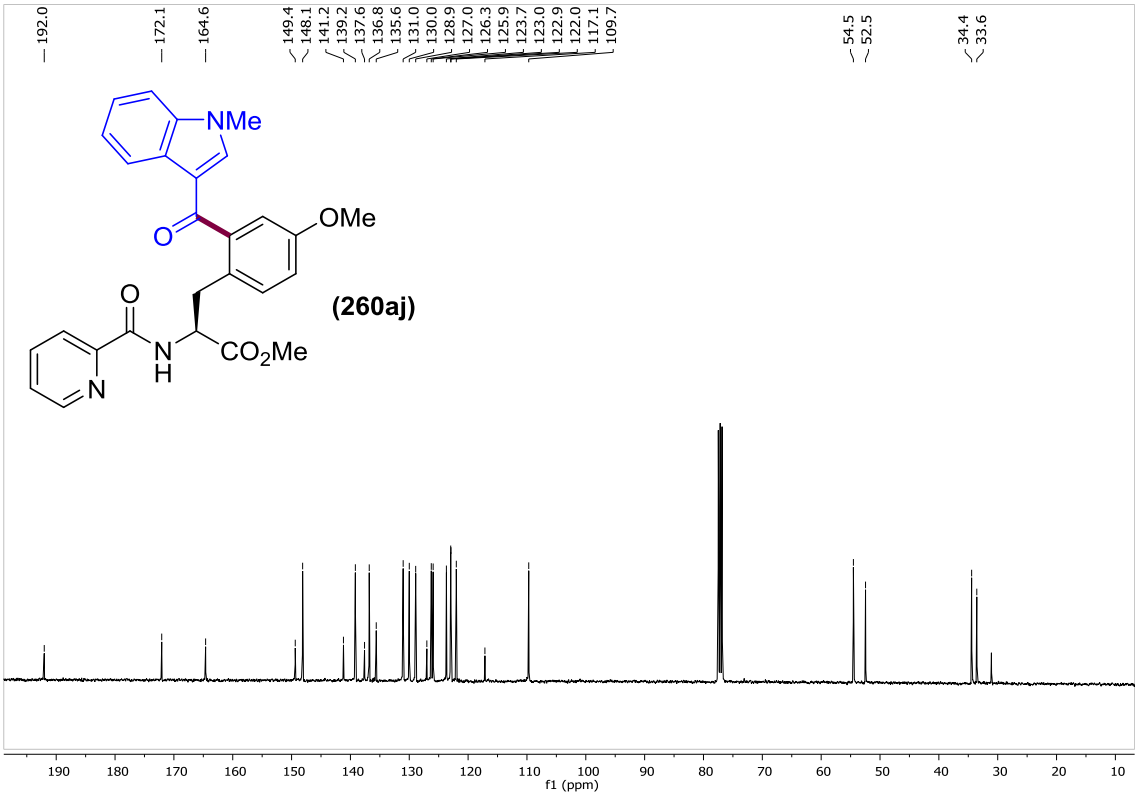


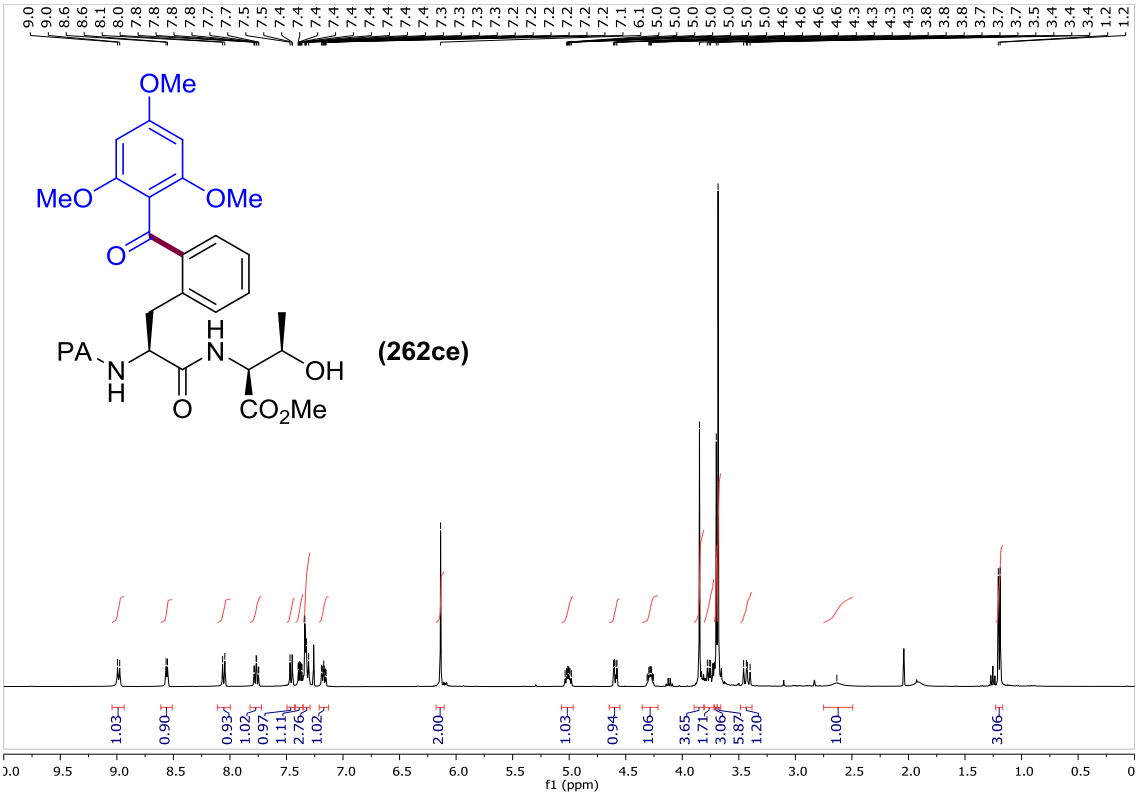
2.3.11.3. ^{1}H NMR and ^{13}C NMR spectra

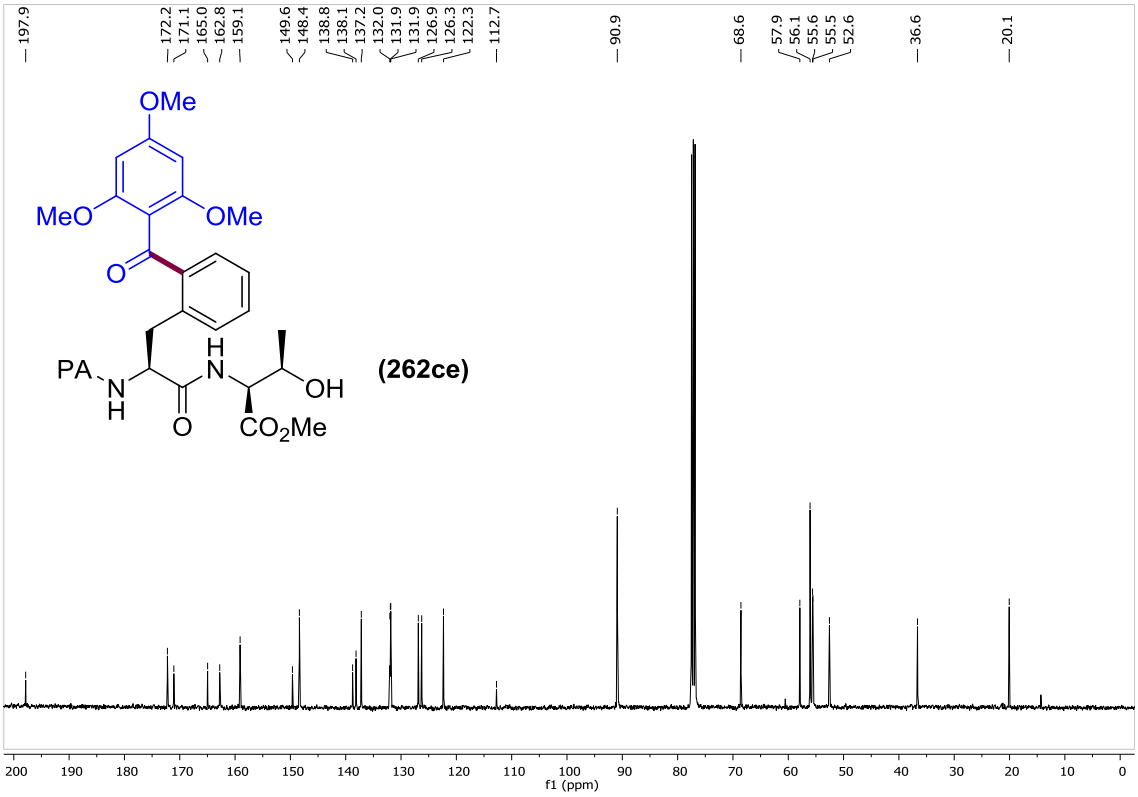


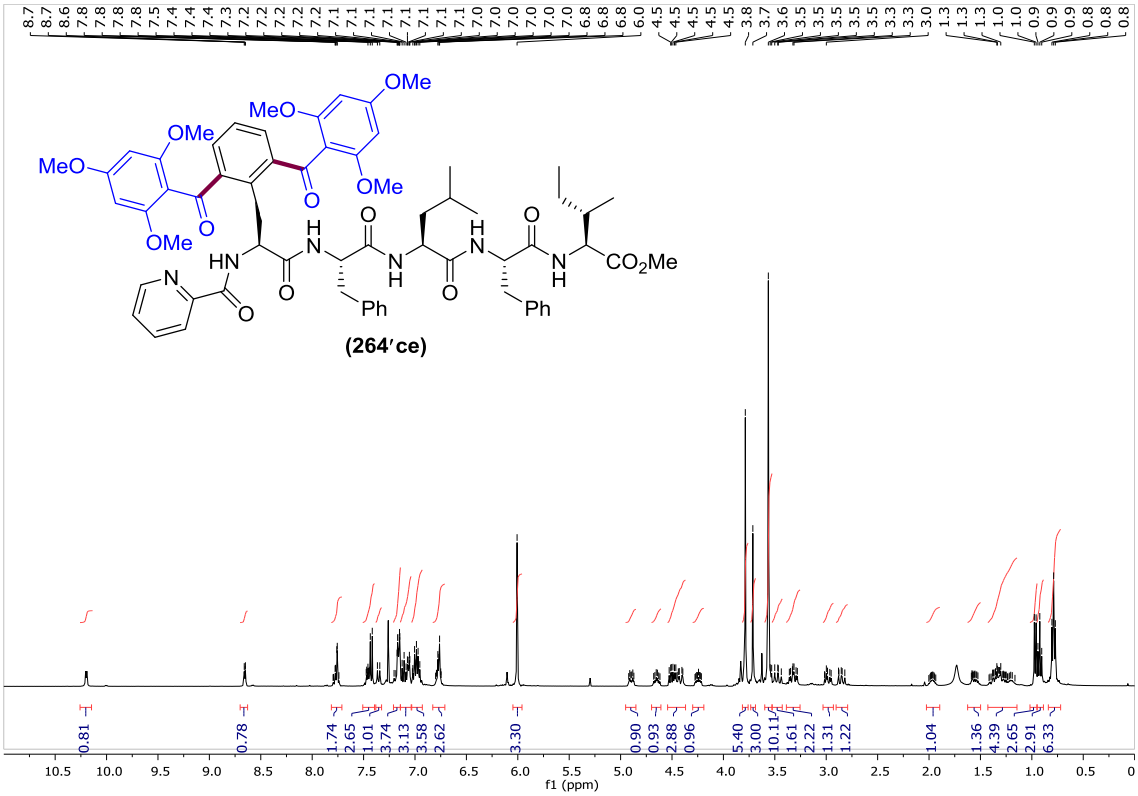


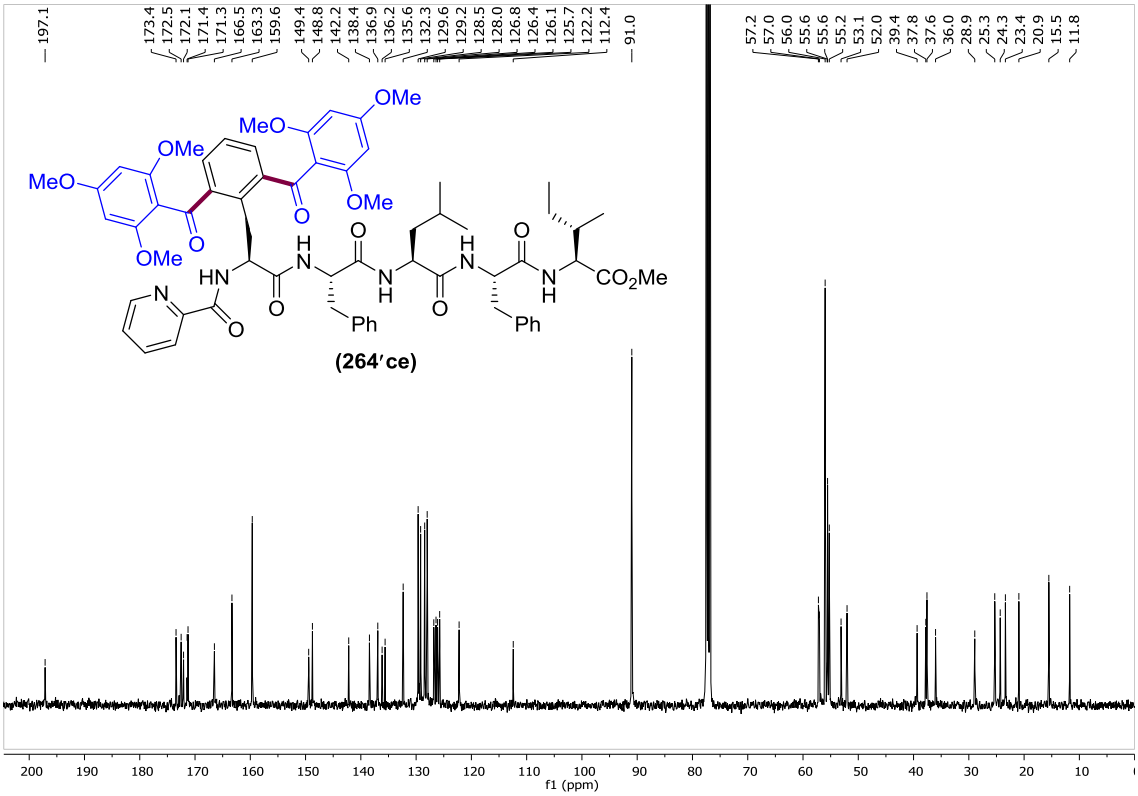

NMe
OMe
O
O
N
H
CO2Me
N
(260aj)
1.04
0.92
0.84
0.85
1.00
2.93
2.07
3.96
1.03
3.00
2.83
2.33
f1 (ppm)


192.0
172.1
164.6
149.4
148.1
141.2
139.2
137.6
136.8
135.6
131.0
130.0
128.9
127.0
126.3
125.9
123.7
123.0
122.9
122.0
117.1
109.7
54.5
52.5
34.4
33.6
NMe
OMe
O
O
N
H
CO2Me
N
(260aj)
f1 (ppm)


OMe
MeO
OMe
O
PA
N
H
H
N
O
OH
CO2Me
(262ce)
f1 (ppm)


OMe
MeO
OMe
O
PA
N
H
H
N
O
OH
CO2Me
(262ce)
f1 (ppm)

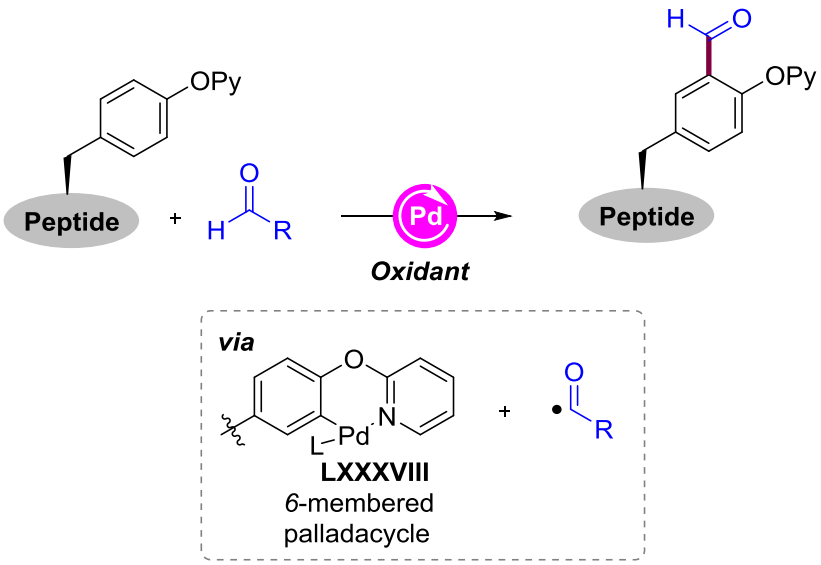

(264′ce)
f1 (ppm)


(264′ce)
f1 (ppm)

2.4. Site-Selective Aqueous C–H Acylation of Tyrosine-Containing Oligopeptides With Aldehydes

As mentioned before, the selective C–H functionalization of amino acid's side-chain represents an unmet challenge of significance importance within peptide chemistry and protein engineering. In the case of aromatic side-chains, most of the protocols entailed the diversification of tryptophan (Trp) or phenylalanine (Phe) with toxic halide-counterparts and organic solvents. Conversely, protocols for the site-selective C–H functionalization of tyrosine moiety remains elusive. The use of transition metals has enabled the introduction of aryl groups,[121] alkenes[129] and trifluoromethyl groups,[126] however, mostly in relatively simple compounds. In addition, some *O*-modifications have been performed capitalizing the nucleophilic character of the hydroxyl group of the tyrosine native structure.[136, 137, 138]

As described in this chapter, we have developed an unprecedented C–H acylation platform of Phe-containing peptides with aldehydes[207] Despite its novelty, the protocol suffered some drawbacks such as the requirement of stoichiometric amounts of silver salts to obtain high yields, the use of an organic solvent (DMF) and the transformation was limited to *N*-terminal Phe residues. Accordingly, we next sought if this radical C–H acylation could be applied in less explored Tyr-containing peptides and, if possible, overcome the limitations mentioned above. We envisioned that a DG could be installed in the hydroxyl group of the Tyr unit, thereby enabling the desired site-selectivity[209] through the formation of a 6-membered palladacycle (**XCVIII**) prone to undergo further oxidative addition of the transient acyl radical species (Scheme 125).



[209] Rej. S.; Ano, Y.; Chatani, N. *Chem. Rev*. **2020**, *120*, 1788.

Scheme 125. General strategy for the site-selective Pd-catalyzed C(sp^2)–H acylation of Tyr-containing peptides.

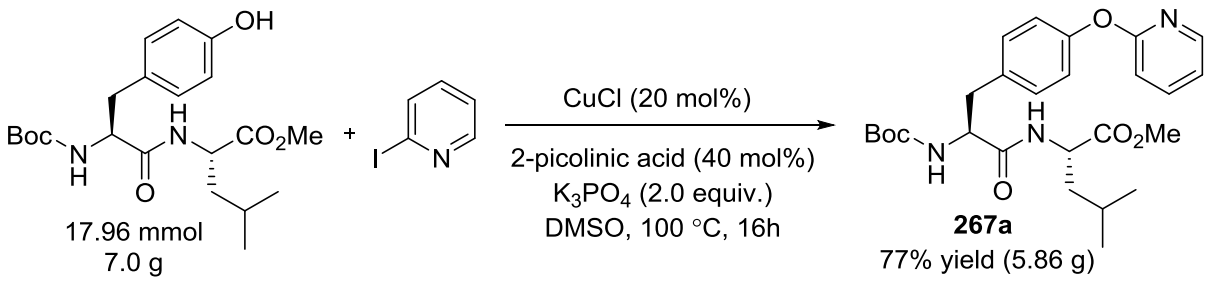
In this regard, we anticipated that the conversion of the native Tyr unit into the corresponding 2-pyridyl ether compound[210] could enable the desired site-selectivity, thus internal or terminal Tyr residues could be selectively modify, upon our acylation strategy.

Taking into account the bibliography within the field of C–H functionalization of Tyr units and our previous works, for this project we stablished the following goals:

- To report the first site-selective C–H acylation of tyrosine residues.
- To stablish an environmentally friendly protocol (silver- free and in aqueous solvent if possible).
- General procedure to modify either internal or terminal Tyr residues.
- To achieve a late-stage acylation process of Tyr-containing complex peptides.

2.4.1. Optimization Process

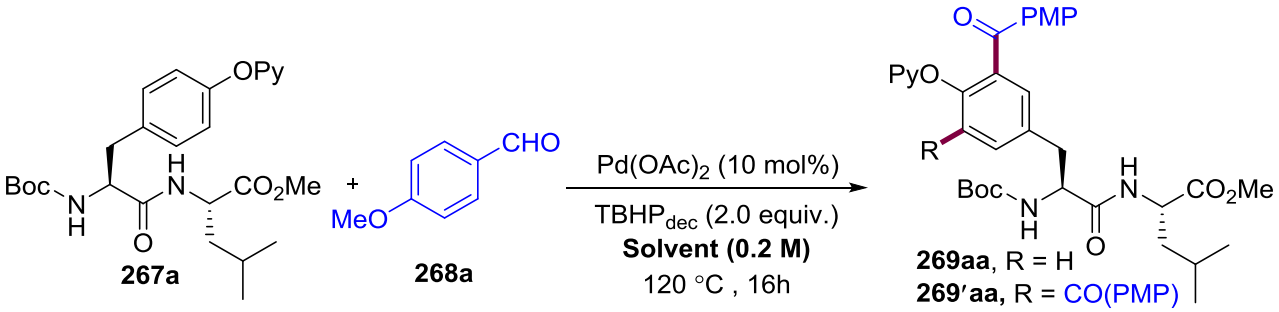
For the optimization process compound Boc-Tyr(OPy)-Leu-OMe (**267a**) was synthesized as model substrate to react with the *p*-anisaldehyde (**268a**) under oxidative conditions. **267a** was easily prepared from Boc-Tyr-Leu-OMe upon a previously described *O*-arylation reaction reaction with 2-iodopyridine. The protocol was scale up and provided the model substrate in gram scale (Scheme 126).[211] On the other hand, $Pd(OAc)_2$ which has been broadly employed in oxidative C–H acylation reactions, was set up as catalyst along with $TBHP_{dec}$ as oxidant. Under these conditions, several solvents were tested as depicted in Table 26. Fortunately,



[210] For selected C–H functionalization reactions directed by 2-pyridyl ether unit on simple phenyl systems, see: a) Lou, S.-J.; Chen, Q.; Wang, Y.-F.; Xu, Z. Y. *ACS Catal*. **2015**, *5*, 2846. b) Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. *Organometallics*, **2015**, *34*, 953.

Scheme 126. Synthesis of the model substrate **267a**.

among the organic solvents, toluene, MeCN and PhCl delivered the acylated peptide **269aa** in good yield and high *mono*-selectivity (entries 1-2, 6, respectively), whereas other polar solvents such as DMF, DMA, 1,4-dioxane or HFIP only delivered trace amounts of the target product **269aa** (entries 3-5, 8, respectively). However, when the reaction was set up under neat water, product **269aa** was obtained with 46% yield and a ratio of 85:15 of *mono*:*di*-acetylated product (entry 7). Even though slightly higher yields were acquired with some organic solvents, it was decided to continue the optimization process with water as solvent driven by its clear cost and environmental benefits.[212]



Entry	Solvent	Yield (%)[b,c]
1	Toluene	60 (8:2)[d]
2	MeCN	56 (87:13)
3	DMF	traces
4	DMA	traces
5	1,4-Dioxane	traces
6	PhCl	66 (75/25)
7	H_2O	46 (85/15)
8	HFIP	traces

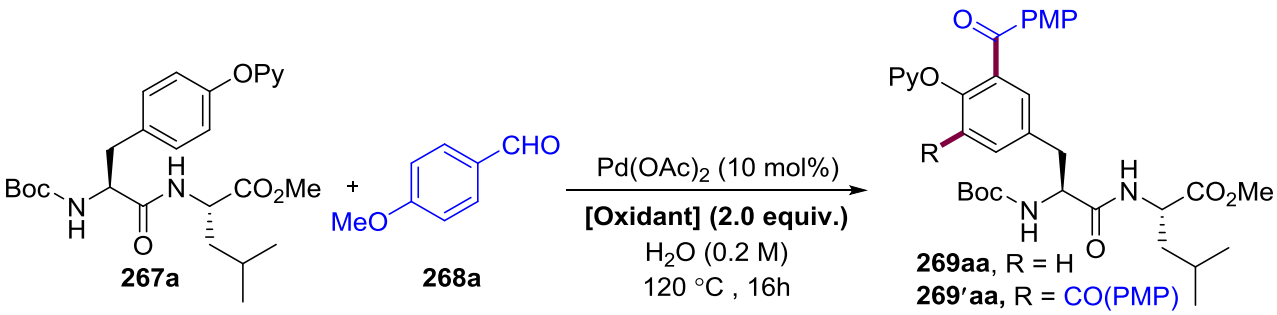
[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHP in decane (2.0 equiv.), solvent (0.75 mL), Ar, 16h at 120 °C. [b] Yield of isolated product after column chromatography. [c]Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 26. Screening of Solvents.

Subsequently, different types of oxidants were texted as shown in the Table 27. The inorganic oxidant $(NH_4)_2S_2O_8$ did not deliver the target product **269aa** (Table 27, entry 3). Common organic solvents such as DTBP and DCP, the latter employed in our Phe acylation protocol, were unsuccessful to deliver the product **269aa**

[212] a) Chanda, A.; Fokin, V. V. *Chem. Rev*. **2009**, *109*, 725. b) Gawande, M. B.; Bonifácio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev*. **2013**, *42*, 5522.

in quantitative amounts (Table 27, entries 4 and 7, respectively). On the other hand, TBPB delivered the final product in low yield and high *mono*-selectivity (Table 27, entry 6), whereas the hydrogen peroxide only delivered traces amounts of **269aa** (Table 27, entry 5). Finally the aqueous solution of TBHP matched the result obtained with the analogous in decane(Table 27, entries 1-2), so the TBHP in aqueous solution was stablished as oxidant for the next screening reactions, due to mayor sustainability and prize over TBHP in decane.

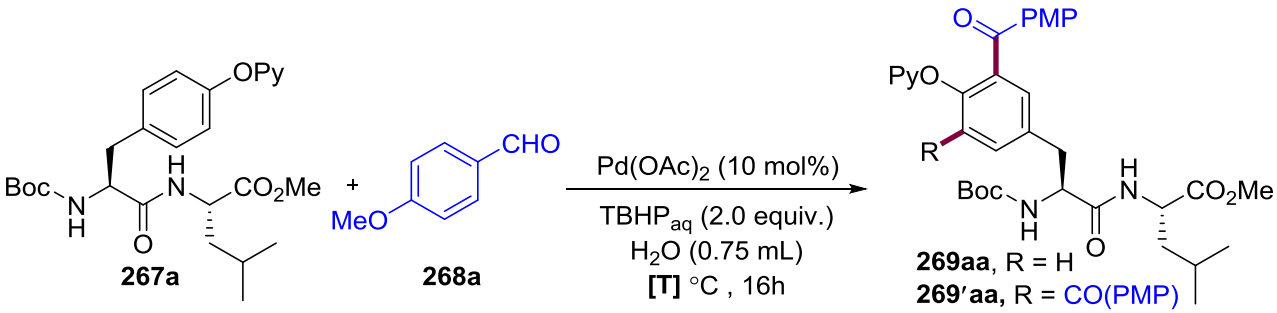


Entry	T (°C)	Yield (%)[b,c]
1	$TBHP_{aq}$	46 (85:15)
2	$TBHP_{dec}$	46 (85:15)
3	$(NH_4)_2S_2O_8$	traces
4	DTBP	traces
5	H_2O_2	traces
6	TBPB	33 (7:3)[c]
7	DCP	Traces

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol%), [oxidant] (2.0 equiv.), H_2O (0.75 mL), Ar, 16h. [b] Yield of isolated product after column chromatography. [c] Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 27. Screening of oxidants.

Then, the reaction temperature was evaluated (Table 28, entries 1-6). Unfortunately, at room temperature the starting material remained unreactive (Table 28, entry 1), so a 10 °C interval was studied ranging from 80 °C to 120 °C (Table 28, entries 2-6). After this screening, the optimal temperature was set up at 90 °C, lower than the boiling point of water, which delivered good yield of the product **269aa** (65%) and excellent *mono*- and *di*-acetylated ratio (93:7) (Table 28, entry 3). Lower temperature did not furnish satisfactory yield (Table 28, entry 2) and even though higher temperatures increased the yield of **269aa**, some *mono*-selectivity was sacrified (Table 28, entries 4-6).



Entry	T (°C)	Yield (%)[b,c]
1	rt	No reaction
2	80	56 (95:5)
3	90	65 (93:7)
4	100	69 (88:12)
5	110	70 (88:12)
6	120	74 (87:13)

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (2.0 equiv.), H_2O (0.75 mL), Ar, 16h. [b] Yield of isolated product after column chromatography. [c] Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 28. Screening of temperature.

Afterwards, other palladium salts and different transition metals were tested as catalyst (

Table **29**, entries 1-9). Among the palladium salts, some furnished the target product 269aa in very low yield (

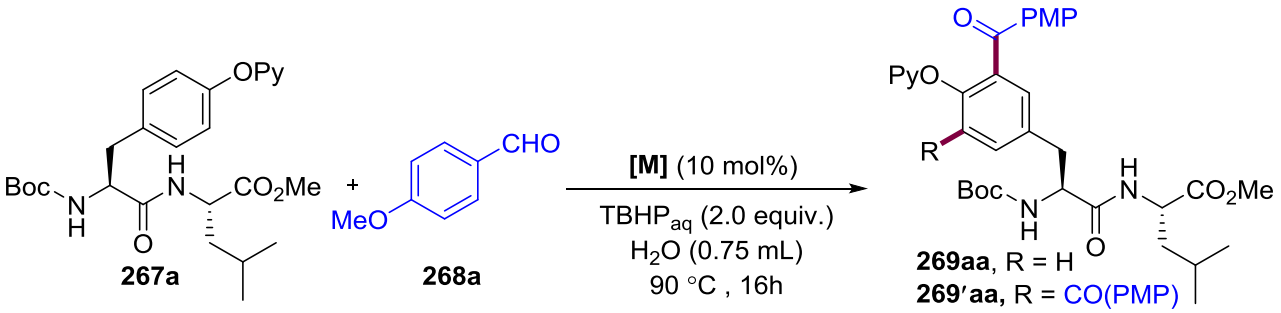
Table **29**, entries 2-4) and some others not even traces of **269aa** were obtained (

Table **29**, entries 5-6). The use of Ruthenium has also been described as a feasible catalyst for C–H acylation reactions, unfortunately, in this particular case the $[RuCl_2(p\text{-cymene})_2]$ catalyst did not afford the acylated product **269aa** (

Table **29**, entry 7). Likewise, nickel salts, were not able to catalyzed the reaction as the formation of **269aa** was not observed (

Table **29**, entries 8-9). As none of the palladium salts or metals improved the yield obtained with $Pd(OAc)_2$ (

Table **29**, entry 1), it was stablished as the catalyst of choice for the next screening reactions.

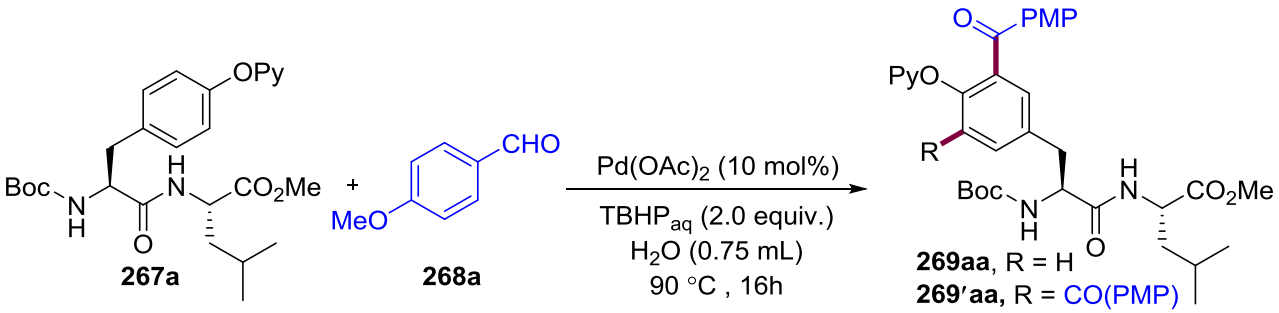


Entry	[M]	Yield (%)[b,c]
1	$Pd(OAc)_2$	65 (93:7)[d]
2	$PdCl_2(MeCN)_2$	15 (100:0)
3	$Pd(TFA)_2$	29 (97:3)
4	$PdCl_2$	23(95:5)
5	PdI_2	0
6	$PhCl_2(PPh_3)_2$	0
7	$[RuCl_2(p\text{-cymene})_2]$	0
8	$NiCl_2(PCy_3)_2$	0
9	$NiCl_2$·DME	0

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45-0.90 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (2.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c]Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 29. Screening of metal Catalyst.

The aldehyde equivalents also could play a crucial role regarding the yield and selectivity of the final product. For this reason, in order to explore this parameter, the model reaction was set up with different amounts of aldehyde **268a** as is shown in Table 30. As expected, more equivalents of aldehyde resulted in higher yield of **269aa**, however the *mono*-selectivity was worsened (Table 30, entries 1-4). Accordingly, the amount of aldehyde was kept at 3.0 equivalents (Table 30, entry 1), as higher amounts of **268a** did not improve significally the final outcome (Table 30, entries 2-4).

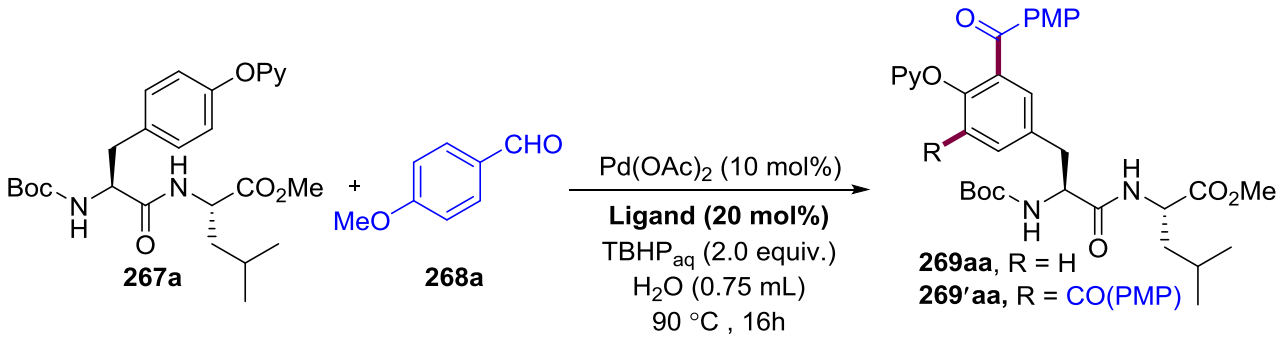


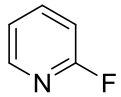
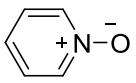
Entry	Equiv. of 176a	Yield (%)[b,c]
1	3	65 (93:7)
2	4	74 (88:12)
3	5	72 (88:12)
4	6	71 (89:11)

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45-0.90 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (2.0 equiv.), H_2O (0.75 ml), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c]Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 30. Screening of aldehyde equivalents.

Afterwards, different type of ligands were explored with the aim of improving the yield of **269aa** while maintaining high *mono*-selectivity (Table 31). In the case of pyridine type ligand **L12** and pyridine *N*-oxide **L16**, the final result was very similar to the reaction without ligand. Phosphine type ligands **L13** and **L14** either had significant influence in the reaction yield or selectivity. Conversely, the use of 1,10-phenantronile **L15** totally inhibited the reaction, probably due to the strong chelation with the catalyst.

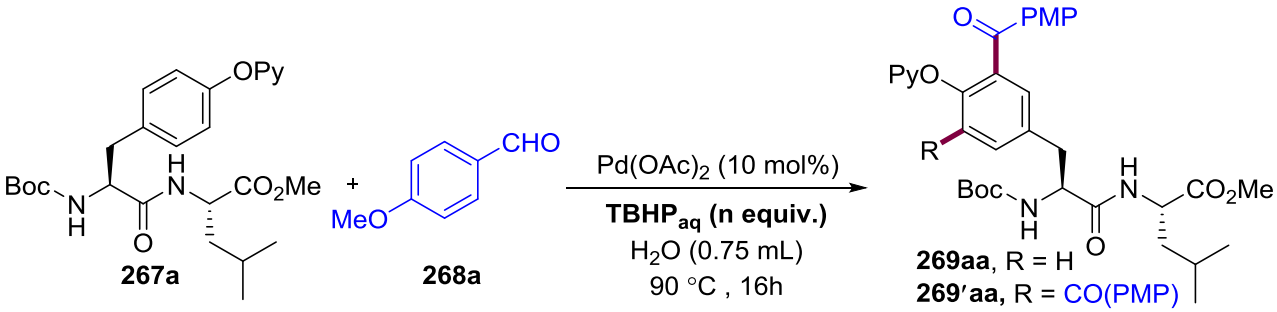


none		XPhos	PPh_3	1,10-Phe	
	L12	**L13**	**L14**	**L15**	**L16**
65 (93:7)[b,c]	67 (88:12)[b,c]	63 (9:1)[b,c]	59 (92:8)[b,c]	0	60 (92:8)[b,c]

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45-0.90 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (2.0 equiv.), Ligand (20 mol%), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c] Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 31. Screening of ligands.

Due to the low-price and availability of TBHP as an aqueous solution, we next sought for the effect of increasing the amount of this oxidant. The result in Table 32 clearly showed that increasing the amount of the oxidant resulted in higher yields. In particular, employing 4.0 equivalents of $TBHP_{aq}$ resulted in a very satisfactory result, obtaining the target product **269aa** with 78% yield while maintaining high selectivity (Table 32, entry 3).

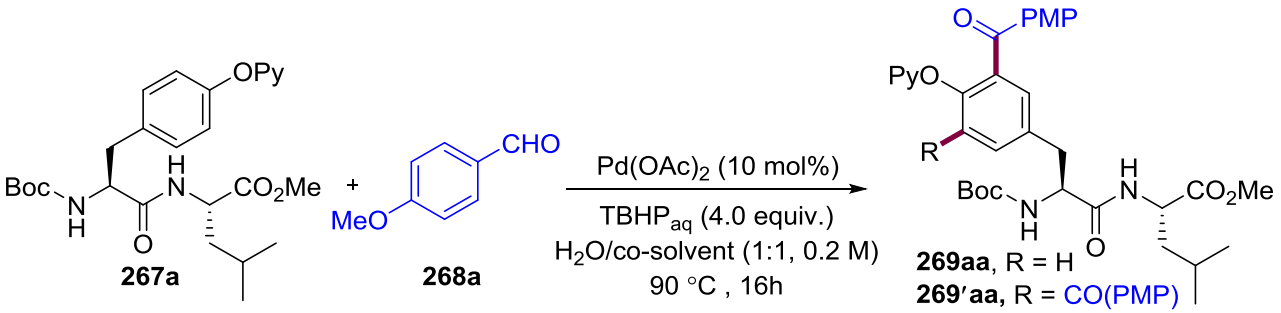


Entry	Equiv. of TBHPaq	Yield (%)[b,c]
1	2	65 (93:7)
2	3	75 (82:18)
3	4	78 (8:2)[d]

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (n equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c]Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**. [d] Yield of isolated product after column

Table 32. Screening of oxidant equivalents.

As shown in Table 33, the employment of a co-solvent was also explored. For this screening, commonly utilized organic solvents such as *t*BuOH, THF and MeCN were tested. However when an organic solvent were used as co-solvent, very low yields of **269aa** were obtained (Table 33, entries 2-4), therefore, neat water was established as the optimal solvent for this transformation, which represents an additional bonus from sustainable standpoint.

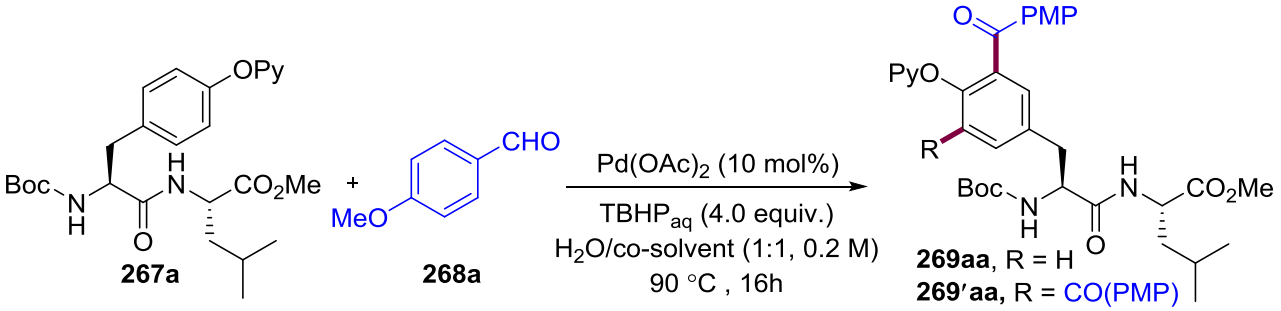


Entry	Co-solvent	Yield (%)[b,c]
1	none	78 (8:2)
2	^{t}BuOH	37 (96:4)
3	THF	14 (100:0)
4	MeCN	18 (100:0)[d]

[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (n equiv.), H_2O (0.4 mL), co-solvent (0.4 mL), Ar, 16h at 90 °C. [b] NMR yield using 1,1-diphenylethylene as internal standard. [c]Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**. [d] Yield of isolated product after column chromatography.

Table 33. Screening of co-solvents.

After a judicious screening of the reaction conditions, the optimal involved the use of 10 mol% of $Pd(OAc)_2$ as catalyst, 4.0 equivalents of inexpensive $TBHP_{aq}$ and water as solvent at 90°C which provided **269aa** in 78% yield as a mixture of *mono*- and *di*-acylated products (8:2 ratio) (Table 34, entry 1). Blank experiments revealed the crucial role of both Pd catalyst and $TBHP_{aq}$ as oxidant in this transformation, as not even traces of **269aa** were detected in their absence (Table 34, entries 2 and 3, respectively). Air atmosphere had a negative effect in the reaction outcome (Table 34, entry 4) and an oxygen atmosphere entirely inhibited the reaction (Table 34, entry 5).



Entry	Change from standard conditions	Yield (%)[b,c]
1	None	78 (8:2)[c]
2	Without $Pd(OAc)_2$	0

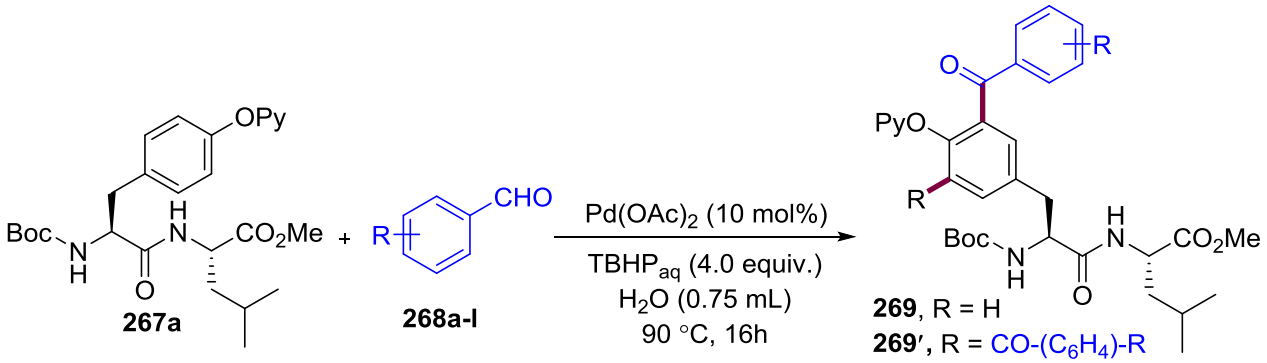
3	Without $TBHP_{aq}$	0
4	Under air	46 (93:7)
5	Under O_2	0

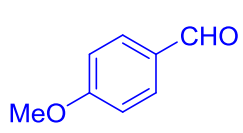
[a]Reaction conditions: **267a** (0.15 mmol), **268a** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (4.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] Yield of isolated product after column chromatography. [c] Ratio of *mono*- and *di*-acylated product **269aa**:**269'aa**.

Table 34. Control experiments.

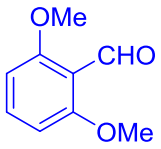
2.4.2. Pd-Catalyzed C(sp²)–H Acylation of Tyr-Containing Dipeptide 267a with Aldehydes

Once we had the optimal conditions in hand, the preparative scope was evaluate began with a broad variety of aldehydes and Boc-Tyr(OPy)-Leu-OMe (**267a**) as substrate as depicted in the Scheme 127. Regardless the electron nature of the aldehydes, in general, the acylated products **269** were obtained in good yields and high preference for the *mono*-acylated product. Benzaldehydes bearing ethers (**269aa-ad**), halides (**269ae-ah**), acetamide (**269ai**) and naphthyl system (**269ak**) were perfectly tolerated, whereas the nitro group was not compatible with the reaction conditions. Ortho- (**269ab**), meta- (**269af**-**ag**) or para- (**269aa**, **269ae**, **269ah**, **269ai** and **269aj**) substituted aldehydes were suitable as well as highly congested aldehydes (**269ab**-**ad**). Interestingly, when highly electron-rich aldehydes were employed, the *mono*-acylated products were exclusively obtained (**269ac**, **269ai**). It is noteworthy that the reaction could be scaled up to gram scale with *p*-(trifluoromethyl)benzaldehyde (**268h**), which verified the robustness of the process and the synthetic utility of our peptide tagging manifold.

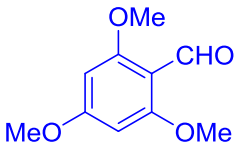




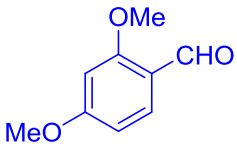
269aa, 78% (8:2)[c]



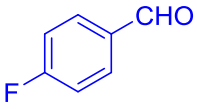
269ab, 74% (8:2)[c]



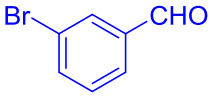
269ac, 54%



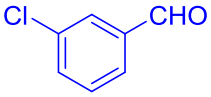
269ad, 48% (83:17)[c]



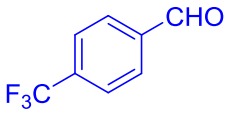
269ae, 76% (75:25)[c]



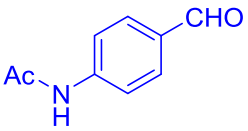
269af, 58% (8:2)[c]



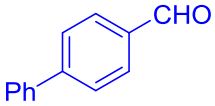
269, 58% (75:25)[c]



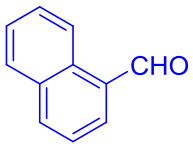
269ah, 73% (75:25)[c,d]



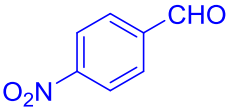
269ai, 52%[e]



269aj, 73% (8:2)[c]



269ak, 73% (8:2)[c]



269al, 0%

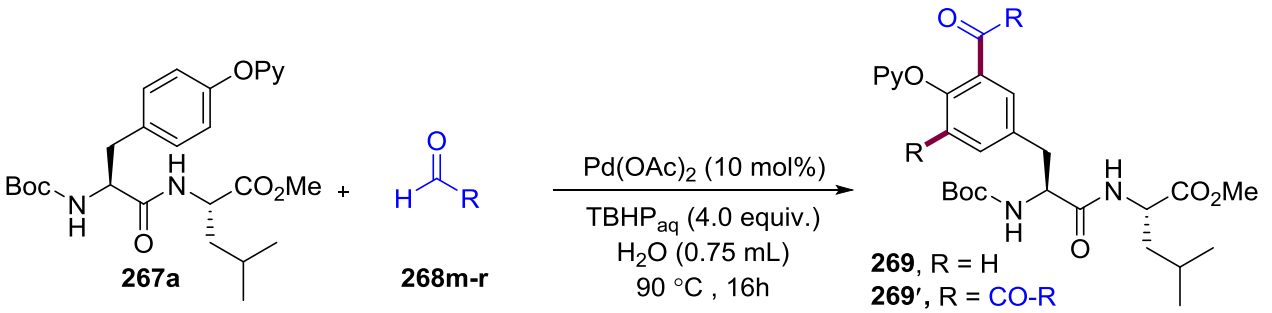
Reaction conditions: **267a** (0.15 mmol), **268a-l** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (4.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of *mono-* and *di-*acylated product **269**:**269'**. [d] Gram scale experiment.

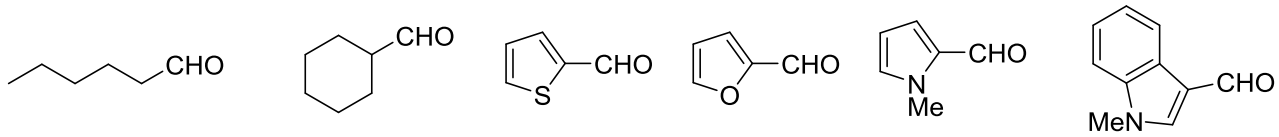
Scheme 127. Pd-catalyzed C(sp^2)–H acylation of Tyr-containing dipeptide **267a** with benzaldehydes.

2.4.3. Pd-Catalyzed C(sp^2)–H Acylation of Tyr-Containing Dipeptide 267a with Aliphatic and Heteroaromatic Aldehydes

Not only benzaldehydes but also the use of aliphatic aldehydes such as heptanal (**268m**) and cyclohexanecarboxaldehyde (**268n**) was explored, which resulted in the exclusive formation of the *mono*-acetylated product **269am** and **269an**, respectively. However, the standard reaction conditions had to be modified, switching the solvent to PhCl and using 5.0 equivalents of aldehyde, in order to obtain slightly higher yields (up to 57%). Likewise, pharmaceutically relevant heterocyclic aldehydes could be employed as coupling partners. In this case, under toluene as solvent at 100°C, which was determinant for the success of the transformation. Accordingly, 2-thiophene (**268ñ**), 2-furan (**268o**), *N*-methyl-2-pyrrole (**268p**) and *N*-methyl-3-

indoyl carboxaldehyde (**268q**) selectively afforded the corresponding *mono*-acetylated products **269añ-aq**. Overall, our Tyr acylation protocol takes place in considerably mild and aqueous conditions compared to related acylation protocols which required higher temperatures along with the use of organic solvents.[178]





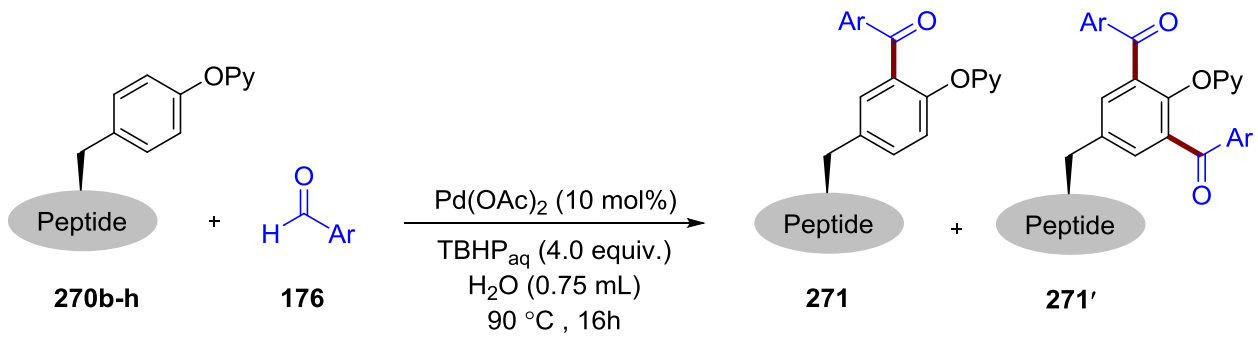
269am, 47% (56%)[f] **269an**, 46% (57%)[f] **269añ**, 62%[g] **269ao**, 55%[g] **269ap**, 44%[g] **269aq**, 61% (95:5)[c,e]

Reaction conditions: **267a** (0.15 mmol), **268m-n** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (4.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of *mono*- and *di*-acylated product **269**:**269'**. [d] Reaction performed in toluene. [e] Reaction performed in PhCl with 5.0 equiv. of aldehyde. [f] Reaction performed in toluene at 100 °C with 5.0 equiv. of aldehyde.

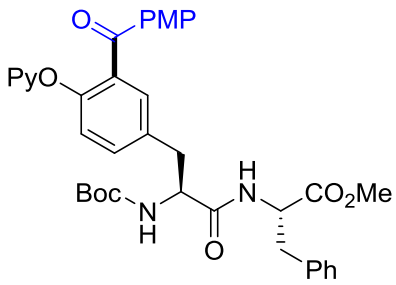
Scheme 128. Pd-catalyzed C(sp²)–H acylation of **175a** with aliphatic and heteroaromatic aldehydes.

2.4.4. Pd-Catalyzed C(sp^2)–H Aroylation of Tyr-Containing Dipeptides with Aldehydes

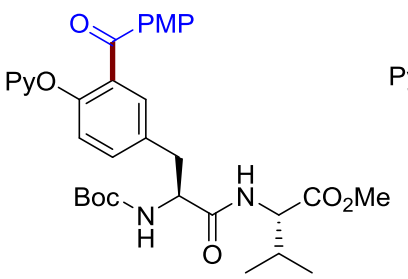
We next turned our attention to the modification of different Tyr-containing dipeptides as shown in the Scheme 129. Fortunately, dipeptides bearing a wide spectrum of amino acid residues were successfully acetylated with PMP (**176a**) or *p*-(trifluoromethyl)benzaldehyde (**176h**), delivering the products **177** in moderate to high yield and high *mono*-selectivity, total *mono*-selectivity (**177**) or unexpectedly *di*-selectivity (**177'**). The latter *di*-acetylated product **177'gh** was obtained when Pro residue was installed within the peptide **175h**, which could enhance the reactivity due to absence of additional N–H bonds as we had observed in our previous investigations,[207] however the selectivity was not reproduced with the use of *p*-methoxybenzaldehyde (**177ga**). Noteworthy, chelating polar amino residues such as protected Lys residue, smoothly delivered the target products (**177ha**). Importantly, the reaction was selective to the Tyr(OPy) moiety as native Tyr residue remained intact after the transformation (**177fa**) and the position of Tyr residues within the peptide, *N*- or *C*-terminal positions, did not change the final outcome.



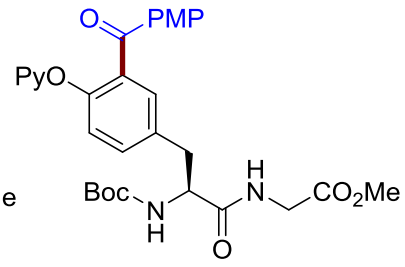
270b-h **176** **271** **271′**



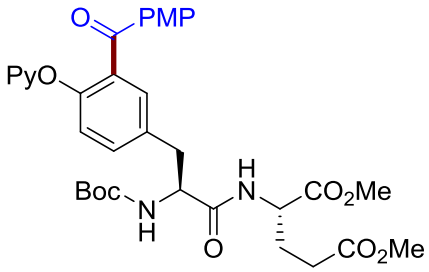
271ba, 49% (8:2)[c]



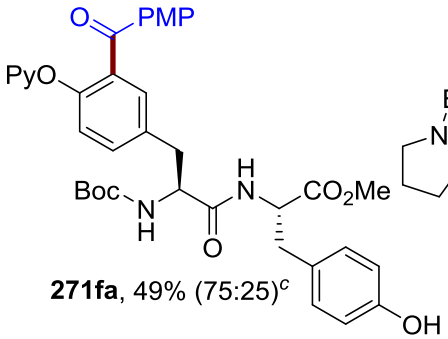
271ca, 49% (8:2)[c]



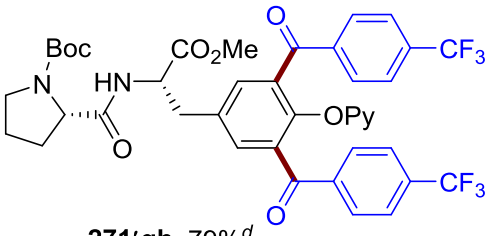
271da, 49% (75:25)[c,d]



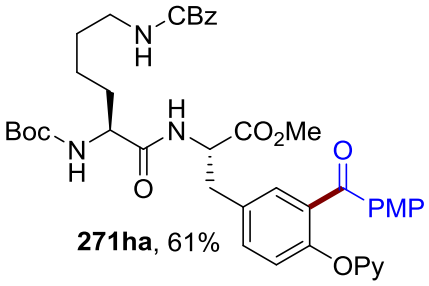
271ea, 50% (9:1)[c]



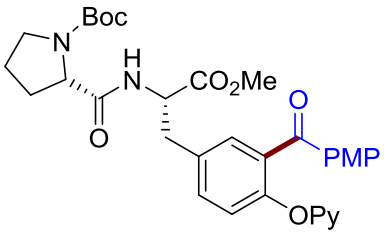
271fa, 49% (75:25)[c]



271′gh, 79%[d]



271ha, 61%



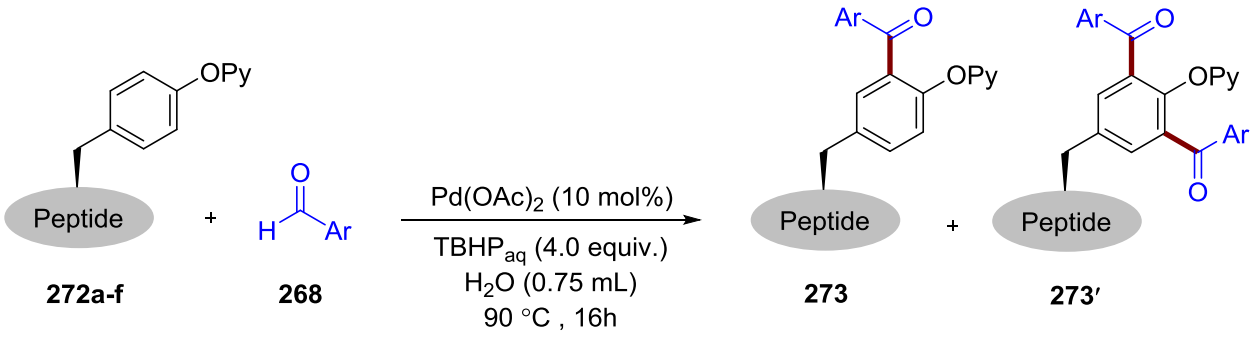
271ga, 81% (8:2)[c,d]

Reaction conditions: **270b-l** (0.15 mmol), **268** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (4.0 equiv.), H_2O (0.75 ml), Ar, 16h at 90 °C. Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of *mono-* and *di-*acylated product **271**:**271'**. [d] Using toluene as solvent.

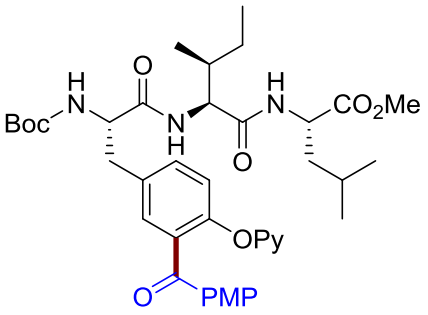
Scheme 129. Pd-catalyzed C(sp²)–H aroylation of Tyr-containing dipeptides with aldehydes.

2.4.5. Pd-Catalyzed C(sp^2)–H Acylation of Tyr-Containing Oligopeptides with Aldehydes

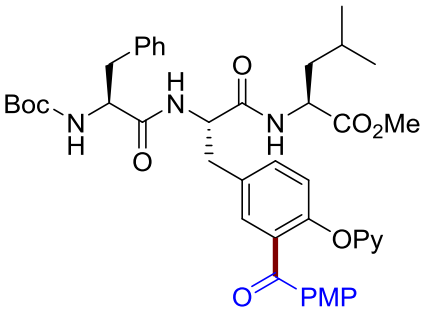
With the aim of capitalize the full potential of this site-selective C–H acylation protocol, the late-stage diversification of more complex oligopeptides **272** was carry out. As shown in the Scheme 130, the process efficiently occurred in highly decorated peptides of different length of tri- and tetrapeptides, including peptides housing the tyr unit in inner position (**273ba**). Remarkably, the biologically active Neuromedin N, was successfully acylated in good yields (**273dh)** which illustrates the high potential of this procedure toward the site-selective modification of biomolecules of high complexity.



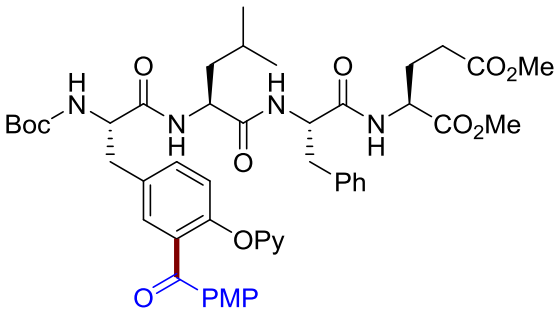
272a-f **268** **273** **273′**



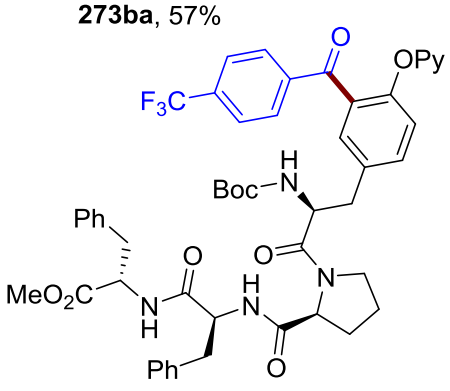
273aa, 62% (85:15)[c]



273ba, 57%



273ca, 64% (8:2)[c]



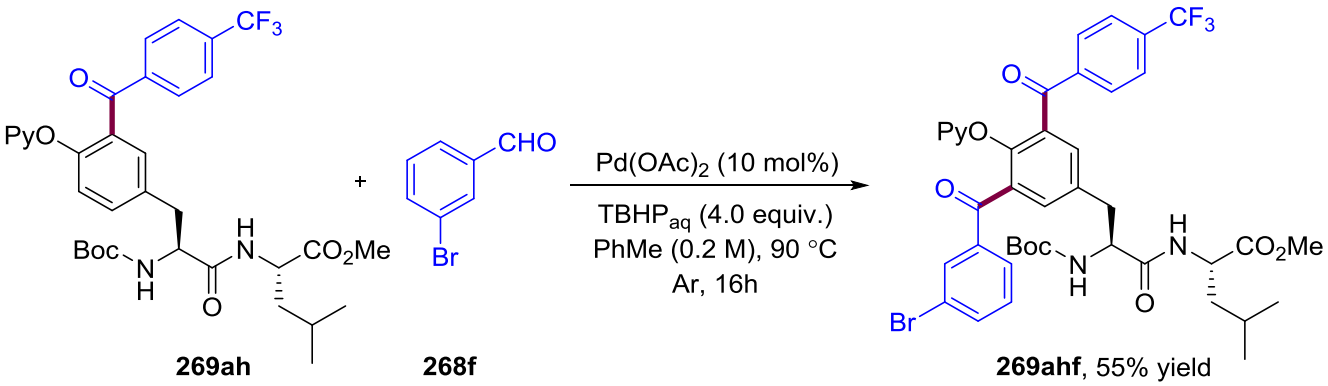
273dh, 61% (8:2)[c,d]
Endomorphin 2 analogue

[a]Reaction conditions: **272a-f** (0.15 mmol), **268** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), TBHPaq (4.0 equiv.), H_2O (0.75 mL), Ar, 16h at 90 °C. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c]Ratio of *mono-* and *di-*acylated product **273**:**273'**. [d] Using toluene as solvent.

Scheme 130. Pd-catalyzed C(sp²)–H aroylation of Tyr-containing oligopeptides with aldehydes.

2.4.6. Consecutive C(sp²)–H Acylation Reaction

The scope was also extended to the orthogonal C–H acylation of Boc-Tyr(OPy)-Leu-OMe (**175a**) with two distinct aldehydes. Firstly, the *mono*-acylated product **269ah** was isolated under standard conditions and it was employed as substrate for a consecutive acylation, in this case using *m*-bromobenzaldehyde (**268f**) as acyl source, which delivered the desired *di*-acylated product **269ahf** in a satisfactory yield (Scheme 131).

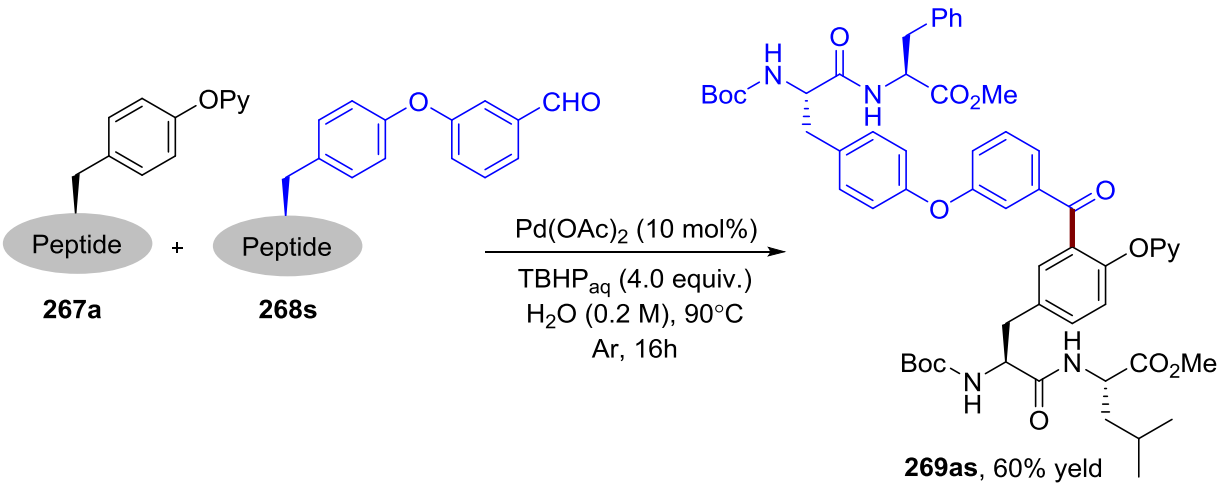


Scheme 131. Consecutive C(sp²)–H aroylation reaction.

2.4.7. Pd-Catalyzed C–H Acylation Toward Chemical Ligation

As previously described by other groups,[103, 118, 152] the chemical ligation of peptides was investigated with our procedure. For this, Tyr-containing peptides were *O*-arylated with 3-iodobenzaldehyde through Cu-catalyzed cross-coupling reaction,[213] thus affording the peptide tethered with the benzaldehyde moiety (**180a**) which was employed as regular benzaldehydes. Herein, by slight modification of the standard conditions (switching the solvent from water to toluene), two Tyr-containing peptides were coupled good yield featuring a unique diaryl ketone cross-linking (Scheme 132). Remarkably, only the *mono*-acetylated products **181aa** was isolated and the undesired *di*-acylation was never observed, probably due to steric hindrance.

[213] Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. *Organometallics*, **2015**, *34*, 953.



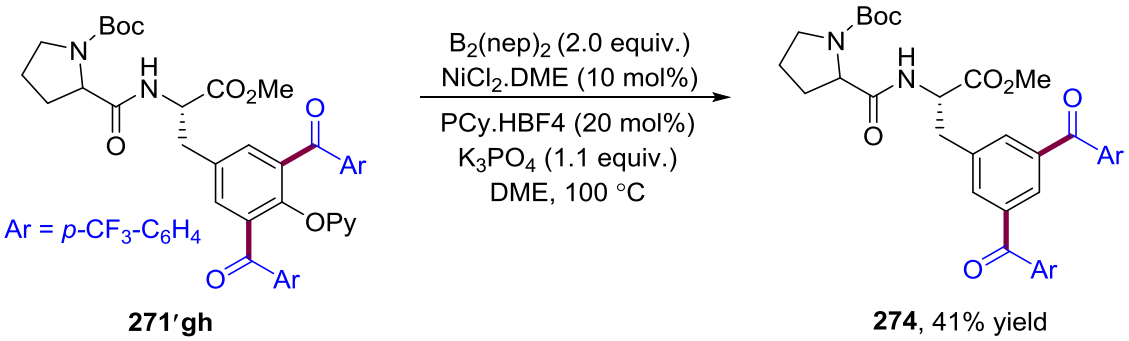
[a]Reaction conditions: **267a** (0.15 mmol), **268s** (0.45 mmol), $Pd(OAc)_2$ (10 mol %), $TBHP_{aq}$ (4.0 equiv.), toluene (0.75 mL), Ar, 16h at 90 °C. [b] Yield of isolated product after column chromatography, average of at least two independent runs.

Scheme 132. Pd-catalyzed C–H acylation toward chemical ligation.

2.4.8. Reductive Cleavage of the DG

A procedure for the removal of the exogenous directing group is always desirable to convert the tyrosine to its native phenol form. This transformation has been described upon a two-step process which consists in *N*-methylation of the pyridine moiety with methyl triflate followed by the cleavage of the resulting C(pyridinium)–O bond by treatment with an alcoholic solution of sodium.[210] Unfortunately, its application resulted in mixture of products along with the racemization of the existing chiral centers. As alternative, the borylative cleavage of OPy directing was explored, which would deliver the highly versatile C–B bond.[214] After evaluation of several protocols involving Rh-,[214c] Ni-[214b] and Fe-catalyzed[214a] borylation reactions, the desired borylation cleavage was never observed, but instead, the reduced product **274** was obtained (Scheme 133).[214b] Although the native structure of tyrosine was altered with the removal of the hydroxyl group, this strategy allows a novel access to *meta*-aroylated Phe-containing peptides from Tyr(OPy) residues.

[214] a) X, Zeng.; Y, Zhang.; Z, Liu.; S, Geng.; Y, He.; Z, Geng. *Org. Lett*. **2020**, *22*, 2950. b) M, Tobisu.; J, Zhao.; H, Kinuta.; T, Furukawa.; T, Igarashi.; N, Chatani. *Adv. Synth. Catal*. **2016**, *358*, 2417. c) H, Kinuta.; M, Tobisu.; N, Chatani. *J. Am. Chem. Soc*. **2015**, *137*, 1593.



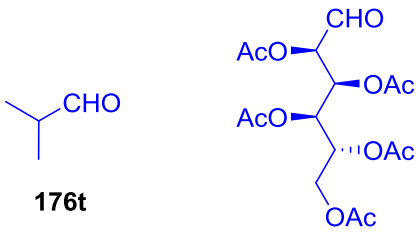
271′gh **274**, 41% yield

Scheme 133. Reductive cleavage of the DG.

2.4.9. Unsuccesful Reactions

2.4.9.1. Unsuccesful Aldehydes

Despite the wide range of aldehydes suitable for this transformation, including aromatic, aliphatic and heteroaromatic aldehydes, a couple of examples did not deliver the target products. As shown in Scheme 134, with the employment of the isobutylaldehyde **176t** and the *O*-acetylated sugar **176u** the corresponding products were not formed. The nature of these aldehydes could be the reason, as depicted in schemes 125 and 126, aliphatic aldehydes were less reactive than benzaldehydes. Furthermore, in the case of the sugar **176u**, the multiple acetoxyl groups of the compound could affect the solubility or inhibit the catalyst through chelation events.



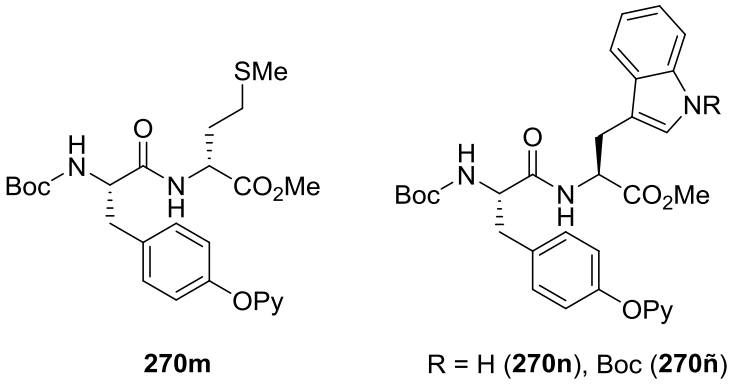
176t **176u**

Scheme 134. Uncussesful aldehydes.

2.4.9.2. Unsuccessful Substrates

Regarding the substrates, dipeptides containing methionine (**270m**) or trypthophan residues (**270n-ñ**) remained unreactive under the standard conditions. Despite the oxidative nature of this transformation the

methionine residue remained intact and in the case of the tryptophan containing-peptides (**270n-ñ**) the plausible competitive C2-acylation of the tryptophan moiety was never observed.

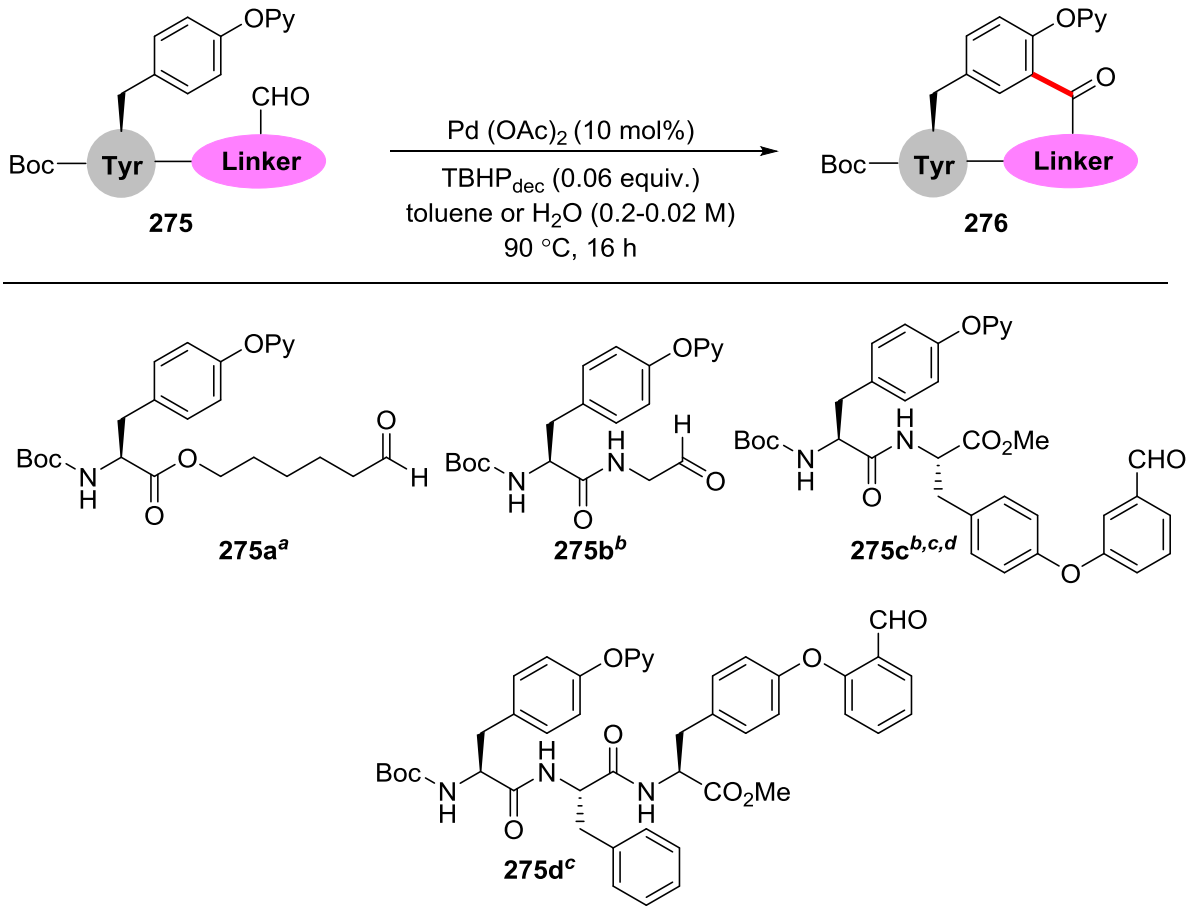


270m R = H (**270n**), Boc (**270ñ**)

Scheme 135. Uncuccesful substrates.

2.4.9.3. Intramolecular Approach

In order to assembly challenging cyclopeptide derivatives, an intramolecular approach was tested by introducing the aldehyde structure into the peptide substrates **275a-d** along with the OPy directing group, which, if successful, would deliver the corresponding cyclic peptides **276**. As shown in Scheme 136, different type of substrates bearing linkers and the aldehyde moiety were designed. Firstly, substrates consisting in the Tyr unit with aliphatic ester or amide bearing the aldehyde (**275a** and **275b**, respectively) were synthesized. The long-chain ester within **275a** would add the optimal flexibility and reduce the strain at the time of the cyclization, whereas in the case of the short-chain **275b** the two reactive groups, the OPy and aldehyde group, would be closer to each other which could facilitate the reactivity. However, when substrates **275a-b** were submitted to the protocol under diluted conditions, the corresponding cyclization was not observed and the substrates remained intact. Afterwards, peptides bearing the 3-benzaldehyde structure **275c-d** were prepared. The aromatic nature of these aldehydes could be the key to achieve the required reactivity toward the cyclization. Unfortunately, substrates **275c-d** did not afford the desired cyclic peptides **276** under different concentrations and only substrates were recovered after the reaction time. Despite our attempts to extend our acylation platform to forge biologically relevant cyclopeptides, the desired intramolecular reaction was not achieved. Accordingly, new tactics should be design in order to pursue this challenging synthetic goal.



[a] Employing 0.02 M of toluene. [b] Employing 0.06 M of toluene. [d] Employing 0.2 M of toluene. [e] Employing 0.2 M of H_2O.

Scheme 136. Intramolecular approach.

2.4.10. Conclusions

In summary, we have developed an unprecedented site-selective acylation of Tyr-containing peptides applicable with a broad spectrum of aldehydes.[215] The transformation was carried out under sustainable conditions and its potential was demonstrated with the successful modification of complex peptides along with the challenging chemical ligation of peptides. Furthermore, the reductive cleavage of the OPy moiety was achieved, which enabled the access to *meta*-acylated Phe-containing peptides. Contrary to most procedures for peptide modification which required halogenated reagent such as iodoarenes, our radical approach allows the direct coupling of two C–H bonds, more convenient from atom-economical standpoint since halogenated waste is avoided. Our protocol broaden the available chemical toolbox for the modification of the ubiquitous

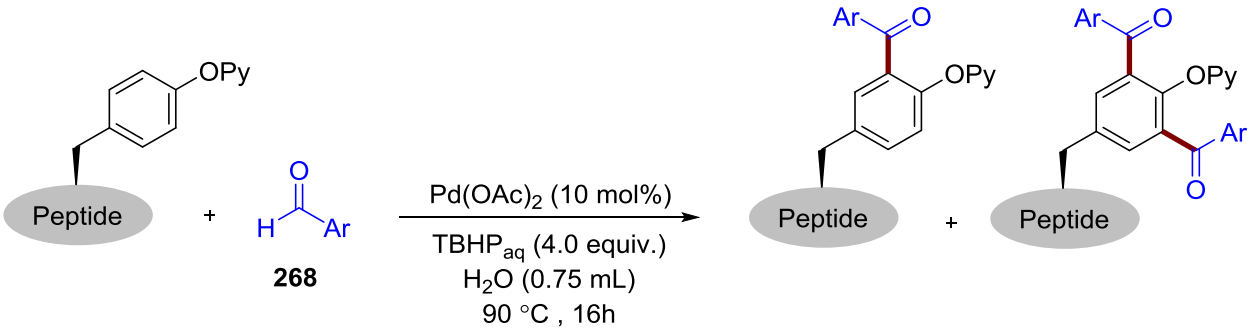
[215] San Segundo, M.; Correa, A. *Chem Sci.* **2020**, *11*, 11531. These results have been protected and an spanish patent application was submitted (P202030131). The corresponding PCT is currently under study.

Tyr residues and demonstrates the applicability of radical processes in the late-stage-functionalization of peptides.

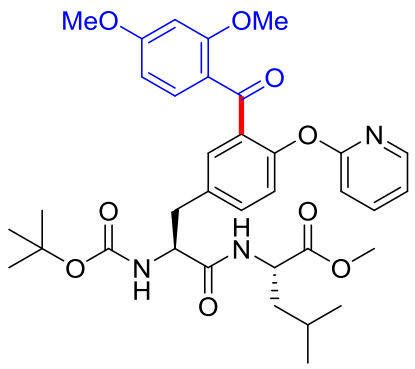
2.4.11. Experimental Procedure

In this section, some representative procedures as well as the characterization of illustrative compounds are provided. For a full detailed experimental description, please see the supporting information of the following article.[215]

2.4.11.1. Pd-Catalyzed C(sp^2)–H Acylation of Tyr-Containing Oligopeptides

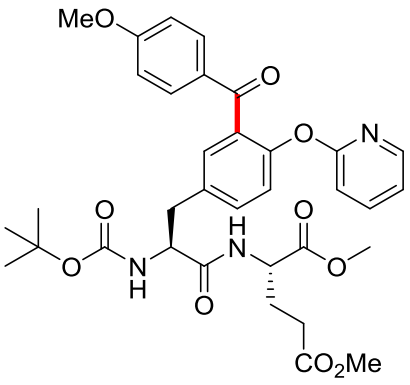


General Procedure: A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol), the aldehyde **268** (0.45 mmol, if solid) and $Pd(OAc)_2$ (10 mol %, 3.4 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, the aldehyde **268** (0.45 mmol, if liquid), a commercially available solution of Luperox® (0.60 mmol, 84 µL) and water (0.75 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to 90 °C in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.



(269ad)

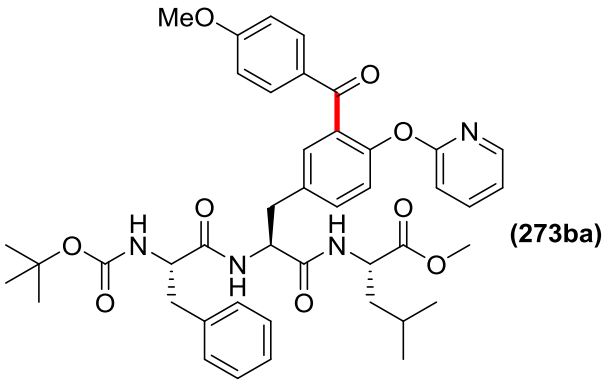
Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(2,4-dimethoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-leucinate (269ad). Following the general procedure, using commercially available 2,4-dimethoxybenzaldehyde **268d** (0.45 mmol, 74.8 mg) and **267a** (0.15 mmol, 73 mg) provided 48 mg (48% yield) (83:17 ratio) of **269ad** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 4.6 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.46 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 6.8 Hz, 1H), 6.33 (s, 1H), 5.15 (s, 1H), 4.61 (q, *J* = 8.3 Hz, 1H), 4.39 (d, *J* = 6.7 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.14 (qd, *J* = 14.1, 6.7 Hz, 2H), 1.69 – 1.53 (m, 3H), 1.44 (s, 9H), 0.93 (dd, *J* = 5.9, 4.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 173.0, 171.0, 164.2, 163.4, 160.8, 155.5, 150.4, 147.0, 139.1, 134.7, 133.3, 132.8, 131.0, 122.9, 122.0, 118.2, 111.1, 104.6, 98.4, 80.4, 55.7, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm^{-1}): 3315, 2957, 1656, 1598, 1465, 1427, 1265, 1244, 1210, 1161. HRMS *caldc* for ($C_{35}H_{43}N_3O_9$): 649.2999, *found* 649.3015.



(271ea)

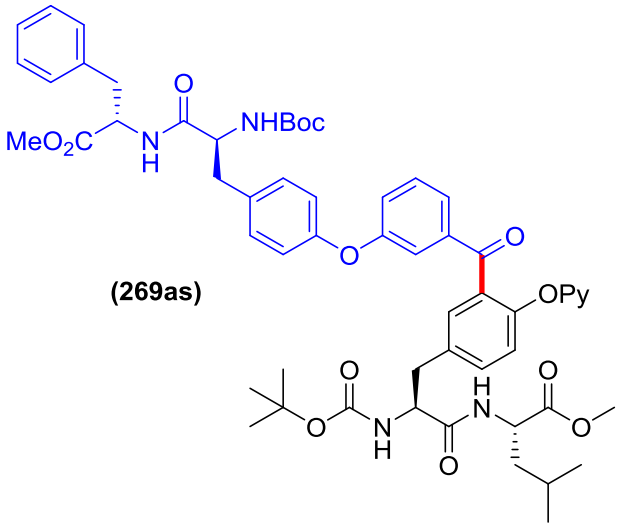
Dimethyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-glutamate (271ea). Following the general procedure, using commercially available 4-methoxybenzaldehyde **268a** (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Glu(OMe)-OMe (**270e**) (0.15 mmol, 77.3 mg) provided 50 mg (50% yield) (9:1 ratio) of **271ea** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.41 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.82 – 6.76 (m, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.23 –

5.11 (m, 1H), 4.64 – 4.55 (m, 1H), 4.40 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 3.26 – 3.02 (m, 2H), 2.46 – 2.28 (m, 2H), 2.28 – 2.14 (m, 1H), 2.03 – 1.91 (m, 1H), 1.43 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 173.3, 171.8, 171.1, 163.6, 163.1, 155.5, 150.4, 147.0, 139.5, 133.1, 132.7, 132.6, 132.5, 130.9, 130.2, 123.0, 118.6, 113.4, 111.6, 80.5, 55.7, 55.6, 52.7, 51.9, 51.8, 37.4, 29.9, 28.3, 27.3. IR (cm^{-1}): 3305, 2953, 1737, 1656, 1595, 1427, 1244, 1165, 730. HRMS *caldc* for ($C_{34}H_{39}N_3O_{10}$): 649.2635, *found* 649.2674.



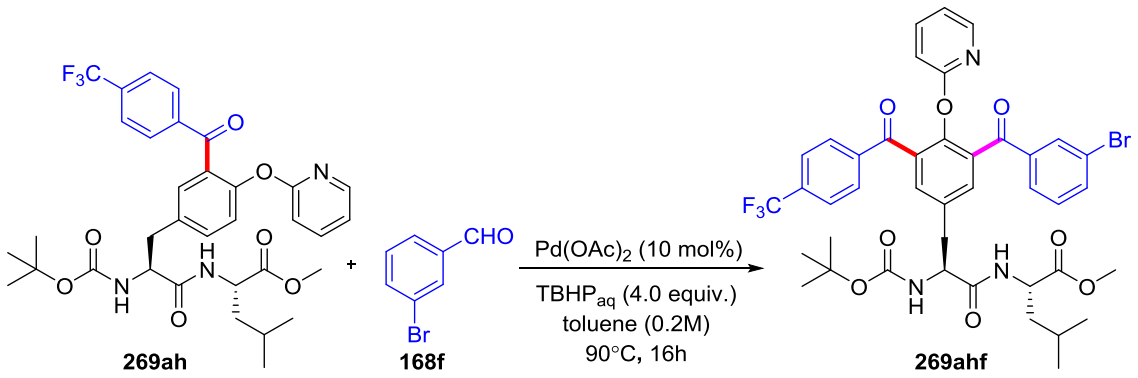
(273ba)

Methyl ((*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-leucinate (273ba). Following the general procedure, using commercially available 4-methoxybenzaldehyde **268a** (0.30 mmol, 36.7 µL) and Boc-Phe-Tyr(OPy)-Leu-OMe (**272b**) (0.10 mmol, 63.0 mg) provided 44 mg (57% yield) of **273ba** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.52 (ddd, *J* = 8.5, 7.2, 2.0 Hz, 1H), 7.32 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.26 (d, *J* = 1.8 Hz, 2H), 7.23 – 7.11 (m, 5H), 6.87 (dd, *J* = 6.6, 5.0 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 6.47 (d, *J* = 6.9 Hz, 1H), 5.14 (d, *J* = 7.2 Hz, 1H), 4.74 – 4.63 (m, 1H), 4.56 – 4.46 (m, 1H), 4.34 (q, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.19 – 3.02 (m, 3H), 3.00 – 2.89 (m, 1H), 1.64 – 1.46 (m, 3H), 1.34 (s, 9H), 0.89 (d, *J* = 5.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 172.8, 171.4, 170.1, 163.7, 163.0, 155.8, 150.2, 146.7, 139.8, 136.6, 133.2, 132.9, 132.8, 132.5, 131.0, 130.2, 129.4, 128.8, 127.1, 123.0, 118.6, 113.5, 111.8, 80.5, 56.2, 55.6, 53.9, 52.4, 51.1, 41.2, 37.9, 37.1, 28.3, 24.8, 22.9, 22.0. IR (cm^{-1}): 3295, 2959, 1646, 1597, 1428, 1254, 1168. HRMS *caldc* for ($C_{43}H_{50}N_4O_9$): 766.3578, *found* 766.3611.



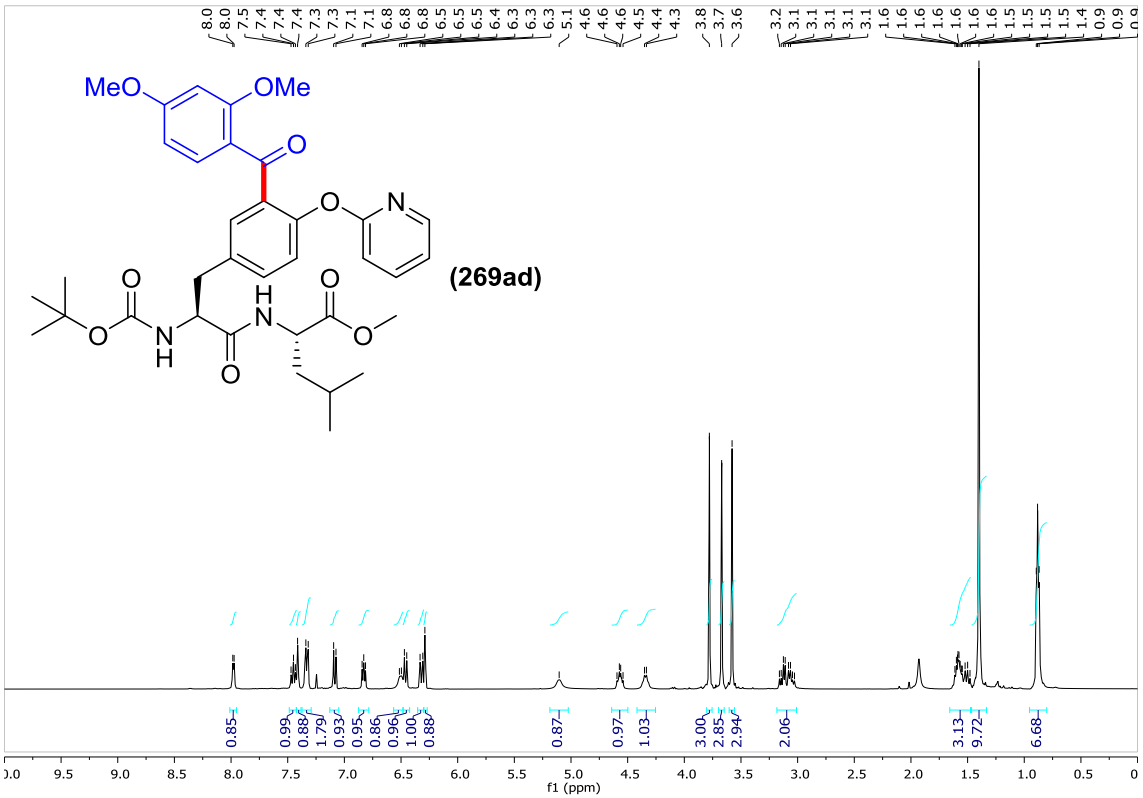
(269as)

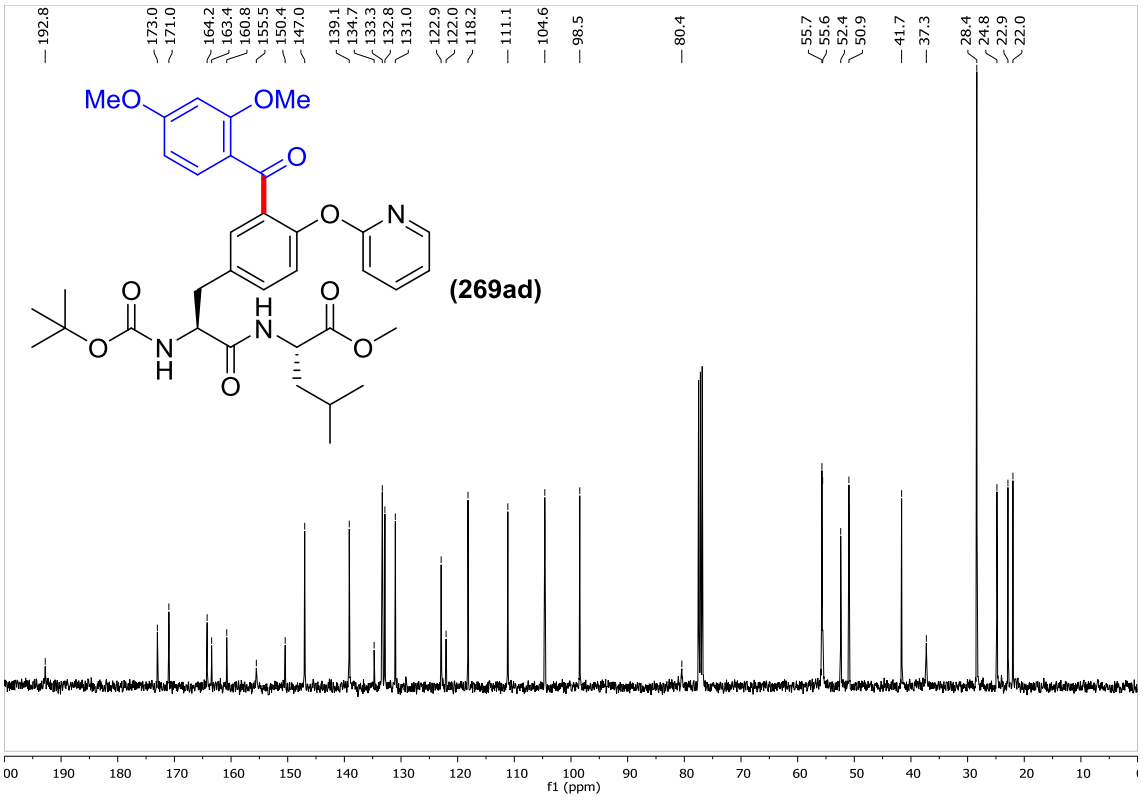
Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(3-(3-(4-((*S*)-2-((tert-butoxycarbonyl)amino)-3-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-*L*-leucinate (269as). Following the general procedure, using methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(3-formylphenoxy)phenyl)propanoyl)-*L*-phenylalaninate **168s** (0.45 mmol, 246 mg) and Boc-Tyr(OPy)-Leu-OMe (**267a**) (0.15 mmol, 73.0 mg) provided 92 mg (60% yield) of **269as** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.56 (ddd, *J* = 8.7, 7.4, 2.0 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.30 – 7.23 (m, 4H), 7.22 – 6.99 (m, 7H), 6.95 – 6.81 (m, 3H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.54 (s, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 8.3 Hz, 1H), 5.03 (t, *J* = 8.1 Hz, 1H), 4.90 – 4.77 (m, 1H), 4.60 (td, *J* = 8.5, 4.4 Hz, 1H), 4.48 – 4.25 (m, 2H), 3.70 (s, 6H), 3.21 – 2.91 (m, 6H), 1.69 – 1.52 (m, 3H), 1.43 (s, 9H), 1.40 (s, 9H), 0.98 – 0.87 (m, 6H). IR (cm^{-1}): 3304, 2957, 1742, 1656, 1505, 1429, 1243, 1167, 732. ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 171.5, 171.3, 170.8, 170.7, 162.8, 156.9, 155.7, 155.4, 155.3, 155.2, 150.5, 146.9, 139.3, 139.1, 135.5, 133.2, 133.2, 131.0, 130.7, 129.3, 129.2, 129.1, 128.6, 128.5, 127.1, 127.1, 125.1, 123.1, 122.9, 119.6, 118.8, 118.5, 111.3, 80.3, 80.2, 55.6, 55.3, 53.2, 53.0, 52.3, 50.7, 41.4, 37.9, 37.5, 37.1, 28.2, 24.6, 22.7, 21.8. IR (cm^{-1}): 3304, 2957, 1742, 1656, 1505, 1429, 1243, 1167, 732. HRMS *caldc* for ($C_{57}H_{67}N_5O_{13}$): 1029.4735, *found* 1029.4761.

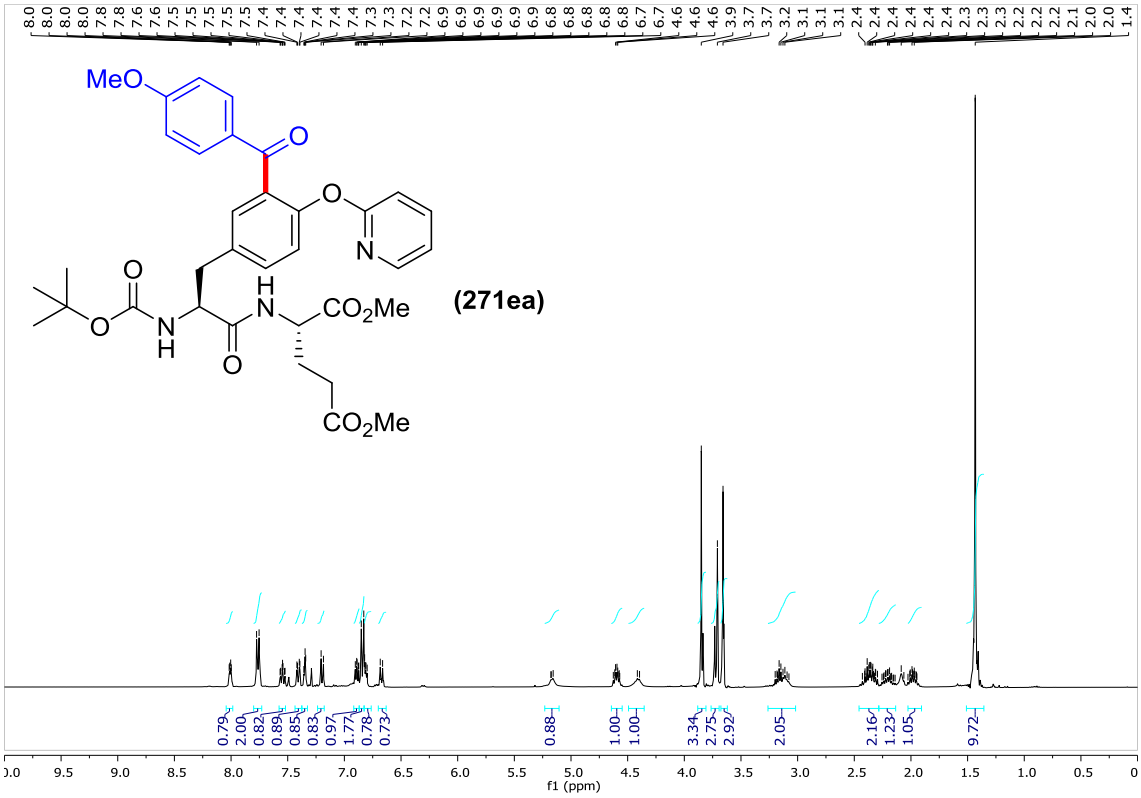


Methyl ((*S*)-3-(3-(3-bromobenzoyl)-4-(pyridin-2-yloxy)-5-(4-(trifluoromethyl)benzoyl)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-*L*-leucinate (269ahf). A reaction tube containing a stirring bar was charged with methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl)-*L*-leucinate **269ah** (0.15 mmol, 98.6 mg), $Pd(OAc)_2$ (10 mol %), TBHP (70 wt. % in H_2O) (4.00 equiv). The reaction tube was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). 3-Bromobenzaldehyde **268f** (0.45 mmol, 52.7 µL) and toluene (0.75 mL) were added under argon atmosphere. The reaction tube was next warmed up to 90 °C and stirred for 16 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and evaporated. The resulting crude was then purified by column chromatography to afford the corresponding product **269ahf** in 55% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 3H), 7.75 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.66 – 7.59 (m, 3H), 7.57 – 7.49 (m, 3H), 7.31 – 7.23 (m, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.75 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 6.08 (d, *J* = 8.3 Hz, 1H), 5.20 (d, *J* = 8.3 Hz, 1H), 4.58 (td, *J* = 8.6, 4.5 Hz, 1H), 4.44 (q, *J* = 7.3 Hz, 1H), 3.62 (s, 3H), 3.29 (dd, *J* = 14.0, 6.6 Hz, 1H), 3.12 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.68 – 1.53 (m, 3H), 1.40 (s, 9H), 0.97 – 0.83 (m, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 193.1, 173.0, 170.4, 161.7, 155.4, 147.9, 146.0, 140.2, 139.7, 139.0, 135.8, 134.2, 134.1, 134.0, 133.2, 132.9, 132.4, 129.9, 129.7, 128.3, 125.1, 125.1, 122.4, 118.9, 110.7, 80.6, 55.3, 52.5, 50.9, 41.5, 37.4, 31.1, 28.3, 24.9, 22.9, 21.9. IR (cm^{-1}): 3325, 2959, 1666, 1410, 1322, 1240, 1166, 1131, 1109, 1065, 732. HRMS *caldc* for ($C_{41}H_{41}BrF_3N_3O_8$): 839.2029, *found* 839.2071.

2.4.11.2. ^{1}H NMR and ^{13}C NMR Spectra



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CO2Me
(271ea)
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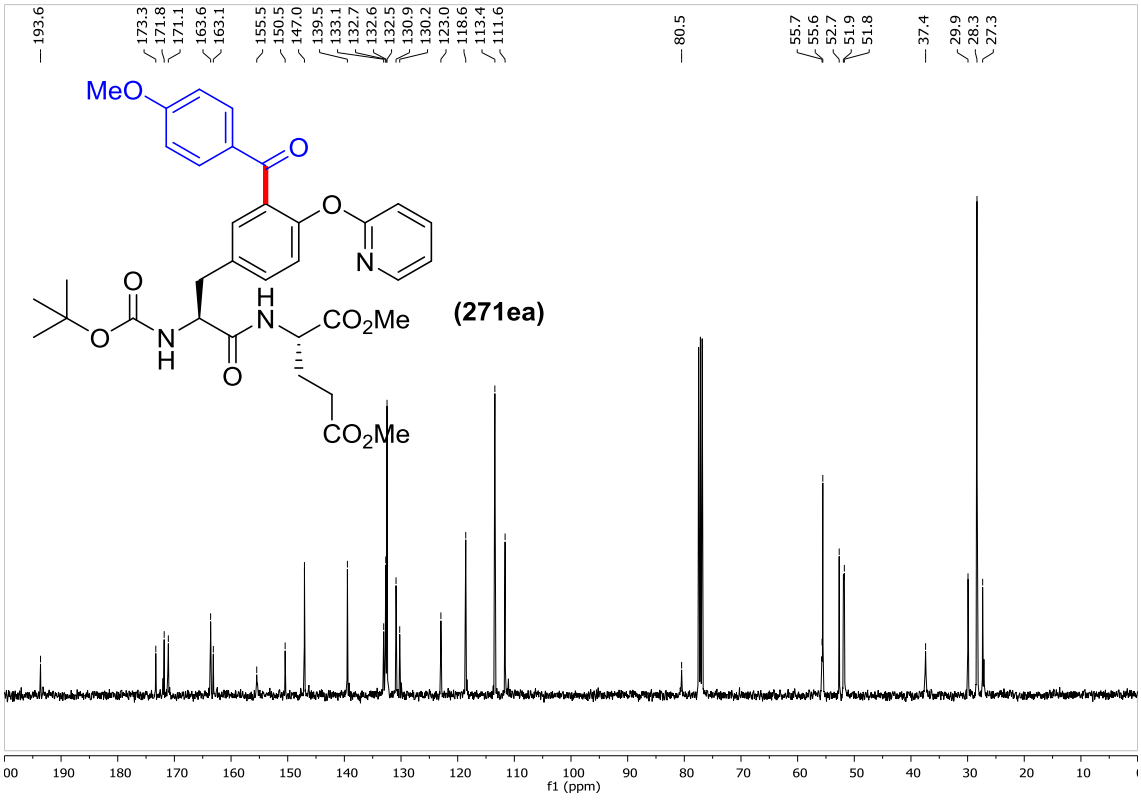
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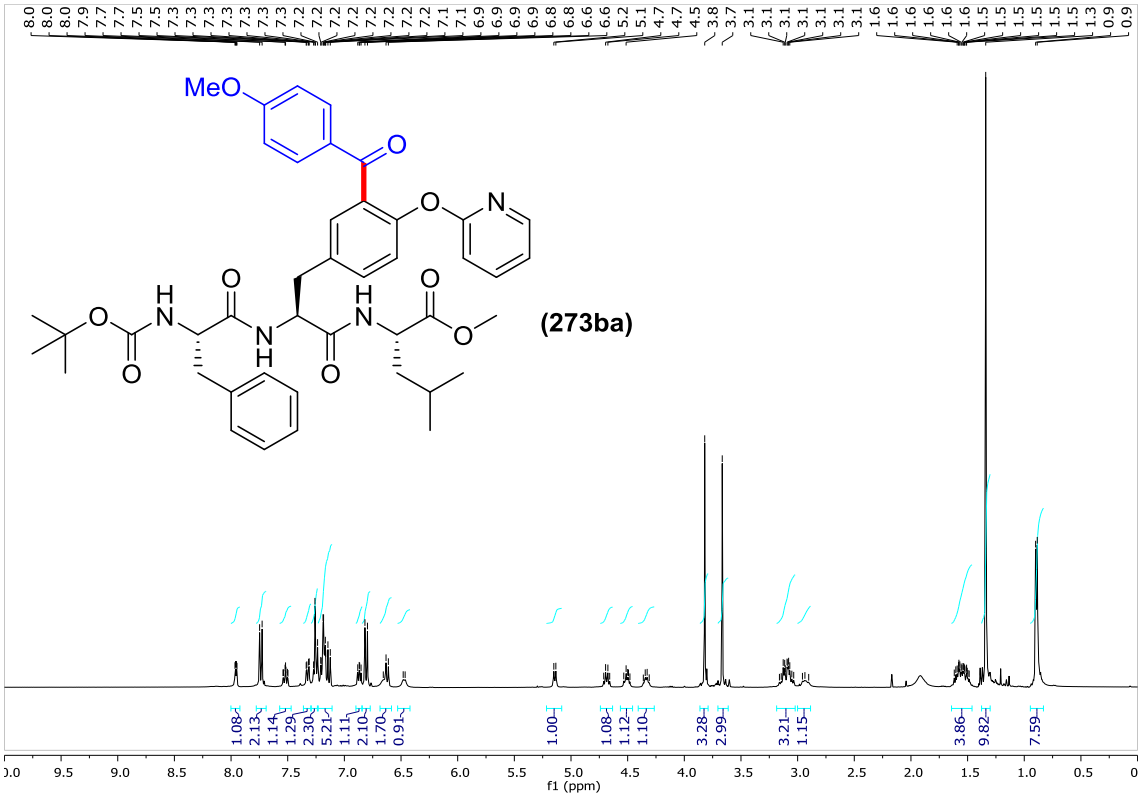
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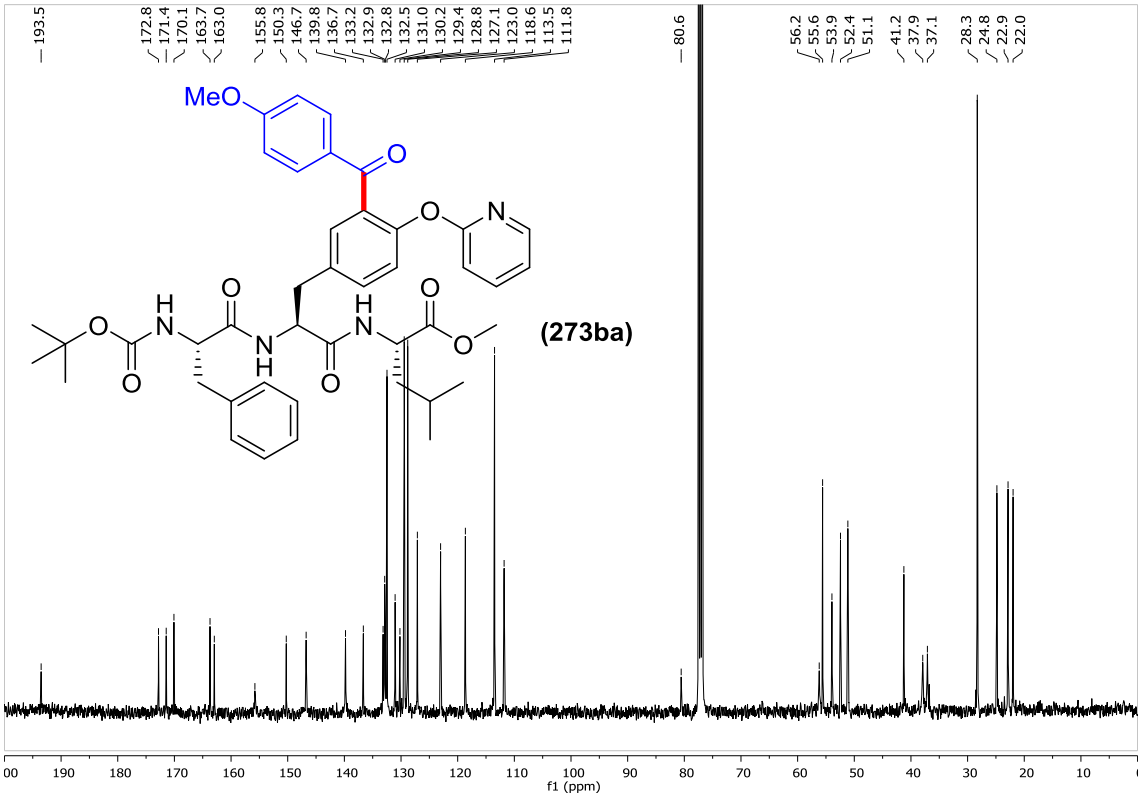
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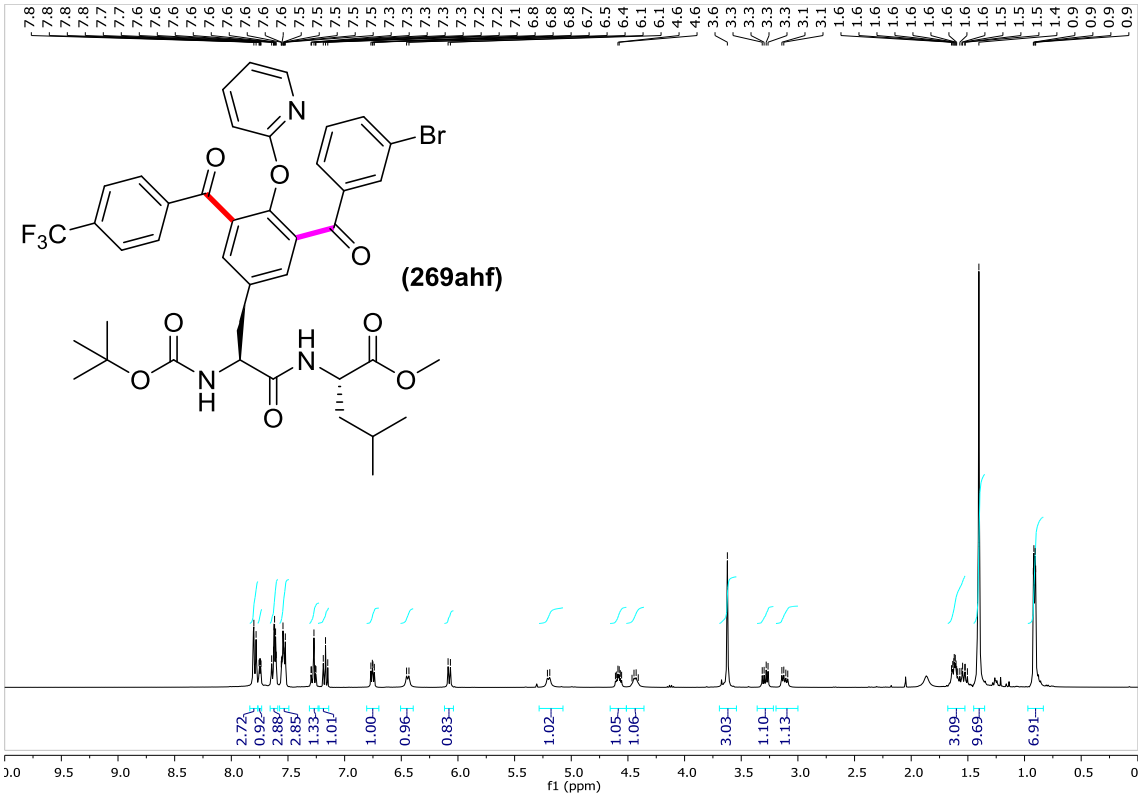
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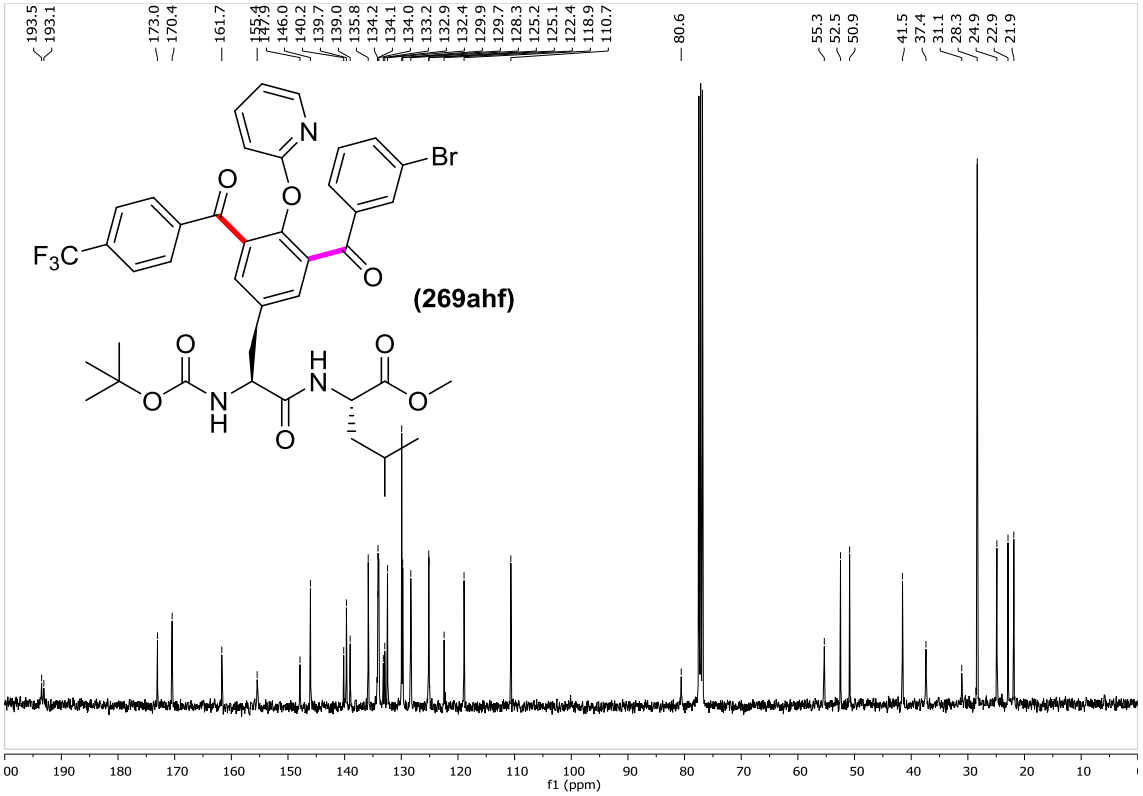
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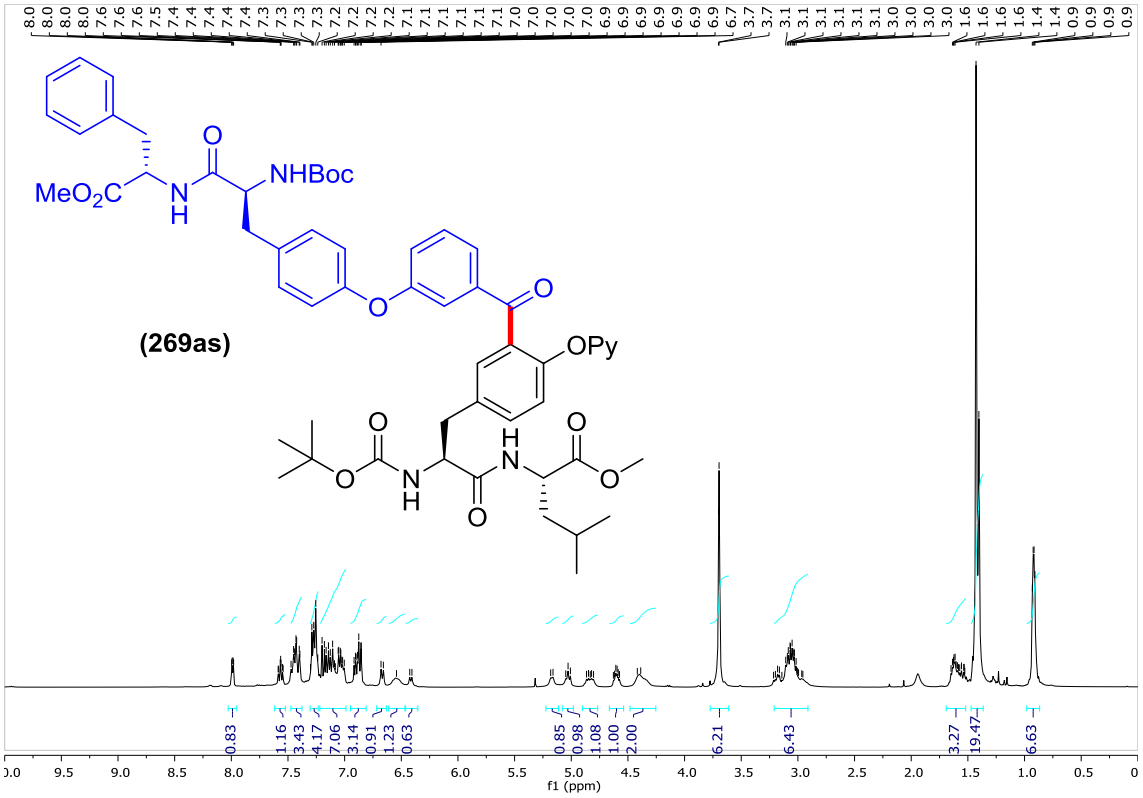
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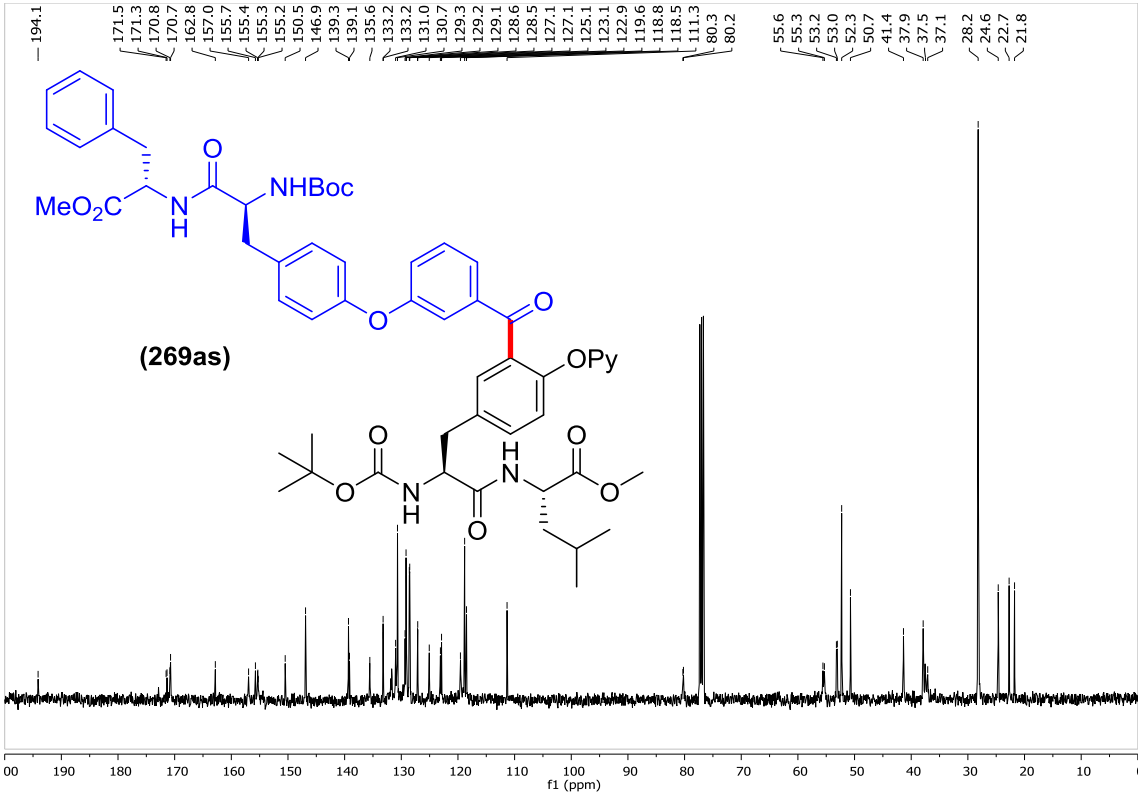
(269as)
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NHBoc
OPy
f1 (ppm)