Universidad del País Vasco/Euskal Herriko Unibertsitatea/ University of the Basque Country

Faculty of Chemistry

Degree in Chemistry

GRADU AMAIERAKO LANA

Pyrrolidin-2,3-diones as pronucleophiles in organocatalytic Michael additions to vinyl sulfones

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Donostia, 2016ko uztaila

SUMARY

This research project has been developed at the Department of Organic Chemistry I at the Faculty of Chemistry in San Sebastian under the guidance of professor Antonia Mielgo from the same department. The research work of this project is a continuation of previous work from the research group on the potential of pyrrolidin-2,3-diones as pronucleophiles in asymmetric organocatalysis. More specifically, in this case the goal has been the investigation of the Michael reaction of C4-substituted pyrrolidin-2,3-diones with vinyl sulfones in the presence of chiral Brønsted bases as catalysts.

LABURPENA

Ikerketa lan hau Kimika Fakultateko Kimika Organikoa I sailean garatu da, Donostin, Antonia Mielgo irakaslearen zuzendaritzapean. Proiektua ikerketa taldean garatzen ari zen pirrolidin-2,3-dionek organokatalisi asimetrikoan pronukleofilo moduan duten potentzialari buruzko lanaren jarraipena da. Zehazki, helburua binil sulfonetara C4-n ordezkatutako pirrolidin-2,3-dionen Michael adizioa ikertzea izan da, Brønsted base kiralen presentzian katalizatzaile moduan.

ABBREVIATIONS AND ACRONYMS

Ac	Acetyl
Ar	Aryl
BB*	Chiral Brønsted base
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
^{i}Bu	*iso*-Butyl
^{t}Bu	*tert*-Butyl
Cat	Catalyst
*m*CPBA	*meta*-chloroperbenzoic acid
DCM	Dichloromethane
DMF	Dimethylformamide
ee	Enantiomeric excess
EPC	Enantiomerically pure compound
Et	Ethyl
EWG	Electron withdrawing group
h	hour(s)
HPLC	High-performance liquid chromatography
Im	Imidazole
IR	Infrared
Me	Mehtyl
Ms	Mesyl
Naphth	Naphthyl
NCA	N-Carboxyanhydride
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PEG	Polyethylene glycol
Ph	Phenyl
r.t.	Room temperature
T	Temperature
t	time
TEA	Triethylamine

TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TMG	1,1,3,3-Tetramethylguanidine
o.n.	Overnight
quan.	Quantitative

INDEX

1. INTRODUCTION

One of the most significant properties of compounds is chirality. Obtaining enantiomerically pure products (EPC synthesis)[1] is a remarkable task in many fields, such as, pharmaceutical, agrochemical and food areas. This is due to the different properties enantiomers can show in a chiral environment, such as biological activity. A remarkable example of this is thalidomide, whose two enantiomers exhibit very different biological properties (Figure 1).[2]
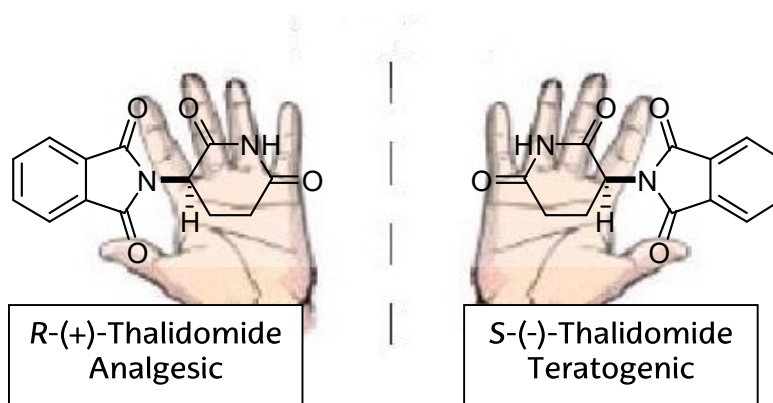

R-(+)-Thalidomide
Analgesic

S-(-)-Thalidomide
Teratogenic

Figure 1. Both enantiomers of thalidomide.

Since the tragedy of thalidomide chemists have focused on the development of methodologies for the synthesis of enantiomerically pure compounds. There are three main strategies for this purpose. When the product is prepared as a racemic mixture the corresponding enantiomers can be separated by *racemate resolution*,[3] which has been for long time the most used protocol in pharmaceutical industries. Other alternative involves the use of the known *chiral pool*,[4] which is based on the employment of natural enantiopure products as starting materials, which are then transformated into the desired compound.

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[1] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis)* in *Modern Synthetic Methods*, Scheffold, R., **1980**, p 94, Salle + Sauerländer, Frankfurt.

[2] Stephens, T.; Brynner, R. *Dark Remedy: The impact of Thalidomide and Its Revival as a Vital Medicine*, **2001**, Perseus, Cambridge, MA.

[3] For general reviews on resolution methods, see: a) Synoradzki, L.; Bernás, U.; Ruśkowski, P. *Org. Prep. Proced. Inc.* **2008**, *40,* 163-200. b) Anderson, N. G. *Org. Proc. Res. Dep.* **2005**, *9*, 800-813. For general reviews on the kinetic dynamic resolution, see: c) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge. d) Matute, B. M. *An. Quim.* **2006**, *102*, 46-52.

[4] For reviews about chiral pool, see: a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*, **2003**, Wiley-VCH. b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, **1996**, Wiley- VCH. c) Hanessian, S. *Pure Appl. Chem.* **1993**, *65*, 1189-1204.

Finally, *asymmetric synthesis*[5] consists of inducting chirality to an achiral compound by using a chiral catalyst,[6] ligand[7] or auxiliary[8] (Figure 2).
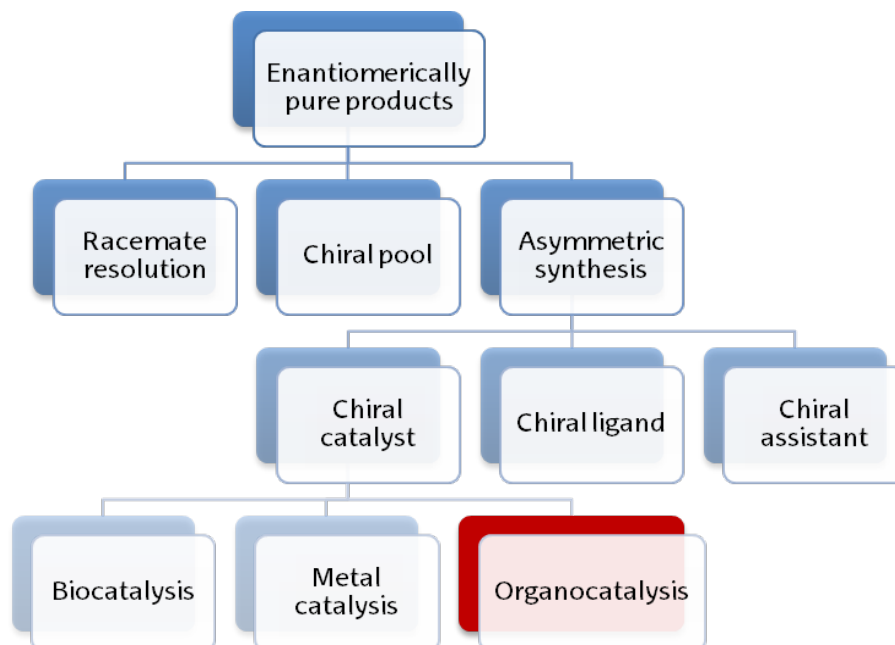
Figure 2. Strategies developed for the synthesis of enantiomerically pure compounds (EPC synthesis)

Catalytic asymmetric reactions can be run using metallic,[9] enzymatic[10] or organic[11] catalysts. This project will focus on organocatalysis as a strategy for the

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[5] For reviews about asymmetric synthesis, see: a) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis 2nd Edition*, **2012**, Pergamon Press, Oxford. b) *Asymmetric Synthesis II: More Methods and Applications*, Eds. Christmann, M.; Bräse, S., **2012**, Wiley-VCH, Weinheim, Germany. c) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials*, **2007**, Wiley-VCH, New York.

[6] For general references on asymmetric catalysis, see: a) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weinhelm. b) Trost, B. M. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 5348-5355.

[7] For more information about chiral ligands, see: a) *Privileged chiral ligands and catalyst*, Ed. Zhou, Q.-L. **2011**, Wiley-VCH, Weinheim. For the use of (–)-sparteine as chiral ligand in asymmetric synthesis, see: b) Schütz, T. *Synlett*, **2003**, *6*, 901-902.

[8] For reviews about chiral auxiliaries, see: a) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. b) Glorious, F.; Gnass, Y. *Synthesis*, **2006**, *12*, 1899-1930. c) Roos, G. *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York.

[9] For general reviews on organometallic catalysis, see: a) Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev.* **2015**, *44*, 433-448. b) Steinborn, D. *Fundamentals of Organometallic Catalysis*, **2011**, Wiley-VCH, Germany. c) Astruc, D. *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag Berlin Heidelberg.

[10] For more information on enzymatic catalysis, see: a) De Gonzalo, G.; Lavandera, I.; Gotor, V. Catalytic *Methods in Asymmetric Synthesis. Advanced material, techniques, and applications*, **2011**, 391-527, Ed. M. Gruttadauria, F. Giacalones, John Wiley & Sons. b) Zagrebelny N. *Russ. Chem. Rev.*

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preparation of enantiopure compounds, which makes use of small organic molecules to catalyze organic reactions. In the field of organocatalysis, chiral Brønsted bases (BB*) have been widely explored.[12] In this context, different nitrogen-containing compounds have been used as BB* catalyst, such as, tertiary amines,[12] guadinines,[13] amidines[12] and imidazoles[14] (Figure 3, a). Some representative Brønstes bases used in organocatalytic reactions are shown in Figure 3, b.

a)

tertiary amines   guanidines   amidines   imidazoles

b)
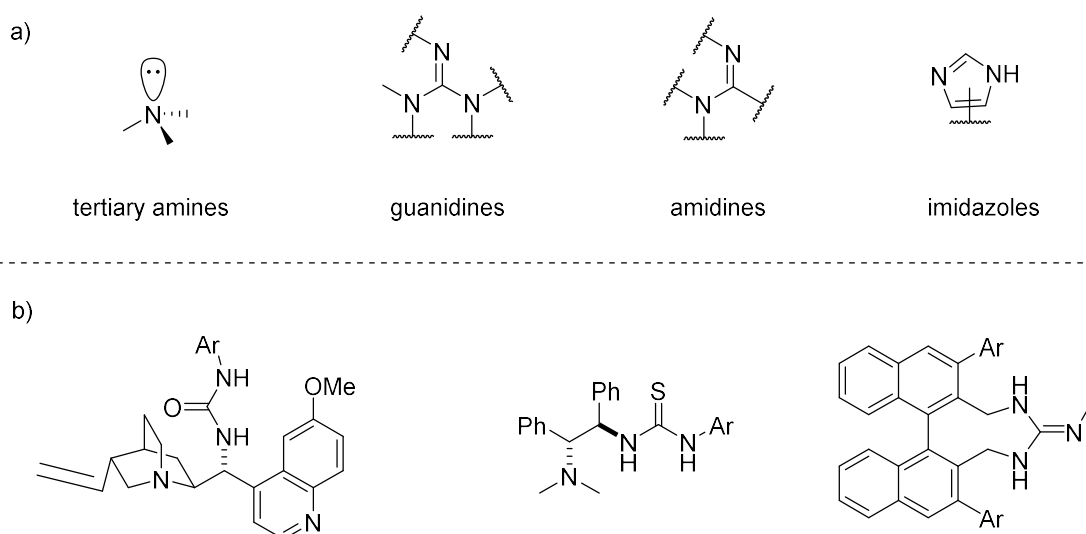
Figure 3. a) Representative nitrogen-containing functionalities used in BB catalysts. b) Some representative examples of chiral BB catalysts.

Among these BB catalysts and, inspired in polyfunctional enzymes, new bifunctional catalysts[15] have been developed. This bifunctionality consist on an

2005, 74, 285-296. c) Reetz, M. T.; Brunner, B.; Schnerider, F.; Schulz, C. M.; Clouthier, M. M.; Kayaser, M. Angew. Chem. Int. Ed. 2004, 43, 4075-4078.

[11] For information about organocatalysis, see: a) Comprehensive Enantioselective Organocatalysis, Reactions and Applications, Ed. Dalko, P. I. 2007, Springer-Verlag Berlin Heidelberg. b) Enantioselective Organocatalysis, Ed. Dalko, P. I. 2007, Wiley-VCH. c) Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis, Ed. Berkessel, A.; Gröger, H. 2005, Wiley-VCH.

[12] For general reviews, see: a) Palomo, C.; Oiarbide, M.; López, R. Chem. Soc. Rev. 2009, 38, 632-653. b) Maruoka, K. Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis; Ed.; Thieme: Stuttgart, 2012. c) Tiang, A.; Gross, J. M.; McDougal, N. T.; Schaus, S. E. Top. Curr. Chem. 2010, 291, 145-200.

[13] a) Leow, D.; Tan, C.-.H. Chem. Asian J. 2009, 4, 488-507. b) Ishikawa, T.; Kumamoto, T. Synthesis 2006, 737-752. c) Ishikawa, T.; Isobe, T. Chem. Eur. J. 2002, 8, 553-557.

[14] Zhang, A.; Xie, F.; Jia, J.; Zhang, W. J. Am. Chem. Soc. 2010, 132, 15939-15941.

[15] For a general review on bifunctional catalysis promoted by Brønsted-base thiourea catalysts, see: a) Fang, X.; Wang, C.-J. Chem. Commun. 2015, 51, 1185–1197. For a general review on bifunctional

active center which plays as BB deprotonating the pronucleophile and another active center which activates the electrophile, generally through hydrogen bonding.

The most representative examples of bifunctional Brønsted bases are (thio)ureas and squaramides. In 2003, Takemoto and coworkers developed the first thiourea derived bifunctional BB catalyst (Figure 4, a).[18] Since then, many research groups have developed different reactions promoted by tiourea-substituted cinchona alcaloid catalysts[16] with excellent results. in 2008, Rawal's group reported a new type of bifunctional Brønsted base carrying a squaramide functionality (Figure 4, b).[19] After this, squaramide based catalyst have been widely employed as an alternative to (thio)ureas in asymmetric catalysis.[17]

organocatalysis, see: b) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, 23, 490–508. For a general review on multiple catalysis with two chiral units, see: c) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem. Int. Ed.* **2011**, 50, 6216–6232. For a mechanistic study of bifunctional catalysis promoted by cinchona alkaloids, see: d) Cucinotta, C.S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. *Chem. Eur. J.* **2009**, 15, 7913–7921. For a general review on bifunctional catalysis promoted by α,α-diarylprolinol catalysts, see: e) Lattanzi, A. *Chem. Commun.* **2009**, 1452–1463. For a general review on bifunctional catalysis promoted by Brønsted-base thiourea/urea catalysts, see: f) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. For a general review on bifunctional catalysis promoted by Cupreine and Cupreidine catalysts, see: g) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, 45, 7496–7504.
[16] For general reviews, see: a) Li, B. J.; Jiang, L.; Liu, M.; Cheng, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, 603–606. b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, 7, 1967–1969. c) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, 44, 6367–6370. d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. For some recent examples, see: e) Han, W.-Y.; Zhao, J.-Q.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2013**, 78, 10541–10547. f) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Angew. Chem. Int. Ed.* **2015**, 54, 6320–6324.
[17] For general reviews on squaramide type catalysts, see: a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, 357, 253–281. b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, 17, 6890–6899. c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, 40, 2330–2346.
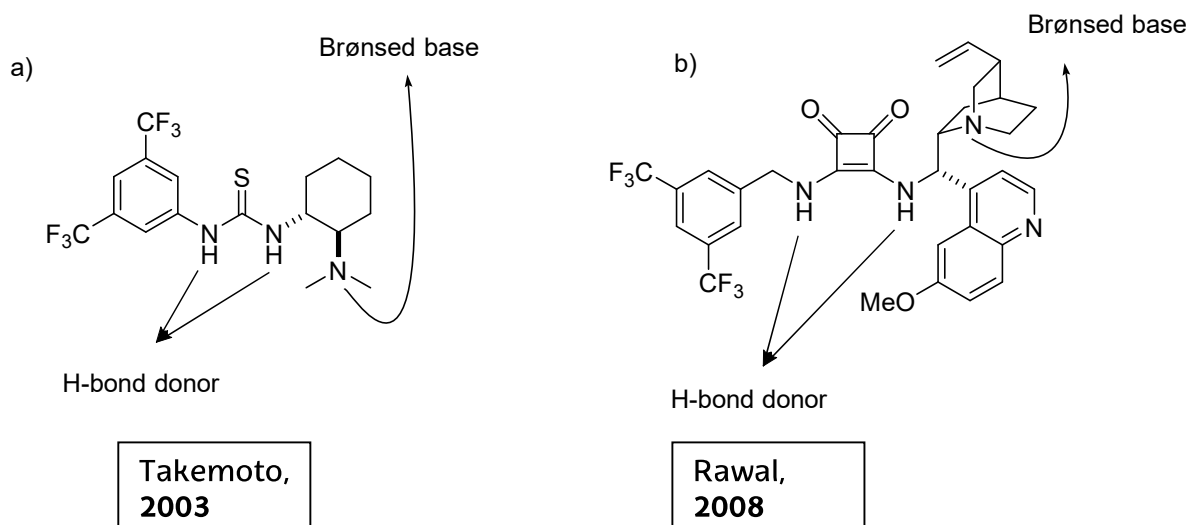
Figure 4. Representative examples of bifunctional Brønsted base catalysts.[18,19]

A remarkable advantage of squaramides over thioureas is their higher acidity.[20] This allows to reduce the catalyst loading in asymmetric transformations. Even more, as it is shown in Figure 5, squaramides offer three possible H-bonding patterns which make them more "bifunctional".
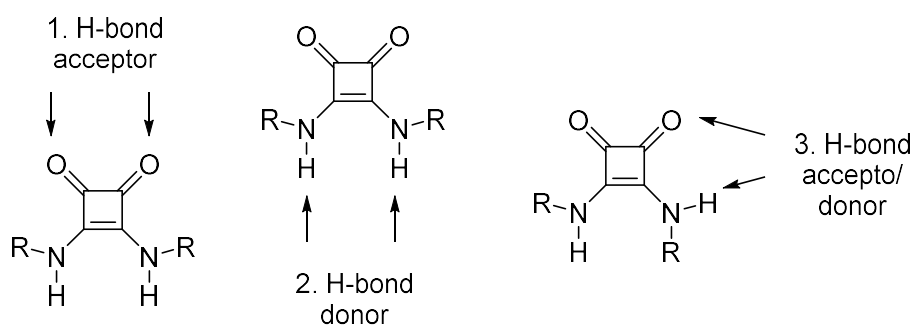

Figure 5. Possible H-bond patterns for squaramides.

When designing catalytic asymmetric reactions, there are many variables to control in order to obtain good results. Besides finding the optimal reaction conditions, changes can be made either in the catalyst or the reactants. This leads

[18] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673
[19] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416-14418.
[20] Ni, X.; Li. X.; Wang, Z.; Cheng, J. P. Org. Lett. 2014, 16, 1786-1789.

to the design of new catalyst and the search for new nucleophiles and electrophiles as the main objective of modern catalytic chemistry.

In this context, the Michael reaction consist of the 1,4 conjugate addition of a nucleophile, also known as Michael donor, to an electron deficient olefin or Michael acceptor (Scheme 1). This is one of the most frequently used C-C and C-heteroatom bond forming reactions in organic synthesis.[21] Since up to two stereocenters can be created, enantio- and diastereo-control are specially significant in these reactions. Michael acceptors are usually α,β-unsaturated carbonyl groups, but also α,β-unsaturated compounds carrying other activating group, such as, nitro, sulfonate, sulfoxide, phosphate or phosphonate are employed.

Michael donor   Michael acceptor

Nu: Nucleophile
EWG: Electronwithdrawing group
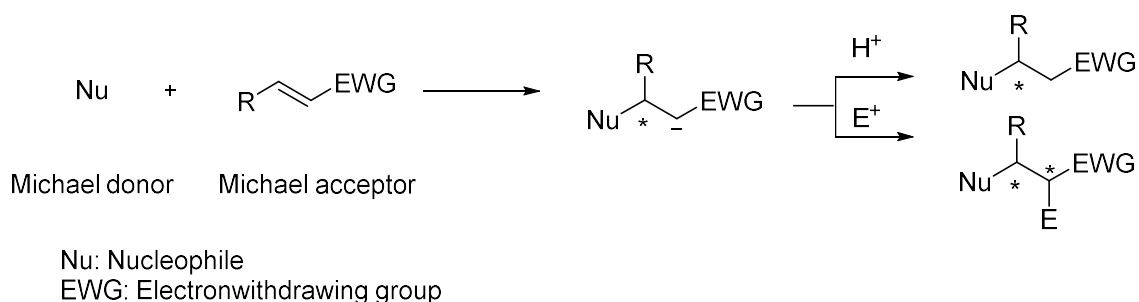
Scheme 1. General scheme for the Michael reaction.

In this context, soft enolization constitutes an efficient tool for the deprotonation of relatively acidic carbonyl compounds. In this strategy a relatively weak Brønsted base is used for the reversible deprotonation of relatively acidic compounds. Most of the developed chiral Brønsed base catalysts fall in this category. At this point, it is worth of noting that esters and carboxylic acid derivatives are challenging proucleophiles for catalysis under soft enolization conditions due to their high pK_a values[22] which makes them hard to enolize with relatively weak Brønsted bases. On the other, α,β-unsaturated esters and

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[21] For information about asymmetric Michael reactions, see: a) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugates Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC, **2010**. For the first example of a Michael reactions, see: b) Michael, A. *Prakt. J. Chem.* **1887**, *36*, 349-356.

[22] For a webpage of Bordwell pKa Table (acidities in DMSO) of different compounds, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

carboxylic acid derivatives have, in turn, shown challenging Michael acceptors because of their limited coordination ability with the catalyst which generates problems of reactivity and stereocontrol. With the aim of solving these problems, new Michael acceptor and donor templates have been designed.
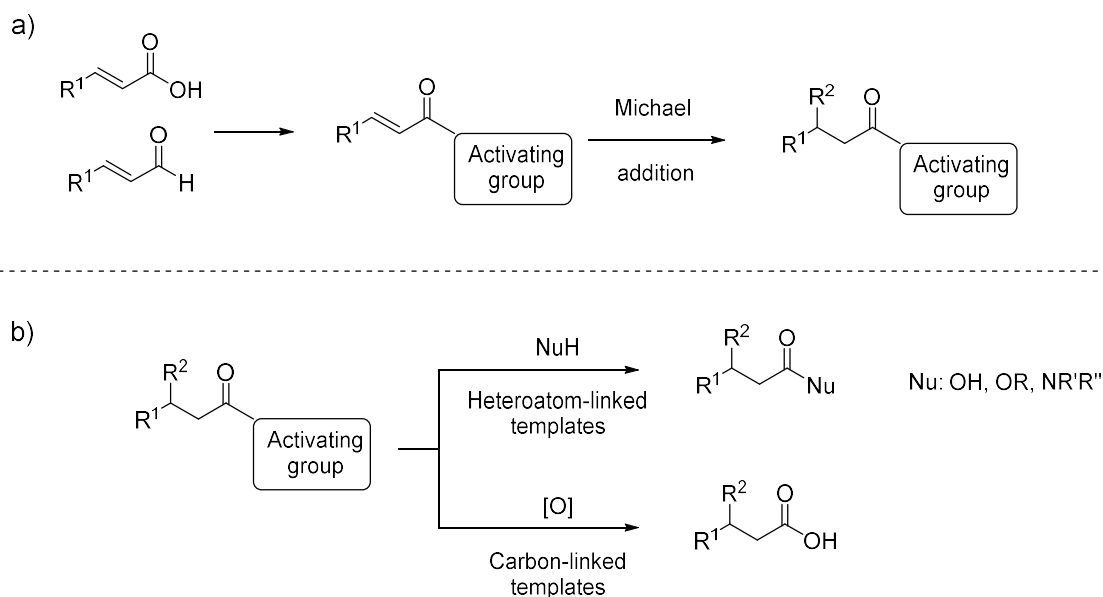
Michael acceptor templates

Conjugate additions to α,β-unsaturated carbonyl compounds as Michael acceptors are of a great significance because the adducts obtained can be widely used. However, as mentioned before, α,β-unsaturated esters and carboxylic acid derivatives are challenging acceptors under soft enolization. In this context, a little developed alternative has been to raise de Brønsted basicity of the catalyst. Likewise, the concentration of the nucleophilic conjugate base increases; and therefore the rate of the addition step.[23,24] However, the most investigated alternative to overcome these problems has been the development of new Michael acceptor templates by incorporating an activating group into the compound (Figure 6, a). This activating electron withdrawing group increases the reactivity of the template as electrophile and can also improve the coordination with the catalyst by providing new coordinating points. The transformation of this activating group can be easily performed upon demand after the Michael addition reaction. Depending on the nature of the adduct, replacement of the activating group can be carried out by acyl substitution with a nucleophile (heteroatom-linked templates) or by C-C oxidative cleavage (carbon-linked templates) (Figure 6, b).[25]

[23] For references related to stronger Brønsted bases, see: a) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Wiley: New York, **2009**. For reviews on chiral guanidines, see: b) Selig, P. *Synthesis* **2013**, *45*, 703–718. c) Fu, X.; Tan, C.-H. *Chem. Commun.* **2011**, *47*, 8210–8222. d) See ref. 13. For a review on chiral iminophosphoranes, see: e) Krawcyk, H.; Dziegielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, L. *Chem. Eur. J.* **2015**, *21*, 10268–10277.

[24] For a representative example of this strategy, see: Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.

[25] For a general review on carboxylic acid surrogate templates in organocatalysis, see: Monge, d.; Jiang, H.; Alvarez-Casao, Y. *Chem. Eur. J.* **2015**, *21*, 4494-4504.

a)

b)

Nu: OH, OR, NR'R"

Figure 6. a) General synthesis for Michael acceptor templates and their Michael addition reaction. b) Activating group replacement in the final Michael adducts.
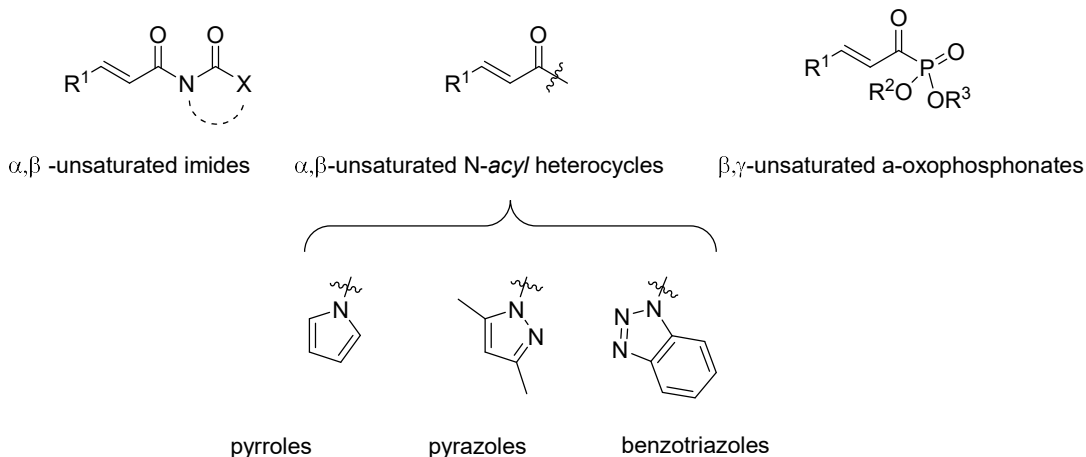
Among the developed templates, the most successful are bidentate ones, since they can provide two coordination points with the catalyst forming cyclic chelates and potentially improving stereocontrol (Figure 7).
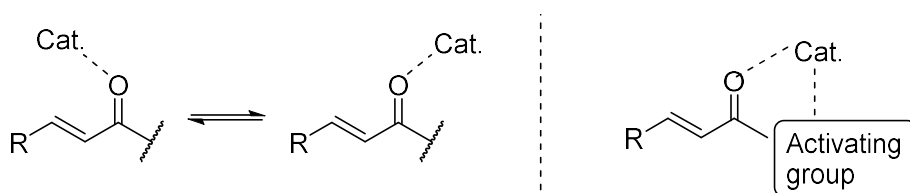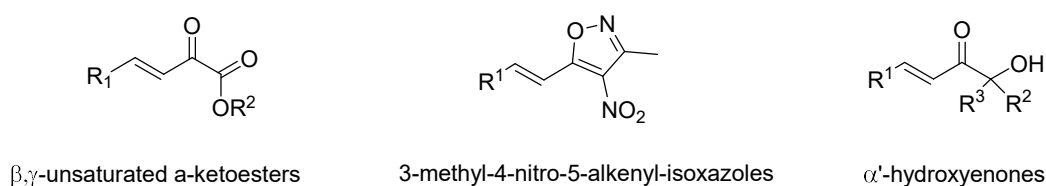

Figure 7. Monodentate vs bidentate templates.

The most representative heteroatom-linked (Figure 8, a) and carbon-linked (Figure 8, b) developed Michael acceptor templates are outlined in Figure 8.

a) HETEROATOM-LINKED TEMPLATES

α,β -unsaturated imides α,β-unsaturated N-*acyl* heterocycles β,γ-unsaturated a-oxophosphonates

pyrroles   pyrazoles   benzotriazoles

b) CARBON-LINKED TEMPLATES

β,γ-unsaturated a-ketoesters   3-methyl-4-nitro-5-alkenyl-isoxazoles α'-hydroxyenones

Figure 8. Some examples of bidentate Michael acceptor templates. a) Heteroatom-linked templates. b) Carbon-linked templates.

Michael donor templates

As mentioned before, the catalytic conjugate addition of carboxylic acid derivatives and esters as nucleophiles is still challenging due to reactivity and/or stereoselectivity problems and this has lead to the need of developing new Michael donor templates. One option to improve the reactivity of these substrates is to prepare more basic catalyst.[23] This strategy has been little investigated since the basicity of the catalyst can cause problems with other functional groups of the reagents. A second option has been the introduction of an electronwithdrawing group in α-position to the ester or equivalent functionality as for instance, α-cyanoacetates[26] and half thioesters[27]. The third alternative is the use of activated

[26] For information about α-substituted cyanoacetates, see: a) Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261–3288. b) Jautza, S.; Peters, R. *Synthesis* **2010**, 365–388.

[27] a) Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844. b) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Perez-Herrera, R.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040.

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ester surrogates which can be later transformed into the desired products. Following this, activated Michael donor templates, both acyclic (Figure 9, a) and cyclic (Figure 9, b) have been documented. The most representative ones are shown in Figure 7.

These heterocyclic templates are, on the one hand, structural building blocks of compounds exhibiting pharmaceutical and medicinal properties; and on the other hand, some of them have been employed as carboxylic acid or ester surrogates. Additionally, most of them are substituted at the α-position of the carbonyl and when reacting with a Michael acceptor a new tetrasubstituted stereocenter is created, which is an added challenge.[28] In asymmetric synthesis controlling the stereochemistry of newly formed tetrasubstituted centers is crucial, and has always shown problematic.

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[28] For more information about tetrasubstituted stereocenter formation, see: a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Ed. Christoffers, J.; Baro, A., **2005**, Wiley-VCH, Weinheim, Germany. b) Liu, Y.; Han, S.-J.; Liu, W.-R.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, 48, 740-751. For organocatalytic formation of tetrasubstituted stereocenters: c) Bella, M.; Casperi, T. *Synthesis.* **2009**, 1583-1614.

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a) Acyclic Michael donor examples
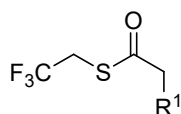
| Trifluoroethyl thioesters | Pyrazoleamides | α-Ketophosphonates | Acylsilanes |
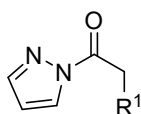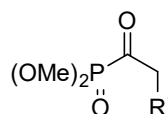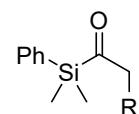
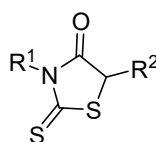- -
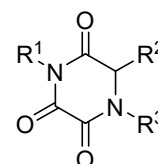
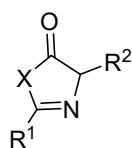a) Heterocyclic Michael donor examples
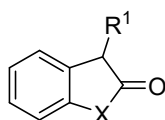
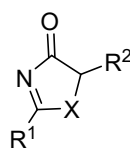X: O   Oxindoles
X: NR   Benzofuran-2(*3H*)-ones

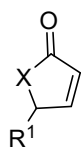Rhodanines

Piperazin-2,3,6-triones

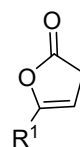X: O   Oxazol-5(*4H*)-ones   X: O   Oxazol-5(*5H*)-ones   X: NR Pyrazol-5(*4H*)-ones
X: S   Thiazol-5(*4H*)-ones   X: S   Thiazol-5(*5H*)-ones   X: O Isoxazol-5(*4H*)-ones
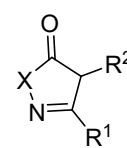
X: NR α,β-unsaturated γ-sustituted
            γ-butyrolactam   deconjugated
X: O γ-butenolide   butenolide

Figure 9. Representative examples of Michael donor templates: a) Acyclic Michael donor templates. b) Heterocyclic Michael donor templates.

Pyrrolidin-2,3-diones as pronucleophiles

Therefore, the search of new pronucleophiles for asymmetric catalysis is still and active research area. In this field, pyrrolidin-2,3-diones seem a good choice because they have been very little investigated in asymmetric catalysis, as explained below, and they are synthetic scaffolds for biologically important compounds.[29]

In this area, 2-pyrrolidinone or γ-butyrolactam skeletons (Figure 8, I) are of remarkable interest in biological terms,[29] as they are precursors of pyrrolidine derivatives with biological activity.[30] Other similar skeletons with biological relevance are α-methylen-2-pyrrolidinones II[31] and pyrrolidin-2,3-diones III (Figure 10). However, while the first two have been widely employed in asymmetric catalysis,pyrrolidin-2,3-diones have been scarcely explored in asymmetric synthesis. Furthermore, no examples of the use of these substrates in catalytic enantioselective synthesis involving the creation of a tetrasubstituted stereocenter at C4 can be found in the literature.

I
2-Pyrrolidinones
or γ-butyrolactams

II
α-Methylene 2-
pyrrolidionenes

III
Pyrrolidin-2,3-diones
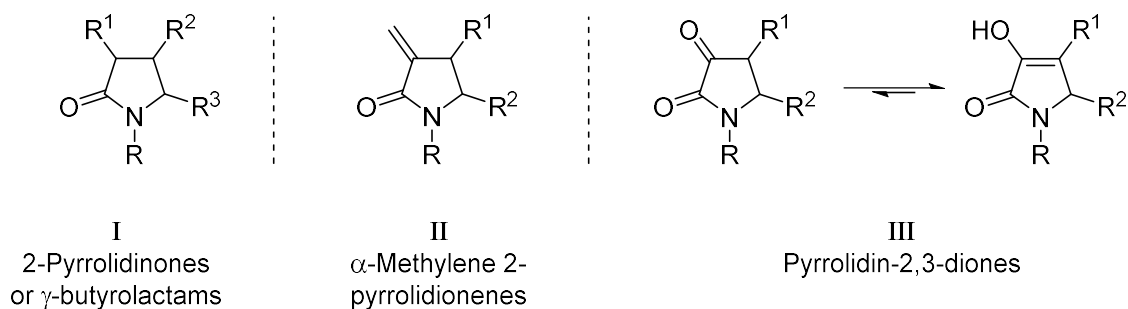
Figure 10. General structure of 2-pyrrolidinones, α-methylene 2-pyrrolidinones and pyrrolidin-2,3-diones.

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[29] a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36-42. b) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1994**, *35*, 7277-7280. c) Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 7057-7060. d) Poli, G.; Baffaloni, S. C.; Renginato, G. *Tetrahedron* **1998**, *54*, 10403-10418.

[30] a) Obst, U.; Betschmann, P.; Lerner, C.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 855-909. b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666-5667. c) Puschl, A.; Tedeschi, T.; Nielsen, P. E. *Org. Lett.* **2000**, *2*, 4161-4163. d) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616-9617. e) Alvarez-Ibarra C.; Csákÿ, A. G.; López de Silanes, I.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 479-484. f) Parson, A. F. *Tetrahedron* **1996**, *52*, 4149-4171.

[31] Albrecht, A.; Albrecht, L.; Janecki, T. *Eur. J. Org. Chem.* **2011**, 2747-2766

The only example of the use of pyrrolidin-2,3-diones in asymmetric catalysis was reported by Xu and co-workers in 2012[32] (Scheme 2). In this case pentacyclic butyrolactam-fused indoloquiolizines are efficiently synthesized. First, a bicyclic hemiacetal is formed through iminium ion activation of the enal by the secondary amine catalyst in a Michael reaction. Then, the hemiacetal is activated under acidic conditions and reacts with tryptamine to generate an iminiun ion. Finally, a diastereoselective Pictet-Spengler cyclization[33] occurs which affords the products in very good results.
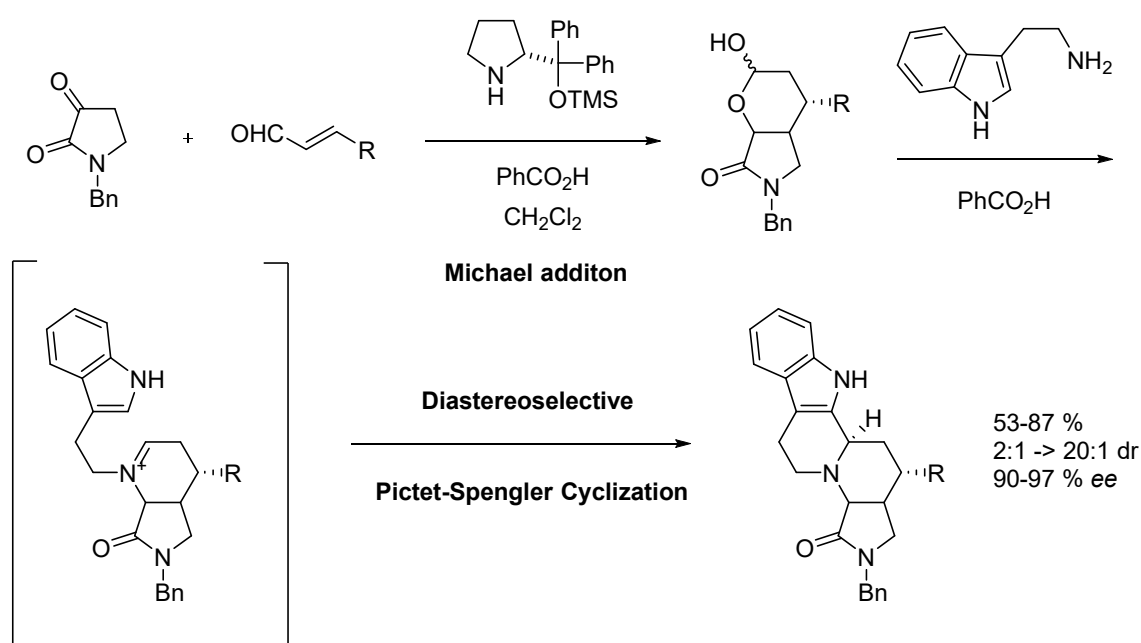
Scheme 2. Only example of the use of pyrrolidin-2,3-diones in asymmetric organocatalysis in literature; Xu and co-workers, **2012**.

Recently, 4-alquiliden pyrrolidin-2,3-diones have also been employed as Michael acceptors in a reaction with sulfur ylides reported by Xu and co-workers (Figure 11).[34] Even if it is not an enantioselective reaction, efficient results are obtained regarding *cis/trans* diastereoselectivity and yield.

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[32] Zhu, H.-L.; Ling, j.-B.; Xu, P.-F. *J. Org. Chem*. **2012**, 77, 7737-7743.

[33] For reviews on organocatalytic Pictet-Spengler reactions, see: a) Taylor, M. S.; Jacobse, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558-10559. b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Stoner, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc*. **2009**, *131*, 10796-10797.

[34] Zhang, S.; Hu, X.-Q.; Wang, Z.-Y.; Xu, P.-F.; *Synthesis*. **2015**, *47*, 2529-2537.

R^1: aryl
R^2: O^{t}Bu, OEt, OBn, aryl
TMG: tetramethylguanidine

28 examples
72-99 % yield
trans/cis 8:1 -> 20:1
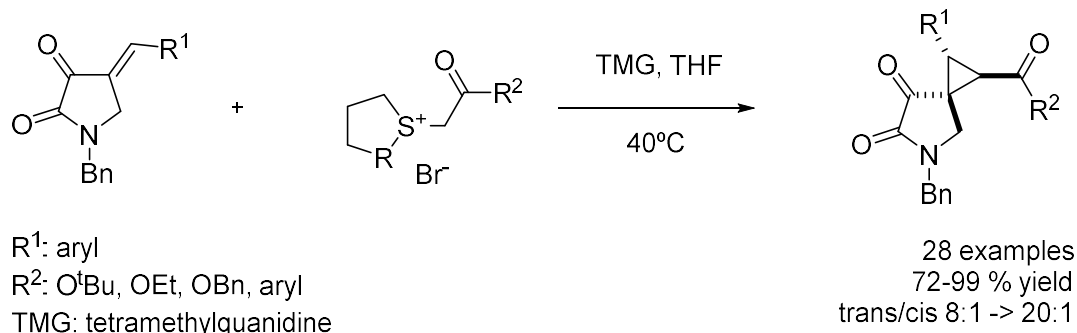
Figure 11. Spiro-cyclopropane synthesis from 4-alquiliden pyrrolidin-2,3-diones; Xu and co-workers, **2015**.

Since these substrates had been little explored, the research group where this work has been developed decided to start a project to investigate the use of 4-substituted pyrrolidin-2,3-diones as Michael donors in organocatalytic asymmetric reactions promoted by chiral Brønsted bases[12] and involving the formation of a tetrasubstituted stereocenter at **C4**.

It was considered that 4-subsituted pyrrolidin-2,3-diones could be easily deprotonated by a chiral Brønsted base since literature data demostrate that they are enolized to a large extent.[35] However, the reaction of these substrates with an electrophile catalyzed by a chiral Bronsted base to create a tetrasubstituted stereocenter was still unrealized. This could be because the alkylation reaction using alkyl halides provides mainly O-alkylated products. Experiments carried out by Southwick in 1962[35] show that sodium enolates obtained from 4-benzyl-pyrrolidin-2,3-diones give a mixture of 3.1 of O-alkylated and C-alkylated products (Scheme 3).

3 : 1   ratio
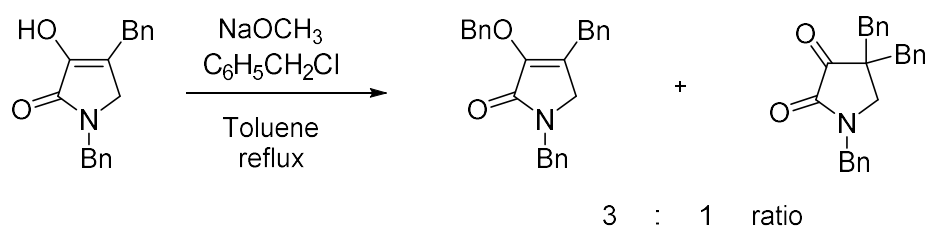
Scheme 3. O- vs C-alkylation regioselectivity in C4-substituted pyrrolidin-2,3-diones.

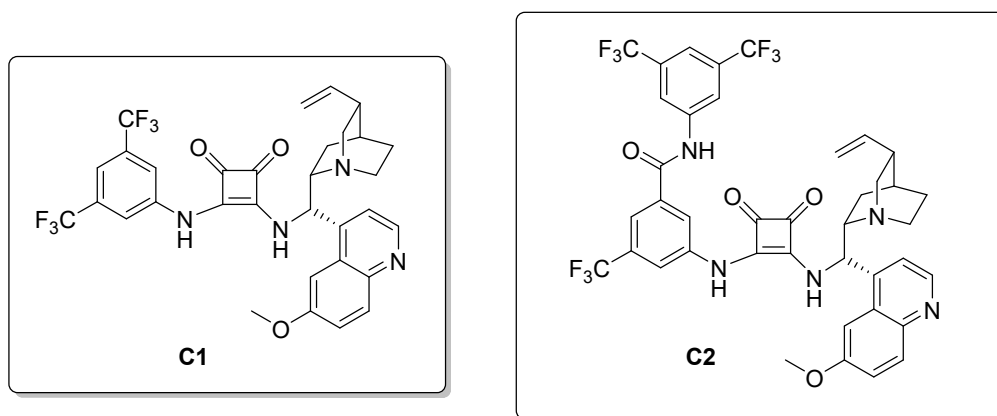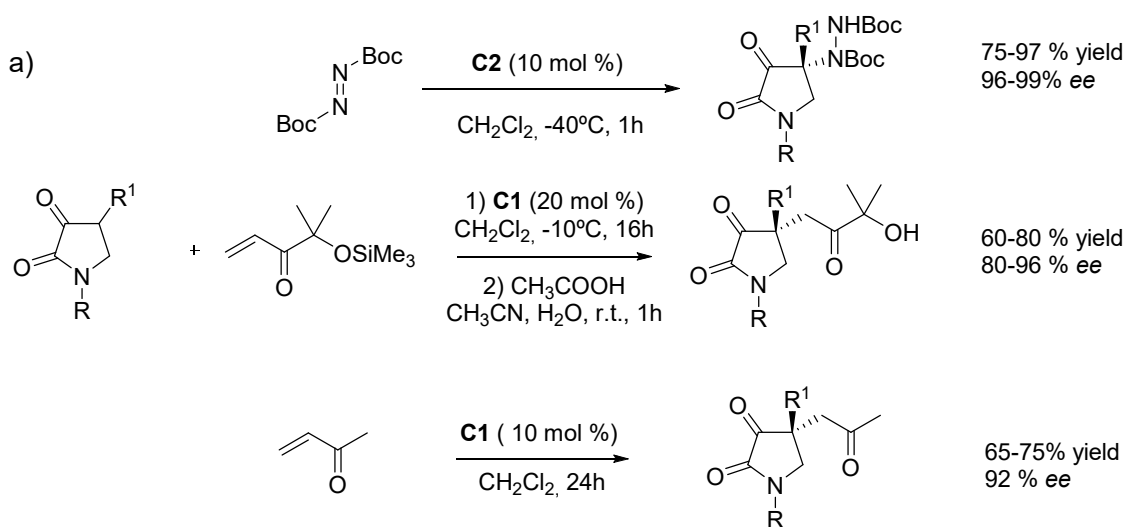[35] Southwick, P. L.; Barnas, E. F. *J. Org. Chem.* **1962**, 27, 98–106.

Preliminary results from the laboratories were this project has been developed obtained by E. Badiola and A. Vázquez show that these substrates give very good yields and enantioselectivities in α-amination reactions and Michael additions to vinyl ketones and sililated α-oxy enones catalyzed by bifunctional Brønsted bases (Scheme 4, a). In addition, transformation of the products coming from these reaction has been efficiently carried out by conversion into the corresponding *N*-carboxy anhydrides upon treatment with *m*CPBA followed by ring opening with a nucleophile to afford $\beta^{2,2}$-amino acids, esters and amides (Scheme 4, b). This is a particular advantageous characteristic of the use of these pyrrolidin-2,3-diones as pronucleophiles, because few enantioselective protocols have been reported for the synthesis of $\beta^{2,2}$-amino acids.[36,37]

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[36] For a review on the synthesis of ^{2,2}-amino acids, see: Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1-5.

[37] For representative examples see: for the use of β-nitroacrylates as Michael acceptors: a) K. Moriyama, T. Sugive, Y. Saito, S. Katsuta, H. Togo *Adv. Synth. Catal.* **2015**, *357*, 2143-2149: b) N. D. Iorio, P. Righi, S. Ranieri, A. Mazzanti, R. G. Margutta, G. Vencivenni *J. Org. Chem.* **2015**, *80*, 7158-7171. c) R. Kaste, H. Wennemers *Angew. Chem. Int. Ed.* **2013**, *52*, 7228-7232; *Angew. Chem.* **2013**, *125*, 7369-7373. d) S. Chen, Q. Lou, Y. Ding, S. Zhang, W. Hu, J. Zhao *Adv. Synth. Catal.* **2015**, *357*, 2437-2441. e) F. G. Zhang, Q.-Q. Yang, J. Xuan, H.-H. Lu, S.-W. Duan, J.-R. Chen, W.-J. Xiao *Org. Lett.* **2010**, *12*, 5636-5639. For the reaction of α-cyanoatetates with vinyl ketones, see: f) T.- Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen *Chem. Eur. J.* **2007**, *13*, 319-327. For the reaction of α-cyanoacetates with vinyl sulfones, see: g) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ving, Y.-C. Chen *Org. Biomol. Chem.* **2006**, *4*, 2097-2099. For the Henry reaction of nitromethane with α-keto esters see: h) Y. Zhang, Z. J. Li, H. S. Xu, Y. Zhang, W. Wang *RSC Adv.* **2011**, *1*, 389-392 For the catalytic acylation of (silyloxy)nitrile anions, see: i) A. Nicewicz, C. M. Yates, J. S. Johnson *Angew. Chem. Inte. Ed.* **2004**, *43*, 2652-2655; *Angew. Chem.* **2004**, *116*, 2706-2709.

a)

75-97 % yield
96-99% *ee*

1) **C1** (20 mol %)
CH$_2$Cl$_2$, -10ºC, 16h

2) CH$_3$COOH
CH$_3$CN, H$_2$O, r.t., 1h

60-80 % yield
80-96 % *ee*

C1 (10 mol %)
CH$_2$Cl$_2$, 24h

65-75% yield
92 % *ee*

C1

C2

b)

m-CPBA

R^{2}OH or R^{3}NH$_2$

N-Carboxyanhidrides
(NCA)

Nu: R^{2}O, R^{3}NH

E:
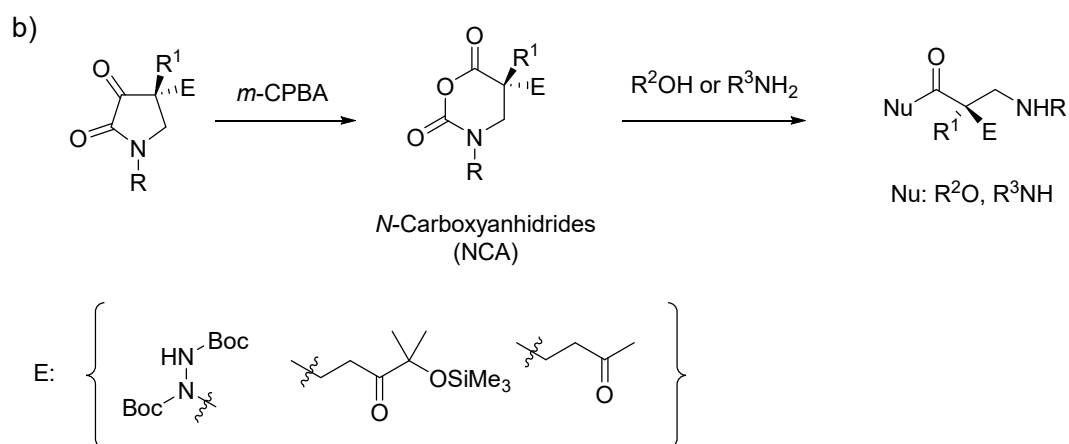
Scheme 4. Precedents from our laboratories: a) Reactions with 4-substituted pyrrolidin-2,3-diones. b) Transformations of the products into β^{2,2}-amino acid derivatives.

2. OBJECTIVES

In this context, the main objective of this project has been to extend the study on the utility of these C4-substituted pyrrolidin-2,3-diones as pronucleophiles to other electrophiles. More specifically, this project has focused on the investagation of vinyl sulfones as Michael acceptors in the presence of bifunctional Brønsted bases as catalysts (Scheme 5).
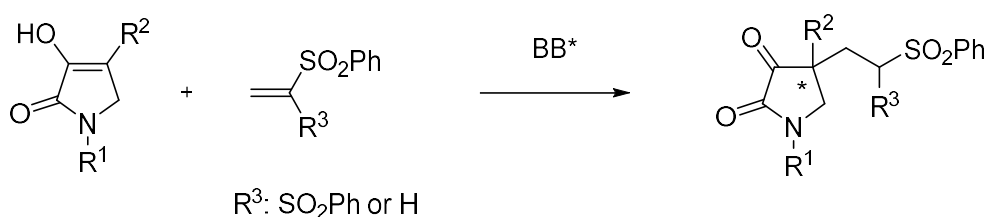
Scheme 5. BB* catalyzed conjugate addition of C4-substituted-pyrrolidin-2,3-diones to vinyl sulfones.

This is a useful reaction since the obtained adducts could be desulfonated[38] following known protocols[39] to give products formally coming from alkylation reactions, which has shown difficulty.
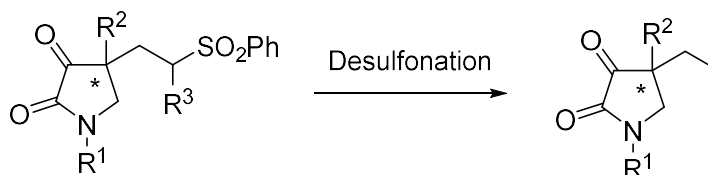
Scheme 6. Desulfonation of the resulting addducts.

These Michael adducts could also be oxidized to the corresponding *N*-carboxyanhydrides, and then opened with a nucleophile to provide $\beta^{2,2}$-amino acid derivatives which are of a great biological significance.

---

[38] For reviews on desulfonation, see: Nájera, C.; Yus, M. *Tetrahedron*, **1999**, *55*, 10547-10658.
[39] There are sweveral desulfonation protocols; but among them the most developed one is the one reported by Brown and Carpino which uses magnesium in MeOH: Brown, A. C.; Carpino, L. A.; *J. Org. Chem.* **1985**, *50*, 1749-1750.
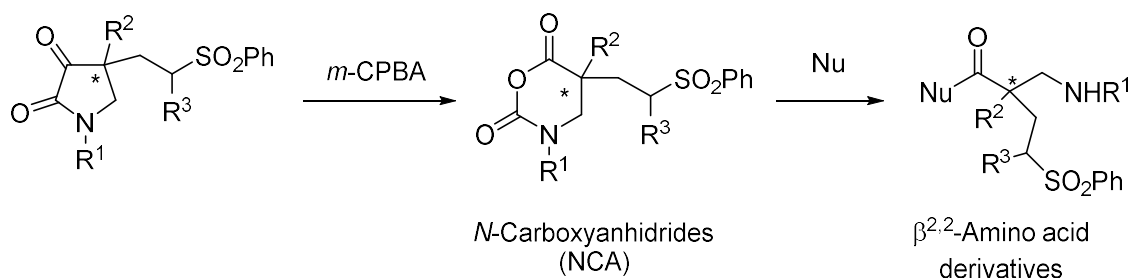
Scheme 7. Transformation of pyrrolidin-2,3-diones into $\beta^{2,2}$-amino acid derivatives.

So, more specifically, the main goals of this project have been the following ones:

a) Synthesis of some C4-substituted pyrrolidin-2,3-diones

b) Investigation of their Michael addition to vinyl sulfones in the presence of some bifunctional Brønsted bases as catalysts.

2. RESULTS AND DISCUSSION

According to the previously established objectives, the first task of this project was to synthesize some C4-substituted pyrrolidin-2,3-diones with different substituents either at the C4 position or at the heterocyclic nitrogen, to then check them in the Michael addition reaction to vinyl sulfones (Scheme 8).
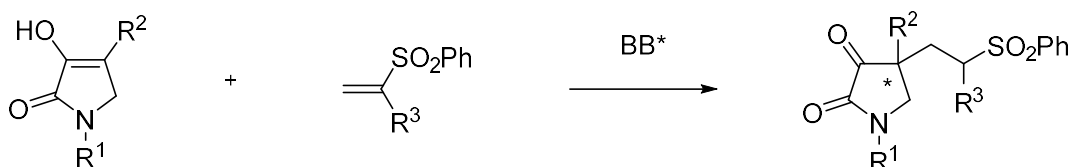
1Aa R^1: Bn R^2: Me
1Ab R^1: 1-Naphth-CH_2 R^2: Me
1Bb R^1: 1-Naphth-CH_2 R^2: ^{i}Bu

2A R: H
2B R: SO_2Ph

Scheme 8. Michael addition reaction of C4-substituted-pyrrolidin-2,3-diones to vinyl sulfones.

More specifically, for first investigations pyrrolidin-2,3-diones **1Aa, 1Ab** and **1Bb** were considered. The synthesis of these starting pyrrolidin-2,3-diones was carried out following protocols previously optimized in the research group based on reported strategies for the preparation of C4-unsubstituted analogs.[40] The synthesis of these unsubstituted derivatives is shown in Scheme 9. They are obtained upon reaction of the corresponding β-amino ester with ethyl oxalate in the presence of NaOEt, to provide *upon in situ* descarboxylation the C4-unsubstituted pyrrolidin-2,3-dione. The β-amino ester is obtained through the aza-Michael addition of the benzylamine to methyl acrylate (Scheme 9).

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[40] Southwick, P. L.; Crouch, R. T. *J. Am. Chem. Soc.* **1953**, *75*, 14, 3413.
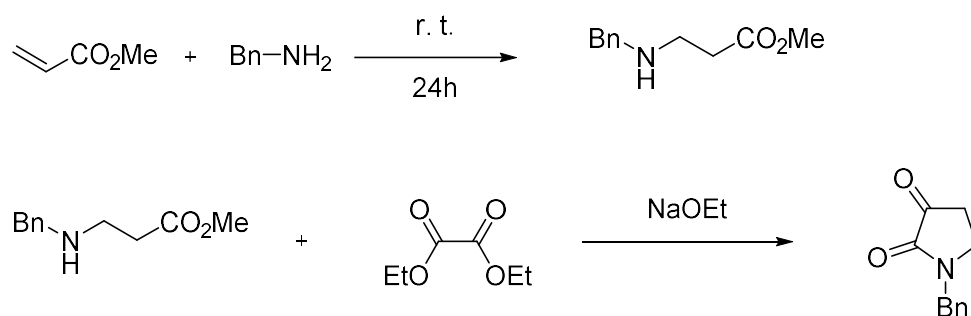
Scheme 9. Reported protocol for the synthesis of non-substituted pyrrolidin-2,3-diones.

According to this, the C4-substituted pyrrolidin-2,3-diones were prepared following the procedure below, which includes first the aza-Michael addition of amines to α-substituted acrylates, and then the cyclization of the resulting β-amino esters with ethyl oxalate (Scheme 10).
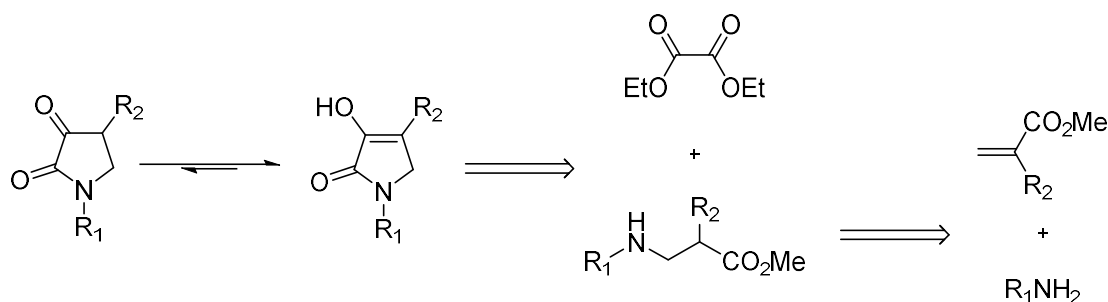

Scheme 10. Retrosynthetic scheme for C4-substituted pyrrolidin-2,3-diones.

3.1. Preparation of α-substituted acrylates

α-Methyl acrylate **5A** is commercially available, and the α-isobutyl analog was prepared following the protocol described in the literature for similar compounds.[41] Alkylation reaction of methyl acetoacetate **3** was run with isobutyl iodide, and then, retro-Claisen reaction of the obtained alkylated product **4** provided acrylate **5B** in 47% yield (not optimized) (Scheme 11).

---

[41] Beddow, J. E; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812-2825.
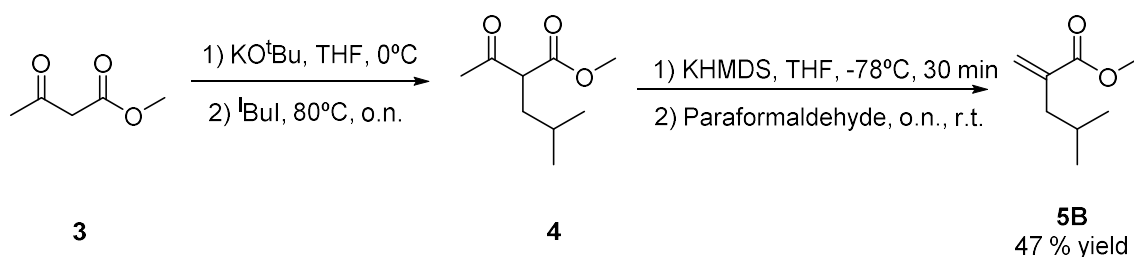
Scheme 11. Procedure for preparation of methyl 4-methyl-2-methylenepentanoate **5B**.

3.2. Preparation of β-amino esters

β-Amino esters were obtained by adding the corresponding amine to the α–substituted acrylate using ruthenium (III) chloride as catalyst and polyethylene glycol as solvent (Table 1).[42]

Table 1. Preparation of racemic β-amino esters.

5A R^2:Me   **6a** R^1: Bn

5B R^2: ^iBu **6b** R^1: 1-Naphth-CH$_2$

(±) **7Aa** R^1: Bn R^2: Me
(±) **7Ab** R^1: 1-Naphth-CH$_2$ R^2: Me
(±) **7Bb** R^1: 1-Naphth-CH$_2$ R^2: ^iBu
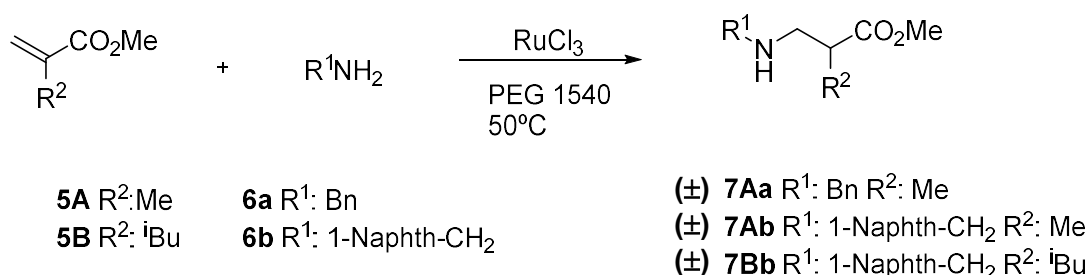
Entry	Product	R^1	R^2	Conversion (%)	Yield (%)
1	**7Aa**	Bn	Me	84	80
2	**7Ab**	1-Naphth-CH$_2$	Me	60	58
3	**7Bb**	1-Naphth-CH$_2$	^iBu	29	11

The 4-methyl derivatives were obtained in good yields, however the 4-isobutyl pyrrolidin-2,3-dione was obtained in only 11%. This yield is not optimized.

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[42] Zhang, H.; Zhang, Y.; Liu, L. Xu, H.; Wang, Y. *Synthesis.* **2005**, *13*, 2129-2136.

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del País Vasco Unibertsitatea

3.3. Cyclization/ decarboxylation reaction

Following the proposed synthetic plan, pyrrolidin-2,3-diones were prepared by reacting ethyl oxalate and the corresponding β-amino ester. Ethanol was distilled to help cyclization and decarboxylation happened simultaneously under the reaction conditions (Table 2).

Table 2. Cyclization/ decarboxylation reaction.
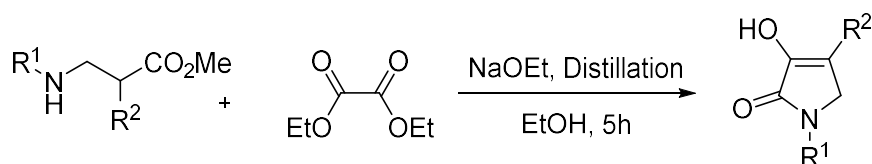
(±) **7Aa** R^1: Bn R^2: Me

(±) **7Ab** R^1: 1-Naphth-CH_2 R^2: Me   **8**

(±) **7Bb** R^1: 1-Naphth-CH_2 R^2: ^{i}Bu

1Aa R^1: Bn R^2: Me

1Ab R^1: 1-Naphth-CH_2 R^2: Me

1Bb R^1: 1-Naphth-CH_2 R^2: ^{i}Bu

Entry	Product	R^1	R^2	Yield (%)
1	**1Aa**	Bn	Me	86
2	**1Ab**	1-Naphth-CH_2	Me	65
3	**1Bb**	1-Naphth-CH_2	^{i}Bu	--

The 4-methyl derivatives were obtained in good yields. Due to the steric hindrance of the isobutyl group, β-amino ester **7Bb** is less reactive and the cyclization product could not be detected under the usual conditions.

It was confirmed by IR that 4-substituted pyrrolidin-2,3-diones are fully enolized as previous studies from Southwick and Barnas showed.[35] The infrared spectrum of 4-methyl pyrrolidin-2,3-dione **1Aa** (Figure 12) shows the presence of a wide band between 3000-3500 cm^{-1}, which corresponds to the OH stretching and the lack of C=O stretching from the ketone supports the literature data. Further support is also given by the ^{1}H NMR spectrum, which confirms that the compound is fully enolized (Figure 13).
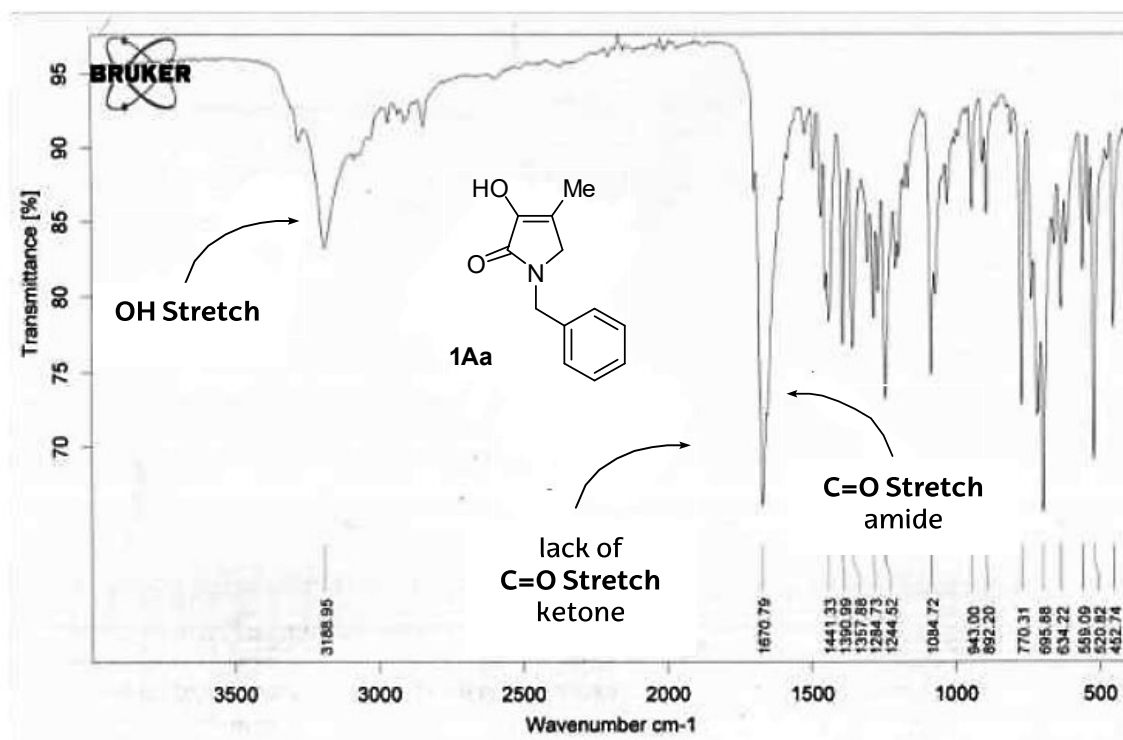
**Figure 12.** IR spectrum of 4-methyl pyrrolidin-2,3-dione **1Aa**.
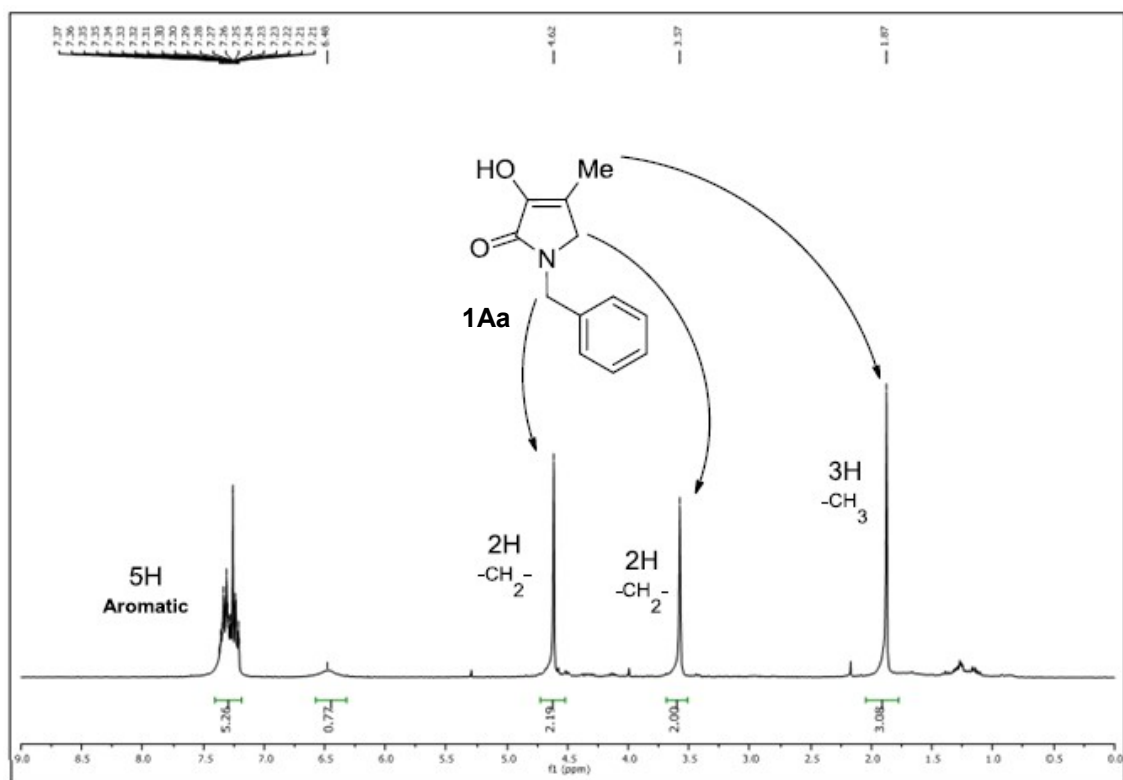
Figure 13. ^{1}H NMR spectrum of 4-methyl pyrrolidin-2,3-dione **1Aa**.

3.4. Michael addition to vinyl sulfones

Previous work from our laboratories has shown that the selection of the electrophile to react with these C4-substituted pyrrolidin-2,3-diones is important, since in some cases the reaction conditions works without catalyst (the starting products are fully enolized) and in other cases retro-Michael addition occurs. Therefore, I started this project by first checking the reaction of pyrrolidin-2,3-dione **1Aa** with (bis)phenyl vinyl sulfone **2A** and phenyl vinyl sulfone **2B** in the absence of catalyst, using CH_2Cl_2 as solvent and at different temperatures as shown in Table 3.

Table 3. Michael addition of pyrrolidin-2,3-dione **1Aa** to vinyl sulfones in the absence of catalyst.

1Aa

2A R: H
2B R: SO$_2$Ph

9AaA R: H
9AaB R: SO$_2$Ph
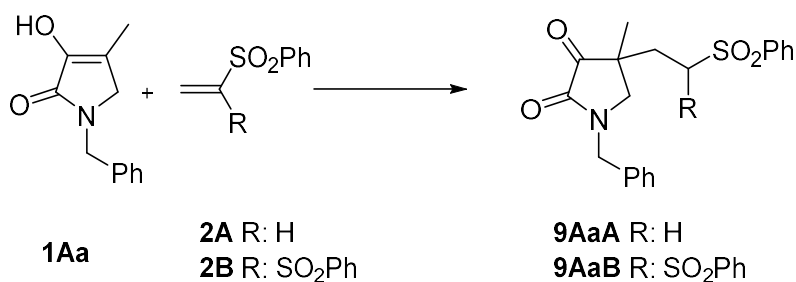
Entry	R	T (°C)	t (h)	Conversion (%)
1	SO$_2$Ph	-20	1	11
2	SO$_2$Ph	-40	16	60
3	H	-20	4	0
4	H	0	16	0
5	H	r.t.	24	0

As Table 3 shows, when the reaction was run with (bis)phenyl vinyl sulfone **2B** at either temperature partial conversion was observed. This means that in the presence of the catalyst both reactions, the enantioselective and the racemic one would be in competition, thus leading to poor enantioselectivity values. However, under similar conditions the addition to the phenyl vinyl sulfone **2A** does not

occur even at room temperature. On this basis, phenyl vinyl sulfone **2A** was selected for the study of the enantioselective version.

As catalysts, squaramide type derivatives introduced by Rawal[19] were selected, because these afforded the best results in the previously investigated reactions with pyrrolidin-2,3-diones. More specifically, the previously described **C1**[43] and the new catalysts (**C2**, **C3** and **C4**) developed in the research group where this project has been carried out were selected (Scheme 12). **C2** was first described by J. Etxabe during his doctoral thesis for the Michael addition of imidazolones to α-silyloxy enones.[44]

C1

C2

C3

C4
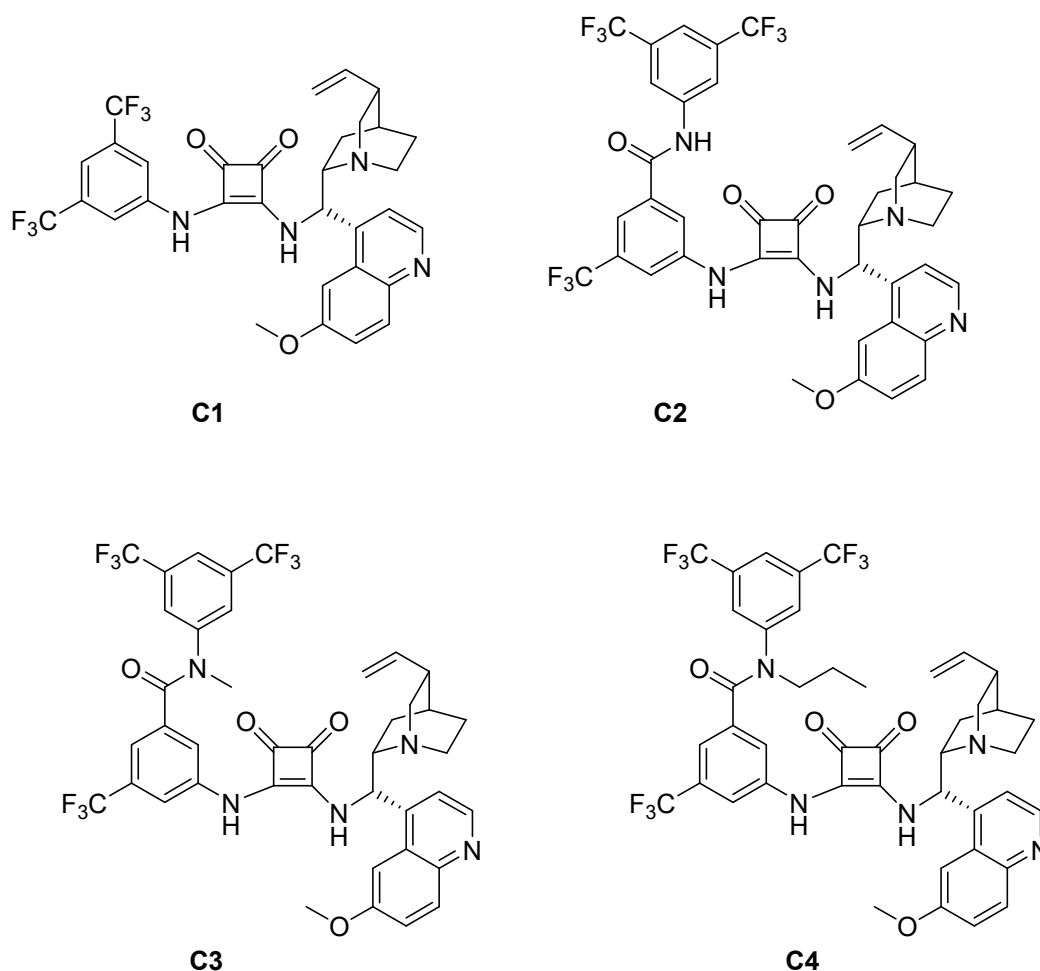
Scheme 12. Catalyst employed in the Micheal addition of pyrrolidin-2,3-diones to vinyl sulfones.

[43] W. Yang, D.-M. *Org. Lett.* **2010**, *12*, 5450-5453
[44] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883-6886

The initial idea when designing catalyst **C2** and related was to incorporate a new electron withdrawing group conected by an amide bond. This amide NH was supposed to either increase the acidity of the NH H-bond donors of the squaramide by intramolecular H-bonding with one of the squaramide carbonyls. The aromatic amide NH could also participate by coordination to one of the substrates.

Catalysts **C1**, **C2** and **C4** were available in the laboratories and **C3** was prepared following the usual sequence described in Scheme 13. First, the corresponding aniline was coupled with the squarate. Then, the resulting product from this reaction was reacted with quinine to provide **C3** in 90% yield.
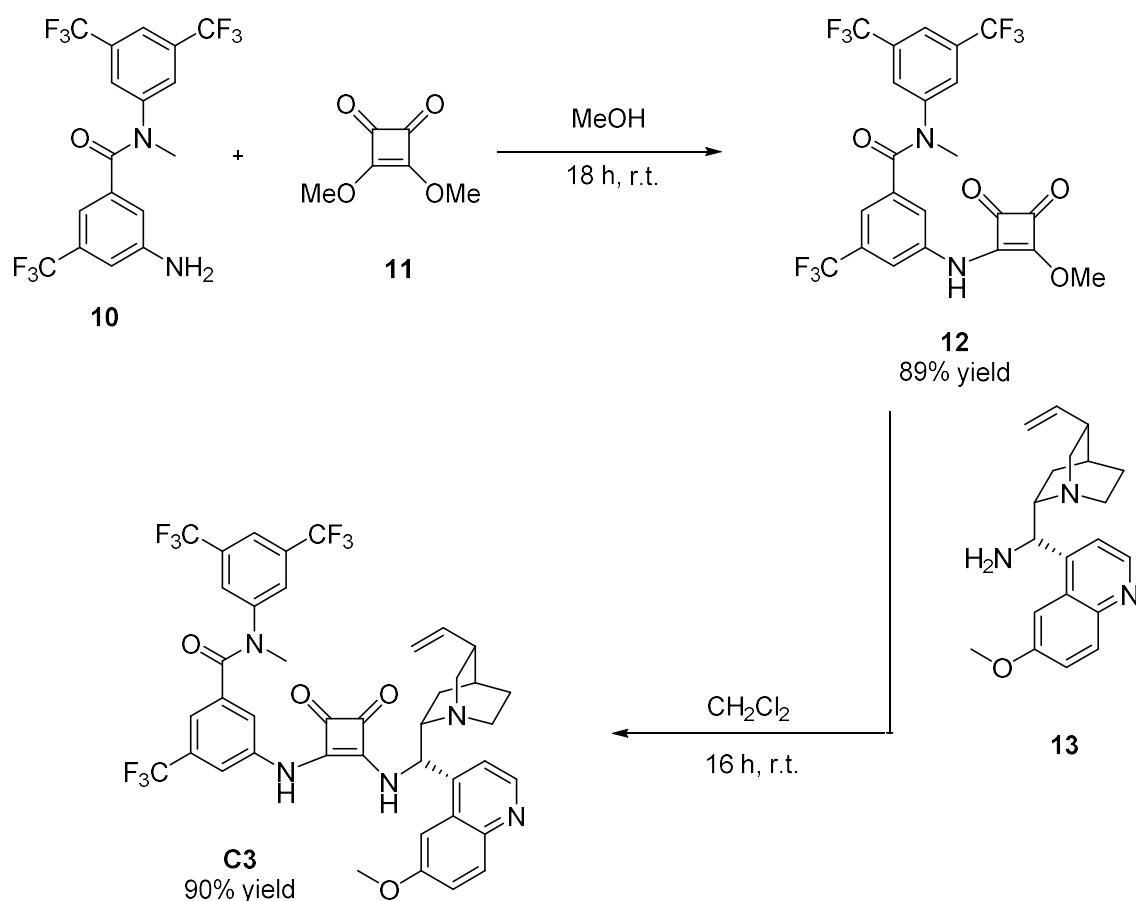
Scheme 13. Scheme for the synthesis of catalyst **C3**.

On this basis, first, catalyst **C1**, **C2** and **C3** were checked in the reaction between pyrrolidin-2,3-dione **1Aa** and phenyl vinyl sulfone **2A**. The racemic reaction was conducted under the same conditions, but using TEA as catalyst. The resulting racemic cyclic adduct **9AaA** could not be appropriately separated in HPLC due to solubility problems, so it was first transformated into the *N*-carboxyanhidride, following the same protocol used in our laboratories with other pyrrolidin-2,3-dione adducts, and then opened with benzylamine. The *ee* values were determined in the opened adduct **14AaA** and are shown in Table 4.

Table 4. Addition of *N*-Benzyl-4-methyl pyrrolidin-2,3-dione to vinyl monosulfone.
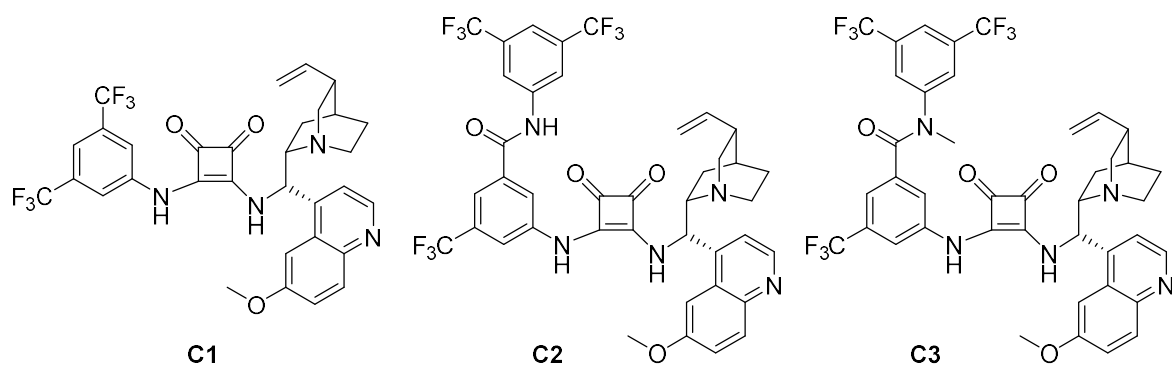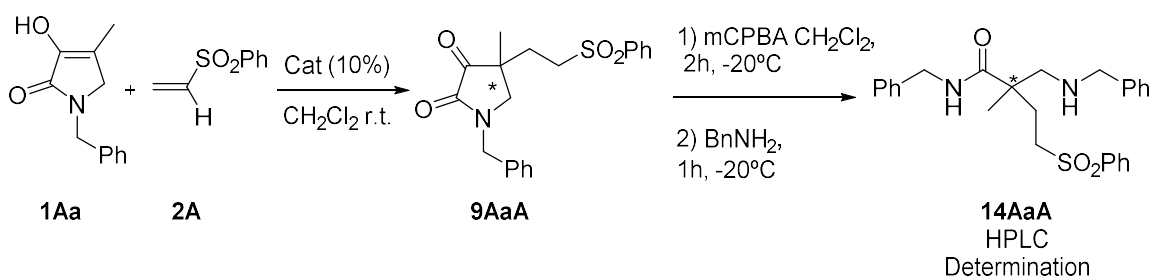
Entry	Catalyst (%)	T (°C)	t (h)	Conversion (%)	Yield[b] (%)	Yield[c] (%)	ee (%)
1	C1 (10 %)	r.t.	24	100	75	70	19
2	C2 (10 %)	r.t.	24	100	81	73	14
3	C3 (10 %)	r.t.	3 days[a]	100	75	69	34

[a] The reaction was not followed. It was left during the weekend. Reaction time might be shorter.

[b] Yields from the conjugate addition reaction.

[c] Yields from the oxidation and ring opening with benzylamine.

Figure 14 shows the corresponding HPLC chromatograms for the racemic
sample and for the enantioselective reactions with catalyst **C1**, **C2** and **C3**.
Unfortunately, in all cases very poor enantioselective values were obtained.
Among all the catalyst tested, squaramide **C3** provided the best results.

a) Racemic (±) 14AaA
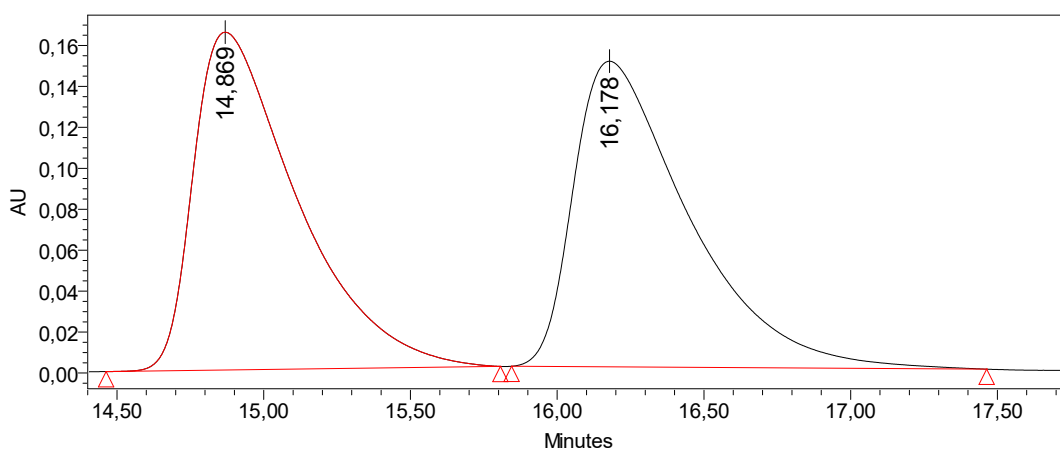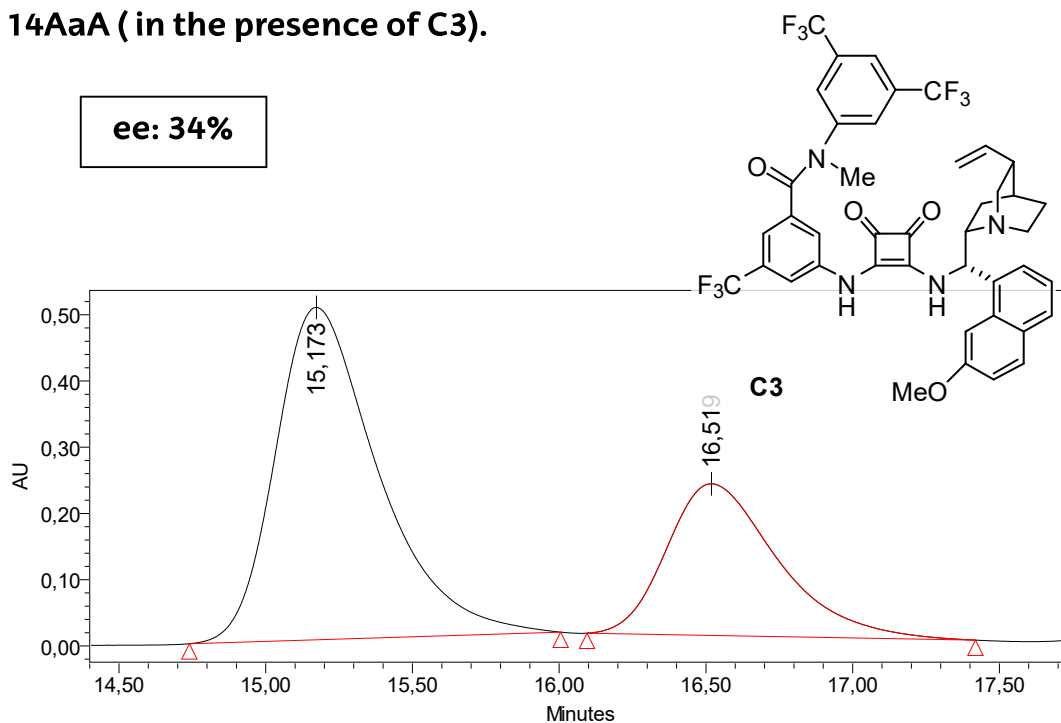

b) 14AaA (in the presence of C1).

ee: 19%
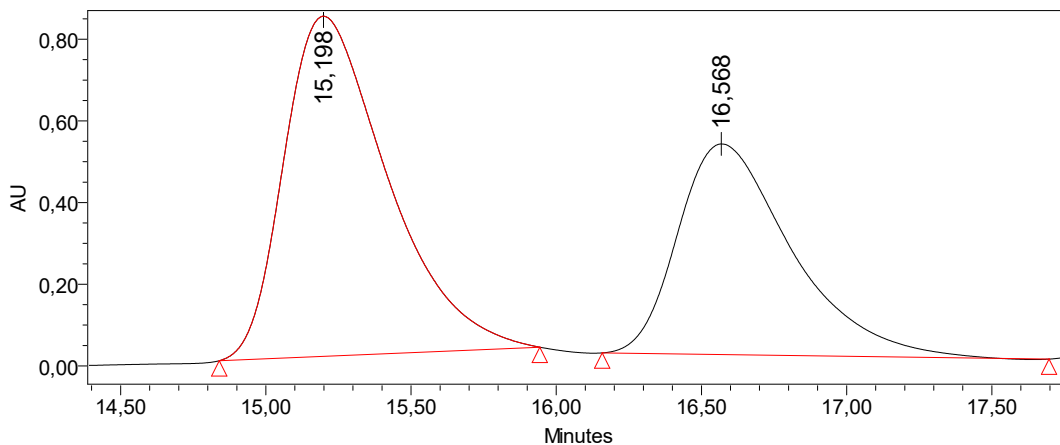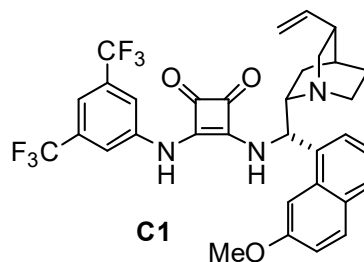
c) **14AaA (in the presence of C2).**
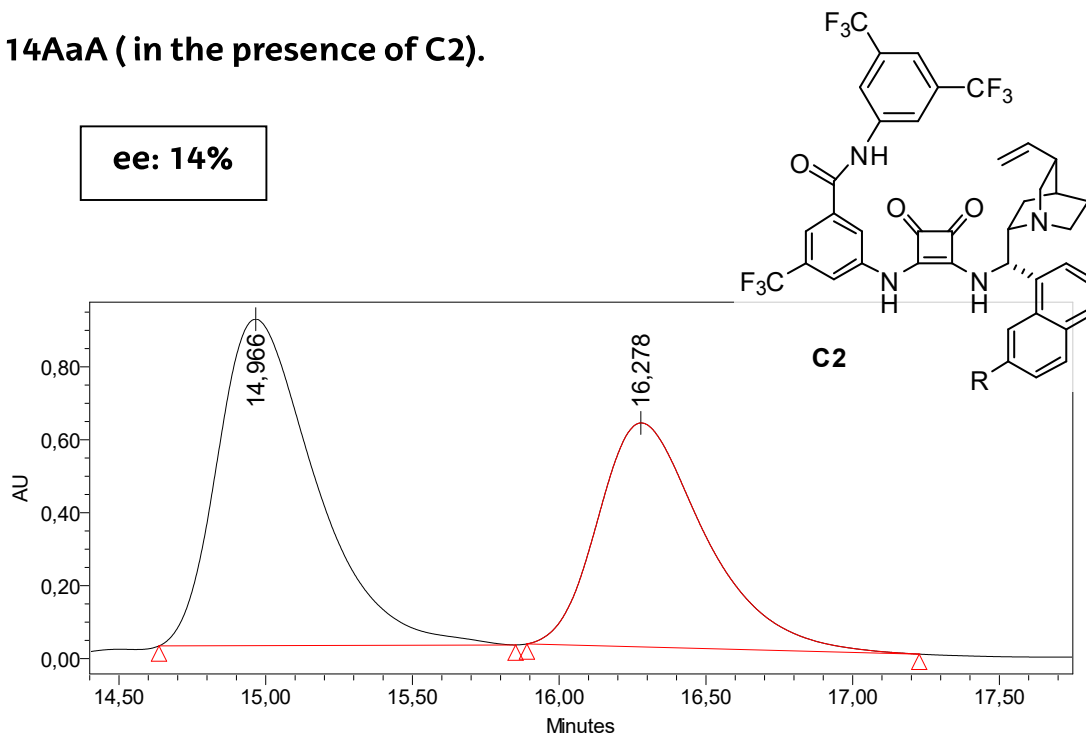
d) **14AaA (in the presence of C3).**

Figure 14. HPLC chromatograms for compound **14AaA**: a) Racemic sample. b) Enantioselective reaction catalyzed by **C1**. c) Enantioselective reaction catalyzed by **C2**. d) Enantioselective reaction catalyzed by **C3**.

With the intention of improving the results, the new catalyst **C4** that had been developed in the lab and efficiently worked in other ongoing research projects was tested in the reaction. The Michael addition product was obtained in 72% yield after three days of reaction.[45] Then the NCA was formed by treatment with *m*CPBA in quantitative yield and the ring was opened providing product **14AaA** in 26% yield (not optimized). The *ee* value was measured in HPLC. However, no significant improvement in enantioselectivity could be observed.

Enantioselective 14AaA, C4

ee: 38%
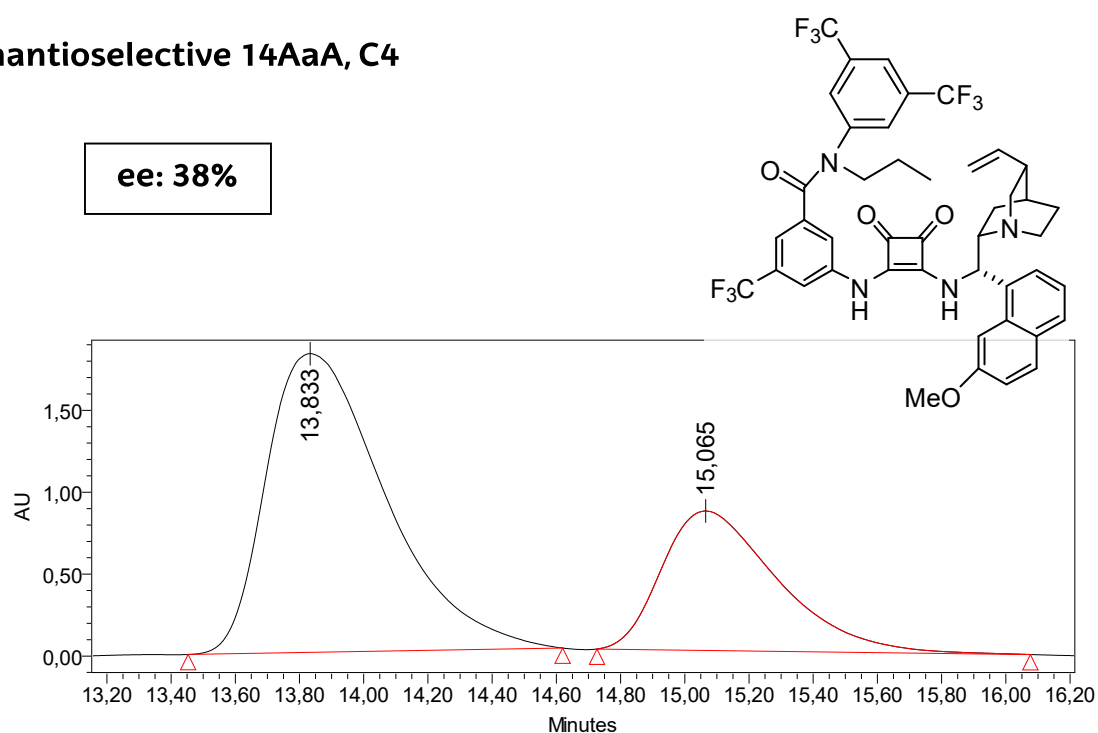
Figure 15. HPLC Chromatogram for enantioselective reaction of **14AaA** catalyzed by **C4**

As mentioned before, another challenge when choosing an appropriate Michael acceptor for the reactions with these pyrrolidin-2,3-diones is to check the possibility of retro Michael reaction, which could account for the poor *ee* values. On this basis and to get more information on this reaction, some preliminary stability studies were carried out with adduct **14AaA** coming from the reaction with catalyst **C3**, which was obtained in 34% *ee* (Scheme 14).

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[45] The reaction was not followed. It was left during the weekend. The reaction time might be shorter.

When this adduct was treated with **C1** in CH_2Cl_2 at r. t. for 3 days no change in the *ee* value and no presence of the starting reactants were observed, thus demonstrating that no retro Michael reaction occurs under these conditions.
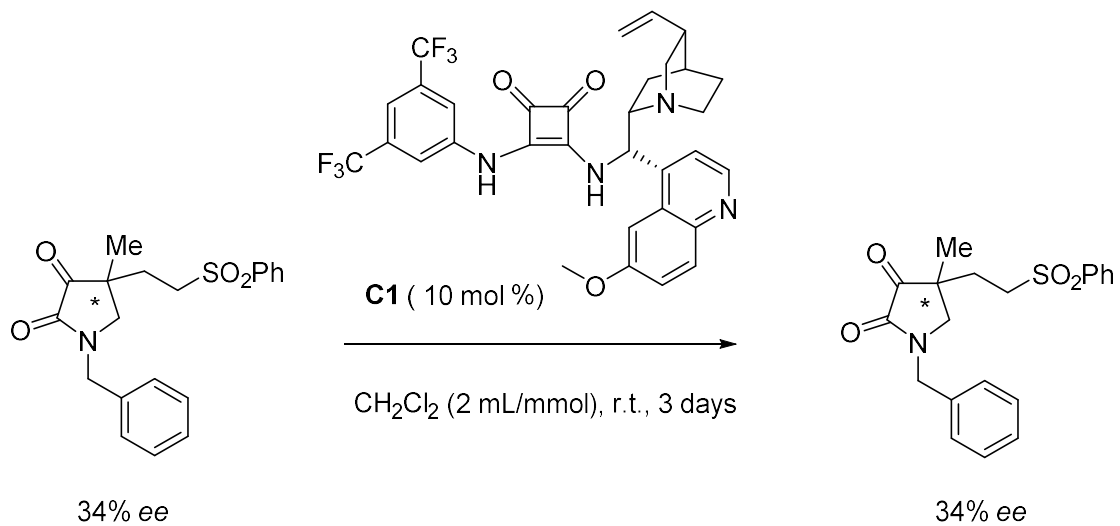
Scheme 14. Retro-Michael study for vinyl monosulfone addition adducts. Enantioselective values determined in the opened adduct **14AaA**.

4. CONCLUSIONS

The main conclusions of the research work described here would be the following:

1. The Micheal addition of pyrrolidin-2,3-diones to phenyl vinyl sulfone works efficiently. But (bis)phenyl vinyl sulfone is not a good electrophile as it is too reactive and the reaction works in the absence of catalyst.

2. The reactions checked take place in good yields but poor stereocontrol has been obtained with the employed catalysts.

3. Derivatization of the adducts to obtain $\beta^{2,2}$-amino acid derivatives works also efficiently.

4. For future research, alternatives for improvement of the results could be modifying either the catalyst or the substrates. The development of new Brønsted base catalyst as well as some modifications in the substituents of the pyrroldin-2,3-diones and the vinyl sulfones could be helpful.

ONDORIOAK

Ikerketa lan honen ondorio nagusiak jarraian aipatzen dira:

1. Fenil binil sulfonetara pirrolidin-2,3-dionen Michael adizioa modu eraginkorrean funtzionatzen du. Baina (bis)fenil binil sulfona ez da elektrofilo egokia erreaktiboegia delako eta erreakzioa katalizatzailearen absentzian gertatzen delako.

2. Ikertutako erreakzioetan etekin onak lortu dira baina estereokontrol apala erabilitako katalizatzaileekin.

3. Aduktoen deribatizazioak $\beta^{2,2}$-amino azido deribatuak lortzeko ere era eraginkorrean gertatzen dira.

4. Etorkizuneko ikerketei begira, emaitzak hobetzeko aukera bat katalizatzailea nahiz sustratoak modifikatzea izan liteke. Brønsted base katalizatzaile berri baten garapena edota pirrolidin-2,3-dionen eta binil sulfonen ordezkatzaileen modifikazioa lagungarria izan liteke.

5. EXPERIMENTAL PART

5.1. Techniques and materials

5.1.1. Nuclear Magnetic Resonance (NMR)

NMR spectra were recorded using a *Bruker Avance DPX* 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C. The solvent used is $CDCl_3$, unless it is otherwise specified. Chemical shifts (δ) are quoted in parts per million referenced to the residual $CDCl_3$ peak, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet. Coupling constants (J) are reported in Hertz (Hz).

5.1.2. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Bioblock lamp VL-4LC, λ= 254 and 365 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 ml of water (limited lifetime), followed by heating.

Chromatographic purification was performed on Merck ROCC 60 silica gel 40-63 μm as stationary phase and a suitable mixture of solvents (typically hexane/ethyl acetate) as eluent.

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]$D) are reported in 10^{-1} deg·cm^{2}g^{-1}; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degree Celsius (°C).

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600 (equipped with

Photodiode Array Detector Waters 2996). The used column is IB and flow/solvent conditions are given for each compound.

5.1.3. Reagents and solvents

Reagents were purchased from different commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, Fluka, TCI, Merck, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

5.1.4. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

5.1.5. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

5.2. Synthesis of catalysts

Catalysts **C1**, **C2** and **C4** were provided by the laboratory where the project was developed. Catalyst **C3** was synthesized following the usual general protocol as outlined below.

12
89% yield

13

C3
90% yield
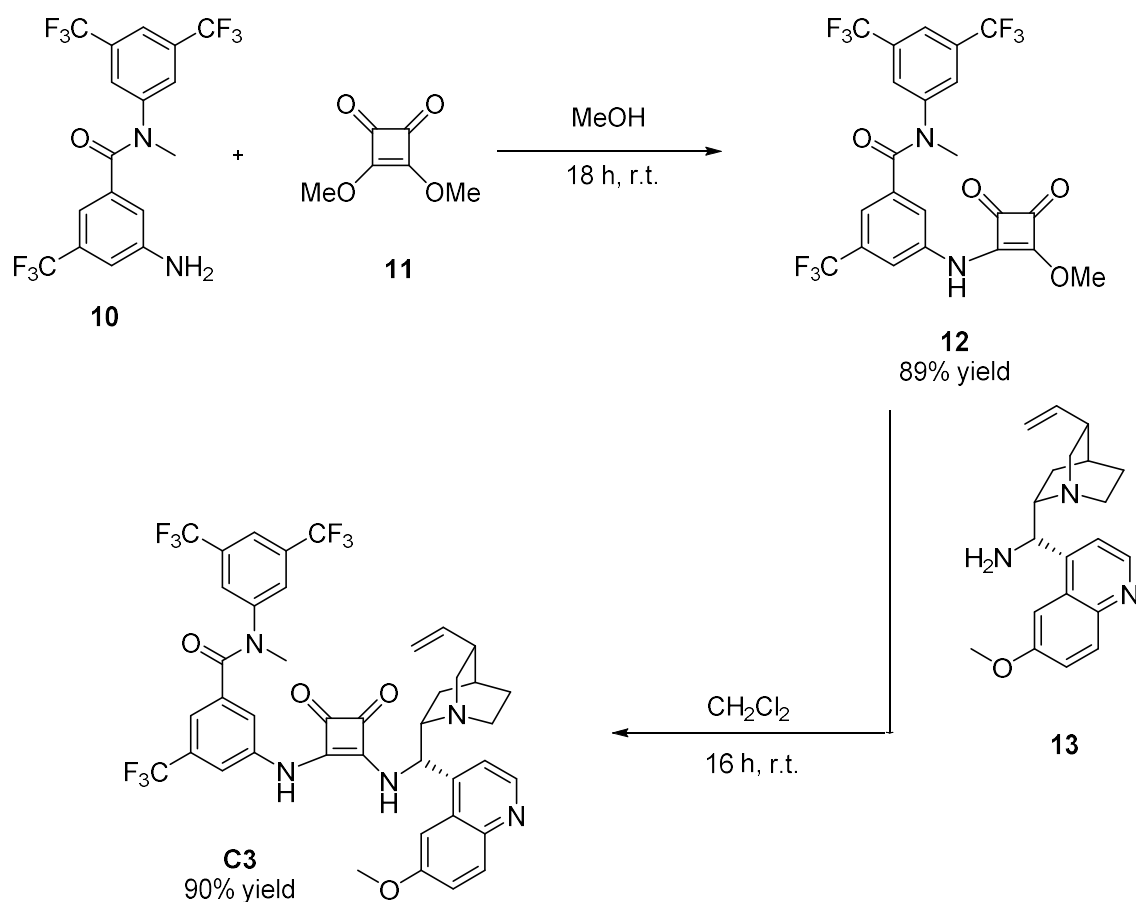
5.2.1. Synthesis of the aniline

Step 1: N-Methyl-3,5-bis(trifluoromethyl)aniline 15[46]

15
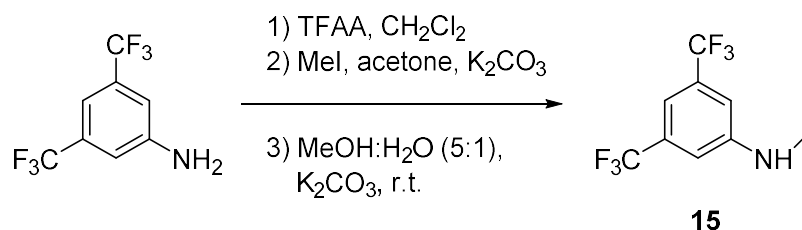
A solution of 3,5-bis(trifluoromethyl)aniline (1 mL, 6.4 mmol, 1 eq) in DCM (14 mL) was cooled down to 0°C. Then, TFAA (2.7 mL, 19 mmol, 3 eq) was added and the mixture was stirred for 20 min at 0°C and then the solvents were evaporated under *vacuum*. Acetone (15 mL), anhydrous K_2CO_3 (1.77 g, 12.8 mmol,

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[46] Koskinen, A. M. P. *ARKIVOC*, **2010**, 205-223.

2 eq) and MeI (1.2 mL, 19 mmol, 3 eq) were added in this order and the mixture was heated to mild reflux for 2h. Potassium carbonate was dissolved when heated. The mixture was filtered and the solvent was evaporated under *vacuum*. MeOH: H_2O (25 mL:5 mL) and anhydrous K_2CO_3 (880 mg, 6.4 mmol, 1 eq) were added. The reaction mixture was stirred at r.t. and completion was determined by ^{1}H-NMR analysis of an aliquot. The solvents were partially evaporated, H_2O (25 mL) was added and the mixture was extracted with DCM (3x10 mL). All the organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to provide the title compound **15** as a yellow oil (1.495 g, 6.19 mmol, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.92 (s, 2H), 4.18 (s, 1H), 2.89 (d, J = 5.2 Hz, 3H).

Step 2: *N-(3,5-Bis(trifluoromethyl)phenyl)-N-methyl-3-nitro-5-(trifluoromethyl)benzamide 16*[47]
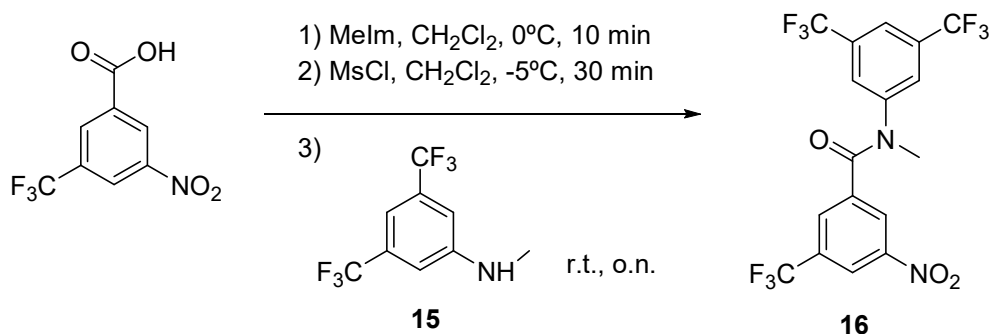
To a solution of 3-nitro-5-(trifluoromethyl)benzoic acid (1.455 g, 6.2 mmol, 1 eq) in CH_2Cl_2 (15.5 mL) at 0°C 1-methylimidazole (1.23 mL, 15.5 mmol, 2.5 eq) was added and the solution was stirred at that temperature for 10 min. Then, MsCl (0.72 mL, 9.3 mmol, 1.5 eq) in CH_2Cl_2 (0.6 mL) was added at -5°C and the mixture stirred for additional 30 min at the same temperature. After the addition of *N*-methyl-3,5-bis(trifluoromethyl)aniline **15** (0.97 mL, 6.2 mmol, 1 eq) the mixture was stirred at r.t. overnight. H_2O (65 mL) was then added and a precipitate was formed which was dissolved in EtOAc (65 mL). The organic layer was separated, washed with brine (3 x 30 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure to give a yellow oil which was crushed with

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[47] Procedure adapted from: Mao, L.; Wang, A.; Li, Y.; Han, X.; Zhou, W. *Synlett.* **2011**, 129-133.

diethyl ether to afford the title compound **16** as a white solid (2.159 g, 4.8 mmol, 78% yield). ^{1}H NMR (300 MHz, CDCl$_3$) 8.44 (s, 1H), 8.36 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.59 (s, 2H), 3.60 (s, 3H).

Step 3: *3-Amino-N-(3,5-bis(trifluoromethyl)phenyl)-N-methyl-5-(trifluoromethyl)benzamide 10*
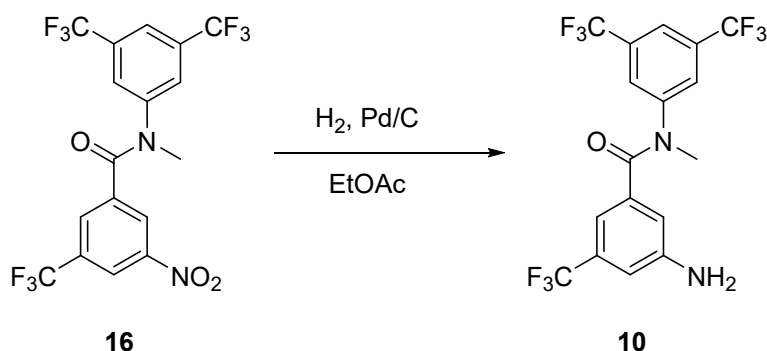
Pd/C was added (216 mg, Pd 10% on activated carbon, 10% in weight) to a solution of N-(3,5-bis(trifluoromethyl)phenyl)-N-methyl-3-nitro-5-(trifluoro methyl)benzamide **16** (2.159g, 4.8 mmol, 1 eq) in EtOAc (10.5 mL) under inert atmosphere. The reaction mixture was stirred under H$_2$ atmosphere (1 atm) at r.t. for 20 h. Then, the mixture was filtered over Celite® and concentrated under reduced pressure to provide the title product **10** as a white solid (1.974 g, 4.7 mmol, 99% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.69 (s, 1H), 7.53 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.69 (s, 1H), 3.92 (s, 2H), 3.53 (s, 3H).

5.2.2 Synthesis of 9-Amino-(9-deoxy) epiquinine 13[48]

17

MsCl, Et₃N

THF, r.t., o.n.

18
quant. yield

NaN₃

DMF, 70°C, 24 h

19
quant. yield

1. PPh₃, 40°C, THF

2. H₂O, 40°C, THF, o.n.

13
56% yield
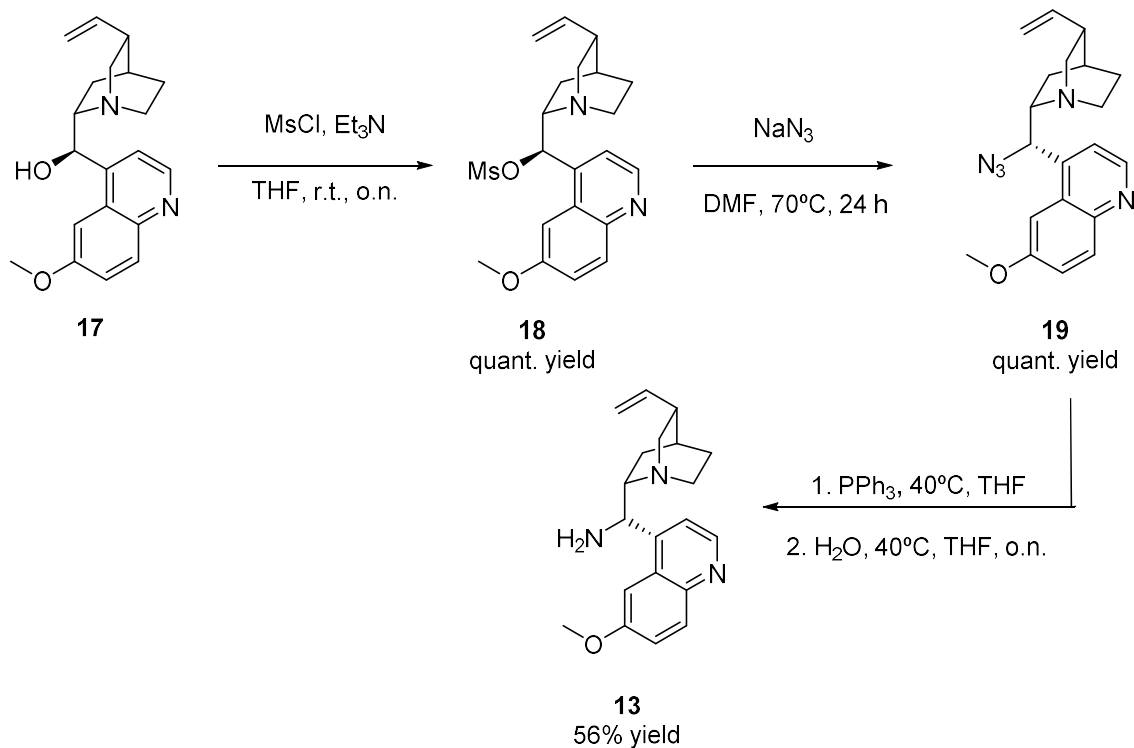
Step 1:[49] To a mixture of quinine **17** (32.4 9, 100 mmol, 1 eq) and Et₃N (50 mL, 360 mmol, 3.6 eq) in dry THF (500 mL) at 0°C MeSO₂Cl (13.9 mL, 180 mmol, 1.8 eq) was added dropwise under inert atmosphere and the mixture was stirred at r.t. overnight. The reaction was quenched with H₂O (40 mL) and THF was removed under *vacuum*. The remaining solid was dissolved in CH₂Cl₂ (60 mL) and extracted with H₂O (40 mL). The organic layer was washed with NaHCO₃ (2 x 40 mL), dried over MgSO₄ and the solvent was evaporated under reduced pressure to provide **18** as a brown dark oil in quantitative yield. The product was used in the next step without further purification.

Step 2:[50] The crude product **18** from the previous step (100 mmol, 1 eq) was dissolved in DMF (300 mL) under inert atmosphere and the resulting solution was cooled down to 0°C. NaN₃ was added portionwise and the mixture was stirred at

[48] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.
[49] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.
[50] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

70ºC for 24h. The reaction was quenched with H_2O (200 mL) and extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (10 x 120 mL) and dried over $MgSO_4$. The solvents were evaporated under *vacuum* to afford the crude solid product **19** in quantitative yield, which was used in the next step without further purification.

Step 3:[50] The crude product **19** from the previous step (100 mmol, 1 eq) was dissolved in dry THF (400 mL) and the resulting solution stirred at 40ºC under inert atmosphere. Then, PPh_3 (26.2 g, 100 mmol, 1 eq) was added portionwise and gas evolution was observed. The mixture was stirred at 40ºC until gas evolution ceased (6h more or less). Then, H_2O (816 mL) was added and the reaction mixture was stirred overnight at the same temperature. The solvents were removed under vaccum providing an orange solid that was dissolved in CH_2Cl_2 (400 mL). The mixture was stirred at 0ºC and quenched by adding HCl 6M (300 mL) portionwise. The aqueous phase was separated and washed with CH_2Cl_2 (3 x 200 mL). Then, the aqueous phase was cooled down to 0ºC and NaOH (first solid and then 40% solution) was added until a precipitate was formed. The mixture was extracted with CH_2Cl_2 (3 x 200 mL), dried over $MgSO_4$ and the solvents were evaporated in *vacuum*. The title product **13** was obtained as a yellow foam. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CDCl3) δ 8.75 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.66 (s, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.39 (dd, J = 9.2, 2.7 Hz, 1H), 5.81 (ddd, J = 17.4, 10.3, 7.5 Hz, 1H), 5.05 − 4.93 (m, 2H), 4.60 (d, J = 10.1 Hz, 1H), 3.97 (s, 3H), 3.34 − 3.03 (m, 4H), 2.87 − 2.74 (m, 2H), 2.29 (s, 1H), 1.86 (s, 2H), 1.66 − 1.37 (m, 2H), 0.77 (dd, J = 13.5, 7.4 Hz, 1H).

5.2.3 Synthesis of N-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-N-methyl-5-(trifluoromethyl)benzamide 12[51]
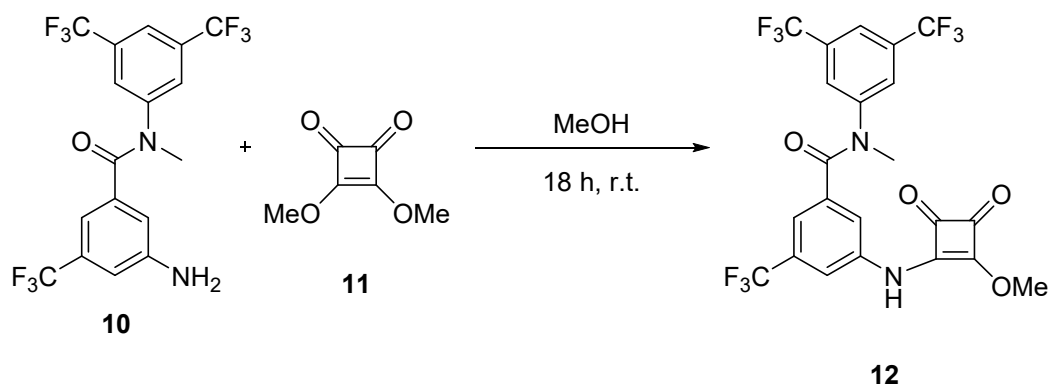
The free aniline **10** (1.97 g, 4.7 mmol, 1.1 eq) and 3,4-dimethoxycyclobut-3-ene-1,2-dione **11** (612.8 mg, 4.3 mmol, 1 eq) were dissolved in MeOH (9 mL) and the mixture was stirred at r.t. for 18 h. The solvents were then removed under reduced pressure and the crude product was purified by silica column chromatography (eluent system: from 95:5 Hexane: EtOAc to 70:30 Hexane: EtOAc). The title compound **12** was obtained as a white solid (2.05 g, 3.8 mmol, 89% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 (d, J = 5.0 Hz, 2H), 7.57 (s, 2H), 7.51 (s, 1H), 7.18 (s, 1H), 4.52 (s, 3H), 3.58 (s, 3H).

5.2.4. Coupling of the squaric ester monoamide to epiquinine. Synthesis of C3[52]

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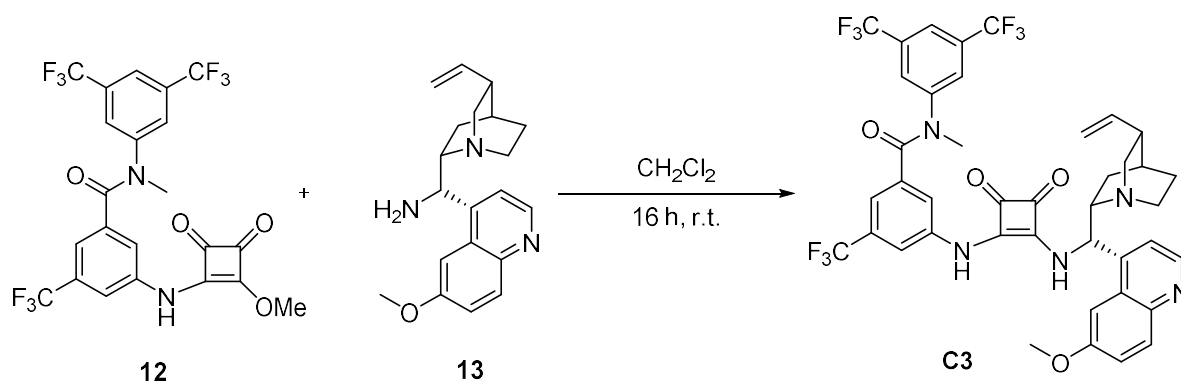
[51] Procedure adapted from: Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*,
3004–3006.
[52] Adapted from: Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

To a suspension of the squaric ester monoamide **12** (593.6 mg, 1.8 mmol, 1 eq) in CH_2Cl_2 (10 mL) epiquinine **13** (0.965 g, 1.8 mmol, 1 eq) was added and the mixture was vigorously stirred at r.t. for 16 h. The solvents were evaporated and the resulting residue was purified by silica column chromatography (eluent system: 98:2 CH_2Cl_2: MeOH). The obtained product was basified with $NaHCO_3$ (2 x 10 mL) and the water phase was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were collected, dried over $MgSO_4$ and concentrated in *vacuum* to give the title product **C3** as a yellow solid (1.353 g, 1.62 mmol, 90% yield). ^1H NMR (300 MHz, Acetone-d_6) 8.77 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.6 Hz, 3H), 7.93 (s, 2H), 7.86 (s, 1H), 7.77 (s, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.42 (dd, J = 9.2, 2.5 Hz, 1H), 7.23 (s, 1H), 6.31 (s, 1H), 5.87 (m , 1H), 4.97 (m, 2H), 4.04 (s, 3H), 3.59 (s, 4H), 3.36 − 3.20 (t, 1H), 2.82 (d, J = 12.4 Hz, 2H), 2.36 (s, 1H), 2.08 (m, 1H), 1.65 (d, J = 15.0 Hz, 4H), 0.89 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) 185.77 , 181.38 , 169.69 , 169.11 , 164.10 , 159.34 , 148.44 , 146.76 , 145.80 , 143.88 , 142.38 , 141.06 , 138.91 , 132.57 , 132.43 (q) , 131.93 (q) , 129.74 , 129.27 , 128.75 , 128.49 , 126.14 , 125.66 , 122.96 , 122.53 , 122.06 , 120.67 , 119.34 , 118.44 , 116.57 , 114.82 , 102.24 , 60.74 , 56.69 , 56.31 , 54.87 , 41.48 , 40.38 , 38.34 , 28.53 , 28.09 , 26.74 . $[\alpha]_D^{23}$ = -115.89° (c=1.0, CH_2Cl_2). mp: 150-152°C.

5.3. Synthesis of starting materials

5.3.1. Synthesis of Methyl 4-methyl-2-methylenepentanoate[53]

Step 1: Alkylation of acetoacetate

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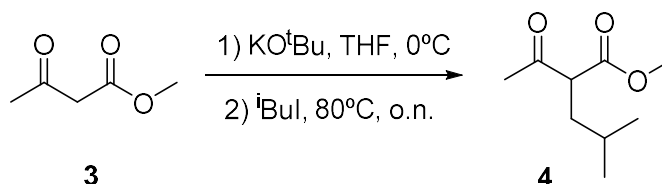
[53] Procedure adapted from: Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812–2825.

To a suspension of potassium *tert*-butoxide (1.1 eq) in THF (2.5mL/mmol) stirring at 0°C methyl acetoacetate **3** (7.56 mL, 70 mmol, 1.0 eq) and *tert*-butanol (0.1 eq) were added. The suspension was stirred for 2 h and isobutyl iodide (7.98 mL, 69.3 mmol, 0.99 eq) was added. The suspension was stirred at 80°C overnight. After this time, a white solid was formed and the reaction was quenched with water until this solid was dissolved. Then, a saturated solution of $NaHCO_3$ was added and the mixture was extracted with ether (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated in *vacuum*. The crude product was purified by silica column chromatography (eluent system 90:10 Hexane: EtOAc) providing 44.4 mmol (7.63 g, 63% yield) of methyl 2-acetyl-4-methylpentanoate **4** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) 3.69 (s, 3H), 3.56 − 3.44 (m, 1H), 2.20 (s, 3H), 1.81 − 1.59 (m, 2H), 1.58 − 1.41 (m, 1H), 0.89 (dd, J = 6.5, 1.4 Hz, 6H).

Step 2: *Retro-Claisen Reaction*

4   KHMDS, THF, -78°C, 30 min / Paraformaldehyde, o.n., r.t.   **5**
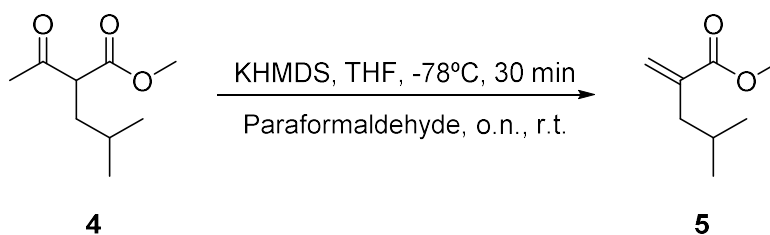
KHMDS (1.1 equiv.) was added dropwise to a solution of methyl 2-acetyl-4-methylpentanoate **4** (7.63 g, 44.4 mmol, 1.0 eq) in THF (8 mL/mmol) at −78 °C. After 30 min, paraformaldehyde (1 equiv.) was added and the resultant mixture was warmed to r.t. overnight. Then reaction mixture was filtered over Celite® and all organic solvents were removed under reduced pressure. The resulting crude was purified by silica column chromatography (eluent system 98:20 Hexane: EtOAc) obtaining 20.8 mmol (2.97 g, 47%) of methyl 4-methyl-2-methylenepentanoate **5** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) 5.89 (s, 1H), 5.23 (s, 1H), 3.54 − 3.42 (m, 3H), 1.99 − 1.83 (m, 2H), 1.70 − 1.46 (m, 1H), 0.63 (dd, J = 6.0, 2.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) 167.05 , 139.45 , 125.05 , 51.06 , 41.12 , 26.82 , 21.83 .

5.3.2. Addition of amines to acrylates[42]
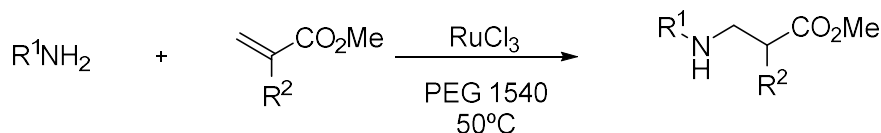
6a R^1: Bn   **5A** R^2:Me
6b R^1: 1-Naphth-CH$_2$ **5B** R^2: ^{i}Bu

($\pm$) **7Aa** R^1: Bn R^2: Me
($\pm$) **7Ab** R^1: 1-Naphth-CH$_2$ R^2: Me
($\pm$) **7Bb** R^1: 1-Naphth-CH$_2$ R^2: ^{i}Bu

RuCl$_3$·H$_2$O (0.5 mol %) was added to a mixture of PEG (average MW 2000, 0.4 g/mmol), the amine (1 eq) and the acrylate (1 eq). The reaction mixture was kept at 50 °C for 16 h by magnetic stirring and then cooled to r.t. The mixture was poured into Et$_2$O (40 mL) and then it was kept cooling in a refrigerator for 30 min to aid precipitation. The precipitate was filtered and washed with further portions of Et$_2$O, and the washings were combined with the initial filtrate. The combined organic phases were washed several times with H$_2$O and dried (MgSO$_4$). After filtration and removal of the solvent, the product was purified by silica column chromatography.

($\pm$) Methyl 3-(Benzylamino)-2-metilpropanoate **7Aa**
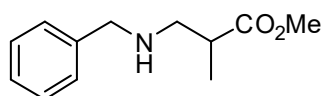
The general procedure for the addition of amines to acrylates was followed using benzylamine (3.27 mL, 30 mmol, 1 eq), methyl methacrylate (3.21 mL, 30 mmol, 1 eq) and RuCl$_3$·H$_2$O (43 mg, 0.5%). The title product was purified by silica column chromatography (eluent system: from 80:20 Hexane: EtOAc to 1:1 Hexane: EtOAc) and isolated as a yellow oil (23.7 mmol, 2.72 g, 80% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 − 7.28 (m, 3H), 7.27 − 7.19 (m, 2H), 3.69 (s, 3H), 2.88 (td, J = 9.9, 3.6 Hz, 1H), 2.75 − 2.61 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H).

*(±) Methyl 2-methyl-3-((naphthalen-1-ylmethyl)amino)propanoate **7Ab***
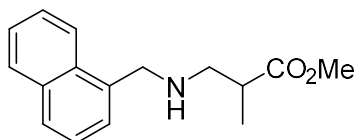
The general procedure for the addition of amines to acrylates was followed using naphthalen-2-ylmethanamine (2.93 mL, 20 mmol, 1 eq), methyl methacrylate (2.14 mL, 20 mmol, 1 eq) and $RuCl_3 \cdot H_2O$ (28.6 mg, 0.5%). The title product was purified by silica column chromatography (eluent system 90:10 Hexane: EtOAc) and isolated as a yellow oil (11.4 mmol, 2.94 g, 58% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 8.0 Hz, 1H), 7.88 − 7.84 (m, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.58 − 7.39 (m, 4H), 4.24 (s, 2H), 3.67 (s, 3H), 3.07 − 2.96 (m, 1H), 2.83 − 2.68 (m, 2H), 1.20 (d, J = 6.9 Hz, 3H).

*(±) Methyl 4-methyl-2-(((naphthalen-1-ylmethyl)amino)methyl) pentanoate **7Bb***
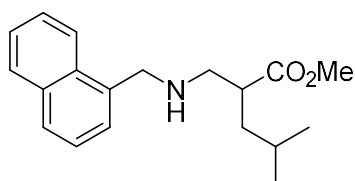
The general procedure for the addition of amines to acrylates was followed using naphthalen-2-ylmethanamine (1.76 mL, 12 mmol, 1 eq), methyl 4-methyl-2-methylenepentanoate (1.71 g, 12 mmol, 1 eq) and recycled PEG+$RuCl_3$ mixture (4.8 g). The title product was purified by silica column chromatography (eluent system 90:10 Hexane: EtOAc) and isolated as a yellow oil (1.4 mmol, 0.355 g, 11% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 7.8 Hz, 1H), 7.93 − 7.74 (m, 2H), 7.59 − 7.38 (m, 4H), 4.30 − 4.16 (m, 2H), 3.66 (s, 2H), 2.96 (dd, J = 11.7, 9.1 Hz, 1H), 2.86 − 2.66 (m, 2H), 1.58 (ddt, J = 19.0, 13.1, 6.3 Hz, 2H), 1.29 (td, J = 9.9, 4.8 Hz, 1H), 0.90 (dd, J = 6.3, 3.7 Hz, 6H).

5.3.3. Cyclization/ decarboxylation reaction.[40]

(±) **7Aa** R^1: Bn R^2: Me   **8**   **1Aa** R^1: Bn R^2: Me
(±) **7Ab** R^1: 1-Naphth-CH$_2$ R^2: Me   **1Ab** R^1: 1-Naphth-CH$_2$ R^2: Me
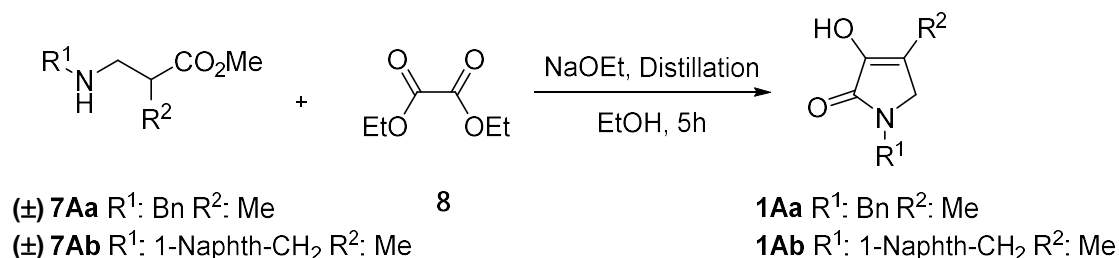
To a solution of the β-amino ester and ethyl oxalate in EtOH (2.3 mL/ mmol), NaOEt was added. The mixture was heated under reflux for 5h and ethanol was removed by distillation leaving a liquid residue, which was dissolved in 50 mL of warm water. Then, the mixture was acidified with HCl 1M and the suspension was extracted with DCM (30 mL x 3. The combined organic phases were dried over MgSO$_4$ and the solvents were evaporated under *vacuum*. The crude product was purified by silica column chromatography.

1-Benzyl-3-hydroxy-4-methyl-1,5-dihydro-2H-pyrrol-2-one *1Aa*
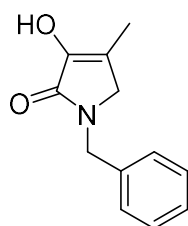
The general procedure for the cyclization reaction was followed using methyl 3-(benzylamino)-2-metilpropanoate (1.600 g, 14 mmol, 1 eq) in EtOH (32.3 mL), diethyl oxalate (2.25 mL, 16.8 mmol, 1.2 eq) and NaOEt (1.218 g, 18.2 mmol, 1.3 eq). The title compound was purified by silica column chromatography (eluent system: 1:1 Hex: EtOAc) and isolated as a white solid (12.0 mmol, 3.36g, 86% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 − 7.19 (m, 5H), 4.62 (s, 2H), 3.57 (s, 2H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) 168.39 , 141.96 , 137.03 , 128.93 , 128.24 , 127.83 , 118.16 , 50.67 , 46.85 , 10.34 .

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Pyrrolidin-2,3-diones as pronucleophiles in
organocatalytic Michael additions to vinyl sulfones

3-Hydroxy-4-methyl-1-(naphthalen-1-ylmethyl)-1,5-dihydro-2H-
*pyrrol-2-one **1Ab***
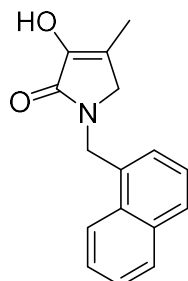
The general procedure for the cyclization reaction was followed using
methyl 2-methyl-3-((naphthalen-2-ylmethyl)amino)propanoate (1.326 g, 5.2
mmol, 1 eq) in EtOH (10 mL), diethyl oxalate (0.84 mL, 6.2 mmol, 1.2 eq) and NaOEt
(0.454 g, 6.8 mmol, 1.3 eq). The title compound was purified by silica column
chromatography (eluent system: from 90:10 Hexane: EtOAc to 80:20 Hexane:
EtOAc) and isolated as a white solid (3.4 mmol, 0.86 g, 65% yield). ^{1}H NMR (300
MHz, CDCl$_3$) δ 8.17 − 8.08 (m, 1H), 7.94 − 7.80 (m, 2H), 7.60 − 7.50 (m, 2H), 7.50 − 7.34
(m, 2H), 5.06 (s, 2H), 3.45 (s, 2H), 1.81 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.07 ,
141.96 , 134.18 , 132.46 , 131.73 , 129.25 , 128.96 , 127.61 , 127.22 , 126.45 , 125.51 ,
123.99 , 118.35 , 50.82 , 45.20 , 10.45 .

5.4. Conjugate addition of pyrrolidin-2,3-diones to vinyl monosulfones

General procedure for the asymmetric reactions
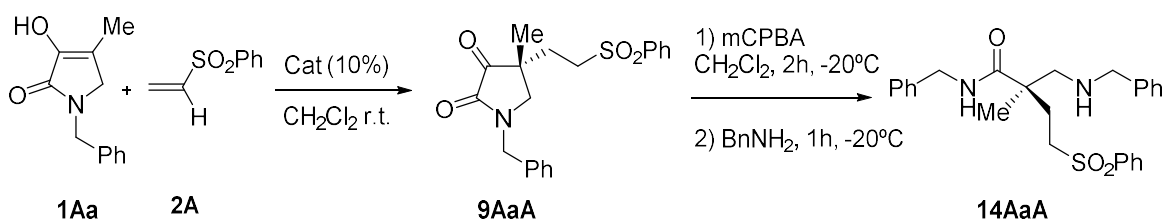
Step 1: Pyrrolidin-2,3-dione **1Aa** (0.2 mmol, 1 eq) and catalyst (0.02 mmol, 10 mol %) were dissolved in CH_2Cl_2 (2 mL/mmol). Then, phenyl vinyl monosulfone **2A** (74 mg, 0.24 mmol, 1.2 eq) was added and the mixture was stirred at r.t. The reaction was followed by ^1H NMR and when complete, the reaction mixture was directly purified by silica column chromatography.

Step 2: The product from the previous step was dissolved in 1 mL of CH_2Cl_2 at -20°C. Then, mCPBA (1.5 eq) was added portionwise *in situ* and the mixture was stirred for 2h. The reaction was followed by TLC analysis and when the reaction was finished, the mixture was dissolved in CH_2Cl_2 and extracted with $NaHSO_3$ 10% (x 2). Then, the aqueous phase was extracted with CH_2Cl_2 (x 2). The organic layers were combined, and extracted with NaOH 1M (x 2). The aqueous phase was washed with CH_2Cl_2 (x 2) and the combined organic layers were dried over $MgSO_4$ and evaporated in under reduced pressure.

Step 3: The crude product from the previous step was dissolved in 1 mL of CH_2Cl_2 at -20°C. Then, benzylamine (2 eq) was added and the reaction mixture was stirred for 1h at the same temperature. The solvent was evaporated in *vacuum*. The crude was purified by silica column chromatography.

(R)-*N*-Benzyl-2-((benzylamino)methyl)-2-methyl-4-(phenylsulfonyl) butanamide **14AaA**
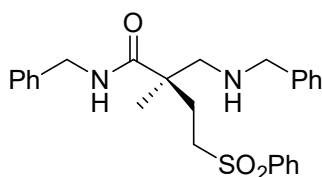
The general procedure was followed using 1-benzyl-3-hydroxy-4-methyl-1,5-dihydro-2H-pyrrol-2-one (40.62 mg, 0.2 mmol, 1 eq). The crude from step 1 was purified by silica column chromatography (eluent system: from 90:10 Hexane: EtOAc to 1:1 Hexane: EtOAc) obtaining a white solid in a range of 72-81% yield. The corresponding NCA was always obtained in quantitative yield. The crude from step 3 was purified by silica column chromatography (eluent system 90:10 Hexane: EtOAc) obtaining a yellow oil (yields between 69-73%). ^1H NMR (300 MHz,

CDCl$_3$) 7.95 − 7.86 (m, 2H), 7.72 − 7.51 (m, 3H), 7.41 − 7.20 (m, 8H), 7.06 (dd, J = 6.4, 3.0 Hz, 2H), 4.35 (dd, J = 5.3, 1.9 Hz, 2H), 3.70 (s, 2H), 3.30 − 3.06 (m, 2H), 2.72 (q, J = 12.5 Hz, 2H), 1.98 (ddd, J = 10.2, 6.8, 3.8 Hz, 2H), 1.13 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) 175.28 , 139.14 , 138.80 , 138.68 , 133.81 , 129.38 , 128.78 , 128.67 , 128.28 , 128.04 , 127.78 , 127.51 , 127.41 , 55.81 , 54.43 , 52.26 , 43.75 , 43.38 , 30.01 , 21.93 .

Procedure for the racemic reaction

The same procedure that for the asymmetric reactions was followed, but using TEA (10 mol%) as catalyst.

4.5.   NMR Spectra
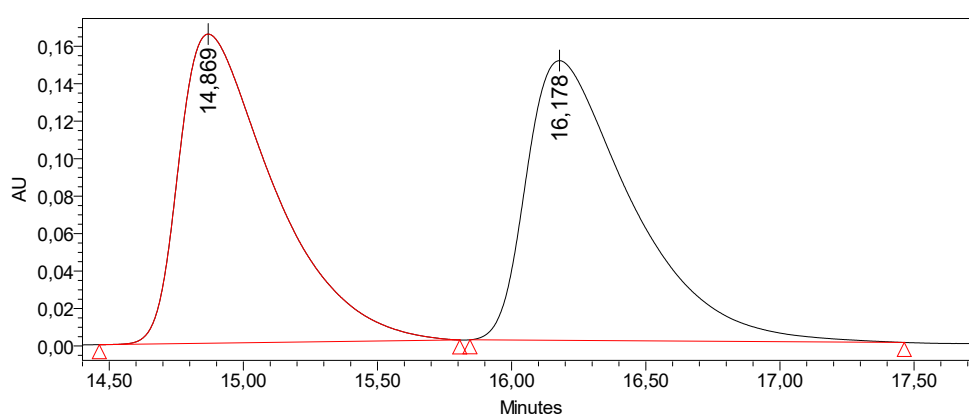
13

9AaA

9AaA
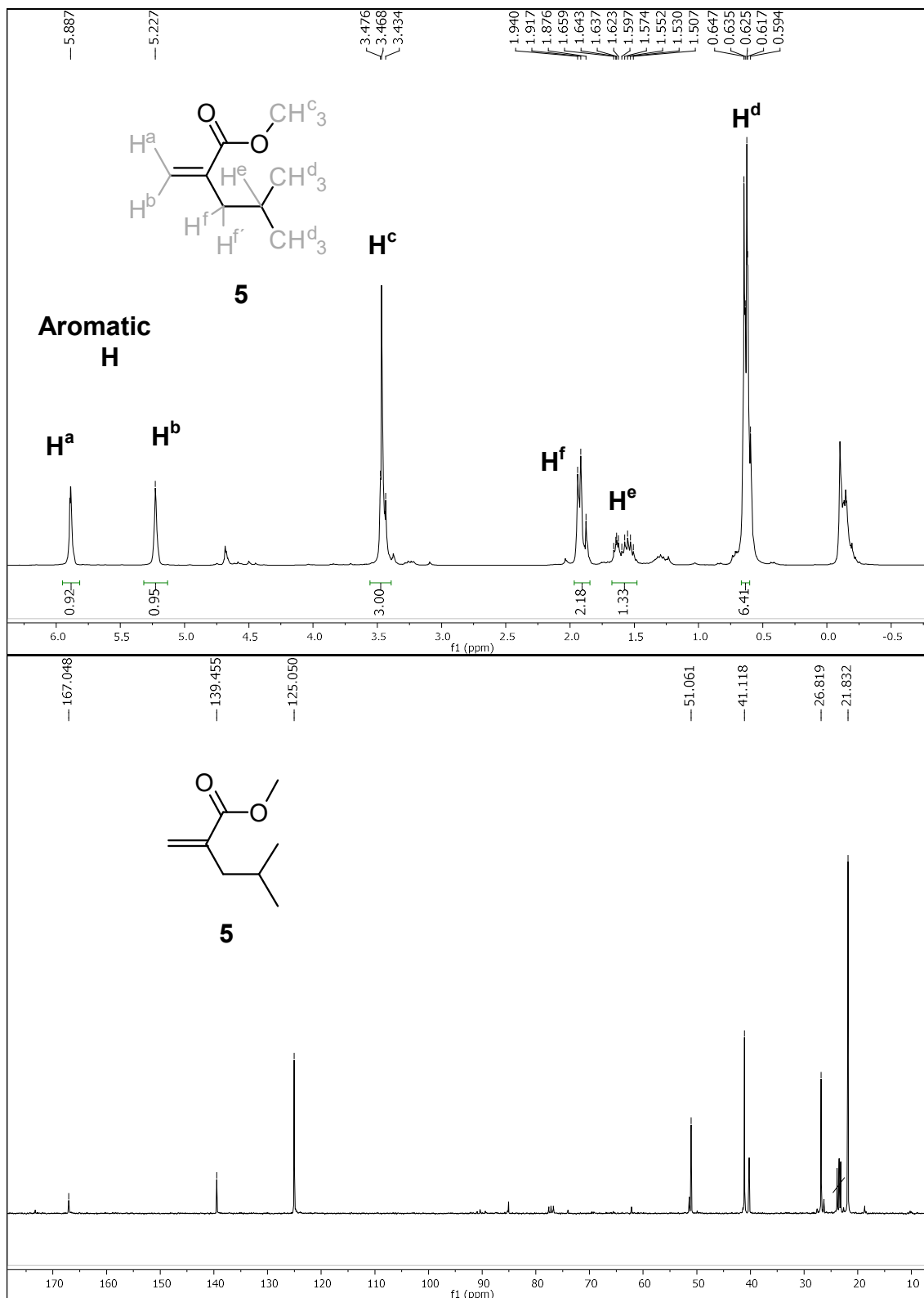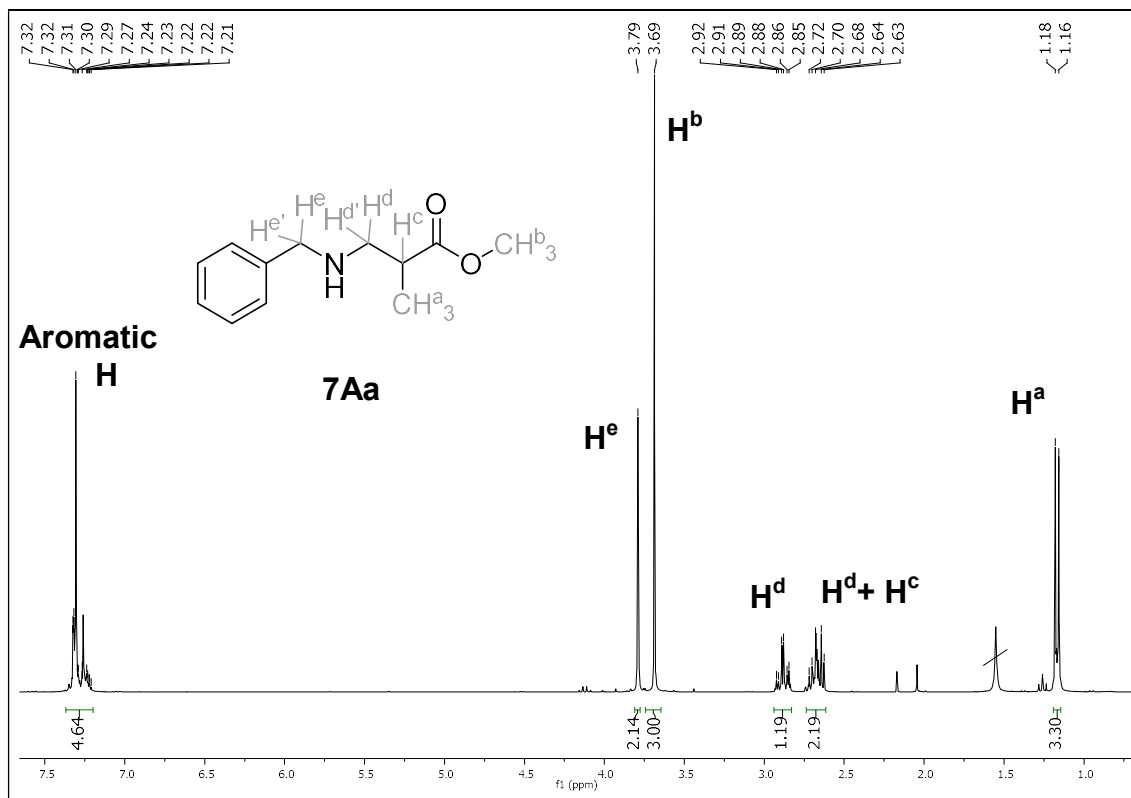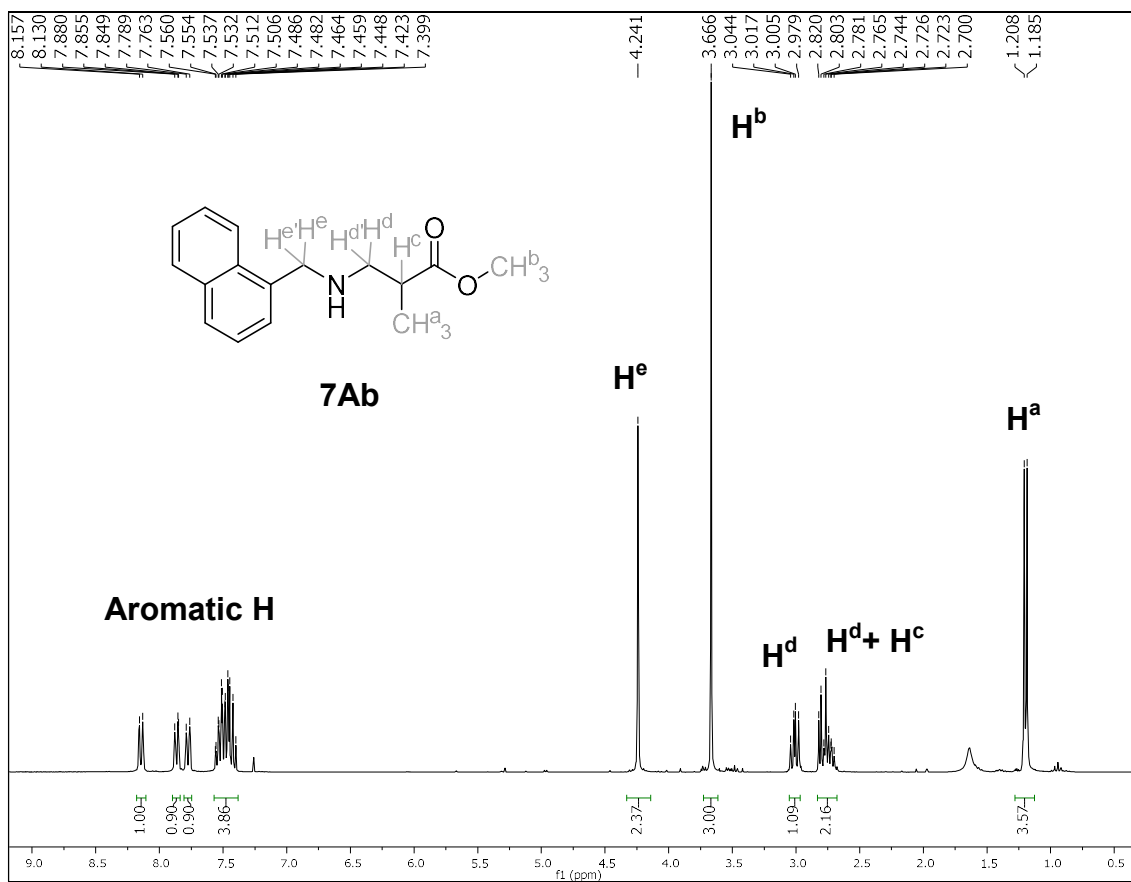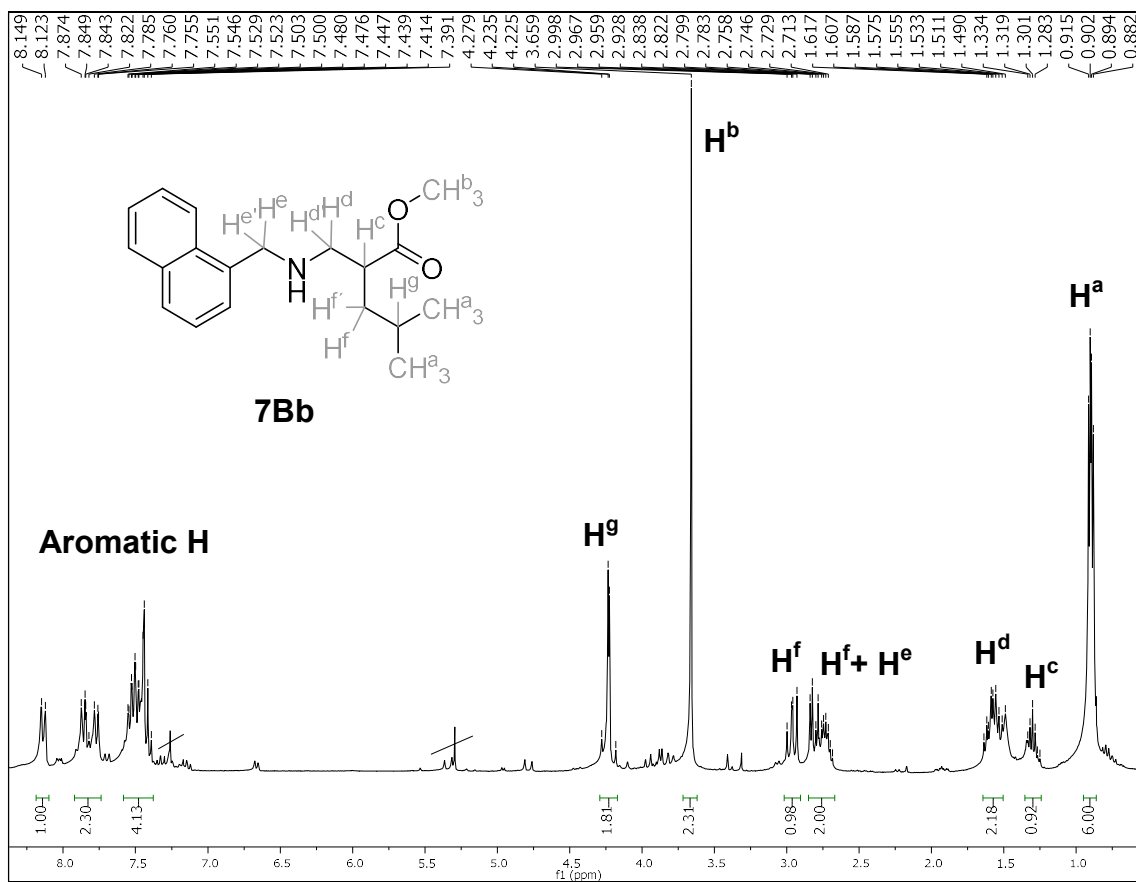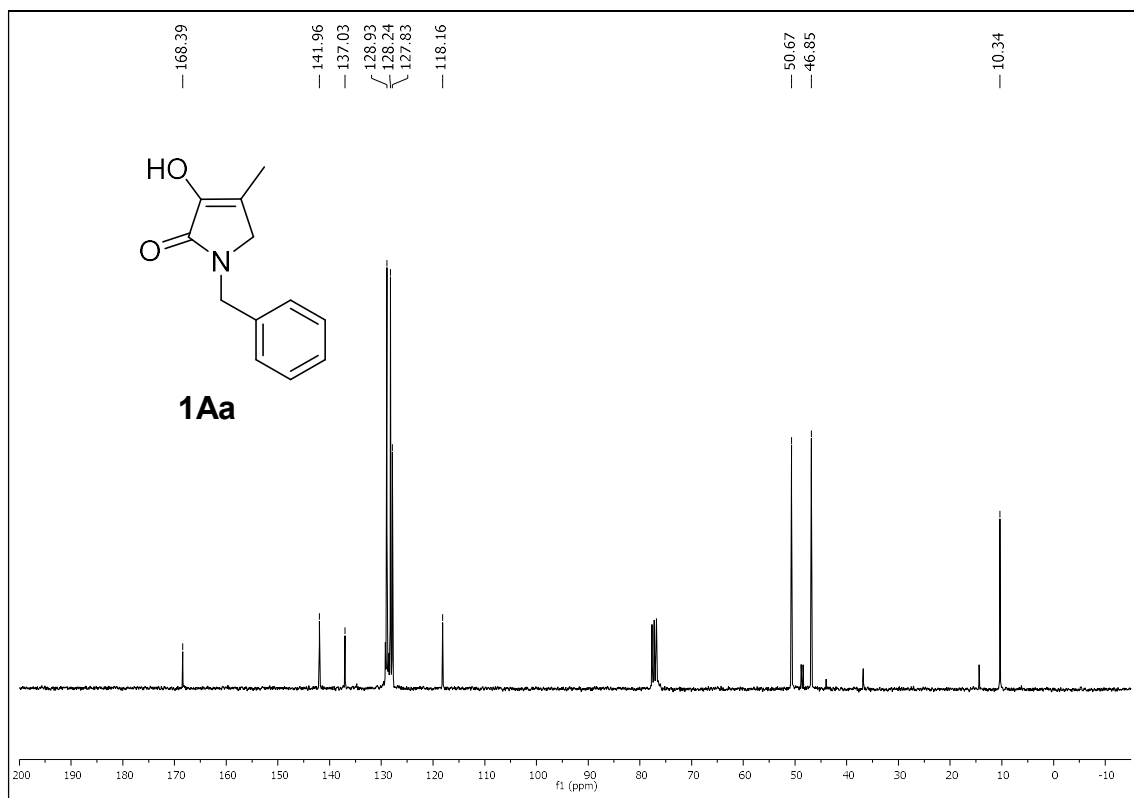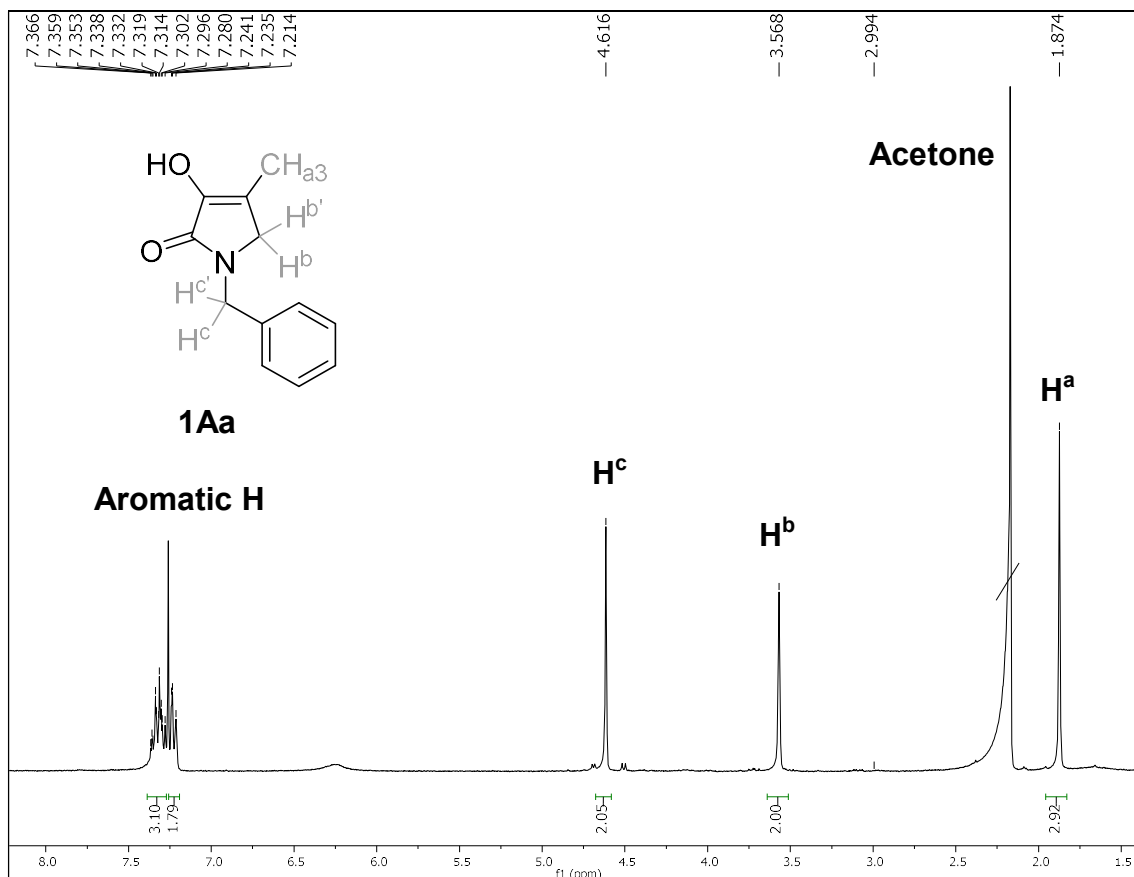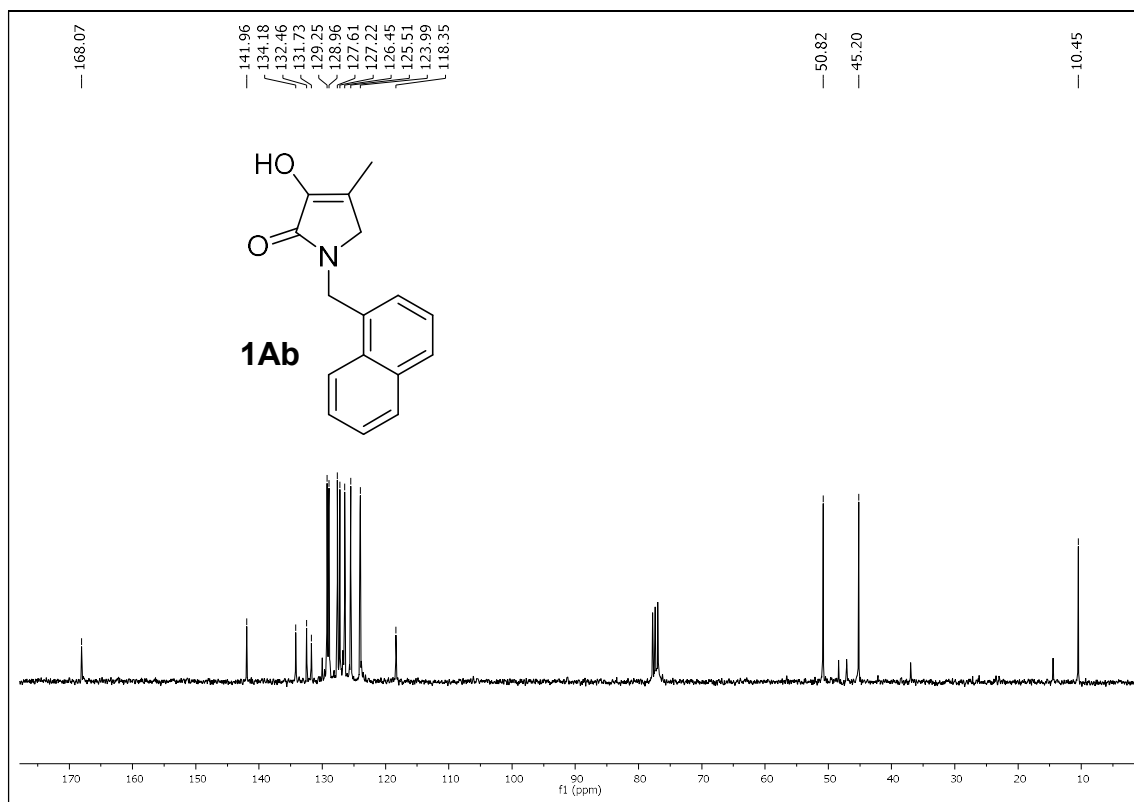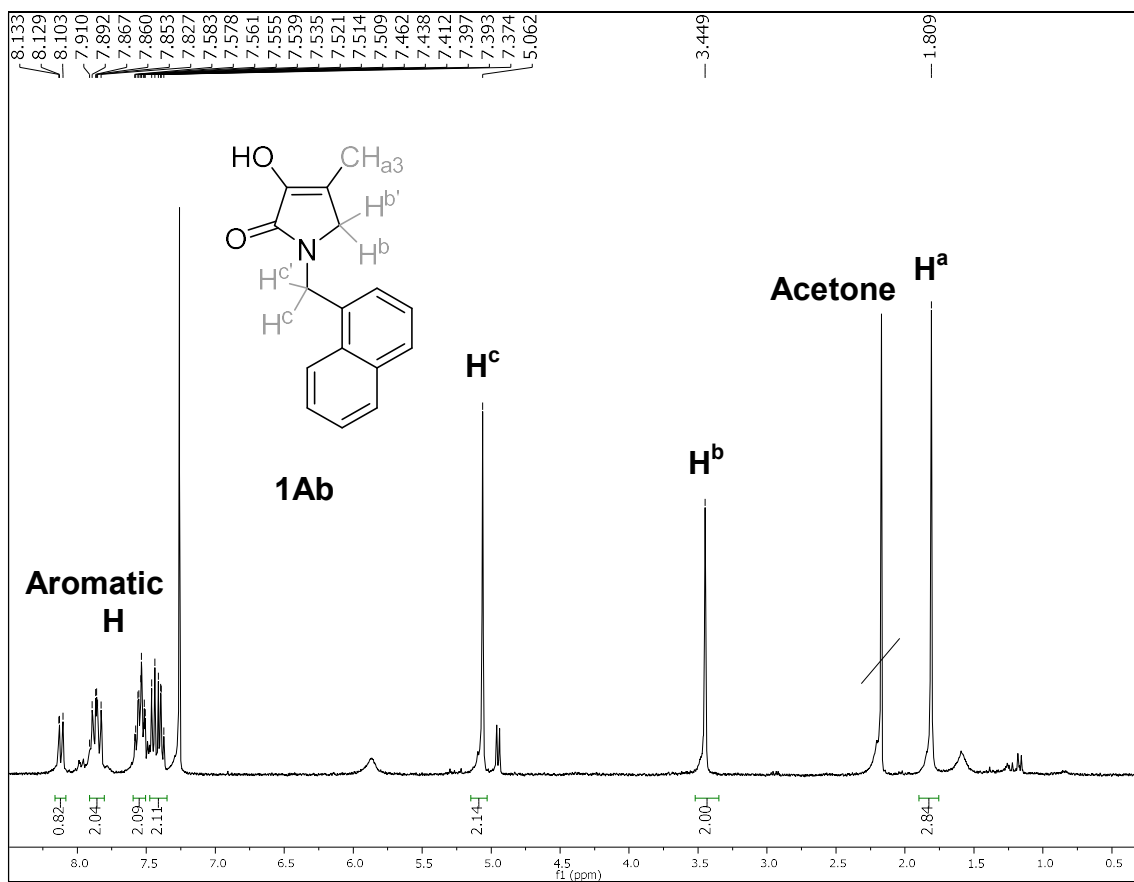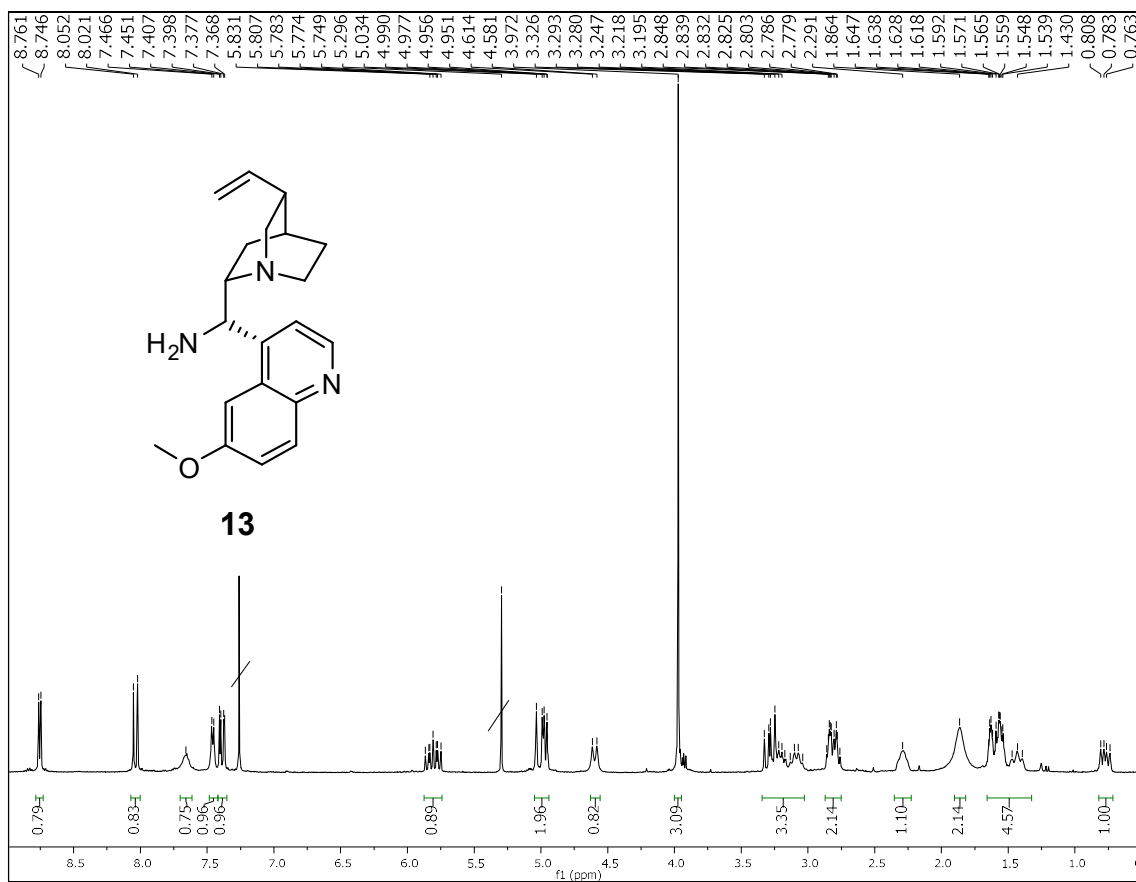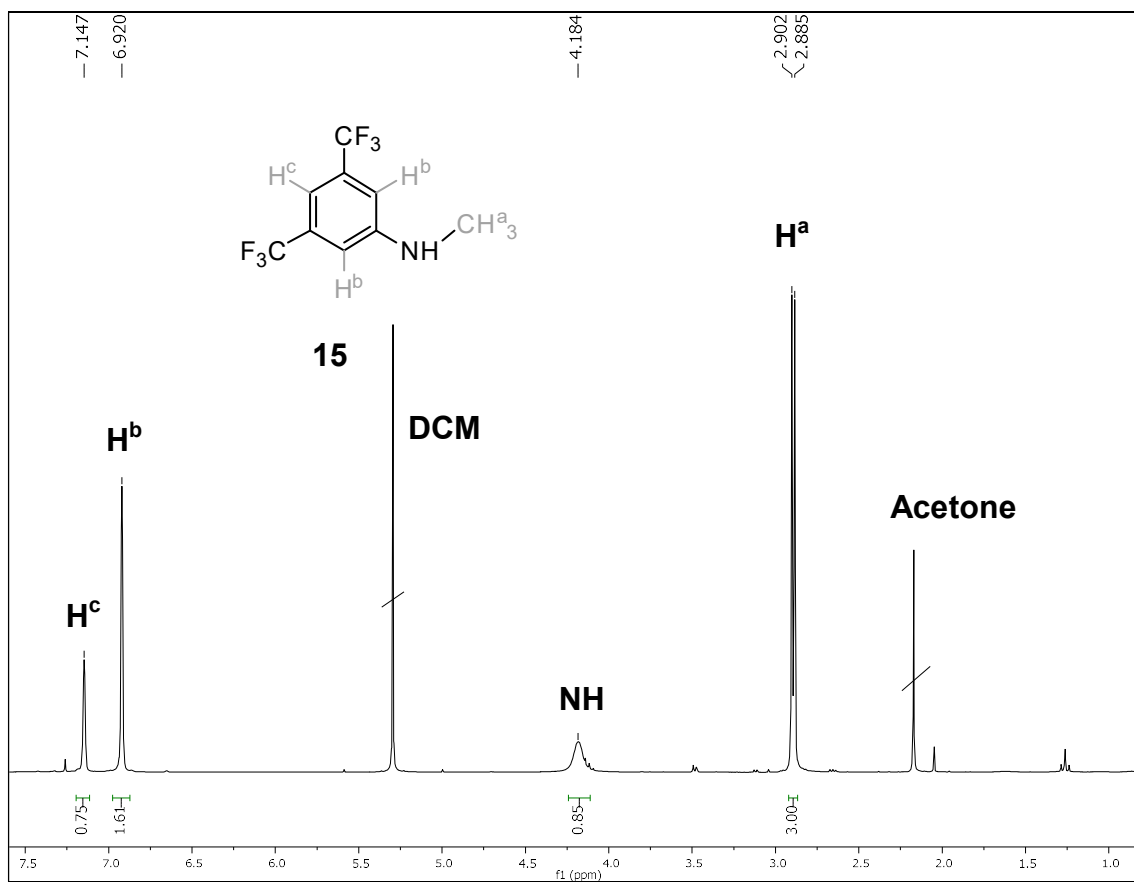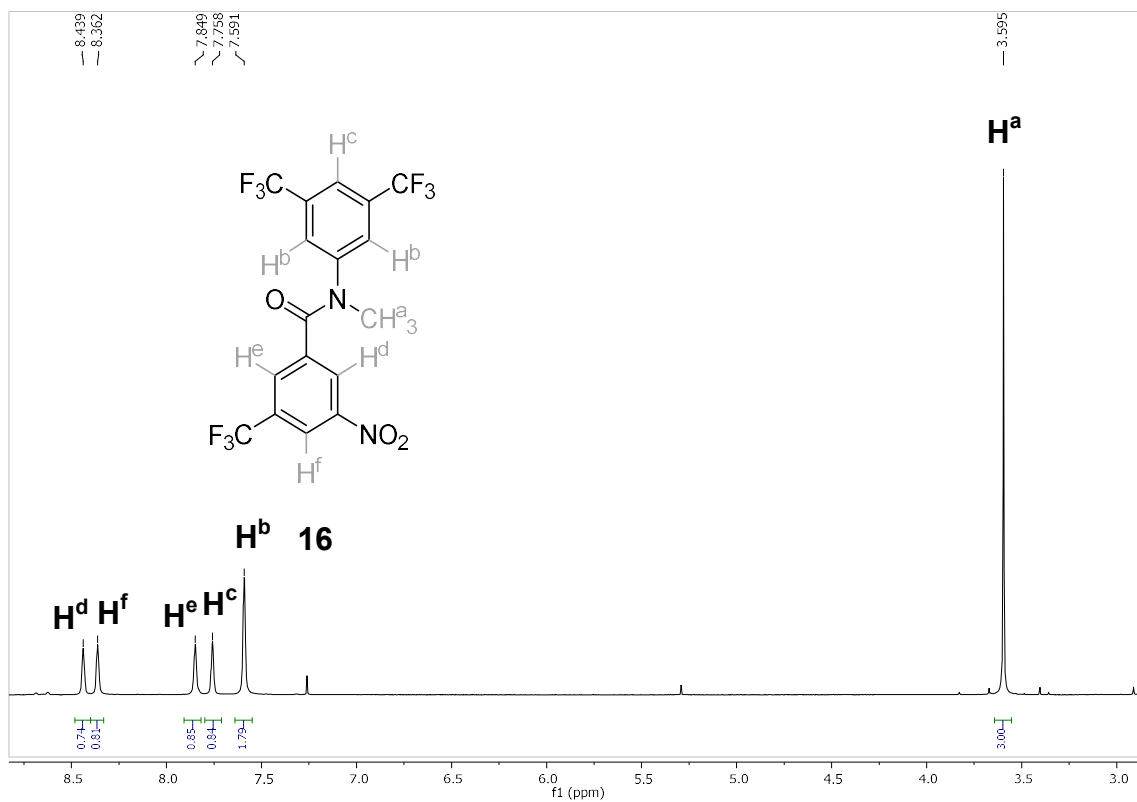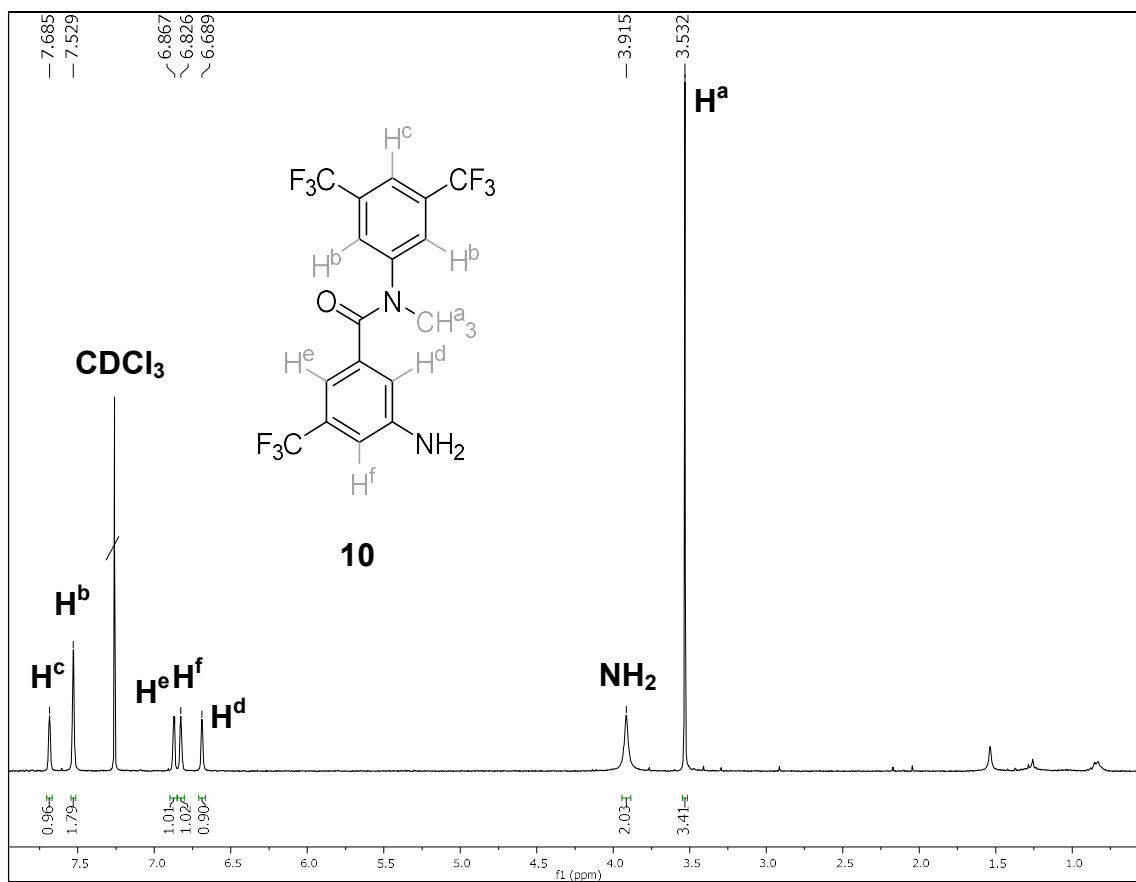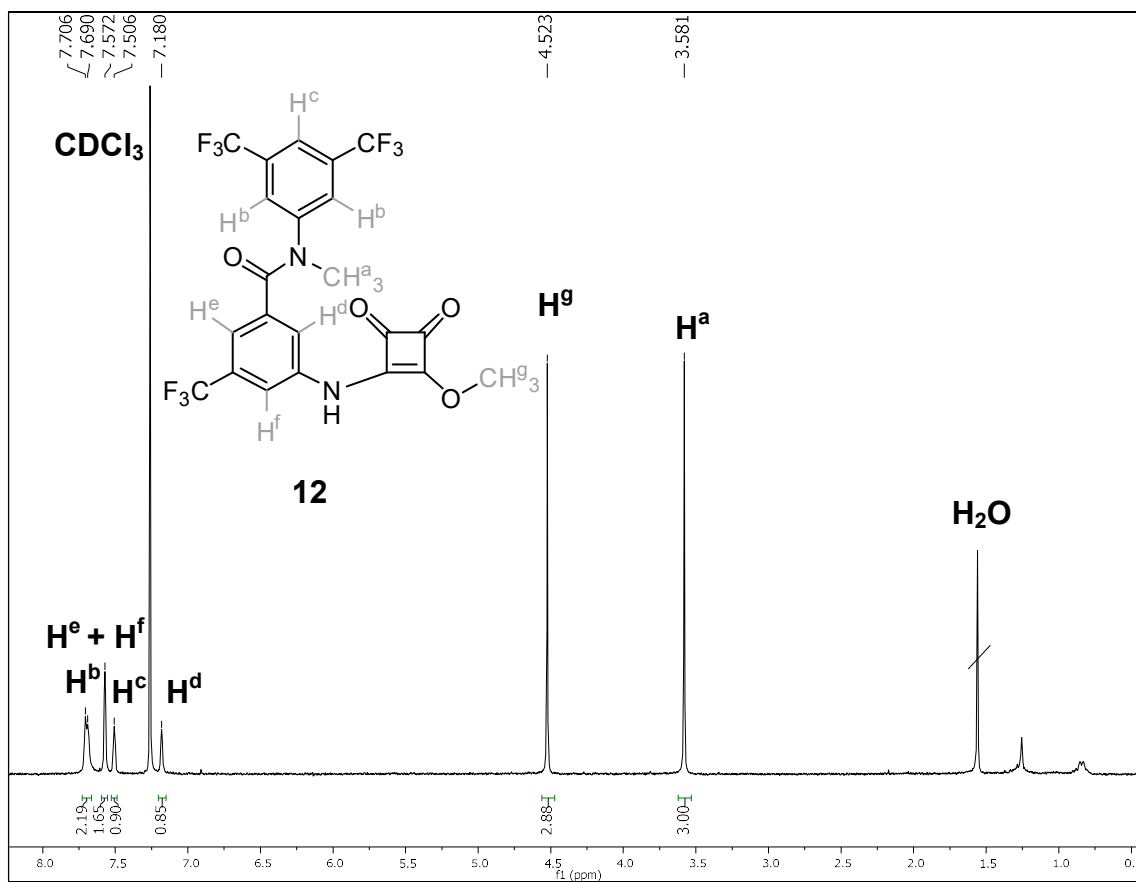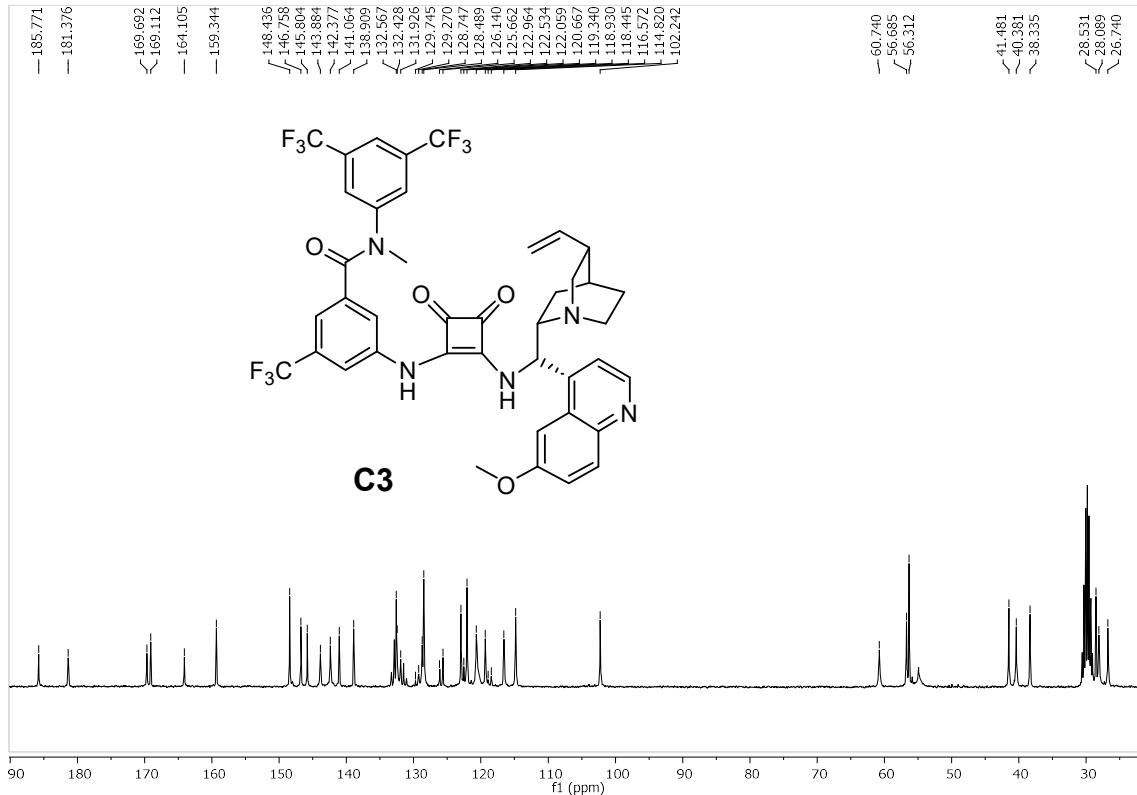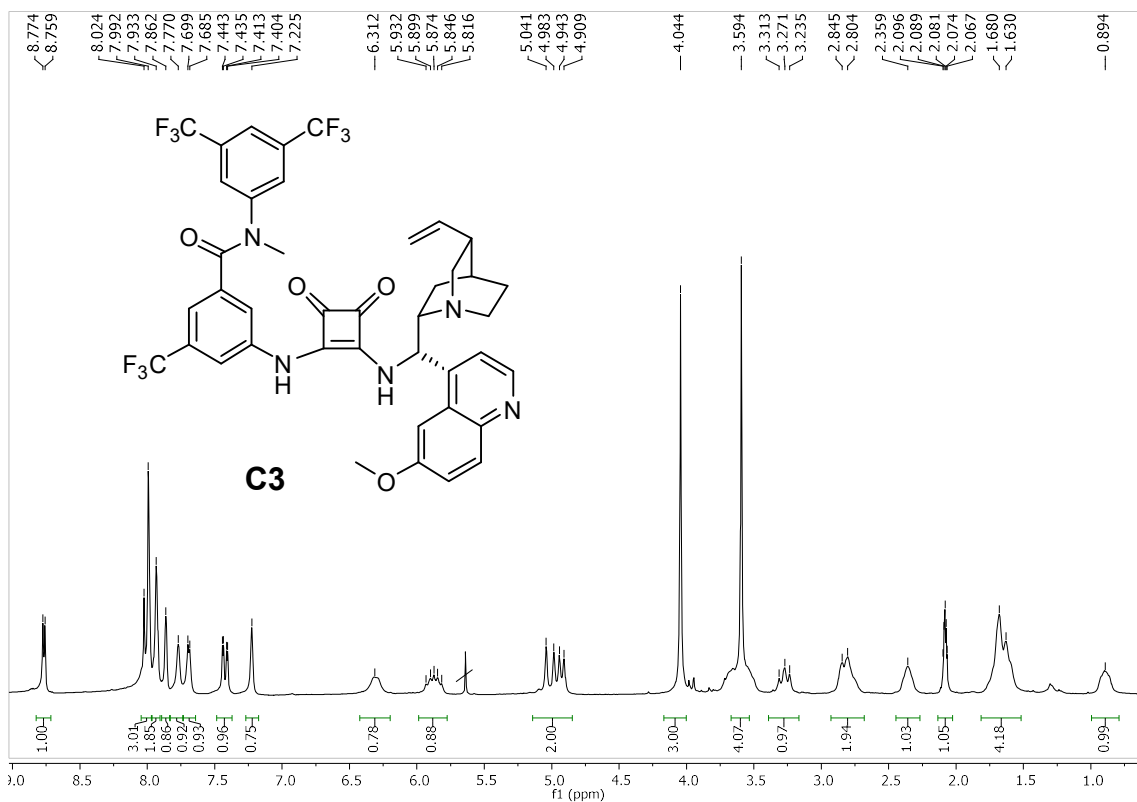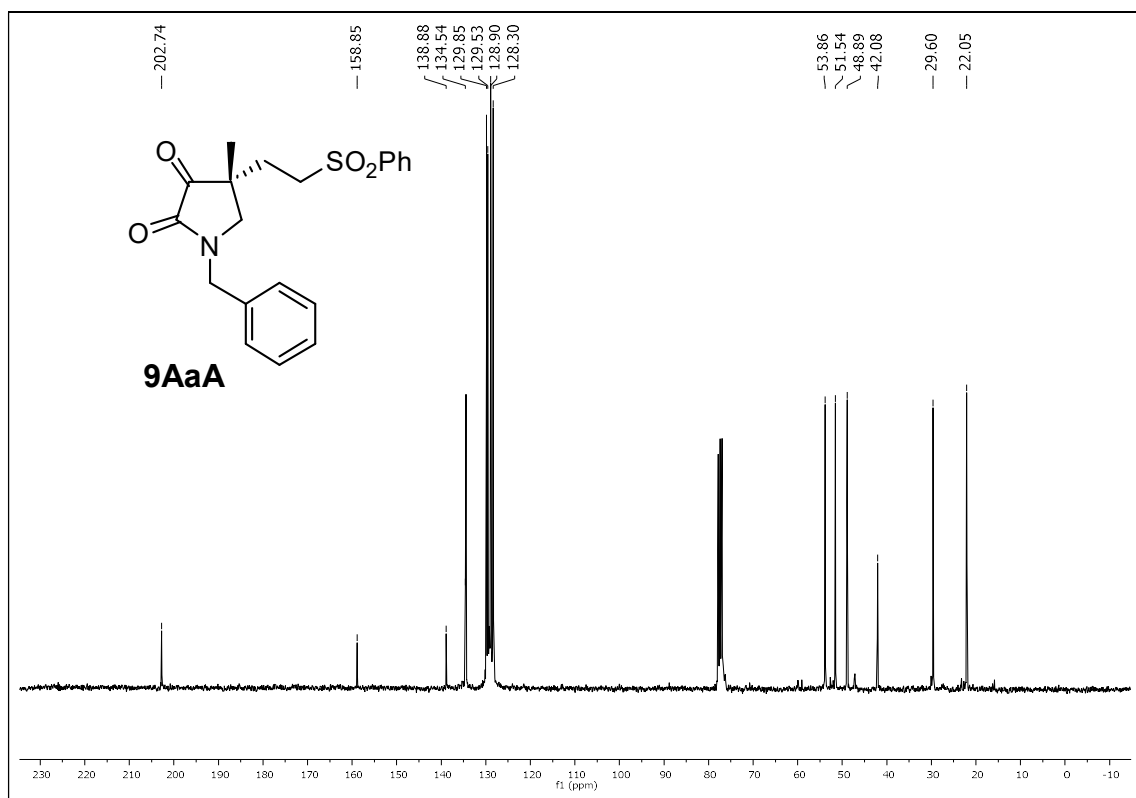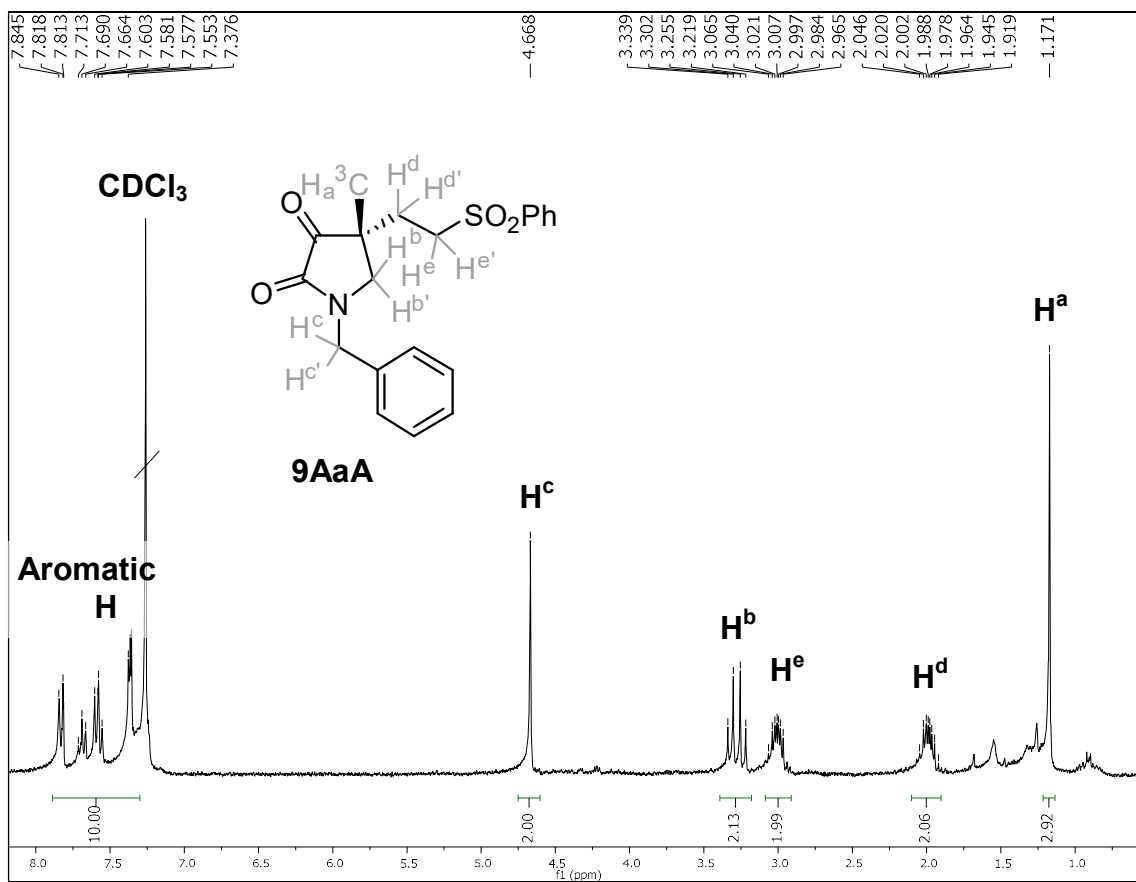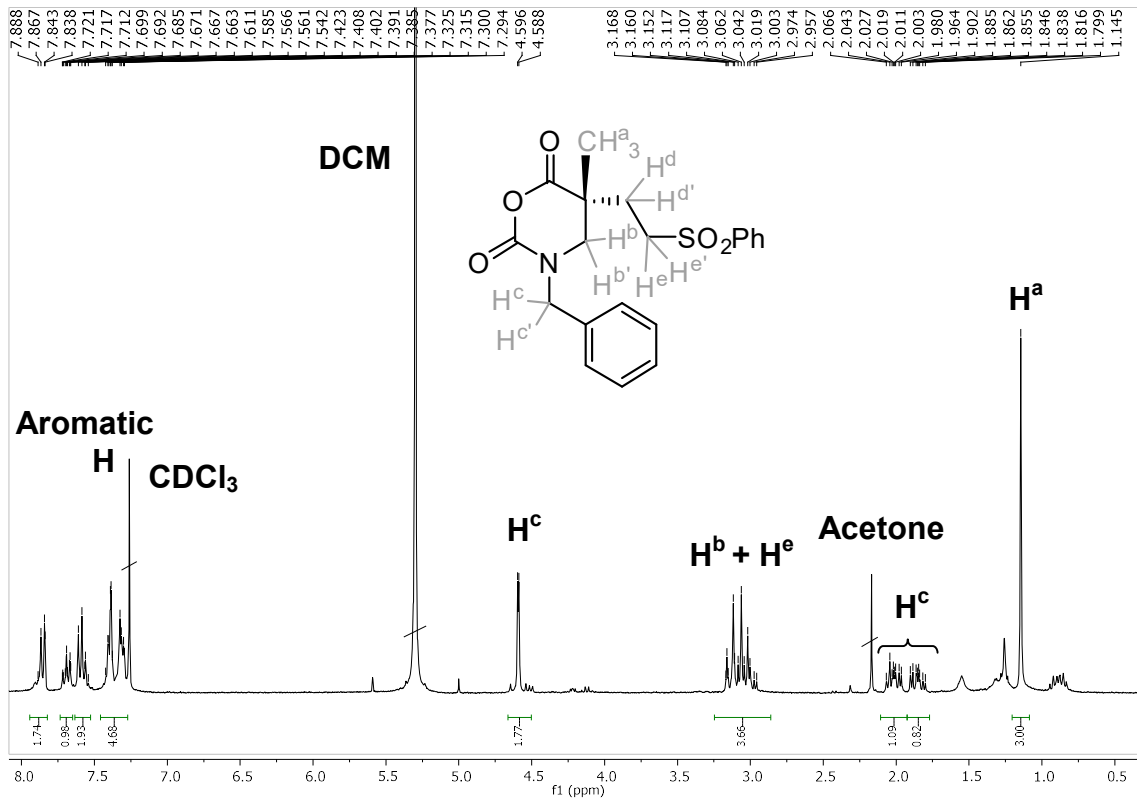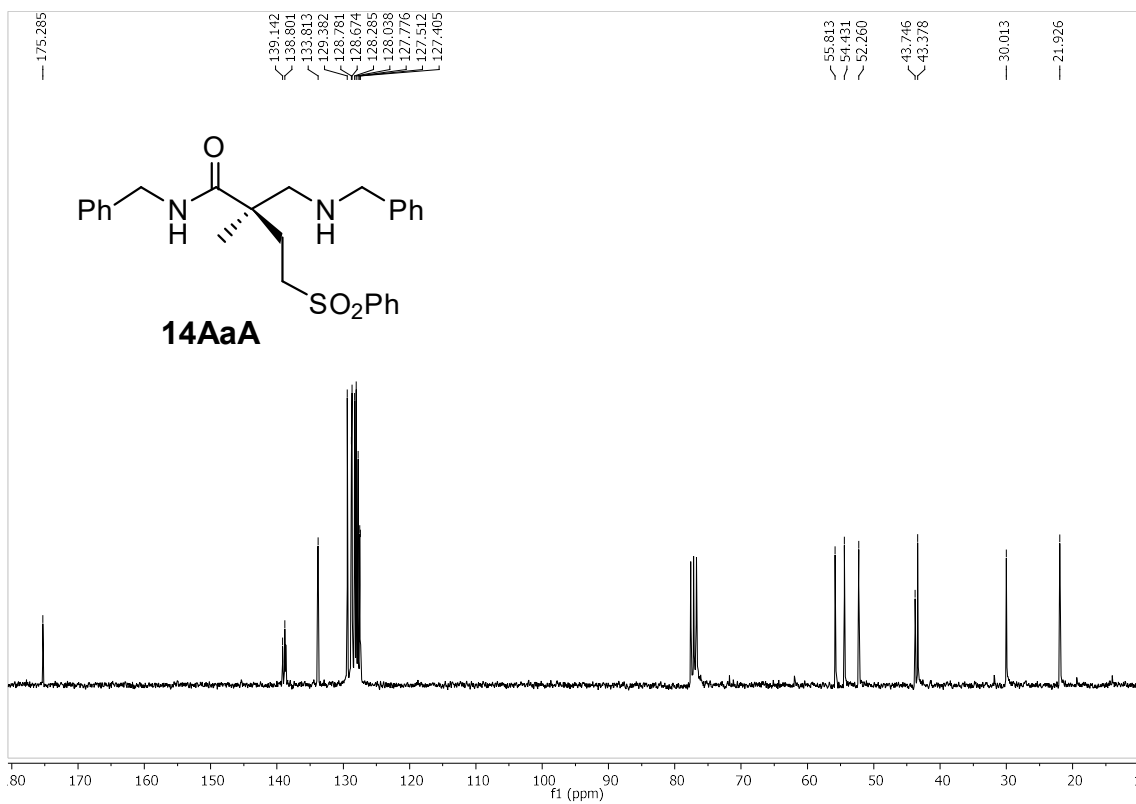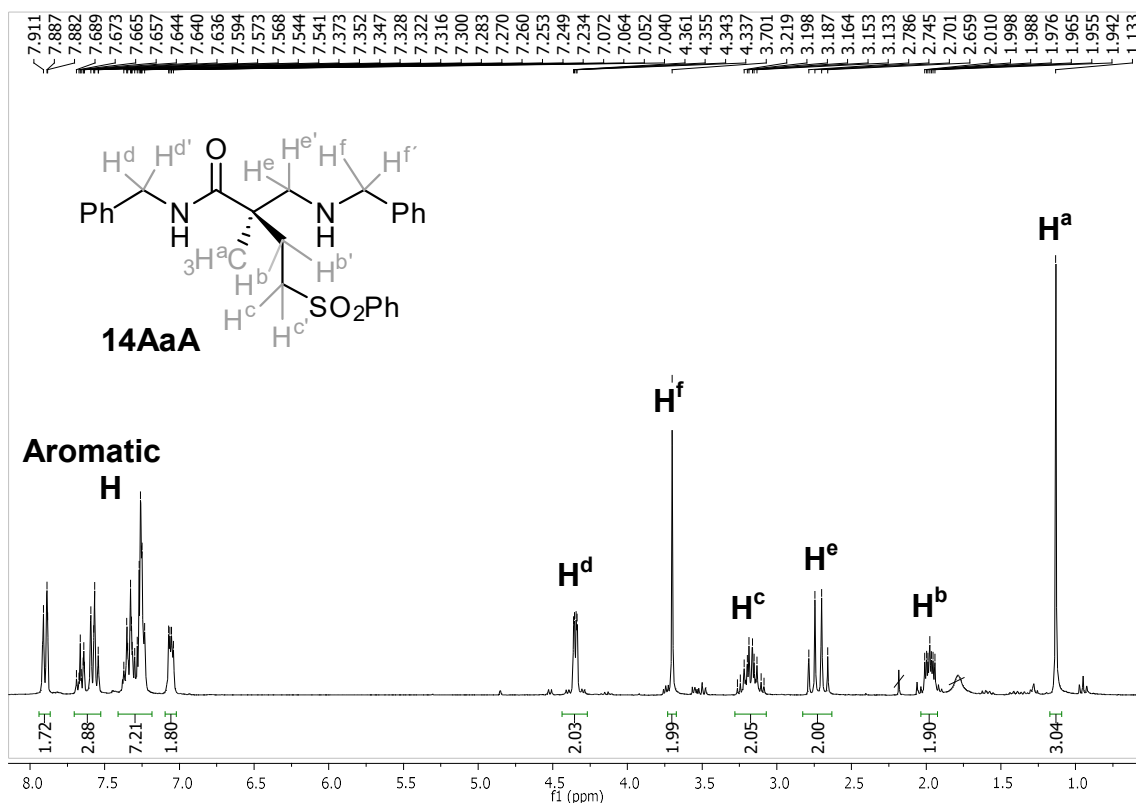
5.6.   HPLC Chromatograms

14AaA
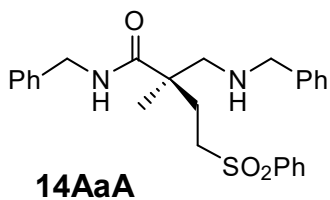
Column: IB
Solvent sistem: Hexane: ^{i}PrOH 50:50
Flow: 0.5 mL/min

Racemic sample:

	Retention Time	% Area
1	14,869	49,92
2	16,178	50,08

C1 catalyst

ee: 19%

C1
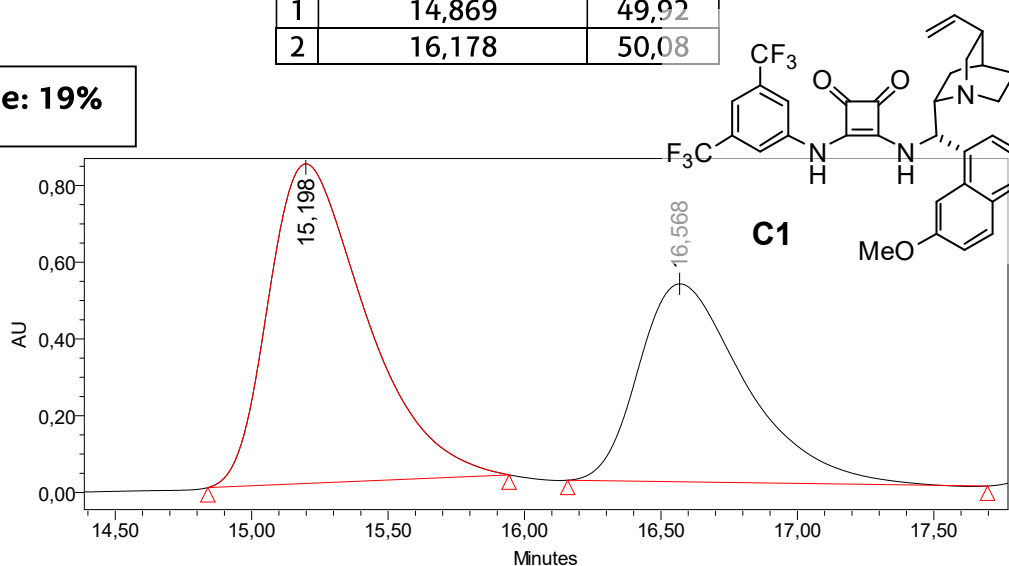
	Retention Time	% Area
1	15,198	59,57
2	16,568	40,43

C2 catalyst

ee: 14%
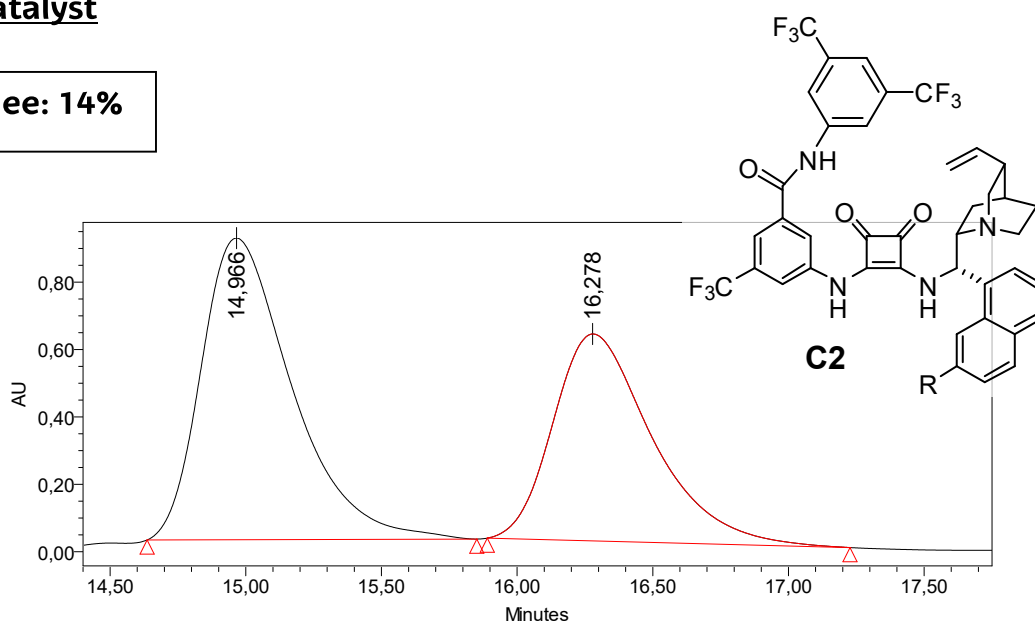
	Retention Time	% Area
1	14,966	57,11
2	16,278	42,89

C3 catalyst

ee: 34%
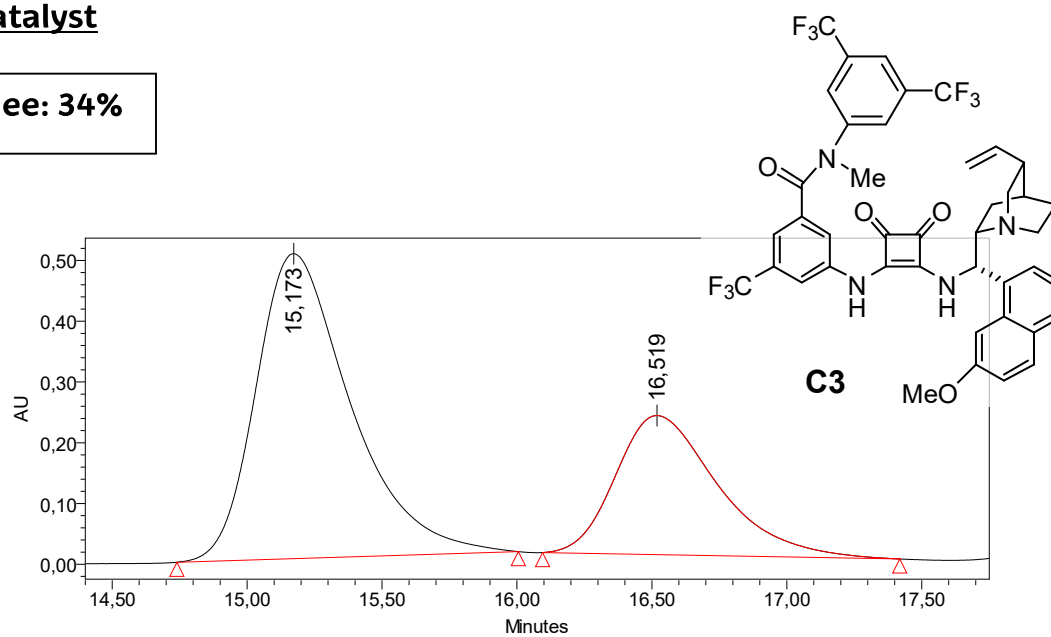
	Retention Time	% Area
1	15,173	67,00
2	16,519	33,00

C4 catalyst

ee: 38%
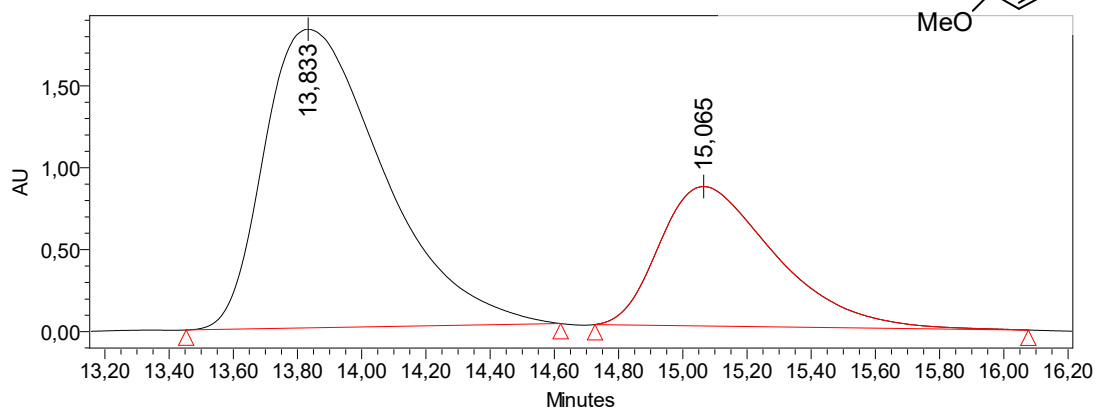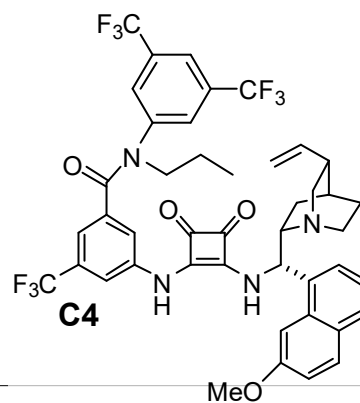
	Retention Time	% Area
1	13,833	68,77
2	15,065	31,23