UNIVERSITÀ DEGLI STUDI DI ROMA "LA SAPIENZA"

Dottorato di ricerca in Scienze Chimiche

XXIX ciclo

Reactivity of trifluoromethyl aldimines with active methylene compounds

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CONTENTS

Introduction

Chapter 1

Trifluoromethyl aldimines

After the isolation of elemental fluorine in 1886 by Henri Moissan, the development of fluorination methodologies and synthesis of fluorinated compounds has been an ongoing topic of current interest to the chemical community.[1]

Indeed, fluorinated compounds have opened new opportunities inherent to the physico-chemical properties of fluorine that could be defined a magic element because of strong electronegativity, low polarizability and a small size.

Fluorinated compounds show advantages such as high thermal, light and chemical stability, oil and water repellency, low dielectric constants, and low flammability, as a result of all this they can be used in many different fields such as polymer science,[2] pharmaceutical and molecular biology.[3]

Since fluorine-containing compounds are almost completely absent in nature, an increasing number of synthetic bioactive pharmaceuticals[4] and agrochemicals contain fluorine, in particular, as many as 35% of agrochemicals and 20% of pharmaceuticals.[5] This popularity of organofluorine compounds has been attributed to the influence that the fluorine substituents could have on several properties, such as the acidity or basicity of neighboring groups, dipole moment, and biological

[1] Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev*. **2015**, *115*, 826–870.
[2] a) Vitale, A.; Bongiovanni, R.; Ameduri, B. *Chem. Rev*. **2015**, *115*, 8835–8866. b) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev*. **2012**, *41*, 31–42.
[3] Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo,G.; Bombelli, F. B.; Metrangolo, P.; Resnati, G. *Chem. Rev*. **2015**, *115*, 1106–1129.
[4] a) Müller, K.; Faeh C.; Diederich, F. *Science* **2007**, *317*, 1881–1886; b) Hagmann, W. K. *J. Med. Chem*. **2008**, *51*, 4359–4369; c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320–330; d) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643
[5] Wang, J.;Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2013**, *114*, 2432.

characteristics such as lipophilicity, metabolic stability, and bioavailability[6] in potentially active molecules.

Thus, for example, a fluorine atom has been used as a replacement for a hydrogen atom or a hydroxyl group, and a $-CF_2$ or $-CF_3$ moiety has been used as a mimic for an oxygen atom; in addition, in many such compounds, a trifluoromethyl group can be considered also as a good mimicry of methyl, isopropyl and phenyl residues.[7] In addition, the presence of the fluorine atoms can confer unusual chemical reactivity and influence the stereochemical transformations of organic compounds compared to their analogous unfluorinated.[8]

Finally, considering the properties of ^{19}F nucleus,[9] the organofluorine compound structural characterization is supported by the use of ^{19}F NMR, coupled with the most usual ^{1}H and ^{13}C NMR spectra.[10]

For these reasons, the synthesis of fluorinated compounds, especially trifluoromethylated, is a topic of considerable interest into the mainstream organic synthesis community. The synthesis of these compounds can occur either through trifluoromethylation techniques[11] or choosing a suitable CF_3-containing precursor that can be subsequently converted into a range of different compounds.

The second approach is considered more efficient, easier and versatile method, obviously the basic issue is that the trifluoromethylated precursor has to be inexpensive, available on large scale, non-toxic, environmentally compatible, and potentially multifunctional for use in various reactions.[12]

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[6] a) Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry Principles and Commercial Applications*, Plenum Press: New York, **1994**.; b) Crowley, P. J. *Chemistry of Organic Fluorine Compounds II*, Hudlicky, M.; Pavlath A. E. Eds., American Chemical Society: Washington, **1995**.

[7] Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev*. **2004**, *104*, 1–16.

[8] a) Catalan, S.; Munoz, S. B.; Fustero, S. *Chimia* **2014**, *68*, 382–409; (b) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed*. **2011**, *50*, 11860–11871; (c) Hunter, L. *Beilstein J. Org. Chem*. **2010**, 6, No. 38; (d) Resnati, G.; Soloshonok, V. A. *Fluoroorganic chemistry: synthetic challenges and biomedical rewards*, In Proceedings of the Tetrahedron Symposia; *Tetrahedron* **1996**, *58*, 1–330.

[9] Saielli, G.; Bini, R.; Bagno, A. *RSC Adv*. **2014**, *4*, 41605–41611.

[10] a) Keita, M.; Kaffy, J.; Troufflard, C.; Morvan, E.; Crousse, B.; Ongeri, S. *Org. Biomol. Chem*. **2014**, *12*, 4576–4581; b) Curtis-Marof, R.; Doko, D., Rowe, M. L.; Richards, K. L.; Williamson, R. A.; Howard, M. J. *Org. Biomol. Chem*. **2014**, *12*, 3808–3812.

[11] Langlois, B. R.; Billard,T. *Synthesis* **2003**, 185−194.

[12] Bégué, J. P.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev*. **2005**, *34*, 562–572.

The main trifluoromethylated intermediate used in the industrial field is trifluoroacetic acid (TFA), as well as its derivates: trifluoroacetic anhydride, esters, amides;[5] unfortunately the corresponding aldehyde, fluoral (CF_3CHO), is an unstable gas, therefore difficult to prepare and use.

Compared to fluoral, its hydrate or hemiacetal derivatives (**Figure 1**) are however widely used in the synthetic field, because of their stability and commercial availability at low cost.

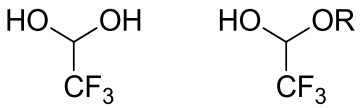
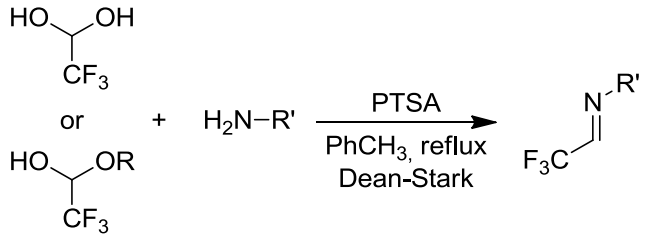


Figure 1. Hydrate or hemiacetal derivatives from fluoral.

Considering that in nature the most biologically active compounds contain nitrogen, the development of efficient synthetic methods for preparing nitrogenated fluorine-containing analogues of natural compounds has received increasing attention in recent years: in particular, 1,2- and 1,3-difunctionalized compounds, including β-amino alcohols and α- and β-amino acids, as well as nitrogen heterocycles, important building blocks for more complex structures.

Hydrate or hemiacetal derivatives of fluoral react with primary amines, in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst at toluene reflux and with a Dean–Stark apparatus, giving the corresponding trifluoromethyl aldimines,[13] as important scaffolds characterized by the presence of both a nitrogenous residue and a $-CF_3$ group (**Scheme 1**).[14]

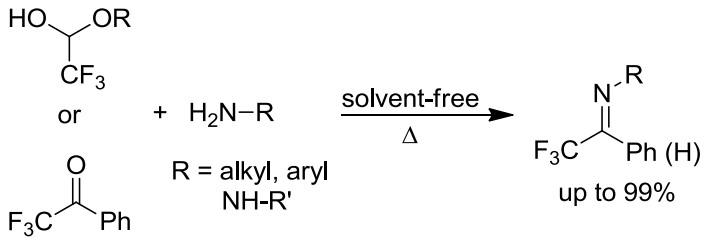
[13] For a very recent review, see: Fioravanti, S. *Tetrahedron* **2016**, *72*, 4449−4489.
[14] Pirkle, W. H.; Hauske, J. R. *J. Org. Chem*. **1977**;*42*, 2436–2439.



Scheme 1. Synthesis of trifluoromethyl aldimines under classical conditions.

However, this methodology does not afford the product in good yields, because of the presence of $-CF_3$ which can stabilize the hemiaminal intermediate and destabilize the carbocationic intermediate. Consequently, different synthetic strategies have been often required, such as the use of ultrasound or microwave,[15] high reaction temperatures or different activation methods.[16]

In this field, an efficient solvent-free methodology for the synthesis of trifluoromethylated aldimines, ketimines, and hydrazones has been developed in the laboratory where I did my PhD thesis (**Scheme 2**).[17]



Scheme 2. Solvent-free synthesis of trifluoromethyl aldimines.

Starting from an equimolar solution of α,α,α-trifluoroacetophenone or trifluoroacetaldehyde ethyl hemiacetal with different aliphatic amines or hydrazines, and heating, the desired products were obtained with excellent yields. In addition, the reaction occurred with complete stereoselectivity, giving only the *E* isomer, as determined by NOE experiments.

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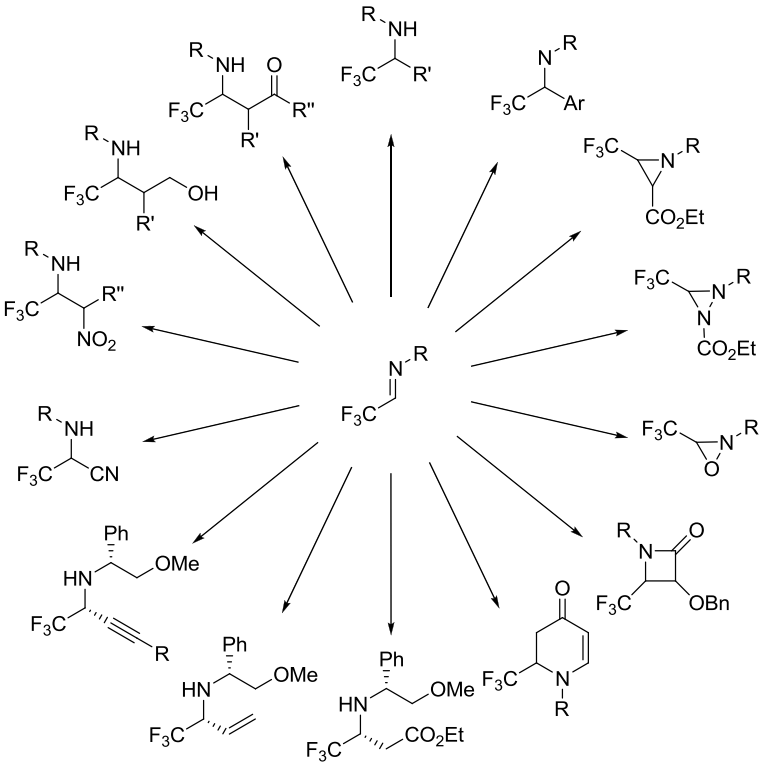
[15] Abid, M.; Savolainen, M.; Landge, S.; Hu, J.; Prakash, G.K. S.; Olah, G. A.; Török B. *J. Fluorine Chem.* **2007**, *128*, 587–594

[16] a) Barney, C. L.; Huber, E. W.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5547−5550; b) Gulevich, A. V.; Shevchenko, N. E.; Balenkova, E. S.; Röschenthaler, G-V.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 11706–11712 and refs therein.

[17] Carroccia, L.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Synthesis* **2010**, 4096–4100.

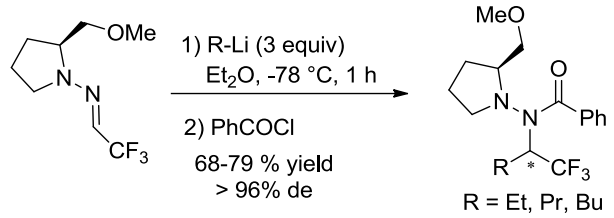
The presence in these compounds of the C=N function allows to use them as interesting electrophiles in several reactions (**Scheme 3**); in addition the presence of electron-withdrawing trifluoromethyl group increases the electrophilicity of the carbon–nitrogen double bond compared with that of nonfluorinated imines.[9]



Scheme 3. Families of compounds after nucleophilic addition on trifluoromethyl aldimines.

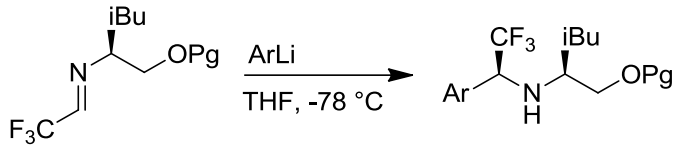
Alkylation and arylation reactions, using organometallic and related reagents, have been widely developed, also in the asymmetric versions. Funabiki and Enders using the SAMP/RAMP-methodology reported a highly diastereoselective alkylation (> 96% de) of hydrazones with alkyllithium reagents, especially with those derived from primary halides (**Scheme 4**).[18]

[18] Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575−1577.



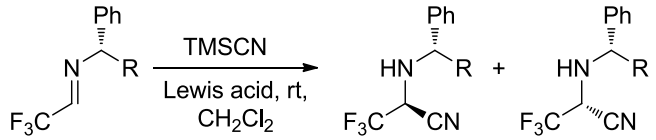
Scheme 4. Organometallic addition to trifluoromethyl hydrazones.

As well as trifluoromethyl aldimines undergo arylation reaction when treated with a broad array of aryllithium reagents (**Scheme 5**), as reported by Gosselin *et al.*[19]



Scheme 5. Organometallic addition to trifluoromethyl aldimines.

Through a Strecker-type reaction, Brigaud and co-workers obtained diastereomerically pure trifluoromethyl amino nitriles (**Scheme 6**) starting from chiral $-CF_3$ aldimines.[20]



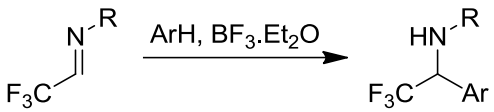
Scheme 6. Strecker-type reactions of chiral fluorinated aldimines.

In all cases, these reactions required the presence of catalytic amount of ytterbium(III) trifluoromethanesulfonate [$Yb(OTf)_3$] or $MgBr_2$.

The reaction of aromatic compounds with trifluoromethyl aldimines by a Friedel–Crafts type reaction can provide an interesting entry to benzylamine

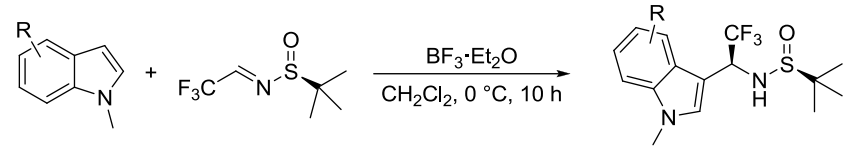
[19] Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.-y.; Volante, R. D. *Org. Lett.* **2004**, *6*, 641−644.
[20] Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 7075−7078.

analogues; in this field Kato reported the synthesis of α-CF_3 α-aryl methylamines in the presence of BF_3•Et_2O (**Scheme 7**).[21]



Scheme 7. Friedel–Crafts type reactions on trifluoromethyl aldimines.

More recently, Soloshonok and co-workers reported Lewis acid catalyzed Friedel–Crafts-type additions on chiral trifluoromethyl *N*-*tert*-butylsulfinylimine with various indoles (**Scheme 8**).[22]

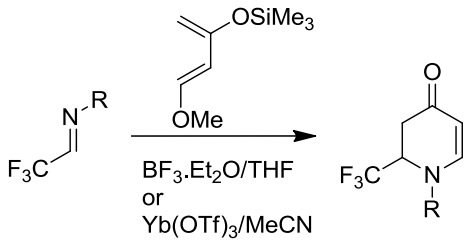


R = 2-Me, 2-CHO, 4-CN, 4-MeO, 5-CN, 5-MeO, 5-CO_2Me, 5-CO_2H, 6-Cl, 6-Br, 7-Br, 7-Me, 2-Me-5-MeO

64-96% yield
up to 99:1 dr

Scheme 8. Friedel–Crafts type reactions on substituted N-methyl indoles.

Aza-Diels–Alder reactions have also been investigated with Danishefsky's diene in order to afford the corresponding dihydropyridinone (**Scheme 9**).[23]

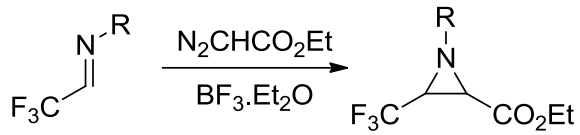


Scheme 9. Aza-Diels–Alder reactions of trifluoromethyl aldimines.

Given that the large majority of modern drugs and agrochemicals contain one or more heterocyclic rings, it is not surprising that the synthesis of trifluoromethyl heterocycles is a topic of current interest to the chemical community. Small CF_3-

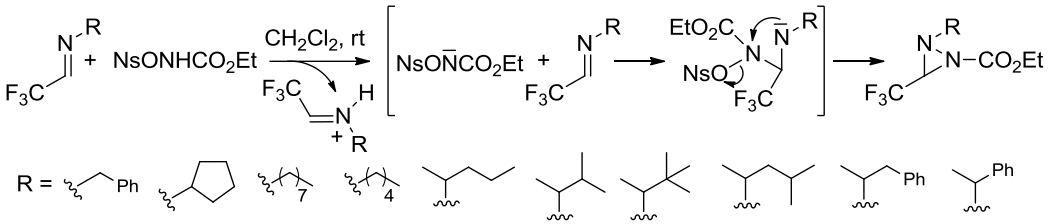
[21] Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 2637–2645.
[22] Wua, L.; Xie, C.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *J. Org. Chem*. **2014**, *79*, 7677−7681.
[23] Crousse, B.; Narizuka, S.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem*. **2000**, *65*, 5009–5013.

containing nitrogen heterocycles, including aziridines, can be integrated in the elaboration of amino acids to create modified peptides with special features.[24] Bégué and co-workers highlighted a straightforward synthesis of aziridine-2-carboxylates, as potential precursors of non-proteogenic α- and β-amino acids, using ethyl diazacetate as nuchelophile and BF_3•Et_2O as catalyst at low temperature (**Scheme 10**).[25]



Scheme 10. Synthesis of trifluoromethyl aziridines.

In the laboratory in which I am attending my PhD, trifluoromethyl aldimines were used to obtain interesting optically active fluorinated diaziridines and oxaziridines.[26] The amination reaction has been developed without any added base and using, as aminating agents, aza-anions formed *in situ* from different alkyl nosyloxycarbamates ($NsONHCO_2R$, Ns=4-$NO_2C_6H_4SO_2$).



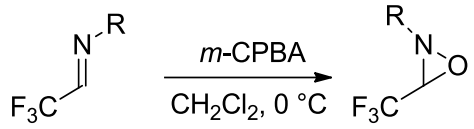
Scheme 11. Synthesis of trifluoromethyl diaziridines.

As reported in **Scheme 11**, the reaction proceeds through an aza-anion nucleophilic attack followed by a ring closure reaction, affording the corresponding trifluoromethyl diaziridines in good yields. It was demonstrated that the stereoselective induction was controlled by steric or electronic effects present on β–

[24] Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. *Chem. Soc. Rev*. **2012**, *41*, 2135–2171.
[25] Crousse, B.; Narizuka, S.; Bonnet-Delpon D.; Bégué, J.-P. *Synlett* **2001**, 679–681.
[26] Carroccia, L.; Fioravanti, S.; Pellacani, L.; Sadun, C.; Tardella, P. A. *Tetrahedron* **2011**, *67*, 5375−5381

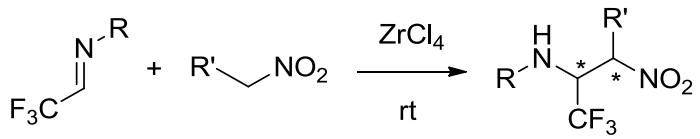
or α–carbon of the aminic residue. In fact, when the phenyl group is present in the α position a very good diastereomeric induction (99:1) was observed, but if this last group is present in the β position a reversal of induction was observed leading to a 1:1.7 mixture of diastereomers

Starting from trifluoromethyl aldimines also trifluoromethyl oxaziridines[26] can be obtained through epoxidation reactions using *m*-CPBA (*m*-chloroperoxybenzoic acid) as oxidant (**Scheme 12**).



Scheme 12. Synthesis of trifluoromethyl oxaziridines.

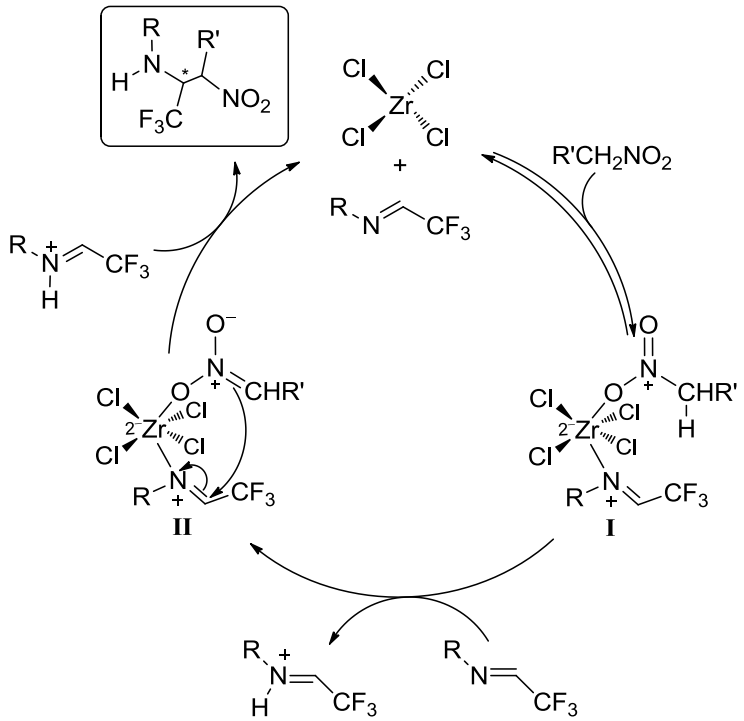
The reactivity of trifluoromethyl aldimines has been also studied in the aza-Henry reactions to successfully synthesize trifluoromethyl β-nitro amines in the presence of catalytic amounts of zirconium tetrachloride ($ZrCl_4$) (**Scheme 13**).[27]



Scheme 13. $ZrCl_4$-catalyzed aza-Henry addition to trifluoromethyl aldimines.

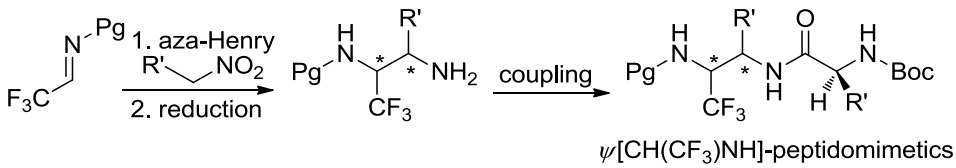
The pathway proposed (**Scheme 14**) for the aza-Henry reaction involves a previous coordination between the imine and Zr(IV), which can coordinate even the nitro compound[28] and this coordination increases the acidity of its hydrogens which can be deprotonated by another imine molecule, thus forming the key intermediate of the reaction (**II**). A final intramolecular attack followed by protonation gave the desired product and restored both the catalyst and the imine.

[27] Fioravanti, S.; Pellacani, L.; Vergari M. C. *Org. Biomol. Chem*. **2012**, *10*, 8207–8210.
[28] a) Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183–1185; b) Nishiwaki, N.; Knudsen, K. R.; Gothelf K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2001**, *40*, 2992–2995.



Scheme 14. Possible pathway of $ZrCl_4$-catalyzed aza-Henry addition.

The β-nitro amines were subsequently considered in a selective reduction of nitro group (**Scheme 15**),



Scheme 15. Synthesis of ψ[CH(CF_3)NH]-peptidomimetics.

followed by a coupling reaction with suitable *N*-Boc-protected L-α-amino acids,[29] to obtain interesting ψ[CH(CF_3)NH]-peptidomimetics.[30,31]

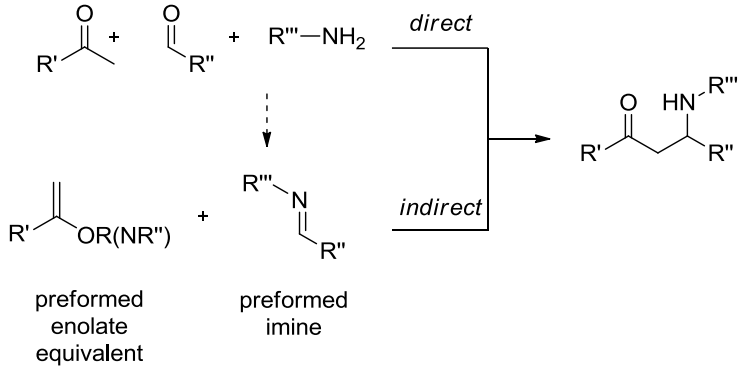
[29] Fioravanti, S.; Pelagalli, A.; Pellacani, L.; Sciubba, F.; Vergari M. C. *Amino Acids* **2014**, *46*, 1961–1970.
[30] Molteni, M.; Bellucci, M. C.; Bigotti, S.; Mazzini, S; Volonterio, A.; Zanda, M. *Org. Biomol. Chem.* **2009**, *7*, 2286–2296.
[31] Sani, M.; Volonterio, A.; Zanda, M. *Med. Chem.* **2007**, *2*, 1693–1700.

Chapter 2

Mannich-type reaction

In 1912, Carl Mannich reported his systematic studies of the three-component reaction (M-3CR) between an enolizable substrate, a primary or secondary amine and a nonenolizable aldehyde, classically formaldehyde, to form β-amino carbonyl compounds, known as Mannich bases.[1]

The classical M-3CR is, however, characterized by a number of serious disadvantages,[2] therefore numerous methods have been developed for the indirect reaction, namely the Mannich-type reaction, through the use of preformed electrophiles (e.g., iminium salts or imines) or nucleophiles (enolates, enol ethers, and enamines) (**Scheme 1**).



Scheme 1. Direct and indirect Mannich reactions.

The nucleophilic species is usually an aromatic or aliphatic aldehyde or ketone, but even derivatives of carboxylic acids, β-dicarbonyl compounds, nitro alkanes, nitriles, or isocyano acetates, showing to be a versatile reaction. Moreover, the obtained products are useful synthetic intermediates, that can be converted into

[1] Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.

[2] a) Tramontini, M.; Angiolini, L. *Mannich Bases–Chemistry and Uses*; New Directions in Organic and Biological Chemistry Series; CRC Press, Boca Raton, FL, **1994**. b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837. c) Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Müller, M.; Regenass, U.; Rösel, J.; Lydon, N. *J. Med. Chem*. **1995**, *38*, 2441–2448. d) Dimmock, J. R.; Sidhu, K. K.; Chen, M.; Reid, R. S.; Allen, T. M.; Kao, G. Y.; Truitt, G. A. *Eur. J. Med. Chem*. **1993**, *28*, 313–322.

a great number of derivatives which possess valuable applications in several fields, especially in medicinal chemistry.[28]

The development of the asymmetric Mannich-type reaction has attracted considerable attention and various methods for conducting highly diastereoselective and/or enantioselective Mannich reactions have been developed in the past.[3]

2.1 Chiral organometallic catalysts

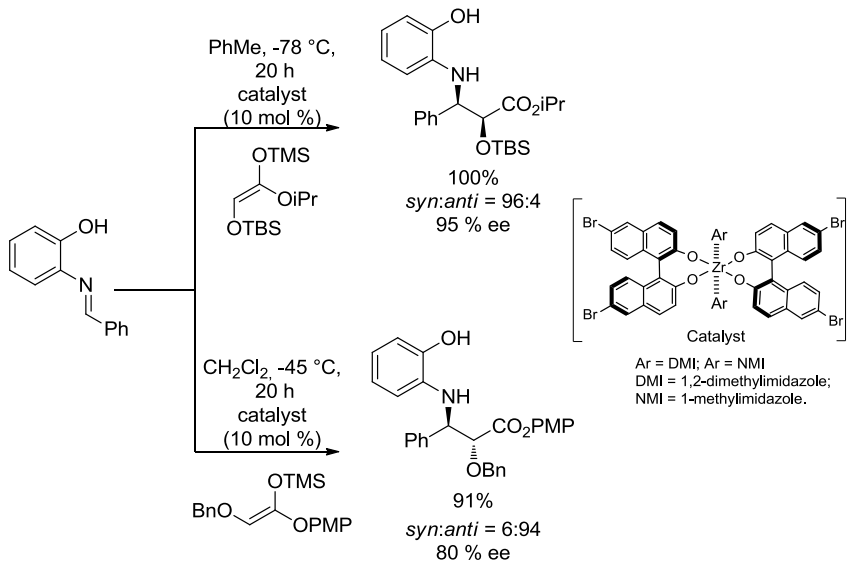
Traditionally, asymmetric Mannich-type reactions are catalyzed by chiral transition-metal complexes.[4]

The first enantioselective Mannich-type reaction on benzaldehyde imine derivatives has been reported by Kobayashi's group; the reaction was catalyzed by a chiral Lewis acid [Zr(IV)-BINOL], able to coordinate the imine towards the addition of silicon enolates and the silyl transfer, facilitating the catalyst recovery. The *syn*- and *anti*-selectivity was controlled by simply choosing the protective groups of the R-alkoxy and the ester moieties of silyl enolates (**Scheme 2**).[5]

[3] a) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569; b) Córdova, A. *Acc. Chem. Res*. **2004**, *37*, 102–112; c) Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069–1094; d) List, B. *Tetrahedron* **2002**, *58*, 5573-5590; e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471–5569.

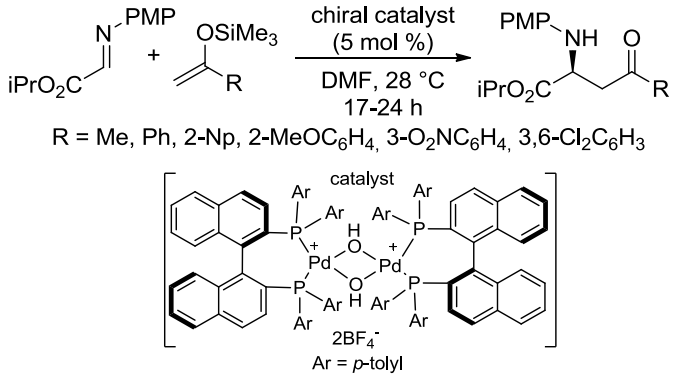
[4] a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R. Wiley, New York, **1994**; b) *Catalytic Asymmetric Synthesis* Ojima I., Wiley, New York, **2000**; c) *Transition Metals for Organic Synthesis, 2nd ed.* Beller, M.; Bolm, C. Wiley-VCH, Weinheim, **2004**; d) GrMger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532;

[5] a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **1997**, *119*, 7153–7154. b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc*. **1998**, *120*, 431–432. c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186.



Scheme 2. Mannich-type reaction catalyzed by a chiral Lewis acid [Zr(IV)-BINOL].

Subsequently, other BINOL- and BINAP-derived catalysts have been used for the asymmetric Mannich-type reactions.[6] In 1998, Sodeoka's group developed a new binuclear palladium complex prepared from chiral Tol-BINAP for the Mannich reactions of imines derived from glyoxylate (**Scheme 3**).[7]



Scheme 3. Mannich type reaction catalyzed by binuclear palladium complex.

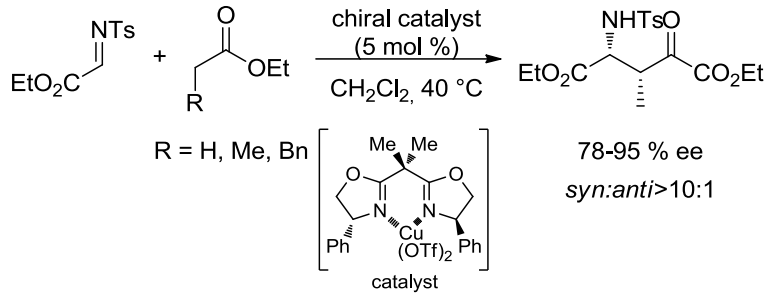
One disadvantage of these stereoselective Mannich reactions is the preparation and stability of the preformed enolate, and a major step for this

[6] a) Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528–15535; b) Yamashita, Y.; Ueno, M.; Kuriyama, Y.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 929–931.

[7] a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475; b) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458.

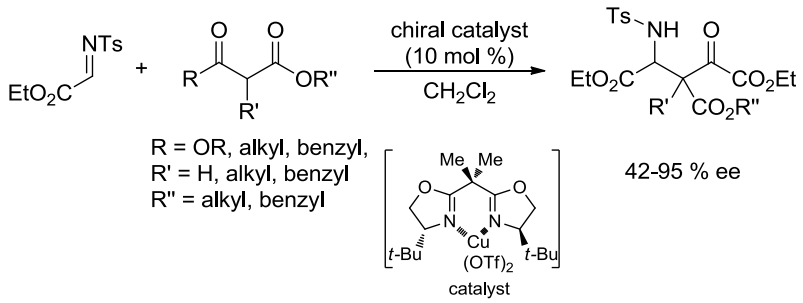
important class of reactions has been to develop catalytic enantioselective version that uses carbonyl compounds, especially aldehydes, as nucleophile precursors.

Subsequently, good results in the asymmetric Mannich-type reactions on α-carbonyl esters were obtained using copper(II) complexes. Jørgensen's group disclosed an approach to asymmetric Mannich reactions that utilizes copper(II)/bisoxazoline complexes. These catalysts are very effective for the addition of α-carbonyl esters to *N*-tosyl α-aldimino ethyl ester which make this method a simple synthetic procedure in order to obtain functionalized α-amino acid derivatives using readily available carbonyl compounds rather than the silyl enol ethers or silyl ketene acetals (**Scheme 4**).[8]



Scheme 4. Mannich type reaction catalyzed by $Cu(OTf)_2$/(*R*)-Ph-BOX.

These same authors disclosed the first asymmetric Mannich-type reaction catalyzed by chiral *tert*-butyl-bisoxazoline/$Cu(OTf)_2$ using malonic esters as pro-nucleophiles or β-keto esters as nucleophiles (**Scheme 5**).[9]

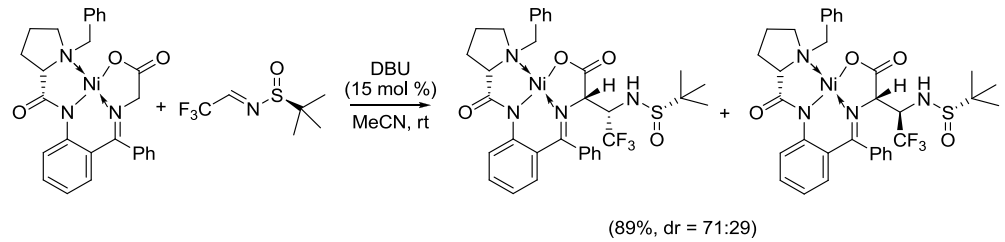


Scheme 5. Mannich type reaction catalyzed by $Cu(OTf)_2$/*t*-Bu-BOX.

[8] Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995–2997.
[9] Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359–2367.

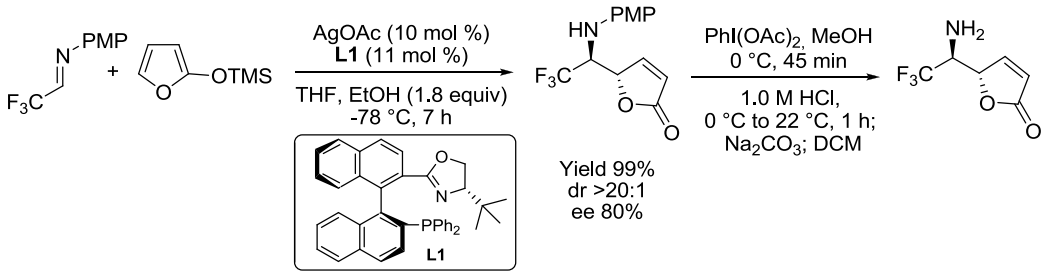
It was found that the best results in terms of yield, diastereo- and enantioselectivity were obtained when β-keto esters bearing the *tert*-butyl group on the ester function were used as the substrate.

Chiral Ni(II) complexes, derived from glycine Schiff bases, were used as Mannich donors in the addition reactions to *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimine (**Scheme 6**).[10] In that case the chiral transition-metal complex is used as a chiral auxiliary, and a perfectly matched between the two reactants provided satisfactory diastereoselectivity.



Scheme 6. Chiral Ni(II) complexes as Mannich donors.

Chiral complex are also used in the asymmetric vinylogous Mannich (AVM)-type reactions that can be regarded as a self-class of Mannich-type additions. In this context, Shi and co-workers[11] reported the silver(I)-catalyzed asymmetric Mannich reaction of fluorinated aldimines with trimethylsiloxyfuran, using chiral phosphine–oxazoline ligands (**Scheme 7**).



Scheme 7. AVM-type reaction of trifluoromethyl aldimine and 2 trimethylsiloxyfuran.

[10] Kawamura, A.; Moriwaki, H.; Röschenthaler, G.-V.; Kawada, K.; Aceña, J. L.; Soloshonok, V. A. *J. Fluorine Chem.* **2015**, *171*, 67–72

[11] Zhao, Q.-Y.; Yuan, Z.-L.; Shi, M. *Tetrahedron*: *Asymmetry* **2010**, *21*, 943–951.

The corresponding adducts were obtained in good to excellent yields and good diastereoselectivities along with moderate to good enantioselectivities.

2.2 Chiral organocatalysts

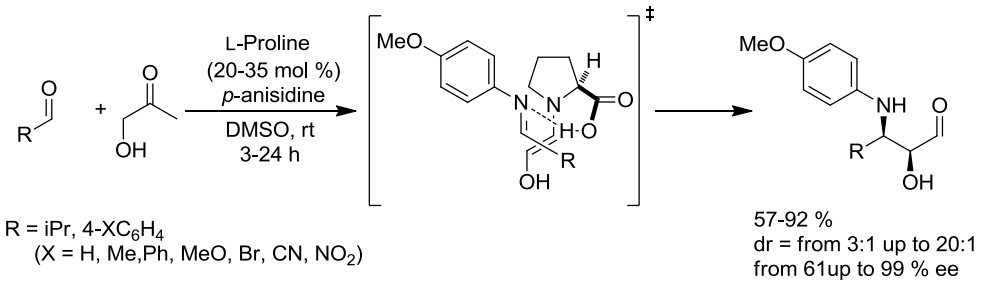
Organocatalytic methods, which generally involves small organic molecules in sub-stoichiometric quantities to promote organic reactions, have emerged as a potent instrument to build chiral intermediates and products. The term "organocatalysis" was coined up by David MacMillan[12] in 2000 to summarize and to describe several classes of organic catalysts that had been used during the last fifty years.

Organocatalysts such as amino acid derivatives, especially those derived from proline,[13] cinchona-type alkaloids,[14] chiral amine thioureas and chiral Brønsted acids[15] have been widely used in the Mannich type reaction.

2.2.1 syn-anti Selective chiral organocatalysts

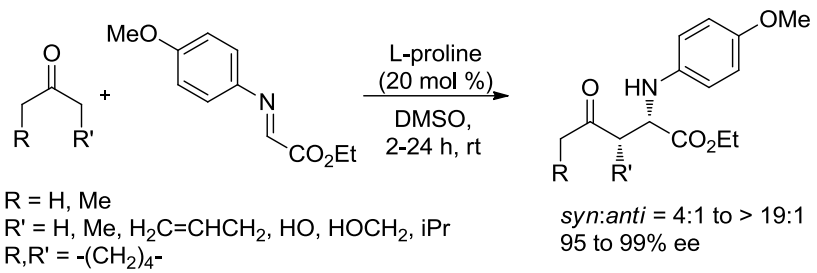
Enamine catalysis using amino acid derivatives has been widely developed[39] since List and co-workers reported the first example of a proline-catalyzed Mannich reaction,[16] to obtain enantiopure *syn*-γ-amino alcohols starting from different aldehydes (**Scheme 8**).

[12] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4224.
[13] a) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; b) Cordova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; c) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101–1104.
[14] a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367–6370; b) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 2653–2664.
[15] a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087; b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764; c) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631–3634; d) Tillman, A. L.; Dixon, D. J. *Org. Biomol. Chem.* **2007**, *5*, 606–609; e) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.
[16] a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.



Scheme 8. Mannich reaction catalyzed by L-proline.

Subsequently Barbas III and co-workers reported results similar to those obtained by List's group concerning the proline-catalyzed Mannich reaction, starting from several ketones and involving preformed imines (**Scheme 9**).[17]



Scheme 9. Mannich type reaction catalyzed by L-proline.

The proline approach has been applied in the Mannich reactions with several nucleophiles and electrophiles.[18] In these transformation the *syn* configuration of the final product is generally controlled by a hydrogen-bond interaction between the imine nitrogen and the hydroxyl hydrogen of proline (**Figure 2**).

[17] a) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131–1140; b) Notz, W.; Tanaka, F.; Watanabe, S. I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F. *J. Org. Chem*. **2003**, *68*, 9624–9634.

[18] a) Marques, M. M. B. *Angew. Chem*. **2006**, *118*, 356–360; *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352; b) Còrdova, A. *Acc. Chem. Res*. **2004**, *37*, 102–112.

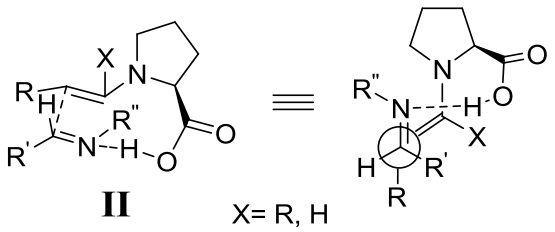


Figure 1. Proposed transition states.

In order to synthetize all possible stereoisomers, recently, other proline derivatives, namely diarylprolinol ethers (**Figure 2**), have been developed.[19]

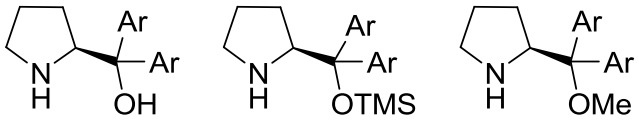


Figure 2. Diarylprolinol ethers.

With these catalysts the relative configuration of the product is controlled by the steric hindrance of the α substituent to the nitrogen (**Figure 3**), in the transition state the only *anti*-type attack being thus favored.

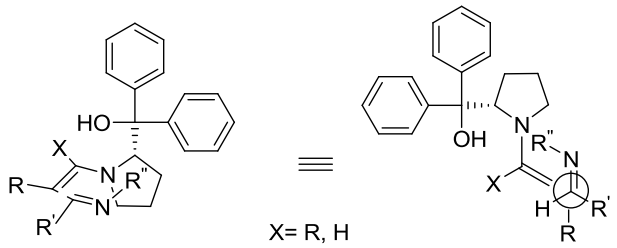
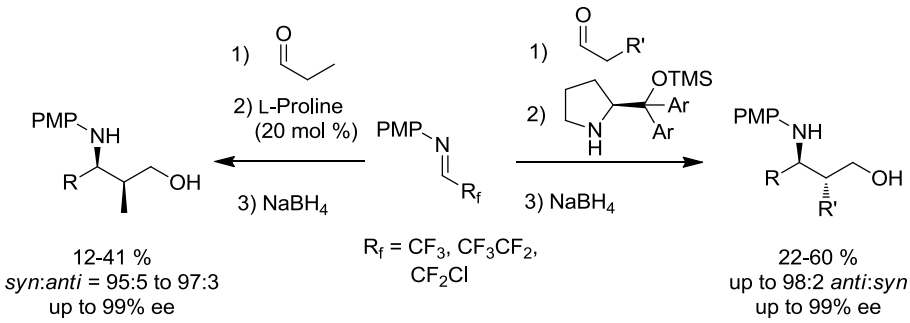


Figure 3. Proposed transition states.

Fustero *et al.*[20] have described the asymmetric Mannich reaction between fluoroalkyl aldimines and propanal catalyzed by proline that, after reduction, gave

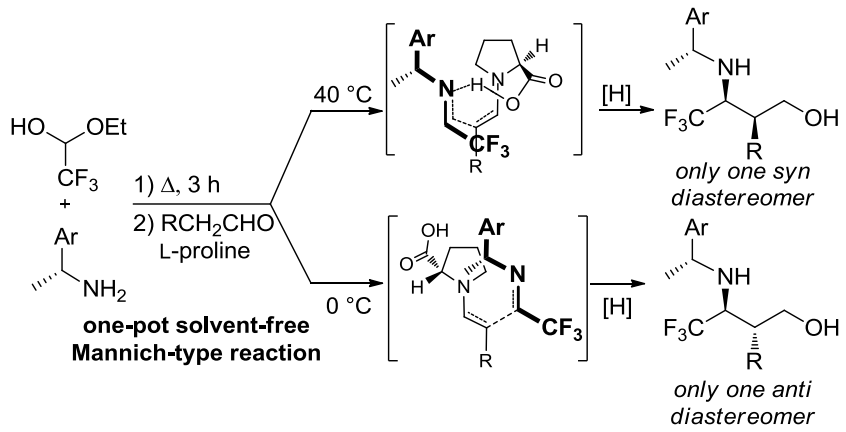
[19] a) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749–7752; b) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631; c) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041; d) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaerd, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; e) Galzerano, P.; Agostino, D.; Bencivenni, G.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.-Eur. J.* **2010**, *16*, 6069–6076.

syn-3-fluoroalkyl-1,3-amino alcohols. Later the same authors described a highly diastereo- and enantioselective synthesis of *anti*-γ-amino alcohols using (*S*)-α,α-diarylprolinol trimethylsilyl ether as catalyst (**Scheme 10**).[21]



Scheme 10. Organocatalyzed Mannich type reaction on fluoroalkyl aldimines.

Recently, in the laboratory in which I am attending my PhD diastereomerically pure fluorinated *syn*- or *anti*-γ-amino alcohols (**Scheme 26**) were obtained by an eco-friendly one-pot solvent free L-proline catalyzed Mannich-type reaction only by changing the reaction temperature (complete selectivity *syn* or *anti* at 40 °C or 0 °C, respectively).[22]



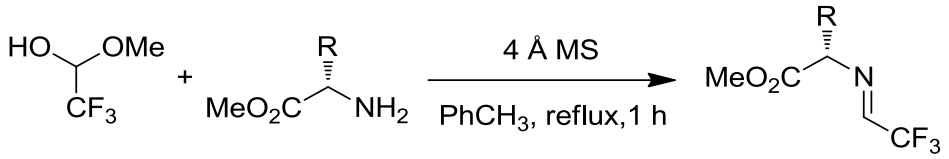
Scheme 11. One-pot solvent-free L-proline-catalyzed Mannich-type reaction on chiral aldimines.

[20] Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433–3436.

[21] Fustero, S.; Mojarrad, F.; Carrion, M. D. P .; Sanz-Cervera, J. F.; Aceña, J. L. *Eur. J. Org. Chem*. **2009**, 5208-5214.

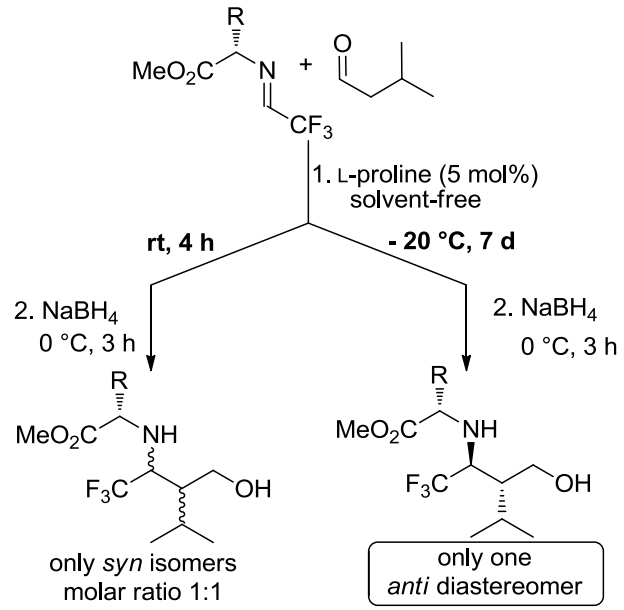
[22] Fioravanti S, Parise L, Pelagalli A, Pellacani L, Trulli L. *RSC Adv*. **2015**, *5*, 29312–29318.

We decided to extend this work to chiral aldimines functionalized with L-α-amino ester moieties.



Scheme 12. Synthesis of functionalized *N*-α-amino ester trifluoromethyl aldimines.

A new methodology, starting from the commercial fluoral ethyl hemiacetal and different L-α-amino esters, has been developed for the synthesis of the aldimines (**Scheme 12**) that subsequently were considered in a proline-catalyzed Mannich-type reaction: again a complete *syn* or *anti* selectivity simply by changing the reaction temperature was observed. (**Scheme 13**).[23]

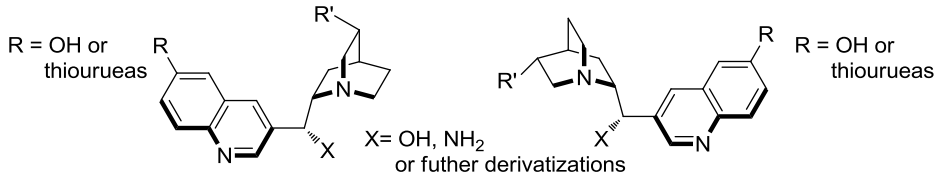


Scheme 13. Synthesis of L-α-amino ester functionalized trifluoromethyl (*S*,*S*,*R*)-anti-γ-amino alcohols.

[23] Fioravanti S, Parise L, Pelagalli A, Pellacani L, Trulli L.; Vergari M. C. *Chirality* **2015**, *27*, 571-575.

2.2.2 Chiral Brønsted Bases

Readily available and inexpensive chincona alkaloids are among the most useful organocatalysts to date. The family of cinchona alkaloids consists of two pseudoenantiomeric pairs, including cinchonine, cinchonidine, quinine and quinidine (**Figure 4**). The presence of 1,2-amino alcohol moiety, containing the basic and bulky quinuclidine, is responsible for the catalytic activity.



R = H
R' = $CH{=}CH_2$; Cinchonidine
R' = CH_2CH_3; Dihydrocinchonidine
R = OMe
R' = $CH{=}CH_2$; Quinine
R' = CH_2CH_3; Dihydroquinine

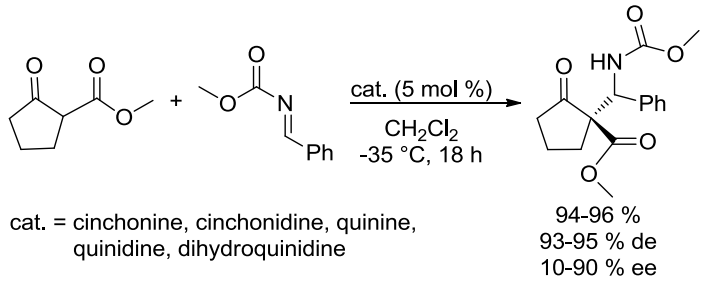
R = H
R' = $CH{=}CH_2$; Cinchonine
R' = CH_2CH_3; Dihydrocinchonine
R = OMe
R' = $CH{=}CH_2$; Quinidine
R' = CH_2CH_3; Dihydroquinidine

Figure 4. Chincona alkaloids organocatalysts.

They are widely used in the asymmetric Mannich-type reaction, especially with active methylene compounds that, after deprotonation, provide a chiral ionic pair whose anion reacts with the imine in a stereoselective way.

In this context, Schaus *et al.* were the first to describe the cinchona alkaloid-catalyzed Mannich reaction of 1,3-dicarbonyl compounds with *N*-carbamoyl aryl imines. They were able to obtain the desired product, characterized by an α-quaternary carbon, in good yield and high diastereo- and enantioselectivities, using several cinchona alkaloid (**Scheme 14**).[24]

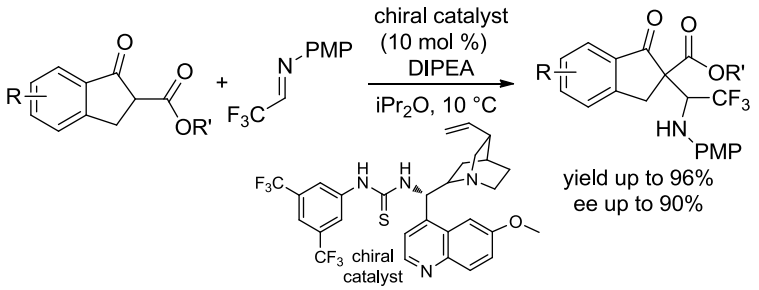
[24] Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003–2006.



Scheme 14. Mannich type reaction catalyzed by chincona alkaloids.

Subsequently, numerous organocatalysts derived from cinchona and structurally simpler thiourea organocatalysts[25] were developed and investigated in several Mannich-type reactions, with a variety of nucleophiles, including isocyano acetates,[26] nitro compounds,[27] phenyl acetates and thioesters.[28]

Recently, the efficiency of bifunctional thiourea catalyst was also studied in the Mannich-type reaction between *N*-PMP trifluoromethyl aldimine and different β–keto esters; the products, characterized by vicinal chiral centers, were obtained in good diastereo- and enantioselectivity (**Scheme 15**).[29]



Scheme 15. Asymmetric organocatalyzed Mannich-type reaction by bifunctional thiourea.

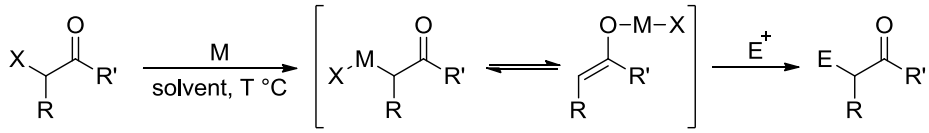
[25] a) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571–2577; b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
[26] Zhang, Z.-W.; Lu, G.; Chen, M.-M.; Lin, N.; Li, Y.-B.; Hayashi, T.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 1715–1721.
[27] Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang S. *Org. Lett.* **2012**, *14*, 704–707.
[28] Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376–3379.
[29] Ji, S.; Alkhalil, A. E.; Su, Y.; Xia, X.; Chong, S.; Wang, K.-H.; Huang, D.; Fu, Y.; Hu, Y. *Synlett* **2015**, *26*, 1725–1731.

Chapter 3

Reformatsky reaction

The Reformatsky reaction, introduced for the first time in 1887,[30] is among the most useful methods for the C−C formation; its classical form involves zinc enolates derived from α-bromo ester and aldehydes or ketones as suitable electrophiles, affording the corresponding β-hydroxy esters.

Nowadays, we can define Reformastky reaction all the transformations resulting from metal (zinc or other metals in low oxidation state) insertion into a carbon-halogen bond, activated by a carbonyl or carbonyl-related groups, followed by addition to the electrophile species (**Scheme 1**).



X = Cl, Br, I
M = Zn, Cr(II), Sm(II), In, Co(0), Ti(III), Sn
R, R' = alkyl, aryl

Scheme 1. Reformatsky-type reaction.

The main advantage of these transformations is that the enolate is formed under mild and neutral reaction conditions; in fact, no activation by strong acids or bases is needed, it follows its excellent functional group tolerance.

In addition, the enolate formation is highly regioselective, in fact, the position of the halogen atom determines unambiguously the site of metal insertion.

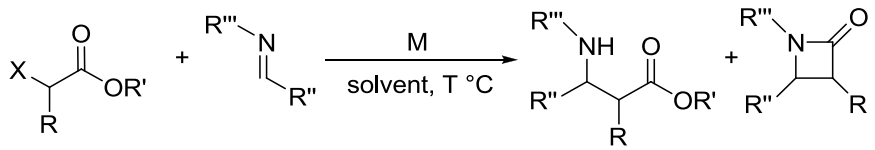
There seems to be no definitive experimental studies defining the mechanism precisely, probably it involves cyclic transition states, for which semiempirical

[30] Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210–1211.

calculations MO (PM3) suggest that the boat like transition state is favored, compared to the chair like transition state, using zinc as a metal.[31]

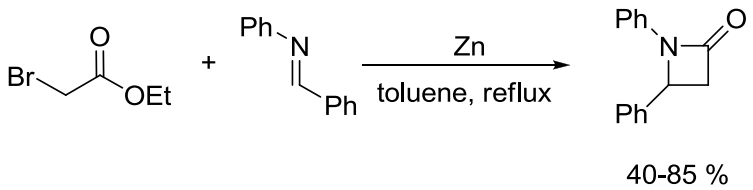
3.1 Aza-Reformatsky reaction

A major extension of the Reformatsky reaction has been achieved by the use of imines as suitable electrophiles. Aza-Reformatsky reaction affords β-amino esters and/or β-lactams, useful and valuable synthetic intermediates in organic synthesis and pharmacologically important compounds (**Scheme 2**).



Scheme 2. Aza-Reformatsky-type reaction.

The first zinc enolate-imine condensation reaction was originally reported by Gilman and Speeter[32] in 1943 who employed a Reformatsky-type reaction between α-bromo esters with an imine for the production of an *N*-aryl-β-lactam (**Scheme 3**).



Scheme 3. Gilman-Speeter reaction.

Subsequently, a great attention has been paid to the study of the aza-Reformatsky reaction,[33] starting from several bromo esters and a variety of imines, with β-amino esters being preferred product especially when an *ortho*-substituent is present in an arylamine-derived imine.

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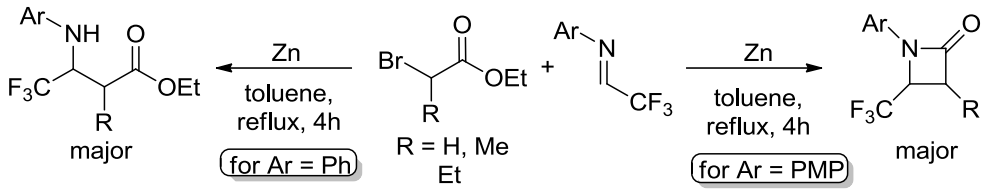
[31] Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J. M.; Cossio, F. P.; Lecea, B. *Tetrahedron Lett.* **1993**, *34*, 6111–6114.

[32] Gilman, H.; Speeter, M. *J. Am. Chem. Soc.*, **1943**, *65*, 2255−2256.

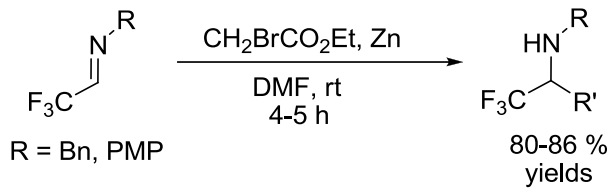
[33] a) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307–308; b) Adrian, J. C.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *34*, 2457–2460; c) Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709–2712: d) Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Clader, J. W.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 4095–4098; e) Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 11329–11340.

In 2001 Gong et al.[34] reported a typical aza-Reformatsky reaction starting from trifluoromethyl aldimines: the corresponding β-lactam was the favored product starting from *N*-*p*-methoxyphenyl (PMP) protected aldimine. On the other hand, using *N*-phenyl protected trifluoromethyl aldimine, the Reformatsky reaction gave the corresponding β-amino esters as major products (**Scheme 4**).



Scheme 4. Aza-Reformatsky-type reaction on trifluoromethyl aldimines.

Later, Bonnet-Delpon reported a modified Reformatsky reaction, between ethyl bromoacetate and trifluoromethyl aldimines, performed under Barbier conditions. The authors were able to obtain the corresponding β-amino β-trifluoromethyl esters in satisfactory yields, using a polar solvent (DMF) (**Scheme 5**).



Scheme 5. Aza-Reformatsky-type reaction on trifluoromethyl aldimine.

However, it is necessary to underline that, even if the aza-Reformatsky reaction has a great potential, the corresponding products are often isolated as a mixture of β-amino esters and β-lactams.

[34] Gong, Y.; Kato, K. *J. Fluorine Chem*. **2001**, *111*, 77–80.

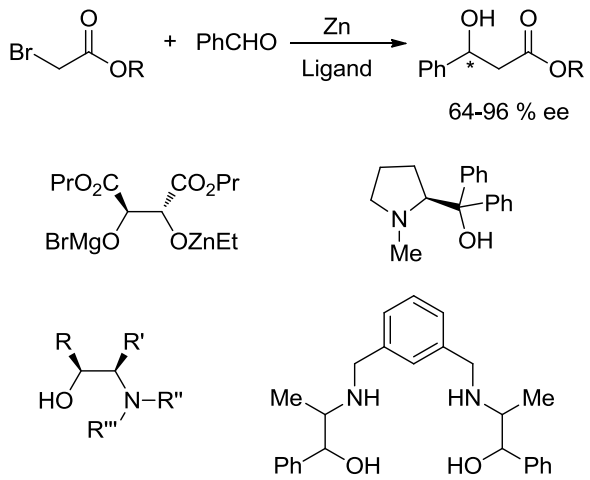
3.2 Stereoselectivity in Reformatsky reactions

The main limitation of the Reformatsky transformations is due to observed low yields and diastereoselectivities, probably because it is classically performed under heterogeneous conditions that made the development of stereoselective variants quite difficult.

To date, a few examples of highly diastereo and enantioselective Reformatsky reactions have been reported.[35]

3.2.1 Heterogeneous conditions

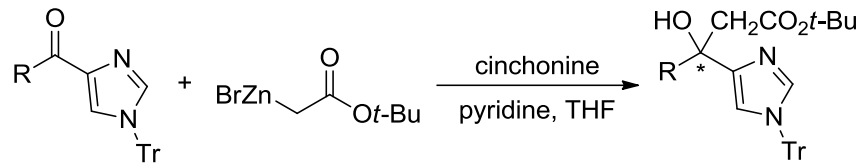
In recent years several ligands, such as carbohydrates,[36] amino alcohols (ephedrines and *N*-alkyl ephedrines),[37] α-amino acid esters,[38] were considered as additives in the Reformatsky reactions performed between benzaldehyde and α-bromo esters in the presence of metallic zinc (**Scheme 6**).



Scheme 6. Enantioselective Reformatsky reactions.

[35] Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert F. *Chem. Soc. Rev*. **2013**, *42*, 937–949.
[36] Ribeiro, C. M. R.; Santos, E. S.; Jardim, A. H. O.; Maia, M. P.; da Silva, F. C.; Moreira, A. P. D.; Ferreira, V. F. *Tetrahedron: Asymmetry* **2002**, *13*, 1703–1706.
[37] a) Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. *Synth. Commun*. **1997**, *27*, 1469–1473; b) Mi, A.; Wang, Z.; Chen, Z.; Jiang, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2641–2642; c) Andrés, J. M.; Martin, Y.; Pedrosa, R.; Perez-Encabo, A.*Tetrahedron* **1997**, *53*, 3787–3794; d) Soai, K.; Kawase, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 781–784; e) Pini, D.; Uccello-Barretta, G.; Mastantuono, A.; Salvadori, P. *Tetrahedron* **1997**, *53*, 6065–6072; f) Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett*. **2003**, *44*, 6161−6163; g) Andrés, J. M.; Martinez, M. A.; Pedrosa, R.; Pèrez-Encabo, A. *Synthesis* **1996**, 1070−1072.
[38] Wang, Z. Y.; Shen, J.; Jiang, C. S.; You, T. P. *Chin. Chem. Lett*. **2000**, *11*, 659–662.

In some specific cases, good enantiomeric excesses have been obtained. Yamano and co-workers reported a highly enantioselective Reformatsky reaction with ketones using cinchona alkaloids as chiral ligands (**Scheme 7**).[39]



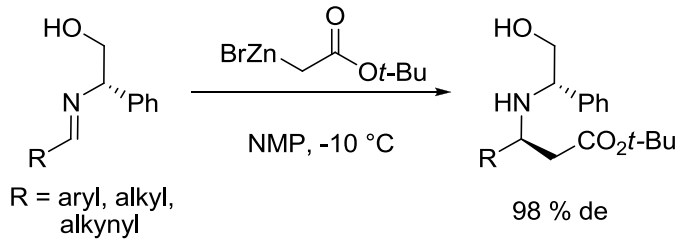
Scheme 7. Enantioselective Reformatsky reaction performed with cinchonine.

In this transformation the high enantioselectivity is due to the chelation of the sp^2-nitrogen with the cinchonine catalyst.

However, in all the above shown examples most of the ligands were used in more than stoichiometric amounts.

In recent years improvements to perform highly diastereoselective Reformastky reactions have been obtained using chiral auxiliaries, either on the electrophile or on the nucleophile.[66]

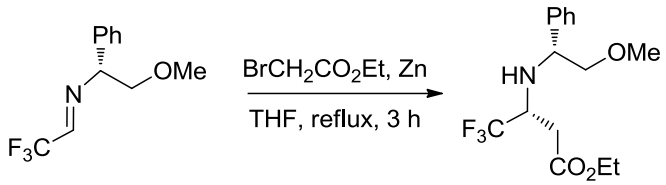
Awasthi *et al.* reported the synthesis of β-amino esters by a Zn-mediated Reformatsky-type reaction, starting from chiral imines derived from (*S*)-phenylglycinol. The desired products were obtained with good yields and stereoselectivities up to 98% (**Scheme 8**).[40]



Scheme 8. Diastereoselective Reformatsky reactions.

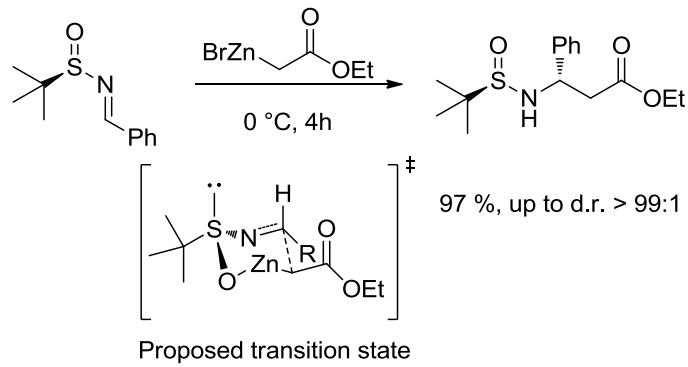
[39] Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051–3054.
[40] Awasthi, A. K.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P.-J.; Doubleday, W. W.; Duran, J. E.; . Farid, P. N. *J. Org. Chem*. **2005**, *70*, 5387–5397.

Chiral trifluoromethyl aldimine, derived from the methyl ether of (*R*)-phenylglycinol, was also studied in the Reformatsky reaction by Bonnet-Delpon's group;[41] using THF at reflux, affordthe corresponding β-amino ester in good yield (80%) and selectivity (81% dr) (**Scheme 9**).



Scheme 9. Diastereoselective Reformatsky reaction on trifluoromethyl aldimine.

In this context, the reactivity of chiral *N*-*tert*-butyl-sulfinylimines with several nucleophiles in the aza Reformatsky reaction also has been widely studied.[42] Poon, Brinner *et al.*[43] explain the observed diastereoselectivity with a chiral *N*-*tert*-butylsulfinylimine by a Zimmerman–Traxler six-membered transition state (**Scheme 10**).

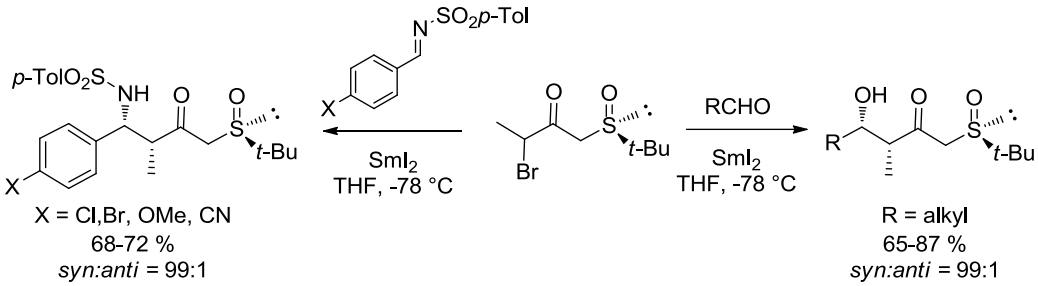


Scheme 10. Diastereoselective Reformatsky reaction on chiral *N*-tert-butylsulfinylimine.

The *tert*-butylsulfinyl group on the nucleophile has also been successfully used as chiral auxiliary in SmI_2-mediated Reformatsky-type reactions. The addition

[41] Dos Santos, M.; Crousse, B.; Bonnet-Delpon, D. *Synlett* **2008**, 399–401.
[42] a) Jing, Z. T.; Huang, Y. G.; Qing, F. L. *Chin. Chem. Lett.* **2011**, *22*, 919–922; b) Concellon, J. M.; Rodriguez-Solla, H.; Simala, C. *Adv. Synth. Catal.* **2009**, *351*, 1238–1242; c) Wang, L.; Shen, C.; Xu, M.-H. *Sci. China Chem*. **2011**, *54*, 61–65.
[43] Brinner, K.; Doughan, B.; Poon, D. J. *Synlett* **2009**, 991–993.

of an α-bromo α-sulfinyl ketone to linear aldehydes[44] or aryl aldimines[45] proceeded with complete *syn* selectivity (**Scheme 11**).

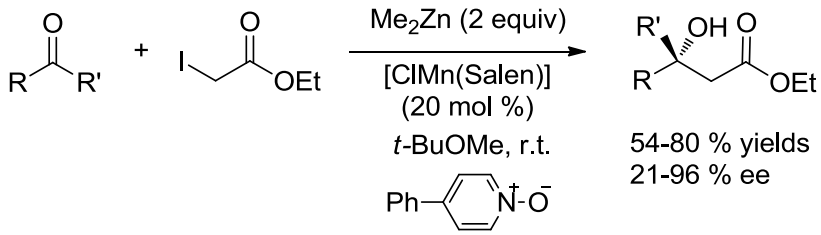


Scheme 11. Diastereoselective Reformatsky reaction on α-bromo α-sulfinyl ketone.

3.2.2 Homogenous conditions

In order to simplify the design of a catalytic asymmetric version of the Reformatsky reaction, homogenous reaction conditions have been considered, using Me_2Zn or Et_2Zn, as zinc sources.[46]

In 2006 Cozzi[47] reported the first example of catalytic asymmetric Reformatsky reaction, between ketones and ethyl α-iodoacetate, in the presence of Me_2Zn, using a chloromanganese–Salen complex (20 mol %) as catalyst and 4-phenylpyridine *N*-oxide (25 mol %) as additive (**Scheme 12**).



Scheme 12. Dimethylzinc-mediated Reformatsky reactions promoted by manganese salen complex.

The reaction shows broad scope and the corresponding products were obtained with moderate to good stereoselection.

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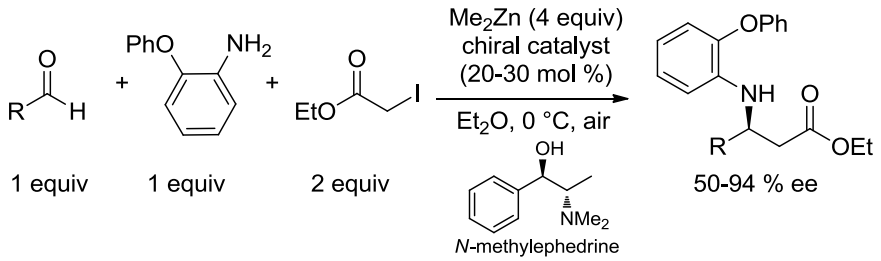
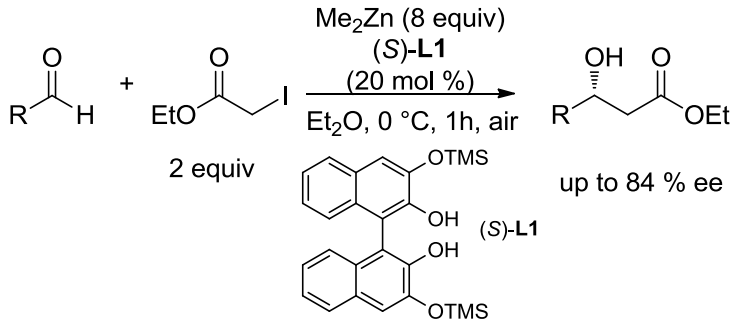
[44] a) Obringer, M.; Colobert, F.; Neugnot B.; Solladié, G. *Org. Lett.* **2003**, *5*, 629–632. b) Obringer, M.; Colobert, F.; Solladié, G. *Eur. J. Org. Chem*. **2006**, 1455–1467.
[45] Barbarotto, M.; Choppin S.; Colobert, F. *Tetrahedron: Asymmetry* **2009**, *20*, 2780–2787.
[46] Cozzi, P. G. *Angew. Chem., Int. Ed*. **2007**, *46*, 2568–2571.
[47] a) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951–2954; b) Cozzi, P. G.; Mignogna, A.; Zoli, L. *Synthesis* **2007**, *17*, 2746–2750.

In the same year Cozzi reported the first catalytic asymmetric aza-Reformatsky reaction using inexpensive and commercially available *N*-methylephedrine as chiral ligand. In addition, in order to obtain reproducible results and initiate the radical process, admission of air into the reaction mixture was necessary (**Scheme 13**).[48]



Scheme 13. One-pot three-component Reformatsky reactions.

Two years later Feringa's group[49] reported a catalytic enantioselective Reformatsky reaction for aldehydes, using BINOL derivative as chiral catalyst (**Scheme 14**); the protocol of these transformations also required air to have a good conversion and good enantiomeric excess.

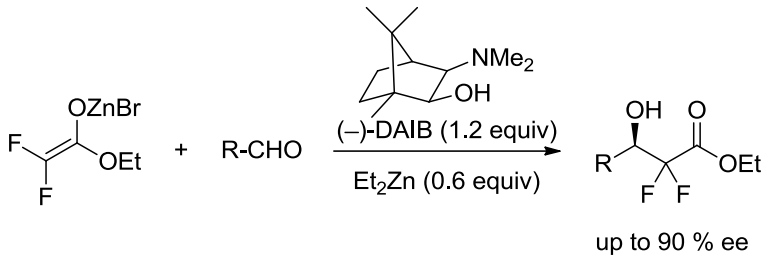


Scheme 14. Reformatsky reactions with aldehydes in the presence of BINOL derivative ligand.

[48] Cozzi, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2075−2079.
[49] Fernández-Ibáñez, M. A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1317–1319.

After the pioneering work of Feringa and Cozzi, different catalytic systems based on the formation of radicals from Me_2Zn have been developed, using Schiff base, bisoxazolidine, or amino alcohol as chiral catalysts.[50]

Recently, given the importance of fluorinated organic compounds, great attention has been paid to the study of fluorinated α-fluoro halogenated esters as reactants in the Reformatsky reactions, especially in the development of asymmetric versions.[51] Knochel *et al.*[82a] described the enantioselective addition of ethyl bromodifluoroacetate to aromatic and aliphatic aldehydes, using (−)-*N*,*N*-dimethylaminoisoborneol [(−)-DAIB] as chiral ligand (**Scheme 15**).



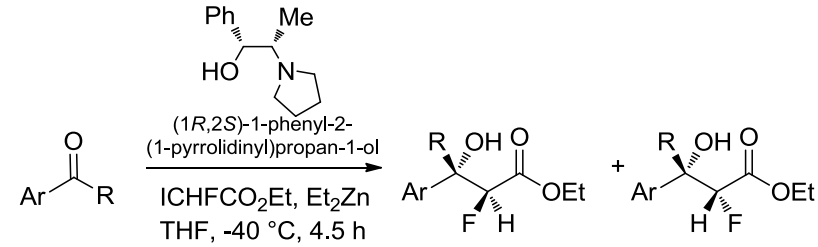
Scheme 15. Reformatsky Reaction in the presence of chiral amino alcohol.

The authors were able to obtain the desired products with good yields and satisfactory enantioselectivities.

Good enantiocontrol was also found through the reaction of ethyl iodofluoroacetate with alkyl and aryl ketones in the presence of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol that unfortunately must be used in stoichiometric amount (**Scheme 16**).[82b]

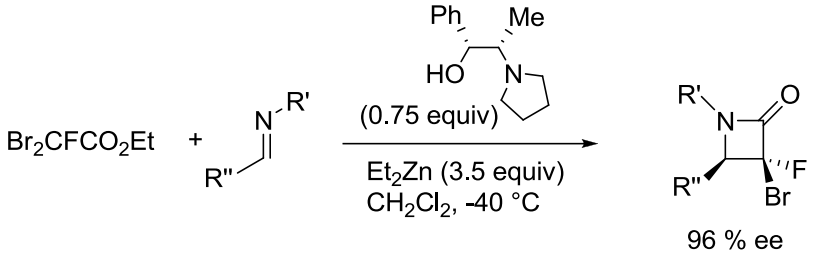
[50] a) Tanaka, T.; Hayashi, M. *Chem. Lett.* **2008**, *37*, 1298–1299. b) Wolf, C.; Moskowitz, M. *J. Org. Chem.* **2011**, *76*, 6372–6376; c) Cozzi, P. G.; Benfatti, F.; Capdevila, M. G.; Mignogna, A. *Chem. Commun.* **2008**, 3317−3318; d) Cozzi, P. G.; Mignogna, A.; Vicennati, P. *Adv. Synth. Catal.* **2008**, *350*, 975−978.

[51] a)Knochel, P.; Kloetzing, R. J.; Thaler, T. *Org. Lett.* **2006**, *8*, 1125−1128; b) Fornalczyk, M.; Singh, K.; Stuart, A. M. *Chem. Commun*. **2012**, *48*, 3500−3502; c) Fornalczyk, M.; Singh, K.; Stuart, A. M. *Org. Biomol. Chem*. **2012**, *10*, 3332−3342



Scheme 16. Reformatsky Reaction in the presence of chiral amino alcohol.

In 2014, the same chiral amino alcohol was reported by Tarui *et al.*[52] in the first asymmetric aza-Reformastky reaction (**Scheme 17**).



Scheme 17. Aza-Reformatsky Reaction in the presence of chiral amino alcohol.

Starting from different aldimines, ethyl dibromofluoroacetate led to enantio-enriched α-bromo-α-fluoro-β-lactams

[52] Tarui, A.; Nishimura, H.; Ikebata, T.; Tahira, A.; Sato, K.; Omote, M.; Minami, H.; Miwa,Y.; Ando, A. *Org. Lett.* **2014**, *16*, 2080−2083.

Thesis Purpose

Chapter 4

Purpose and aims

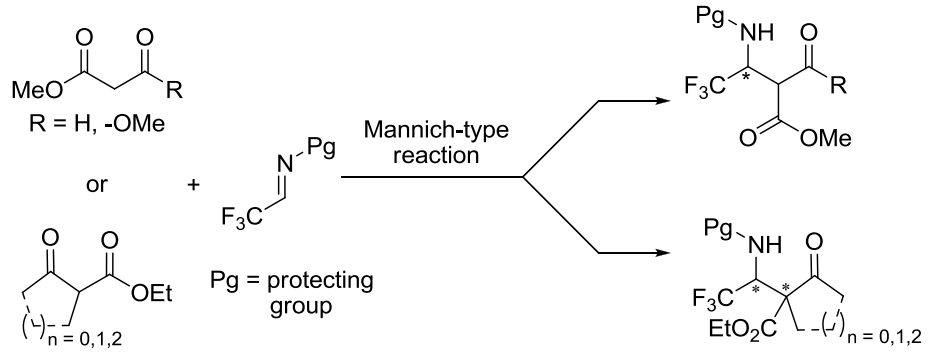
1,2- and 1,3-Difunctionalized compounds, including β-amino esters or more generally β-amino carbonyl compounds as well as nitrogen heterocycles, have all been found to possess a variety of biological properties, making them valuable and useful synthetic intermediates in organic synthesis and in medicinal chemistry. Considering the relevance of the presence of fluorine in bioactive molecules, the synthesis of fluorine-containing analogues of before mentioned compounds was the prevalent scope of this PhD thesis.

The studies focused on the reactivity of different active methylene compounds towards different *N*-protected trifluoromethyl aldimines, optimal scaffolds for the construction of fluorinated molecules, in order to obtain interesting potentially bioactive highly functionalized molecules, suitable for further chemoselective transformations.

Among the various methods involving nucleophilic additions on trifluoromethyl imines, Mannich-type and aza-Reformatsky reactions have been considered as powerful approaches to obtain interesting trifluoromethyl compounds.

To the best of our knowledge, few examples of Mannich-type additions of active methylene compounds on trifluoromethyl imines are reported in the literature[1] and so the reactivity of *C*-CF_3 substituted *N*-protected aldimines with malonate or β-keto esters has been here studied (**Scheme 1**).

[1] a) Ji, S.; Alkhalil, A. E.; Su, Y.; Xia, X.; Chong, S.; Wang, K.-H.; Huang, D.; Fu, Y.; Hu, Y. *Synlett* **2015**, *26*, 1725–1731; b) Shibata, N.; Nishimine, T.; Shibata, N.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. *Org. Biomol. Chem*. **2014**, 12, 1454–1462; c) Shibata, N.; Nishimine, T.; Shibata, N.; Tokunaga, E.; Kawada, K.; Kagawa, T.; Sorochinsky, A. E.; Soloshonok, V. A. *Chem. Commun*. **2012**, 4124−4126.



Scheme 1. Mannich-type reactions on malonate or β-keto esters.

The aim was to find an efficient methodology to obtain interesting compounds, characterized by different sites that can allow a further molecular growth. In addition, the usefulness of these Mannich-type reactions may be enhanced by a decarboxylation reaction of the newly obtained β-keto esters. Indeed, it is well-known that the direct addition reaction of enolizable ketones to imines suffers from low yields and/or low selectivity.[2]

Just as interesting is the synthesis of heterocycles that constitute a major family of pharmaceuticals and agrochemicals.[3] Therefore, trifluoromethyl-functionalized heterocyclic compounds are becoming modern attractive targets in medicinal chemistry.[4] Thus, the attention has been directed towards the synthesis of 2-imidazoline derivatives which have attracted considerable interest because of their wide applications in the synthesis of biologically active compounds such as α,β-diamino acids and also their presence in some biologically active natural products.[5]

---

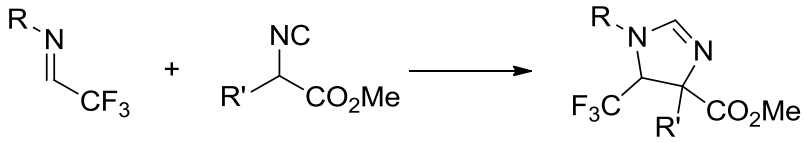
[2] Funabiki, K.; Nagamori, M.; Goushi, S.; Matsui, M. *Chem. Commun*. **2004**, 1928−1929.

[3] a) Eguchi, S. *Bioactive Heterocycles I*, Springer, Heidelberg, **2006**; b) Joule J. A.; Mills, K. *Heterocyclic Chemistry at a Glance*, Blackwell, Oxford, **2007**.

[4] a) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, Wiley, Hoboken, New Jersey, **2009**; b) Kirsch, P. *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; c) Muzalevskiy,V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, 3905−3929; d) Erian, A. W. *J. Heterocycl. Chem*. **2001**, *38*, 793−808; e) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635−3638; f) Silvester, M. J. *Adv. Heterocycl. Chem*. **1994**, *59*, 1−38; g) Welch, J. T. *Tetrahedron*, **1987**, *43*, 3123−3198.

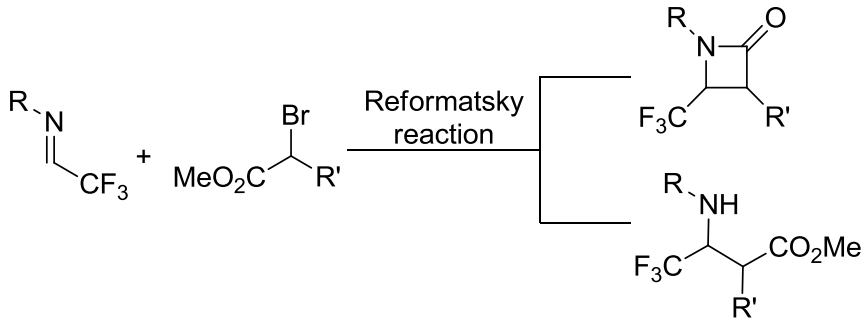
[5] a) Viso, A.; Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev*. **2005**, *105*, 3167−3196. b) Liu, H.; Du, D. M. *Adv. Synth. Catal*. **2009**, *351*, 489−519.

One of the most efficient methods for the synthesis of imidazolines is the Mannich-type addition/cyclization cascade reaction between imines and suitable α-isocyano acetates. With the aim to obtain trifluoromethyl functionalized imidazolines, this reaction was then studied during my thesis for the first time starting from trifluoromethyl aldimines and several substituted α-isocyano acetates (**Scheme 2**).



Scheme 2. Mannich-type reactions on isocyano acetates.

Trifluoromethyl aldimines were also considered in the aza-Reformatsky reaction with different α-bromo esters, hoping to find also an efficient methodology to obtain univocally β-lactam or β-amino ester (**Scheme 3**).



Scheme 3. Aza-Reformatsky reactions on trifluoromethyl aldimines.

The β-amino esters, β-amino keto esters, and β-amino malonates obtained through aza-Reformatsky and Mannich type-reactions respectively, are characterized by the [CH(CF_3)] group.

The [CH(CF_3)] group can be introduced into a peptidic structure to obtain a fluorinated ψ[CH(CF_3)NH]-peptidomimetic.[6] Indeed, this group is a known isoster of the carbonyl group and can mimic his behavior. The term of "isoster" was

[6] See ref.30 and 31 in the **Chapter 1**.

coined by Langmuir, indicating a group of similar steric and electronic profile to the original functional group. This definition has been also extended to the compounds with similar biological properties or compounds eliciting a similar biological effect, the terms used in this case is "bioisoster".

And it is precisely the synthesis of molecules characterized by an acetyl lysine bioisoster portion, the aim of the project carried out at the University of Oxford (UK) under the supervision of Professor Darren J. Dixon and in collaboration with the SGC (Structural Genomics Consortium).

The project was focused on the development of epigenetic probes against PCAF (p300/CBP-associated factor). Starting from the lead compound reported in **Figure 1**,

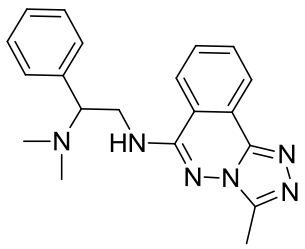


Figure 1. Lead compound.

compound that showed a weak affinity for the bromodomain module of PCAF, a library of compounds was developed in order to clarify the key binding elements and therefore increase the affinity for the abovementioned site.

Results and Discussion

Chapter 5

Mannich type reactions of 1,3-dicarbonyl compounds with trifluoromethyl aldimines

The reactivity of 1,3-dicarbonyl compounds in the Mannich type reaction is well established, especially in the asymmetric version. Nowadays, there are few data reported in literature about the reactivity of trifluoromethyl aldimines towards 1,3-dicarbonyl compounds.[1]

However, these nitrogen containing organofluorine are extremely attractive synthetic targets.

5.1 Preliminary studies

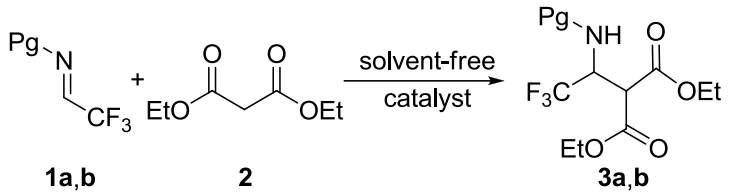
The entire trifluoromethyl (*E*)-aldimines tested in the subsequent Mannich-type reactions were synthesized followed the reported solvent-free protocol between the trifluoroacetaldehyde ethyl hemiacetal and amines[2] and used without further purification.

The investigation of Mannich-type reaction with 1,3-dicarbonyl compounds started with the reaction of trifluoromethyl aldimines **1a**,**b** and diethyl malonate **2** in equimolar ratio. As reported in **Table 1**, different reaction conditions were considered.

[1] See ref.13 in the **Chapter 1**.

[2] See ref.17 in the **Chapter 1**.

Table 1. Optimization of the reaction conditions on diethyl malonate **2**.



1a,**b** **2** **3a**,**b**

Pg: **a** = Bn; **b** = MeO–C6H4–(PMP)

Entry	Pg	Catalyst	Molar (%)	Time (min)	T (°C)	Yield (%)[a]
1	Bn	$CuCl_2$	25	5	25	50
2			25	30	0	35
3			25	60	–20	40
4		$AlCl_3$	50	30	25	–
5			25	30	25	–
6			10	30	25	–
7		$ZrCl_4$	10	10	25	75
8	PMP	$CuCl_2$	50	30	25	–
9			25	30	25	–
10			10	30	25	–
11		$AlCl_3$	50	30	25	–
12			25	30	25	–
13			10	30	25	–
14		$ZrCl_4$	10	30	25	79

[a]After flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

To promote the Mannich-type reaction, the Lewis acid catalysis was considered hoping to increase, through the coordination with the carbonyl groups, the acidity of methylene protons. These latter could be deprotonated by trifluoromethyl aldimines **1**, giving the nucleophilic species and activating themselves through self-protonation at the same time. Three Lewis acids were considered as catalysts, $CuCl_2$,[3] widely used to promote different addition

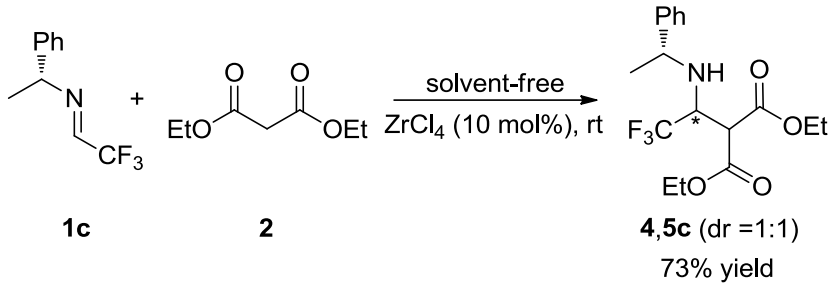
[3] a) Li, J.-L.; Liu, L.; Pei, Y.-N.; Zhu, H.-J. *Tetrahedron* **2014**, *70*, 9077−9083; b) Liu, Y.; Wan, J.-P. *Org. Biomol. Chem*. **2011**, *9*, 6873−6894; c) Le Engers, J.; Pagenkopf, B. L. *Eur. J. Org. Chem*. **2009**, *2009*, 6109−6111, d) Shintani, R.; Hayashi, T. *In New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; Wiley: New York, **2007**; Ch 3, pp 59−100.
e) Gonzalez, A. S.; Arrayas, R. G.; Carretero, J. C. *Org. Lett*. **2006**, *8*, 2977−2980.

reactions, $AlCl_3$, and $ZrCl_4$,[4]as easily disposable, eco-friendly, and efficient Lewis acid.[5]

All the reactions were performed under solvent-free condition; in the presence of $AlCl_3$ no reaction occurs starting from either **1a** or **1b** (entries 4-6 and 11-13). On the other hand, the use of $ZrCl_4$ (entries 7 and 14) as catalyst gave the corresponding Mannich adducts **3a**,**b** in higher yields and shorter times than when the reactions were performed with $CuCl_2$ (entries 1-3 and 8-10).

Thus, in order to study the stereofacial induction of reaction, a diastereoselective $ZrCl_4$-catalyzed Mannich-type reaction was performed, under the fixed optimal reaction conditions, starting from optically pure trifluoromethyl aldimine (*R*)-**1c** (**Scheme 1**).

The desired products **4**,**5c** were obtained in satisfactory yield, but no induction was observed. The reaction was repeated by varying the temperature (0 and –20 °C), but no significant changes in the diastereomeric ratio (dr) were determined by the ^{19}F NMR analysis performed on the crude mixtures.



Scheme 1. $ZrCl_4$-Catalyzed Mannich-type reaction on optically pure **1c**.

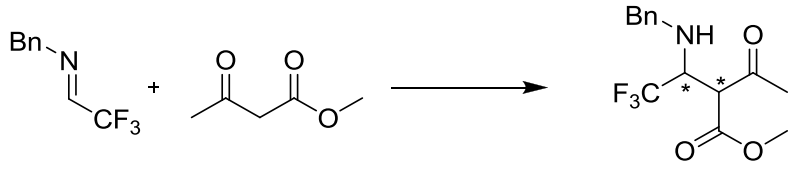
Therefore, the interest has been directed towards the reactivity of β-keto esters.

In order to find the optimal reaction conditions for direct catalytic Mannich-type additions of β-keto esters to trifluoromethyl aldimines, the trifluoromethyl

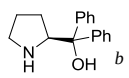
[4] a) See ref. 27 and ref 28 in the **Chapter 1**; b) Morandi, B.; Carreira, E. M. *Angew. Chem.* **2011**, *123*, 9251−9254*; Angew. Chem., Int. Ed.* **2011**, *50*, 9085−9088.
[5] a) Zhang, Z.-H.; Li, T.-S. *Curr. Org. Chem.* **2009**, *13*, 1−30; b) Smitha, G.; Chandrasekhar, S.; Reddy, C. S. *Synthesis* **2008**, *2008*, 829−855.

aldimine **1a** and the simplest β-keto ester, methyl acetoacetate (**6**), were considered as reactants in equimolar ratio under different reaction conditions (**Table 2**).

Table 2. Optimization of the reaction conditions of β-keto ester **6**.



1a **6** **7**,**7'a**

Entry	Catalyst	Molar (%)	Solvent	Time	T (°C)	Yield (%)[a]
1	–	–	–	2 d	25	–
2	Et_3N	100	THF	4 h	25	–
3	KF	100	THF	4 h	25	–
4	Cinchonidine	10	CH_2Cl_2	1 d	25	–
5	L-proline	10	–	24 h	25	–
6		30	–	2 h	25	–
7		10	DMSO	24 h	25	–
8		10	NPM	3 h	25	<5[c]
9		10	THF	2 d	25	<5[c]
10	 *b*	10	–	1 d	25	–
11		10	NPM	3 d	25	<5[c]

[a]After flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2). [b](*S*)-α,α-diphenylprolinol (Hayashi's catalyst).[c]Conversion determined by ^{19}F NMR.

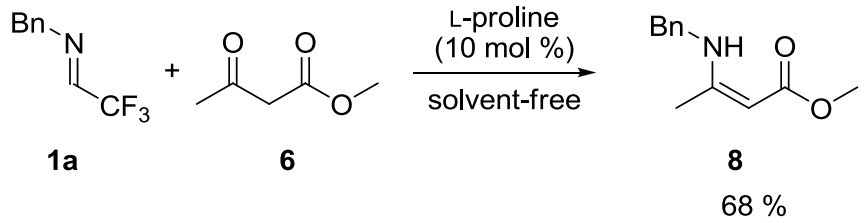
Considering the higher acidity of the β-keto esters compared to the malonates, at first, the Mannich-type reaction was performed without catalyst (entry 1), to test if the same imine could generate *in situ* the nucleophile, acting as both base and substrate.[6] Unfortunately,the reaction did not give the expected product, and both reagents were quantitatively recovered (entry 1).

Subsequently, the most common organic or inorganic bases (entries 2 and 3) were considered to promote the formation of nucleophilic species, but once again, both aldimine **1a** and methyl acetoacetate **6** were quantitatively recovered in every cases.

[6]In the aziridination reactions with ethyl nosyloxycarbamate the same fluorinated imines were able to deprotonate *in situ* the aminating agent, acting as both base and substrate: see ref. 26 in the **Chapter 1** and Barani, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 3829−3834.

It is possible to suppose that, once obtained the nucleophile, it is necessary also an activation of the imine in order that the Mannich addition could occur. Then bifunctional catalysts (entry 4-11), able to activate both the imine and the β-keto ester, were considered.

As shown in **Table 2,** while no reaction occurs with cinchonidine, using L-proline (entries 8 and 9) or (*S*)-α,α-diphenylprolinol (entry 11) in the presence of a suitable solvent the formation of expected Mannich adducts was observed, but only in traces (<5%) by NMR. On the contrary, working under solvent-free conditions, the β-enamino ester **8** (**Scheme 2**), was obtained as major product, resulting from a L-proline-catalyzed nucleophilic addition of benzylamine, *in situ* formed by hydrolysis of **1a**, to the ketone moiety of **6**.[7]



1a **6** **8**

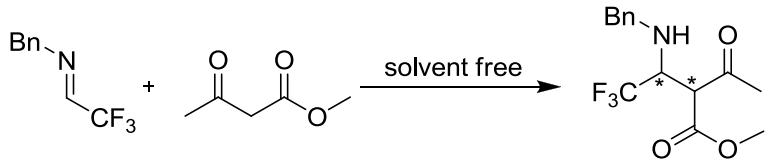
68 %

Scheme 2. Synthesis of β-enamino ester **8**.

Finally, based on previous results, a Lewis acid catalysis was considered (**Table 3**).

[7] Kundu, D.; Majee, A.; Hajra, A. *Chin. J. Chem.* **2008**, *26*, 1545–1548.

Table 3. Lewis acid catalyzed Mannich-type reactions.



1a **6** **7,7'a**

syn/*anti* = 1:1

Entry	Catalyst	Molar (%)	Time	T (°C)	Yield (%)[a]
1	$CuCl_2$	25	5 min	25	50
2		25	30 min	0	35
3		25	1 h	–20	40
4	$AlCl_3$	25	15 min	25	40
5		25	25 min	0	36
6		25	45 min	–20	30
7	$ZrCl_4$	10	10 min	25	75
8		10	1 h	0	35
9		10	3 h	–20	30
10		10	6 h	–70	–
11		25	6 h	–70	–

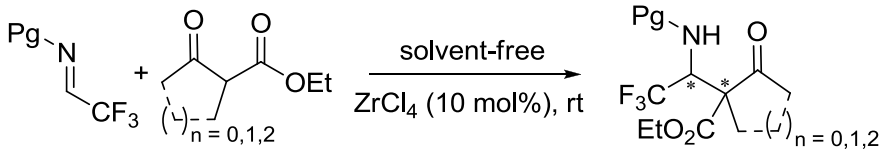
[a] After flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

The reactions, performed under solvent-free conditions, gave the expected products **7**,**7'a**. The best reaction conditions, reported in entry 7, involve the $ZrCl_4$ as catalyst allowing to obtain the desired products in only 10 min and in good yield. No diastereoselectivity was observed; in fact, the two *syn*/*anti* diastereomers were obtained in equimolar ratio even by changing the reaction temperature, in lower yields and longer reaction time (entries 8-9).

Fixed the best conditions and in order to investigate the scope of addition, $ZrCl_4$-catalyzed Mannich-type reactions were performed starting from different β-keto esters **9-11** and *N*-protected trifluoromethyl aldimines **1a**,**b** (**Table 4**).

In all cases the reactions took successfully place in a short time, and the expected Mannich adducts were obtained in satisfactory yields after flash chromatography on silica gel. In addition very high stereoselectivity was achieved, especially when six-membered cyclic β-keto ester **11** was used (entries 3 and 6).

Table 4. Solvent-free $ZrCl_4$-catalyzed Mannich-type reaction of different β-keto esters.

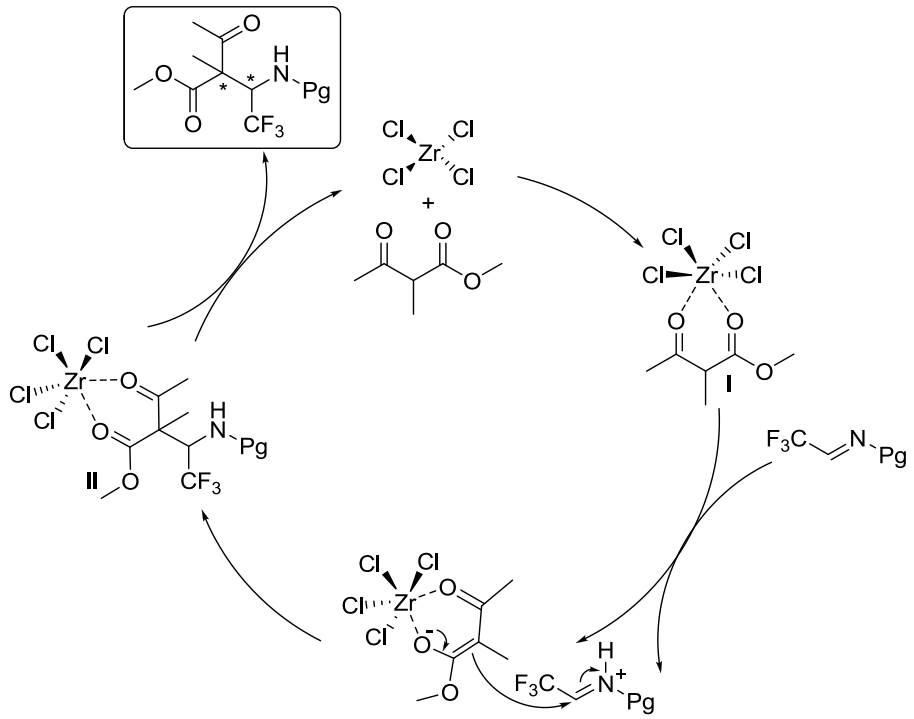


1a,b **9-11** **12/12'a,b 13/13'a,b, 14a,b**

Entry	Pg	n	Product	Time (min)	major/minor[a]	Yield (%)[b]
1	Bn	0	**12a/12'a**	30	7:3[c]	65
2		1	**13a/13'a**	10	7:3[c]	75
3		2	**14a**	10	9.9:0.1	78
4	PMP	0	**12b/12'b**	30	7:3[c]	68
5		1	**13b/13'b**	10	7:3[c]	73
6		2	**14b**	10	9.9:0.1	85

[a]Determined by ^{19}F NMR spectra performed on the crude mixtures. [b]After flash chromatography on silica gel. [c]The ratio did not change by working at lower temperatures.

In order to explain the $ZrCl_4$-catalyzed Mannich-type reaction pathway performed on trifluoromethyl (*E*)-aldimines a catalytic cycle can be proposed (**Scheme 3**).

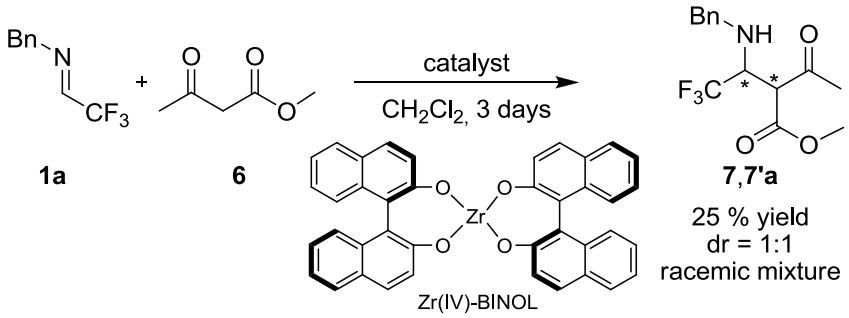


Scheme 3. Proposed pathway for $ZrCl_4$-catalyzed Mannich-type addition of **6**.

As shown in the **Scheme 3**, Zr (IV) could coordinate both β-dicarbonyl oxygen atoms (**I**) so determining an increase in acidity of methylene protons, which can then be deprotonated by trifluoromethyl aldimine. Finally, an intermolecular nucleophilic attack to form **II** brings to the formation of the expected fluorinated β-amino β-dicarbonyl compounds and restores the catalytic cycle.

Subsequently, in order to develop a catalytic asymmetric Mannich-type reaction, the use of chiral ligand was considered. As reported in the introduction of this thesis, Zr(IV)-BINOL is an efficient organometallic catalyst widely used in the Mannich-type reactions of silyl enol ethers with aldimines.[8] Thus, on the basis of the collected data, the same chiral catalyst was considered for the reaction between the aldimine **1a** and the methyl acetoacetate **6** (**Scheme 4**).

[8]a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154. b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431–432; c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186.



Scheme 4. Mannich-type reaction catalyzed by Zr(IV)-BINOL.

The catalyst was prepared *in situ* starting from zirconium-(IV) *tert*-butoxide [Zr(O*t*-Bu)$_4$] and (*R*)-(+)-1,1′-bi(2-naphthol) as ligand. Unfortunately, the desired product was obtained in low yield and neither diastereo- or enantioselectivities were observed even by changing the reaction temperature.

Therefore, considering the proposed reaction pathway (**Scheme 3**), the optically pure trifluoromethyl aldimine (*R*)-**1c** was considered as suitable chiral auxiliary in the Mannich type reaction with β-keto esters, hoping that the chiral centre on the aldimine could give diastereoselective addition.

The Mannich type reactions were performed with different β-keto esters, $ZrCl_4$ as catalyst and under solvent free conditions. The results are reported in **Table 5**.

Table 5. $ZrCl_4$-catalyzed Mannich-type reaction on optically pure **1c**.

1c **6**: R = CH_3, R' = H, R'' = CH_3
9: R, R' = CH_3, R'' = C_2H_5
10: R-R' = -$(CH_2)_3$-, R'' = C_2H_5
11: R-R' = -$(CH_2)_4$-, R'' = C_2H_5
15: R = CH_3, R' = H, R'' = $C(CH_3)_3$
16: R, R' = CH_3, R'' = $C(CH_3)_3$

anti-**17**,**18** *syn*-**17'**,**18'**
19
20
21
anti-**22**,**23** *syn*-**22'**,**23'**
24

Entry	β-Keto ester	Time (min)	Product	dr[a]	*anti/syn* [a]	Yield (%)[b]
1	**6**	30	*anti*-**17,18** *syn*-**17',18'**	5:5	5:5	72
2	**9**	10	**19**	≥ 9.9	9.9:0.1	68
3	**10**	10	**20**	≥ 9.9	9.9:0.1	78
4	**11**	20	**21**	≥ 9.9	9.9:0.1	78
5	**15**	30	*anti*-**22,23** *syn*-**22',23'**	5:5	5:5	65
6	**16**[9]	30	**24**	≥ 9.9	9.9:0.1	64

[a]Determined by ^{19}F NMR spectra performed on the crude mixtures. [b]After flash chromatography on silica gel.

Starting from (*R*)-**1c** and methyl acetoacetate (**6**), the reaction was successful leading to *syn*-**17/18'***anti*-**17/18'** addition products in good yield, but the stereoselective control failed; in fact all the four possible diastereomers were obtained (entry 1).

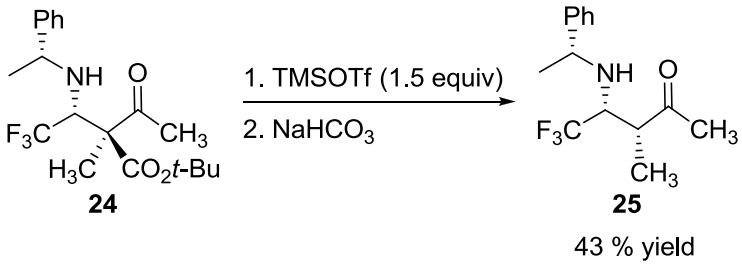
As shown in the entry 5, also the presence of a bulky group in the ester residue did not influence the reaction stereochemistry,[10] in fact with *tert*-butyl ester **15** (entry 5), dr and *anti*/*syn* ratio did not change compared with methyl ester **6** (entry 1). On the contrary, the presence of the ever-increasing steric hindrance on the nucleophilic site led to highly stereocontrol (entry 16).

[9] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834−8837.

[10] See ref.40 in the **Chapter 2**. The authors reported that the absolute configuration of Mannich adducts was reversed when going from a β-keto ester with an ester group derived from a secondary to a tertiary alcohol.

High diastereomeric and *anti*/*syn* ratios were obtained starting from methyl substituted or cyclic methylene active compounds **9-11** and **16** (entries 2-4, 6): in all cases only one of the four possible diastereomers, characterized by the presence of a quaternary chiral center, was obtained.

In order to unequivocally assign the absolute configuration of the quaternary chiral center, as well as the relative configuration *syn* or *anti* of the obtained diastereomers, the diastereoselective decarboxylation of compound **24** was performed (**Scheme 5**), following the procedure reported in the literature.[10]



Scheme 5. Decarboxylation reaction of **24**.

Treatment of the Mannich adduct **24** with trimethylsilyltrifluoromethanesulfonate and saturated aqueous $NaHCO_3$ gave the corresponding ketone **25** and a high diastereoselectivity was maintened in this transformation.

Following an already reported methodology,[11] 2D NOESY ^1H NMR analysis (**Figure 1**).were acquired on **24** and **25** that, coupled with computational studies, permits to assign the relative and the absolute configurations to the C_β and to the C_α, respectively.

[11] a) Fioravanti, S.; Parise, L.; Pellacani, L., Sciubba, F.; Trulli, L. *J. Org. Chem*. **2015**, *80*, 8300−8306 and see ref.29, 54 in the **Chapter 1** and **2**.

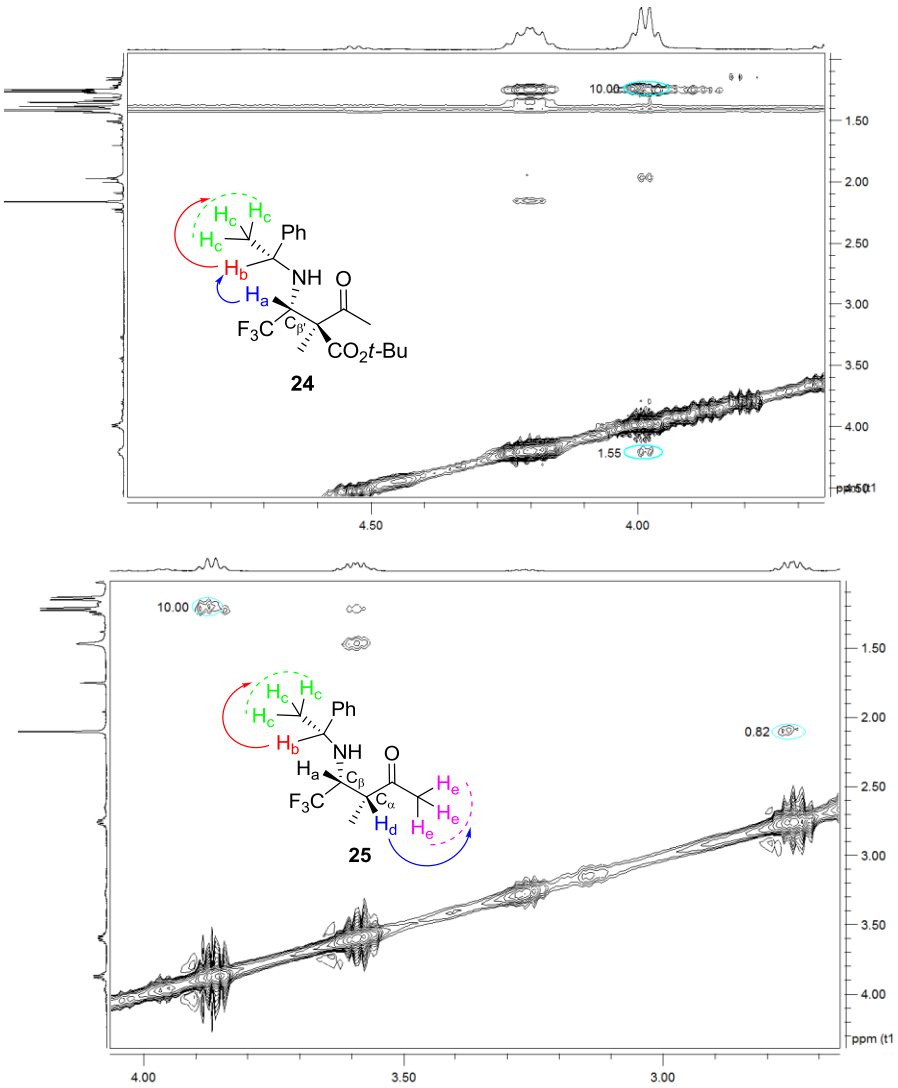


Figure 1. NOESY ^{1}H NMR spectra of **24** and **25**.

The 2D NOESY ^{1}H NMR analysis permitted to determinate the relative interproton distances and thus molecular geometry, by the following equation:

$$\frac{V_X}{V_R} = \left(\frac{d_R}{d_X}\right)^6$$

in which V_R is the volume of the reference cross peak, d_R is the corresponding interproton distance and V_X is the volume relative to the unknown distance d_X.

Therefore, starting from a reference cross peak whose interproton distance is known, it is possible to calculate the distances between other protons.

Since the chiral center on the amine residue has *R* configuration, the interproton distance between H_b and the protons H_c in both **24** and **25** can be considered as a fixed value and used to determine the distance between H_a and H_b in **24** and the distance between H_d and H_e in **25** through the previous equation.

Subsequently, the comparison between the values measured by NOESY spectra with those determined by minimization structure permitted to assign the *R* absolute configuration to C_β for **24**, and the *R* absolute configuration to C_α for *syn*-**25**. As a consequence, the (*R*,*R*,*S*) absolute configuration and the *anti* relative configuration can be assigned to the starting β'-amino β-keto ester **24**. The same (*R*,*R*,*S*) absolute configuration can be assigned to all obtained β'-amino β-keto ester *anti*-isomer **19**, **20**, and **21**(**Figure 2**), for which 2D NOESY ^{1}H NMR spectra were also performed on the purified compounds.

All optimized geometries were located using hybrid functional theory (B3LYP)[12] and the 6-31G(d, p)[13] basis set using the continuum solvation model[14] with chloroform (ε = 4.71) as the solvent conforming to the experimental conditions. All calculations were carried out using the Gaussian 09 program.[15]

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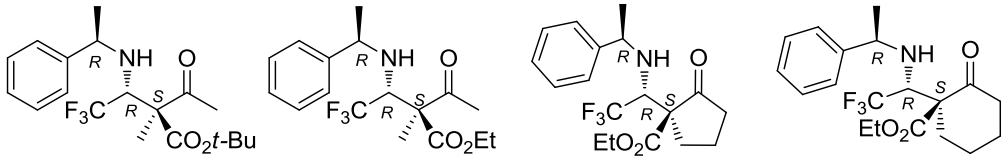
[12]Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 1372–1377.

[13]a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys*. **1971**, *54*, 724–728; b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys*.**1972**, *56*, 2257–2261; c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–223.

[14] Barone, V.; Cossi, M.; Tomasi, J. *J. Comp. Chem*. **1998**,*19*, 404–17.

[15]Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.;Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A. J.; Peralta, E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2013**.



24 **19** **20** **21**

Figure 2. Assigned absolute configurations.

Considering the previously supposed mechanism (**Scheme 3**), it is possible to rationalize the stereochemical outcome of these Zr-catalyzed Mannich-type reactions.

The enolate, coordinated in an octahedral-like intermediate around the zirconium center, is constrained in a planar geometric disposition, which allows the nucleophilic attack take place only on the sterically less hindered prochiral *Re* face of optically pure aldimine (*R*)-**1c** (**Figure 3**).

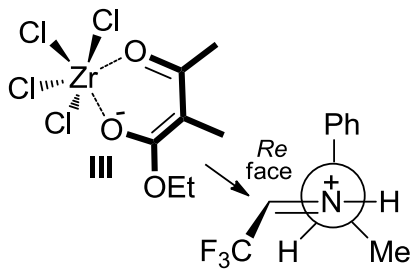
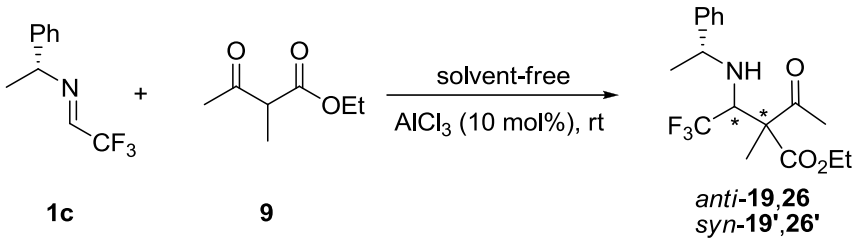


Figure 3. Proposed transition state.

Considering the stereochemical results reported in **Table 5**, a steric hindrance on the *E* double bond of zirconium complex **III** was required to obtain complete stereoselective control.

In fact, starting from unsubstituted acyclic β-keto esters **6** or **16** low dr values and no *syn*/*anti* selectivity was observed.

Therefore, in order to study the importance of zirconium on the high diastereoselectivity observed, the Mannich-type addition reaction between (*R*)-**1c** and **8** was repeated but using $AlCl_3$ as catalyst (**Scheme 6**).



Scheme 6. $AlCl_3$-catalyzed Mannich-type reaction.

As shown by the ^{19}F NMR analysis performed on the crude mixture, $AlCl_3$-catalyzed Mannich-type reaction led to all the four possible diastereomers in equimolar ratios (**Figure 4**).

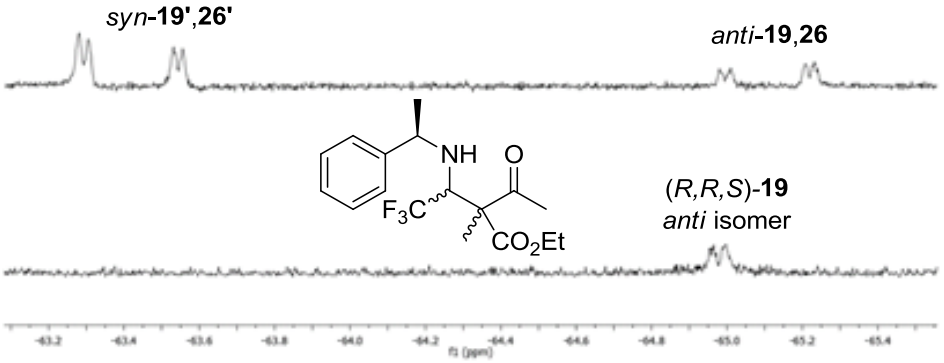
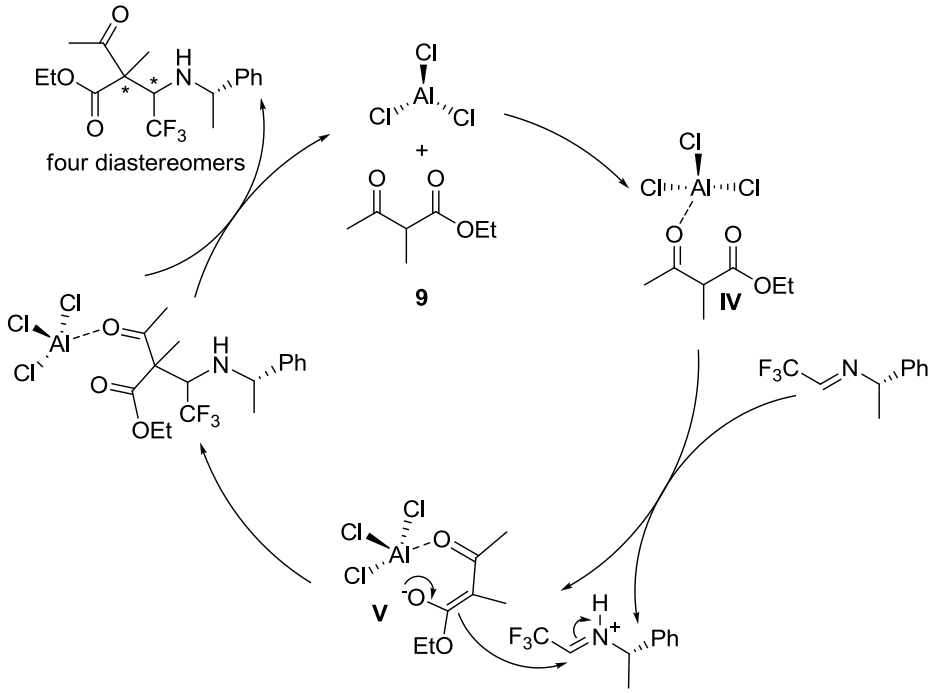


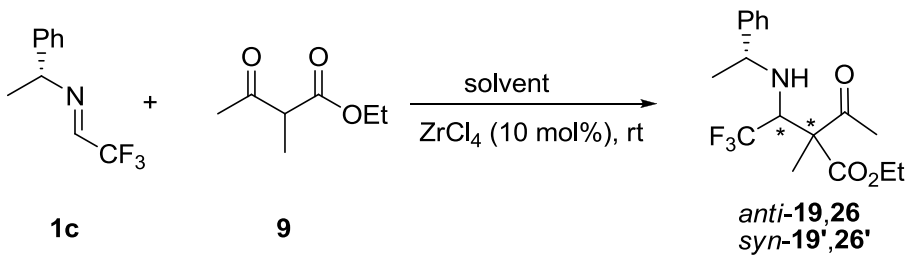
Figure 4. ^{19}F NMR spectra of a mixture of *anti*-**19**, **26** and *syn*-**19′**,**26′** obtained in the presence of $AlCl_3$; only *anti*-**19** isomer obtained in the presence of $ZrCl_4$.

In order to explain the obtained results, a reaction pathway is proposed, in which Al coordinates only the carbonyl oxygen (**IV**) giving, consequently, the acyclic anionic intermediate **V** (**Scheme 7**).



Scheme 7. Proposed pathway for $AlCl_3$-catalyzed Mannich-type addition of **9**.

Finally, the solvent effect on the stereoselective reaction outcome was investigated. Thus, the $ZrCl_4$-catalyzed Mannich-type reaction of **9** with chiral aldimine (*R*)-**1c** (**Scheme 8**)was performed by using some different organic solvents (DMSO, THF, $CHCl_3$, and $PhCH_3$).



Scheme 8. $ZrCl_4$-catalyzed Mannich-type reaction on optically pure **1c** in the presence of the solvent.

The reaction did not occur using DMSO as solvent, probably because $ZrCl_4$ is coordinated to the solvent and no longer available to promote the catalytic cycle. On the other hand, performing the reaction in almost non polar toluene, the Mannich addition takes place in satisfactory yields (68%), but all the four possible diastereomers *anti*-**19**,**26** and *syn*-**19'**,**26'** are formed in equimolar ratios. Indeed,

the use of less polar THF or $CHCl_3$ gave only the diastereomerically pure **19**, although in yields lower than those obtained in reactions performed under solvent-free conditions (32 and 43%, respectively).

Chapter 6

Synthesis of trifluoromethyl 2-imidazolines through Mannich-type reactions with isocyano acetates

The reaction of α-isocyano acetates with imines represents a convenient method for the synthesis of 2-imidazolines, an interesting class of five-membered ring,[1] which can be found in natural product chemistry, in medicinal chemistry, in organic synthesis, in coordination chemistry, and even in homogeneous catalysis.[2] Therefore, the broad utility of these heterocyclic compounds have prompted considerable interest to develop an efficient method for the preparation of trifluoromethyl 2-imidazolines, considering even the general relevance of $-CF_3$ group.

A traditional synthetic approach towards 2-imidazolines usually involves the use of BuLi to generate the nucleophile.[3] Other synthetic methods concerning the use of metal catalyst complexes (Cu, Ag, Au, Pd, Ni),[4] or of weaker bases,[5] or the simultaneous use of both[6] have also been developed.

An alternative strategy involves a direct reaction between primary amines, α-isocyano acetates, and carbonyl compounds performed in the presence of a metal catalyst or even without catalyst,[7] the same imine being able to act as a base.

---

[1] Grimmett, M. R. *Comprehensive Heterocyclic Chemistry*, Eds.: A. R. Katrizky, C. W. Rees, E. F. V. Scriven, Pergamon, Oxford, **1996**, *3*, 77–120.

[2] a) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010–5017; b) Rondu, F.; Bihan, G. L.; Godfroid, J. J. *J. Med. Chem.* **1997**, *40*, 3793–3803, c) Haiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586–3591; d) Liu, H.; Du, D.-M. *Adv. Synth. Catal.* **2009**, 351, 489–519 and references therein; e) Dalko, P. I.; Langlois, Y. *Chem. Commun.* **1998**, 331–332.

[3] Both activated and unactivated isocyanides can successfully be deprotonated because of the high basicity of BuLi. a) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs Ann. Chem.* **1977**, 1183−1193, b) van Leusen, D.; van Leusen, A. M. *Org. React.* **2001**, *57*, 417−666.

[4] Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969−4972.

[5] Zhang, Z.; Lu, G.; Chen, M.; Lin, N.; Li, Y.; Hayashi, T.; Chan, A. S. C. *Tetrahedron:Asymmetry* **2010**, *21*, 1715–1721.

[6] Qi, X.; Xiang, H.; Yang, C. *Org. Lett.* **2015**, *17*, 5590–5593.

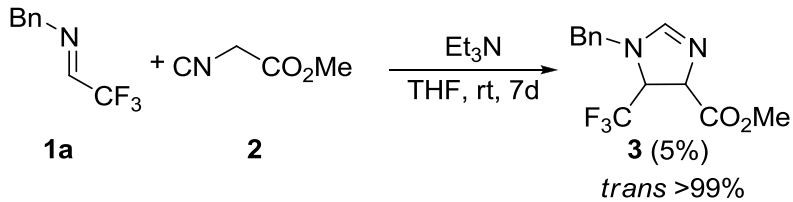
[7] a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L. *Org. Lett.* **2003**, *5*, 3759-3762. b) Bon, R. S.; van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; de Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2005**, *70*, 3542–3553. c)

Recently also catalytic asymmetric Mannich-type/cyclization cascade reactions between α-isocyano acetates and imines has received much attention.[8]

6.1 Preliminary studies

At first an equimolar ratio of (*E*)-1-phenyl-*N*-(2,2,2-trifluoroethylidene)methanamine (**1a**) and methyl 2-isocyanoacetate (**2**) was reacted without catalyst but no reaction occurred, not even changing the reaction conditions (solvent, temperature, molar ratio), and both reagents were quantitatively recovered.

Therefore, starting from data reported in the literature,[5] different inorganic or organic bases were considered to promote the nucleophile formation: the expected product was obtained only by using Et_3N as added base and THF as solvent in very low yield (**Scheme 1**) but high diastereoselectivity, only *trans* isomers being detected.[9]



Scheme 1. Base catalyzed Mannich-type reaction.

Therefore, to increase the reaction yield, a Lewis acid catalysis was attempted, hoping that the coordination of a metal at the terminal isocyano acetate carbon allows for an easier α-deprotonation.

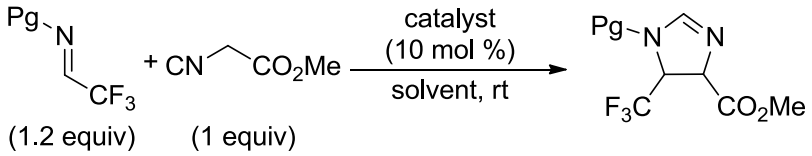
Elders, N.; Schmitz, R. F.; de Kanter, F.J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem*. **2007**, *72*, 6135–6142.

[8] a) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855−862. b) Shao, P.-L.; Liao, J.-Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5435−5439. c) Nakamura, S.; Maeno, Y.; Ohara, M.; Yamamura, A.; Funahashi,
Y.; Shibata, N. *Org. Lett.* **2012**, *14*, 2960−2963. d) Ortín, I.; Dixon, D. J. *Angew. Chem., Int. Ed*. **2014**, *53*, 3462−3465. e) de la Campa, R.; Ortín, I.; Dixon, D. J. *Angew. Chem., Int. Ed*. **2015**, *54*, 4895–4898.

[9] The *trans* relative configuration was assigned by comparing H/H coupling constant values ($^3J_{trans}$ = 5.0−6.0 Hz) reported in the literature for similar compounds. a) Xie, H., Zhu, J.; Chen, Z.; Li, S.; Wu, Y. *J. Org. Chem*. **2010**, *75*, 7468–7471. b) Aydin, J.; Kumar, K. S.; Eriksson, L.; Szabò, K. J. *Adv. Synth. Catal*. **2007**, *349*, 2585–2594

Considering the successful use of $ZrCl_4$ as catalyst in the Mannich-type reactions of 1,3-dicarbonyl compounds (see **Chap. 5**), this Lewis acid was added in catalytic amounts in the reaction between **1a** and **2**, but only a complex reaction mixture was formed. Thus, to promote the Mannich-type/cyclization cascade reaction of isocyano acetate **2** with *N*-protected trifluoromethyl aldimine **1a** some classic silver derivatives were considered (**Table 1**).

Table 1. Optimization of the reaction conditions of **2**.



(1.2 equiv) (1 equiv)

1a-b **2** **3a**,**b**

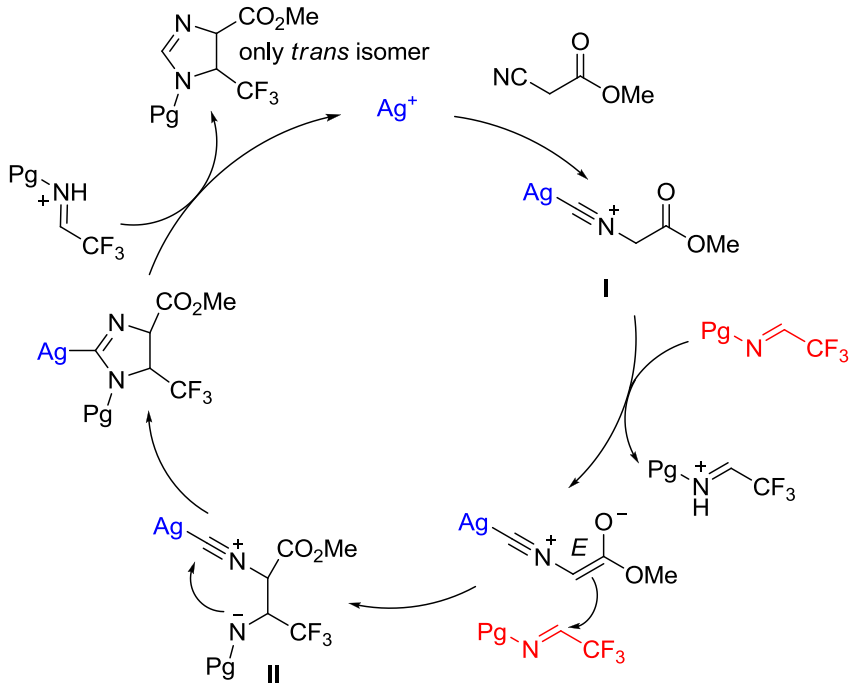
Pg: **a** = Bn, **b**= PMP *trans* > 99%

Entry	Pg	Product	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	Bn	**3a**	AgOAc	THF	22	46
2			$AgNO_3$	THF	24	52
3			Ag_2O	THF	18	60
4			Ag_2O	CH_2Cl_2	20	62
5			Ag_2O	DMSO	15	66
6			Ag_2O	NMP	15	63
7			Ag_2O	DMF	15	65
8			Ag_2O	EtOH	16	45
9			Ag_2O	iPrOH	15	40
10			Ag_2O	-	5	85
11	PMP	**3b**	Ag_2O	-	5	88

[a] After flash chromatography on silica gel.

As shown in **Table 1**, Ag_2O turned out to be the best catalyst compared to AgOAc and $AgNO_3$ (entries 1-3); in fact the desired product *trans*-**3a** was obtained in higher yield and in shorter time. Then, the Ag_2O-catalyzed Mannich-type reaction was repeated by changing the solvent, ranging from polar aprotic and protic (entries 3−9), but the performance of addition does not seem to be influenced by the solvent nature. On the contrary, working under solvent-free condition (entry 10), *trans*-**3a** was obtained in shorter time and in very high yield and purity. Working under the same solvent-free conditions, imidazoline *trans*-**3b** (entry 11)

was successfully obtained starting from *N*-protected trifluoromethyl aldimine **1b.** On the basis of collected data, a possible reaction mechanism is proposed in **Scheme 2**.



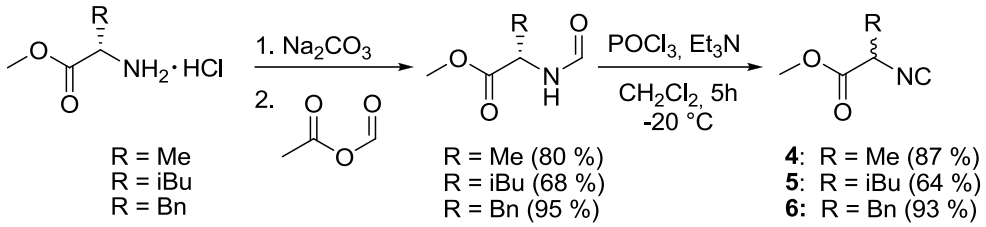
Scheme 2. Possible reaction mechanism.

The silver-isocyano acetate complex **I**, generated according to the literature,[10] is deprotonated by a molecule of trifluoromethyl aldimine and, then, the attack of a second molecule of aldimine, leads to **II**. The ring closure reaction followed by the exchange silver(I) cation/proton provides the 2-imidazoline.

[10] a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev*. **2010**, *110*, 5235–5331; b) Bon, R. S.; van Vliet, B.; Sprenkels, N. E.; Schmitz, R. F.; Kanter, F. J. J.; Stevens, C. V.; Swart, M.; Bickelhaupt, F. M.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem*. **2005**, *70*, 3542–3553

6.2 Reaction scope

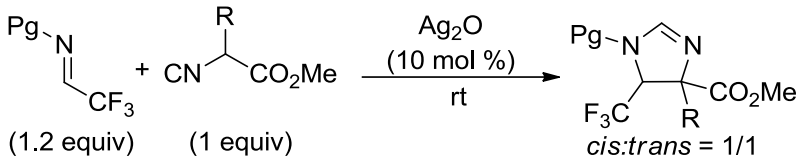
In order to explore the reaction scope, additional α-isocyano esters (**4-6**), prepared by α-amino acid methyl ester hydrochlorides were obtained in high purity and yield (**Scheme 3**), through slight modifications of standard protocols,[11]



Scheme 3 Synthesis of different α-isocyano esters.

and then considered in the Mannich-type reactions with aldimines **1a-b**. The results are reported in **Table 2**.

Table 2. Mannich-type reactions of α-isocyano esters **4-6**.



1a,b **4-6** **7/7'-9/9'a,b**

Entry	R	Pg	Product	Solvent	Time (h)	Yield (%)[a]
1	Bn	Me	**7/7'a**	–	4	60
2	PMP		**7/7'b**	–	4	48
3	Bn	iBu	**8/8'a**	CH_2Cl_2	16	45
4	PMP		**8/8'b**	CH_2Cl_2	16	55
5	Bn	Bn	**9/9'a**	CH_2Cl_2	12	38
6	PMP		**9/9'b**	CH_2Cl_2	10	40

[a] After flash chromatography on silica gel.

While in all cases the stereoselectivity was completely lost,[12] the reactions involving **4** proceeded as expected under solvent-free conditions (entries 1-2). On

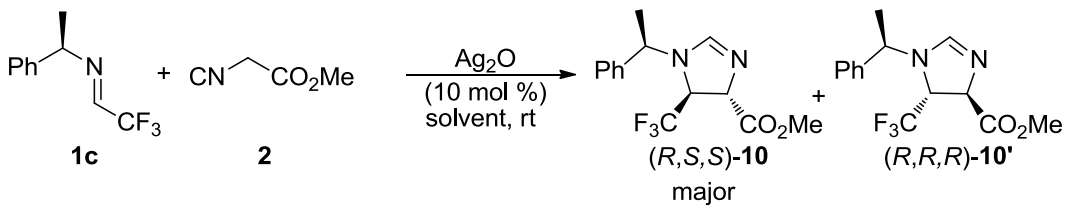
[11] Elders, N.; Schmitz, R. F.; Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135-6142.

[12] Even by changing the reaction conditions (molar ratios, silver catalysts, and temperature) no improvements of stereoselectivity were observed.

the contrary, starting from **5** or **6** the use of CH_2Cl_2 as solvent was required to afford the desired products albeit in moderate yields (entries 3-6), showing that these reactions suffer from the steric hindrance on the α carbon, that can determine the decrease of yields and the increase of reaction time. Moreover, the substituent on the nucleophile carbon could be responsible also for the similar energy between the *E* and *Z* enolates, resulting in a total loss of geometric selectivity, which instead is controlled by the formation of the only *E* enolate isomer of α-isocyano acetate **2**.

6.3 Control of stereofacial induction

Turning the interest towards the possible stereofacial attack, the Mannich-type additions were performed starting from the optically pure aldimine **1c**. The presence of an α-alkyl substituent on the imine nitrogen coupled with an R group of isocyano acetates **4-6** seems to approach the limits for these Mannich-type reactions, the expected products being obtained only in traces. On the contrary, the Mannich-type reaction between methyl 2-isocyanoacetate (**2**) and the imine **1c**, performed under solvent-free conditions, afforded the expected *trans* 2-imidazolines (**Scheme 4**) but in very low diastereomeric ratio (dr = 6:4), even when the reactions were attempted at lower temperatures (from −20 to 0 °C). Anyway, the diastereomers could be separated between them by flash chromatography on silica gel, and diastereomerically pure compounds **10** (major isomer) and **10′** (minor isomer) were obtained.[13]



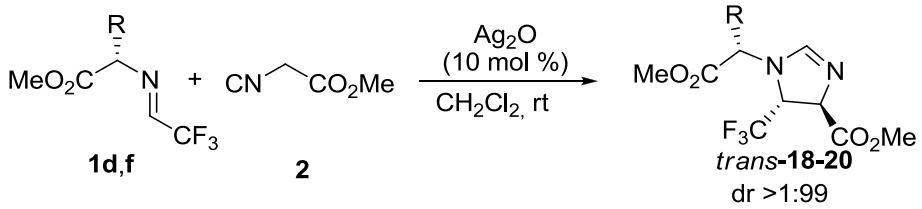
Scheme 4. Mannich-type reactions on optically pure aldimine **1c**.

[13] For these latter, the absolute configurations were determinate using the same previously described methodology (see **Chap 5**, pp. 59−60) involving computational studies coupled with the data obtained from 2D NOESY NMR spectra.

With the hope to increase the stereofacial induction, very interesting optically active trifluoromethyl aldimines deriving from L-α-amino esters[14] were considered.

The additions of **2** to aldimines **1d-f** occurred with very high diastereoselectivity, leading in all cases only to (*S*,*R*,*R*) diastereomers. The results are reported in **Table 3**.

Table 3. Mannich-type reactions on aldimines **1d-f**.



Entry	**1**	R	Product	Yield (%)[a]
1	**d**	iPr	**18**	39
2	**e**	iBu	**19**	30
3	**f**	Bn	**20**	28

[a]After flash chromatography on silica gel.

To explain the high diastereoselectivity and the absolute configurations obtained, a possible transition state could be suggested (**Figure 1**).

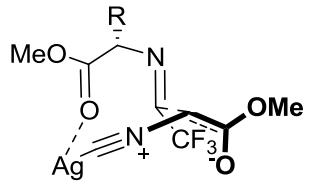


Figure 1. Proposed transition state.

The imine ester group could be coordinate by silver of the activated methyl 2-isocyanoacetate (**2**). This interaction could create a well-defined chiral pocket that can readily differentiate the enantiotopic faces of aldimine, favoring the attack of the enolate preferentially to the *Re* imine face and the formation of enantiopure valuable trifluoromethyl imidazolidines, enriched by an α-amino acid residue.

[14] See ref. 54 in the **Chapter 2**.

Chapter 7

Aza-Reformatsky reactions on trifluoromethyl aldimines

Fluorinated 1,2- and 1,3-difunctionalized compounds, including β-amino esters as well as nitrogen heterocycles like β-lactams, could have a variety of interesting biological properties, making them useful and versatile synthetic intermediates in organic synthesis. β-Amino esters and β-lactams could be obtained through the aza-Reformatsky reaction. Thus, the aim of this chapter is the study of the reactivity of trifluoromethyl aldimines in the aza-Reformastky reaction.

7.1 Heterogeneous conditions

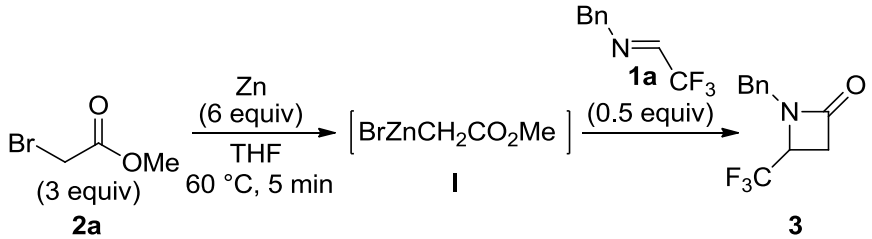
7.1.1 Preliminary studies

The preliminary aza-Reformatsky reaction was performed between methyl-2-bromoacetate (**2a**) and trifluoromethyl aldimine **1a**. A two-step procedure was used: in the first step the Reformatsky reagent (**I**) was synthesized by refluxing **2a** with freshly-activated zinc dust; after 5 min at 60 °C, 0.5 equiv of aldimine **1a**[1] were added.

Different reaction conditions were screened in order to find an efficient methodology: in all cases the reaction lead to the formation of only β-lactams (**Table 1**).

[1] See ref.17 in the **Chapter 1**.

Table 1. Optimization of the reaction conditions on methyl-2-bromoacetate (**2a**).

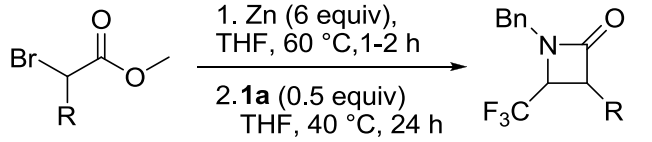


Entry	Solvent	T[b](°C)	Time (h)[b]	Yield **3** (%)[c]
1	THF	25	36	–
2	THF	40	18	79
3[a]	THF	40	20	35
4	CH_2Cl_2	40	36	20
5	$PhCH_3$	40	36	36

[a]Reaction performed by using the following molar ratios **1a**/Zn/**2a** = 3:3:0.5. [b]Relative to the second step. [c]After flash chromatography on silica gel.

Initially, using THF as solvent, the addition of **1a** was carried out at room temperature (entry 1), but after 36 h only the same aldimine was recovered. Increasing the addition step temperature (40 °C, entry 2), the expected product was obtained in very good yields. Decreasing the amount of metal Zn (entry 3), β-lactam **3** was obtained in lower yield as well as changing the reaction solvent (entries 4 and 5). Interestingly, following the reactions by ^{1}H NMR spectroscopy, in all cases only the simultaneous disappearance/appearance of the aldimine **1a** signals and those of β-lactam **3**, respectively, was observed. It is important to underline that the signals relating to a possible β-amino ester intermediate were not detected.

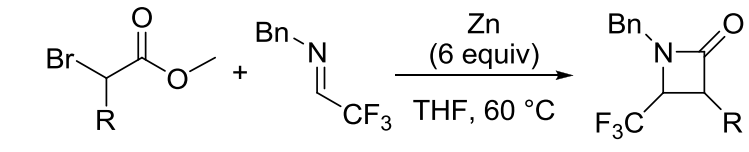
With the optimal two-step reaction conditions in hand, the heterogeneous aza-Reformatsky reaction was investigated starting also from α-bromo esters **2b**,**c** (**Scheme 1**).



Scheme 1. Aza-Reformatsky reactions on α-bromo esters **2b**,**c**.

Unexpectedly, while the reaction with α-bromo ester **2b** proceeded smoothly leading to *trans*-**4**,[2] although in very low yield, the reaction did not occur by using **2c**, even by chancing some reaction conditions (solvent, temperature and/or molar ratios). Hoping to get better results, a one-pot procedure was tested, following a procedure reported in the literature (**Table 2**).[3]

Table 2. One-pot Aza-Reformatsky reactions on α-bromo esters **2b**,**c**.



Entry	R	Time (h)	Product	*trans*:*cis*[a]	Yield (%)[b]
1	Me	18	*trans*-**4**	>99:1	70
2	Ph	10	*trans*-**5**	>99:1	83

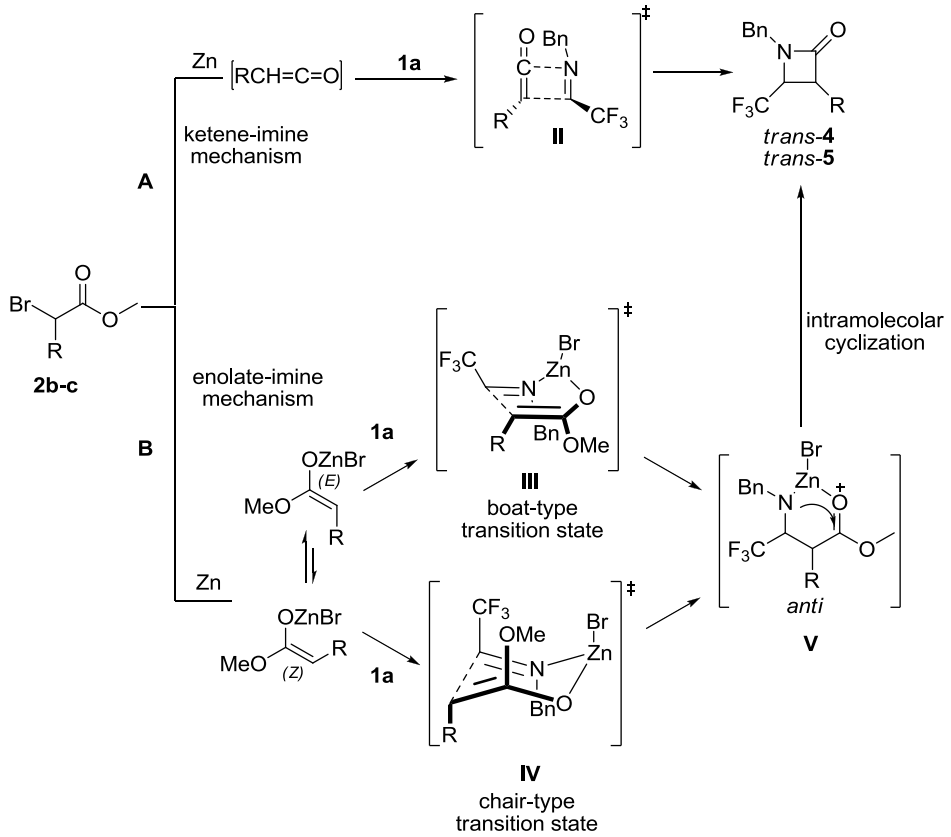
[a]Determined by ^{19}F NMR spectra of the crude reaction mixture. [b]After flash chromatography on silica gel.

As shown in **Table 2**, aldimine **1a** was converted into the products *trans*-**4**,**5** in good yield by a convenient one-pot protocol. Once again, only β-lactams in *trans* configuration were achieved, showing that reactions proceeded also with high diastereoselectivity.

[2] The *trans* relative configuration was assigned by comparing the H/H coupling constant values ($^3J_{trans}$ = 1.5−2.5 Hz; $^3J_{cis}$ = 4.5−6.0 Hz) of ring protons and the δ values of −CF_3 group on the ^{19}F NMR spectra recorded by us with those reported in the literature for similar compounds: Bevilacqua P. F.; Keith D. D.; Roberts J. L. *J. Org. Chem*. **1984**, *49*, 1430−1434.

[3] Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Lett*. **2010**, *51*, 2000−2003.

To explain this, two possible reaction pathways can be suggested: a *via* ketene-imine mechanism[4] or an addition-cyclization mechanism[5] (**Scheme 2**).[6] The former hypothesized that the reaction was occurring *via* a ketene Staudinger-type mechanism (**A**). The ketene, formed by α-bromo ester due to the presence of Zn,[7] could add to imine through a formal [2+2] cycloaddition, leading to *trans* β-lactam *via* the favored transition state **II**.



Scheme 2. Proposed reaction pathways.

Alternatively, the zinc enolate addition to the (*E*)-aldimine could lead to the *anti*-β-amino ester (**V**), never detected during these reactions, which quickly cyclize giving the corresponding *trans* β-lactam (**Scheme 2**, **B**).

[4] Jian, S.-Z.; Ma, C.; Wan, Y.-G. *Synthesis* **2005**, *5*, 725–730.

[5] Hart, D. J.; Ha, D. C. *Chem. Rev*. **1989,** *89,* 1447-1465.

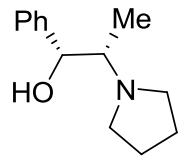
[6] For brevity only the synthesis of one enantiomer has been reported.

[7] Hafner, A.; Ley, S. V. *Synlett* **2015,** *26*, 1470–1474

In the last hypothesis, the stereochemical data could be rationalized through a rigid cyclic chair- and/or a boat-type transition states, depending by the *E* or *Z* enolate configuration. Whereas the *E* isomer should be the most stable, only the boat-like transition state **III** could be invoked to explain the observed *trans* diastereoselectivity of the addition,[8] because the chair Zimmerman-Traxler transition state would give *cis* β-lactam. However, such as reported in the literature,[9] it cannot be excluded that both isomers are in fast equilibrium between them and that the minor *Z* isomer reacts, through a chair-type transition state (**IV**), much faster than the *E* enolate, leading to the *anti*-β-amino ester (**V**).

7.1.2 Enantio- and diastereoselective studies

In order to achieve optically pure *trans* β-lactams, a suitable chiral ligand was considered, namely the inexpensive and commercially available amino alcohol (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**6**, **Figure 1**), already used in the asymmetric Reformatsky reaction.[10]



(1*R*,2*S*)-**6**

Figure 1. (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol.

To test the enantioselective addition, methyl 2-bromoacetate (**2a**) and imine **1a** were reacted both under two-step (**A**) and one-pot (**B**) conditions (**Scheme 3**).

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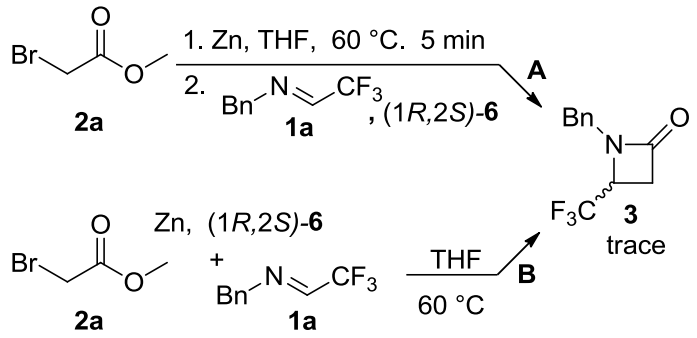
[8] a) Georg, G. I.; Harriman, G. C. B.; Hepperle, M.; Clowers, J. S.; Vander Velde, D. G.; Himes, R. H. *J. Org. Chem* **1996**, *61*, 2664−2676. b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Martini, O.; Molteni, V. *Tetrahedron*. **1996**, *52*, 2583−2590. c) Ishihara, T.; Ichihara, K.; Yamanaka, H. *Tetrahedron*, **1996**, *52*, 255−262. d) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron*. **1996**, *52*, 1685−1698. e) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry, Stereoselective Aldol Condensations*, ed. by N.L. Allinger, E. L, Eliel and S. H. Wilen, Wiley, New York (**1982**).

[9] a) Maanen, H.; Kleijn, H.; Jastrzebski, J. T. B. H.; Van Koten, G. *Bull Soc Chim Pr* **1995,** *132*, 86−94. b) Van der Steen, F.H.; Kleijn, H.; Jastrzebski, J. T. B. H.; Van Koten, G. *J. Org. Chem*. **1991**, *56*, 5147−5158. c) Van der Steen, F.H.; Kleijn, H.; Britovsek, G. J.P.; Jastrzebski, J. T. B. H.; Van Koten, G. *J. Org. Chem*. **1992**, *57*, 3906−3916.

[10] a) Andrés, J. M.; Martinez, M. A.; Pedrosa, R.; Pèrez-Encabo, A. *Synthesis* **1996**, 1070−1072. b) Kloetzing, R. J.; Thaler, T.; Knochel, P. *Org. Lett.* **2006**, *8*, 1125−1128

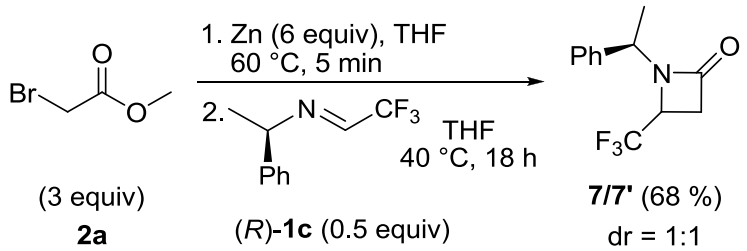


Scheme 3. Enantioselective Reformatsky reactions.

The classical two-step reaction was attempted at high temperature (the second step was performed at a range between 40−60 °C) also by using a large excess (12 equiv) of Zn metal, but **3** was still obtained in very low yield (10 and 18 % respectively) and as a racemic mixture, as determined by chiral HPLC analyses. On the contrary, working at lower temperature (0 and 25 °C) no reaction occurred and both aldimine **1a** and α-bromo ester **2a** were recovered in all cases.

Consequently, a one-pot procedure was considered, but again the β-lactam was obtained only in trace and as a racemic mixture.

Failed the enantioselective control, we attempted to obtain chiral β-lactams starting from optically pure trifluoromethyl aldimine (*R*)-**1c**,[1] still bearing a benzyl residue on the nitrogen atom easily removable under mild hydrogenolytic conditions (**Scheme 4**).

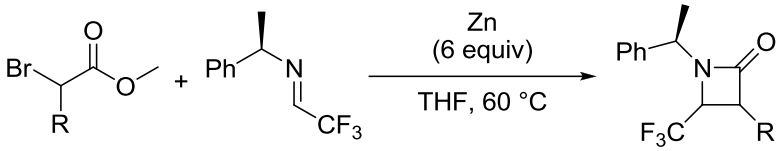


Scheme 4. Aza-Reformatsky reactions on optically pure **1c**.

The reaction successfully gave the expected β-lactams **7/7′** in satisfactory yield, but once again no selectivity was observed. However, hoping that an

increasead steric hindrance on the pre-nucleophile species could give better results, the one-pot aza-Reformatky reactions were performed even by using α-bromo esters **2b-c** (**Table 3**).

Table 3. Aza-Reformatsky reactions on optically pure **1c**.



2b-c (3 equiv) (*R*)-**1c**
R: **b** = Me, **c** = Ph (0.5 equiv)

trans-**8/8'**
trans-**9/9'**

Entry	R	Time (h)	Product	dr[a]	*trans*:*cis*[a]	Yield (%)[b]
1	Me	12	**8/8′**	1:1	>99:1	65
2	Ph	15	**9/9′**	1:1	>99:1	61

[a]Determined by ^{19}F NMR spectra of the crude reaction mixture.
[b]After flash chromatography on silica gel.

Once again, high yields and high geometric selectivity were obtained, the only diastereomers *trans*-**7/7′** and **8/8′** being obtained, but no stereoinduction was observed (dr = 1/1), probably due to the high required reaction temperature.

All diastereomers were purified by flash chromatography on silica gel to obtain optically pure compounds; absolute configurations of the newly formed stereocenters (**Figure 2**) was assigned by 2D NOESY ^{1}H NMR spectra coupled with geometric optimization processes through the reported methodology (see **Chap 5**, pp 58-59).[11]

[11] See ref.11 in the **Chapter 5**.

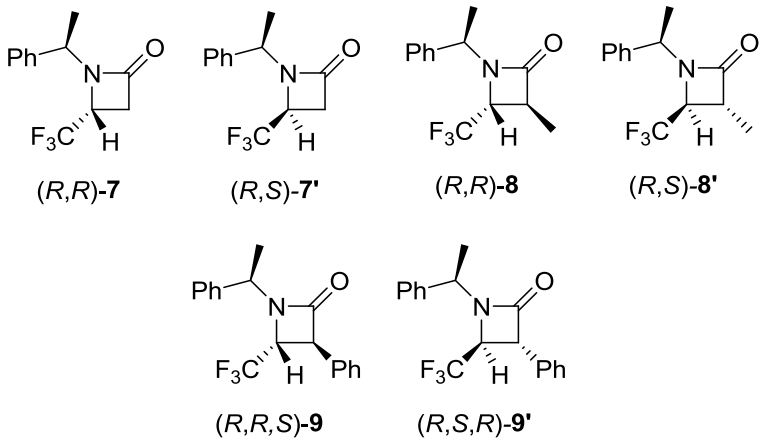


Figure 2. Assigned absolute configurations.

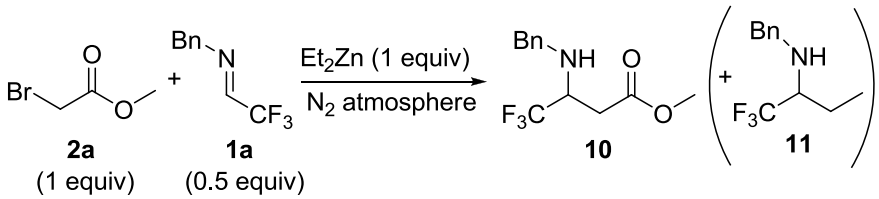
7.2 Homogeneous conditions

Then, the interest has been directed towards the aza-Reformatsky reactions on trifluoromethyl aldimines under homogeneous conditions, by using commercially available Et_2Zn as source of metal.

7.2.1 Preliminary studies

The investigation begin by reacting methyl 2-bromoacetate (**2a**) and trifluoromethyl aldimine **1a** in the presence of diethylzinc, changing some reaction parameters (**Table 4**).

Table 4. Optimization of the homogeneous aza-Reformatsky reaction conditions on **1a**.



Entry	Solvent	T(°C)	Time	Yield of **10** (%)[a]
1	THF	40	12 h	-
2	THF	25	36 h	5
3	THF	0	3 d	-
4	THF	−10	3 d	-
5[b]	THF	25	36 h	-
6	CH_2Cl_2	25	24 h	68

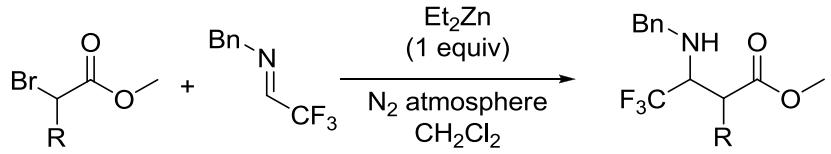
[a]After flash chromatography on silica gel. [b]Performed by using 1 equiv of **2a**

Working in THF at 40 °C (entry 1), a very complex crude mixture was recovered after 12 h. At room temperature, only β-amino ester **10** was formed but in trace (entry 2). Furthermore, decreasing the reaction temperature (entries 3, 4), the major observed product was the adduct **11**, resulting from the addition of diethylzinc to aldimine **1a**, even working in equimolar ratios (entry 5). Finally by changing the reaction solvent (from THF to CH_2Cl_2, entry 6), only **10** was achieved in satisfactory yield.

It must be emphasized that, working under homogeneous conditions, β-lactam **3** was not observed in any case even in trace, on the contrary to what reported in the literature for analogous aza-Reformatsky reactions performed on unfluorinated aldimines.[12]

Thanks to the more reactivity of diorganozinc reagents (R_2Zn)[13] obtained using Et_2Zn, we are able to promote the reaction at room temperature and, since only β-amino esters were obtained, the enolate-imine mechanism is the only reasonable Then, the best homogeneous aza-Reformatsky reaction conditions has been extended to the α-bromo esters **2b-c**. The results are reported in **Table 5**.

Table 5. Homogeneous aza-Reformatsky reactions.



2b-c (1 equiv) (0.5 equiv) *syn*-**12**
R: **b** = Me, **c** = Ph **1a** *anti*-**13**

Entry	R	Temp (°C)	Time (d)	Product	*syn*:*anti*[a]	Yield (%)[b]
1	Me	25	3	*syn*-**12**	>99:1	44
2		0	3		>99:1	56
3		−20	9		>99:1	60
4	Ph	25	3	*anti*-**13**	>1:99	40
5		0	5		>1:99	48
6		−20	10		>1:99	57

[a]Determined by ^{19}F NMR spectra of the crude reaction mixture. [b]After flash chromatography on silica gel.

[12] Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Miwa, Y.; Minami, H.; Ando, A. *Tetrahedron Letters* **2010**, *51*, 2000–2003.

[13]a) Knochel, P; Perea, J. J. A.; Jones, P. *Tetrahedron*, **1998**, *54*, 8275−8319; b) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*, Oxford Press, **1999.**

As shown in **Table 5**, the reactions proceeded smoothly to afford only β-amino esters in satisfactory yields, which increase when temperatures decrease (entries 3 and 6). Concerning the diastereoselective reaction outcome, the *syn* or *anti* selectivity was observed depending from the different starting α-bromo esters **2b-c**, namely starting from **2b**, only β-amino ester *syn*-**12** was obtained and from **2c** only the isomer *anti*-**13** was formed.[14]

Assuming the enolate in the only *E* configuration, two possible transition states, chair-like transition state **VI** for *syn*-**12** and boat-like transition state **VII** for *anti*-**13**, can be invoked in order to rationalize the different stereochemical results (**Figure 3**).[8] This difference is probably due to the increased planarity of the (*E*)-enolate resulting from **2c**, by favouring the boat-like transition state **VII**.[15]

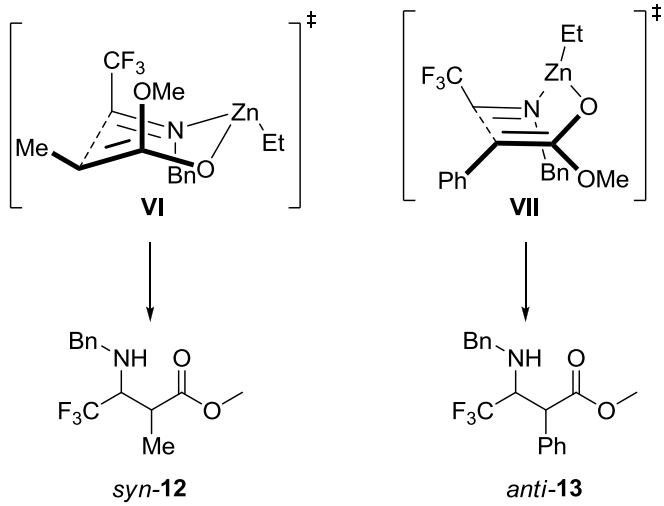


Figure 3. Proposed transitions states.

In order to confirm the relative configuration of both, the homogeneous aza-Reformatsky reactions were repeated and the obtained β-amino ester crude mixtures were allowed to rise to 25 °C to promote the intramolecular cyclization (14 d, **Scheme 5**).

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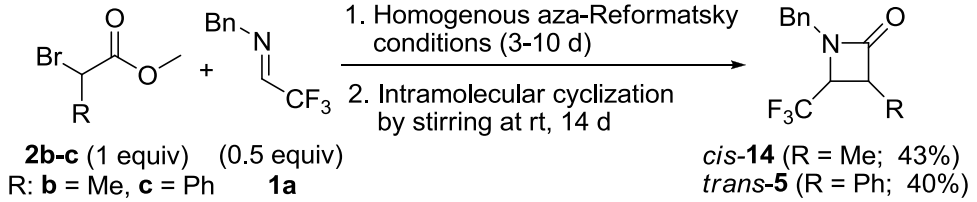
[14] The *syn* and *anti* relative configurations were assigned by comparing H/H coupling constant values ($^3J_{syn}$= 6.5−7 Hz; $^3J_{anti}$= 8.5−9 Hz) with the data reported in the literature. Stiles, M.; Winkler, R. R.; Chang, Y.-L.; Traynor, L. *J. Am. Chem. Soc.*, **1964**, *86*, 3337–3342.

[15] The *anti*- stereochemistry could be also explained through a chelated six-membered chair transition involving the *Z* enolate (see p. 78, ref. 9).



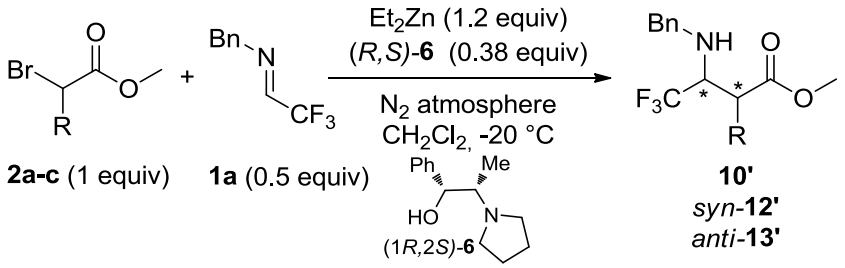
Scheme 5. Homogeneous aza-Reformatsky reactions followed by intramolecular cyclization.

As expected, β-lactams *cis*-**14** and *trans*-**5** were obtained starting from *syn*-**12** and *anti*-**13**, respectively.

7.2.2 Enantio- and diastereoselective studies

As reported in the introduction (see **Chap. 3**) homogeneous conditions could make the development of asymmetric aza-Reformatsky reaction easier. Therefore, in order to achieve enantioselective reaction control, the aza-Reformatsky additions of α-bromo ester **2a-c** on **1a** were performed in the presence of chiral amino alcohol (*R,S*)-**6** by using a moderate excess of Et_2Zn. The results are reported in **Table 6**.

Table 6. Enantioselective homogeneous aza-Reformatsky reactions.



Entry	R	Time (d)	Product	*syn*:*anti*[a]	Yield(%)[b]	ee (%)[c]
1	H	5	**10′**	–	50	98
2	Me	6	*syn*-**12′**	>99:1	52	98
3	Ph	9	*anti*-**13′**	>1:99	58	91

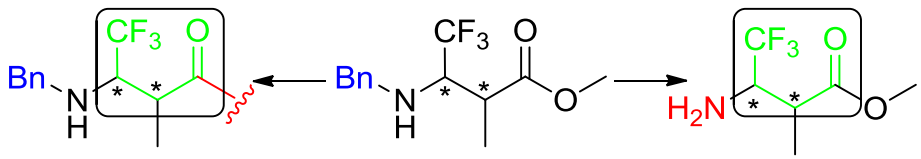
[a]Determined by ^{19}F NMR spectra of the crude reaction mixture. [b]After flash chromatography on silica gel. [c]Determined by chiral HPLC.

The expected β-amino esters **10′**, *syn*-**12′** and *anti*-**13′** were obtained in satisfactory yields and excellent enantioselectivity.

7.3 Synthetic elaboration of obtained compounds: synthesis of ψ[CH(CF$_3$)NH]-peptidomimetic precursors

In order to demonstrate the utility of optically pure β-amino β-trifluoromethyl ester *syn*-**12′**, the synthesis of small ψ[CH(CF$_3$)NH]-peptidomimetic precursors was considered through appropriate chemical transformations.

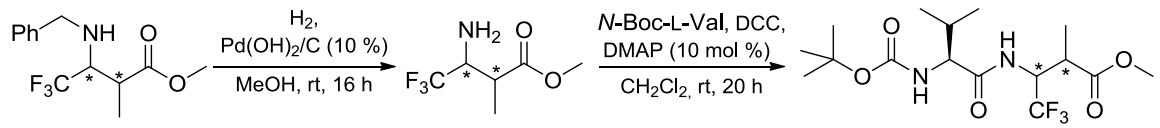
In fact, the obtained compounds can be considered as starting point for the synthesis of peptidomimetics precursors characterized by a chiral ψ[CH(CF$_3$)NH][16] cores in which a carbonyl group is replaced by its isoster, the -CHCF$_3$ group. Two are the possible molecular growth sites: the carboxylic group, that after methyl ester group removal permits a *C*-terminal molecular growing or to fix the trifluoromethylated core to solid matrix, and a free NH$_2$ moiety obtainable by a benzyl group hydrogenolysis reaction (**Scheme 6**).



Scheme 6. Molecular growth sites.

The second chemical elaboration was considered, to obtain the primary amine group as molecular growing site.

After removal of the benzylic residue, DCC coupling reaction with the *N*-Boc-L-Val was performed on *syn*-**14′** following the classical conditions (**Scheme 7**).[17]



12' **14'** (98% ee; 30%) **15'** (43%) only one diastereomer

Scheme 7. Synthesis of **15′**.

[16] a) Aresu, E.; Fioravanti, S.; Gasbarri, S.; Pellacani, L.; Sciubba, F. *RSC Adv*. **2013**, *3*, 13470-13476; b) Aresu, E.; Fioravanti, S.; Gasbarri, S.; Pellacani, L.; Ramadori, F. *Amino Acids* **2013**, *44*, 977-982 and see ref.30 in the **Chapter 1**.

[17] Fioravanti, S.; Massari, D.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2008**, *64*, 3204−3211.

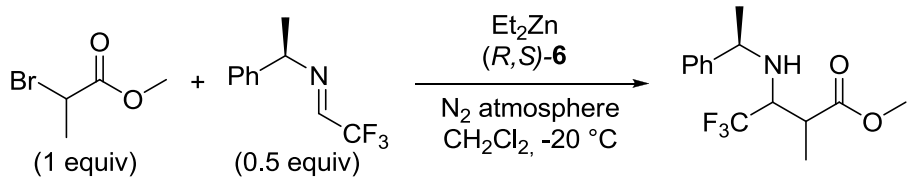
The coupling reaction gave in satisfactory yields the corresponding **15′** as a pure diastereomer compound.

7.4 Determination of the absolute configuration

In order to assign unequivocally the absolute configuration of the new chiral centers formed in the organocatalyzed aza-Reformatsky reactions and hence to the diastereomer **15′**, the addition reactions was repeated starting from the chiral aldimine (*R*)-**1c** and further chemical modifications were required.

To begin the study, trifluoromethyl aldimine (*R*)-**1c** and **12b** were reacted, either in the presence or in the absence of the chiral ligand **6** (**Table 7**).

Table 7. Homogeneous aza-Reformatsky reactions on optically pure **1c**.

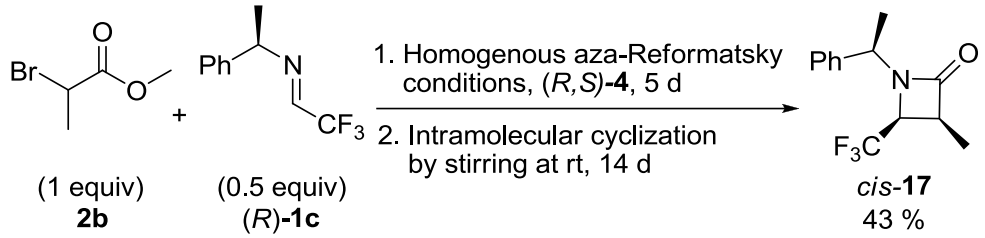


(1 equiv) **2b** (0.5 equiv) (*R*)-**1c** *syn*-**16**,**16'**

Entry	Time (d)	**6** (equiv)	Et_2Zn (equiv)	Product	dr[a]	*syn:anti*[a]	Yield (%)[b]
1	6	-	1	**16/16′**	1:1	>99:1	68
2	5	0.38	1.2	**16′**	>99:1	>99:1	49

[a]Determined by ^{19}F NMR spectra of the crude reaction mixture. [b]After flash chromatography on silica gel.

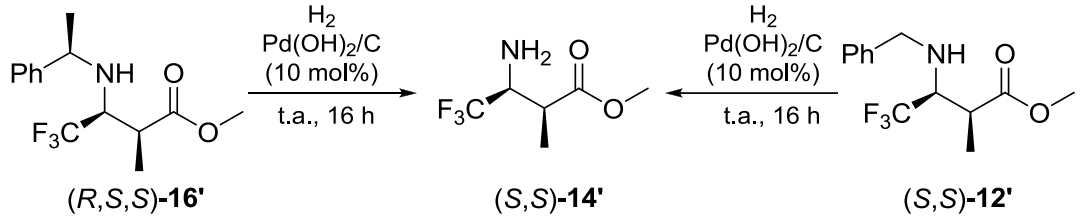
As shown in **Table 7**, performing the addition without chiral ligand only the geometric stereocontrol was achieved, being controlled by the nucleophilic species (entry 1). The result showed also that a resident chiral center of the imine cannot influenced the facial selectivity. On the contrary, adding to the reaction (*R*,*S*)-**6**, a complete stereofacial selectivity was obtained (entry 2), only one *syn* diastereomer having been formed. Then, the organocatalyzed homogenous aza-Reformatsky reactions was brought at room temperature (14 d) to form the corresponding *cis*-β-lactam **17** (**Scheme 8**).



Scheme 8. Homogeneous aza-Reformatsky reactions followed by intramolecular cyclization.

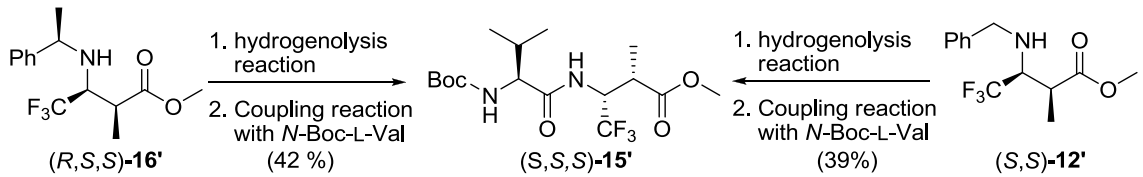
The same previously described methodology, based on the 2D NOESY ^{1}H NMR spectra and geometric optimization processes, permitted to assign the (*S*,*S*) absolute configuration to the newly chiral centers of **17**, and as a consequence even to those of starting β-amino ester **16'**.

After removal of chiral benzyl group of (*R*,*S*,*S*)-**16'**, chiral HPLC analysis showed that the obtained primary amine (*S*,*S*)-**14′** is the same isomer formed by hydrogenolysis reaction carried out from *syn*-**12′** to which, therefore, the same configuration can be attributed (**Scheme 9**).



Scheme 9. Hydrogenolysis reactions on **16′** and **12′**.

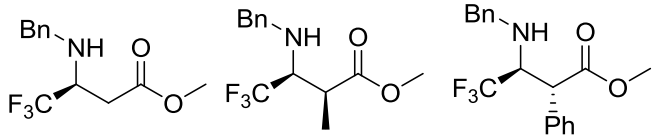
In order to confirm this, DCC coupling reaction with the *N*-Boc-L-Val was also performed on the β-amino ester obtained by hydrogenolysis of (*R*,*S*,*S*)-**16'** (**Scheme 10**).



Scheme 10. Synthesis of **15′**.

The coupling reaction gave, as expected, the same diastereomer **15′**, already obtained starting from (*S*,*S*)-**12′**, thus confirming the matching between the absolute configurations.

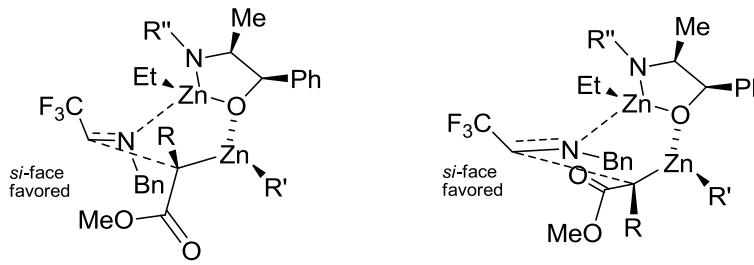
Extending these studies even to the other enantioriched β-amino esters (**Table 6**, entry 1 and 3), the absolute configurations of the new synthesized chiral trifluoromethyl compounds are reported below (**Figure 4**).



(*S*)-**10'** (*S,S*)-**12'** (*S,R*)-**13'**

Figure 4. Assigned absolute configurations.

Considering the found absolute configuration, the chiral ligand **6** promotes the nucleophilic attack preferentially on the *Si* face of the starting imine and Noyori's representative transition model can be used to explain the stereoselectivity of this Reformatsky reaction (**Figure 5**).[18]



VIII **IX**

R= H, Me
R'= Et or $CHRCO_2Me$
R''= $-(CH_2)_4-$

R= Ph
R'= Et or $CHRCO_2Me$
R''= $-(CH_2)_4-$

Figure 5. Proposed transitions states.

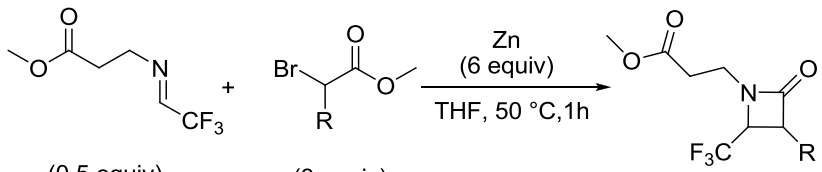
Transition model **VIII** and **IX** provide the products with the observed stereochemistry. The proposed stereochemical models are based on the formation

[18] Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842.

of a coordination network involving the imine nitrogen, zinc ion, ligand, and Reformatsky reagent, which would allow for the successful formation of multiple chiral inductions.

In order to investigate how the presence of a further ester group could influence the chemical outcome, the trifluoromethyl aldimine **1g**[19] derived from β-alanine was reacted under one-pot heterogeneous aza-Reformatsky conditions with α-bromo esters **2a-c** to give, as expected, only β-lactams. The results are showed in **Table 8**.

Table 8. Aza-Reformatsky reactions on **1g**.



(0.5 equiv) **1g**

(3 equiv) R = H, Me, Ph **2a-c**

18 *trans*-**19** *trans*-**20**

Entry	R	Time (h)	Product	*trans*:*cis*[b]	Yield (%)[c]
1[a]	H		**18**	-	34
2	Me	18	*trans*-**19**	>99:1	40
3	Ph	10	*trans*-**20**	>99:1	42

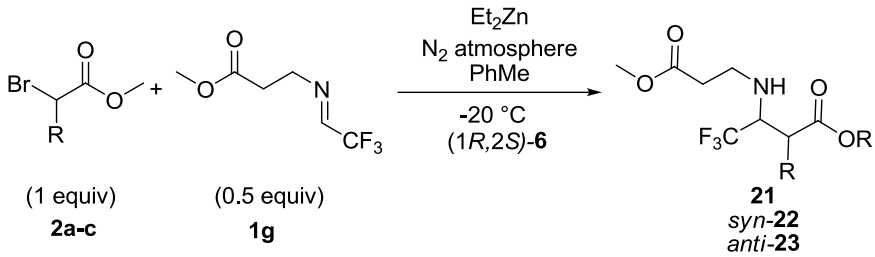
[a]Higher yields in the one-procedure compared to the two-step protocol. [b]Determined by ^{19}F NMR spectra of the crude reaction mixture. [c]After flash chromatography on silica gel.

While lower yields compared to those obtained starting from imine **1g** (**Table 1** and **2**) were observed, the same high *trans* diastereoselectivity (entry 2-3) and chemoselectivity were found. One again the compounds can be derived by the two different pathways before reported: *via* ketene-imine mechanism and a condensation-cyclization mechanism (see **Chap. 7**, pp 76-77). It is noteworthy to stress that, if the second suggested mechanism was the one involved, no trace of a possible β-lactam resulting by cyclization of aza-Reformastky adduct on the imine

[19] See ref.54 in the **Chapter 2**.

ester group was observed, consistent with a high reaction chemoselectivity.[20] Next, the homogeneous Et_2Zn-promoted aza-Reformatsky reactions, were performed, even in the asymmetric version (**Table 9**).

Table 9. Homogeneous aza-Reformatsky reactions on **1g**.



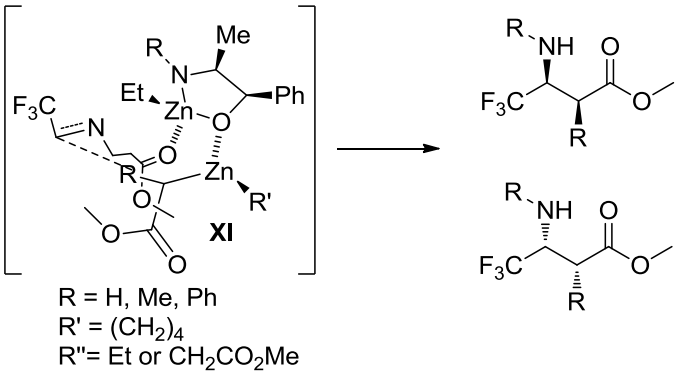
Entry	R	Time (h)	Et_2Zn (equiv)	**6** (equiv)	Product	*syn/anti*[a]	Yield (%)[b]
1[d]	H	18	1.0	-	**21**	-	40
2[d]	Me	18			*syn*-**22**	>99:1	45
3[d]	Ph	12			*anti*-**23**	>1:99	56
4	H	72	1.2	0.38	**21'** (74% ee)	-	50
5	Me	72			*syn*-**22'**	>99:1	48
6	Ph	72			*anti*-**23'**	>1:99	51

[a]Determined by ^{19}F NMR spectra of the crude reaction mixture [b]After flash chromatography on silica gel. [c]Determined by chiral HPLC. [d] Reaction performed at room temperature.

As shown in **Table 9**, the expected β-amino esters **21-23** were obtained in satisfactory yields; however, a change of the solvent was required ($PhCH_3$ instead of CH_2Cl_2). In addition, while a high *syn*/*anti* stereochemical outcome was observed, a lower enantiocontrol was found (see **Table 6**).

A reasonable explanation, taking into account the ester group on the *N*-chain of the aldimine, may be given. On the basis of the stereochemical model proposed before, another transition state could be suggested (**Figure 6**). In this latter the network of coordination involves the ester moiety of the β-alanine chain, instead of the imine nitrogen, thereby giving lower stereoselectivity of attack.

[20] The presence of the strong electron-withdrawing $–CF_3$ group increases the electrophilicity of the ester moiety in the β-position of β-amino ester intermediate, so directing the nucleophilic attack



R = H, Me, Ph
R' = $(CH_2)_4$
R"= Et or CH_2CO_2Me

Figure 6. Proposed transitions state

Chapter 8

Work towards the discovery of selective and potent PCAF inhibitors

During my PhD, I spent a period of six months at the University of Oxford (UK) under the supervision of Professor Darren J. Dixon and in collaboration with the SGC (Structural Genomics Consortium).

During this period the attention was focused on the development of different phthalazine-based derivatives in order to obtain epigenetic probes able to clarify key binding elements for the good affinity with the bromodomain module of PCAF (p300/CBP-associated factor).

The chemical probes are selective small-molecules that specifically bind and potently control the activity of a cellular target in order to deciphering biochemical pathways.[1,2,3] They can rapidly and reversibly inhibit a protein or a protein domain in cells or animals, modulate individual functions of multifuctional proteins and they can be used in almost any cell type and disclose temporal features of target inhibition;[4] in addition a probe that shows a positive effect can serve as a chemical starting point for drug discovery and in this way they can be quite useful at invalidating drug targets.[5] Target discovery currently uses a number of tools to associate a protein target with a disease, including the use of chemical probes in cellular or animal disease models.

[1] Knapp, S.; Arruda, P.; Blagg, J.; Burley, S.; Drewry, D. H.; Edwards, A.; Fabbro, D.; Gillespie, P.; Gray, N. S.; Kuster, B.; Lackey, K. E.; Mazzafera, P.; Tomkinson, N. C.; Willson, T. M.; Workman, P.; Zuercher, W. J. *Nat. Chem. Biol* **2013**, *9*, 3-6.
[2] Kroeze, W. K.; Sassano, M. F.; Huang, X. P.; Lansu, K.; McCorvy, J. D.; Giguère, P. M.; Sciaky, N.; Roth, B. L. *Nat. Struct. Mol. Biol.* **2015,** *22*,362–369.
[3] King, R.; Finley, D. *Nat. Chem. Biol.* **2014**, *10*, 870-874.
[4] Arrowsmith, C.; Audia, J.; Austin, C.; Baell, J.; Bennett, J.; Blagg, J.; Bountra, C.; Brennan, P. et al. *Nat. Chem. Biol* **2015**, *11*, 536-541.
[5] Sweis, R. F. *ACS Med. Chem. Lett.* **2015**, *6*, 618–621.

In fact, in order to find new medicines for diseases, like Alzheimer's disease, cancer and chronic inflammation, we first need to discover a new disease-associated protein target.

Epigenetic is an exciting new area for target discovery: especially epigenetic chemical probes, allowing the investigation of the epigenome, are having a strong impact in biological discovery and target validation for several classes of chromatin-interacting proteins.[6]

We can consider three classes of epigenetic proteins, discovered through the study of post-translational modification (PTM) of lysine and/or arginine residues in histones and other proteins through methylation and acetylation: a) those which add a methyl or acetyl group (writers) using *S*-adenosylmethionine (methylation) and acetyl-CoA (acetylation) as co-factors, b) those which remove a methyl or acetyl group (erasers) and c) those which bind histones/proteins containing a particular PTM (readers).

Therefore, as long as it is recognized that these proteins contribute to the control of various genes and they represent a rich source of potential therapeutic targets, it is important to unravel the biology of these proteins by developing small-molecule inhibitors and antagonists with the following properties:[4]

- IC_{50} or K_d < 100 nM
- Selectivity > 30-fold over proteins in the same family
- Significant cellular activity below 1 μM.

8.1 Bromodomain

The interest has been directed towards the development of chemical probes against the bromodomain proteins family in recent years. The bromodomain, named for the *Drosophilia* gene *brahma* from which it was first identified,[7] is a conserved module that has been found in a number of proteins involved in

[6] Huston, A.; Arrowsmith, C. H.; Knapp, S.; Schapira, M. *Nat. Chem. Biol* **2015**, *11*, 542-545.
[7] Haynes, S. R.; Dollard, C.; Winston, F.; Beck, S.; Trowsdale, J.; Dawid, I. B. *Nucleic Acids Res*. **1992**, *20*, 2603

transcription regulation that selectively recognize ε-*N*-acetylated lysine residues,[8,9] acting as "readers" of the histone code. The bromodomain family shall consist of 61 diverse domains in humans that have been described in 41 nuclear proteins,[10,11] (**Figure 1**)

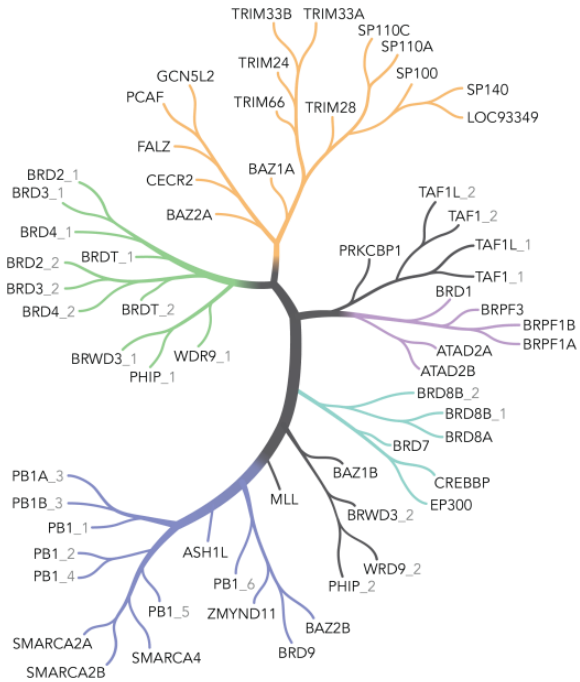


Figure 1. Human bromodomain family.

all of these characterized by 110 amino acids arranged in a characteristic structure made up of four α-helices (αZ, αA, αB, αC) connected by interhelical loops, termed the BRD fold (**Figure 2**).

[8] Müller, S.; Knapp, S. *Med. Chem. Commun*. **2014**, *5*, 288–296.
[9] Mujtaba, S.; Zeng, L.; Zhou, M. *Oncogene* **2007**, *26*, 5521–5527.
[10] Filippakopoulos, P.; Picaud, S.; Mangos, M.; Keates, T; Lambert, J. P.; Barsyte-Lovejoy, D.; Felletar, I.; Volkmer, R.;. Muller, S.; Pawson, T.; Gingras, A. C.; Arrowsmith, C. H.; Knapp, S. *Cell* **2012**, *149*, 214–231.
[11] Filippakopoulos, P.; Knapp, S. *FEBS Lett.* **2012**, *586*, 2692–2704.

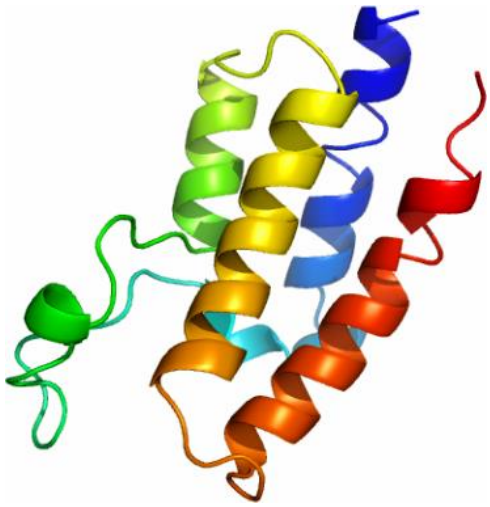


Figure 2. General structure of a bromodomain module.

The interaction with the acetylated lysine residue occurs *via* a hydrogen bond with a conserved asparagine. In addition the water molecules in the binding pocket can mediate further interaction between the anchored acetylated lysine and the hydroxyl of a conserved tyrosine residue.[12] Bromodomains have recently been implicated in the development of cancer and have been shown to contain a "druggable" binding pocket, however their precise biological role is still poorly understood.

Hence development of selective chemical probes targeting the bromodomain-histone interaction is highly desirable for our understanding of the biological roles of these proteins within the human genome and to provide starting points for new molecular therapeutics against cancer.

8.1.1 p300/CBP-associated factor, PCAF

PCAF, also known as K(lysine) acetyltransferase 2B, KAT2B, is a transcriptional coactivator that works both as a histone lysine acetyltransferase, through its HAT domain which is highly homologous to the yeast GCN5

[12] Liu, Y.; Wang, X.; Zhang, J.; Huang, H.; Ding, B.; Wu, J.; Shi, Y. *Biochemistry*, **2008**, *47*, 6403–6417.

(yGCN5),[13] and as an acetyl-lysine reader through its conserved bromodomain located directly C-terminal to the HAT domain.[14,15]

The simultaneous presence of these two domains is a sign of the importance of PCAF and a direct link between transcriptional regulation and chromatin modification. Given the significant role in regulation of gene expression, PCAF has been implicated in numerous types of cancer.

The Hedgehog signaling pathway, that plays an important role in embryonic patterning and development of many tissues and organs as well as in maintaining and repairing mature tissues in adults, has been implicated in developmental abnormalities as well as in several types of cancer, including brain tumors like medulloblastoma and glioblastoma, and PCAF is involved as a cofactor of the genes involved in this pathway.[16]

In addition it has been found that PCAF can acetylate and stabilize overexpressed ATP-citrate lyase that promotes tumor growth of human lung cancers.[17] PCAF has also been found to regulate the stability of β-catenin, which is involved in colorectal tumors.[18] No probes against the bromodomain of PCAF have yet been described; on the contrary the HAT domain of PCAF has been targeted with a number of broad-activity HAT inhibitors. Therefore, given the number of diseases in which PCAF is involved, it is necessary to develop selective inhibitors to treat these pathologies.

In the group where I spent a period of my PhD they are making progress toward the development of PCAF inhibitors, starting from different acetyl lysine bioisosters (**Figure 3**),

[13] Marcus, G.A.; Silverman, N.; Berger, S.L.; Horiuchi, J.; Guarente, L. *EMBO J.* **1994**, *13*, 4807–4815.
[14] Marmorstein, R. *Cell Mol Life Sci*, **2001**, *58*, 693–703.
[15] Carrozza, M.J.; Utley, R.T.; Workman, J.L. *Trends Genet*, **2003**, *19*, 321–327.
[16] Malatesta, M.; Steinhauer , C.; Mohamma, F.; Pandey, D. P.; Squatrito, M.; Helin, K. *Cancer Res*. **2013**, *73*, 6323-6333.
[17] Lin, R.; Tao, R.; Gao, X.; Li, T.; Zhou, X.; Guan, K. L.; Xiong, Y.; Lei, Q. Y. *Mol. Cell.* **2013**, *51*, 506–518.
[18] Xinjian, G.; Qihuang, J.; Fang, Z.; Tingting, Y.; Qiwei, Z. *Mol. Biol. Cell.* **2009**, *20*, 419–427.

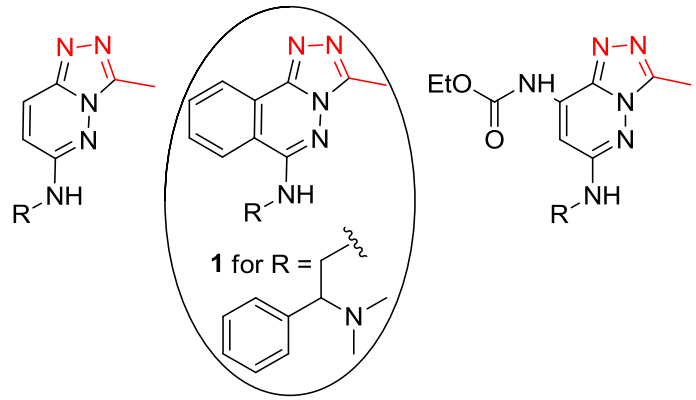


Figure 3. Families of compounds to be synthesized against PCAF, the acetyl lysine mimic motif of each structure is highlighted (red).

and the best compound **1** in the different families is reported to have a K_D of 1.0 μM a significantly weak affinity.

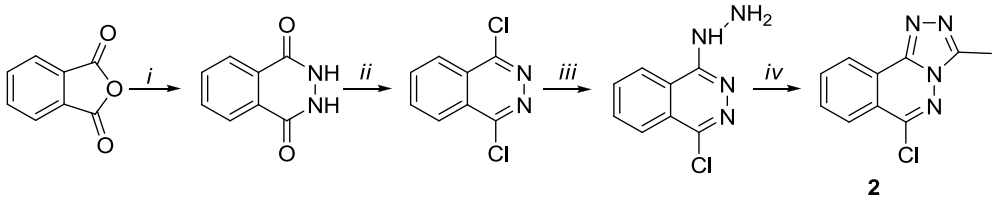
However all the molecular portions, the position of the phenyl ring, the length of the chain and the tertiary amine, that could be responsible binding elements, they were simultaneously changed.

The aim of my project was to understand the key binding elements from **1**, especially the phenyl residue position, the importance of terminal tertiary amine and the effect of chain; in addition my goal was to try to investigate a range of *N*-substituents derivatives in order to explore new binding elements and to optimize the terminal H-bond

The measuring of biological activity of potential probes, through biophysical assay [Differential Scanning Fluorimetry (DSF)], was used to guide the optimization process toward a future design of high-affinity PCAF probes.

The synthetic approach of potential PCAF ligands was based on the condensation between different amines and an acetyl lysine mimic, namely the 6-chloro-3-methyl-[1,2,4]triazolo[3,4-a]phthalazine (**2**), that can be obtained following the procedure reported in the literature[19] (**Scheme 1**).

[19] Xue, D.; Zhang, Y.; Wang, C.; Zhu, N.; Shao, K.; Zhang, X.; Zhang, Z. *Eur. J. Med. Chem.* **2014**, *85*, 235-244.



(*i*) H_2N-NH_2 H_2O, CH_3COOH, 120 °C, 4h, 85%; (*ii*) $POCl_3$, 110 °C, 1h, 70%;
(*iii*) EtOH, H_2N-NH_2 H_2O, 78 °C, 0.5h, 86%; (*iv*) CH_3COCl, dioxane, NEt_3, 110 °C, 3h, 53%

Scheme 1. Synthesis of **2**.

Starting from the lead compound **1**, several amines were chosen in order to understand the important moieties (**Figure 4**).

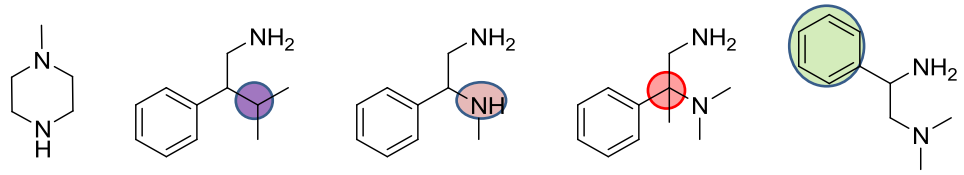
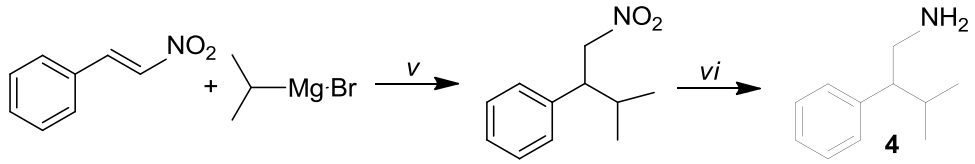


Figure 4 Amines chosen, the modified moieties of each structure are highlighted.

The amines **4-7** were obtained by classical reactions of organic chemistry, because they are either expensive or not commercially available.

The synthesis of amine **4** involved a Michael addition reaction of an opportune Grignard reagent to β-nitrostyrene,[20] followed by nitro group reduction.[21]



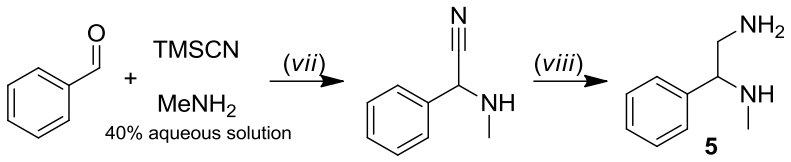
(*v*) THF, -20 °C, 1.1h, 40%; (*vi*) $NiCl_2 \cdot 6H_2O$/ $NaBH_4$, MeOH, 25 °C,1h, 90%

Scheme 2 Synthesis of **4**.

The *gem*-diamine **5**, characterized by the presence of both a primary and secondary amine moiety, was obtained through a Strecker reaction, involving

[20] Yao, C.; Kao, K.; Liu, J.; Wang, Y.; Chen, W.; Lin, Y.; Yan, M.; *Tetrahedron* **1998**, *54*, 791−822.
[21] Martinelli, E.; Vicini, A. C.; Mancinelli, M.; Mazzanti, A.; Zania, P.; Bernardi, L.; Fochi, M. *Chem. Commun.* **2015**, *51*, 658-660.

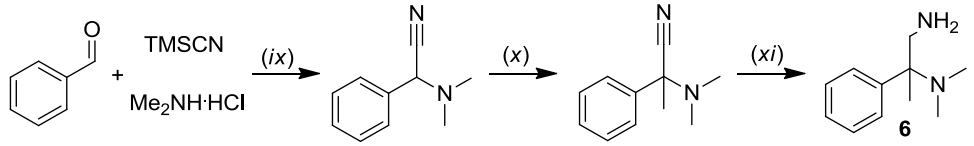
benzaldeyde, methylamine solution and trimethylsilyl cyanide (TMSCN),[22] followed by a nitrile reduction with $LiAlH_4$ (**Scheme 3**).



(*vii*) MeOH, 25 °C, 24h, 90%; (*viii*) $LiAlH_4$, Et_2O, 0° C to rt, 52%

Scheme 3 Synthesis of **5**.

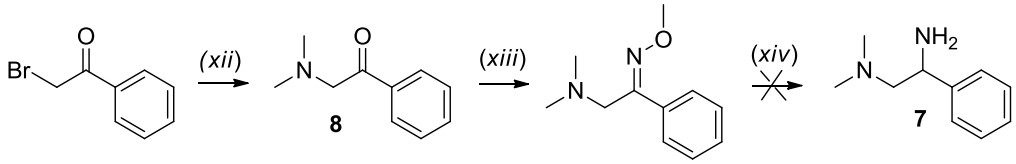
A similar Strecker reaction,[23] followed by alkylation with iodomethane and nitrile group reduction, leads to the amine **6** (**Scheme 4**).



(*ix*) $NaHSO_3$, H_2O, K_2CO_3, 25 °C, 24h, 87%; (*x*) LDA, CH_3I, THF, -78 °C to rt, 16h, 80%;
(xi) $LiAlH_4$, Et_2O, 18h, 44%

Scheme 4 Synthesis of **6**.

Finally, to synthesize amine **7** a procedure reported in the literature[24] was followed (**Scheme 5**), but strangely the last step of reported synthetic pathway did not give the desired product.



(*xii*) Me_2NH, K_2CO_3, MeCN, 25 °C, 18h, 88%; (*xiii*) $CH_3ONH_2 \cdot HCl$, Pyridine, 25 °C, 12h, 79%;
(*xiv*)H_2, Pd/C, MeOH

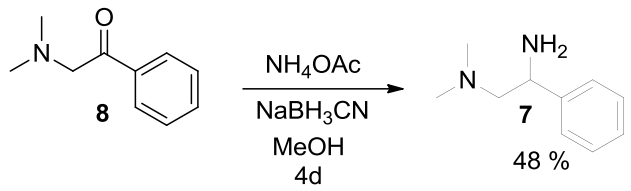
Scheme 5. Attempted synthesis of **7.**

[22] Vongvilai, P.; Linder, M.; Sakulsombat, M.; Svedendahl Humble, M.; Berglund, P.; Brinck, T.; Ramstrm, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 6592 –6595.

[23] Taylor, H. M.; Hauser, C. R. *Organic Syntheses*, *Coll. Vol. 5*, p.437 (**1973**).

[24] Gomtsyan, A.; Bayburt, E.; Keddy, R.; Turner, S.; Jinkerson, T.; Didomenico, S.; Perner, R.; Koenig, J.; Drizin, I.; McDonald, H.; Surowy, C.; Honore, P.; Mikusa, J.; Marsh, Wetter, J.; Faltynek C.; Lee C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3894–3899.

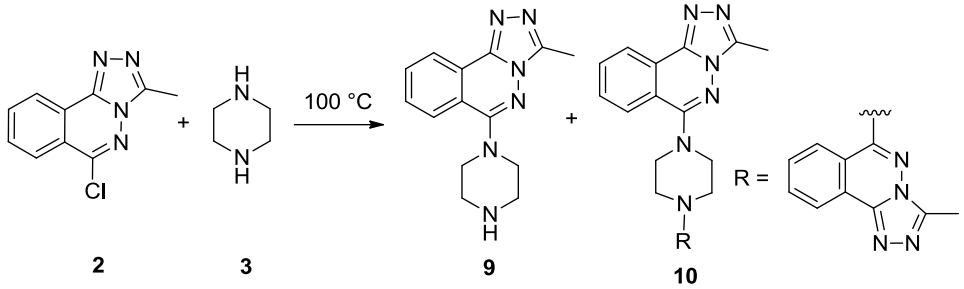
Then, in order to obtain **7**, a new synthetic approach, involving a reductive amination reaction with ammonium acetate, was developed starting from the ketone **8** (**Scheme 6)**.



Scheme 6 Synthesis of **7**.

The commercial piperazine **3** was the first tested amine and its reaction with **2** was performed in the presence of NaOH, following a procedure reported in the literature[19] (**Table 1**).

Table 1 Optimization of the coupling reaction.



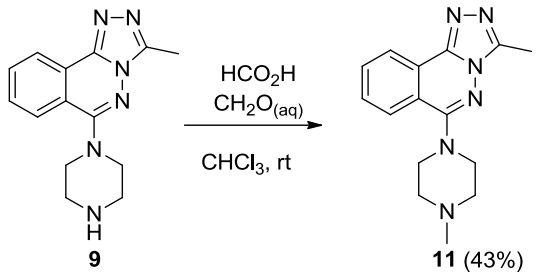
2 **3** **9** **10**

Entry	**2**:**3** ratio	Conditions	**9**/**10**[a] (Yield of **9**)
1	1:1.2	NaOH (3 equiv), DMF	2/8
2	1:1.2	NaOH (1.5 equiv), DMF	2/8
3	1:3	NaOH (1.5 equiv), DMF	2/8
4	1:2	KI (0.1 equiv), HCl (0.2 equiv), EtOH	>9.9/0.1 (63)[b]

[a]Determined by ^{1}H NMR performed on the crude mixture. [b]After flash chromatography on silica gel.

Once again, the reaction, performed by following the literature conditions (entry 1), gave the undesired bifunctionalized **10** as major product in all cases, even by changing some parameters (entries 2–3). Then, to obtain only **9**, a methodology developed by the Dixon's group was followed, using catalytic KI and HCl (entry 4) to form *in situ* a more reactive aryl iodide. Under these conditions, the substitution

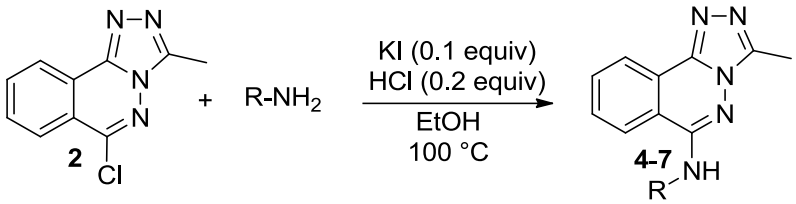
reaction lead to **9** as the only product from which **11** was obtained through the Eschweiler-Clarke reaction.[25]

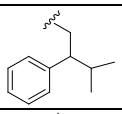
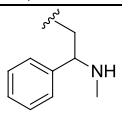
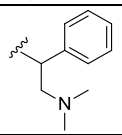
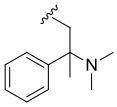


Scheme 7. Synthesis of **11**.

The same tandem procedure was repeated starting from synthesized amines **4**–**7** and the expected products **12-15** were obtained as the only products (**Table 2**).

Table 2 S_{NAr} coupling reaction with different amines.



Entry	R	Time	Product	Yield[a] (%)
1		7d	**12**	35
2		4d	**13**	30
3		12h	**14**	21
4		12h	**15**	17

[a]After flash chromatography on silica gel.

[25] Sahakitpichana, P.; Ruchirawat, S.; *Tetrahedron Lett.* **2003**, *44*, 5239–5241.

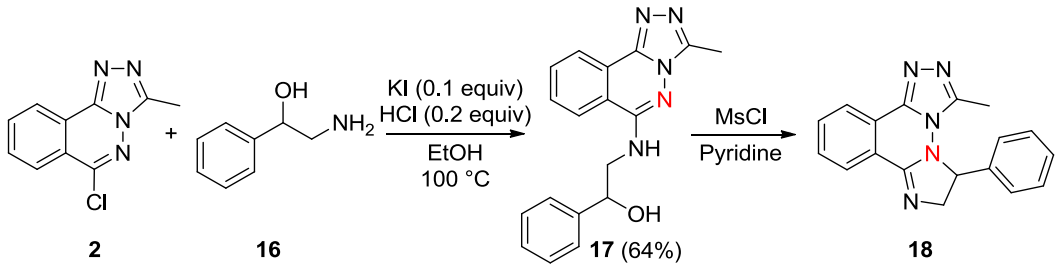
Unfortunately, the DSF[26] analysis performed on all obtained compounds (**Figure 4**) suggested a general very low affinity of these compounds for PCAF, only the compound **13** resulting to be better than the lead compound **1**, whose value to cause ΔT_m is 1.7 °C.

Average of CompScreen: Tm Shift (C)	Column Labels						
Row Labels	BRD4A	BRD9A	CECR2A	CREBBPA	PCAFA	TAF1A	Grand Total
LT053	0.07	0.4	0.41	-0.48	-0.46	0.53	0.078333333
LT056	1.04	0.97	0.42	0.18	0.05	0.34	0.5
LT074	0.08	1.54	0.53	-0.07	2.13	0.47	0.78
LT077	-0.82	2.56		-0.08	1.01	2.28	0.99
LT101	0.27	0.48	0.37	0.28	0.44	0.31	0.358333333
LT103	0.29	0.43	0.31	0.06	0.71	0.22	0.336666667

Figure 4. Thermal shifts of **11-15**.

Encouraged by the results, we decided to create a series of different homologous of **13** generating a library of compounds from which structure-activity relationships (SARs) can be readily explored.

So, we thought that a nucleophilic substitution of a suitable leaving group, such as the methanesulfonate group, with different primary amines could be a simple and quick methodology to obtain different compounds (**Schema 8**).



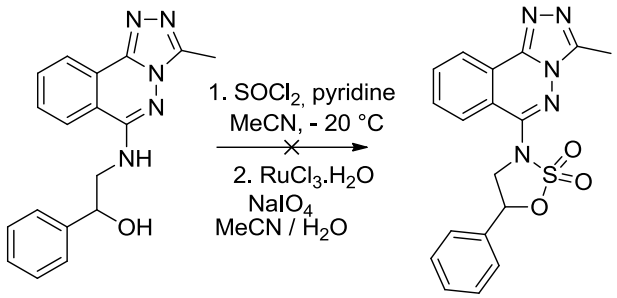
Schema 8. Synthesis of **17** followed by mesylation reaction.

However during the mesylation of the hydroxylic group of **17**, formed through S_{NAr} coupling reaction between **2** and phenylethanolamine (**16**), the expected product undergoes a very fast nucleophilic intramolecular attack, giving **18** as major compound.

[26] DSF is an inexpensive and rapid screening method to detect low-molecular-weight ligand interactions promoting protein stability: Niesen, F. H.; Berglund, H.; Vedadi, M. *Nat. Protoc.* **2007**, *2*, 2213.

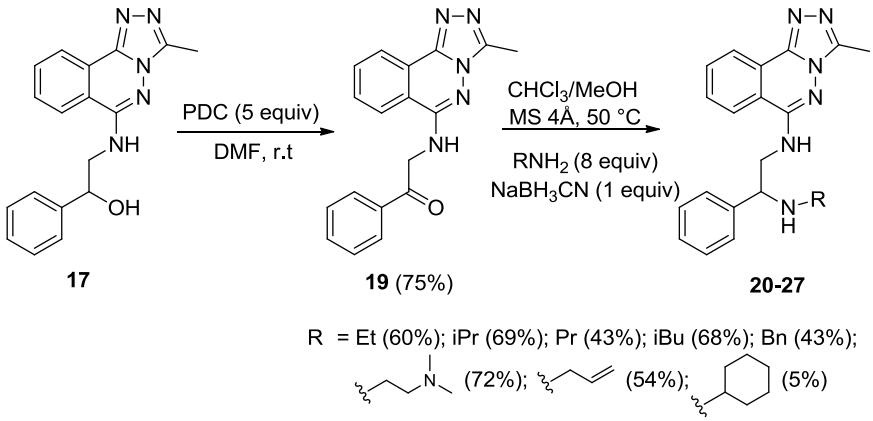
Therefore, we attempted to convert the amino alcohol **16** in the corresponding cyclic sulfamidate, which, used in its asymmetric version,[27] could moreover provide enantioenriched products after ring-opening reaction.

But once again, following the classical mesylation procedure (**Scheme 9**),[26] the reaction did not occur and only a complete crude mixture was obtained.



Scheme 9. Attempted synthesis of cyclic sulfamidate.

Then, we decided to completely change the synthetic strategy and, after oxidation of **16**, a reductive amination finally gave the synthetic targets in good yield (**Scheme 10**).

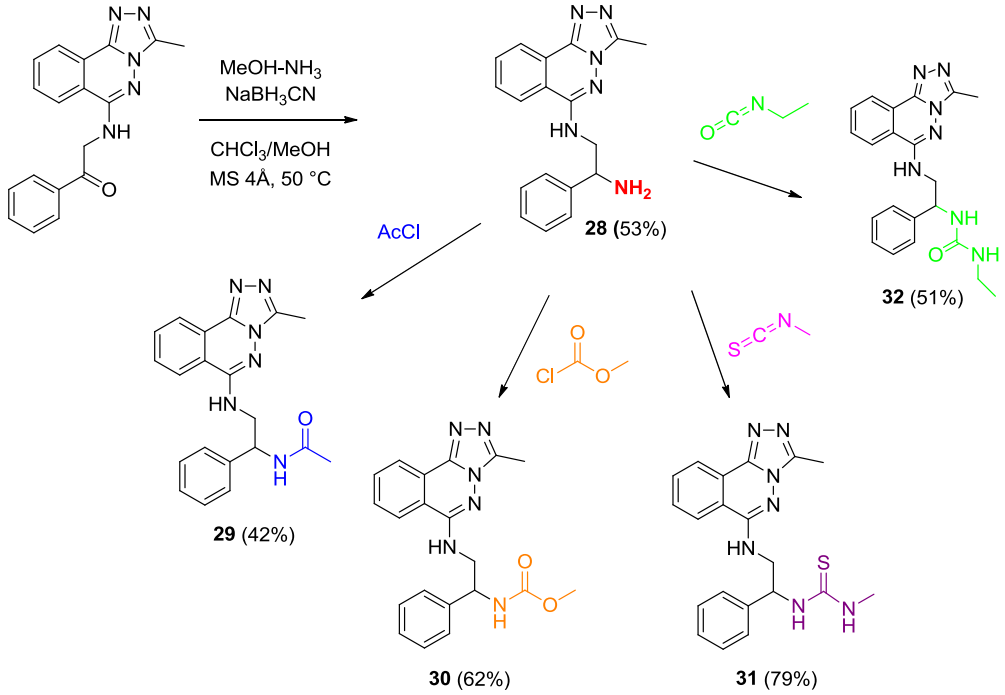


Scheme 10. Synthesis of **20-27**.

Given the relevance of H-bond donors and acceptors in the pocket, the reductive amination was used to obtain the primary amine **28** allowing also the

[27]Moss, T. A.; Alonso, B.; Fenwick, D. R.; Dixon, D. J. *Angew. Chem*. **2010**, *122*, 578–581; *Angew. Chem*., *Int. Ed.* **2010**, *49*, 568–571.

derivatization of the terminal position with alternative H-bond donors and acceptors (**Scheme 11**).



Scheme 11. Synthesis of **28-32**.

In conclusion a series of potential epigenetic probe was generated and to date biophysical assay are currently underway to test the affinity with the bromodomanin module of PCAF.

Chapter 9

Conclusions

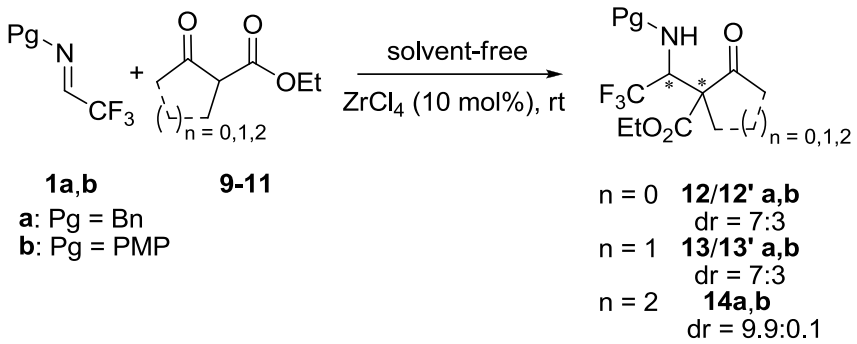
In this thesis the reactivity of *N*-protected trifluoromethyl (*E*)-aldimines towards different active methylene compounds in the Mannich-type and aza-Reformatsky reactions was studied.

At first, suitable trifluoromethyl aldimines were reacted with β-dicarbonyl compounds, including diethyl malonate and several β-keto esters. The presence of a trifluoromethyl group, lowering both nitrogen basicity and carbon electrophilicity of the imine C=N group, greatly affects the Mannich-type addition of β-dicarbonyl compounds. In fact, the most common organic or inorganic bases, such as some organocatalysts (cinchonidine, L-proline or their derivatives), frequently used to promote Mannich-type reactions between aromatic aldimines and β-dicarbonyl compounds,[1] did not give the expected results.

Excellent results were obtained only through a Lewis acid catalysis, indeed an efficient solvent-free Zr-catalyzed Mannich-type reaction has been developed for the synthesis of fluorinated β-amino β-dicarbonyl compounds starting from *N*-protected trifluoromethyl aldimines and cyclic or acyclic β-keto esters bearing different ester residues.

The presence of an alkyl substituent on the nucleophilic carbon and the use of Zr as coordinating metal lead to a high stereoselective control of reactions (**Scheme 1**).

[1] a) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003−2006; b) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603−606, c) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043−2046.



Scheme 1. Solvent-free $ZrCl_4$-catalyzed Mannich-type reaction of different β-keto esters.

Instead, contrary to what reported in the literature for similar reaction,[2] the ester residue did not affect the reaction outcome: in fact, no difference in reactivity was found by changing the ester moiety.

Then, in order to develop a catalytic asymmetric Mannich-type reaction, failing all attempts using an added chiral catalyst, we successfully developed a new asymmetric Zr-catalyzed Mannich-type reaction at low cost starting from the optically pure aldimine derived by the inexpensive chiral (*R*)-α-methylbenzylamine. A complete facial and geometric stereoselective induction with formation of a chiral quaternary center was so obtained, the same chiral substrate acting as chiral ligand (**Figure 1**).

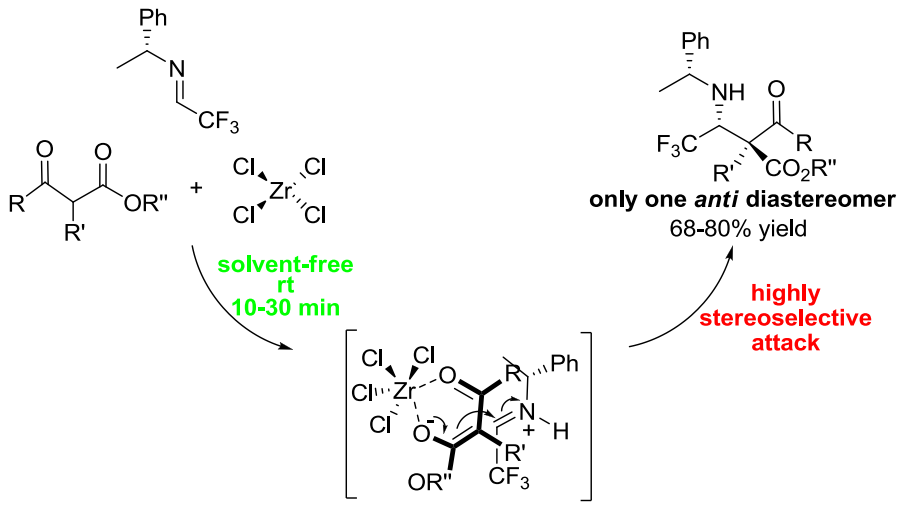
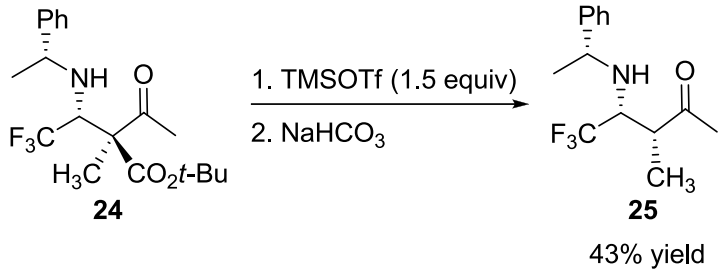


Figure 1. Proposed transition state.

[2]See ref. 40 in the **Chapter 2**.

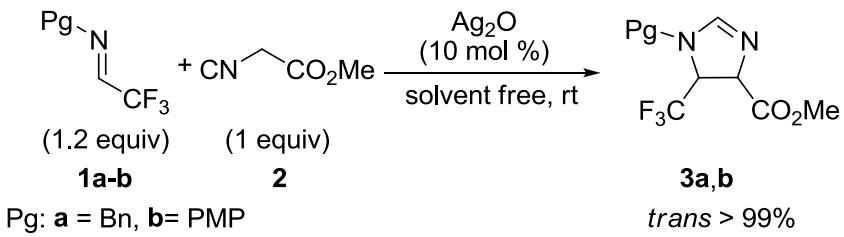
The nucleophilic attack takes place only on the sterically less hindered prochiral *Re* face of optically pure aldimine, giving *R,R,S* pure diastereomeric compounds bearing a quaternary chiral center.

In addition, the diastereoselective catalytic Mannich-type reaction represents, thanks to a diastereoselective decarboxylation reaction of the new obtained β-keto esters, a valid approach to obtain optically active trifluoromethyl β-amino ketones.



Scheme 2. Decarboxylation reaction.

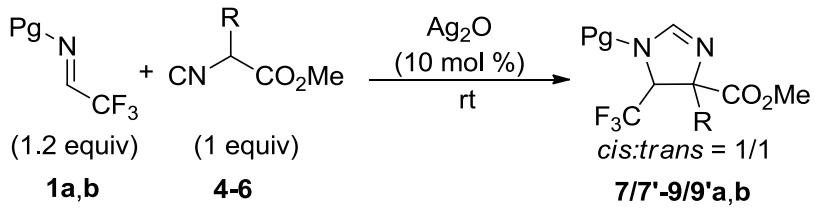
Extending my studies, the interest has been directed towards the possibility to synthesize attractive trifluoromethylated 2-imidazolines by Mannich-type addition/cyclization cascade reaction of α-isocyano acetates on trifluoromethyl aldimines. Silver(I) oxide is turned out to be a very efficient catalyst for the reaction performed under solvent-free conditions between methyl 2-isocyanoacetate (**2**) and trifluoromethyl aldimines **1a**,**b** (**Scheme 3**).



Scheme 3. Ag_2O-catalyzed Mannich-type ractions.

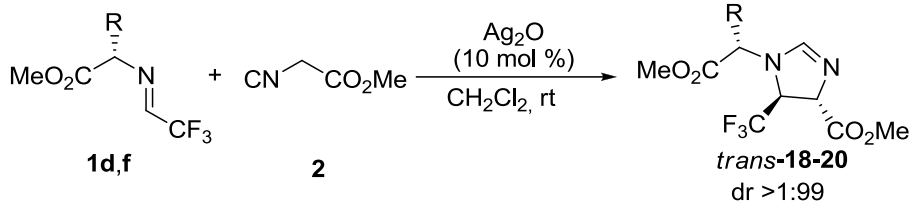
High *cis*/*trans* stereoselective control was obtained, the reaction affording only *trans* imidazolines **3a**,**b**.

Subsequently, the study has been extended to the reactivity of α-isocyano esters bearing a tertiary carbon center. Though the silver(I) catalysis appeared once again to be a good reaction catalyst, the use of dichloromethane as solvent was required and the total loss of geometric selectivity was recorded because of the steric hindrance on the nucleophilic site (**Scheme 4**).



Scheme 4. Ag_2O-catalyzed Mannich-type reactions.

Excellent stereoselectivity was obtained starting from the trifluoromethyl (*E*)-aldimines **1d**,**f** deriving from L-α-amino esters (**Scheme 5**).



Scheme 5. Ag_2O-catalyzed Mannich-type reactions on **1d-f**.

A complete stereoselective control was obtained and the reactions lead to the formation of the only optically pure *trans* isomers. To explain the high diastereoselectivity observed and the stereochemical outcome, a transition state can be proposed (**Figure 2**).

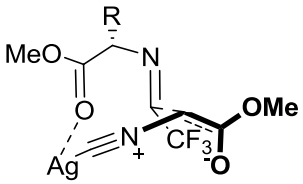


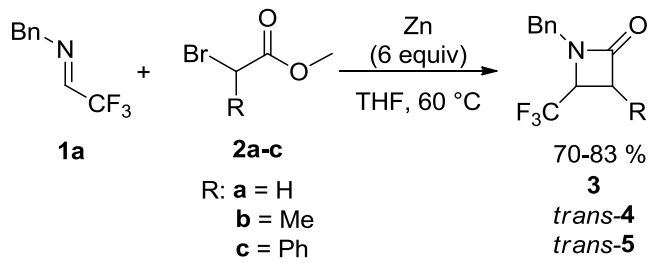
Figure 2. Proposed transition state.

The coordination of the imine ester group to the silver promotes the enolate attack preferentially to the *Re* imine face, obtaining enantiopure valuable trifluoromethyl imidazolines enriched by an α-amino ester residue.

As a further and last class of active methylene compounds, α-bromo esters have been considered in the aza-Reformatsky reactions, always with different trifluoromethyl aldimines.

The reactions were studied under two different conditions: heterogeneous conditions, using activated metal zinc as catalyst, and homogenous conditions, using Et_2Zn as source of the metal.

Working under heterogeneous conditions, only β-lactams in good yields and high *trans* geometric selectivity were achieved when the reactions were performed starting from α-bromo esters (**Scheme 6**).

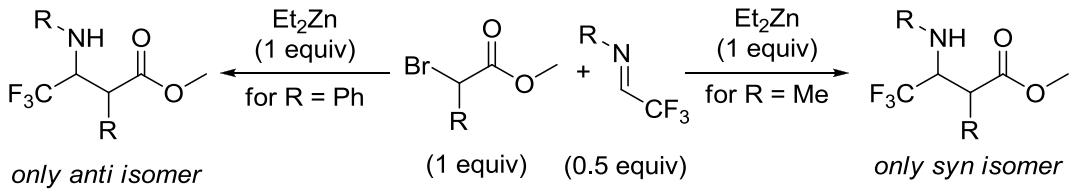


Scheme 6. Aza-Reformatsky reaction under heterogeneous conditions.

However, adding (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol as chiral ligand no enantioselective control was obtained. Even the presence of a chiral center on the aldimine does not seem able to control the facial attack selectivity.

Then, we moved on to study the homogeneous reaction outcome.

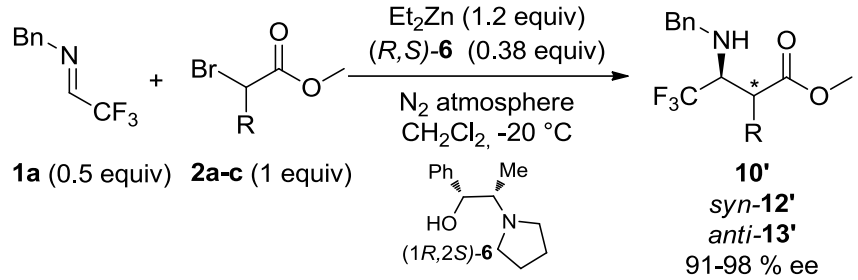
Under optimal conditions, the additions lead to the only β-amino esters, in good isolated yields and high geometric selectivity, the *syn* or *anti* isomer formation depending from the R substituent. In fact, while a complete *syn* selectivity was achieved starting from methyl substituted α-bromo ester **2b**, the *anti* β-amino ester was obtained starting from phenyl substituted α-bromo ester **2c** (**Scheme 7**).



Scheme 7. Aza-Reformatsky reaction under homogeneous conditions.

Subsequently, the first example of a convenient enantioselective aza-Reformatsky reaction on trifluoromethyl aldimines has been successfully developed.

Using diethyl zinc and substoichiometric amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol as chiral ligand, trifluoromethyl enantioenriched β-amino esters in good yields and enantioselectivities (up to 91% ee) were synthesized (**Scheme 8**).



Scheme 8. Enantioselective aza-Reformatsky reaction.

The *S* absolute configuration assigned to *C*-CF_3 substituted chiral center suggested that the *Si*-face of the coordinate imine was preferentially exposed, as shown in the proposed transition model reported below (**Figure 3**).

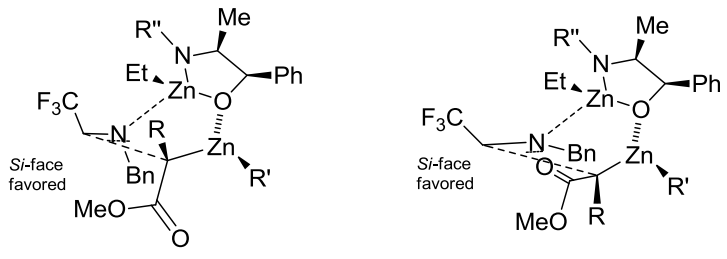
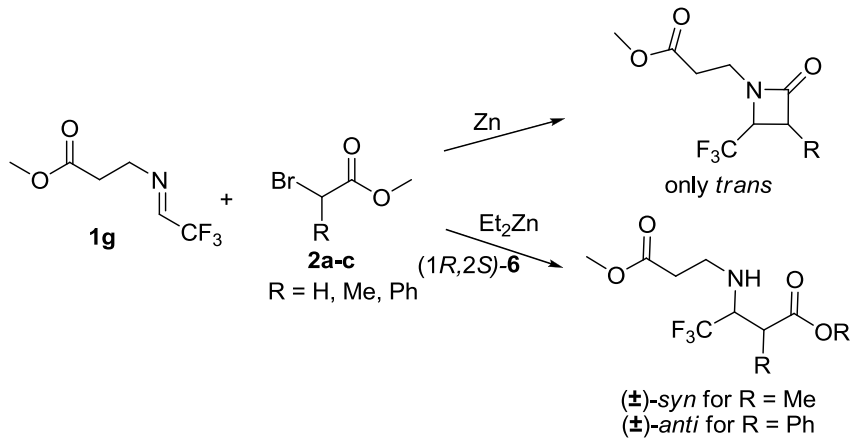


Figure 3. Proposed transition states in the presence of (1*R*,2*S*)-**6**.

Finally, in order to investigate how the presence of a further ester group could influence the chemical outcome, the trifluoromethyl aldimine **1g**[3] derived from β-alanine was considered in the two different approaches (**Scheme 9**).



Scheme 9. Aza-Reformatsky reactions performed on **1g** under homogeneous and heterogeneous condition.

Under heterogeneous conditions, the reactions lead to the expected β-lactams with high chemoselectivity and also high *trans* diastereoselectivity. In addition, corresponding expected β-amino esters were obtained under homogeneous conditions. Confirming our proposed transition states, the presence of an ester group on the β position of imine nitrogen, is responsible for the low or absent enantiocontrol found in the asymmetric aza-Reformatsky reactions.

[3] See ref. 54 in the **Chapter 2**.

β-Amino esters, keto esters, and malonates obtained through aza-Reformatsky and Mannich type-reactions respectively, allow to approach, through appropriate chemical transformations, new ψ[CH(CF_3)NH]-peptidomimetics. In fact, the [CH(CF_3)] group is a known isoster of the carbonyl group.

Similarly, the synthesis of bioisoster has been the aim of the project carried out at the University of Oxford (UK) under the supervision of Professor Darren J. Dixon and in collaboration with the SGC (Structural Genomics Consortium).

I have turned the attention on the development of potential epigenetic probes, characterized by a portion of acetyl lysine bioisoster, in order to draw conclusions about the binding elements, which are important for affinity with the bromodomain module of PCAF. A library of 20 compounds was developed and improvements in terms of affinity, compared to the lead compound, were obtained.

Experimental section

General Experimental Methods

IR spectra were recorded on a Perkin-Elmer 1600 Series FT/IR spectrophotometer in $CHCl_3$ as the solvent, and reported in . ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Varian-Mercury 300 instrument and on a Bruker Avance III 400 instrument, and reported in δ units. $CDCl_3$ was used as the solvent and $CHCl_3$ as the internal standard. ESI MS analyses were performed using a quadrupole-time of flight (Q-TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode.

HPLC analyses were performed with a Varian 9001 instrument using an analytical column (3.9 × 300 mm, flow rate 1.3 mL/min; detector: 254 nm) equipped with a Varian RI-4 differential refractometer, or a Varian 9050 UV/VIS detector. Eluents were HPLC grade. Enantiomeric excess were determined using analytical high performance liquid chromatography (HPLC) performed on Varian 9001 instrument (column and solvent conditions are given with the compound).

Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel plates.

Silica gel 230-400 mesh was used for column chromatography.

Computational details

All optimized geometries were located using hybrid functional theory (B3LYP) and the 6-31G(d, p) basis set using the continuum solvation model with chloroform (ε = 4.71) as the solvent conforming to the experimental conditions. All calculations were carried out using the Gaussian 09 program.[1]

[1] Gaussian 09, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A. J.; Peralta, E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.;

Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2013**.

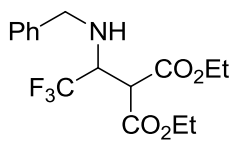
Chapter 10

Mannich type reactions of 1,3-dicarbonyl compounds with trifluoromethyl aldimines

Synthesis of trifluoromethyl imines (1a-c). The trifluoromethyl imines were synthesized following a procedure reported in the literature.[1] **1a-c** are known compounds.

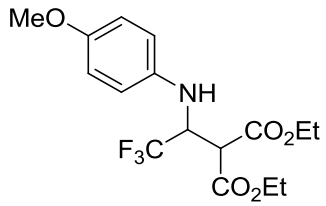
General procedure for the $ZrCl_4$-Catalyzed Mannich-type reactions.

To a mixture of trifluoromethyl aldimines **1a-c** (1 mmol) and diethyl malonate (**2**) or *β*-keto esters **6**, **9-11**, and **15-16** (1 mmol), $ZrCl_4$ (10 mol %) was added. The reactions were performed under solvent-free conditions and stirred at room temperature for 10-30 min. After H_2O addition, the crude mixtures were extracted with Et_2O. The collected organic layers were dried on anhydrous Na_2SO_4, the solvent evaporated *in vacuo* and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

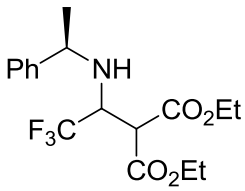


Diethyl 2-[1-(benzylamino)-2,2,2-trifluoroethyl]malonate (3a). Yellow oil (299 mg, 80%). IR: 1748, 1760. ^{1}H NMR ($CDCl_3$): 1.22–1.33 (m, 6H), 2.40 (br, 1H), 3.71 (d, *J* = 6.0 Hz, 1H), 3.86–4.07 (m, 3H), 4.15–4.29 (m, 4H), 7.21–7.31 (m, 5H). ^{19}F NMR ($CDCl_3$):–72.2 (d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 13.8, 13.9, 52.0, 52.3, 58.7 (q, *J* = 28.4 Hz), 61.8, 62.1, 125.8 (q, *J* = 286.3 Hz), 127.2, 128.1 (2C), 128.2 (2C), 139.2, 166.5, 166.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_4$ 348.1423, found 348.1424.

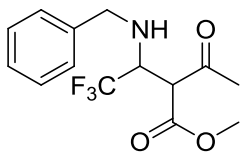
[1] See ref.17 in the **Chapter 1**.



Diethyl 2-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]malonate (3b). Brown oil (287 mg, 79%). IR: 1750, 1758. ^{1}H NMR ($CDCl_3$): 1.15 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 3.74 (s, 3H), 3.82 (d, *J* = 3.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.61–4.76 (m, 2H), 6.69–6.79 (m, 4H). ^{19}F NMR ($CDCl_3$): –74.1 (d, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 13.8, 13.9, 50.7, 55.6, 57.3 (q, *J* = 30.2 Hz), 62.1, 62.5, 114.7 (2C), 115.7 (2C), 125.1 (q, *J* = 284.7 Hz), 139.8, 153.3, 166.0, 167.0. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_5$ 364.1372, found 364.1375.

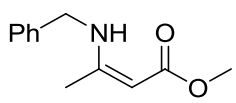


Diethyl 2-[2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]malonate (4/5c). Colorless oil (263 mg, 73%). IR: 1743, 1751. ^{1}H NMR ($CDCl_3$): 1.28–1.35 (m, 18H), 2.73 (br, 2H), 3.64 (d, *J* = 5.1 Hz, 1H), 3.71 (d, *J* = 5.1 Hz, 1H), 3.93–4.31 (m, 12H), 7.24–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): –73.4 (d, *J* = 7.4 Hz), –70.66 (d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 13.8, 13.9 (2C), 14.0, 23.6, 25.1, 51.3, 51.7, 55.4, 55.7, 56.4 (q, *J* = 28.0 Hz), 56.5 (q, *J* = 28.8 Hz), 61.7, 61.8, 62.0, 62.2, 125.5 (q, *J* = 284.3 Hz), 126.0 (q, *J* = 288.4 Hz), 126.8 (2C), 127.1 (2C), 127.2, 127.3, 128.3 (2C), 128.4 (2C), 143.7, 144.7, 166.4, 166.8 (2C), 166.9. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_4$ 362.1579, found 362.1582.

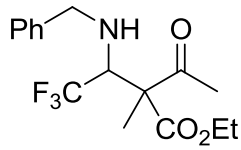


Methyl 2-acetyl-3-(benzylamino)-4,4,4-trifluorobutanoate (7/7'a). Yellow oil (227 mg, 75%). IR: 1740, 1715. ^{1}H NMR ($CDCl_3$): 1.84 (br, 1H), 2.01 (br, 1H), 2.20 (s, 3H), 2.24 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.78 (d, *J* = 2.1 Hz, 1H), 3.79 (d, *J* = 3.7 Hz, 1H), 3.82–3.86 (m, 2H), 3.92–4.05 (m, 4H), 7.23–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): –72.0 (d, *J* = 7.2 Hz) –71.9 (d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 29.1, 29.8, 52.3 (2C), 52.7, 52.9, 58.0 (q, *J* = 28.6 Hz), 58.6, 58.9 (q, *J* = 28.1 Hz), 59.4, 127.3, 127.4,

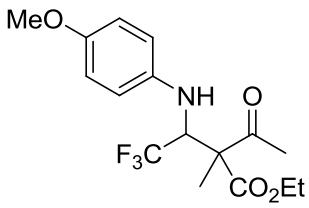
127.5 (q, *J* = 282.5 Hz, 2C), 128.3 (4C), 128.4 (4C), 138.8, 139.1, 167.2, 167.5, 198.8, 199.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO_3$ 304.1161, found 304.1165.



Methyl (*Z*)-3-(benzylamino)but-2-enoate (8). Colorless oil (68%). IR: 1740, 1650. ^{1}H NMR ($CDCl_3$): 1.93 (s, 3H), 3.65 (s, 3H), 4.44 (d, *J* = 6.4 Hz, 2H), 4.55 (s, 1H), 7.22−7.42 (m, 5H), 8.95 (br, 1H). ^{13}C NMR ($CDCl_3$): 19.4, 46.8, 50.0, 82.8, 126.7 (2C), 127.3, 128.8 (2C), 138.7, 161.9, 179.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1203.

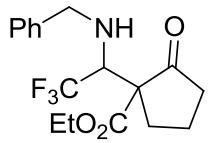


Ethyl 2-acetyl-3-(benzylamino)-4,4,4-trifluoro-2-methylbutanoate (12/12'a). Red oil (215 mg, 65%). IR: 1743, 1720. ^{1}H NMR ($CDCl_3$): 1.21–1.28 (m, 6H), 1.40 (s, 3H, minor *syn* isomer), 1.48 (s, 3H, major *anti* isomer), 1.83 (br, 2H), 2.18 (s, 6H), 3.79–3.85 (m, 2H), 4.07–4.30 (m, 7H), 4.38 (q, *J* = 7.3 Hz, 1H), 7.26–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): –65.60 (d, *J* = 7.6 Hz, minor *syn* isomer), –65.4 (d, *J* = 7.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): 13.4, 13.8, 13.9, 15.5, 25.8, 26.3, 52.7, 53.1, 61.9, 62.1, 62.2 (q, *J* = 26.6 Hz), 62.3, 62.6 (q, *J* = 26.7 Hz), 63.2, 126.0 (q, *J* = 288.6 Hz), 126.2 (q, *J* = 288.2 Hz), 127.3, 127.5, 128.0 (2C), 128.2 (2C), 128.3 (2C), 128.4 (2C), 138.8, 139.3, 169.4, 169.5, 200.7, 202.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_3$ 332.1474, found 332.1570.

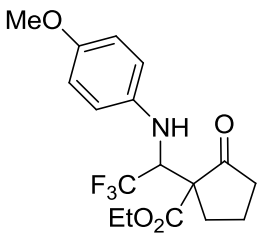


Ethyl 2-acetyl-4,4,4-trifluoro-3-(4-methoxyphenylamino)-2-methylbutanoate (12/12'b). Red oil (236 mg, 68%). IR: 1750, 1729. ^{1}H NMR ($CDCl_3$): 1.16 (t, *J* = 7.1 Hz, 3H, major *anti* isomer), 1.25 (t, *J* = 7.0 Hz, 3H, minor *syn* isomer), 1.54 (s, 3H, *syn* isomer), 1.56 (s, 3H, major *anti* isomer), 2.19 (s, 6H), 3.73 (s, 6H), 4.02–4.27 (m, 6H), 4.76–4.87 (m,

1H, major *anti* isomer), 4.92–5.03 (m, 1H, minor *syn* isomer), 6.67–6.78 (m, 8H). ^{19}F NMR ($CDCl_3$): –67. 3 (d, J = 7.4 Hz, minor *syn* isomer), –67.6 (d, J = 8.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): 13.7, 13.8, 15.1, 16.4, 26.2, 26.5, 55.5 (2C), 58.7 (q, J = 28.4 Hz), 59.8 (q, J = 28.2 Hz), 61.3 (2C), 62.0, 62.3, 114.7 (2C), 114.8 (2C), 115.2 (2C), 115.5 (2C), 125.3 (q, J = 286.9 Hz), 125.4 (q, J = 286.5 Hz), 139.3, 139.6, 153.2, 153.4, 169.5, 169.6, 201.8, 202.0. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{21}F_3NO_4$ 348.1423, found 348.1425.

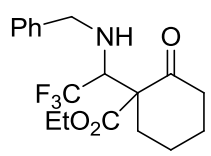


Ethyl 1-[1-(benzylamino)-2,2,2-trifluoroethyl]-2-oxocyclopentanecarboxylate (13/13'a). Red oil (257 mg, 75%). IR: 1758, 1725. ^{1}H NMR ($CDCl_3$): 1.21–1.31 (m, 6H), 1.59 (br, 2H), 1.98–2.05 (m, 6H), 2.17–2.76 (m, 6H), 3.78–4.09 (m, 4H), 4.12–4.41 (m, 6H), 7.24–7.34 (m, 10H). ^{19}F NMR ($CDCl_3$): –65.25 (d, J = 8.4 Hz, minor *syn* isomer), –65.5 (d, J = 8.4 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): 13.8, 13.9, 19.5, 20.2, 27.0, 27.1, 37.2, 38.5, 52.7, 54.2, 62.0, 62.2 (q, J = 26.5 Hz, 2C), 62.2, 63.1, 64.5, 125.9 (q, J = 287.6 Hz, 2C), 127.3, 127.4, 128.0 (4C), 128.3 (4C), 139.0, 139.3, 166.7, 166.8, 210.1, 210.4. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_3$ 344.1474, found 344.1471.

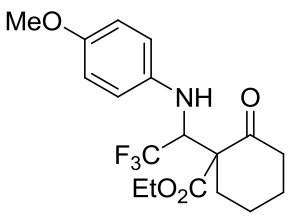


Ethyl 2-oxo-1-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]cyclopentanecarboxylate (13/13'b). Brown oil (262 mg, 73%). IR: 1762, 1759. ^{1}H NMR ($CDCl_3$): 1.04 (t, J = 7.1 Hz, 3H, major *anti* isomer), 1.23 (t, J = 7.1 Hz, 3H, minor *syn* isomer), 1.93–2.47 (m, 10H), 2.54–2.83 (m, 2H), 3.54 (br, 1H), 3.74 (s, 6H), 3.85 (br, 1H), 3.90–4.04 (m, 2H), 4.10–4.25 (m, 2H), 4.82–4.96 (m, 2H), 6.69–6.78 (m, 8H). ^{19}F NMR ($CDCl_3$): –69.9 (d, J = 7.2 Hz, minor *syn* isomer), –68.37 (d, J = 7.0 Hz, major *anti* isomer). ^{13}C NMR ($CDCl_3$): 13.7, 13.9, 19.5, 20.0, 27.2, 28.2, 37.1, 38.3, 55.6 (2C), 59.7 (q, J = 28.1 Hz), 61.0 (q, J = 27.7 Hz), 62.0, 62.3, 62.5, 63.9, 114.7 (4C), 115.7 (2C), 116.4 (2C), 125.1 (q, J = 285.9 Hz), 125.6 (q, J = 286.6 Hz), 139.5, 139.9, 153.5,

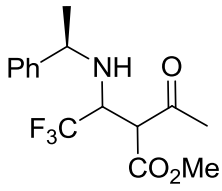
153.8, 166.4, 167.2, 209.4, 210.7. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{21}F_3NO_4$ 360.1423, found 360.1427.



Ethyl 1-[1-(benzylamino)-2,2,2-trifluoroethyl]-2-oxocyclohexanecarboxylate (14a). White oil (278 mg, 78%). IR: 1743, 1729.^{1}H NMR ($CDCl_3$): 1.21 (t, *J* = 7.1 Hz, 3H), 1.64–1.94 (m, 6H), 2.36–2.52 (m, 3H), 3.73–4.10 (m, 2H), 4.13–4.28 (m, 3H), 7.22–7.33 (m, 5H). ^{19}F NMR ($CDCl_3$): –63.8 (d, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$): 13.8, 21.9, 25.9, 30.9, 40.7, 52.8, 61.6 (q, *J* = 27.4 Hz), 61.9, 64.3, 126.0 (q, *J* = 288.7 Hz), 127.3, 128.1 (2C), 128.3 (2C), 139.1, 168.5, 203.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_3$ 358.1630, found 358.1635.

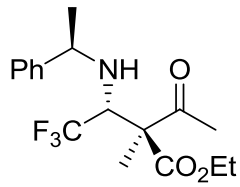


Ethyl 2-oxo-1-[2,2,2-trifluoro-1-(4-methoxyphenylamino)ethyl]cyclohexanecarboxylate (14b). White oil (317 mg, 85%). IR: 1745, 1728. ^{1}H NMR ($CDCl_3$): 1.11 (t, *J* = 7.1 Hz, 3H), 1.63–2.03 (m, 6H), 2.42–2.54 (m, 3H), 3.73 (s, 3H), 3.97 (q, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 1H), 4.83–4.91 (m, 1H), 6.66–6.76 (m, 4H). ^{19}F NMR ($CDCl_3$): –67.0 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 13.7, 22.0, 26.2, 31.4, 40.8, 55.7, 58.9 (q, *J* = 29.1 Hz), 62.2, 63.8, 114.8 (2C), 115.3 (2C), 125.1 (q, *J* = 286.2 Hz), 139.8, 153.3, 168.3, 203.9. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_4$ 374.1579, found 374.1571.

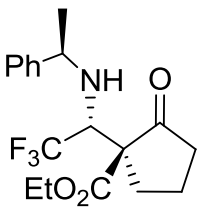


Methyl 2-acetyl-4,4,4-trifluoro-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-17,18/*syn*-17',18'). Yellow oil (228 mg, 72%). IR: 1739, 1725. ^{1}H NMR ($CDCl_3$): 1.29–1.34 (m, 12H), 1.67 (br, 1H), 2.05 (s, 3H), 2.12 (s, 3H), 2.21 (br, 1H), 2.29 (s, 3H), 2.32 (s, 3H), 2.50 (br, 1H), 3.65–3.81 (m, 20H), 3.98–4.09 (m, 5H), 7.23–7.36 (m, 20H). ^{19}F NMR ($CDCl_3$): –73.2 (d, *J* = 7.6 Hz), –72.63 (d, *J* = 6.9 Hz), –70.52 (d, *J* = 6.9 Hz), –70.07 (d, *J* = 7.9 Hz). ^{13}C NMR ($CDCl_3$):

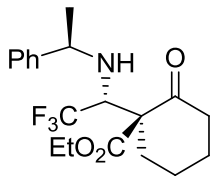
22.7, 23.1, 24.7, 24.8, 28.7, 29.3, 29.9, 30.9, 52.5, 52.7 (2C), 52.9, 55.3, 55.4, 55.6 (q, *J* = 26.3 Hz), 55.7 (2C), 55.7 (q, *J* = 27.8 Hz), 56.6 (q, *J* = 28.3 Hz), 56.7 (q, *J* = 27.7 Hz), 57.6, 58.2, 59.0, 59.1, 125.6 (q, *J* = 277.4 Hz), 126.0 (q, *J* = 288.1 Hz), 126.6 (2C), 126.7 (2C), 127.1 (q, *J* = 284.4 Hz), 127.2 (q, *J* = 280.4 Hz), 127.3 (2C), 127.4 (4C), 127.6 (2C), 128.3 (2C), 128.4 (4C), 128.5 (2C), 143.1, 143.2, 144.7, 144.8, 167.3, 167.5, 167.7, 167.8, 199.0, 199.1, 200.4 (2C). HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{19}F_3NO_3$ 318.1317, found 318.1312.



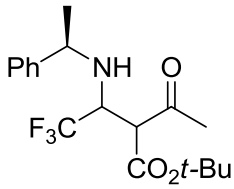
Ethyl (2*S*,3*R*)-2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (19). Light yellow oil (234 mg, 68%). $[\alpha]_D$ = +86.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1742, 1726. ^1H NMR ($CDCl_3$): 1.28–1.31 (m, 6H), 1.46 (s, 3H), 1.97 (br, 1H), 2.22 (s, 3H), 4.04 (q, *J* = 6.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 1H), 4.36 (q, *J* = 8.1 Hz, 1H), 7.22−7.32 (m, 5H). ^{19}F NMR ($CDCl_3$): –65.0 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): 13.9, 15.3, 21.6, 26.6, 55.5, 59.1 (q, *J* = 26.7 Hz), 62.1, 63.2, 126.0 (q, *J* = 288.4 Hz), 126.5 (2C), 127.4, 128.5 (2C), 145.5, 169.4, 202.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_3$ 346.1630, found 346.1633.



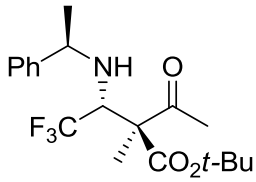
Ethyl (1*S*)-2-oxo-1-[(1*R*)-2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]cyclopentanecarboxylate (20). Light yellow oil (278 mg, 78%). $[\alpha]_D$ = +54.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1731, 1718. ^1H NMR ($CDCl_3$): 1.23–1.28 (m, 6H), 1.60 (br, 1H), 1.85–1.96 (m, 3H), 2.12–2.23 (m, 1H), 2.19–2.28 (m, 1H), 2.59–2.63 (m, 1H), 3.96 (q, *J* = 6.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 1H), 7.16−7.29 (m, 5H). ^{19}F NMR ($CDCl_3$): –65.0 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): 14.0, 19.6, 21.6, 27.2, 37.2, 55.3, 59.2 (q, *J* = 26.3 Hz), 62.3, 64.5, 126.5 (2C), 126.9 (q, *J* = 288.4 Hz), 127.5, 128.6 (2C), 146.4, 166.8, 210.0. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{23}F_3NO_3$ 358.1630, found 358.1636.



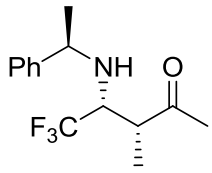
Ethyl (1*S*)-2-oxo-1-[(1*R*)-2,2,2-trifluoro-1-{[(*R*)-1-phenylethyl]amino}ethyl]cyclohexanecarboxylate (21). Colorless oil (289 mg, 78%). $[\alpha]_D$ = +79.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1740, 1715. ^{1}H NMR ($CDCl_3$): 1.26–1.30 (m, 6H), 1.57–1.67 (m, 3H), 1.84–1.99 (m, 4H), 2.37–2.41 (m, 1H), 2.52–2.65 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 1H), 7.23−7.33 (m, 5H). ^{19}F NMR ($CDCl_3$): –65.0 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): 13.9, 21.5, 22.1, 25.7, 30.3, 40.9, 55.2, 58.2 (q, *J* = 26.6 Hz), 61.9, 64.3, 126.4 (q, *J* = 287.8 Hz), 126.5 (2C), 127.4, 128.5 (2C), 146.6, 168.4, 203.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{25}F_3NO_3$ 372.1787, found 372.1785.



***tert*-Butyl 2-acetyl-4,4,4-trifluoro-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-22,23/*syn*-22',23').** Colorless oil (233 mg, 65%). IR: 1737, 1712. ^{1}H NMR ($CDCl_3$): 1.48–1.58 (m, 52H), 2.04 (s, 3H), 2.07 (s, 3H), 2.29–2.30 (m,6H), 3.50– 3.73 (m, 6H), 3.99–4.08 (m, 6H), 7.26−7.36 (m, 20H). ^{19}F NMR ($CDCl_3$): –70.1 (d, *J* = 8.6 Hz), –70.50 (d, *J* = 7.7 Hz), –72.21 (d, *J* = 8.5 Hz), –72.83 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 22.6, 23.3, 24.9, 25.5, 27.6 (2C), 27.8 (12C), 28.3 (2C), 54.6, 55.3, 55.4, 55.6, 56.1 (q, *J* = 28.0 Hz), 56.3 (q, *J* = 27.5 Hz), 56.4 (q, *J* = 30.0 Hz), 56.5 (q, *J* = 28.0 Hz), 59.2, 59.7, 59.9, 60.5, 82.8, 82.9, 83.0, 83.1, 125.7 (q, *J* = 278.8 Hz), 125.8 (q, *J* = 279.8 Hz), 125.9 (q, *J* = 285.5 Hz), 126.1 (q, *J* = 288.5 Hz), 126.7 (2C), 126.9 (2C), 127.0 (2C), 127.3 (2C), 127.4, 127.5, 127.6 (2C), 128.4 (4C), 128.5 (2C), 128.7 (2C), 143.0, 143.4, 143.8, 144.8, 165.9, 166.1, 166.7, 166.8, 199.7, 199.8, 200.5, 200.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{25}F_3NO_3$ 360.1787, found 360.1789.



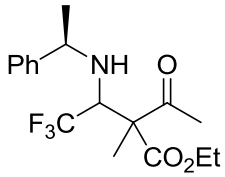
***tert*-Butyl (2*S*,3*R*)-2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (24).** Yellow oil (238 mg, 64%). $[\alpha]_D$ = +123.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1752, 1719. ^1H NMR ($CDCl_3$): 1.25 (d, *J* = 6.4 Hz, 3H) 1.34 (s, 3H), 1.40 (s, 9H), 1.95 (br, 1H), 2.15 (s, 3H), 3.98 (q, *J* = 6.4 Hz, 1H), 4.15−4.24 (m, 1H), 7.14−7.26 (m, 5H). ^{19}F NMR ($CDCl_3$): –64.3 (d, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$): 15.8, 21.4, 26.5, 27.7 (3C), 55.3, 59.5 (q, *J* = 26.5 Hz), 63.6, 82.7, 126.1 (q, *J* = 288.9 Hz), 126.4 (2C), 127.2, 128.4 (2C), 146.5, 168.4, 202.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{27}F_3NO_3$ 374.1943 found 374.1941.



(3*R*,4*R*)-5,5,5-trifluoro-3-methyl-4-{[(*R*)-1-phenylethyl]amino}pentan-2-one (25). Yellow oil (75 mg, 43%). $[\alpha]_D$ = +72.0 (*c* = 1 g/100 mL, $CHCl_3$). IR: 1715. ^1H NMR ($CDCl_3$): 1.19 (d, *J* = 7.1 Hz, 3H), 1.26 (d *J* = 6.4 Hz, 3H), 1.51 (br, 1H), 2.15 (s, 3H), 2.76–2.83 (m, 1H), 3.60–3.67 (m, 1H), 3.91 (q, *J* = 6.4 Hz, 1H), 7.20−7.29 (m, 5H). ^{19}F NMR ($CDCl_3$): –72.3 (d, *J* = 8.9 Hz). ^{13}C NMR ($CDCl_3$): 11.1, 23.3, 28.6, 46.4, 55.6, 56.4 (q, *J* = 27.0 Hz), 126.8 (2C), 127.4, 127.7 (q, *J* = 245.8 Hz), 128.5 (2C), 144.7, 208.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{19}F_3NO$ 274.1419, found 274.1421.

*General procedure for the $AlCl_3$-Catalyzed Mannich-type reactions of β-keto ester **9** with aldimine **1c**.*

To a mixture of trifluoromethyl aldimines **1c** (1 mmol) and *β*-keto esters **9** (1 mmol), $AlCl_3$ (10 mol %) was added. The reaction was performed under solvent-free conditions and stirred at room temperature for 30 min. After H_2O addition, the crude mixtures were extracted with Et_2O. The collected organic layers were dried on anhydrous Na_2SO_4, the solvent evaporated *in vacuo* and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 8:2).

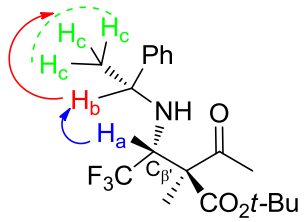


Ethyl 2-acetyl-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (*anti*-19,26/*syn*-19',26'). Yellow oil (169 mg, 49%). IR: 1751, 1715. ^{1}H NMR ($CDCl_3$): 1.12−1.41 (m, 36H), 1.46−1.58 (br, 4H), 1.81 (s, 3H), 2.04 (s, 3H), 2.22 (s, 3H), 2.32 (s, 3H), 3.89–4.39 (m, 16H), 7.22−7.35 (m, 20H). ^{19}F NMR ($CDCl_3$): –63.3 (d, *J* = 7.0 Hz), –63.54 (d, *J* = 6.7 Hz), –64.99 (d, *J* = 8.3 Hz), –65.22 (d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$): 13.6, 13.7, 13.8, 13.9, 14.2, 15.2, 16.5 (2C), 21.3 (2C), 21.6 (2C), 24.3, 24.8, 26.1, 26.4, 53.1, 55.3, 55.5, 55.8, 59.0 (q, *J* = 27.3 Hz), 59.1 (q, *J* = 26.6 Hz), 60.0 (q, *J* = 26.6 Hz), 60.8 (q, *J* = 26.3 Hz), 61.9, 62.0, 62.2 (2C), 62.6 (3C), 63.2, 125.8 (q, *J* = 280.8 Hz), 125.9 (q, *J* = 267.5 Hz), 125.9 (q, *J* = 288.1 Hz), 126.4 (2C), 127.0 (2C), 127.4 (4C), 127.7 (2C), 128.0 (2C), 128.3 (2C), 128.4 (2C), 128.6 (4C), 127.7 (q, *J* = 245.8 Hz), 142.8, 143.4, 145.2, 145.5, 169.4 (2C), 169.8, 169.9, 201.2, 201.3, 202.4, 202.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO_3$ 346.1630 found 346.1623.

2D NMR spectra and optimized geometries to determine the absolute configuration of the new chiral centers.

1. To determine the absolute configuration of the new trifluoromethyl substituted chiral-center (C_β), 2D NMR spectra and optimized geometries of β'-amino β-dicarbonyl compound **24** was considered.

2D NMR spectra and optimized geometries of 24



24

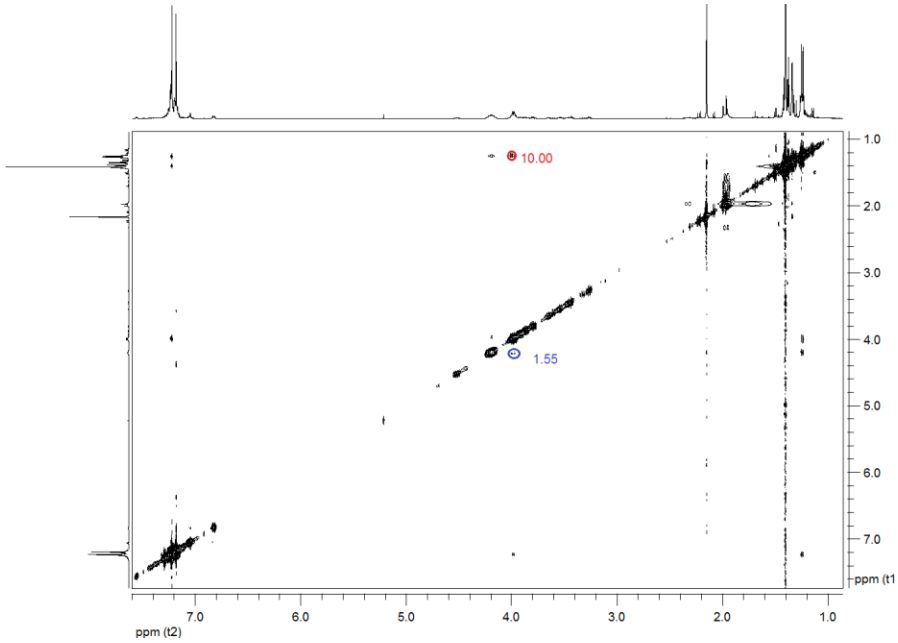
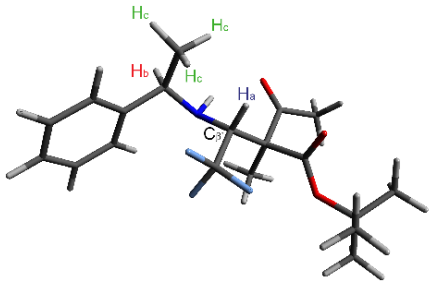
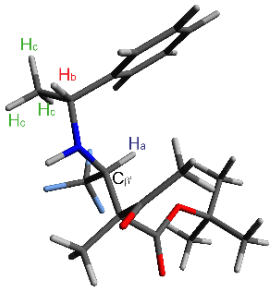


Figure 1. 2D NOESY spectrum of **24**.

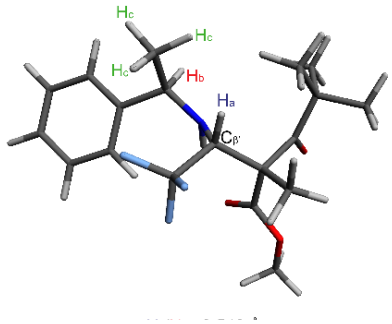
The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_b and H_a was measured 1.55 a.u. (corresponding to an interproton distance of 3.62 Å), in order to determine the absolute configuration.



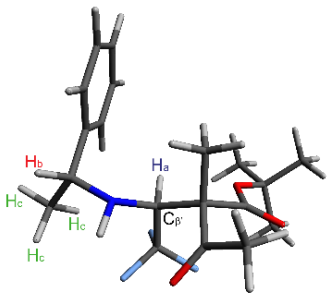
H_a/H_b : 3.616 Å
(*R*,*R*,*S*)
possible diastereomer *anti*-**24**



H_a/H_b : 3.646 Å
(*R*,*S*,*R*)



H_a/H_b : 3.540 Å
(*R*,*R*,*R*)
possible diastereomer *syn*-**24**



H_a/H_b : 3.605 Å
(*R*,*S*,*S*)

Figure 2. Optimized geometries of all possible diastereomers. By NOESY analysis coupled with computational studies the *R* absolute configuration can be assigned to C_β

Calculated Coordinates:

(*R*,*R*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	1.353000	1.281210	0.374545
2	6	0	2.634923	1.445779	0.369280
3	6	0	0.231243	0.578607	0.257404
4	6	0	-1.117646	0.914567	0.484439
5	6	0	0.511232	-0.935341	-0.281814
6	1	0	0.073892	0.849472	-1.310867
7	6	0	-1.441875	2.440723	0.389550
8	6	0	-2.865231	2.872160	0.684341
9	8	0	-0.600533	3.274706	0.102997
10	6	0	-1.071981	0.539603	1.983105
11	1	0	-1.00374	-0.541088	2.104431
12	1	0	-0.194811	0.994347	2.446201
13	6	0	-2.278150	0.247562	-0.298806
14	8	0	-2.456305	0.492086	-1.478559
15	8	0	-3.038662	-0.528972	0.469784
16	6	0	-4.207689	-1.283163	-0.065690
17	6	0	-3.733754	-2.270561	-1.133846
18	6	0	-5.257150	-0.302849	-0.592669
19	6	0	-4.715811	-2.01815	1.174932
20	1	0	-3.364603	-1.75216	-2.019084
21	1	0	-4.572380	-2.909560	-1.426748

22	1	0	-2.938509	-2.908240	-0.739137
23	9	0	0.914712	-1.426436	0.905353
24	9	0	1.469300	-1.231893	-1.18866
25	9	0	-0.583459	-1.653149	-0.647891
26	1	0	1.009073	2.221562	0.535895
27	6	0	3.650213	0.345746	-0.037899
28	6	0	4.530156	-0.181004	-0.991362
29	1	0	4.468211	0.136904	-2.026467
30	6	0	5.496458	-1.125954	-0.634165
31	1	0	6.164617	-1.522293	-1.393812
32	6	0	5.601617	-1.560287	0.686400
33	1	0	6.352222	-2.294445	0.964846
34	6	0	4.729534	-1.041666	1.647458
35	1	0	4.799334	-1.372365	2.680247
36	6	0	3.766839	-0.100539	1.287030
37	1	0	3.080078	0.290652	2.030027
38	1	0	3.052143	2.358590	0.077756
39	6	0	2.472565	1.743256	-1.868307
40	1	0	2.154168	0.863492	-2.433473
41	1	0	3.414766	2.095842	-2.296937
42	1	0	1.730530	2.534912	-2.008778
43	1	0	-1.967867	0.877623	2.506345
44	1	0	-3.399926	2.181477	1.338202
45	1	0	-2.852409	3.873062	1.118320
46	1	0	-3.406698	2.919852	-0.266848
47	1	0	-4.895210	0.232370	-1.470620
48	1	0	-5.529449	0.420705	0.181669
49	1	0	-6.159239	-0.857538	-0.868492
50	1	0	-3.943714	-2.680225	1.576588
51	1	0	-5.589010	-2.622905	0.914945
52	1	0	-5.006395	-1.308683	1.954920

(*R*,*S*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstrom) X	Y	Z
1	7	0	-1.357758	-1.547574	0.569733
2	6	0	-2.737391	-1.227190	0.117875
3	6	0	-0.161322	-1.002971	0.044267
4	6	0	1.027518	-1.130858	0.971198
5	1	0	-0.326339	0.055219	0.246899
6	6	0	0.196281	-1.621553	1.417692
7	6	0	0.506876	-0.611060	2.360289
8	6	0	0.036108	0.821188	2.482677
9	8	0	0.544968	-1.345084	3.327657
10	6	0	2.235864	-0.246981	0.577982
11	8	0	3.377847	-0.531952	0.878236
12	8	0	1.855242	0.861662	-0.071816
13	6	0	3.759187	1.164273	-1.607990
14	6	0	3.594969	2.496152	0.557829
15	6	0	1.926260	2.866530	-1.297122
16	1	0	-1.273111	-2.549523	0.706910
17	6	0	-2.971902	0.277920	0.036463
18	6	0	-2.735238	1.021414	-1.129193
19	1	0	-2.360108	0.530388	-2.019906
20	6	0	-2.972016	2.398061	-1.160270
21	1	0	-2.782174	2.954415	-2.073611
22	6	0	-3.454846	3.055559	-0.028180
23	1	0	-3.644447	4.124525	-0.055476
24	6	0	-3.697350	2.327540	1.138604
25	1	0	-4.078726	2.827021	2.024462
26	6	0	-3.456342	0.953578	1.166667
27	1	0	-3.649128	0.392318	2.077304
28	1	0	-3.356209	-1.580920	0.951382
29	6	0	-3.219497	-2.000065	-1.124199
30	1	0	-2.687255	-1.723840	-2.034258
31	1	0	-4.287393	-1.818905	-1.282992
32	1	0	-3.080605	-3.075034	-0.968602
33	1	0	-0.696248	1.083477	1.717574
34	1	0	-0.401138	0.959412	3.472275
35	1	0	0.886536	1.501451	2.370226

36	9	0	-0.522373	-1.057478	-2.421792
37	9	0	-0.054337	-2.949735	-1.454945
38	9	0	1.499142	-1.458361	-1.756726
39	6	0	2.832733	1.850528	-0.601249
40	1	0	1.359755	2.391514	-2.103088
41	1	0	2.531503	3.669945	-1.726287
42	1	0	1.219468	3.306671	-0.588057
43	1	0	3.172176	0.640254	-2.367216
44	1	0	4.420529	0.449888	-1.117299
45	1	0	4.370368	1.921739	-2.108129
46	1	0	2.899188	2.946779	1.272439
47	1	0	4.237466	3.291862	0.168112
48	1	0	4.218276	1.768164	1.077371
49	6	0	1.516452	-2.578072	1.148035
50	1	0	1.915510	-2.976366	0.214741
51	1	0	0.706474	-3.221009	1.497136
52	1	0	2.305542	-2.607223	1.897568

(*R*,*R*,*R*)

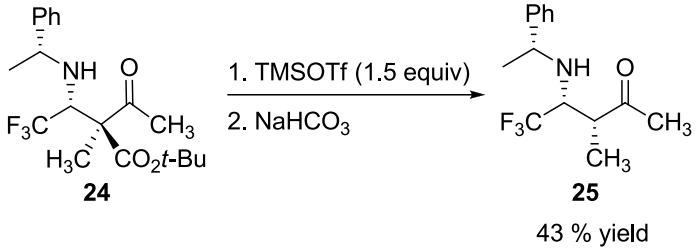
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	4.364189	1.189489	-0.795717
2	6	0	5.498809	0.394555	-0.949026
3	6	0	5.374628	-0.994514	-0.862977
4	6	0	4.129563	-1.570876	-0.618485
5	6	0	2.981107	-0.781221	-0.442337
6	6	0	3.117385	0.607359	-0.548181
7	6	0	1.632525	-1.487461	-0.214327
8	7	0	0.444864	-0.624902	-0.310054
9	6	0	-0.317848	-0.088201	0.797005
10	6	0	-1.675542	0.474218	0.239694
11	6	0	-1.406783	1.687834	-0.691771
12	8	0	-2.382213	2.599583	-0.623172
13	6	0	-2.252407	3.726103	-1.515894
14	6	0	1.644334	-2.357673	1.052430
15	6	0	0.380646	0.933748	1.735659
16	9	0	1.628871	0.539159	2.065999
17	9	0	-0.300483	1.051073	2.904362
18	9	0	0.489555	2.181468	1.221785
19	6	0	-2.682616	0.858813	1.352993
20	6	0	-2.344597	-0.572208	-0.724749
21	6	0	-2.871403	-1.981158	-0.320302
22	8	0	-2.583139	-0.195658	-1.860348
23	8	0	-0.442473	1.805199	-1.424018
24	1	0	-0.562615	-0.899275	1.484564
25	6	0	-4.418346	-1.859894	-0.306626
26	6	0	-2.409387	-2.571300	1.022005
27	6	0	-2.452155	-2.950216	-1.449777
28	1	0	-1.332144	4.273644	-1.303850
29	1	0	-3.124168	4.349611	-1.324475
30	1	0	-2.241368	3.384539	-2.552627
31	1	0	0.507556	0.048692	-1.065530
32	1	0	2.251900	1.250533	-0.443103
33	1	0	4.442485	2.270539	-0.870227
34	1	0	6.466582	0.848359	-1.141397
35	1	0	6.246339	-1.629859	-0.992760
36	1	0	4.049542	-2.654360	-0.573951
37	1	0	1.537299	-2.188920	-1.056859
38	1	0	1.765243	-1.762000	1.958268
39	1	0	2.475434	-3.064080	1.006137
40	1	0	0.725709	-2.945542	1.130591
41	1	0	-3.665299	1.055787	0.922328
42	1	0	-2.775701	0.064589	2.093415
43	1	0	-2.364253	1.763363	1.870647
44	1	0	-2.867185	-3.944105	-1.254624
45	1	0	-2.815344	-2.600812	-2.417552
46	1	0	-1.362484	-3.035914	-1.501983
47	1	0	-4.858958	-2.850689	-0.155515
48	1	0	-4.768480	-1.212193	0.503312
49	1	0	-4.783168	-1.458016	-1.254670
50	1	0	-2.914923	-3.531289	1.169846

51	1	0	-1.337074	-2.773881	1.031340
52	1	0	-2.660475	-1.947113	1.882333

(*R*,*S*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.022367	1.192352	0.748443
2	6	0	3.117871	0.035683	-0.036349
3	6	0	3.637700	0.156904	-1.334034
4	6	0	4.050025	1.391146	-1.833729
5	6	0	3.946591	2.537378	-1.040494
6	6	0	3.430802	2.433605	0.250785
7	6	0	2.670064	-1.338303	0.456772
8	6	0	2.829155	-1.536212	1.974907
9	7	0	1.335535	-1.675461	-0.096017
10	6	0	0.191399	-0.835655	0.195053
11	6	0	-0.499815	-1.147072	1.559181
12	9	0	-0.123349	-2.326988	2.088490
13	6	0	-0.803303	-0.811568	-1.019619
14	6	0	-0.058746	-0.236222	-2.253616
15	6	0	-2.000101	0.132148	-0.764460
16	8	0	-3.131012	-0.073377	-1.161388
17	8	0	-1.590159	1.221643	-0.105738
18	6	0	-2.518217	2.299757	0.328318
19	6	0	-3.103721	2.993475	-0.902617
20	6	0	-1.585669	3.232094	1.102701
21	6	0	-3.593401	1.716080	1.247855
22	6	0	-1.324299	-2.239340	-1.322864
23	8	0	-1.133613	-3.135791	-0.517695
24	6	0	-2.014019	-2.510743	-2.639813
25	9	0	-1.854869	-1.164485	1.501147
26	9	0	-0.177619	-0.194702	2.479838
27	1	0	-2.151416	4.079812	1.499178
28	1	0	0.543747	0.190421	0.302327
29	1	0	1.109340	-2.649820	0.072279
30	1	0	2.630302	1.133473	1.758708
31	1	0	3.347876	3.316849	0.877602
32	1	0	4.269642	3.500162	-1.425487
33	1	0	4.456715	1.458866	-2.838740
34	1	0	3.722089	-0.731149	-1.955310
35	1	0	3.336713	-2.065903	-0.022596
36	1	0	2.178075	-0.881286	2.557406
37	1	0	3.864114	-1.343625	2.275853
38	1	0	2.583013	-2.567302	2.243546
39	1	0	-1.272116	-2.515597	-3.446745
40	1	0	-2.488358	-3.492030	-2.595309
41	1	0	-2.750517	-1.737111	-2.862059
42	1	0	-1.122467	2.698643	1.937452
43	1	0	-0.793796	3.616447	0.453430
44	1	0	-3.131411	1.151321	2.061744
45	1	0	-4.269136	1.057250	0.702176
46	1	0	-4.175444	2.534435	1.682429
47	1	0	-2.303131	3.341916	-1.562071
48	1	0	-3.685287	3.864328	-0.584818
49	1	0	-3.757427	2.322564	-1.460974
50	1	0	0.323451	0.760906	-2.023620
51	1	0	-0.727796	-0.156093	-3.113125
52	1	0	0.787182	-0.876519	-2.506377

2. In order to determine the absolute configuration of the new quaternary chiral center (C_α) of β'-amino β-dicarbonyl compound **24**, and thus also the *syn* or *anti* configuration, a diastereoselective decarboxylation, in which the same high selectivity was retained, was performed (**Scheme 1**), following the procedure reported in the literature.[2] Then, the absolute configuration of α-methyl substituted carbon in **25** was determined.



Scheme 1. Decarboxylation reaction of **24**.

2D NMR spectra and optimized geometries of (*R*,*R*,*R*)-β-amino ketone 25

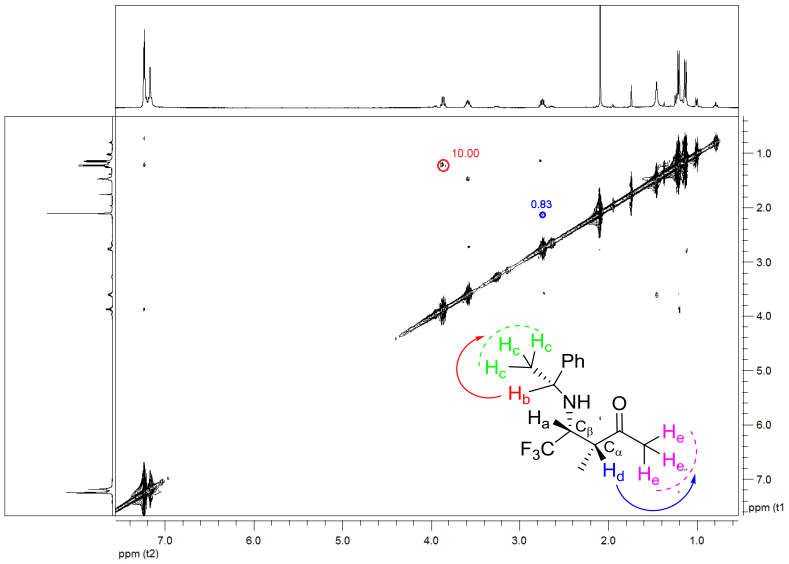
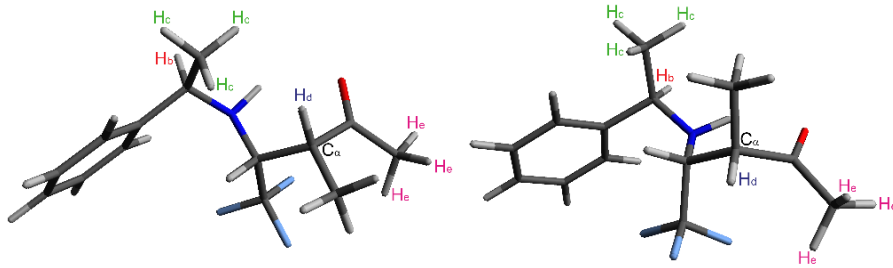


Figure 3. 2D NOESY spectrum of **25**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_d and H_e was measured 0.83 a.u. (corresponding to an interproton distance of 4.03 Å), in order to determine the absolute configuration.

[2] See ref.40 in the **Chapter 2**.



H_a/H_e : 3.857 Å
(*R*,*R*,*R*)-**25**

H_a/H_e : 2.950 Å
(*R*,*R*,*S*)-**25**

Figure 4. Optimized geometries of obtained (*R*,*R*,*R*)-**25** and of its possible diastereomer (*R*,*R*,*S*).

Calculated Coordinates:

(*R*,*R*,*R*)-**25** obtained diastereomer

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.344535	0.480449	2.184862
2	6	0	1.942853	0.800232	0.736815
3	6	0	3.086614	0.743194	-0.290658
4	6	0	4.337350	-0.044564	0.023824
5	6	0	0.684603	0.009201	0.218786
6	6	0	0.966201	-1.480156	-0.019376
7	9	0	1.518605	-2.084496	1.065269
8	7	0	0.096047	0.541655	-1.001704
9	6	0	-1.070497	1.440629	-0.882846
10	6	0	-2.286049	0.670209	-0.360558
11	6	0	-2.679599	-0.499106	-1.031769
12	6	0	-3.797120	-1.221543	-0.622346
13	6	0	-4.547314	-0.792287	0.477278
14	6	0	-4.166820	0.363776	1.155381
15	6	0	-3.045578	1.089791	0.737902
16	9	0	-0.155196	-2.163222	-0.309526
17	9	0	1.829788	-1.668867	-1.048802
18	1	0	-0.063960	0.032050	1.018203
19	1	0	-2.775562	1.990685	1.278480
20	1	0	-4.739794	0.708062	2.011724
21	1	0	-5.418619	-1.355180	0.799360
22	1	0	-4.084433	-2.121256	-1.159236
23	1	0	-2.087541	-0.843324	-1.873351
24	6	0	-0.797691	2.764820	-0.148884
25	1	0	0.820975	0.972254	-1.570260
26	8	0	2.964770	1.341347	-1.351838
27	1	0	4.858309	0.394096	0.881788
28	1	0	4.997038	-0.039321	-0.844410
29	1	0	1.474041	0.571917	2.842134
30	1	0	3.095935	1.193728	2.536793
31	1	0	-0.585157	2.620208	0.915712
32	1	0	-1.656514	3.439101	-0.226594
33	1	0	0.062067	3.266991	-0.602235
34	1	0	-1.299927	1.705807	-1.923667
35	1	0	2.745551	-0.525740	2.306368
36	1	0	1.615239	1.843051	0.708745
37	1	0	4.084161	-1.074091	0.294140

(*R*,*R*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-3.408971	-2.079919	1.591569

2	6	0	-2.384202	-1.876822	1.265944
3	9	0	-1.460800	1.967745	-0.711449
4	6	0	-0.679765	1.481862	0.288022
5	9	0	0.574479	1.898513	0.051212
6	6	0	-2.256478	-0.426248	0.769538
7	6	0	-3.232134	-0.226168	-0.401133
8	6	0	-4.374564	0.739268	-0.200064
9	6	0	-0.785533	-0.047729	0.401086
10	7	0	-0.268273	-0.656401	-0.811994
11	6	0	0.924780	-1.526402	-0.762197
12	6	0	2.172723	-0.731461	-0.376654
13	6	0	2.801353	-0.853864	0.867452
14	6	0	3.940944	-0.102135	1.173469
15	6	0	4.473103	0.779173	0.234334
16	6	0	3.856873	0.907445	-1.014573
17	6	0	2.719554	0.161000	-1.311306
18	9	0	-1.088166	2.091580	1.433177
19	8	0	-3.104837	-0.869018	-1.434173
20	6	0	0.751070	-2.828372	0.039202
21	1	0	-0.161709	-0.305504	1.266022
22	1	0	2.413833	-1.543891	1.610241
23	1	0	4.412182	-0.212826	2.146061
24	1	0	5.361007	1.359209	0.468660
25	1	0	4.265553	1.588271	-1.755966
26	1	0	2.237191	0.271935	-2.278910
27	1	0	-1.019322	-1.077434	-1.349456
28	1	0	-4.953923	0.457411	0.686969
29	1	0	-5.021247	0.750572	-1.078268
30	1	0	0.526288	-2.646806	1.094413
31	1	0	1.660222	-3.436431	-0.009064
32	1	0	-0.070392	-3.416685	-0.379514
33	1	0	1.069154	-1.822990	-1.808486
34	1	0	-3.976143	1.742520	-0.016514
35	1	0	-1.720880	-2.053169	2.117470
36	1	0	-2.137252	-2.585291	0.473356
37	1	0	-2.554959	0.240150	1.583569

As a consequence of the results obtained from the above reported procedure, the (*R*,*R*,*R*) absolute configuration can be assigned to the obtained *syn* isomer **25**. As a consequence, the (R,R,S) absolute configuration can be assigned to the starting β′-amino β-keto ester anti isomer **24**. The (*R*,*R*,*S*) absolute configuration can be assigned to all obtained β'-amino β-keto ester *anti*-isomer **19**, **20**, and **21**.

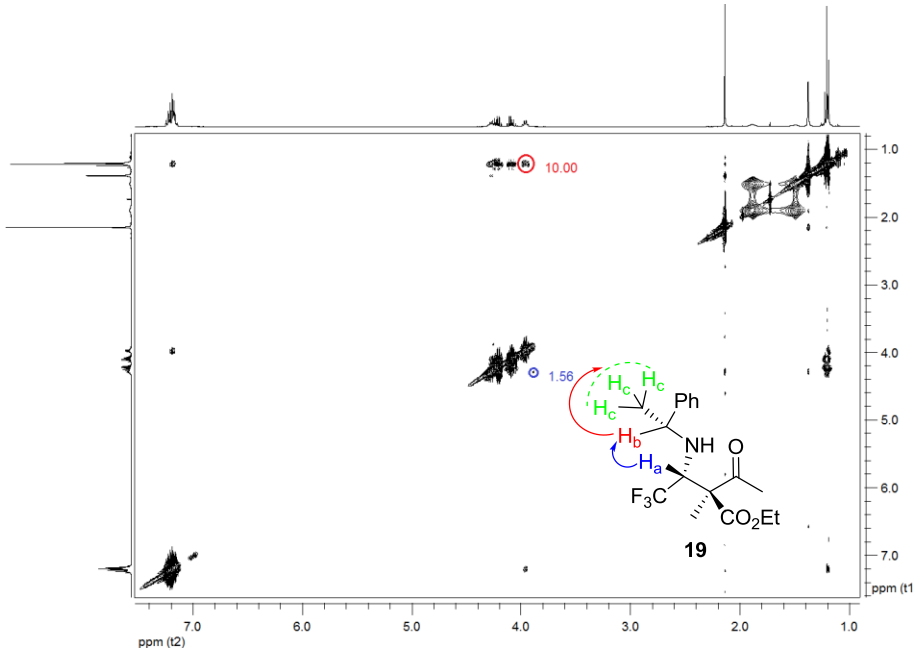
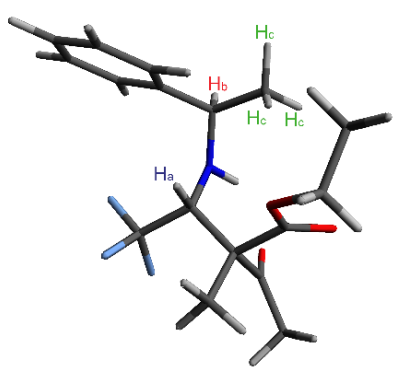
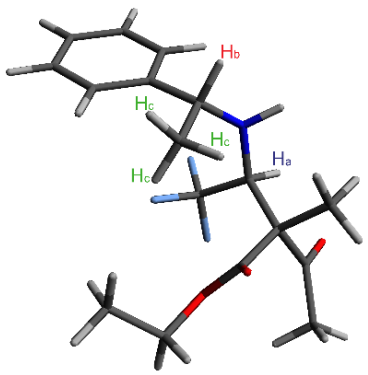


Figure 5. 2D NOESY spectrum of **19**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_b and H_a was measured 1.56 a.u. (corresponding to an interproton distance of 3.61 Å), in order to determine the absolute configuration.



H_a/H_b : 3.634 Å
(*R*,*R*,*S*)-**19**
obtained diastereomer



H_a/H_b : 4.027 Å
(*R*,*S*,*R*)

Figure 6. Optimized geometries of obtained (*R*,*R*,*S*)-**19** and of its possible diastereomer (*R*,*S*,*R*).

Calculated Coordinates:

(*R*,*R*,*S*)-**19** obtained diastereomer

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.142829	-0.801206	-1.767907
2	6	0	-1.734012	-0.468322	-0.304854
3	6	0	-2.628199	-1.243960	0.717752
4	6	0	-4.047223	-1.580227	0.315303
5	6	0	-0.187537	-0.703983	-0.067084
6	6	0	0.222576	-2.118281	-0.569691
7	9	0	0.317187	-2.159946	-1.925040
8	7	0	0.286530	-0.509381	1.277207
9	6	0	1.265387	0.515652	1.667517
10	6	0	2.494556	0.501241	0.758756
11	6	0	3.469702	-0.489728	0.949495
12	6	0	4.608582	-0.544692	0.149161
13	6	0	4.794697	0.393651	-0.870333
14	6	0	3.833867	1.382435	-1.075001
15	6	0	2.695192	1.436295	-0.264596
16	9	0	1.417430	-2.498918	-0.094626
17	9	0	-0.669000	-3.080658	-0.213814
18	1	0	0.338558	-0.022446	-0.742604
19	1	0	1.966713	2.222061	-0.437376
20	1	0	3.967928	2.118571	-1.862589
21	1	0	5.682192	0.354167	-1.495190
22	1	0	5.352537	-1.317463	0.320676
23	1	0	3.326002	-1.226455	1.735023
24	6	0	0.662608	1.914668	1.870415
25	1	0	-0.405777	-0.732865	1.978013
26	8	0	-2.215187	-1.553332	1.821299
27	1	0	-4.568029	-0.693467	-0.055736
28	1	0	-4.569968	-1.977847	1.185517
29	1	0	-1.462086	-0.315758	-2.467164
30	1	0	-3.151872	-0.440204	-1.978788
31	1	0	0.266669	2.325393	0.940803
32	1	0	1.409933	2.613659	2.261618
33	1	0	-0.162419	1.858809	2.587043
34	1	0	1.618632	0.183616	2.652371
35	1	0	-2.122074	-1.875013	-1.952893
36	6	0	-2.095589	1.016274	-0.094934
37	1	0	-4.055234	-2.329389	-0.482785
38	8	0	-2.902007	1.405059	0.727379
39	8	0	-1.500000	1.811329	-0.999156
40	6	0	-2.045654	3.156828	-1.167659
41	6	0	-1.396787	4.185731	-0.260586
42	1	0	-3.122793	3.106276	-0.996042
43	1	0	-1.857050	3.379382	-2.219627
44	1	0	-1.592864	3.965445	0.790638
45	1	0	-1.817224	5.170646	-0.488893
46	1	0	-0.316505	4.235519	-0.421855

(*R*,*S*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.949619	-1.491353	-0.228916
2	6	0	-1.898939	-0.718703	0.637835
3	6	0	-2.164727	-1.223182	2.076314
4	6	0	-0.440441	-1.226806	0.205589
5	1	0	-0.653741	-2.281273	0.001859
6	7	0	0.626570	-1.240046	1.179931
7	6	0	1.513037	-0.152371	1.641990
8	6	0	2.772322	-0.028278	0.764244
9	6	0	3.452605	-1.196417	0.388248
10	6	0	4.634845	-1.138827	-0.346250
11	6	0	5.165204	0.097047	-0.727804
12	6	0	4.498460	1.265802	-0.365085

13	6	0	3.313849	1.202414	0.375883
14	6	0	0.038678	-0.720460	-1.158281
15	1	0	2.816438	2.128285	0.642540
16	1	0	4.895150	2.233744	-0.658773
17	1	0	6.085614	0.145625	-1.302553
18	1	0	5.142648	-2.058437	-0.623929
19	1	0	3.032847	-2.158051	0.666501
20	6	0	0.842889	1.190683	1.958193
21	1	0	0.431437	-1.905083	1.911278
22	8	0	-2.726175	-2.642348	-0.556385
23	1	0	0.506885	1.701608	1.054344
24	1	0	1.547267	1.850278	2.473757
25	1	0	-0.017243	1.047328	2.613270
26	1	0	1.878014	-0.538252	2.602878
27	6	0	-2.156242	0.793094	0.601840
28	8	0	-2.374521	1.473330	1.586154
29	8	0	-2.164398	1.272831	-0.652967
30	6	0	-2.465670	2.683917	-0.841177
31	6	0	-1.205744	3.531360	-0.797379
32	1	0	-3.184628	2.991474	-0.079410
33	1	0	-2.937811	2.723769	-1.824705
34	1	0	-0.769133	3.531559	0.204257
35	1	0	-1.452491	4.564267	-1.062687
36	1	0	-0.463629	3.157966	-1.507388
37	6	0	-4.274772	-0.835987	-0.545835
38	1	0	-4.636721	-0.220202	0.282741
39	1	0	-5.004942	-1.608739	-0.788571
40	1	0	-4.147618	-0.178475	-1.411172
41	1	0	-3.193111	-1.011462	2.378343
42	1	0	-1.503823	-0.726963	2.786733
43	1	0	-2.006761	-2.303540	2.128497
44	9	0	-0.948488	-0.778700	-2.081975
45	9	0	1.044907	-1.490010	-1.620675
46	9	0	0.494215	0.554577	-1.141594

2D NMR spectra and optimized geometries of 20

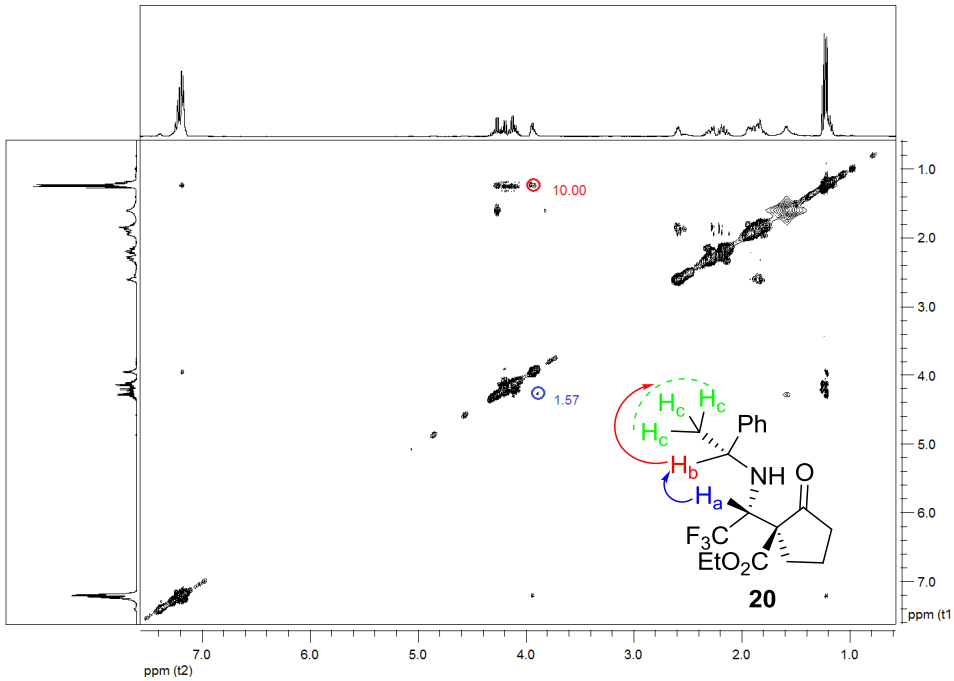
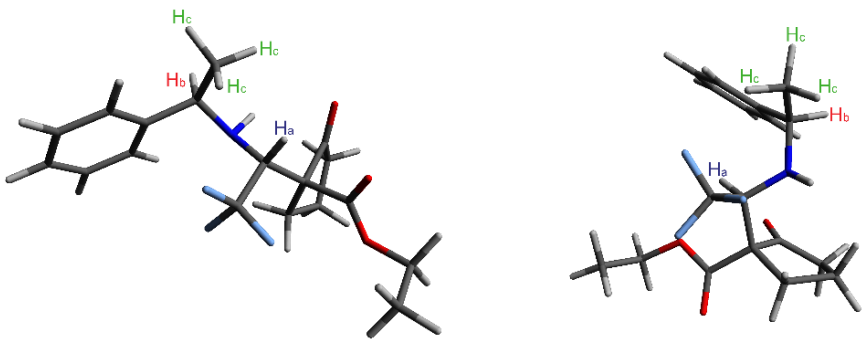


Figure 7. 2D NOESY spectrum of **20**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_b and H_a was measured 1.57 a.u. (corresponding to an interproton distance of 3.61 Å), in order to determine the absolute configuration.



H_a/H_b : 3.615 Å
(*R*,*R*,*S*)-**20**
obtained diastereomer

H_a/H_b : 3.583 Å
(*R*,*R*,*S*)

Figure 8. Optimized geometries of obtained (*R*,*R*,*S*)-**20** and of its possible diastereomer (*R*,*S*,*R*).

Calculated Coordinates:

(*R*,*R*,*S*)-**20** obtained diastereomer

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.862956	1.225425	0.198722
2	6	0	-2.132198	1.218481	0.984814
3	6	0	0.153985	0.202471	0.465011
4	6	0	1.530362	0.635273	-0.130648
5	6	0	-0.277195	-1.155892	-0.111881
6	1	0	0.326749	0.024372	1.533161
7	6	0	1.906503	2.076895	0.357338
8	6	0	2.474554	2.869516	-0.810408
9	8	0	1.729569	2.481466	1.486013
10	6	0	2.646758	1.859576	-1.954065
11	1	0	3.382120	3.400180	-0.509103
12	1	0	1.727818	3.636021	-1.058391
13	6	0	1.593368	0.766876	-1.668243
14	1	0	3.649824	1.426612	-1.927932
15	1	0	2.504735	2.314007	-2.937443
16	1	0	1.825118	-0.179841	-2.156772
17	1	0	0.609490	1.094874	-2.015147
18	6	0	2.623099	-0.266267	0.490096
19	8	0	2.643807	-0.558994	1.667715
20	8	0	3.554093	-0.636056	-0.400137
21	6	0	4.617088	-1.508410	0.082576
22	6	0	4.194043	-2.965328	0.005591
23	1	0	4.871242	-1.214421	1.102439
24	1	0	5.457799	-1.294770	-0.579659
25	1	0	3.341057	-3.157105	0.660739
26	1	0	5.024013	-3.603971	0.323730
27	1	0	3.921683	-3.239008	-1.017496
28	9	0	-0.741206	-1.076232	-1.372722
29	9	0	-1.243368	-1.725244	0.642632
30	9	0	0.757022	-2.038996	-0.132626
31	1	0	-0.429229	2.120474	0.394294
32	6	0	-3.247416	0.444947	0.273319
33	6	0	-4.149838	-0.378983	0.956289
34	1	0	-4.041610	-0.542161	2.023038
35	6	0	-5.199746	-1.009165	0.281747
36	1	0	-5.884490	-1.647160	0.833497
37	6	0	-5.366630	-0.823833	-1.089820
38	1	0	-6.182163	-1.312950	-1.614681
39	6	0	-4.472686	-0.002728	-1.782699
40	1	0	-4.590814	0.149772	-2.852037
41	6	0	-3.426918	0.622794	-1.106858
42	1	0	-2.726404	1.249882	-1.648589
43	1	0	-2.444051	2.270815	0.944556
44	6	0	-1.956457	0.878359	2.472381
45	1	0	-1.739880	-0.180880	2.633428
46	1	0	-2.862358	1.125384	3.032758
47	1	0	-1.135798	1.467330	2.893027

(*R*,*S*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.477806	-0.623951	-0.415874
2	6	0	-2.286933	0.677486	-0.531469
3	8	0	-3.494352	0.719174	-0.665353
4	8	0	-1.490842	1.756511	-0.542970
5	6	0	-2.130624	3.055209	-0.679719
6	6	0	-2.573629	3.588738	0.672536
7	6	0	-0.192058	-0.450617	0.450391
8	6	0	-0.530152	-0.130249	1.924491

9	9	0	-0.705918	-1.259982	2.656594
10	6	0	-2.376563	-1.827863	-0.037501
11	6	0	-1.983970	-2.997219	-0.973276
12	6	0	-1.559461	-2.320512	-2.280137
13	6	0	-0.993069	-0.969748	-1.874804
14	8	0	-0.317222	-0.235935	-2.558329
15	7	0	0.662856	-1.615673	0.286938
16	6	0	2.129789	-1.558811	0.541650
17	6	0	2.526409	-1.790160	2.009279
18	6	0	2.754507	-0.325862	-0.102736
19	6	0	2.862658	-0.276302	-1.500903
20	6	0	3.437388	0.821291	-2.138793
21	6	0	3.918976	1.895316	-1.385789
22	6	0	3.815869	1.860423	0.004457
23	6	0	3.236406	0.758925	0.640638
24	9	0	-1.658517	0.602910	2.074734
25	9	0	0.464490	0.570103	2.519293
26	1	0	0.338693	0.420867	0.066175
27	1	0	-2.297793	-2.095072	1.018218
28	1	0	-2.813070	-3.695716	-1.110778
29	1	0	-1.144848	-3.564780	-0.561336
30	1	0	-2.431304	-2.112997	-2.916883
31	1	0	-0.839633	-2.874954	-2.886967
32	1	0	-2.970902	2.958955	-1.369773
33	1	0	-1.360987	3.684526	-1.129875
34	1	0	-3.349761	2.953367	1.105583
35	1	0	-2.981401	4.597371	0.551968
36	1	0	-1.730630	3.638039	1.367118
37	1	0	0.273714	-2.417169	0.773935
38	1	0	3.168321	0.751784	1.722868
39	1	0	4.187155	2.689702	0.599761
40	1	0	3.512110	0.837443	-3.222176
41	1	0	2.484570	-1.105524	-2.091258
42	1	0	2.520239	-2.420094	-0.016867
43	1	0	2.173923	-1.001774	2.675078
44	1	0	3.614934	-1.860583	2.101764
45	1	0	2.101683	-2.736724	2.359570
46	1	0	-3.413824	-1.539206	-0.222015
47	1	0	4.371243	2.750398	-1.879688

2D NMR spectra and optimized geometries of 21

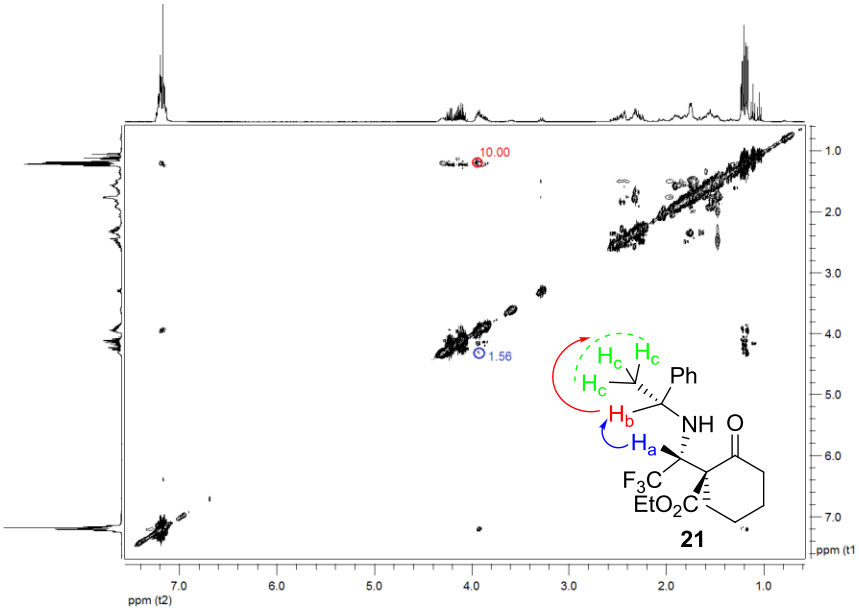
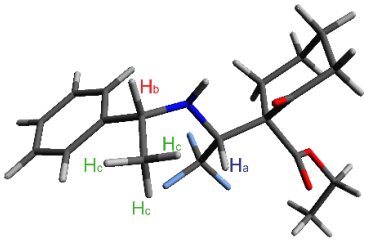
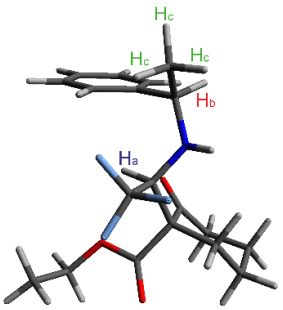


Figure 9. 2D NOESY spectrum of **21**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_b and H_a was measured 1.56 a.u. (corresponding to an interproton distance of 3.61 Å), in order to determine the absolute configuration.



H_a/H_b : 3.607 Å
(*R*,*R*,*S*)-**21**
obtained diastereomer



H_a/H_b : 3.572 Å
(*R*,*S*,*R*)-**21**

Figure 10. Optimized geometries of obtained (*R*,*R*,*S*)-**21** and of its possible diastereomer (*R*,*S*,*R*).

Calculated Coordinates:

(*R*,*R*,*S*)-**21** obtained diastereomer

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.477156	-0.539713	0.013753
2	6	0	1.947897	-1.846825	-0.703341
3	6	0	3.210569	-2.479387	-0.158697
4	6	0	3.084815	-2.732384	1.357325
5	6	0	2.774328	-1.427048	2.093691
6	6	0	1.506195	-0.745579	1.556793
7	8	0	1.325770	-2.337111	-1.628262
8	6	0	0.049652	-0.151379	-0.523639
9	6	0	-0.425052	1.211751	-0.000192
10	9	0	-1.518285	1.634389	-0.674223
11	6	0	2.490379	0.510424	-0.509716
12	8	0	3.135376	1.162016	0.463315
13	6	0	4.108528	2.170007	0.058245
14	6	0	3.444865	3.518991	-0.157671
15	7	0	-0.919777	-1.193787	-0.166584
16	6	0	-2.213996	-1.287592	-0.903414
17	6	0	-2.111551	-1.005100	-2.410637
18	6	0	-3.349639	-0.551174	-0.183778
19	6	0	-4.387576	0.084320	-0.876689
20	6	0	-5.452499	0.676680	-0.191975
21	6	0	-5.499737	0.642618	1.201095
22	6	0	-4.470386	0.010879	1.903698
23	6	0	-3.409897	-0.578637	1.217537
24	8	0	2.686375	0.675269	-1.698355
25	9	0	0.517731	2.174016	-0.178639
26	9	0	-0.737905	1.210203	1.309918
27	1	0	1.366746	0.220595	2.044780
28	1	0	4.614006	1.819811	-0.843569
29	1	0	4.818094	2.197795	0.886972
30	1	0	2.748323	3.482960	-0.997810
31	1	0	4.212525	4.267756	-0.376954
32	1	0	2.901486	3.834078	0.737118
33	1	0	-4.374521	0.128372	-1.960304
34	1	0	-6.243294	1.167143	-0.752870
35	1	0	-6.326647	1.103078	1.734069
36	1	0	-4.493377	-0.021984	2.989643
37	1	0	-2.604173	-1.056475	1.764151
38	1	0	-2.463175	-2.353468	-0.809514
39	1	0	-1.988124	0.059656	-2.625104
40	1	0	-3.009101	-1.351231	-2.930375
41	1	0	-1.257382	-1.546384	-2.827071
42	1	0	2.637143	-1.622886	3.163000
43	1	0	3.627521	-0.746407	2.004758
44	1	0	4.051718	-1.797059	-0.341652
45	1	0	3.395404	-3.397575	-0.721219
46	1	0	2.288285	-3.466114	1.536107
47	1	0	4.013462	-3.178319	1.728019
48	1	0	-0.450674	-2.074042	-0.340929
49	1	0	0.164073	-0.013778	-1.606784
50	1	0	0.631773	-1.352982	1.810218

(*R*,*S*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.725579	1.110976	-1.264172
2	6	0	2.214487	1.149765	-1.326188
3	6	0	-0.034435	0.005918	-0.712750
4	6	0	-0.289675	-1.093547	-1.760522
5	6	0	-2.271443	1.278030	-1.083433
6	6	0	-3.369571	2.154830	-0.465566
7	1	0	-2.717403	0.545906	-1.761350
8	6	0	-2.031952	2.415855	1.648365

9	6	0	-0.971691	1.456002	1.137521
10	8	0	0.107935	1.355442	1.683008
11	6	0	-2.165996	-0.620252	0.596942
12	8	0	-3.348844	-0.831590	0.424899
13	8	0	-1.385370	-1.328409	1.430106
14	6	0	-1.997595	-2.445254	2.133882
15	6	0	-1.963912	-3.713150	1.297078
16	1	0	-3.019105	-2.168530	2.402059
17	1	0	-1.398550	-2.545968	3.040588
18	1	0	-2.582437	-3.609091	0.403136
19	1	0	-2.351054	-4.548327	1.889366
20	1	0	-0.941473	-3.952069	0.992252
21	1	0	0.355876	1.386270	-2.167465
22	6	0	2.897212	0.562773	-0.096525
23	6	0	3.195576	-0.802853	0.022324
24	1	0	2.906655	-1.492618	-0.762740
25	6	0	3.858287	-1.295349	1.148758
26	1	0	4.078848	-2.356649	1.220282
27	6	0	4.242212	-0.430050	2.173995
28	1	0	4.762857	-0.812883	3.046967
29	6	0	3.954016	0.931757	2.067102
30	1	0	4.248733	1.615825	2.857679
31	6	0	3.287861	1.418044	0.942532
32	1	0	3.063613	2.478525	0.867758
33	1	0	2.448579	2.222079	-1.311333
34	6	0	2.789212	0.609434	-2.649470
35	1	0	2.618002	-0.460010	-2.777409
36	1	0	3.866907	0.796078	-2.696500
37	1	0	2.325148	1.127004	-3.496764
38	6	0	-2.783075	3.156355	0.531003
39	1	0	-1.546374	3.094825	2.354073
40	1	0	-2.753686	1.813942	2.220853
41	1	0	-4.110108	1.522621	0.033961
42	1	0	-3.890468	2.682875	-1.272301
43	1	0	-2.093348	3.837748	0.016308
44	1	0	-3.570576	3.777258	0.971137
45	9	0	0.840941	-1.789296	-2.036624
46	9	0	-0.721747	-0.576925	-2.937936
47	9	0	-1.210695	-2.011251	-1.380107
48	6	0	-1.370063	0.533223	-0.061755
49	1	0	0.542399	-0.454878	0.089021
50	1	0	-1.625069	1.927755	-1.682227

Chapter 11

Synthesis of trifluoromethyl 2-imidazolines through Mannich-type reactions with isocyano acetates

*General procedure for the synthesis of isocyano acetates (**4-6**).* The methyl ester·HCl salt (100 mmol) was added to a semisaturated Na_2CO_3 (aq) (100 mL) solution, and the mixture was extracted with DCM (4 × 100 mL). The organic layers were combined and dried over $MgSO_4$. Removal of the solvent under reduced pressure allowed isolation of the corresponding methyl ester. Acetic formic anhydride (prepared by stirring 1 equiv of acetic anhydride and 1.1 equiv of formic acid for 2 h at 55 °C; 15 mL, 16.8 g, 110 mmol) was added dropwise at 0 °C to a stirred solution of the appropriate methyl ester (50 mmol) in DCM (135 mL), and the mixture was stirred for 2 h at room temperature. All volatiles were evaporated under reduced pressure, and the corresponding formamides **7-9** were isolated (68-95%).

A solution of $POCl_3$ (2.9 mL, 4.8 g, 31 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of a formamide (25 mmol) in Et_3N (17 mL) and CH_2Cl_2 (60 mL) at -25 °C. The reaction mixture was stirred for 5 h at the same temperature, and the resulting red mixture was added to cold H_2O (60 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined, washed with H2O (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield the desired (racemic) isocyano acetates **4-6** (64-93%), which was sufficiently pure for follow-up chemistry.

The formamides **7**-9 and the isocyano acetates **4-6** are known in literature.[1]

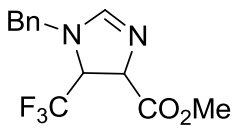
[1] Elders, N.; Schmitz, R. F.; Kanter, F. J. J.; Ruijter, E.; Groen, M. B.; Orru, R. V. A. *J. Org. Chem.* **2007**, *72*, 6135-6142

Synthesis of trifluoromethyl imines (1a-f). The trifluoromethyl imines were synthesized following the procedures reported in the literature.[2,3] **1a-f** are known compounds.

General procedure for the Ag_2O-Catalyzed Mannich-type reactions.

Method A: To a mixture of trifluoromethyl aldimines **1a-c** (0.18 mmol) and Ag_2O (0.015 mmol), isocyano acetates **2** or **4** (0.15 mmol) was added. The reactions were performed under solvent-free conditions and stirred at room temperature (3-5 h, see **Tables 1**,**2**, **Chap. 6**). EtOAc was added to the mixture and the mixture filtered through a pad of celite. Then, the solvent was evaporated *in vacuo* and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 3:7).

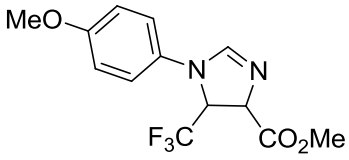
Method B: To a mixture of trifluoromethyl aldimines **1a-c** (0.18 mmol) and Ag_2O (0.018 mmol) in CH_2Cl_2, isocyano acetates (0.18 mmol) was added. The reactions were stirred at room temperature (see **Tables 2**,**3**, **Chap.6**). EtOAc was added to the mixture and the mixture filtered through a pad of celite. Then, the solvent was evaporated *in vacuo* and the residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 3:7).



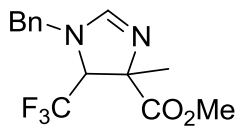
Methyl 1-benzyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (*trans*-3a).

Method A: colorless oil (44 mg, 85 %). ^{1}H NMR ($CDCl_3$): 3.77 (s, 3H), 4.25−4.39 (m, 2H), 4.77 (d, J = 15.1 Hz, 1H), 7.20–7.43 (m, 6H). ^{19}F NMR ($CDCl_3$): –74.6 (d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 50.6, 52.9, 60.9 (q, J = 31.9 Hz), 70.3, 124.8 (q, J = 280.3 Hz), 128.0 (2C), 128.4, 129.0 (2C), 134.5, 157.4, 169.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{14}F_3N_2O_2$ 287.1007, found 287.1068.

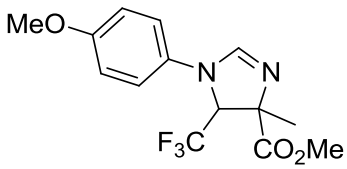
[2] See ref.17 in the **Chapter 1**.
[3] See ref.17 in the **Chapter 2**.



Methyl 1-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (*trans*-3b). Method A: red oil (48 mg, 88 %). ^{1}H NMR ($CDCl_3$): 3.79 (s, 3H), 3.85 (s, 3H), 4.87−4.99 (m, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.20 (s, 1H). ^{19}F NMR ($CDCl_3$): –74.8 (d, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$): 53.2, 55.5, 63.1 (q, *J* = 31.7 Hz), 70.3, 114.9 (2C), 123.8 (2C), 124.4 (q, *J* = 281.2 Hz), 131.3, 155.5, 158.1, 170.0. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{14}F_3N_2O_3$ 303.0957, found 303.0905.



Methyl 1-benzyl-4-methyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (*cis*-7a, *trans*-7′a). Method A: yellow oil (32 mg, 26 %). ^{1}H NMR ($CDCl_3$): 1.38 (s, 3H), 1.58 (s, 3H), 3.50 (q, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 4.19–4.29 (m, 3H), 4.37 (d, *J* = 7.5 Hz, 1H), 4.56–4.64 (m, 1H), 6.93 (s, 1H), 7.09 (s, 1H), 7.19–7.39 (m, 10H). ^{19}F NMR ($CDCl_3$): –69.3 (d, *J* = 7.3 Hz), –67.1 (d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): 19.7 (q, *J* =3.0 Hz, 2C), 50.6 (2C), 52.2, 52.7, 52.8, 53.0, 62.8 (q, *J* = 30.4 Hz), 67.8 (q, *J* = 31.0 Hz), 124.3 (q, *J* = 282.0 Hz), 124.9 (q, *J* = 282.3 Hz), 128.1 (2C), 128.2 (2C), 128.3, 128.5, 128.9 (2C), 129.1 (2C), 134.5, 134.7, 155.5, 156.2, 170.8, 173.0. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1189.

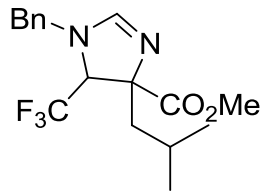


Methyl 1-(4-methoxyphenyl)-4-methyl-5-(trifluoromethyl)-4,5 dihydro-1*H*-imidazole-4-carboxylate (*cis*-7b).

Method A: red oil (15 mg, 26 %). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 30:70). ^{1}H NMR ($CDCl_3$): 1.71 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 5.08 (q, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.01 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 2H). ^{19}F NMR ($CDCl_3$): –67.8 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 19.5 (q, *J* = 2.9 Hz), 53.3, 55.5, 60.3, 65.4 (q, *J* = 30.2 Hz), 114.8 (2C), 124.5 (q, *J* = 281.2 Hz), 124.9 (2C), 131.7, 154.1, 158.3,

173.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1113, found 317.1154.

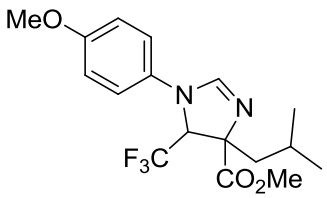
***trans*- 7′b**: **Method A**: red oil (8 mg, 14 %). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 30:70). ^{1}H NMR ($CDCl_3$): 1.68 (s, 3H), 3.81 (s, 6H), 4.23 (q, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 7.17 (s, 1H). ^{19}F NMR ($CDCl_3$): –69.5 (d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 27.6, 53.0, 55.5, 70.8 (q, *J* = 30.4 Hz), 76.0, 114.9 (2C), 123.8 (q, *J* = 282.3 Hz), 124.1 (2C), 131.7, 153.9, 158.0, 170.7. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1113, found 317.1137.



Methyl 1-benzyl-4-isobutyl-5-(trifluoromethyl)-4,5-dihydro-1H-imidazole-4-carboxylate (*cis*-8a). Method B: colorless oil (12 mg, 19 %). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 0.86 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.72 (dd, *J* = 5.2, 13.9 Hz, 1H), 1.83–1.92 (m, 1H), 2.02 (dd, *J* = 5.7, 13.5 Hz, 1H), 3.62 (s, 3H), 3.84 (q, *J* = 7.6 Hz, 1H), 4.21 (d, *J* = 15.2 Hz, 1H), 4.58 (d, *J* = 15.2 Hz, 1H), 7.06 (s, 1H), 7.15 (d, *J* = 6.6, 2H), 7.28–7.37 (m, 3H). ^{19}F NMR ($CDCl_3$): –66.9 (d, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 23.4, 24.5, 25.3, 41.3 (q, *J* = 2.5 Hz), 50.6 (q, *J* = 1.4 Hz), 52.6, 64.6 (q, *J* = 30.0 Hz), 80.2, 124.8 (q, *J* = 283.7 Hz), 128.0 (2C), 128.3, 128.9 (2C), 135.1, 155.7, 174.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_2$ 343.1633, found 343.1659.

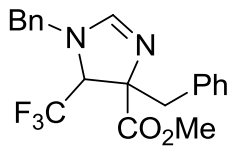
(*trans*-8′a): Method B: colorless oil (10 mg, 16%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 0.81 (d, *J*=6.7 Hz, 3H), 0.83 (d, *J*=6.7 Hz, 3H), 1.19 (dd, *J* = 5.3, 13.5 Hz, 1H), 1.66–1.70 (m, 1H), 1.93 (dd, *J* = 6.6, 13.6 Hz, 1H), 3.45 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 4.21 (d, *J* = 15.1 Hz, 1H), 4.61 (d, *J* = 15.0 Hz, 1H), 7.09 (s, 1H), 7.21 (d, *J* = 6.6, 2H), 7.29–7.45 (m, 3H). ^{19}F NMR ($CDCl_3$): –69.2 (d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 23.1, 24.2, 24.6, 49.8,

50.9, 52.6, 67.4 (q, *J* = 30.4 Hz), 79.7, 124.5 (q, *J* = 283.2 Hz), 128.5 (3C), 129.0 (2C), 134.6, 156.0, 170.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_2$ 343.1633, found 343.1602.



Methyl 4-isobutyl-1-(4 methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (*cis*-8b). Method B: brown oil (15 mg, 23%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 0.92 (d, *J*=6.5 Hz, 3H), 1.04 (d, *J*=6.5 Hz, 3H), 1.83–1.85 (m, 1H), 1.89–2.00 (m, 1H), 2.11 (dd, *J* = 5.1, 13.3 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.67 (q, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.16 (s, 1H). ^{19}F NMR ($CDCl_3$): –67.2 (d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$): 23.7, 24.5, 25.2, 41.5, 52.9, 55.5, 67.4 (q, *J* = 29.4 Hz), 80.3, 114.8 (2C), 124.2 (2C), 124.3 (q, *J* = 284.9 Hz), 131.9, 153.6, 157.9, 174.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_3$ 359.1583, found 359.1553.

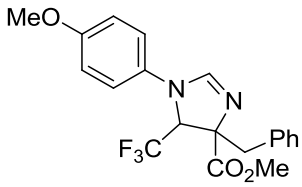
(*trans*-8′b): Method B: brown oil (10 mg, 15%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 0.94 (d, *J*=6.7 Hz, 3H), 1.00 (d, *J*=6.7 Hz, 3H), 1.67 (dd, *J* = 5.1, 13.3 Hz, 1H), 1.90–1.99 (m, 1H), 2.21 (dd, *J* = 13.4, 6.7 Hz, 1H), 3.81 (s, 6H), 4.20 (q, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 7.20 (s, 1H). ^{19}F NMR ($CDCl_3$): –69.5 (d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 23.2, 24.5, 24.7, 50.2, 52.7, 55.5, 70.4 (q, *J* = 29.9 Hz), 79.6, 114.9 (2C), 123.4 (2C), 123.4 (q, *J* = 284.3 Hz), 132.1, 153.3, 157.7, 170.7. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{22}F_3N_2O_3$ 359.1583, found 359.1565



Methyl 1,4-dibenzyl-5-(trifluoromethyl) 4,5-dihydro-1*H*-imidazole-4-carboxylate (*cis*-9a). **Method B:** yellow oil (12 mg, 17%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 3.13 (d, *J*=13.1 Hz, 1H), 3.34–3.37 (m, 4H), 4.13 (q, *J* = 7.5 Hz, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.75

(d, *J* = 15.2 Hz, 1H), 7.14–7.33 (m, 10H), 7.51 (s, 1H). ^{19}F NMR ($CDCl_3$): –67.3 (d, *J* = 9.9 Hz). ^{13}C NMR ($CDCl_3$): 39.2, 51.0, 52.5, 64.2 (q, *J* = 30.5 Hz), 80.2, 124.6 (q, *J* = 284.0 Hz), 127.1, 128.0 (2C), 128.1 (2C), 128.4, 129.0 (2C), 130.4 (2C), 134.6, 135.2, 156.6, 172.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_2$ 377.1477, found 377.1405.

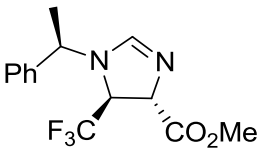
***trans*-9′a: Method B**: yellow oil (12 mg, 17%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 3.09 (d, *J* = 13.7 Hz, 1H), 3.33 (d, *J*=13.4 Hz, 1H), 3.78 (s, 3H), 4.04 (q, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 15.0 Hz, 1H), 4.63 (d, *J* = 15.1 Hz, 1H), 6.91 (s, 1H), 7.13–7.39 (m, 10H). ^{19}F NMR ($CDCl_3$): –68.5 (d, *J* = 9.9 Hz). ^{13}C NMR ($CDCl_3$): 38.8, 51.4, 52.9, 64.6 (q, *J* = 30.8 Hz), 78.8, 124.2 (q, *J* = 284.2 Hz), 127.4, 128.2 (2C), 128.4 (2C), 128.7, 129.1 (2C), 130.3 (2C), 133.9, 134.3, 157.7, 171.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_2$ 377.1477, found 377.1428.



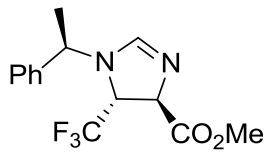
Methyl 4-benzyl-1-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (*cis*-9b). Method B: brown oil (14 mg, 19%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 3.26 (d, *J*=12.6 Hz, 1H), 3.45 (d, *J*=13.2 Hz, 1H), 3.52 (s, 3H), 3.80 (s, 3H), 4.93 (br, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.22–7.35 (m, 6H). ^{19}F NMR ($CDCl_3$): –67.4 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 39.5, 52.7, 55.5, 66.8 (br), 80.9, 114.8 (2C), 124.0 (2C), 124.3 (q, *J* = 286.0 Hz), 127.1, 128.2 (2C), 130.3 (2C), 131.5, 135.5, 153.7, 158.0 173.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1426, found 393.1432.

(*trans*-9′b): **Method B**: brown oil (10 mg, 14%). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 3.34 (d, *J*=13.9 Hz, 1H), 3.46 (d, *J*=13.7 Hz, 1H), 3.73 (s, 3H), 3.85 (s, 3H), 4.39 (q, *J* = 6.8 Hz, 1H), 6.40 (d, *J* = 8.8

Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 7.22–7.33(m, 6H). ^{19}F NMR ($CDCl_3$): –68.7 (d, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): 44.2, 53.2, 55.4, 67.6 (q, J=30.8 Hz,), 79.1, 114.5 (2C), 123.8 (q, J = 287.7 Hz), 125.2 (2C), 127.5, 128.5 (2C), 131.3 (2C), 130.0, 134.4, 155.3, 158.4 170.2. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_3$ 393.1426, found 393.1468.



Methyl (4*S*,5*S*)-1-[(*R*)-1-phenylethyl]-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (10). **Method A**: colorless oil (17 mg, 38 %). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 1.62 (d, J = 6.9 Hz, 3H), 3.82 (s, 3H), 4.48−4.62 (m, 1H), 4.69 (q, J = 6.8 Hz, 1H), 4.78 (d, J = 5.6 Hz, 1H), 6.91 (s, 1H), 7.30–7.48 (m, 5H). ^{19}F NMR ($CDCl_3$): –75.0 (d, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$): 18.4, 53.3, 56.2, 61.7 (q, J = 31.5 Hz), 68.9, 124.6 (q, J = 280.7 Hz), 127.2 (2C), 128.6, 129.1 (2C), 138.5, 156.4, 169.5. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1103.



Methyl (4*R*,5*R*)-1-[(*R*)-1-phenylethyl]-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (10′). **Method A**: colorless oil (11 mg, 24 %). Separated by HPLC (eluent: hexane/ethyl acetate = 70:30). ^{1}H NMR ($CDCl_3$): 1.71 (d, J = 7.0 Hz, 3H), 3.72 (s, 3H), 4.03−4.16 (m, 1H), 4.57 (q, J = 6.8 Hz, 1H), 4.73 (d, J = 5.9 Hz, 1H), 7.15–7.39 (m, 6H). ^{19}F NMR ($CDCl_3$): –75.1 (d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 22.1, 52.9, 56.8, 61.3 (q, J = 34.5 Hz), 69.8, 124.5 (q, J = 280.4 Hz), 126.2 (2C), 128.4, 129.1 (2C), 137.7, 154.5, 160.5. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{16}F_3N_2O_2$ 301.1164, found 301.1153.

2D NMR spectra and optimized geometries to determine the absolute configuration of the new chiral centers.

1. To determine the absolute configuration of the new chiral centers 2D NOESY NMR spectra and optimized geometries of the 2-imidazolines *trans*-**10** and *trans*-**10′** were considered.

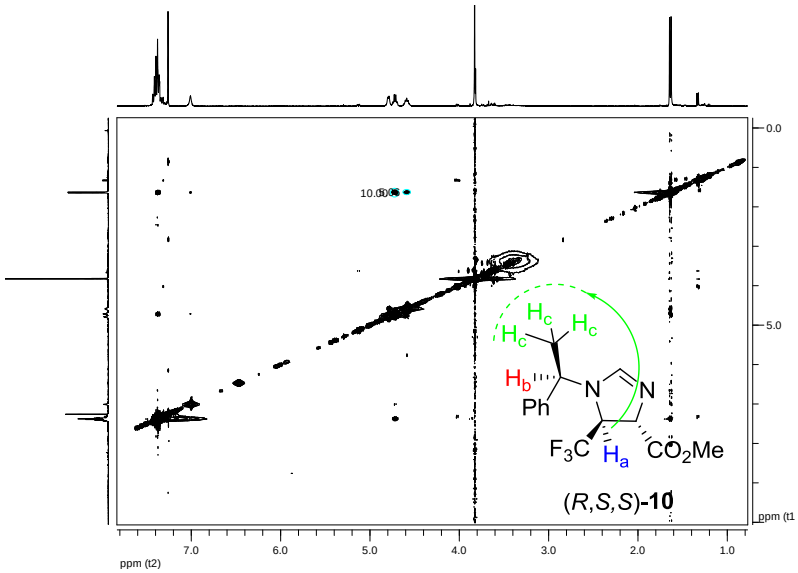


Figure 1. 2D NOESY spectrum of *trans*-**10**.

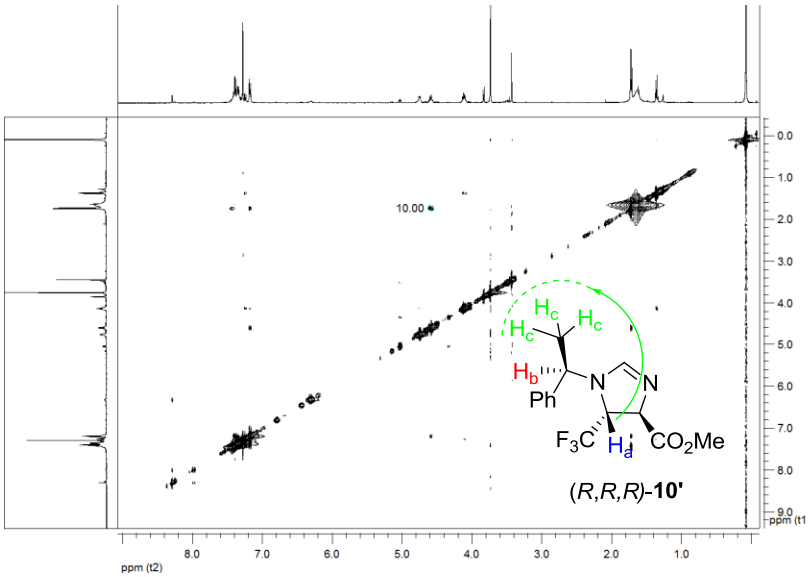
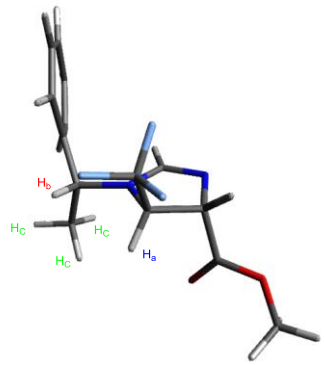
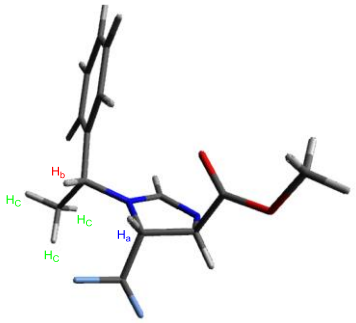


Figure 2. 2D NOESY spectrum of *trans*-**10′**

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_a and the protons H_c of the methyl group can be easily determinate for **10**, the value is 5.06 a.u. (corresponding to an interproton distance of 2.99 Å). The NOESY spectrum of **10′** did not show the correlation between H_a and H_c



H_c/H_a : 3.590 Å
(*R*,S,*S*)
possible diastereomer *trans*-**10**



H_c/H_a : 4.308 Å
(*R*,*R*,*R*)
possible diastereomer *trans*-**10′**

Figure 3. Optimized geometries of (*R*,*S*,*S*)-**10** and (*R*,*R*,*R*)-**10′**.

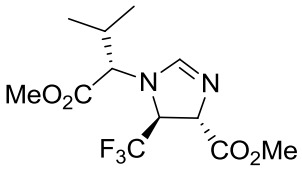
(*R*,*S*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-1.140000	-4.367000	-3.224000
2	1	0	-2.572000	-1.001000	0.074000
3	6	0	-0.407000	-3.878000	-2.574000
4	1	0	0.589000	-4.027000	-3.000000
5	7	0	-4.081000	-0.060000	-1.064000
6	6	0	-4.240000	-0.082000	-2.336000
7	8	0	-2.743000	-2.906000	-1.636000
8	6	0	-1.880000	-2.137000	-2.046000
9	7	0	-3.176000	-0.322000	-3.029000
10	8	0	-0.656000	-2.470000	-2.510000
11	6	0	-2.652000	-0.234000	-0.703000
12	1	0	-0.428000	-4.313000	-1.571000
13	6	0	-5.155000	0.088000	-0.042000
14	6	0	-2.092000	-0.634000	-2.055000
15	9	0	-2.598000	1.440000	0.941000
16	6	0	-2.055000	1.073000	-0.239000
17	1	0	-1.165000	-0.116000	-2.322000
18	9	0	-0.726000	0.958000	-0.067000
19	9	0	-2.288000	2.063000	-1.122000
20	1	0	-4.660000	0.317000	0.909000
21	6	0	-5.836000	-1.272000	0.133000
22	6	0	-6.065000	1.237000	-0.386000
23	6	0	-5.613000	2.608000	-0.144000

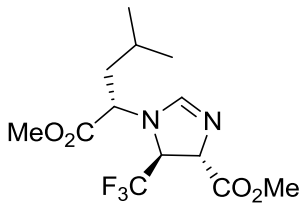
24	6	0	-6.266000	3.738000	-0.792000
25	6	0	-7.370000	3.557000	-1.541000
26	6	0	-7.936000	2.228000	-1.718000
27	6	0	-7.326000	1.064000	-1.097000
28	1	0	-4.880000	2.827000	0.627000
29	1	0	-5.860000	4.733000	-0.629000
30	1	0	-7.881000	4.398000	-2.002000
31	1	0	-8.925000	2.141000	-2.159000
32	1	0	-7.937000	0.176000	-0.976000
33	1	0	-6.628000	-1.217000	0.888000
34	1	0	-6.279000	-1.641000	-0.799000
35	1	0	-5.115000	-2.028000	0.468000
36	1	0	-5.225000	0.101000	-2.794000

(*R*,*R*,*R*)

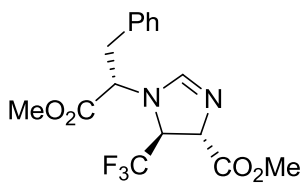
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-1.140000	-4.367000	-3.224000
1	1	0	-2.258000	0.060000	-0.121000
2	6	0	-1.658000	0.071000	-2.673000
3	1	0	-5.293000	4.448000	-1.995000
4	1	0	-4.090000	2.621000	-0.871000
5	6	0	-2.730000	-0.816000	-0.579000
6	6	0	-2.274000	-1.145000	-1.990000
7	6	0	-2.600000	-2.007000	0.329000
8	6	0	-5.864000	3.571000	-1.704000
9	6	0	-5.168000	2.520000	-0.973000
10	1	0	-4.393000	0.655000	0.823000
11	7	0	-3.523000	-1.522000	-2.718000
12	7	0	-4.159000	-0.532000	-0.868000
13	1	0	-7.678000	4.210000	-2.597000
14	6	0	-7.160000	3.436000	-2.040000
15	6	0	-4.465000	-0.949000	-2.041000
16	6	0	-5.046000	0.182000	0.078000
17	6	0	-5.841000	1.275000	-0.601000
18	1	0	-5.505000	-0.896000	-2.397000
19	1	0	-5.294000	-1.553000	1.392000
20	6	0	-7.895000	2.238000	-1.670000
21	6	0	-7.254000	1.153000	-0.948000
22	6	0	-5.906000	-0.853000	0.816000
23	1	0	-6.582000	-0.363000	1.526000
24	1	0	-6.511000	-1.456000	0.128000
25	1	0	-8.955000	2.184000	-1.891000
26	1	0	-7.881000	0.349000	-0.583000
27	9	0	-3.396000	-3.032000	-0.053000
28	9	0	-2.986000	-1.667000	1.585000
29	9	0	-1.338000	-2.466000	0.416000
30	8	0	-2.243000	1.166000	-2.457000
31	8	0	-0.515000	-0.243000	-3.382000
32	6	0	0.014000	0.852000	-4.128000
33	1	0	0.338000	1.661000	-3.465000
34	1	0	0.892000	0.491000	-4.672000
35	1	0	-0.711000	1.215000	-4.865000
36	1	0	-1.570000	-1.986000	-2.013000



Methyl (4*S*,5*S*)-1-[(*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (18). Method B: colorless oil (22 mg, 39 %). $[\alpha]_D$ = 22.6 (*c* = 1 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.00 (d, *J* = 6.6 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 2.20−2.29 (m, 1H), 3.52 (d, *J* = 10.4 Hz, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 4.29–4.35 (m, 1H), 4.70 (dd, *J* = 1.97, 6.5 Hz, 1H), 7.14 (s, 1H) ^{19}F NMR ($CDCl_3$): –75.3 (d, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$): 19.2, 19.6, 29.8, 52.4, 53.4, 62.7 (q, *J* = 31.8 Hz), 67.3, 69.9, 124.8 (q, *J* = 279.9 Hz), 154.7, 169.9, 171.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{18}F_3N_2O_4$ 311.1219, found 311.1274.



Methyl (4*S*,5*S*)-1-[(*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (19). Method B: colorless oil (14 mg, 30 %). $[\alpha]_D$ = 31.3 (*c* = 2 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.96 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.2 Hz, 3H), 1.74−1.88 (m, 3H), 3.73 (s, 3H), 3.84 (s, 3H), 4.03 (dd, *J* = 10.3, 5.0 Hz, 1H), 4.38 (p, *J* = 6.6 Hz, 1H), 4.74 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.07 (s, 1H) ^{19}F NMR ($CDCl_3$): –75.2 (d, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$): 21.0, 22.8, 24.5, 39.5, 52.8, 53.3, 58.5, 62.8 (q, *J* = 31.5 Hz), 68.8, 124.6 (q, *J* = 279.6 Hz), 155.3, 169.3, 171.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{20}F_3N_2O_4$ 325.1375, found 325.1342.



Methyl (4*S*,5*S*)-1-[(*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl]-5-(trifluoromethyl)-4,5-dihydro-1*H*-imidazole-4-carboxylate (20). **Method B**: colorless oil (18 mg, 28 %). $[\alpha]_D$ = 19.3 (*c* = 1 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 3.10 (dd, *J* = 8.6, 14.2 Hz, 1H), 3.31 (d, *J* = 6.6, 14.2 Hz, 1H), 3.67 (s, 3H), 3.76 (s, 3H), 4.20 (dd, *J* = 6.7, 8.6 Hz, 1H), 4.33 (p, *J* = 6.5 Hz, 1H), 4.61 (dd, *J* = 2.0, 6.7 Hz, 1H), 6.98 (s, 1H), 7.12–7.28 (m, 5H). ^{19}F NMR ($CDCl_3$):

–75.6 (d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 37.2, 52.7, 53.1, 58.6, 62.6 (q, J = 31.6 Hz), 70.1, 124.6 (q, J = 279.9 Hz), 127.3, 128.7 (2C), 128.9 (2C), 135.5, 154.3, 169.9, 170.8. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}F_3N_2O_4$ 359.1219, found 359.1258.

2D NMR spectra and optimized geometries to determine the absolute configuration of the new chiral centers.

1. To determine the absolute configuration of the new chiral centers 2D NOESY NMR spectra and optimized geometries of the 2-imidazoline and **20** was considered.
   The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_a and the protons H_b can be easily determinate for **20**, the value is 3.19 a.u. (corresponding to an interproton distance of 3.38 Å).

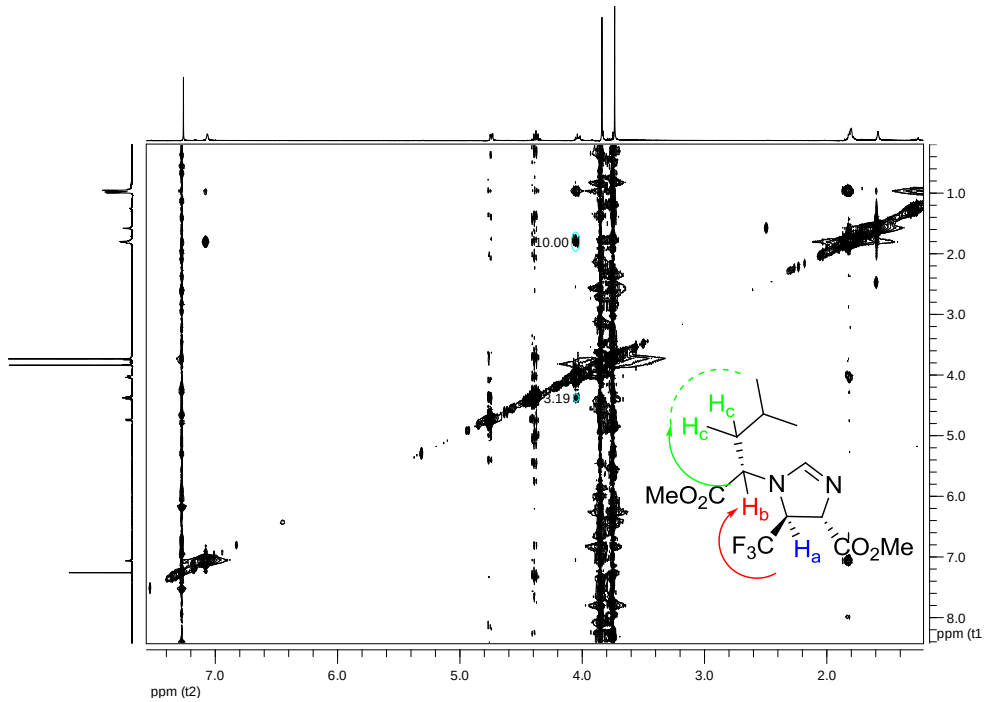
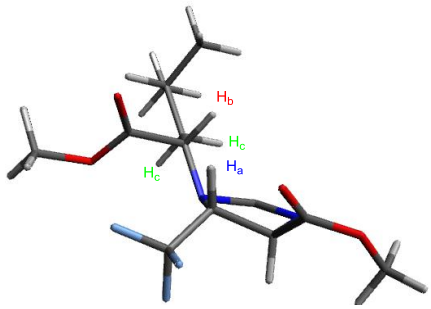
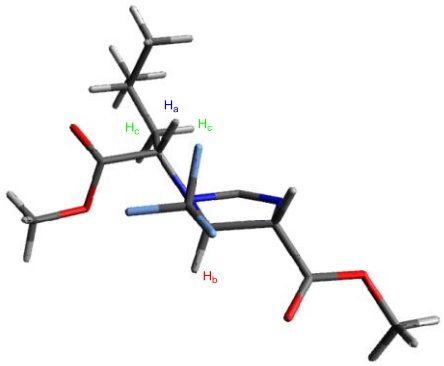


Figure 4. 2D NOESY spectrum of **20**.



H_b/H_a : 3.21 Å
(*S*,*R*,*R*)
possible diastereomer **20**



H_b/H_a: 3.646 Å
(*S*,*S*,*S*)

Figure 5. Optimized geometries of obtained (*S*,*S*,*S*)-**20** and of its possible diastereomer (*S*,*R*,*R*).

(*S*,*R*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-1.140000	-4.367000	-3.224000
1	7	0	-3.219000	1.078000	-0.121000
2	6	0	-3.408000	-0.277000	-0.690000
3	6	0	-2.022000	0.978000	0.661000
4	7	0	-1.248000	-0.066000	0.343000
5	6	0	-1.942000	-0.776000	-0.744000
6	6	0	-1.868000	-2.293000	-0.623000
7	8	0	-2.870000	-3.008000	-0.576000
8	8	0	-0.643000	-2.887000	-0.668000
9	6	0	0.565000	-2.121000	-0.747000
10	6	0	-4.305000	1.813000	0.562000
11	6	0	-4.390000	3.289000	0.066000
12	6	0	-5.690000	1.138000	0.461000
13	8	0	-6.024000	0.133000	1.081000
14	8	0	-6.531000	1.801000	-0.390000
15	6	0	-7.809000	1.189000	-0.554000
16	6	0	-4.038000	-0.355000	-2.094000
17	1	0	-1.516000	-0.508000	-1.722000
18	1	0	0.517000	-1.352000	-1.522000
19	1	0	1.368000	-2.810000	-1.025000
20	1	0	0.816000	-1.706000	0.232000
21	1	0	-8.393000	1.810000	-1.239000
22	1	0	-8.339000	1.141000	0.402000
23	1	0	-7.707000	0.192000	-0.993000
24	9	0	-5.349000	-0.001000	-2.080000
25	9	0	-3.433000	0.466000	-2.991000
26	9	0	-3.995000	-1.600000	-2.629000
27	1	0	-3.985000	-0.902000	0.004000
28	6	0	-3.201000	4.191000	0.285000
29	6	0	-3.061000	4.958000	1.553000
30	6	0	-2.042000	4.123000	-0.655000
31	1	0	-4.122000	1.851000	1.647000
32	1	0	-4.623000	3.300000	-1.007000
33	1	0	-5.252000	3.768000	0.551000
34	1	0	-4.028000	5.357000	1.877000
35	1	0	-2.387000	5.811000	1.417000
36	1	0	-2.660000	4.323000	2.348000
37	1	0	-2.266000	3.505000	-1.529000

38	1	0	-1.161000	3.709000	-0.156000
39	1	0	-1.794000	5.126000	-1.016000
40	1	0	-3.713211	4.995265	-0.200486
41	1	0	-1.778613	1.651815	1.403805

(*S*,*S*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-3.968970	0.886210	-1.132160
1	7	0	-3.658000	1.157000	-0.838000
2	6	0	-3.698000	-0.336000	-0.644000
3	6	0	-2.347000	1.461000	-1.3100000
4	7	0	-1.569000	0.396000	-1.539000
5	6	0	-2.232000	-0.774000	-0.899000
6	1	0	-1.752000	-0.917000	0.0850000
7	6	0	-4.281000	2.059000	0.143000
8	6	0	-4.062000	3.568000	-0.167000
9	6	0	-4.709000	4.574000	0.815000
10	6	0	-4.437000	6.005000	0.338000
11	6	0	-4.197000	4.404000	2.246000
12	6	0	-5.805000	1.840000	0.207000
13	8	0	-6.471000	1.978000	1.233000
14	8	0	-6.354000	1.585000	-1.016000
15	6	0	-7.735000	1.248000	-0.980000
16	1	0	-4.362000	-0.693000	-1.441000
17	6	0	-1.974000	-2.095000	-1.676000
18	1	0	-3.865000	1.839000	1.132000
19	1	0	-4.436000	3.782000	-1.177000
20	1	0	-2.987000	3.787000	-0.173000
21	1	0	-5.797000	4.440000	0.816000
22	1	0	-4.922000	6.733000	0.997000
23	1	0	-4.830000	6.159000	-0.673000
24	1	0	-3.364000	6.223000	0.323000
25	1	0	-4.622000	5.171000	2.903000
26	1	0	-3.106000	4.491000	2.289000
27	1	0	-4.478000	3.432000	2.660000
28	1	0	-8.040000	0.956000	-1.989000
29	1	0	-8.331000	2.114000	-0.676000
30	1	0	-7.913000	0.401000	-0.310000
31	6	0	-4.203000	-0.960000	0.671000
32	9	0	-3.617000	-0.411000	1.775000
33	9	0	-5.543000	-0.721000	0.829000
34	9	0	-4.073000	-2.298000	0.802000
35	8	0	-2.991000	-2.739000	-2.057000
36	8	0	-0.699000	-2.627000	-1.498000
37	6	0	0.249000	-1.902000	-2.268000
38	1	0	1.095000	-2.570000	-2.463000
39	1	0	0.637000	-1.052000	-1.700000
40	1	0	-0.145000	-1.582000	-3.240000
41	1	0	-2.022708	2.428644	-1.463375

Chapter 12

Reactivity of trifluoromethyl aldimines in the aza-Reformatsky reaction

All experiments were carried out under nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

*Synthesis of trifluoromethyl imines (**1a,c,g**).* The trifluoromethyl imines were synthesized following the procedures reported in the literature.[1,2] **1a,c** and **1g** are known compounds.

Activation Zinc dust. Zinc dust was activated by stirring with dilute HCl during 10-15 min, and then washed several times with distilled H_2O, EtOH and absolute Et_2O before rigorous drying. This procedure removes oxides from the surface of zinc, which form slowly upon standing in air.

*Preparation of the solution of Reformatsky reagent.*Under N_2 atmosphere, to a two-neck round bottom flask were added the above activated zinc (3 mmol) and dry THF (4 mL). The suspension was warmed to 40−50 °C, and methyl bromoacetate (**2a**, 3 mmol) in THF (1 mL) was added dropwise. After insoluble matter precipitated, the light yellow supernatant solution was decanted and used for subsequent experiments.

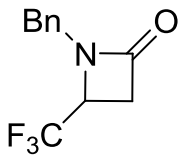
General procedure for the zinc promoted aza-Reformatsky reaction.

Method **A** (two-step protocol): to a solution of trifluoromethyl aldimines (**1a,c** 0.5 mmol) in THF (1 mL) warmed to 40 °C, the above methyl bromozincacetate/THF

[1] See ref.17 in the **Chapter 1**.
[2] See ref.54 in the **Chapter 2**.

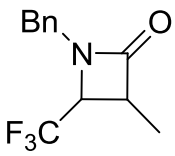
solution was added. The resulting mixture was stirred at the same temperature for 18 h. The mixture was quenched with saturated aqueous NH_4Cl, and then extracted with AcOEt. The organic layer was concentrated *in vacuo* to give the crude oil. The residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 80:20).

Method **B** (one-pot protocol): Under N_2 atmosphere, to a two-neck round bottom flask the above activated zinc (3 mmol), dry THF (4 mL), the trifluoromethyl aldimines **1a,c** or **1g** (0.5 mmol) and α-bromo esters (**2b-c**) were added. The suspensions were warmed to 40-60 °C. The resulting mixtures were stirred at same temperature for the reaction time shown in **Table 2-3** and **8** (**Chap. 7**). The mixture was quenched with saturated aqueous NH_4Cl, and then extracted with AcOEt. The organic layer was concentrated *in vacuo* to give the crude mixture. The residues purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 80:20).



1-Benzyl-4-(trifluoromethyl)azetidin-2-one (3).

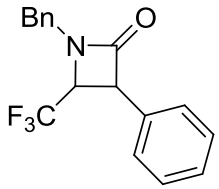
Method A: colorless oil (90 mg, 79 %). IR: 1788, 1200. ^{1}H NMR ($CDCl_3$): 2.92−3.07 (m, 2H), 3.70–3.78 (m, 1H), 3.92 (d, *J* = 15.1 Hz, 1H), 4.75 (d, *J* = 15.1 Hz, 1H), 7.35–7.14 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.9 (d, *J* = 5.9 Hz). ^{13}C NMR ($CDCl_3$): 38.5 (q, *J* = 1.8 Hz), 45.7, 49.6 (q, *J* = 35.0 Hz), 124.4 (q, *J* = 279.3 Hz), 128.1, 128.4 (2C), 128.9 (2C), 134.5, 165.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{11}F_3NO$ 230.0793, found 230.0785.



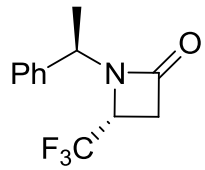
1-Benzyl-3-methyl-4-(trifluoromethyl)azetidin-2-one (*trans*-**4**).

Method B: colorless oil (85 mg, 70 %). IR: 1782. ^{1}H NMR ($CDCl_3$): 1.31 (d, *J* = 7.4 Hz, 3H), 3.30 (qd, *J*= 7.8, 1.9 Hz, 1H), 3.39 (qd, *J* = 6.0, 2.2 Hz, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 4.85 (d, *J* = 15.2 Hz, 1H), 7.24–7.42 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.1 (d, *J* = 5.8 Hz). ^{13}C NMR ($CDCl_3$): 12.3, 45.4, 46.9 (q, *J* = 1.8 Hz), 57.2 (q, *J* = 34.2 Hz), 124.4 (q, *J* = 279.3 Hz),

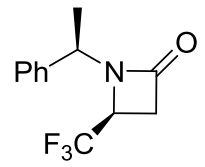
128.1, 128.4 (2C), 129.0 (2C), 134.8, 169.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0949, found 244.0953.



1-Benzyl-3-phenyl-4-(trifluoromethyl)azetidin-2-one (*trans*-**5**). **Method B**: colorless oil (126 mg, 83 %). IR: 1780. ^1H NMR ($CDCl_3$): 3.80 (qd, *J* = 5.9, 2.4, 1H), 4.05 (d, *J* = 15.1 Hz, 1H), 4.46 (*J* = 2.1 Hz, 1H), 4.98 (d, *J* = 15.0 Hz, 1H), 7.14–7.42 (m, 10H). ^{19}F NMR ($CDCl_3$): –73.8 (d, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$): 45.7, 56.3, 57.9 (q, *J* = 34.0 Hz), 124.3 (q, *J* = 279.9 Hz), 127.2 (2C), 128.3 (2C), 128.5 (2C), 129.0 (2C), 129.1 (2C), 132.6, 134.6, 166.5. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{15}F_3NO$ 306.1106, found 306.1153.

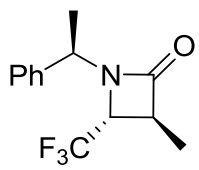


(*R*)-1-[(R)-1-Phenylethyl]-4-(trifluoromethyl)azetidin-2-one (7). Method A: colorless oil (38 mg, 31 %) Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1775. $[\alpha]_D$ = 43.8 (*c* = 4 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.82 (d, *J* = 7.2 Hz, 3H), 3.01 (m, 2H), 3.71–3.87 (m, 1H), 4.51 (q, *J* = 7.1 Hz, 1H), 7.28–7.39 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.8 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 19.7, 37.9, 49.4 (q, *J* = 34.9 Hz), 56.0, 124.5 (q, *J* = 279.6 Hz), 126.6 (2C), 128.0, 128.9 (2C), 135.8, 165.3. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0949 found 244.0955.

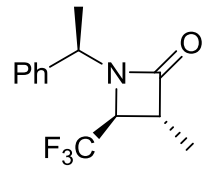


(*S*)-1-[(*R*)-1-Phenylethyl]-4-(trifluoromethyl)azetidin-2-one (7′). Method A: colorless oil (40 mg, 33 %) Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1778. $[\alpha]_D$: 28.2 (*c* = 4 g/100 mL, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.62 (d, *J* = 7.3 Hz, 3H), 2.92–3.09 (m, 1H), 3.68–3.73 (m, 1H), 5.06 (q, *J* = 7.3 Hz, 1H), 7.31–7.41 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.8 (d, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$): 18.0, 38.1, 49.7 (q, *J* = 35.7 Hz), 52.1, 124.3 (q, *J* = 279.0 Hz), 127.2, 128.1 (2C), 128.9 (2C),

138.6, 165.3. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0949, found 244.0951.

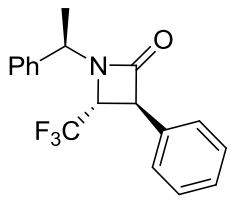


(3*S*,4*R*)-3-Methyl-1-[(*R*)-1-phenylethyl]-4-(trifluoromethyl)azetidin-2-one (*trans*-8). **Method B**: colorless oil (43 mg, 33 %). Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1780. $[\alpha]_D$ = 30.1 (*c* = 3 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.30 (d, *J* = 7.4 Hz, 3H), 1.82 (d, *J* = 7.2 Hz, 3H), 3.20 (qd, *J*=7.4, 2.1 Hz, 1H), 3.36 (qd, *J*=6.0, 2.2 Hz, 1H), 4.48 (q, *J*=7.2 Hz, 1H), 7.27–7.41 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.1 (d, *J*= 6.4 Hz). ^{13}C NMR ($CDCl_3$): 12.4, 19.9, 46.0, 55.8, 57.0 (q, *J*=34.0 Hz), 124.4 (q, *J*=279.4 Hz), 126.5 (2C), 127.9, 128.9 (2C), 140.9, 169.3. HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO$ 258.1106, found 258.1115.



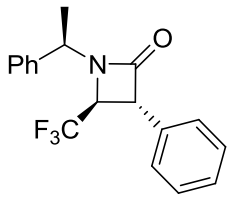
(3*R*,4*S*)-3-Methyl-1-[(*R*)-1-phenylethyl]-4-(trifluoromethyl)azetidin-2-one (*trans*-8′).

Method B: colorless oil (40 mg, 31 %). Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1779. $[\alpha]_D$ = 38.3 (*c* = 3 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.25 (d, *J* = 7.3 Hz, 3H), 1.60 (d, *J* = 7.4 Hz, 3H), 3.16–3.28 (m, 2H), 5.10 (q, *J* = 7.4 Hz, 1H), 7.30–7.41 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.1 (d, *J* = 6.0 Hz). ^{13}C NMR ($CDCl_3$): 12.2, 17.6, 46.3, 51.3, 57.2 (q, *J* = 34.7 Hz), 124.3 (q, *J* = 279.1 Hz), 127.2 (2C), 128.1, 128.9 (2C), 138.5, 169.3 HR-MS (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO$ 258.1106, found 258.1130.



(3*S*,4*R*)-3-Phenyl-1-[(*R*)-1-phenylethyl]-4-(trifluoromethyl)azetidin-2-one (*trans*-9). Method B colorless oil (40 mg, 25 %). Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1779, 1500. $[\alpha]_D$: 38.3 (*c* = 3 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.89 (d, *J* = 7.2 Hz, 3H), 3.77 (qd, *J* = 5.9,

2.4 Hz, 1H), 4.36 (d, *J* = 2.4 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 1H), 7.15–7.52 (m, 10H). ^{19}F NMR ($CDCl_3$): –73.7 (d, *J* = 5.9 Hz). ^{13}C NMR ($CDCl_3$): 19.8, 55.5 (q, *J* = 1.7 Hz), 56.1, 57.7 (q, *J* = 33.9 Hz), 124.3 (q, *J* = 280.01 Hz), 126.7 (2C), 127.3 (2C), 128.1, 128.2, 128.9 (2C), 129.1 (2C), 132.9, 140.7, 166.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{17}F_3NO$ 320.1262, found 320.1280.



(3*R*,4*S*)-3-Phenyl-1-[(*R*)-1-phenylethyl]-4-(trifluoromethyl)azetidin-2-one (*trans*-9′). Method B: colorless oil (59 mg, 37 %). Separated by HPLC (eluent: hexane/ethyl acetate = 90:10). IR: 1779, 1500. $[\alpha]_D$ = 19.5 (*c* = 3 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.68 (d, *J* = 7.2 Hz, 3H), 3.69 (qd, *J* = 5.8, 2.4 Hz, 1H), 4.33 (d, *J* = 2.4 Hz, 1H), 5.20 (q, *J* = 7.2 Hz, 1H), 7.15–7.39 (m, 10H). ^{19}F NMR ($CDCl_3$): –73.7 (d, *J* = 5.9 Hz). ^{13}C NMR ($CDCl_3$): 17.8, 52.0, 55.8 (q, *J* = 1.77 Hz), 58.0 (q, *J* = 34.5 Hz), 124.2 (q, *J* = 279.4 Hz), 127.3 (4C), 128.2 (2C), 128.9 (2C), 129.1 (2C), 132.8, 138.5, 166.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{17}F_3NO$ 320.1262, found 320.1235.

2D NMR spectra and optimized geometries to determine the absolute configuration of the new chiral centers.

1. To determine the absolute configuration of the new chiral centers 2D NOESY NMR spectra and optimized geometries of the β-lactams **8** and **8′** were considered.

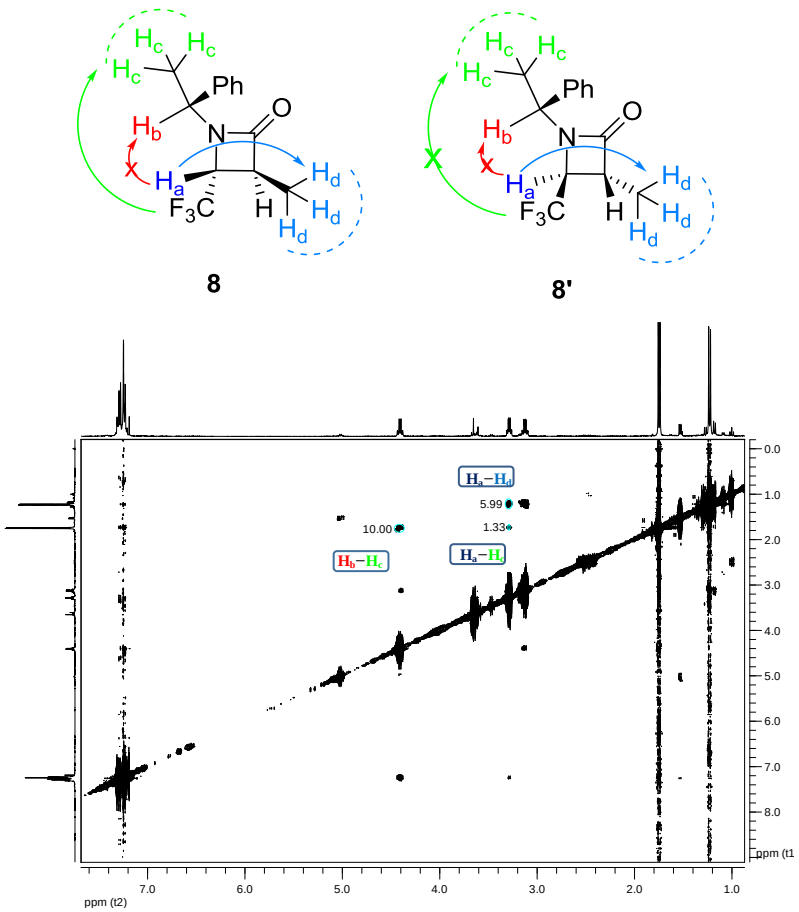


Figure 1. 2D NOESY NMR spectrum of **8**.

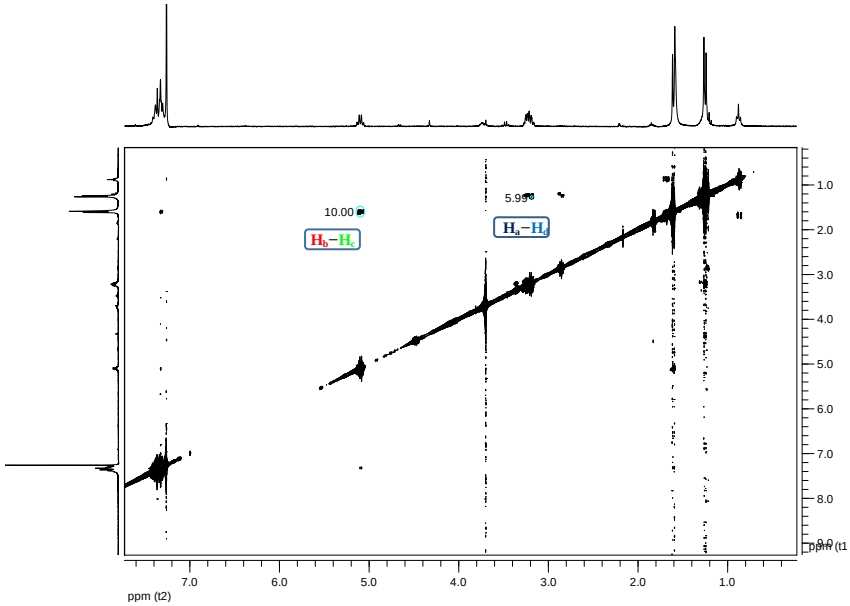


Figure 2. 2D NOESY NMR spectrum of **8′**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_a and the protons H_c of the methyl group can be easily determinate for **8**, the value is 1.33 a.u. (corresponding to an interproton distance of 3.73 Å). The NOESY spectrum of **8′** did not show the correlation between H_a and H_c. The same correlation value (5.99 a.u. corresponding to an interproton distance of 2.90 Å) was found for the cross peak between H_a and the protons H_d of the methyl group in the NOESY spectra of **8** and **8′**.[3]

[3] The 2D NOESY ^{1}H NMR analysis permit to determinate the relative interproton distances and thus molecular geometry, by the following equation:

$$\frac{V_X}{V_R} = \left(\frac{d_R}{d_X}\right)^6$$

in which V_R is the volume of the reference cross peak, d_R is the corresponding interproton distance and V_X is the volume relative to the unknown distance d_X. As suggested by the equation, if the protons are too far apart do not generate a NOESY correlation.

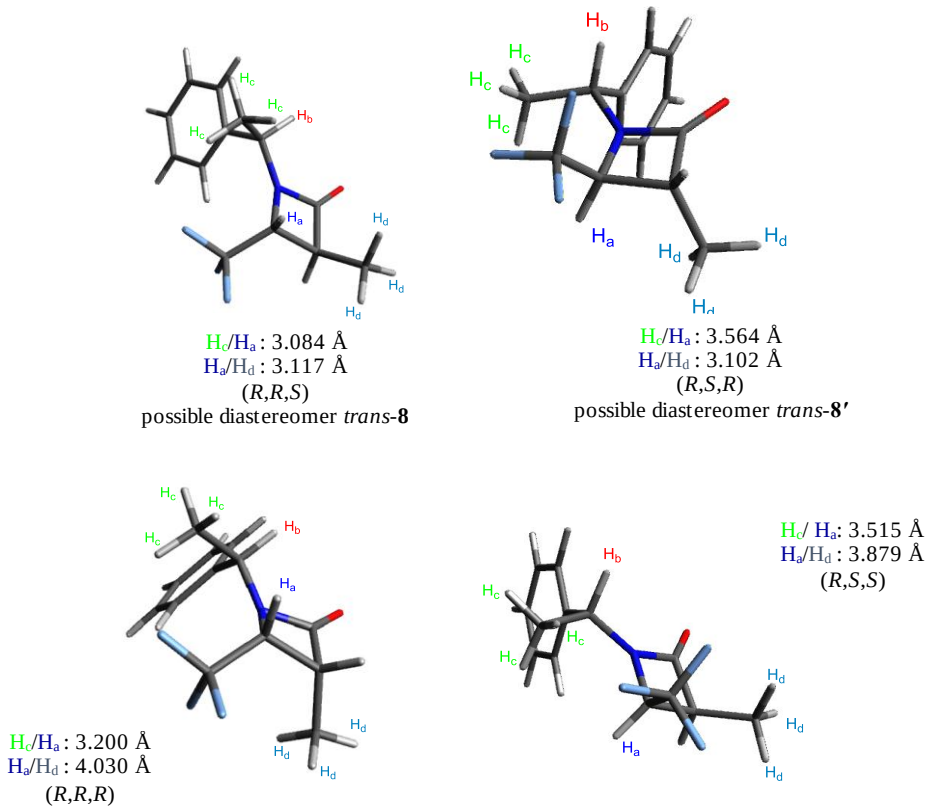


Figure 3. Optimized geometries.

By NOESY analysis coupled with computational studies, the (*R*,*R*,*S*) absolute configurations can be assigned to *trans*-**8**, and the (*R*,*S*,*R*) to *trans*-**8′.**

Calculated Coordinates:

(*R*,*R*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.030770	0.044215	0.016045
2	7	0	0.050861	-0.112647	1.480246
3	6	0	1.414475	0.115317	1.535185
4	6	0	1.492488	0.417950	0.033493
5	8	0	2.206231	0.014185	2.449538
6	6	0	1.952799	1.822866	-0.358470
7	1	0	2.080738	-0.336511	-0.493770
8	1	0	-0.238063	-0.878839	-0.537118
9	6	0	-1.016806	1.083784	-0.492209
10	6	0	-0.727092	-0.888853	2.471065
11	6	0	-1.023381	-0.032013	3.696199
12	6	0	-0.747454	-0.520739	4.975982
13	1	0	-0.283746	-1.497887	5.086563
14	6	0	-1.060909	0.234255	6.108360
15	1	0	-0.838996	-0.158893	7.096141
16	6	0	-1.649838	1.491348	5.969295
17	1	0	-1.891049	2.081565	6.848118

18	6	0	-1.919493	1.991736	4.691728
19	1	0	-2.368084	2.974164	4.575472
20	6	0	-1.608736	1.235263	3.563105
21	1	0	-1.793014	1.639930	2.572501
22	1	0	-0.079694	-1.715513	2.787095
23	6	0	-1.998635	-1.478539	1.852358
24	1	0	-2.693364	-0.697718	1.540980
25	1	0	-2.495171	-2.101700	2.600967
26	1	0	-1.764710	-2.107832	0.989057
27	9	0	-2.281525	0.599509	-0.515700
28	9	0	-0.706061	1.427025	-1.763571
29	9	0	-1.033302	2.207830	0.255023
30	1	0	1.396566	2.592325	0.180243
31	1	0	1.824333	1.987713	-1.430422
32	1	0	3.014291	1.931289	-0.118777

(*R*,*S*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.098754	-0.173634	0.049758
2	7	0	0.007023	-0.373175	1.504604
3	6	0	1.296867	0.099245	1.593654
4	6	0	1.330596	0.483710	0.103792
5	8	0	2.070444	0.173283	2.526327
6	1	0	1.225414	1.568660	0.001578
7	6	0	2.505259	-0.007080	-0.734670
8	6	0	-0.207741	-1.439734	-0.793839
9	1	0	-0.902477	0.496261	-0.270421
10	6	0	-0.887377	-0.827922	2.583427
11	6	0	-0.945260	0.194939	3.715779
12	6	0	-0.782006	-0.223409	5.039791
13	1	0	-0.555983	-1.266156	5.247888
14	6	0	-0.899504	0.684452	6.094454
15	1	0	-0.765125	0.343100	7.116695
16	6	0	-1.178304	2.026637	5.834310
17	1	0	-1.264905	2.735665	6.652296
18	6	0	-1.339770	2.454427	4.513859
19	1	0	-1.553742	3.498124	4.302345
20	6	0	-1.225623	1.544354	3.463570
21	1	0	-1.347995	1.886840	2.439669
22	1	0	-0.459983	-1.753232	2.989608
23	6	0	-2.297135	-1.139284	2.062791
24	1	0	-2.764700	-0.250109	1.629027
25	1	0	-2.915432	-1.463216	2.903179
26	1	0	-2.288662	-1.932992	1.315667
27	1	0	2.388798	0.271013	-1.784867
28	1	0	2.629737	-1.089707	-0.674365
29	1	0	3.419683	0.459984	-0.357816
30	9	0	-1.463966	-1.945910	-0.806072
31	9	0	0.609672	-2.420651	-0.360995
32	9	0	0.107587	-1.166687	2.079470

(*R*,*R*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.069121	0.098485	0.093862
2	7	0	0.251663	-0.144559	1.510361
3	6	0	1.609352	0.023121	1.333152
4	6	0	1.436182	0.440595	-0.140369
5	8	0	2.545265	-0.175393	2.079123
6	1	0	1.600662	1.512482	-0.282614

7	6	0	2.200665	-0.379192	-1.171220
8	1	0	-0.411679	-0.788633	-0.448298
9	6	0	-1.052235	1.218094	-0.195151
10	6	0	-0.427576	-0.880433	2.583959
11	6	0	-0.933109	0.011217	3.718325
12	6	0	-1.222973	-0.586203	4.953905
13	1	0	-1.056533	-1.652739	5.086940
14	6	0	-1.713185	0.169737	6.017506
15	1	0	-1.927733	-0.311359	6.967425
16	6	0	-1.917998	1.543298	5.863545
17	1	0	-2.296512	2.136180	6.690935
18	6	0	-1.623070	2.147353	4.641699
19	1	0	-1.770408	3.215928	4.513236
20	6	0	-1.132915	1.387434	3.575965
21	1	0	-0.892711	1.874249	2.638820
22	1	0	0.346815	-1.532772	3.006829
23	6	0	-1.543812	-1.768510	2.011373
24	1	0	-2.321188	-1.163263	1.538974
25	1	0	-2.005538	-2.342669	2.817459
26	1	0	-1.145574	-2.474820	1.276492
27	9	0	-2.291597	0.947588	0.274300
28	9	0	-1.152809	1.400747	-1.529142
29	9	0	-0.670836	2.396768	0.348081
30	1	0	1.901018	-0.104949	-2.186754
31	1	0	2.026518	-1.451602	-1.038253
32	1	0	3.274044	-0.196349	1.070399

(*R*,*S*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.021747	-0.051731	0.036410
2	7	0	0.014262	-0.203351	1.500542
3	6	0	1.331175	0.172964	1.623394
4	6	0	1.455429	0.441039	0.117030
5	8	0	2.072158	0.231045	2.582172
6	6	0	1.734319	1.883501	-0.291653
7	1	0	2.151161	-0.248511	-0.370060
8	6	0	-0.169826	-1.318382	-0.802772
9	1	0	-0.745172	0.684344	-0.330035
10	6	0	-0.881625	-0.732212	2.548785
11	6	0	-0.974406	0.260767	3.699293
12	6	0	-0.673779	-0.146090	5.003085
13	1	0	-0.333318	-1.163065	5.182805
14	6	0	-0.801265	0.742141	6.073074
15	1	0	-0.560930	0.412046	7.079611
16	6	0	-1.227133	2.050873	5.847927
17	1	0	-1.322043	2.744565	6.677950
18	6	0	-1.524342	2.468513	4.548055
19	1	0	-1.851937	3.488180	4.366127
20	6	0	-1.400154	1.578998	3.481726
21	1	0	-1.626302	1.914081	2.472882
22	1	0	-0.417792	-1.650818	2.927123
23	6	0	-2.268327	-1.080240	2.002013
24	1	0	-2.749043	-0.204791	1.555211
25	1	0	-2.901597	-1.425420	2.824407
26	1	0	-2.213678	-1.871168	1.255628
27	9	0	-1.459051	-1.702618	-0.949362
28	9	0	0.511016	-2.358855	-0.277842
29	9	0	0.309988	-1.094877	-2.048280
30	1	0	1.024296	2.570717	0.178949
31	1	0	1.660305	1.995882	-1.376781
32	1	0	2.742980	2.175103	0.014936

As a consequence of the reported procedure the following absolute configurations can be assigned: (*R*,*R*)-**7,** (*R*,*S*)-**7′**, (*R*,*R*,*S*)-**9**, (*R*,*R*,*S*)-**9′**.

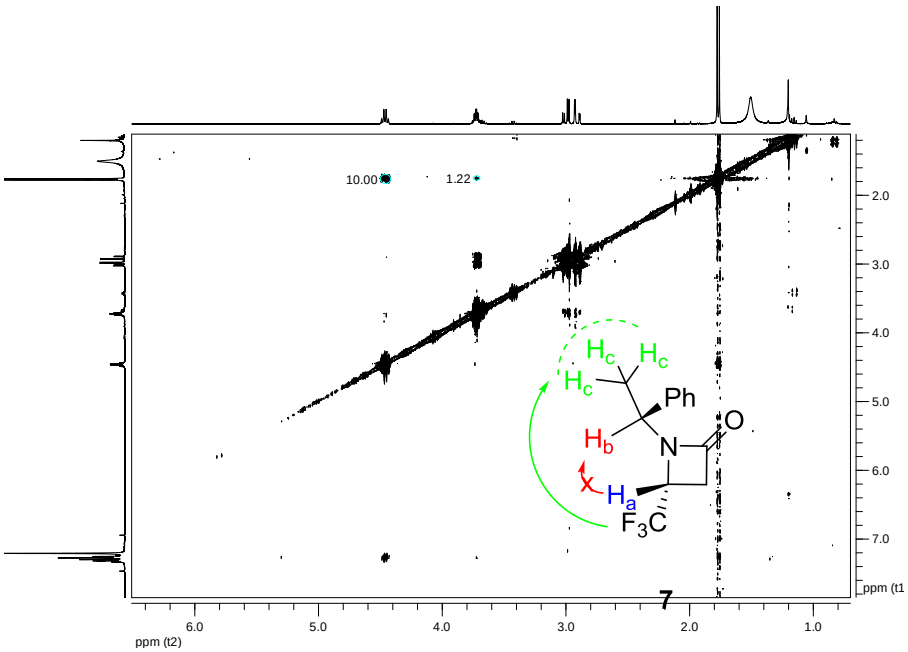


Figure 4. 2D NOESY NMR spectrum of **7**.

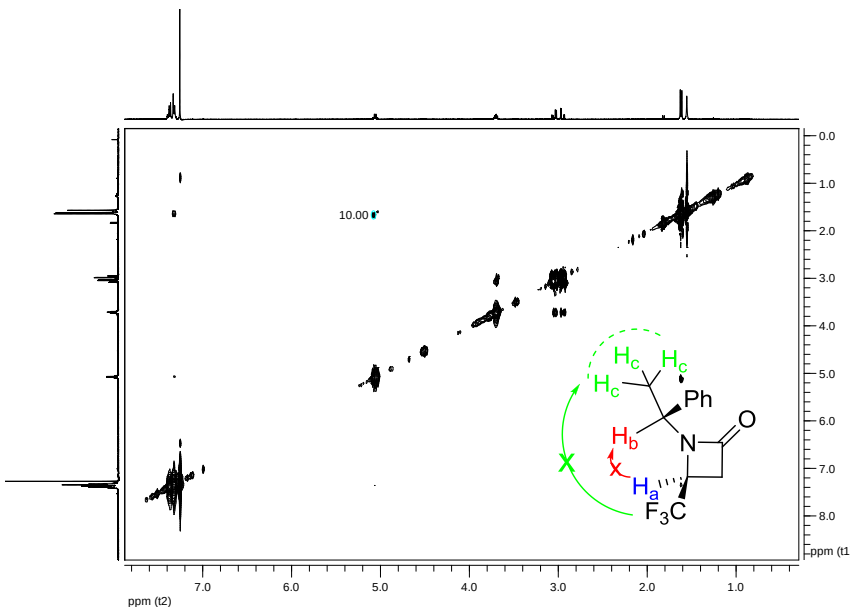
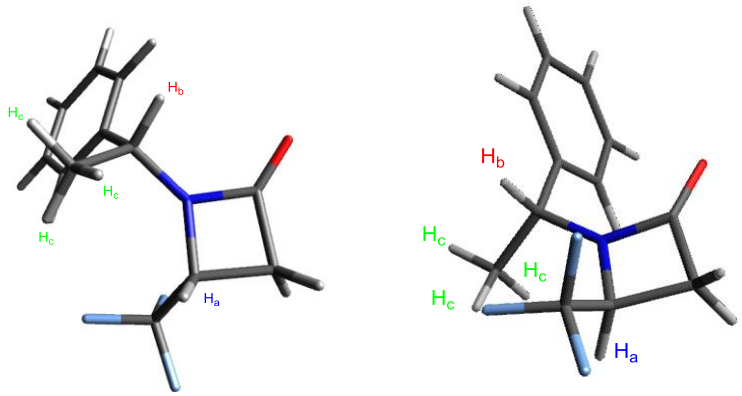


Figure 5. 2D NOESY NMR spectrum of **7′**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u. The cross peak between H_a and the protons H_c of the methyl group can be easily determinate for **7**, the value is 1.22 a.u. (corresponding to an interproton

distance of 3.791 Å). The NOESY spectrum of **7′** did not show the correlation between H_a and H_c.



H_c/H_a : 3.020 Å
(*R*,*R*)
possible diastereomer **7**

H_c/H_a : 3.450 Å
(*R*,*S*)
possible diastereomer **7′**

Figure 6. Optimized geometries of obtained (*R*,*R*)-**7** and of (*R*,*R*)-**7′**.

Calculated Coordinates:

(*R*,*R*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.028801	0.319294	0.300927
2	7	0	0.715638	0.981742	0.322350
3	6	0	1.085742	1.992429	-0.533913
4	6	0	2.486676	1.388023	-0.732120
5	8	0	0.493405	2.982503	-0.910293
6	1	0	2.683296	1.012710	-1.737874
7	1	0	3.308552	2.024038	-0.400594
8	1	0	2.566211	0.341955	1.253854
9	6	0	2.050834	-1.110589	-0.210281
10	6	0	-0.482403	0.894058	1.174012
11	6	0	-1.651047	0.215583	0.461519
12	6	0	-2.720813	0.999103	0.012164
13	1	0	-2.696649	2.074350	0.168955
14	6	0	-3.811076	0.419241	-0.639666
15	1	0	-4.631410	1.044585	-0.979708
16	6	0	-3.842915	-0.958895	-0.853860
17	1	0	-4.688681	-1.414516	-1.360364
18	6	0	-2.778233	-1.749468	-0.414323
19	1	0	-2.793979	-2.822955	-0.579476
20	6	0	-1.690923	-1.168176	0.238356
21	1	0	-0.871723	-1.798432	0.565975
22	1	0	-0.772685	1.938067	1.336354
23	6	0	-0.139963	0.276548	2.534084
24	1	0	0.223514	-0.749042	2.435687
25	1	0	-1.033771	0.260546	3.162295
26	1	0	0.626988	0.867485	3.043609
27	9	0	1.372789	-1.254345	-1.363371

28	9	0	1.514919	-1.978148	0.686917
29	9	0	3.325132	-1.502386	-0.424013

(*R*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.928509	0.385909	0.700578
2	7	0	-0.519464	0.296556	0.292456
3	6	0	-0.423043	1.632777	-0.057770
4	6	0	-1.854828	1.912608	0.434081
5	8	0	0.458896	2.297556	-0.554536
6	1	0	-1.908099	2.529374	1.332515
7	1	0	-2.532966	2.299026	-0.327996
8	6	0	-2.900352	-0.348107	-0.210706
9	1	0	-2.131445	0.082407	1.731244
10	6	0	0.347349	-0.881456	0.126494
11	6	0	1.810751	-0.482483	-0.000373
12	6	0	2.542097	-0.875347	-1.125476
13	1	0	2.044071	-1.416417	-1.925870
14	6	0	3.903126	-0.578857	-1.231292
15	1	0	4.455810	-0.890893	-2.112594
16	6	0	4.546714	0.119776	-0.210198
17	1	0	5.603858	0.354989	-0.290747
18	6	0	3.822768	0.518522	0.917111
19	1	0	4.316132	1.066416	1.714650
20	6	0	2.466418	0.216755	1.022110
21	1	0	1.911553	0.536711	1.899511
22	1	0	0.054284	-1.389881	-0.801556
23	6	0	0.135999	-1.859275	1.294956
24	1	0	0.405012	-1.395141	2.247981
25	1	0	0.771771	-2.736164	1.148954
26	1	0	-0.900912	-2.198203	1.346883
27	9	0	-2.751097	-1.692433	-0.131841
28	9	0	-2.734356	-0.006220	-1.504928
29	9	0	-4.173983	-0.063958	0.133326

2D NMR spectra and optimized geometries of 9 and 9′

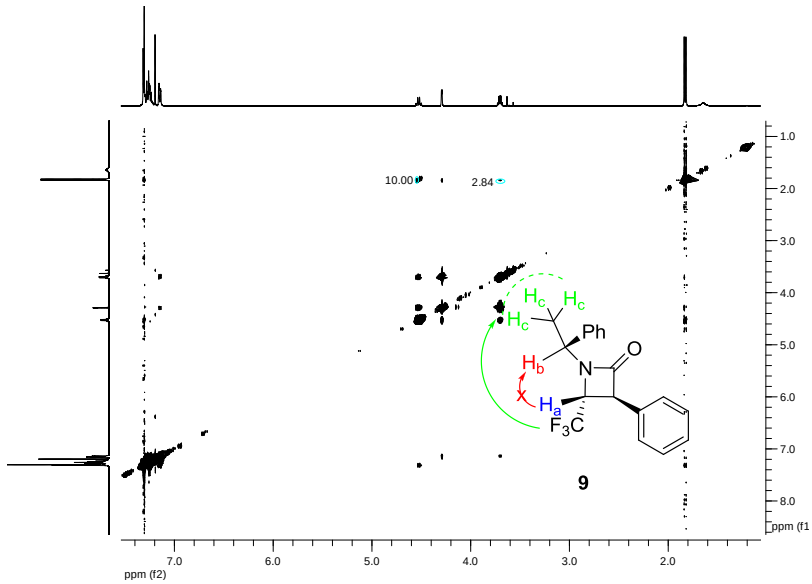


Figure 7. 2D NOESY NMR spectrum of **9**.

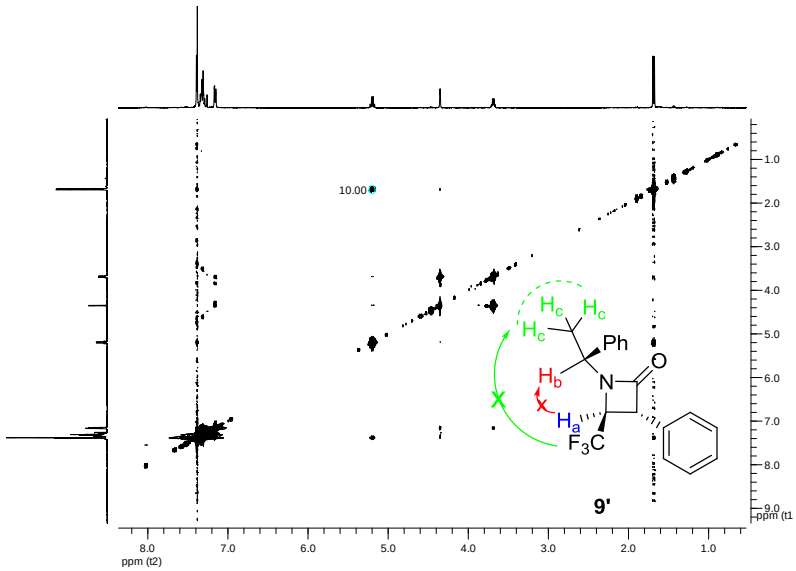
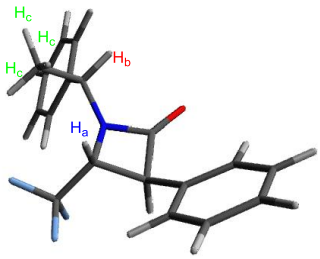
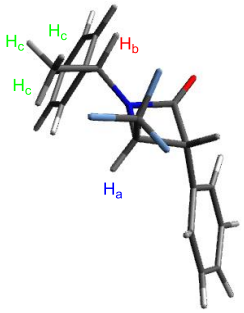


Figure 8. 2D NOESY NMR spectrum of **9′**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_a and the protons H_c of the methyl group can be easily determinate for **9**, the value is 2.84 a.u. (corresponding to an interproton distance of 3.041 Å). The NOESY spectrum of **9′** did not show the correlation between H_a and H_c

H_c/H_a : 3.041 Å
(R,R,R)
possible diastereomer **9**





H_c/H_a : 3.608 Å
(R,R,S)
possible diastereomer **9′**

Figure 9. Optimized geometries of obtained (*R,R,S*)-**9** and of (*R,S,S*)-**9′**.

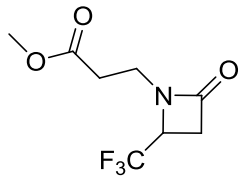
Calculated Coordinates:

(*R,R,S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.696227	-0.562460	0.347369
2	7	0	0.531688	0.240467	-0.091987
3	6	0	1.255292	0.968340	-0.992088
4	6	0	2.442949	-0.031342	-0.913761
5	8	0	1.002826	2.009651	-1.550193
6	1	0	2.439984	-0.716517	-1.773065
7	6	0	3.865988	0.639264	-0.708583
8	1	0	2.108799	-0.198162	1.296351
9	6	0	1.498787	-2.062538	0.347213
10	6	0	-0.545201	0.805136	0.701029
11	6	0	-1.906254	0.446549	0.121153
12	6	0	-2.932336	1.406022	0.109780
13	1	0	-2.749032	2.412074	0.481552
14	6	0	-4.202961	1.088087	-0.374881
15	1	0	-4.987065	1.840765	-0.377140
16	6	0	-4.466607	-0.191975	-0.855870
17	1	0	-5.454426	-0.438513	-1.235732
18	6	0	-3.461777	-1.155939	-0.849394
19	1	0	-3.664895	-2.155451	-1.225246
20	6	0	-2.192564	-0.841878	-0.358726
21	1	0	-1.431066	-1.616982	-0.357301
22	1	0	-0.431355	1.896336	0.646291
23	6	0	-0.498861	0.416927	2.180474
24	1	0	-0.612593	-0.661842	2.325031
25	1	0	-1.304044	0.908062	2.739048
26	1	0	0.448531	0.721882	2.636932
27	9	0	0.685154	-2.443929	1.356831
28	9	0	2.687486	-2.686126	0.518116
29	9	0	0.961577	-2.501512	-0.813244
30	6	0	4.879939	-0.023623	0.018427
31	6	0	4.220591	1.889060	-1.255376
32	1	0	3.496886	2.446494	-1.850175
33	6	0	5.486687	2.453535	-1.066980
34	6	0	6.449864	1.775892	-0.329560
35	1	0	5.716084	3.422594	-1.503295
36	6	0	6.148166	0.532742	0.211364
37	1	0	7.434495	2.211995	-0.184820
38	1	0	6.899523	-0.010551	0.778906
39	1	0	4.684970	-1.007935	0.442339

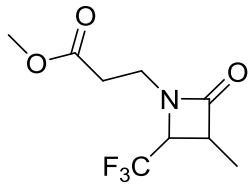
(*R*,*R*,*S*)

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.690260	0.248200	-0.559510
2	7	0	0.334370	0.173480	0.034880
3	6	0	0.544110	1.207990	0.896600
4	6	0	1.854740	1.609410	0.182300
5	8	0	-0.048530	1.554390	1.891600
6	6	0	1.793260	2.834660	-0.657400
7	6	0	2.730360	-0.761510	-0.116680
8	1	0	1.632030	0.322400	-1.652150
9	6	0	-0.551560	-0.938470	0.303950
10	6	0	-1.993180	-0.515910	0.045030
11	6	0	-2.916470	-0.473690	1.100830
12	1	0	-2.606200	-0.719680	2.114280
13	6	0	-4.242610	-0.102010	0.871260
14	1	0	-4.946850	-0.070370	1.698480
15	6	0	-4.661720	0.236260	-0.413610
16	1	0	-5.693450	0.528580	-0.589360
17	6	0	-3.754060	0.211610	-1.469860
18	1	0	-4.077770	0.485340	-2.470460
19	6	0	-2.427550	-0.158770	-1.242930
20	1	0	-1.731480	-0.161810	-2.078390
21	1	0	-0.443400	-1.179130	1.369820
22	6	0	-0.243630	-2.206930	-0.492370
23	1	0	-0.107890	-2.002050	-1.559780
24	1	0	-1.046100	-2.946350	-0.387670
25	1	0	0.667360	-2.683080	-0.120920
26	9	0	2.657280	-1.889810	-0.856570
27	9	0	2.584990	-1.093310	1.185090
28	9	0	3.973600	-0.251540	-0.282500
29	6	0	2.817560	3.017670	-1.690690
30	6	0	2.884480	4.261960	-2.443960
31	1	0	3.641830	2.318090	-1.780320
32	6	0	0.937890	3.964660	-0.297720
33	1	0	2.697200	1.653410	0.885540
34	6	0	1.016000	5.210390	-1.048040
35	1	0	0.336970	3.946090	0.606310
36	6	0	1.997050	5.364620	-2.110230
37	1	0	0.465140	6.076050	-0.699400
38	1	0	3.720260	4.437780	-3.111000
39	1	0	2.181620	6.347350	-2.528900



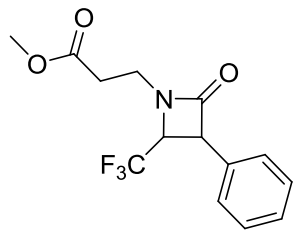
Methyl 3-[2-oxo-4-(trifluoromethyl)azetidin-1-yl]propanoate (18).

Method B: colorless oil (38 mg, 34 %). purified by flash chromatography on silica gel (eluent CH2Cl2 with 2% of MeOH). ^{1}H NMR ($CDCl_3$): 2.59−2.74 (m, 2H), 2.95−3.17 (m, 1H), 3.34–3.42 (m, 1H), 3.67–3.75 (m, 4H), 4.07–4.15 (m, 1H). ^{19}F NMR ($CDCl_3$): −75.3 (d, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$): 32.3, 37.9, 38.5, 51.2 (q, *J* = 34.9 Hz), 52.0, 124.5 (q, *J* = 279.4 Hz), 165.3, 171.4. (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_8H_{11}F_3NO_3$ 226.0691, found 226.0635.



Methyl 3-[3-methyl-2-oxo-4-(trifluoromethyl)azetidin-1-yl]propanoate (*trans*-19).

Method B: colorless oil (48 mg, 40 %). The residue purified by flash chromatography on silica gel (eluent CH_2Cl_2 with 2% of MeOH). ^{1}H NMR ($CDCl_3$): 1.35 (d, *J* = 7.4 Hz, 3H), 2.6 (dt, *J* = 16.3, 6.6 Hz, 1H), 2.68–2.78 (m, 1H), 3.22 (qd, *J* = 7.2, 1.7 Hz, 1H), 3.29–3.43 (m, 1H), 3.63–3.77 (m, 5H). ^{19}F NMR ($CDCl_3$): −74.7 (d, *J*=6.5 Hz). ^{13}C NMR ($CDCl_3$): 12.4, 32.3, 37.8, 46.9, 51.9, 58.8 (q, *J* = 34.1 Hz), 124.5 (q, *J* = 279.2 Hz), 169.1, 171.4. (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_9H_{13}F_3NO_3$ 240.0848, found 240.0865.



Methyl 3-[2-oxo-3-phenyl-4-(trifluoromethyl)azetidin-1-yl]propanoate (*trans*-20).

Method B: colorless oil (63 mg, 42 %). The residue purified by flash chromatography on silica gel (eluent hexane/ethyl acetate = 80:20). ^{1}H NMR ($CDCl_3$): 2.63 (dt, *J* = 16.2, 6.3 Hz, 1H), 2.73–2.87 (m, 1H), 3.37–3.51 (m, 1H), 3.67 (s, 3H), 4.07–4.13 (m, 1H), 4.39 (s, 1H), 7.23–7.40 (m, 5H). ^{19}F NMR ($CDCl_3$): −74.3 (d, *J*=6.3 Hz). ^{13}C NMR ($CDCl_3$): 32.3, 37.9, 51.9, 56.2, 59.3 (q, *J* = 33.9 Hz), 124.3 (q, *J* =

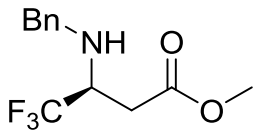
279.7 Hz), 127.2 (2C), 128.2, 129.0, 132.6, 166.3, 171.2. (ESI Q-TOF) (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{15}F_3NO_3$ 302.1004, found 302.1052.

General procedure of the racemic Et_2Zn-promoted aza-Reformatsky reaction

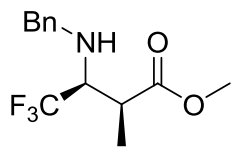
α-Bromo ester **2a-c** (1.0 mmol) was added to a solution of the corresponding imine **1a,c** or **1g** (0.5 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. Then, 1.0 M Et_2Zn in hexane (1.0 mL, 1.0 mmol) was slowly added to the mixture at the appropriate temperature (reported in **Table 4**,**5**,**7** and **9 Chap. 7**, pp. 80, 81, 85, 89). The whole mixture was stirred at the same temperature for the appropriate time. The mixture was quenched with saturated aqueous $NaHCO_3$, and was extracted with AcOEt. Then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt: hexane = 5:95) to afford the corresponding β-amino esters.

General procedure of the Et_2Zn-promoted asymmetric aza-Reformatsky reaction

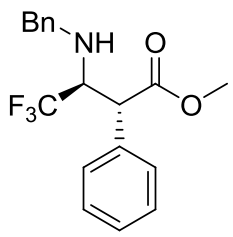
α-Bromo ester **2a-c** (1.0 mmol) was added to a solution of the corresponding imine **1a,c** or **1g** (0.5 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol **6** (0.38 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. Then the mixture was cooled to −20 °C, and 1.0 M Et_2Zn in hexane (1.2 mL, 1.2 mmol) was slowly added to the mixture at the same temperature. The whole mixture was stirred at the same temperature for the appropriate time (reported in **Table 6**, **Chap 7**, p. 83). The mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with AcOEt. Then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt: hexane: 5:95) to afford the corresponding β-amino esters.



Methyl (*S*)-3-(benzylamino)-4,4,4-trifluorobutanoate (10'). Colorless oil (65 mg, 50%). IR: 1745. $[\alpha]_D$ = −15.8 (*c* = 2.7 g/100 mL, $CHCl_3$). The ee was determined to be 98% by HPLC (Column Lux 5u Amylose-2), hexane/EtOH = 95:5, 0.7 ml/min, 206 nm, major 7.77 min and minor 6.91 min). ^{1}H NMR ($CDCl_3$): 1.65 (br, 1H), 2.50 (dd, *J* = 15.6, 9.7 Hz, 1H), 2.70 (dd, *J* = 15.5, 4.0 Hz, 1H), 3.56–3.68 (m, 1H), 3.69 (s, 3H), 3.87 (d, *J* = 13.0 Hz, 1H), 4.01 (d, *J* = 13.0 Hz, 1H), 7.21–7.38 (m, 5H). ^{19}F NMR ($CDCl_3$): –74.8 (d, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$): 34.7, 51.8, 52.1, 55.9 (q, *J* = 28.7 Hz), 126.2 (q, *J* = 284.4 Hz), 127.4, 128.4 (4C), 138.8, 170.4. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{15}F_3NO_2$ 262.1055, found 262.1068.



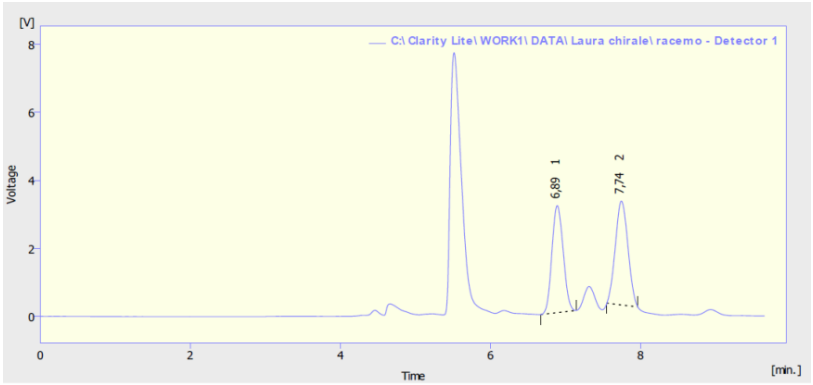
Methyl (2*S*,3*S*)-3-(benzylamino)-4,4,4-trifluoro-2-methylbutanoate (*syn*-12'). Colorless oil (71 mg, 52%). IR: 1758. $[\alpha]_D$ = −20.0 (*c* = 2.4 g/100 mL, $CHCl_3$) The ee was determined to be 98% by HPLC (Column Lux 5u Amylose-2), hexane/EtOH = 95:5, 0.7 mL/min, 206 nm, major 9.12 min and minor 9.62 min). ^{1}H NMR ($CDCl_3$): 1.24 (d, *J* = 7.1 Hz, 3H), 1.76 (br, 1H), 2.86 (qd, *J* = 7.1, 4.5 Hz, 1H), 3.63 (s, 3H), 3.64–3.73 (m, 1H), 3.84 (d, *J* = 13.1 Hz, 1H), 4.03 (d, *J* = 13.0 Hz, 1H), 7.23–7.40 (m, 5H). ^{19}F NMR ($CDCl_3$): –71.1 (d, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): 10.8, 39.5, 52.0, 52.3, 59.4 (q, *J* = 27.0 Hz), 126.6 (q, *J* = 286.1 Hz), 127.3, 128.3 (2C), 128.4 (2C), 139.3, 173.7. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{17}F_3NO_2$ 276.1211, found 276.1258.



Methyl (2*R*,3*S*)-3-(benzylamino)-4,4,4-trifluoro-2-phenylbutanoate (*anti*-13'). Colorless oil (98 mg, 58%). IR: 1779. $[\alpha]_D$ = 18.3 (*c* = 1.5 g/100 mL, $CHCl_3$). The ee was determined to be 91% by HPLC of *trans*-**5**, obtained after cyclization of *anti*-**13'** (Column Lux 5u Amylose-2), hexane/EtOH = 95:5, 1.0 mL/min, 206 nm, major 5.24 min and minor 5.91 min). ^{1}H NMR ($CDCl_3$): 1.64 (br, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 3.68 (s, 3H), 3.81 (d, *J*

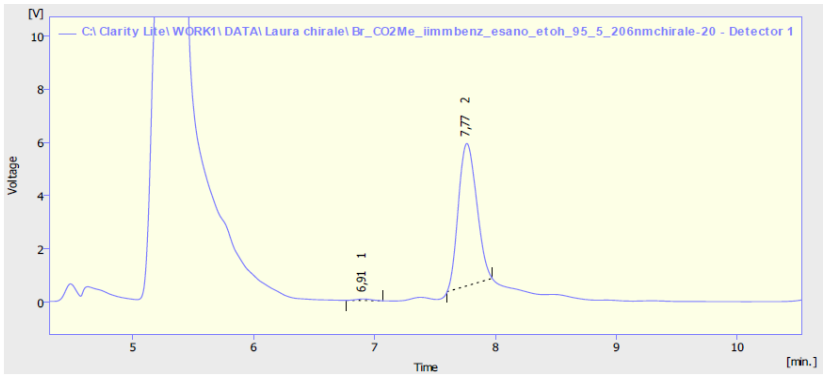
= 12.9 Hz, 1H), 3.88 (d, *J* = 9.1 Hz, 1H), 3.93−4.03 (m, 1H), 6.97–7.35 (m, 10H). ^{19}F NMR ($CDCl_3$): –73.0 (d, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$): 51.4z, 52.5, 52.8, 60.1 (q, *J* = 27.3 Hz), 126.3 (q, *J* = 284.6 Hz), 127.3, 128.3 (4C), 128.4, 128.9 (2C), 129.3 (2C), 133.6, 138.8, 171.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{19}F_3NO_2$ 338.1368, found 338.1397.

HPLC trace of racemic 10



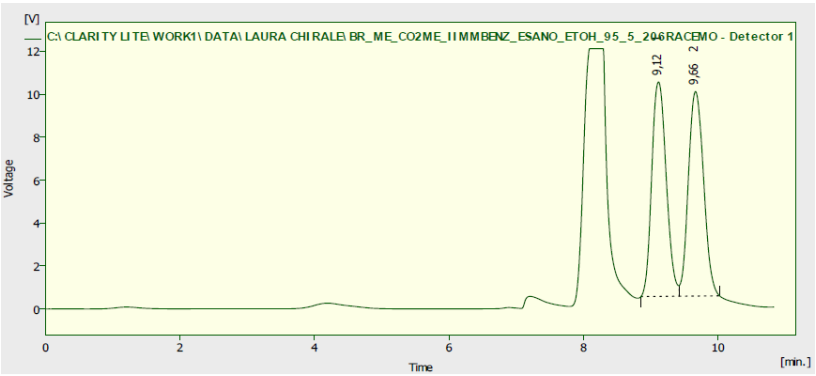
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	6,892	32880,261	3147,022	48,1	50,8	0,17	
2	7,744	35468,478	3053,556	51,9	49,2	0,19	
	Total	68348,739	6200,577	100,0	100,0		

HPLC traces of 10'



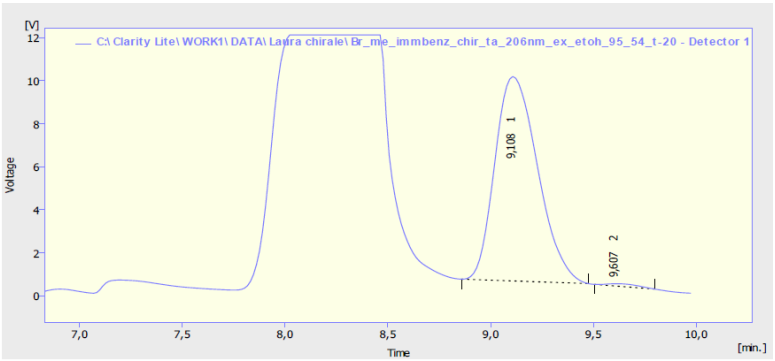
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	6,907	517,332	59,125	0,9	1,1	0,15	
2	7,767	56070,923	5345,700	99,1	98,9	0,17	
	Total	56588,255	5404,824	100,0	100,0		

HPLC trace of racemic *syn*-12



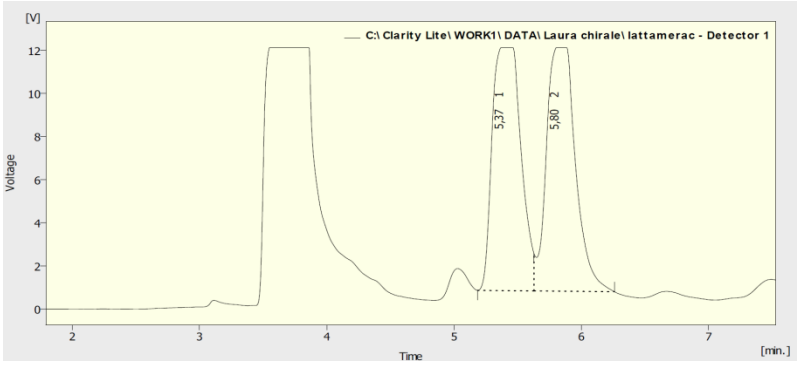
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	9,120	149445,427	9985,941	49,9	51,2	0,25	
2	9,664	150006,748	9530,184	50,1	48,8	0,26	
	Total	299452,175	19516,125	100,0	100,0		

HPLC trace of *syn*-12'



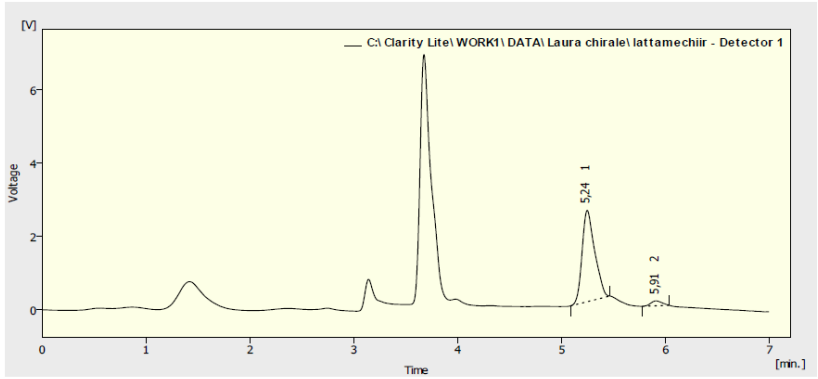
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	9,108	137665,648	9500,182	99,0	98,9	0,23	
2	9,607	1390,206	108,624	1,0	1,1	0,19	
	Total	139055,854	9608,806	100,0	100,0		

HPLC trace of racemic *trans*-5



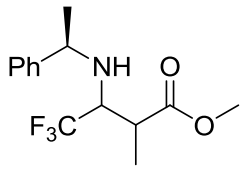
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5,368	176622,428	11271,893	49,5	49,9	0,26	
2	5,804	180545,968	11296,712	50,5	50,1	0,24	
	Total	357168,396	22568,606	100,0	100,0		

HPLC trace of enantioriched *trans*-5[4]

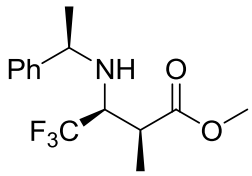


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5,244	20998,183	2492,955	95,5	94,9	0,14	
2	5,908	997,719	133,942	4,5	5,1	0,13	
	Total	21995,902	2626,897	100,0	100,0		

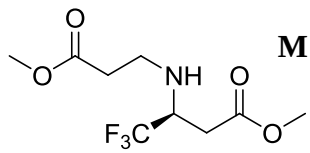
[4] Obtained from the cyclization of *anti*-**13'**



Methyl 4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (*syn*-16, 16'). Colorless oil (98 mg, 68%). IR: 1780, 1785. ^{1}H NMR ($CDCl_3$): 1.15 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.80 (br, 2H), 2.67–2.75 (m, 1H), 2.81–2.89 (m, 1H), 3.38–3.44 (m, 4H), 3.61–3.68 (m, 4H), 3.92 (q, *J* = 6.3 Hz, 1H), 4.03 (d, *J* = 6.2 Hz, 1H), 7.20–7.30 (m, 10H). ^{19}F NMR ($CDCl_3$): –70.0 (d, *J* = 10.0 Hz), –72.1 (d, *J* = 6.2 Hz). ^{13}C NMR ($CDCl_3$): 10.3, 10.7, 23.5, 24.8, 39.0, 39.3, 51.8, 52.1, 55.6, 55.9, 57.2 (q, *J* = 26.4 Hz), 57.4 (q, *J* = 27.1 Hz), 126.2 (q, *J* = 284.8 Hz), 126.7 (q, *J* = 287.6 Hz), 126.8 (2C), 127.3 (2C), 127.4 (2C), 128.3 (2C), 128.5 (2C), 143.7, 144.6, 173.3, 173.9. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{19}F_3NO_2$ 290.1368, found 290.1394.



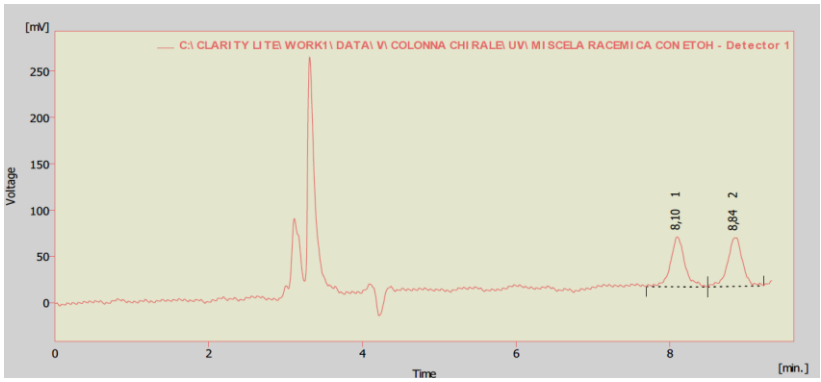
Methyl (2*S*,3*S*)-4,4,4-trifluoro-2-methyl-3-{[(*R*)-1-phenylethyl]amino}butanoate (16'). Colorless oil (70 mg, 49 %). IR: 1785. ^{1}H NMR ($CDCl_3$): 1.25 (d, *J* = 7.2 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.81 (br, 1H), 2.86−2.94 (m, 1H), 3.67–3.73 (m, 4H), 3.98 (q, *J* = 6.2 Hz, 1H), 7.26–7.39 (m, 5H). ^{19}F NMR ($CDCl_3$): –72.2 (d, *J* = 7.9 Hz). ^{13}C NMR ($CDCl_3$): 10.7, 23.5, 39.1, 52.0, 55.5, 57.4 (q, *J* = 27.1 Hz), 126.3 (q, *J* = 284.8 Hz), 126.7 (2C), 127.4, 128.5 (2C), 144.8, 173.9. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{19}F_3NO_2$ 290.1368, found 290.1385.



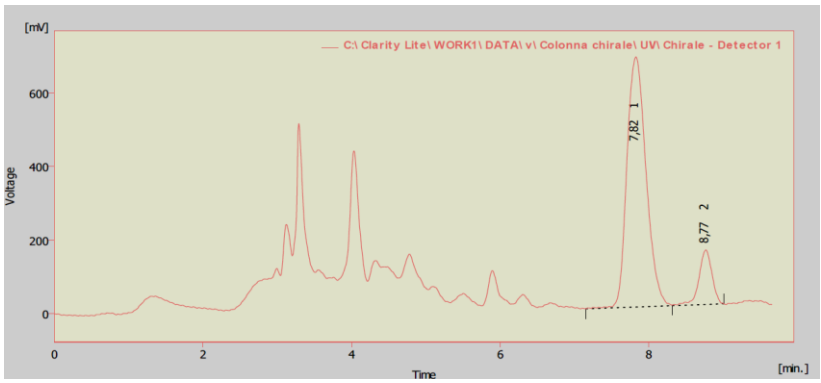
Methyl (*S*)-4,4,4-trifluoro-3-[(3 methoxy-3-oxopropyl)amino]butanoate (21'). Colorless oil (64 mg, 50%). $[\alpha]_D$ = 23.2 (*c* = 3 g/100 mL, $CHCl_3$). The ee was determined to be 74% by HPLC (Column Lux 5u Amylose-2), hexane/EtOAc = 95:5, 1.0 mL/min, 203 nm, major 7.82 min and minor 8.77 min). ^{1}H NMR ($CDCl_3$): 2.47–2.55 (m, 4H), 2.7 (dd, *J* = 15.8, 3.9 Hz, 1H), 2.93−3.01

(m, 1H) , 3.0.9−3.17 (m 1H), 3.58–3.64 (m, 1H), 3.68 (s, 3H), 3.73 (s, 3H). ^{19}F NMR ($CDCl_3$): −75.5 (d, *J*=7.9 Hz). ^{13}C NMR ($CDCl_3$): 34.1, 43.4, 51.7, 52.2, 56.7 (q, *J* = 29.4 Hz), 125.6 (q, *J* = 283.7 Hz), 170.2, 172.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_9H_{15}F_3NO_4$ 258.0953 found 258.0908.

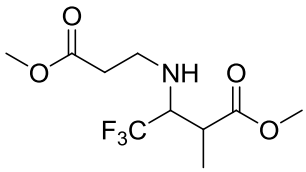
HPLC trace of 21.



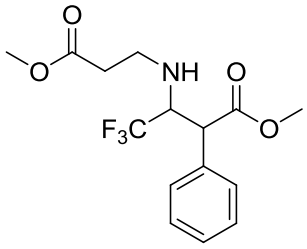
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	8,096	697,357	53,849	49,5	50,6	0,18	
2	8,844	712,594	52,545	50,5	49,4	0,20	
	Total	1409,951	106,394	100,0	100,0		



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	7,824	12182,682	680,149	87,1	82,1	0,28	
2	8,768	1809,883	148,318	12,9	17,9	0,19	
	Total	13992,565	828,467	100,0	100,0		



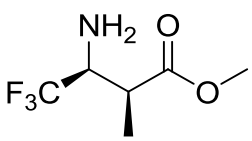
Methyl 4,4,4-trifluoro-3-[(3-methoxy-3-oxopropyl)amino]-2-methylbutanoate (*syn*-22). Colorless oil (65 mg, 48%). ^{1}H NMR ($CDCl_3$): 1.21 (d, *J* = 7.1 Hz, 3H), 1.65 (br, 1H), 2.45 (t, *J* = 6.3 Hz, 2H), 2.77–2.94 (m, 2H), 3.08–3.16 (m, 1H), 3.56–3.71 (m, 4H), 3.75 (s, 3H). ^{19}F NMR ($CDCl_3$): −72.1 (d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$): 11.2, 34.8, 39.4, 44.3, 51.6, 52.2, 60.7 (q, *J* = 27.1 Hz), 126.2 (q, *J* = 217.9 Hz), 172.8, 173.6. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{17}F_3NO_4$ 272.1110 found 272.1118.



Methyl 4,4,4-trifluoro-3-(3-methoxy-3-oxopropylamino)-2-phenylbutanoate (*anti*-23). Colorless oil (84 mg, 51%). ^{1}H NMR ($CDCl_3$): 2.25 (t, *J* = 6.3 Hz, 2H), 2.71−2.79 (m, 1H), 2.87−2.94 (m, 1H), 3.55 (s, 3H), 3.68 (s, 3H), 3.77−3.92 (m, 2H), 7.26 −7.48 (m, 5H). ^{19}F NMR ($CDCl_3$): −73.6 (d, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$): 35.0, 44.5, 51.4, 51.5, 52.4, 61.1 (q, *J* = 27.3 Hz), 126.2 (q, *J* = 284.1 Hz), 128.3, 128.8 (2C), 129.3 (2C), 133.6, 171.6, 172.4. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{19}F_3NO_4$ 334.1266 found 334.1208.

General procedure for the benzyl group hydrogenolysis reaction

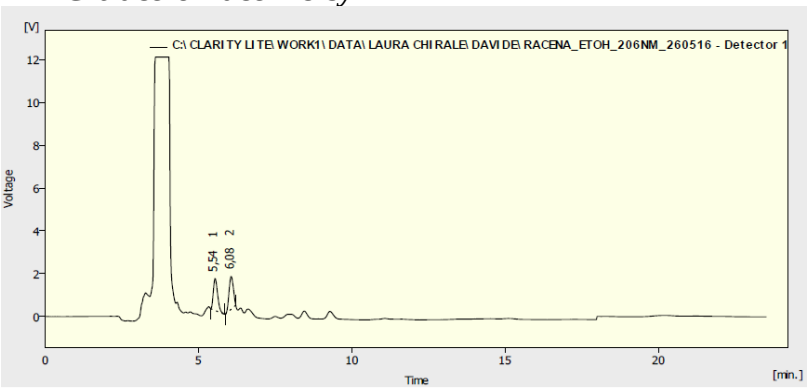
To a solution of β-amino esters *syn*-**12'** or **16'** (0.5 mmol) in MeOH (15 mL), 10 mol % $Pd(OH)_2$ on carbon (0.05 mmol) was added while being exposed to H_2. After 12 hours, the reaction mixture was filtered through celite pad and concentrated *in vacuo*. The corresponding amines were used in the next experiments without further purification.



Methyl (2*S*,3*S*)-3-amino-4,4,4-trifluoro-2methylbutanoate (*syn*-14'). Colorless oil (52 mg, 43 %). IR: 3338, 3400, 1788. The ee was determined to be 98% by

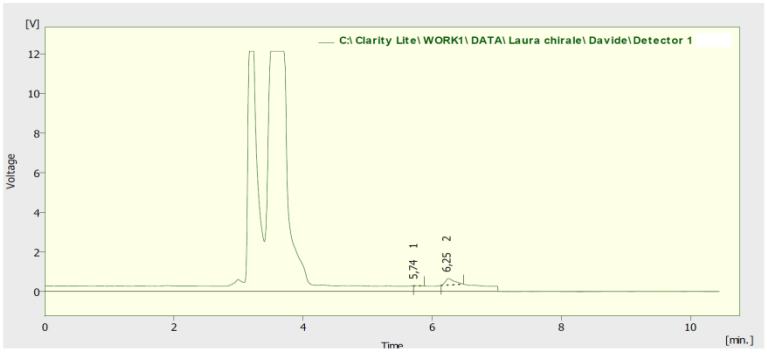
HPLC (Column Lux 5u Amylose-2), hexane/EtOH = 95:5, 1.0 mL/min, 203 nm, major 5.74 min and minor 6.25 min). ^{1}H NMR ($CDCl_3$): 1.26 (d, *J* = 7.1 Hz, 3H), 1.65 (br, 2H), 2.85 (qd, *J* = 7.2, 4.6 Hz, 1H), 3.58–3.87 (m, 4H). ^{19}F NMR ($CDCl_3$): –75.8 (d, *J* = 7.9 Hz). ^{13}C NMR ($CDCl_3$): 12.3, 37.55, 53.0, 54.1 (q, *J* = 29.7 Hz), 123.8 (q, *J* = 283.3 Hz), 172.1. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_6H_{11}F_3NO_2$ 186.0742, found 186.0758.

HPLC trace of racemic *syn*-14



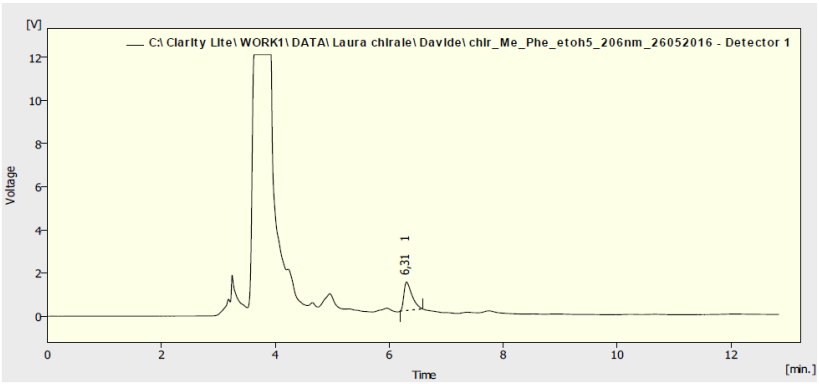
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5,540	14554,295	1492,541	49,9	49,6	0,16	
2	6,080	14629,226	1517,141	50,1	50,4	0,20	
	Total	29183,521	3009,682	100,0	100,0		

HPLC trace of *syn*-14', obtained starting from *syn*-12'

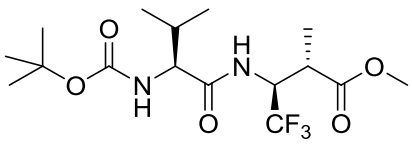


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	5,736	29,838	4,264	0,9	1,3	0,06	
2	6,252	3172,984	327,225	99,1	98,7	0,17	
	Total	3202,823	331,489	100,0	100,0		

HPLC trace of *syn*-14', obtained starting from 16'



Coupling reactions: general procedure. To a solution of *syn*-**14′** (0.25 mmol) in 7 mL of CH_2Cl_2 equimolar amounts of *N*-Boc-L-Val, *N*,*N*'-dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP, 10 mol %) were added. After 24 h of stirring at room temperature, the crude mixture was filtered off to remove the formed *N*,*N*'-dicyclohexylurea (DCU) and the solvent was evaporated under vacuum. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2)

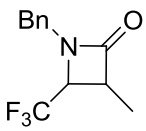


Methyl (2*S*,3*S*)-3-{(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanamido}-4,4,4-trifluoro-2-methylbutanoate (15'). White viscous oil. (80 mg 56%). IR: 3440, 3342, 1708, 1670. $[\alpha]_D$= 21.2 (*c* =1 g/100 mL, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 0.93–0.97 (m, 6H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 2.09–2.23 (m, 1H), 2.82–2.91 (m, 1H), 3.71 (s, 3H), 3.83 (t, *J* = 7.6 Hz, 1H), 4.98–5.13 (m, 2H), 6.60 (d, *J* = 7.2 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) –73.3 (br). ^{13}C NMR (75 MHz, $CDCl_3$) 12.4, 19.1 (2C), 28.2 (3C), 30.0, 38.8, 51.6 (q, *J* = 30,3 Hz), 52.3, 60.7, 80.5, 124.6 (q, *J* = 282.2 Hz), 156.0, 171.8, 172.6. HRMS: *m/z* [M + H]$^+$ calcd for $C_{16}H_{28}F_3N_2O_5$ [M+H]$^+$ 385.1950, found 385.1934.

*Synthesis of the **cis-14** and **trans-5** by Et_2Zn promoted aza-Reformatsky reaction*

α-Bromo ester **2b-c** (1.0 mmol) was added to a solution of the corresponding imine **1a** (0.5 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. Then the mixture was cooled to −20 °C, and 1.0 M Et_2Zn in hexane (1.0 mL, 1.0 mmol) was slowly added to the mixture at same temperature. The whole mixture was stirred at the same temperature for appropriate time (reported in **Table 5**, **Chap 7**, p. 83). The temperature was allowed to rise to room temperature and quenched with saturated aqueous $NaHCO_3$ after 14 days. The mixture was extracted with AcOEt and then

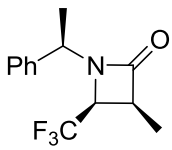
the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt: hexane: 5:95) to afford the corresponding β-lactams *cis*-**14** and *trans*-**5**.



1-benzyl-3-methyl-4-(trifluoromethyl)azetidin-2-one (*cis*-14). Colorless oil (52 mg, 43 %). IR: 1788. ^{1}H NMR ($CDCl_3$): 1.35 (d, *J* = 7.7 Hz, 3H), 3.40–3.52 (m, 1H), 3.77–3.88 (m, 1H), 3.97 (d, *J* = 15.1 Hz, 1H), 4.85 (d, *J* = 15. Hz, 1H), 7.22–7.41 (m, 5H). ^{19}F NMR ($CDCl_3$): –68.8 (d, *J* = 9.2 Hz). ^{13}C NMR ($CDCl_3$): 8.9, 45.3, 47.3, 53.9 (q, *J* = 32.8 Hz), 124.4 (q, *J* = 280.3 Hz), 128.1, 128.5 (2C), 128.9 (2C), 134.7, 169.3. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{13}F_3NO$ 244.0949, found 244.0965.

*Synthesis of the **cis-17** by asymmetric Et_2Zn promoted aza-Reformatsky reaction*

α-Bromo ester **2b** (1.0 mmol) was added to a solution of the corresponding imine **1c**(0.5 mmol) and (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol **6** (0.38 mmol) in CH_2Cl_2 (5 mL) at ambient temperature. Then the mixture was cooled to −20 °C, and 1.0 M Et_2Zn in hexane (1.2 mL, 1.2 mmol) was slowly added to the mixture at the same temperature. The whole mixture was stirred at the same temperature for 5 days. The temperature was allowed to rise to room temperature and quenched with saturated aqueous $NaHCO_3$ after 14 days. The mixture was extracted with AcOEt and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt: hexane: 1:9) to afford the corresponding β-lactam *cis*-**17**.



(3*S*,4*S*)-3-methyl-1-[(*R*)-1-phenylethyl]-4-(trifluoromethyl)azetidin-2-one (*cis*-17). White solid (55 mg, 43 %). IR: 1769. $[\alpha]_D$ = 12.3 (*c* = 3 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.32 (dq, *J* = 7.6, 3.4 Hz, 3H), 1.62 (d, *J* = 7.3 Hz, 3H), 3.33–3.40 (m, 1H), 3.64–3.74 (m, 1H), 5.07 (q, *J* = 7.4 Hz, 1H), 7.27–7.39 (m, 5H). ^{19}F NMR ($CDCl_3$): –68.5 (d,

J = 6.9 Hz). ^{13}C NMR ($CDCl_3$): 9.0, 17.9, 46.6, 51.6, 53.7 (q, *J*=34.7 Hz), 124.4 (q, *J*=279.8 Hz), 127.2 (2C), 128.0, 128.8 (2C), 138.6, 169.4. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{15}F_3NO$ 258.1106, found 258.1167.

2D NMR spectra and optimized geometries to determine the absolute configuration of the new chiral centers of *cis*-17.

1. To determine the absolute configuration of the new chiral centers 2D NOESY NMR spectra and optimized geometries of the β-lactam *cis*-**17** were considered.

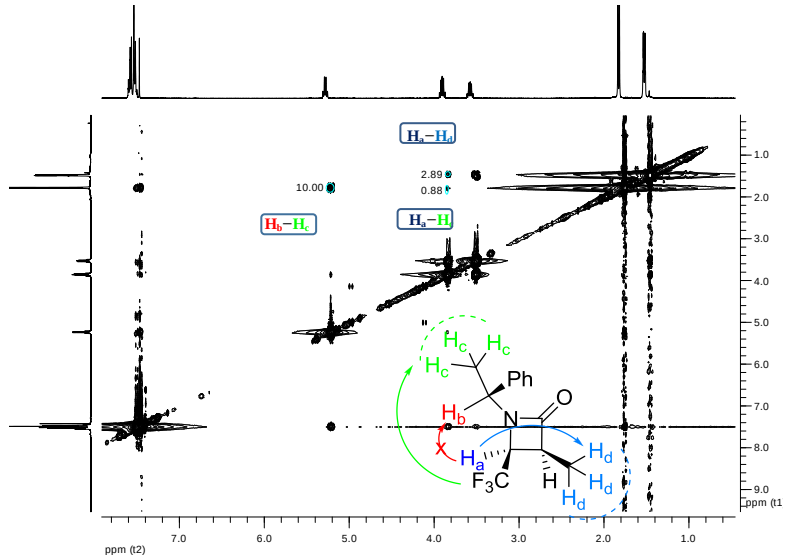


Figure 10. 2D NOESY spectrum of *cis*-**17**.

The cross peak between the protons H_b and H_c was used as a distance ruler and its volume was set to 10.00 a.u.; the cross peak between H_a and the protons H_c of the methyl group can be easily determinate for *cis*-**17**, the value is 0.88 a.u. (corresponding to an interproton distance of 4.034 Å). The correlation between H_a and H_d shows a value equal to 2.89 a.u., corresponding to an interproton distance of 3.27 Å, that confirms the *cis* configuration (compared to the distance determinate for the *trans*-**8** and **8'**).

The optimized geometries of all possible diastereomers (see pp.166-168) coupled with NOESY analysis permits to assign the (*R*,*S*,*S*) to *cis*-**16**

Chapter 13

Work towards the discovery of selective and potent PCAF inhibitors

Synthesis of 6-chloro-3-methyl[1,2,4]triazolo[3,4-a]phthalazine (2). Multistep procedure for the synthesis of **2** was followed.[1]

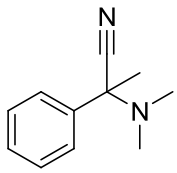
*Synthesis of amines **5-8***

Synthesis of 3-methyl-2-phenylbutan-1-amine (4). The amine **5** was synthesized starting from (*E*)-(2-nitrovinyl)benzene which, following a reported procedure of Michael addition reaction with Grignard reagent,[2] gave the corresponding adduct**.** The reported procedure of reduction of the nitro group[3] lead to the amine **4**. The Michael adduct[4] and **4** are known.[5]

Synthesis of *N*^{1}-methyl-1-phenylethane-1,2-diamine (5). **Procedure**: To a stirred suspension of $LiAlH_4$, (237.2 mg, 6.30 mmol) in Et_2O (10 mL) under N_2 was added dropwise, over 0.5 h, a solution of 2-(methylamino)-2-phenylacetonitrile (230.0 mg, 1.57 mmol) in Et_2O (500 mL) at 0 ˚C. The mixture was stirred at this temperature for 5 h and then at room temperature overnight. H_2O was then added, followed by 15% NaOH (2 mL), and finally another 10 mL of H_2O. Inorganic material was removed by filtration. The solution was extracted with EtOAc, dried over $MgSO_4$, filtered and the solvent was evaporated to give the product as yellow

[1] See ref. 19 in the **Chapter 7**.
[2] Yao, C.; Kao, K.; Liu, J.; Wang, Y.; Chen, W.; Lin, Y.; Yan, M.; *Tetrahedron* **1998**, *54*, 791-822.
[3] Martinelli, E.; Vicini, A. C.; Mancinelli, M.; Mazzanti, A.; Zania, P.; Bernardi, L.; Fochi, M. *Chem. Commun.* **2015**, *51*, 658-660.
[4] Yao, C.; Kao, K.; Liu, J.; Wang, Y.; Chen, W.; Lin, Y.; Yan, M.; *Tetrahedron* **1998**, *54*, 791-822.
[5] Brenna, E.; Fuganti, C.; Gatti, F. G.; Passoni, M.; Serra, S. *Tetrahedron Asymmetry* **2003** , *14*, 2401 -2406

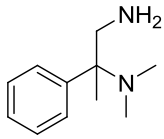
oil. The crude product (52% yield) was used in the next step without further purification. **5** is a known compound.[6]



Synthesis of 2-(dimethylamino)-2-phenylpropanenitrile

Procedure: LDA was prepared by adding BuLi (0.69 mL, 1.1 mmol, 1.6 M in hexanes) to a solution of diisopropylamine (0.17 mL, 1.2 mmol) in 2.5 mL of THF, at 0 °C under N_2. The solution was stirred 15 min at 0 °C and then cooled to –78 °C. A solution of 2-(dimethylamino)-2-phenylacetonitrile (160 mg, 1 mmol) in THF (2.5 mL) was added to the LDA solution and the mixture was stirred for 30 min at –78 °C. CH_3I (0.07 mL, 1.1 mmol) was then added to the solution. The reaction mixture was stirred for 16 hours, while the temperature was allowed to rise to 0 °C and quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl ether (3x20 mL), the combined organic phases were dried ($MgSO_4$) and concentrated. The crude product (72% yield) was used in the next step without further purification.

2-(Dimethylamino)-2-phenylpropanenitrile. Colorless oil. IR: 2230. ^{1}H NMR ($CDCl_3$): 1.60 (s, 3H), 2.17 (s, 6H), 7.19−7.28 (m, 3H), 7.46−7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): 29.3, 40.7 (2C), 67.2, 117.6, 125.4 (2C), 141.0, 128.3, 128.7 (2C). HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{15}N_2$ 175.1235, found 175.1242.



Synthesis of N_2,N_2-dimethyl-2-phenylpropane-1,2-diamine (6)

Procedure: To a stirred suspension of $LiAlH_4$, (90.4 mg, 2.4 mmol) in Et_2O (5 mL) under N_2 was added dropwise, over 0.5 h, a solution of 2-(dimethylamino)-2-phenylpropanenitrile (105 mg, 0.6 mmol) in Et_2O (5 mL) at 0 ˚C. The mixture was stirred at this temperature for 5 h

[6] Malkov, A.V.; Stewart-Liddon, A. J. P.; McGeoch, G. D.; Ramirez-Lopez, P.; Kocovsky, P. *Org. Biomol. Chem*. **2012** , *10*, 4864-4877

and at room temperature overnight. H_2O (1 mL) was then added, followed by 15% NaOH (1 mL), and finally another 2 mL of H_2O. Inorganic material was removed by filtration. The solution was extracted with Et_2O, dried over $MgSO_4$, filtered and the solvent was evaporated to give the product (44%) as yellow oil. Purification by FCC (MeOH 10%/ EtOAc) yielded **6** (44%) as colorless oil.

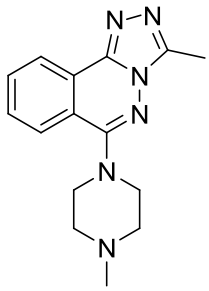
***N*$_2$,*N*$_2$-Dimethyl-2-phenylpropane-1,2-diamine.** Colorless oil. IR: 3335. ^{1}H NMR ($CDCl_3$): 1.29 (s, 3H), 2.18 (s, 6H), 2.58 (d, J = 13.4 Hz, 1H), 2.99 (d, J = 13.4 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.48 (dd, J = 8.2, 0.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 12.6, 38.8 (2C), 52.2, 63.8, 126.5, 127.1 (2C), 128.0 (2C), 144.7. HR-MS (ESI Q-TOF) (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{19}N_2$ 179.15428, found 179.15434.

Synthesis of *N*$_1$,*N*$_1$-dimethyl-2-phenylethane-1,2-diamine (7). Procedure: Ammonium acetate (1.5 g, 20 mmol) and 2-(dimethylamino)-1-phenylethan-1-one (0.163 g, 1 mmol) were mixed in methanol (20 mL) and then treated with sodium cyanoborohydride (0.314 g, 5 mmol). The mixture was stirred at room tempearture under a N_2 atmosphere for 4 days. The reaction mixture was quenched by adding 1N NaOH, and the product was extracted with EtOAc (3 x 50 mL). The organic extract was dried ($MgSO_4$) and the solvent was evaporated to give the crude free base. Purification by FCC (5% MeOH/CH_2Cl_2). 49% yield. **7** is a known compound.[7]

Synthesis of 3-methyl-6-(4-methylpiperazin-1-yl)-[1,2,4]triazolo[3,4-a]phthalazine (11). Procedure: 3-Methyl-6-(piperazin-1-yl)-[1,2,4]triazolo[3,4-a]phthalazine (**11**) (87.6 mg, 0.32 mmol) was added to $CHCl_3$ followed by a formaldehyde solution 37 % (0.15 ml. 1.92 mmol) and formic acid (0.07 ml, 1.92 mmol). The mixture was heated at 70 °C for 3h. The mixture was charged with aqueous 1N NaOH (50 mL), and the layers were separated. The aqueous layer was

[7] Ooka, H.; Arai, N.; Azuma, K.; Kurono, N.; Ohkuma, T. *J. Org. Chem.*, **2008**, *73*, 9084−9093.

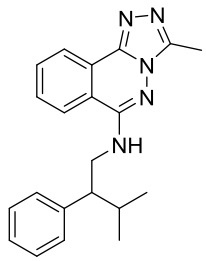
extracted with $CHCl_3$ (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by FCC (MeOH-NH_3 10%/ EtOAc) yielded **11** (43%) as a white solid.



White solid. Mpt: 210-212 ◦C; IR: 3400, 2938, 2847, 2800, 2360, 2341, 1510, 708. ^{1}H NMR ($CDCl_3$): 8.58 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 7.2, 1H), 7.69 (t, *J* = 7.2, 1H), 3.43 (s, 4H), 2.72 (s, 3H), 2.70 (s, 4H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): 157.5, 147.7, 142.4, 132.7, 129.8, 126.3, 125.0, 123.7, 120.0, 54.7 (2C), 51.1 (2C), 46.1, 9.7. LR-ESI-MS: $C_{15}H_{19}N_6$ (*m/z*) $[M + H]^+$found 283.1 calcd 283.2. HR-ESI-MS: $C_{15}H_{19}N_6$ (*m/z*) $[M + H]^+$ found 283.16656 calcd 283.16657.

*General procedure for the coupling reactions of **2** with amines **4-7***

In a pressure tube, 6-chloro-3-methyl[1,2,4]triazolo[3,4-a]phthalazine (**2**) (20 mg, 0.092 mmol) was dissolved in EtOH (0.2 mL), amine **4-7** (0.21 mmol), KI (1.5 mg, 0.009 mmol) and concentrated HCl (2 μL, 0.002 mmol) were added, the tube was sealed and the reaction was stirred at 100 °C, until the complete disappearance of reactants was observed by TLC. The reaction mixture was concentrated, 1M NaOH (aq) (20 mL) was added and the aqueous phase was extracted with $CHCl_3$-MeOH (10%) (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The compound **9** is known.[8]

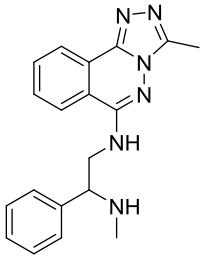


3-Methyl-*N*-(3-methyl-2-phenylbutyl)[1,2,4]triazolo[3,4-a]phthalazin-6-amine (12).

Brown oil (22 %). IR: 3292, 2957, 2928, 2800, 2360, 2341, 1514, 701. ^{1}H NMR ($CDCl_3$): 0.82 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 2.04 (ddt, *J* = 13.3, 8.5, 6.7 Hz, 1H),

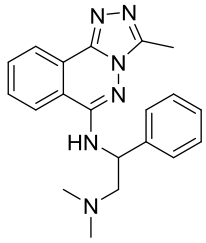
[8] See ref. 18 in the **Chapter 7**.

2.72–2.80 (m, 1H2.73 (s, 3H), 3.49 (ddd, *J* = 14.0, 10.7, 3.5 Hz, 1H), 4.21 (ddd, *J* = 13.0, 7.3, 4.5 Hz, 1H), 4.78 (d, *J* = 3.8 Hz, 1H), 7.20–7.38 (m, 6H), 7.53–7.61 (m, 1H), 7.74–7.78 (m, 1H), 8.55 (dd, *J* = 7.9, 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 21.0, 21.1, 31.6, 44.9, 52.2, 118.2, 121.7, 123.8, 124.2, 127.0, 128.4 (2C), 128.8 (2C), 150.7, 147.3, 142.0, 141.9, 132.4, 129.9. LR-ESI-MS: $C_{21}H_{24}N_5$ (*m/z*) [M + H]$^+$ found 346.2 calcd 346.2. HR-ESI-MS: $C_{21}H_{24}N_5$ (*m/z*) [M + H]$^+$ found 346.20216.



N^1-Methyl-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (13).

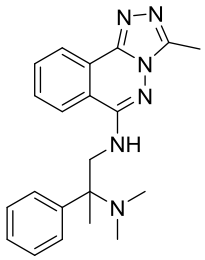
White solid (30%). IR: 3275, 2926, 2853, 2360, 2343, 1518, 701. ^{1}H-NMR ($CDCl_3$): 2.43 (s, 3H), 2.65 (s, 3H), 3.52–3.65 (m, 1H), 3.81 (dt, *J* = 13.2, 5.3 Hz, 1H), 4.01 (dd, *J* = 8.2, 4.9 Hz, 1H), 6.06 (br, 1H), 7.31–7.48 (m, 5H), 7.66–7.71 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.5 Hz, 1H), 8.56 (d, *J* = 7.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$): 9.7, 33.8, 47.0, 62.9, 118.3, 122.5, 123.7, 123.9, 127.2 (2C), 128.2, 129.0 (2C), 130.0, 132.5, 140.1, 141.9, 147.2, 151.0. LR-ESI-MS: $C_{19}H_{21}N_6$ (*m/z*) [M + H]$^+$ found 333.1 calcd 333.2. HR-ESI-MS: $C_{19}H_{21}N_6$ (*m/z*) [M + H]$^+$ found 333.18205 calcd 333.18222.



N^2,N^2-Dimethyl-N^1-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1 phenylethane-1,2-diamine 14).

Yellow oil (21%). IR: 3334, 2926, 2856, 2360, 2342, 1510, 701. ^{1}H NMR ($CDCl_3$): 2.39–2.40 (m, 9H), 2.54 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.90 (t, *J* = 11.7 Hz, 1H), 4.85 (dd, *J* = 11.4, 3.7 Hz, 1H), 6.77 (br, 1H), 7.21–7.26 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.40–7.49 (m, 2H), 7.70–7.78 (m, 1H), 7.78–7.85 (m, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.56 (dd, *J* = 7.9, 0.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.5, 45.1 (2C), 54.2, 64.9, 118.8, 122.8, 123.7, 124.2, 126.7 (2C), 127.3, 128.3 (2C), 130.0, 132.5, 141.5, 141.8,

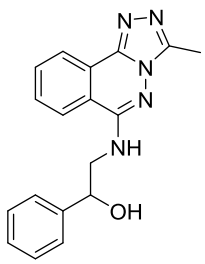
147.3, 150.6. LR-ESI-MS: $C_{20}H_{23}N_6$ (*m/z*) $[M + H]^+$ found 347.2 calcd 347.2. HR-ESI-MS: $C_{20}H_{23}N_6$ (*m/z*) $[M + H]^+$ found 347.19788 calcd 347.19787 error = 0.01 ppm.



***N*²,*N*²-Dimethyl-*N*¹-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-2-phenylpropane-1,2-diamine (15).**

Brown oil (17 %). IR: 3368, 2941, 2829, 2784, 2360, 2341, 1513, 701. ^{1}H NMR ($CDCl_3$): 1.53 (s, 3H), 2.31 (s, 6H), 2.66 (s, 3H), 3.64 (s, 2H), 5.70 (br, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.39 (dd, *J* = 10.6, 5.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.67–7.72 (m, 1H), 7.78–7.83 (m, 1H), 8.56 (dd, *J* = 7.9, 0.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 14.9, 38.9 (2C), 50.6, 60.4, 118.4, 121.9, 123.8, 124.2, 126.6 (2C), 127.2, 128.4 (2C), 129.9, 132.4, 141.9, 143.9, 147.2, 150.8. LR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 361.2 calcd 361.2. HR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 361.21362 calcd 361.21352 error = 0.28 ppm.

Synthesis of 2-{(3-methyl[1,2,4]triazolo[3,4-α]phthalazin-6-yl)amino}-1-phenylethan-1-ol (17). Procedure: In a pressure tube, 6-chloro-3-methyl[1,2,4]triazolo[3,4-a]phthalazine (**1**) (601 mg, 2.76 mmol) was dissolved in EtOH (2 mL), 2-amino-1-phenylethan-1-ol (862 mg, 6.29 mmol), KI (45.3 mg, 0.27 mmol) and concentrated HCl (0.055ml) were added, the tube was sealed and the reaction was stirred at 100 °C for 4d. The reaction mixture was cooled to room temperature and filtered through a buchner funnel. The filter cake was washed with DCM and dried in vacuum. **23** (505mg, 57%) was obtained as a white solid.

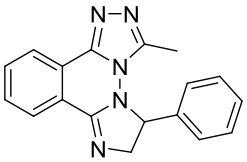


2-{(3-Methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethan-1-ol (17).

White solid (57 %). IR: 3400, 2938, 2801, 2360, 1511, 701. Mpt: 218-220 °C. ^{1}H NMR (DMSO): 2.61 (s, 3H), 3.39 (ddd, *J* = 13.5, 8.5, 5.1 Hz, 1H), 3.71 (ddd, *J* = 13.4, 5.9, 3.9 Hz, 1H),

5.12 (dt, *J* = 8.3, 4.0 Hz, 1H), 5.55 (d, *J* = 4.4 Hz, 1H), 8.36–8.40 (m, 2H), 7.25 (dd, *J* = 10.4, 4.3 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.81–7.87 (m, 2H), 7.91–7.97 (m, 1H). ^{13}C NMR (DMSO): 9.4, 50.0, 69.4, 118.3, 122.5, 123.4, 124.3, 125.8 (2C), 127.0, 128.1 (2C), 130.2, 132.8, 141.1, 144.1, 146.0, 151.2; LR-ESI-MS: $C_{18}H_{18}N_5O$ (*m/z*) $[M + H]^+$ found 320.2 calcd 320.2. HR-ESI-MS: $C_{18}H_{18}N_5O$ (*m/z*) $[M + H]^+$ found 320.15037 calcd 320.15059.

Synthesis of 3-methyl-6-phenyl-6,7-dihydroimidazo[2,1-a][1,2,4]triazolo[4,3-c]phthalazine (18). Procedure: To a solution of **17** (0.123 mmol) in pyridine (3.7 mL) was added methanesulfonyl chloride (5.5 mmol) and the mixture was stirred at room temperature for 1 h. Then, water (0.6 mL) was added to the solution. The mixture was concentrated to a small volume and the residue was partitioned between $CHCl_3$ (20 mL) and water (20 mL). The organic layer was dried over $MgSO_4$ and evaporated to give **18.**

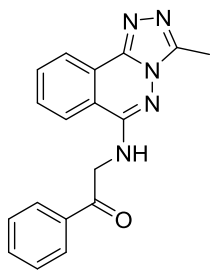


3-Methyl-6-phenyl-6,7-dihydroimidazo[2,1 a][1,2,4]triazolo[4,3-c]phthalazine (18).

White solid (68 %). ^{1}H-NMR ($CHCl_3$): 2.42 (s, 3H), 4.09 (dd, *J* = 14.5, 2.6 Hz, 1H), 4.44 (dd, *J* = 14.5, 8.9 Hz, 1H), 5.62 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.03–7.29 (m, 5H), 7.64 (td, *J* = 7.8, 1.1 Hz, 1H), 7.76 (td, *J* = 7.8, 1.1 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (DMSO): 12.3, 61.8, 68.6, 121.6, 123.6, 123.8, 125.3 (2C), 127.1, 129.0, 129.6 (2C), 130.9, 133.2, 137.5, 144.7, 144.9, 156.6; LR-ESI-MS: $C_{18}H_{16}N_5$ [(*m/z*) $[M + H]^+$ found 320.1 calcd 320.2.

Synthesis of 2-{(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethan-1-one (19). Procedure: To a solution of **23** (700 mg, 2.2 mmol) in DMF (11ml) was added pyridinium dichromate (5.640 g, 15 mmol). The mixture was stirred at room temperature for 14 hours. The mixture was poured into water (60 mL), and then filtered through a buchner funnel. The filter cake was washed

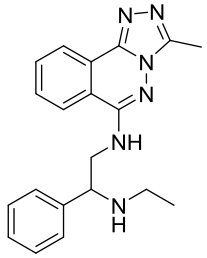
with EtOAc and filtered through the silica gel ($CHCl_3$-MeOH). **25** was obtained (75% yield) as a beige solid.



2-{(3-Methyl[1,2,4]triazolo[3,4-α]phthalazin-6-yl)amino}-1-phenylethan-1-one (19). Beige solid (75 %). IR: 3268, 2929, 2360, 1698, 1516, 700. Mpt: 240-242 °C; ^{1}H NMR ($CDCl_3$): 2.63 (s, 3H), 4.90 (d, *J* = 4.1 Hz, 2H), 6.51 (br, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.59–7.63 (m, 1H), 7.66 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 8.02–8.05 (m, 2H), 8.53 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 48.0, 118.1, 122.5, 123.8, 124.2 (2C), 128.0, 129.0 (2C), 130.1, 132.8, 134.4 (2C), 142.0, 147.2, 150.3, 194.5. LR-ESI-MS: $C_{18}H_{15}N_5O$ (*m/z*) $[M + H]^+$ found 318.1 calcd 318.1. HR-ESI-MS: $C_{18}H_{15}N_5O$ (*m/z*) $[M + H]^+$ found 318.13459 calcd 318.13603.

General procedure for the reductive amination reaction

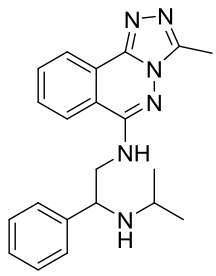
To a solution of ketone **19** (0.1mmmol) in 0.5 mL of a mixture $CHCl_3$/MeOH (2:1), the amine (0.88 mmol) was added. AcOH was added until the pH is 5, then $NaBH_3CN$ (0.12 mmol), and stirred to 50 °C until the reactants are consumed. The reaction mixture was quenched by adding 1N NaOH, and the product was extracted with $CHCl_3$/MeOH (10%) (3 × 50 mL). The organic extract was dried ($MgSO_4$) and the solvent was evaporated to give the crude free base. Purification by FCC ($CHCl_3$-iPrOH 5%).



***N*^{1}-Ethyl-*N*^{2}-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (20)**

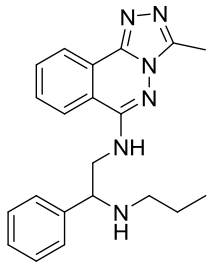
White solid (43 %). IR: 3232, 3068, 2963, 2361, 1515, 669. Mpt: 228-230 °C. ^{1}H NMR ($CDCl_3$): 1.20 (t, *J* = 7.0 Hz, 3H), 2.73–2.62 (m, 4H), 3.58–3.68 (m, 1H), 3.75–3.83 (m, 1H), 4.20 (br, 1H), 6.23 (br, 1H), 7.31–7.51 (m, 5H), 7.61–7.73 (m, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 8.52 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): 9.7, 15.0,

41.6, 47.1, 61.0, 118.3, 122.5, 123.7, 124.0, 127.1 (2C), 128.1, 129.0 (2C), 130.1, 132.5, 141.9 (2C), 147.2, 151.0. LR-ESI-MS: $C_{20}H_{24}N_6$ (*m/z*) $[M + H]^+$ found 347.2 calcd 347.2. HR-ESI-MS: $C_{20}H_{24}N_6$ (*m/z*) $[M + H]^+$ found 347.19784 calcd 347.19787.



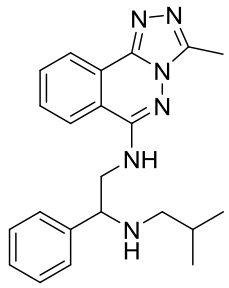
N^1-Isopropyl-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (21)

White solid (69 %). IR: 3228, 2968, 2360, 1517, 701. Mpt: 258-260 °C; ^{1}H NMR ($CDCl_3$): 1.13 (d, *J* = 6.1 Hz, 6H), 2.64 (s, 3H), 2.89– 2.80 (m, 1H), 3.50 (t, *J* = 10.2 Hz, 1H), 3.79 (dt, *J* = 13.1, 5.6 Hz, 1H), 4.22 (br, 1H), 6.25 (br, 1H), 7.47–7.32 (m, 5H), 7.71–7.65 (m, 2H), 7.79 (t, *J* = 7.4 Hz, 1H), 8.53 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 22.1, 23.9, 45.8, 47.5, 58.4, 118.4, 122.2, 123.7, 124.1, 126.9 (2C), 127.9, 128.9 (2C), 130.0, 132.5, 141.9 (2C), 147.2, 151.0. LR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 409.2 calcd 409.2. HR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 361.21348 calcd 361.21352.



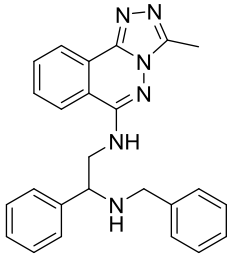
N^2-(3-Methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenyl-N^1-propylethane-1,2-diamine (22)

White solid (28 %). IR: 3067, 2900, 2854, 2359, 2341, 1515, 700. Mpt: 216-218 °C. ^{1}H NMR ($CDCl_3$): 0.94 (t, *J* = 7.4 Hz, 3H), 1.55 (dq, *J* = 21.8, 7.2 Hz, 2H), 2.56 (ddd, *J* = 25.4, 14.7, 7.6 Hz, 2H), 2.66 (s, 3H), 3.49–3.58 (m, 1H), 3.75– 3.84 (m, 1H), 4.06 (dd, *J* = 7.7, 5.0 Hz, 1H), 6.10 (br, 1H), 7.47–7.30 (m, 5H), 7.71 (s, *J* = 14.0 Hz, 2H), 7.81 (d, *J* = 7.7 Hz, 1H), 8.58 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 151.0, 147.3, 142.0, 141.6, 132.5, 130.0, 128.9 (2C), 127.8, 126.9 (2C), 124.2, 123.8, 122.2, 118.4, 61.2, 49.1, 47.3, 23.3, 11.8, 9.8. LR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ 361.2 calcd 361.2. HR-ESI-MS: $C_{21}H_{25}N_6$ (*m/z*) $[M + H]^+$ 361.21341 calcd 361.21352.



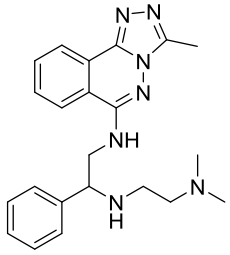
N^1-Isobutyl-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (23)

White solid (68 %). IR: 3228, 3068, 2952, 2813, 1514, 700. Mpt: 218-220 °C. ^{1}H NMR ($CDCl_3$): 0.95 (dd, *J* = 6.6, 5.5 Hz, 6H), 1.76 (tt, *J* = 13.3, 6.7 Hz, 1H), 2.41 (ddd, *J* = 42.4, 11.5, 6.7 Hz, 2H), 2.66 (s, 3H), 3.51 (ddd, *J* = 8.4, 6.0, 3.0 Hz, 1H), 3.82–3.77 (m, 1H), 4.02 (dd, *J* = 8.2, 5.0 Hz, 1H), 6.14 (s, 1H), 7.31–7.44 (m, 5H), 7.70 (d, *J* = 3.8 Hz, 2H), 7.79 –7.85 (m, 1H), 8.60 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 20.6, 20.8, 28.7, 47.3, 55.2, 61.4, 118.5, 122.1, 123.9, 124.3, 126.8 (2C), 127.8, 128.8 (2C), 130.0, 132.5, 141.8, 142.0, 147.3, 151.0. LR-ESI-MS: $C_{22}H_{27}N_6$ (*m/z*) $[M + H]^+$ found 375.2 calcd 375.2. HR-ESI-MS: $C_{22}H_{27}N_6$ (*m/z*) $[M + H]^+$ found 375.22882 calcd 375.22917.



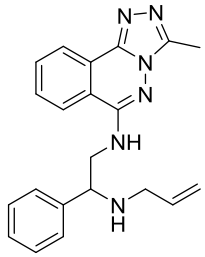
N^1-Benzyl-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (24)

White solid (34%). IR: 3230, 2970, 2360, 1515, 700. Mpt: 258-260 °C; ^{1}H NMR ($CDCl_3$): 2.64 (s, 3H), 3.58–3.51 (m, 1H), 3.66 (d, *J* = 13.2 Hz, 1H), 3.76–3.83 (m, 1H), 3.85 (d, *J* = 13.2 Hz, 1H), 4.10 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.90 (br, 1H), 7.48 – 7.26 (m, 10H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.69–7.74 (m, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 8.59 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 47.5, 51.1, 60.2, 118.4, 122.1, 123.9, 124.3, 127.1 (2C), 127.3, 128.0, 128.3 (2C), 128.5 (2C), 129.0 (2C), 130.0, 132.6, 140.0, 141.3, 142.0, 147.3, 150.9. LR-ESI-MS: $C_{25}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 409.2 calcd 409.2. HR-ESI-MS: $C_{25}H_{25}N_6$ (*m/z*) $[M + H]^+$ found 409.21341 calcd 409.21352.



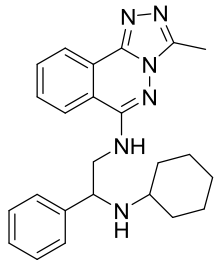
N^1-(2-(Dimethylamino)ethyl)-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (25)

White solid (72 %). IR: 3230, 2970, 2360, 1514, 751, 700. Mpt: 218-220 °C. ^{1}H NMR ($CDCl_3$): 2.23 (s, 6H), 2.47–2.37 (m, 1H), 2.58–2.65 (m, 2H), 2.66 (s, 3H), 2.67–2.74 (m, 1H), 3.52 (ddd, *J* = 13.1, 8.9, 4.0 Hz, 1H), 3.85 (ddd, *J* = 13.3, 6.0, 4.7 Hz, 1H), 8.56 (d, *J* = 7.9 Hz, 1H), 6.48 (br, 1H), 4.08 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.29–7.45 (m, 5H), 7.64–7.73 (m, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 44.0, 44.9 (2C), 47.6, 58.5, 61.2, 118.6, 122.8, 123.6, 124.1, 126.9 (2C), 127.8, 128.8 (2C), 129.9, 132.4, 141.5, 142.0, 147.2, 151.1. LR-ESI-MS: $C_{22}H_{28}N_7$ (*m/z*) $[M + H]^+$ found 390.3 calcd 390.2. HR-ESI-MS: $C_{22}H_{28}N_7$ (*m/z*) $[M + H]^+$ found 390.23943 calcd 390.24007.



N^1-Allyl-N^2-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (26)

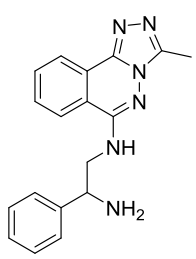
White solid (54 %). IR: 3228, 3069, 2927, 2361, 2341, 1515, 700. Mpt: 246-247 °C. ^{1}H NMR ($CDCl_3$): 2.66 (s, 3H), 3.18 (dd, *J* = 14.1, 6.2 Hz, 1H), 3.30 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.53–3.66 (m, 1H), 3.81 (dt, *J* = 13.2, 5.4 Hz, 1H), 4.13 (t, *J* = 7.1 Hz, 1H), 5.09–5.27 (m, 2H), 5.93 (ddd, *J* = 16.3, 11.0, 5.9 Hz, 1H), 6.02 (s, 1H), 7.28–7.48 (m, 5H), 7.65–7.76 (m, 2H), 7.76–7.87 (m, 1H), 8.58 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 47.3, 49.6, 60.4, 116.5, 118.4, 122.2, 123.8, 124.2, 127.0 (2C), 128.0, 128.9 (2C), 130.0, 132.5, 136.2, 141.1, 142.0, 147.3, 150.9. LR-ESI-MS: $C_{21}H_{23}N_6$ (*m/z*) $[M + H]^+$ found 359.2 calcd 359.2; HR-ESI-MS: $C_{21}H_{23}N_6$ (*m/z*) $[M + H]^+$ found 359.19799 calcd 359.19787.



***N*¹-Cyclohexyl-*N*²-(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylethane-1,2-diamine (27).**

White solid (5 %). IR: 3235, 2970, 2930, 950, 816. Mpt: 208-210 °C. ^{1}H NMR ($CDCl_3$): 1.14–1.27 (m, 6H), 1.53–1.83 (m, 6H), 2.48 (s, 1H), 2.65 (s, 3H), 3.43–3.53 (m, 1H), 3.74–3.82 (m, 1H), 4.24 (dd, *J* = 8.5, 4.7 Hz, 1H), 6.30 (s, 1H), 7.30–7.47 (m, 5H), 7.65–7.77 (m, 2H), 7.81 (dd, *J* = 11.6, 4.6 Hz, 1H), 8.57 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 24.5 (2C), 24.9, 25.9 (2C), 47.6, 53.5, 57.9, 118.5, 122.3, 123.8, 124.1, 126.9 (2C), 127.8, 128.9 (2C), 130.1, 132.5, 141.6, 142.0, 147.2, 151.0. LR-ESI-MS: $C_{24}H_{29}N_6$ (*m/z*) $[M + H]^+$ found 401.3 calcd 401.2; HR-ESI-MS: $C_{24}H_{29}N_6$ (*m/z*) $[M + H]^+$ found 401.24466 calcd 401.24482.

Synthesis of *N*¹-(3-methyl[1,2,4]triazolo[3,4-α]phthalazin-6-yl)-2-phenylethane-1,2-diamine (28). Procedure: To a solution of ketone **19** (10 mg, 0.03 mmol) in 0.5 mL of a mixture $CHCl_3$/MeOH (2:1) a solution of MeOH/NH_3 (0.5 ml) was added. Then, AcOH was added until the pH is 5, followed by adding $NaBH_3CN$ (2.25 mg, 0.036 mmol) and stirring to 50 °C for 18h. The reaction mixture was quenched with 1N NaOH, and the organic layer was extracted with $CHCl_3$/ MeOH (10%) (3 × 50 mL). The organic extract was dried ($MgSO_4$) and the solvent was evaporated to give the crude free base. Purification by FCC ($CHCl_3$-iPrOH 5%).



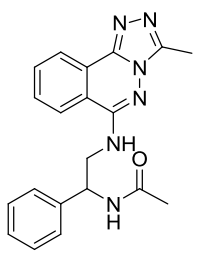
***N*¹-(3-Methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-2-phenylethane-1,2-diamine (28).**

Yellow solid (52 %). IR: 3277, 3065, 2925, 2854, 2359, 2341, 1515, 700. Mpt: 210-212 °C; ^{1}H NMR ($CDCl_3$): 2.69 (s, 3H), 3.52 (ddd, *J* = 13.0, 8.7, 4.2 Hz, 1H), 3.87 (ddd, *J* = 13.2, 6.0, 4.8 Hz, 1H), 4.38 (dd, *J* = 8.7, 4.7 Hz, 1H), 5.91 (br, 1H), 7.31–7.45 (m, 5H), 7.71 (ddd, *J* = 12.3, 9.3, 4.4 Hz, 2H), 7.79–7.85 (m, 1H), 8.60 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): 9.8, 48.9, 54.4, 118.4, 122.2, 123.9, 124.3, 126.1 (2C), 127.8, 128.9

(2C), 130.1, 132.6, 142.0, 143.8, 147.3, 151.0. LR-ESI-MS: $C_{18}H_{19}N_6$ (*m/z*) [M + H]$^+$ found 319.1 calcd 319.2. HR-ESI-MS: $C_{18}H_{19}N_6$ (*m/z*) [M + H]$^+$ found 319.16652 calcd 319.16657.

Synthesis of *N*-(2-((3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6 yl)amino)-1-phenylethyl)acetamide (29).

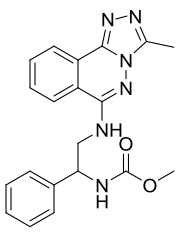
Procedure: Triethylamine (0.015 mL, 0.11 mmol) was added to a solution of **28** (31.8 mg, 0.1 mmol) in $CHCl_3$/MeOH (2:1, 0.5 mL), the mixture was cooled to 0 °C, and acetyl chloride (7 µL, 0.104 mmol) was slowly added. The reaction mixture was stirred for 3h, warmed to room temperature and stirred overnight. The mixture was quenched with saturated sodium bicarbonate solution (20 mL). The phases were separated and the aqueous layer was washed with $CHCl_3$/MeOH (2:1, 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude product was purified by washing with EtOAc and $CHCl_3$.



***N*-(2-{(3-Methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethyl)acetamide (29).**

White solid (42 %). IR: 3270, 3065, 2925, 2853, 1625, 1517, 701. Mpt: 216-218 °C. ^{1}H-NMR (MeOD): 1.99 (s, 3H) 2.71 (s, 3H), 3.75 (dd, *J* = 13.6, 8.6 Hz, 1H), 3.91 (dd, *J* = 13.6, 5.6 Hz, 1H), 5.58 (dd, *J* = 8.6, 5.6 Hz, 1H), 7.27 (ddd, *J* = 7.3, 3.9, 1.2 Hz, 1H), 7.35 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.42–7.46 (m, 2H), 7.82 (dt, *J* = 8.4, 3.7 Hz, 1H), 7.92 (dd, *J* = 11.5, 4.4 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.43 (d, *J* = 7.4 Hz, 1H). ^{13}C-NMR (MeOD): 9.5, 22.7, 48.3, 53.1, 120.4, 124.2, 124.3, 124.9, 128.0 (2C), 128.6, 126.6 (2C), 132.2, 134.1, 141.7, 143.3, 148.6, 153.4, 173.2. LR-ESI-MS: $C_{20}H_{21}N_6O$ (*m/z*) [M + H]$^+$ found 361.2 calcd 361.2, HR-ESI-MS: $C_{20}H_{21}N_6O$ (*m/z*) [M + H]$^+$ found 361.17714 calcd 361.17714.

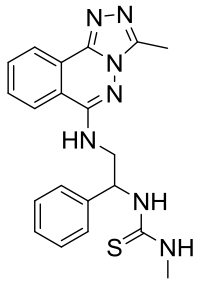
Synthesis of methyl (2-{(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethyl)carbamate (30). Procedure: Into a well stirred solution of **28** (10.0 mg, 0.03 mmol) in $CHCl_3$/MeOH (2:1, 0.3 mL), cooled in a water-bath, was added dropwise a solution of methyl chloroformate (3 µL, 0.035mmol). The mixture was stirred for 1 h to 0 °C, warmed to room temperature, and stirred overnight. The mixture was concentrated. Purification by FCC (DCM/ MeOH: 98/2) yielded **29** (62%) as a white solid.



White solid (62 %). IR: 3270, 3065, 2929, 2858, 1628, 1517, 701. Mpt: 240-242 °C. ^{1}H NMR (DMSO): 2.61 (s, 3H), 3.48 (s, 3H), 3.60 (ddd, *J* = 13.2, 8.1, 4.9 Hz, 1H), 3.73 (dd, *J* = 12.4, 6.1 Hz, 1H), 5.19 (dd, *J* = 13.8, 8.1 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.75–7.80 (m, 2H), 7.80–7.86 (m, 1H), 7.90–7.94 (m, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 8.38 (dd, *J* = 7.9, 0.9 Hz, 1H). ^{13}C NMR (DMSO): 9.4, 47.1, 51.3, 53.0, 118.1, 122.5, 123.4, 124.2, 126.6 (2C), 127.0, 128.2 (2C), 130.2, 133.0, 141.1, 141.9, 146.1, 151.1, 156.4. LR-ESI-MS: $C_{20}H_{21}N_6O_2$ (*m/z*) $[M + H]^+$ found 377.2 calcd 377.2. HR-ESI-MS: $C_{20}H_{21}N_6O_2$ (*m/z*) $[M + H]^+$ found 377.17214 calcd 377.17205.

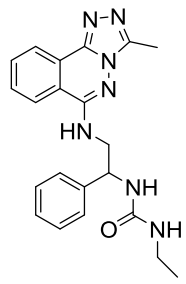
1-Methyl-3-(2-{(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethyl)thiourea (31)

Procedure: Into a well stirred solution of **29** (10.0 mg, 0.03 mmol) in $CHCl_3$/MeOH (2:1, 0.3 mL), was added methyl isothiocyanate (10.9 mg, 0.15 mmol). The mixture was stirred for 16 h to room temperature. The mixture was concentrated. Purification by washing with $CHCl_3$ yielded **31** (79%) as a white solid.



White solid (79 %). IR: 3031, 2952, 1516, 1018, 797. Mpt: 262-264 °C. ^{1}H NMR (DMSO): 2.63 (s, 3H), 2.79 (d, *J* = 4.2 Hz, 3H), 3.68–3.84 (m, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.70 (br, 1H), 8.37 (d, *J* = 7.6 Hz, 1H), 7.88–7.95 (m, 2H), 8.29 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (DMSO): 9.5, 30.9, 46.9, 55.6, 118.2, 122.5, 123.3, 124.3, 126.8 (2C), 126.9, 128.1 (2C), 130.2, 132.9, 141.1, 141.6, 146.1, 151.1, 175.8. LR-ESI-MS: $C_{20}H_{22}N_7S$ (*m/z*) $[M + H]^+$ found 392.2 calcd 392.2. HR-ESI-MS: $C_{20}H_{22}N_7S$ (*m/z*) $[M + H]^+$ found 392.16518 calcd 392.16519.

1-Ethyl-3-(2-{(3-methyl[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino}-1-phenylethyl)urea (32). **Procedure:** Into a well stirred solution of **29** (10.0 mg, 0.03 mmol) in $CHCl_3$/MeOH (2:1, 0.3 mL), was added ethyl isocyanate (0.01 mL, 0.15mmol). The mixture was stirred for 16 h to r.t. The mixture was concentrated. Purification by washing with $CHCl_3$ yielded **32** (51%) as a beige solid.



Beige solid (51 %). IR: 3035, 2958, 1519, 1018, 797. Mpt: 240-242 °C. ^{1}H NMR (MeOD): 1.02 (t, *J* = 7.2 Hz, 3H), 2.90 (s, 3H), 3.09 (q, *J* = 7.2 Hz, 2H), 3.69–3.76 (m, 1H), 3.90 (dd, *J* = 13.7, 4.6 Hz, 1H), 5.42 (dd, *J* = 8.9, 4.6 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.3 Hz, 2H), 8.00–8.08 (m, 2H), 8.34 (d, *J* = 7.9 Hz, 1H), 8.46 (dd, *J* = 7.6, 1.0 Hz, 1H). ^{13}C NMR (MeOD): 9.2, 15.7, 35.8, 49.4, 53.3, 121.6, 121.7, 125.2, 125.5, 127.7 (2C), 128.6, 129.7 (2C), 134.7, 134.9, 142.4, 142.5, 148.1, 155.1, 160.9. LR-ESI-MS: $C_{21}H_{24}N_7O$ (*m/z*) $[M + H]^+$ found 390.2 calcd 390.2. HR-ESI-MS: $C_{20}H_{22}N_7S$ (*m/z*) $[M + H]^+$ found 390.20500 calcd 390.20368.