UNIVERSITÀ DEGLI STUDI DI ROMA "LA SAPIENZA"

Dottorato di ricerca in Scienze Chimiche

XXVI ciclo

TRIFLUOROMETHYL IMINES IN AZA-HENRY REACTIONS: STEREOCHEMICAL STUDIES.

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INTRODUCTION

Chapter 1

Trifluoromethyl imines

Fluorine is a magic element: thanks to its properties and to its small steric size, it is able to induce about dramatic, and often unexpected, changes in physical and chemical properties, reactivity and biological features of organic molecules.[1]

In bioorganic and medicinal chemistry, judicious introduction of fluorine atoms or appropriate fluorinated functions into a molecule has become a method widely used to modify and tune its biological properties.[2] Thus, for example, a fluorine atom has been used with great success as a replacement for a hydrogen atom or a hydroxyl group. In particular, the xenobiotic trifluoromethyl group is well accepted in medicinal chemistry as a substituent of distinctive qualities. In fact, it is both highly hydrophobic, electron-rich and sterically demanding; moreover, it can provide high *in vivo* stability and features a good mimicry with several naturally

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

[2] Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*, ACS Books, American Chemical Society: Washington, D.C., 1996.

occurring residues such as methyl, isopropyl, phenyl, etc.[3] As a consequence, the synthesis of selectively fluorinated compounds and, in particular, of nitrogen-containing ones like biological relevant targets, might be of particular interest. This concerns especially trifluoromethylated compounds, as shown by the increasing number of CF_3-containing drugs and drug-candidates which are clinically used or in the development.[4] The synthesis of these compounds can be achieved either by the trifluoromethylation techniques,[5] or through the ‘‘building block’’ path from a readily available trifluoromethylated material. The last strategy remains the most powerful route to structurally elaborated molecules and the fundamental question in this approach is the choice of the right starting CF_3-containing chemical, which has to be readily available at an industrial scale, inexpensive, non-toxic and environmentally compatible.

Fluoral (CF_3CHO) is recognized as a highly useful starting chemical: the strong electron-withdrawing character of the trifluoromethyl moiety enhances the electrophilicity of the carbonyl group and, indeed, fluoral presents a higher reactivity

[3] Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16.
[4] Bégué, J.-P.; Bonnet-Delpon, D. *Chimie Bioorganique et Médicinale du Fluor*, Edisciences-CNRS Publishers: 2005.
[5] Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185−194.

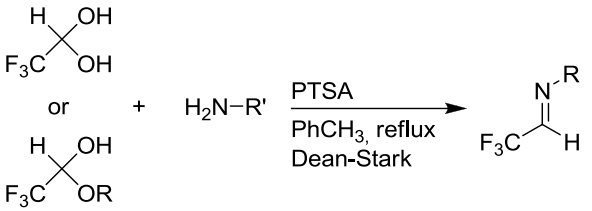
compared to that of other aldehydes. Fluoral itself is an unstable gas, difficult to prepare and use. On the contrary, its hydrate and hemi-acetal derivatives [$CF_3CH(OH)_2$ and $CF_3CH(OH)(OR)$, respectively] are very stable and commercially available in bulk at reasonable costs. Those compounds are largely used in the synthesis of trifluoromethyl imines, interesting versatile building blocks which can provide nitrogen-containing fluorinated molecules with wide structural and functional diversities. The importance of those imines lies in the fact that they present within the same substrate both the nitrogen atom and the trifluoromethyl moiety. Moreover the presence of the C=N function allows to use them as interesting electrophiles in many different nucleophilic addiction reaction[6].

1.1 *Trifluoromethyl imines synthesis*

The classical synthesis of trifluoromethyl imines involves a condensation reaction between fluoral derivatives and nucleophilic amines performed at toluene reflux with a

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

Dean–Stark apparatus involving *p*–toluenesulfonic acid (PTSA) as catalyst (Scheme 1).



Scheme 1

This method however does not always provide the expected product in good yields: the very strong electron–withdrawing nature of the CF_3 group destabilizes the carbocationic intermediate while it stabilizes the hemiaminal intermediate that can be easily isolated.[7] Consequently, it is often required to use different synthetic strategies,[8] high reaction temperatures or different activation methods.[9]

In the last years, the developments in the synthesis of trifluoromethyl nitrogen-containing molecules starting from

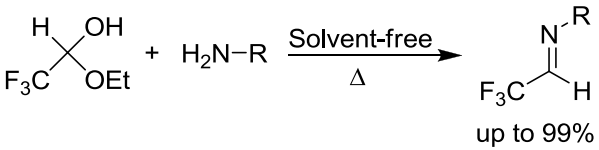
[7] Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 3086–3089.

[8] Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer R. A.; Chen, C-Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 355–358.

[9] 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.

trifluoromethyl imines encouraged us to focus our attention on a new univocal synthesis of such compounds.

Recently in the laboratory in which I am attending my PhD it was studied a new efficient solvent-free synthesis of different trifluoromethyl aldimines,[10] easily obtained by heating an equimolar solution of trifluoroacetaldehyde ethyl hemiacetal with different aliphatic amines (Scheme 2).



Scheme 2

The reaction give the corresponding fluorinated aldimines in very good yields, and occurs with complete stereoselectivity giving rise to the only the *E* isomer, as determined by NOE experiments (Figure 1).

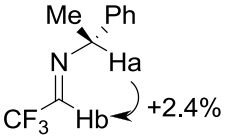


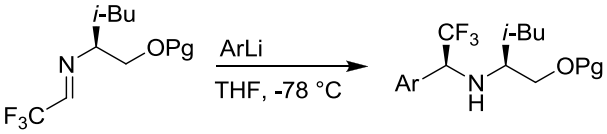
Figure 1

[10] Carroccia, L.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Synthesis* **2010**, *23*, 4096−4100.

1.2 *Trifluoromethyl imines reactivity*

The addition of organometallic species to imines is a common approach to obtain amines, including optically active ones. The electron-withdrawing effect of the CF_3 moiety can often favour the addition of nucleophiles on C=N bonds, without the need of additives, or *N*-activated substrates. In this field, some nucleophilic addition reaction on fluorinated imines are reported in the literature.

Trifluoromethyl aldimines can undergo arylation reaction with a highly diastereoselective outcome when treated with aryl lithium compounds at low temperature (Scheme 3).[11]



Scheme 3

Different Mannich-type reactions performed with enol silyl ethers,[12] acetone[13] or aldehydes,[14] in the presence of suitable catalyst are reported (Scheme 4).

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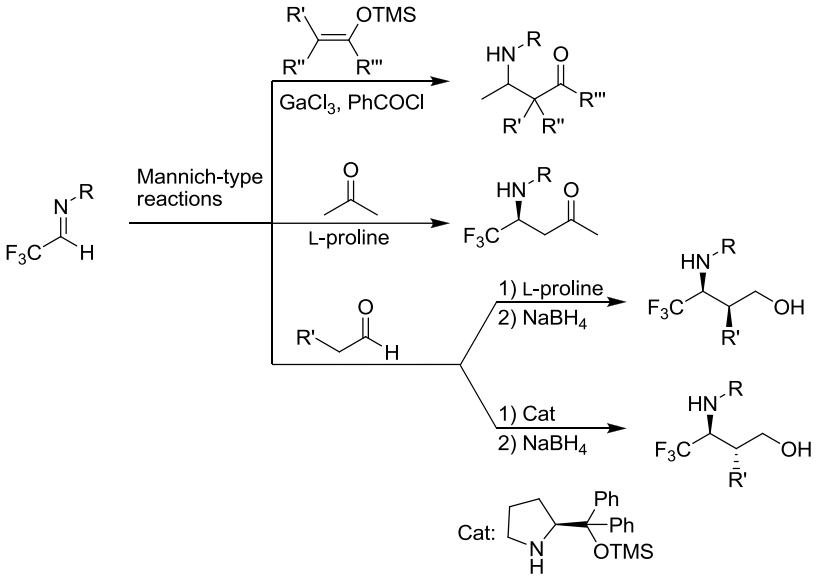
[11] a) Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.-y.; Volante, R. D. *Org. Lett.* **2004**, *6*, 641−644 ; b) Roy, A.; Gosselin, F.; O'Shea, P. D.; Chen C.-y. *J. Org. Chem.* **2006**, *71*, 4320−4323.

[12] Takaya, J.; Kagoshima, H.; Akiyama, T. *Org. Lett.* **2000**, *2*, 1577−1579.

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



Scheme 4

Alternatively, trifluoromethyl imines were considered as suitable substrate in the Reformatsky[15] and Strecker reactions (Scheme 5).[16]

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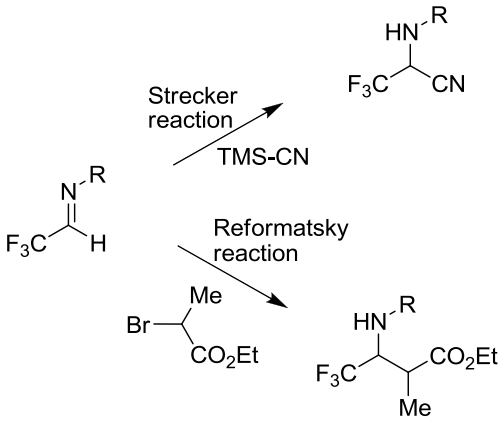
[14] a) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433–3436; b) Fustero, S.; Mojarrad, F.; Pérez Carrión, M. D.; Sanz-Cervera, J. F.; Aceña, J. L. *Eur. J. Org. Chem.* **2009**, 5208–5214.

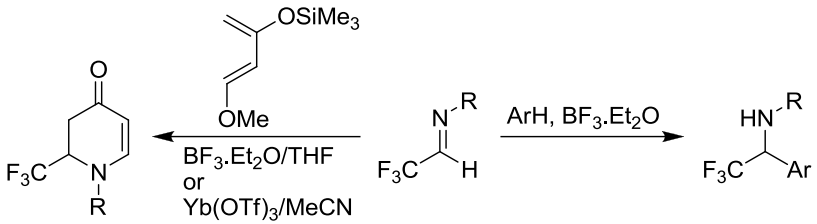
[15] Gong, Y.; Kato, K. *J. Fluorine Chem.*, **2001**, *111*, 77−80.

[16] a) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 7075−7078; b) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379−1381



Scheme 5

In the literature other reactions are reported involving trifluoromethyl imines such as: Friedel-Crafts-type reactions,[17] or aza-Diels-Alder reactions[18] (Scheme 6).

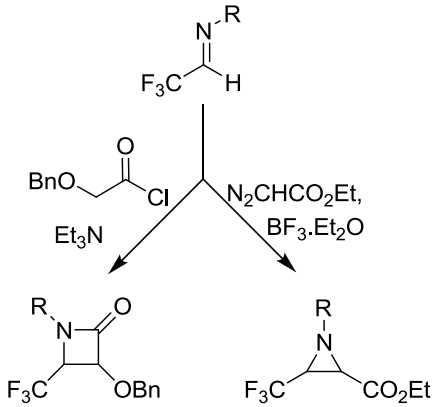


Scheme 6

[17] Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn*, **2002**, *75*, 2637–2645.

[18] Crousse, B.; Narizuka, S.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009–5013.

In addition, trifluoromethyl imines were employed to synthesize functionalized small heterocycles such as β-lactam[19] and aziridine[20] derivatives (Scheme 7).



Scheme 7

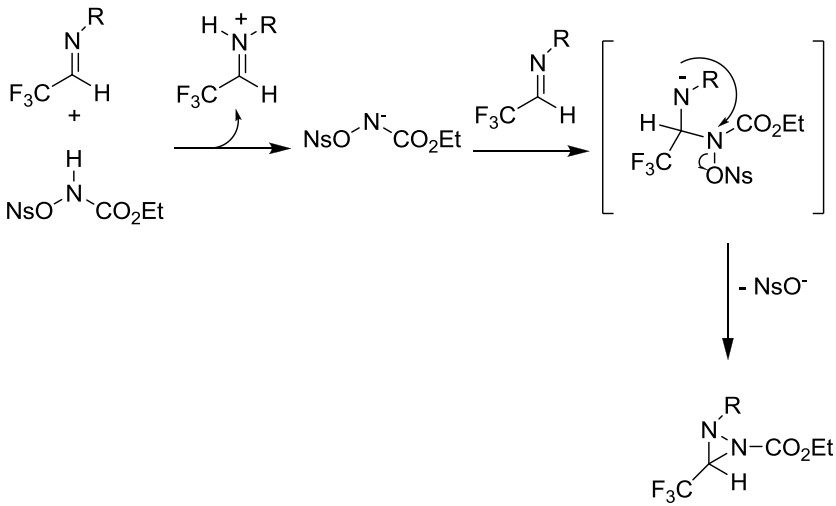
In the laboratory in which I am attending my PhD, trifluoromethyl imines were used to obtain interesting optically active fluorinated diaziridines and oxaziridines.[21] At first it was studied the direct amination reaction of different trifluoromethyl imines with aza-anions deriving from alkyl nosyloxycarbamates ($NsONHCO_2R$) in CH_2Cl_2, at room

[19] Abouabdellah, A.; Bégué, J.-P; Bonnet-Delpon, D. *Synlett*, **1996**, 399−400.

[20] Crousse, B.; Narizuka, S.; Bonnet-Delpon, D.; Bégué, J.-P *Synlett*, **2001**, 679−681.

[21] Carroccia, L.; Fioravanti, S.; Pellacani, L.; Sadun, C.; Tardella, P. A. *Tetrahedron* **2011**, *67*, 5375−5381.

temperature in the absence of external bases. The reactions proceed through a first nucleophilic attack by the *in situ* formed aza-anion, followed by the ring closure, thus giving the corresponding trifluoromethyl diaziridines (Scheme 8)

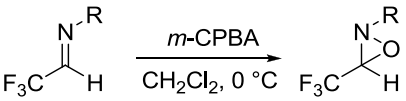


Scheme 8

As reported in the scheme above, during the direct amination reaction, the trifluoromethyl imines act as both base, deprotonating the starting carbamate and generating the real nucleophilic species, and substrate, undergoing the key nucleophilic attack. In all cases, trifluoromethyl substituted diaziridines were obtained in high yields and purity with total retention of the starting imine configurations, moreover it was demonstrated that the stereoselective induction was controlled

by steric or electronic effect present on the β– or α–carbon of the aminic residue.

In the same paper it was reported the synthesis of trifluoromethyl oxaziridines by epoxidation reaction using *m*-CPBA as oxidant (Scheme 9).



Scheme 9

The expected compounds were obtained in good yield and the observed diastereoselectivity was higher than the one of aziridination and it was found to be related to the steric hindrance of the *N*-substituent.

Chapter 2

Nitro compounds

The remarkable synthetic importance of nitro compounds has ensured long-standing studies of their utilization in organic synthesis. Historically nitro compounds, especially aromatic ones, were been used as important precursor of azo dyes and explosives; while in organic chemistry they have proven to be valuable reagents for the synthesis of complex target molecules.

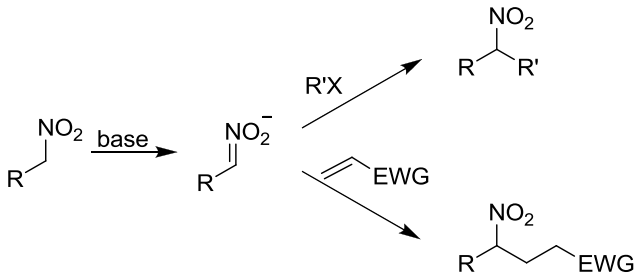
The nitro group is the strongest electron-withdrawing known substituent[22] and this property dominates the chemistry of the molecules containing this functional group. The high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position. This property is mainly due to the nitro stabilization of the corresponding nitronate ion (Scheme 10).

Scheme 10

[22] Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18.

2.1 *Nitro compounds reactivity*

The importance of nitro alkanes in the organic synthesis is mainly due to their easy conversion into the corresponding nitronate which can act as carbon nucleophiles with a range of electrophiles such as halo alkanes[23] or Michael acceptors,[24] leading to the carbon–carbon bond formation (Scheme 11).



Scheme 11

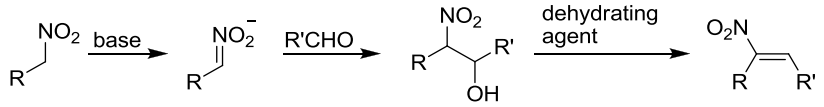
Another widely studied reaction involves nitronate additions to aldehydes (Henry reaction),[25] the corresponding β-

[23] Seebach, D.; Lehr, F. *Angew. Chem. Int. Ed.* **1976**, *15*, 505–506.

[24] Perlmutter, P. *Conjugate addition reactions in organic synthesis*; Pergamon: Oxford, 1992.

[25] a) Henry, L. C. R. *Acad. Sci. Paris* **1895**, *120*, 1265−1270; b) Rosini, G. *Comprehensive organic synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, p 321; c) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945; d) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–33; e) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.

nitro alcohols under opportune conditions[26] can undergo a dehydration reaction thus forming the corresponding nitro alkenes (Scheme 12), very useful and versatile compounds in organic synthesis.[27]



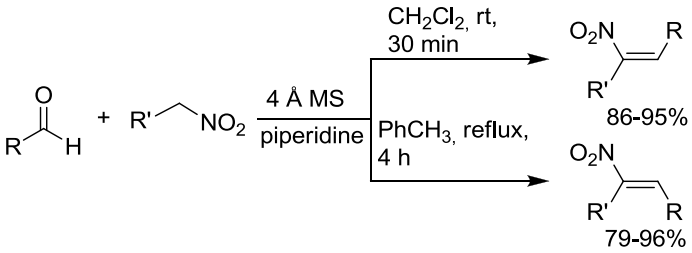
Scheme 12

(*E*)- and (*Z*)-nitro alkenes were synthesized by our research group trough a simple and efficient stereoselective one-pot reaction between nitro alkanes and different aldehydes[28] (Scheme 13).

[26] a) Melton, J.; Mc Murry, J. E. *J. Org. Chem.* **1975**, *40*, 2138−2139; b) Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, R. *J. Org. Chem.* **1980**, *45*, 1185−1189; c) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017−1018; d) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897–3900; e) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261−283; f) Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, 1014−1016; g) Rosini, G.; Ballini, R.; Petrini, M.; Sorrenti, P. *Synthesis* **1985**, 515−517; h) Ballini, R.; Castagnani, R.; Petrini M. *J. Org. Chem.* **1992**, *57*, 2160−2162.

[27] a) Barrett, A. G. W.; Graboski, G. G. *Chem. Rev.* **1986**, *86*, 751−762; b) Barrett, A. G. M. *Chem. Soc Rev.* **1991**, *20*, 95−127.

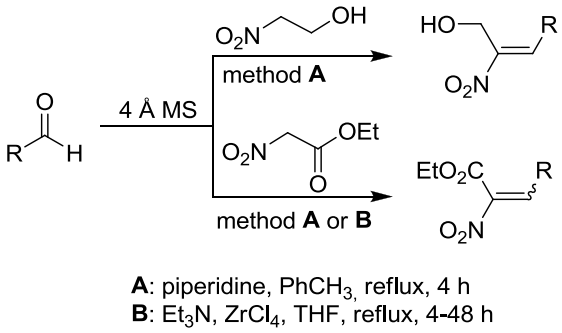
[28] Fioravanti, S.; Pellacani, L.; Tardella, P. A.; Vergari M. C. *Org. Lett.* **2008**, *10*, 1449–1451.



Scheme 13

As reported in the Scheme 13, simply by changing reaction conditions (solvent and temperature) it is possible to control the stereochemical outcome of the reactions, obtaining pure (*E*)- or (*Z*)-nitro alkenes in high to excellent yields.

More recently, we used 2-nitroethanol and ethyl nitroacetate as opportune substrate for the synthesis of various α-substituted nitro alkenes (Scheme 14).[29]



Scheme 14

[29] Fioravanti, S.; Pellacani, L.; Vergari, M. C. *Org. Biomol. Chem.* **2012**, *10*, 524−528.

When using 2-nitroethanol the reaction proceeded with total stereoselectivity, giving corresponding (*E*)-nitro alkenes as the only isomer; on the contrary, the desired α-nitro cinnamates and acrylates were always obtained as a (*E*/*Z*)-mixture. Nevertheless the most interesting aspect of the proposed synthesis is that it was reported, for the first time, the addition of zirconium tetrachloride ($ZrCl_4$) as Lewis acid. $ZrCl_4$ was chosen, instead of titanium tetrachloride,[30] being easier to handle, stronger Lewis acid, cheaper and more environmentally friendly.[31]

2.2 *Nitro group versatility*

Another fundamental property which makes nitro compounds very useful scaffolds in organic synthesis is the NO_2 moiety versatility, as reported by Ballini, one of the most recognised leader in this field.[32] Likewise, the nitro group has been described as a "synthetic chameleon"[33] because it serves as a masked precursor to many useful functionalities. In fact, once introduced in a molecular framework, the NO_2 moiety is

[30] Lehnert, W. *Tetrahedron* **1972**, *28*, 663–666.
[31] Bora, U. *Synlett*, **2003**, 1073−1074.
[32] Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099−12121.
[33] Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1995**, *68*, 1592−1604.

amenable to further transformations. It can be converted into primary amines[34] or hydroxyl amines[35] by reduction reaction, into carbonyl group through the Nef reaction[36] or using Cr(II) compounds.[37] Moreover, it can be removed by radical route using appropriate initiators[38] or removed as nitrous acid to introduce a double bond into the molecular structure[39] (Scheme 15).

[34] a) Larock, R. C. *Comprehensive Organic Transformations*, VCH, New York, **1989**, pp. 411 – 415; b) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897–2911; c) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733–5734; d) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608−5609.

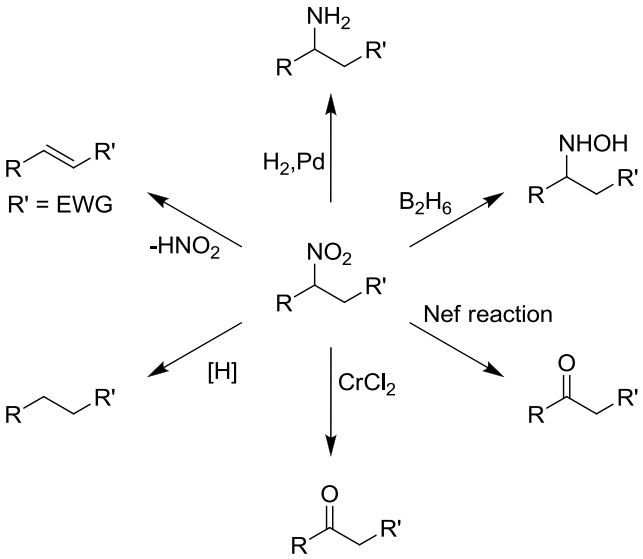
[35] Feuer, H.; Bartlett, R. S.; Vincent, B. F. Jr.; Anderson, R. S. *J. Org. Chem.* **1965**, *30*, 2880–2882.

[36] a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263–291; b) Ballini, R.; Petrini, M. *Tetrahedron* , **2004**, *60*, 1017–1047.

[37] Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett*. **1985**, *26*, 3777–3778.

[38] a) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705−1708; b) Rosini, G.; Ballini, R.; Zanotti, V. *Synthesis* **1983**, 137−139; c) Shen, B.; Johnston, J. N. *Org. Lett*. **2008**, *10*, 4397–4400.

[39] Ballini, R.; Bosica, G. *Tetrahedron* **1995**, *51*, 4213−4222.


NH2
R
R'
H2,Pd
NHOH
B2H6
R
R'
R
R'
R' = EWG
-HNO2
NO2
R
R'
Nef reaction
[H]
CrCl2
O
R
R'
R
R'
O
R
R'

Scheme 15

Chapter 3

Aza-Henry reaction

The addition reactions of active C−H nucleophiles to C=X bonds represent some of the most important carbon−carbon bond-forming processes in organic chemistry. The aldol,[40] nitroaldol (Henry),[25] and Mannich[41] reactions are the main examples of such type of reactions and they have been studied extensively (Scheme 16). Another member of this family of carbon−carbon bond-forming reaction is the aza-Henry (or nitro-Mannich) reaction,[42] involving nucleophilic addition of a nitronate species to an electrophilic imine, but it is the one studied to a far lesser extent.

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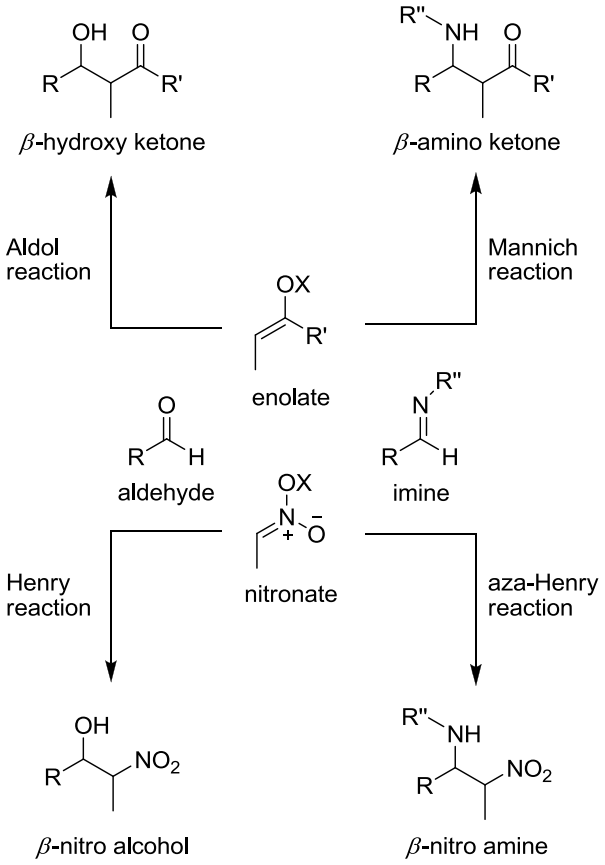
[40] a) Wurtz, A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436–442; b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374; c) Palomo, C.; Oiarbide, M.; Garci, J. M. *Chem.−Eur. J.* **2002**, *8*, 36–44; d) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Berlin, 2004; e) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.

[41] a) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29−41;b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626−2704.

[42] a) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. *Eur. J. Org. Chem.* **2009**, 2401−2420; b) Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151−153; c) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887–2939.

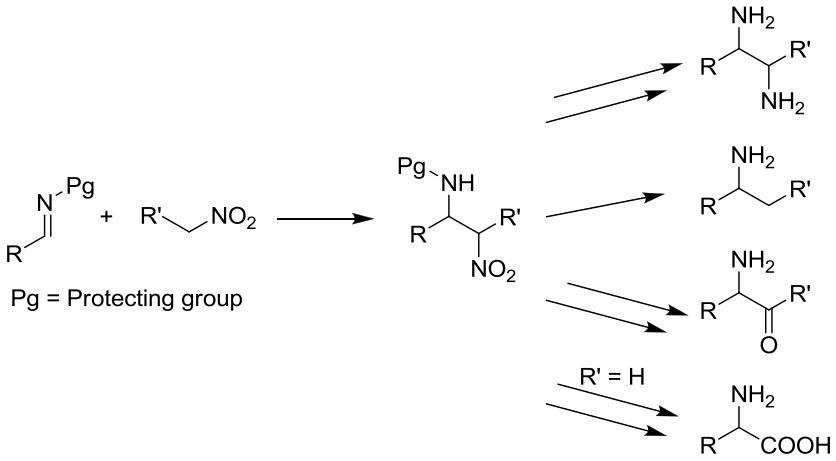


Scheme 16

Interest in the aza-Henry reaction arises from the value of the resulting β-nitro amines. Those compounds represent rather useful synthetic building blocks since two vicinal nitrogenated functions are present in different oxidation states,

thus giving access to further transformations with complete chemoselectivity.

Furthermore, the versatility of the nitro group allows access to other important structural motifs such as 1,2-diamines (via nitro reduction), monoamines (via reductive denitration), and α-amino ketones or α-amino acids (via the Nef reaction) (Scheme 17)



Scheme 17

Several natural products possessing valuable biological properties contain 1,2-diamino moieties.[43] Many synthetic

[43] a) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135–149; b) Merino, P.; Lanaspa, A.; Merchán, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629–646; c) Viso, A.; Pradilla, R.; García; A. Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196; d). Kotti, S. R. S. S; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101–114.

diamine derivatives have also been used as medicinal agents, in particular as anticancer and antiviral drugs,[44] antihypertensives,[45] antiarrhythmics,[46] analgesics,[47] antidepressant agents[48] and as antiparasitic agents.[49]

In organic synthesis vicinal diamines are widely used in catalytic asymmetric synthesis both as ligands[50] and organocatalysts.[51]

The biological and synthetic importance of 1,2-diamines has stimulated significant activity in the past, and

---

[44] Mibu, N.; Yokomizo, K.; Miyata, T.; Sumoto, K. *Chem. Pharm. Bull.* **2007**, *55*, 1406–1411.

[45] Szilagyi, G.; Kasztreiner, E.; Matyus, P.; Kosary, J.; Czako, K.; Cseh, G.; Huszti, Z.; Tardos, L.; Kosa, E.; Jaszlits, L. *Eur. J. Med. Chem.* **1984**, *19*, 111–117.

[46] Zubovics, Z.; Toldy, L.; Varró, A.; Rablokzky, G.; Kürthy, M.; Dvortsák, P.; Jerkovich, G.; Tomori, E. *Eur. J. Med. Chem.* **1986**, *21*, 370–378.

[47] González-Sabin, J.; Gotor, V.; Rebolledo, F. *Chem. Eur. J.* **2004**, *10*, 5788–5794.

[48] Szmuszkovicz, J.; Von Voigtlander, P. F.; Kane, M. P. *J. Med. Chem.* **1981**, *24*, 1230–1236.

[49] Rebollo, O.; Del Olmo, E.; Ruiz, G.; López-Pérez, J. L.; Giménez, A.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 184–187.

[50] a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935–952; b) Soai, K.; Niwa, S. ; *Chem. Rev.* **1992**, *92*, 833–856; c) Jacobsen, E. N. *Catalytic Asymmetric Synthesis* Ed.: I. Ojima, Wiley-VCH, Weinheim, **1993**, p. 159; d) Kolb, H. C.;. VanNieuwenhze, M. S; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; e) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431–8434; f) Savoia, D. *Top. Organomet. Chem.* **2005**, *15*, 1–58.

[51] a) Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005**, *17*, 39–403; b) Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423–9429.

several conceptually different strategies for their preparation have been developed.[52]

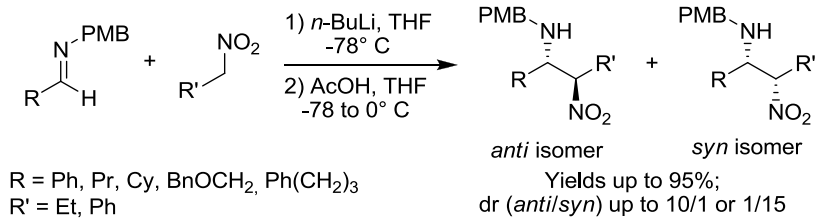
Because of the high imine reactivity with nucleophiles, the development of new chiral non-racemic catalysts to promote the production of enantiomerically pure β-nitro amines has been a challenging task.

Although the first nucleophilic addition of nitro alkanes to imines was reported by Louis Henry in 1896,[53] significant interest in the nitro-Mannich reaction has been paid starting from 1998, prior to this, reports of nitro-Mannich reactions were limited to unselective uncatalyzed examples. In 1998 Anderson and co-workers reported the first acyclic diastereoselective aza-Henry reactions[54] describing the addition of the lithium salts of various nitro alkanes to *N*-(*p*-methoxybenzyl)imines (Scheme 18).

[52] a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; b) Viso, A.; Fernández de la Pradilla, R. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 327–334.

[53] Henry, L. *Bull. Acad. R. Belg.* **1896**, *32*, 33.

[54] Adams, H.; Anderson, J. C.; Peace, S.; Pennel, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932−9934.



Scheme 18

The presence of acetic acid was found to be crucial for the nitro-Mannich reaction to occur, ruling out the possibility of the addition of a nitronate anion followed by a protonation. This is because addition of a nitronate anion to an imine is thermodynamically disfavored, primarily due to the difference in pKa values between the nitronate (pKa 9) and the aza-anion product (pKa 35). Therefore the aza-Henry reaction should take place either through a nitronic acid or through a protonated imine as the key intermediate. This paper represented an important turning point for development of the nitro-Mannich reaction as it provided a method for reliable synthesis of β-nitro amines with good diastereoselectivity. Since then many protocols have been reported providing access to a wide variety of β-nitro amines with high levels of stereoselectivity, including both organocatalyzed and metal-catalyzed examples. Moreover, the utility of this reaction has recently begun to be

demonstrated through its successful application to target synthesis.

3.1 Organocatalytic aza-Henry Reactions

Organocatalysis has emerged as a very powerful tool for asymmetric synthesis and has been successfully applied to a whole host of C−C bond-forming processes.[55]

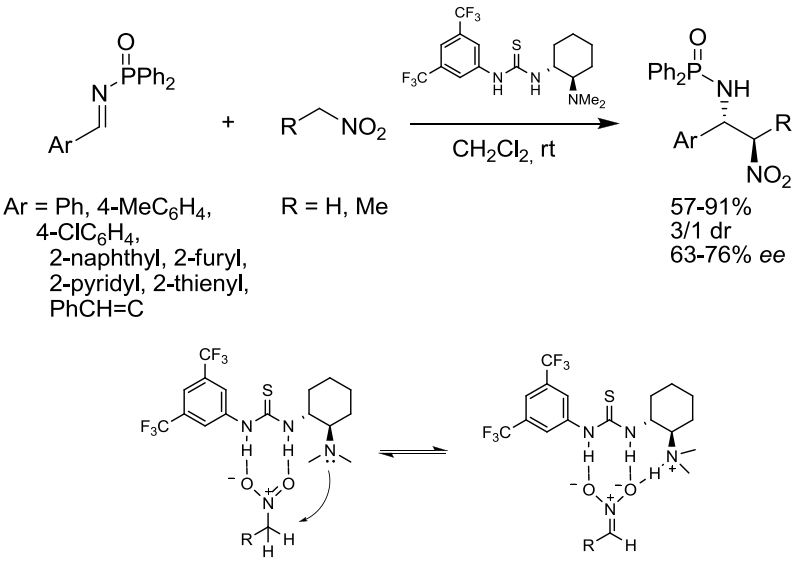
Therefore, a number of different organocatalysts have been developed as efficient catalysts for nitro-Mannich reactions. These include a variety of different chiral thioureas, Brønsted acids, and phase-transfers catalysts.

3.1.a Urea/thiourea Catalysts

The first organocatalytic aza-Henry reaction was reported by Takemoto and co-workers, who used a thiourea as bifunctional catalyst in the reactions of *N*,*N*-

[55] a) Berkessel, A.; Gröger, H.*Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; b) Dalko, P. I. *Enantioselective Organocatalysis: Reaction and Experimental Procedures*, JohnWiley & Sons, New York, 2007.

diphenylphosphinoyl imines with an excess of nitromethane (Scheme 19).[56]



Scheme 19

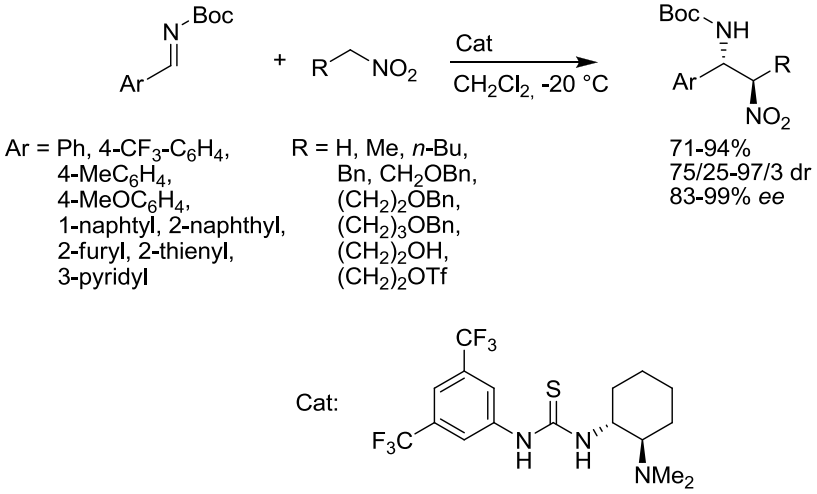
It has been reported that urea and thiourea moieties can interact with different polar compounds such as nitro and related compounds through hydrogen bond interactions.[57]

[56] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627.

[57] a) Bordwell, F. G.; Ji, G. *J. Am. Chem. Soc.* **1991**, *113*, 8398–8401; b) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415–8426; c) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080.

This catalyst can act as a base through its tertiary amino moiety and as a mild Brønsted acid with the two protons of the thiourea group,[58]thus activating both the nitro alkane and the imine.

Takemoto's group later reported an improvement to the thiourea-catalyzed method: using *N*-Boc-imines[59] they increased the enantiomeric excess, furthermore they used different nitro compounds demonstrating the versatility of the reactions (Scheme 20).

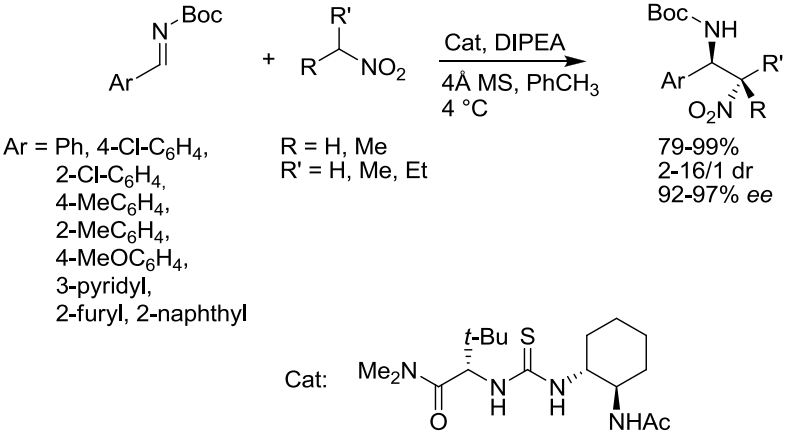


Scheme 20

[58] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[59] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.−Eur. J.* **2006**, *12*, 466−476.

The use of thiourea as efficient catalyst for the aza-Henry reaction between nitroethane and aryl *N*-Boc-imines was also demonstrated by Jacobsen[60] (Scheme 21).



Scheme 21

Since the reports by Takemoto and Jacobsen on the application of thiourea-based organocatalysts to asymmetric aza-Henry reactions, there have been a large number of publications from other groups demonstrating the use of thiourea bearing various chiral scaffolds[61]. These include catalyst-derived structures including from cinchona alkaloids,

[60] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
[61] Wang, C.-J.; Dong, X.-Q.; Zhang, Z.-H.; Xue, Z.-Y.; Teng, H.- L. *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607.

such as hydroquinine[62] and quinine[63], chiral sulfonamides,[64] glycosides,[65] and steroids.[66] Alternatively it is documented the use of chiral oxazoline thiourea,[67] or BINAP-based bisthiourea[68] as efficient organocatalysts

3.1.b Brønsted Acid Catalysts.

Almost simultaneously with Takemoto's work, Johnston and co-workers reported the use of an alternative organocatalyst in asymmetric aza-Henry reactions.[69] They investigated the use of a chiral proton catalyst for the enantio- and diastereoselective reactions of aryl *N*-Boc-imines with nitromethane and nitroethane (Scheme 22).

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[62] Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499–11505.

[63] Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375–380.

[64] Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110–15111.

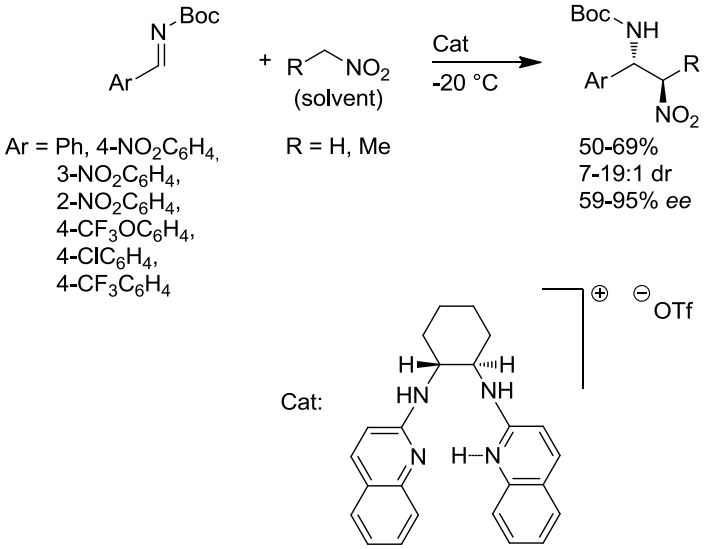
[65] Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707–1710.

[66] Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal*. **2009**, *351*, 2096–2100.

[67] Chang, Y.-W.; Yang, J.-J.; Dang, J.-N.; Xue, Y.-X. *Synlett* **2007**, 2283−2285.

[68] Rampalakos, C.; Wulff, W. D. *Adv. Synth. Catal*. **2008**, *350*, 1785−1790.

[69] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419.



Scheme 22

The authors hypothesized that the bisamidine ligand takes the proton from solvent interactions, thereby avoiding achiral solvent coordinated Brønsted-acid catalysis, to create a chiral proton coordination complex which can induce enantioselectivity.

Johnston's group later extended the scope of their methodology to include reaction of α-nitro esters[70] and aryl nitro alkanes.[71] The same group recently improved the efficiency of aza-Henry reactions by using a bisamidine

[70] a) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397–4400; b) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867.
[71] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076−1079.

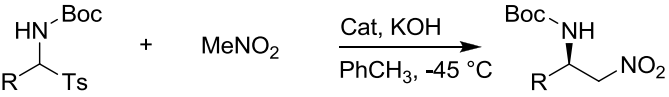
catalyst,[72] which gave rise to higher yields and stereoselectivity over a wide range of aryl *N*-Boc-imines and several nitro alkanes.

3.1.c Phase-transfer catalyst.

Hererra's and Palomo's groups independently reported the use of cinchona derived phase-transfer catalyst (PTC) in the aza-Henry reaction of α-amido sulfones with nitro alkanes (Scheme 23).[73,74]

[72] Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880–2882.
[73] Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975−7978.
[74] Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622−17623.

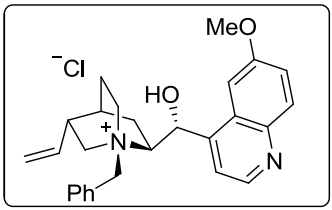
Herrera:



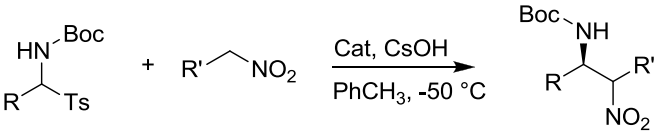
R = Ph, 2-BrC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-furyl, $BnCH_2$, Cy, *i*-Pr, Et, Me

70-98%
75-98% *ee*

Cat:



Palomo:



R = Ph, 4-$MeOC_6H_4$, 4-$ClOC_6H_4$, 4-$CF_3C_6H_4$, 3-$NO_2C_6H_4$, 2-furyl, 1-naphthyl, $BnCH_2$, Cy, Pr, Hexyl, *i*-Bu, *i*-Pr, Et

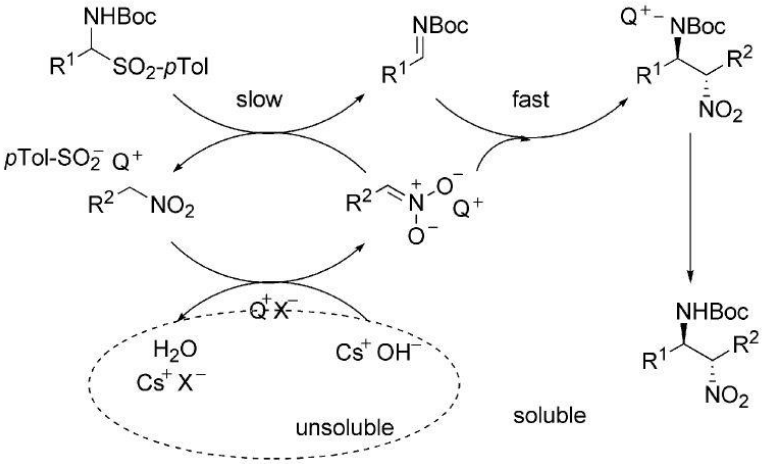
R' = H, Me

72-80%
3-13/1 dr
78-98% *ee*

Scheme 23

Both groups reported the same reaction conditions except for the type of inorganic base used for the formation *in situ* of the *N*-Boc-imines from the α-amido sulfones. The method is particularly useful for imines derived from enolizable aldehydes: the formation of the *N*-Boc-imines *in situ* avoids the need to isolate these unstable substrates. The

corresponding β-nitro amines were achieved in excellent yields and enantioselectivity. Later Palomo et al. extended the scope of this reaction with respect to both nitro alkanes and α-amido sulfones and reported a reaction mechanism for this process using a combination of experimental observations and quantum calculations[75] (Scheme 24).



Scheme 24

The initially generated nitronate anion is the active base that promotes elimination of sulfinic acid from α-amido sulfones to provide the intermediate *N*-acyl imines (slow step), then a second molecule of nitronate anion adds to the

[75] Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955−7966.

performed (*in situ*) imine (fast step) to provide the final product after protonation.

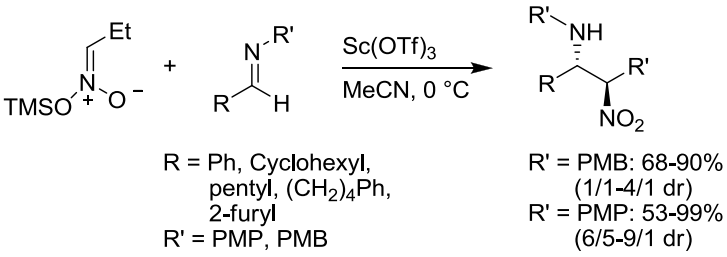
3.2 Metal-Catalysed aza-Henry Reactions

The recognition that the aza-Henry reaction was proton centered,[54] invited the use of many different chiral Lewis acids as catalysts.

3.2.a Indirect Reaction

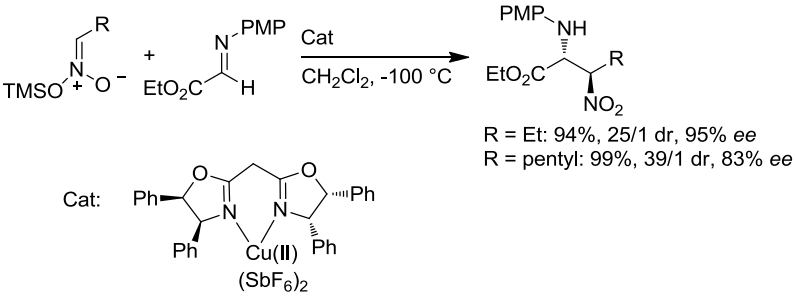
The first racemic version involves $Sc(OTf)_3$, as catalyst, and trimethylsilyl (TMS) nitronates, which, differently from lithium nitronates, allowed to use catalytic quantities of Lewis acid. The reaction brings to the desired compounds in in good yields and with moderate to good *anti* selectivity[76] (Scheme 25).

[76] Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, 850–852.



Scheme 25

In 2001 Jørgensen at al. reported the first asymmetric nitro-Mannich reactions between TMS-nitronates and ethyl glyoxylate-*N*-PMP-imine. They used Cu(II)−*cis*-DiPh-BOX catalyst to achieve excellent yields and enantio- and diastereoselectivity[77] (Scheme 26)



Scheme 26

The Authors justified the stereochemical outcome by proposing a mechanism which involves the α-imino ester bond

[77] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2001**, *123*, 5843–5844.

to the catalyst in a bidentate fashion followed by coordination of the TMS-nitronate to the copper center (Figure 2).

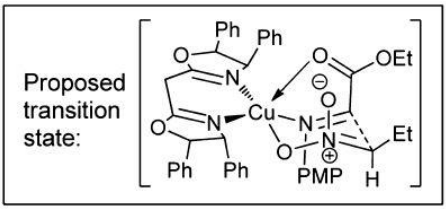


Figure 2

3.2.b Direct reaction

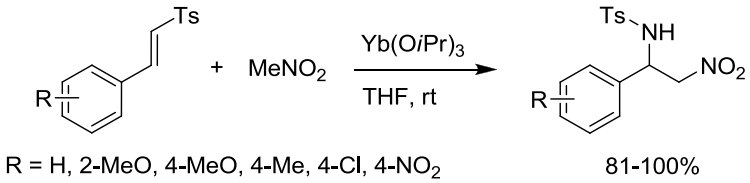
Although the indirect metal-catalyzed nitro-Mannich reactions offer efficient access to β-nitro amines in high yield and stereoselectivity, the requirement to pre-form the silyl nitronates limits their synthetic utility. A more attractive method would involve direct coupling of nitro alkanes with imines via *in situ* nitronate formation.

To date there have been a considerable number of papers of both racemic and asymmetric direct metal-catalyzed nitro-Mannich reactions, providing ready access to a wide variety of β-nitro amines with high diastereo- and enantioselectivity.[42] Here I will report the most significant.

The effectiveness of lanthanide derivatives as catalysts for aza-Henry reactions was confirmed by Qian and Shibasaky

who reported respectively the first catalytic racemic[78] and the first asymmetric[79] direct metal-catalyzed aza-Henry reactions.

Qian and co-workers[78] reported the reaction of nitromethane with *p*-toluenesulfonyl (Ts) imines, effectively catalyzed by $Yb(OiPr)_3$; the corresponding products were formed in excellent yield for a range of aryl imines (Scheme 27).



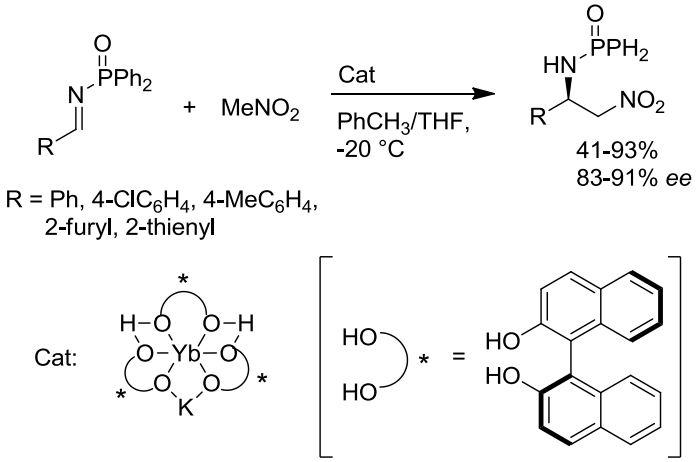
Scheme 27

Since the used Lewis acid is the only promoter of the reaction which proceeds in the absence of any base, it has been proposed that the alkoxide moiety of the catalyst deprotonates nitromethane, thus transforming the ytterbium derivative into a bifunctional catalyst.

Shibasaki and co-workers[79] in 1999 reported the first asymmetric direct metal-catalyzed reaction: they investigated several catalysts prepared from $Yb(OiPr)_3$, KO*t*-Bu and (*R*)-

[78] Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.* 2001, *42*, 4673−4675.
[79] Yamada, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3504–3506.

binaphthol in different ratios. The complex prepared in 1:1:3 ratio afforded the best results, furnishing the desired β-nitro amines with good yields and enantioselectivity. No base was needed because the formed Yb/K heterobimetallic complex contains both Lewis-acidic and Brønsted-basic sites, capable of activating both the electrophilic *N*-phosphinoyl aryl imines and the nucleophilic nitromethane (Scheme 28).



Scheme 28

An important drawback of the catalyst is that it is not able to promote the aza-Henry reaction with bulkier substituted nitro alkanes. This lack of activity was attributed to the reduced size of the binding pocket of the catalyst, which could have insufficient space to accommodate both the imine and the nitro

alkane. In 2001, the same research group reported the use of Al/Li/binaphthoxide-KO*t*-Bu catalyst (Figure 3), which presents a larger binding pocket, to promote reactions of larger nitro alkanes with *N*-phosphinoyl aryl imines.[80]

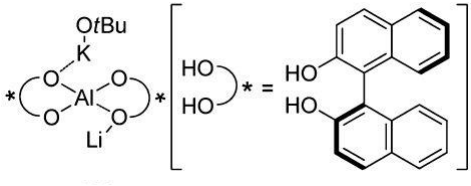
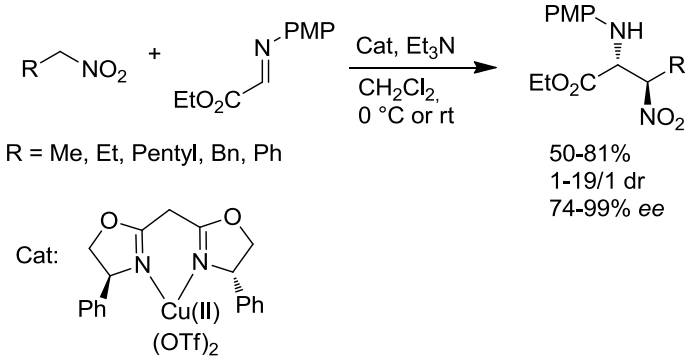


Figure 3

Jørgensen et al. reported an improvement to their Cu(II)−cis-DiPh-bis(oxazoline) (BOX)-catalyzed nitro-Mannich reactions of TMS-nitronates in which the use of TMS-nitronates was avoided through the use of catalytic amounts of organic base. In the reaction they used both Cu(II)−Ph-BOX catalyst and catalytic amount of triethylamine to promote direct nitro-Mannich reaction between a variety of nitro alkanes and α-imino esters.(Scheme 29).[81]

[80] Yamada, K.-I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982.
[81] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992–2995.

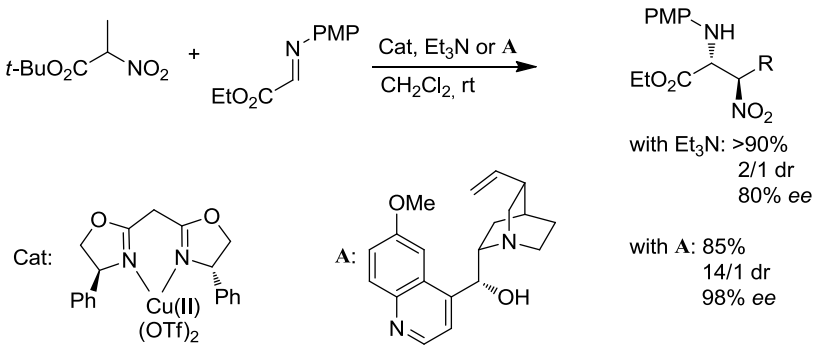


Scheme 29

As reported in the scheme, the reaction gave moderate to good yields and stereoselectivity; however, just the reported imine was compatible with the reaction conditions limiting its substrate scope.

Later Jørgensen et al. reported that the Cu(II)−BOX-catalyzed nitro-Mannich methodology could be applied to the synthesis of β-amino α-nitro acid derivatives bearing quaternary chiral centers (Scheme 30).[82]

[82] Knudsen, K. R.; Rahbek, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362−1364.

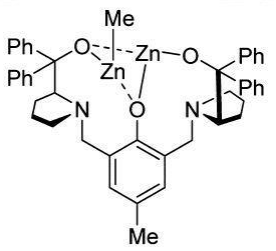


Scheme 30

At first, they used Et_3N to promote the nitronate formation, obtaining good enantioselectivity but poor diastereoselectivity. They then investigated the effect of a series of cinchona alkaloids instead of triethylamine. Use of quinine **A** as a co-catalyst resulted in a drastic improvement in diastereoselectivity. Therefore, they state that the chiral Lewis acid is responsible for the high enantioselectivity, whereas the cinchona alkaloid controls the reaction diastereoselectivity. As a consequence, the combination of both is crucial to achieve highly stereoselective reactions.

The use of the dinuclear zinc catalyst **B** (Figure 4) as effective catalyst for aza-Henry was reported at first by Qian[83] and then by Trost.[84]

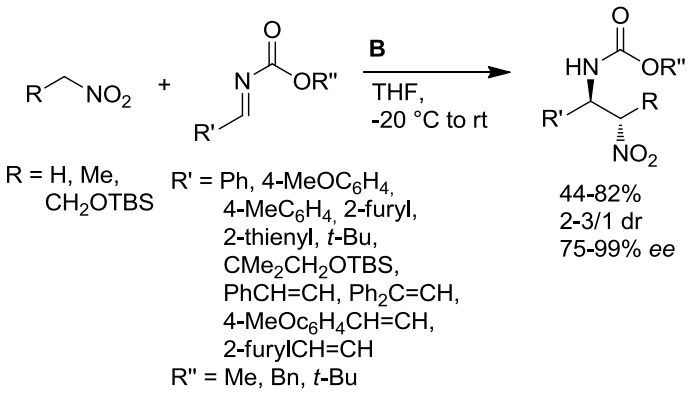
[83] Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality* **2006**, *18*, 741–745.



B

Figure 4

The first Author added nitromethane to *N*-tosyl imines, while Trost, extended the use of the catalyst considering different nitro compounds and, more interesting, many different imine type including α,β-unsaturated imines (Scheme 31).

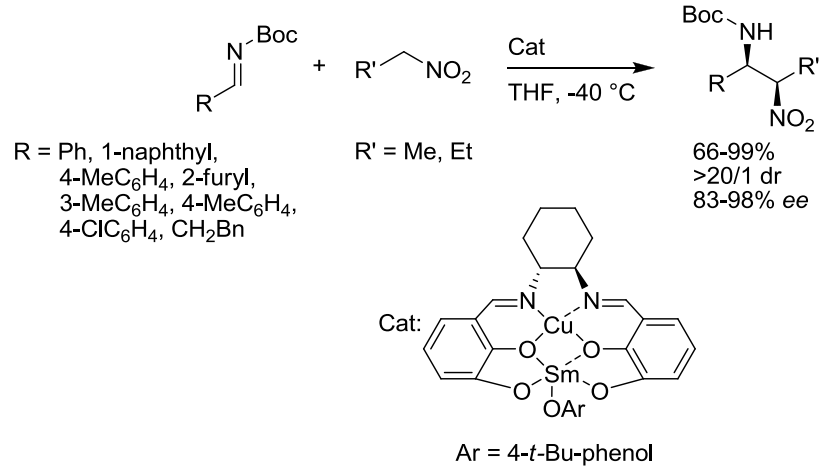


Scheme 31

[84] Trost, B. M.; Lupton, D. W. *Org. Lett*. **2007**, *9*, 2023–2026.

The authors proposed a catalytic cycle that highlights the dual Lewis-acid/Lewis-basic functionality of the catalyst **B**, involving a preliminary deprotonation of nitromethane to form a zinc nitronate intermediate followed by binding of the imine and subsequent attack by the nitronate.

The most successful direct metal-catalyzed nitro-Mannich reaction to date is reported by Shibasaki.[85] The authors used an heterobimetallic Cu−Sm−Schiff base complex to achieve highly *syn*-selective nitro-Mannich reactions between a range of *N*-Boc aryl and alkyl imines and nitroethane and 1-nitropropane (Scheme 32).



Scheme 32

[85] Handa, S.; Gnanadesikan, V.; Matsunga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900–4901.

This work represents an important milestone in the field of the aza-Henry reactions because it was the first catalytic asymmetric method in which *syn* adducts were obtained as the only observed products.

In a later publication the same group reported a development of a second-generation catalyst which demonstrated greater activity and an improved substrate scope, especially with respect to *N*-Boc alkyl imines.[86]

In the literature there are reported many other procedure to perform metal-catalyzed aza-Henry reactions which involve the use of silica-grafted Cu(II)−BOX catalyst,[87] combination of $Zn(OTf)_2$, (–)-*N*-methylephedrine (NME), Hünig's base and molecular sieves,[88] or employing supramolecular Cu(II) complex[89].

[86] Handa, S.; Gnanadesikan, V.; Matsunga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925–4934.
[87] Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595−2598.
[88] a) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884; b) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117–120.
[89] Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal*. **2009**, *351*, 1255–1262.

THESIS PURPOSE

Chapter 4

Purpose and aims

This thesis focuses on the study of the reactivity of different nitro compounds towards *N*-substituted trifluoromethyl aldimine. Continuing our studies on the reactivity of these last ones,[21] we explored a new aza-Henry reaction which gave rise, in a single step, to a new carbon-carbon bond with simultaneous generation of two vicinal stereocenters.

Despite the importance of the CF_3 moiety in bioorganic and medicinal chemistry and the well-known utility of nitro compounds as nucleophiles, to the best of our knowledge, no aza-Henry reactions performed on fluorinated imines are documented in the literature.

The emerging importance of fluorinated nitrogen-containing molecules in biological, pharmaceutical and medical fields[90] prompt us to develop an efficient method for the synthesis of trifluoromethylated β-nitro amines. These compounds, obtained through an aza-Henry reaction, are

[90] Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology* Wiley: Chichester, 2009.

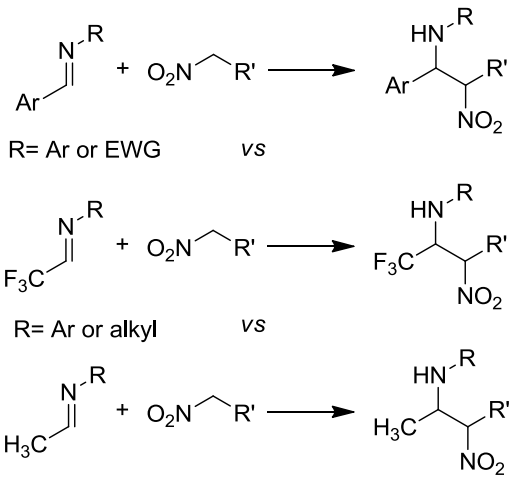
interesting highly functionalized molecules, being present in the same structure the CF_3 group and two nitrogen atoms in different oxidation state, suitable for further chemoselective transformations.

4.1 *Trifluoromethyl imines and nitro alkanes in the aza-Henry reaction*

At first it was investigated the influence that the CF_3 group exerts on the reactivity of the imine carbon towards simple nitro alkanes. Starting from the data reported in the literature,[6] it was tested whether and how the strong electron-withdrawing inductive effect of the trifluoromethyl group can influence the reactivity of the electrophilic imine carbon in the aza-Henry reaction.

The majority of the aza-Henry reactions reported in the literature[42] involves, as electrophiles, imines derived by condensation reaction between aromatic aldehydes and aromatic or EWG-substituted primary amines. These substituents play a crucial role on the reactivity of the imine double bond, exerting electronic effects, which makes the imine carbon a good electrophile. Moreover, those compounds are widely used because obtained only in the *E* configuration.

Considering that, it is interesting to compare the well-documented reactivity of aromatic imines with that of the trifluorometyl imines in which the CF_3 group exerts a strong electron-withdrawing inductive effect (Scheme 33).



Scheme 33

Therefore, the reactivity of fluorinated imines were compared even with that of alkyl non-fluorinated analogues, performing the nitro alkane additions under different reaction conditions, like different catalysts, solvents and temperature.

Furthermore, trifluoromethyl imine reactivity was studied considering the influence of alkyl or aromatic residues on the imine nitrogen and using different nitro compounds

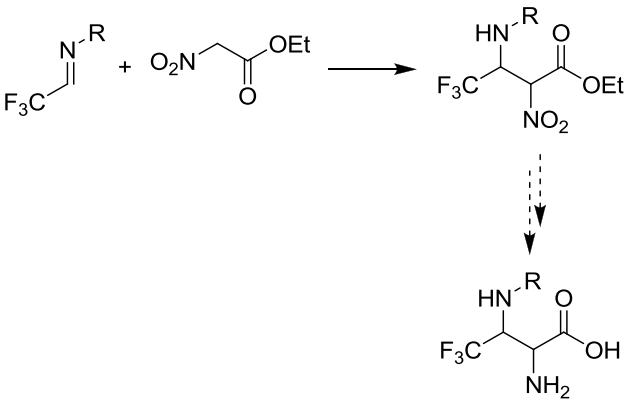
(linear, branched, or bearing a hetero atom) to explore the reaction applicability.

Since the control of contiguous stereocenters in flexible acyclic molecules is the maximum challenge,[91] and with the aim of controlling the reaction stereochemical outcome, they were employed different Lewis acids or in the presence of opportune chiral ligands or in the presence of starting optically pure trifluoromethyl imines.

4.2 *Trifluoromethyl imines and ethyl nitro acetate in the aza-Henry reaction*

In order to extend the study and to obtain more complex and interesting fluorinated compounds, ethyl nitroacetate was considered as reaction partner. The aza-Henry addition gave rise to different trifluoromethyl β-amine α-nitro esters, suitable precursor of very interesting α,β-diamino acids (Scheme 34).

[91] Trost, B. M.; Jiang, C. H. *Synthesis* **2006**, 369−396.

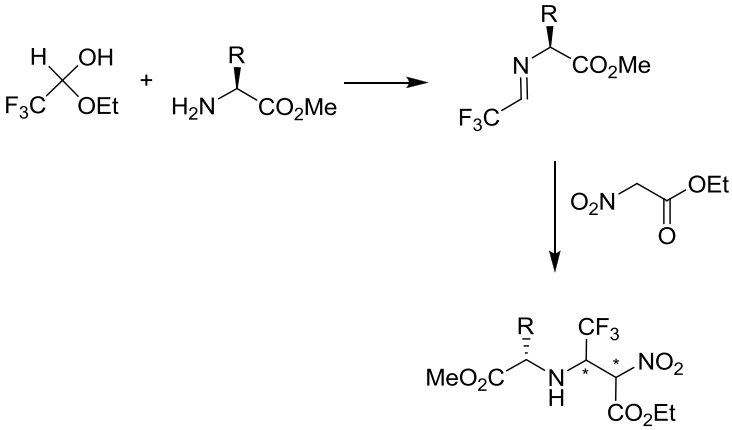


Scheme 34

The reaction conditions were modulate considering the major acidity of ethyl nitroacetate and different R residues were tested.

In this reaction the stereochemical control is even more significant. Thus, in addition to the use of chiral ligands or of opportune chiral *N*-protecting groups, it was studied a new, univocal synthesis of very interesting optical active trifluoromethyl aldimines deriving from L-α-amino esters.

Those valuable compounds were then considered as remarkable optically pure substrate in the aza-Henry reaction especially considering the potential chemical transformations of obtained molecules (Scheme 35).



Scheme 35

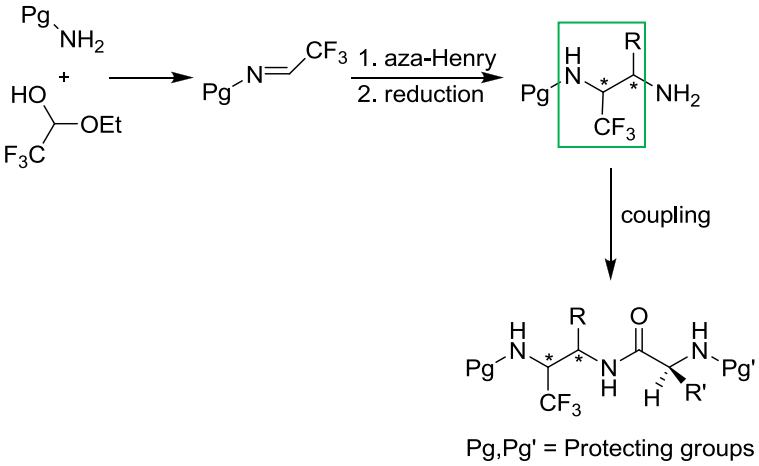
4.3 *Chemoselective tranformation of obtained compounds: nitro group reduction reaction and synthesis of ψ[CH(CF$_3$)NH]-peptidomimetics*

Among all the possible transformations which the nitro group can undergo, its reduction reaction, to form the corresponding primary amines, is the most reported and it requires the mildest conditions.

In order to obtain vicinal primary diamines, compounds difficult to synthesize, it was necessary to introduce a protecting group on the imine nitrogen: the PMP (4-MeOC$_6$H$_4$) moiety or benzyl residues were considered as suitable removing groups. The latter case is the only one that allows to

introduce a stereogenic center on the starting imines, but required a chemoselective nitro group reduction. Thus, controlled reaction conditions were optimized to achieve only the NO_2 reduction without incurring the benzyl residues hydrogenolysis.[92] The benzyl group can be removed later.

More importantly, the reduction reaction leads to the formation of new interesting ψ[CH(CF_3)NH]-peptidomimetics[93] when a protecting group is present on the imine nitrogen (Scheme 36).



Scheme 36

[92] Primary vicinal diamines are unstable compounds, therefore it is necessary to maintain at any time almost one protected nitrogen.

[93] Molteni, M.; Bellucci, M. C.; Bigotti, S.; Mazzini, S; Volonterio, A.; Zanda, M. *Org. Biomol. Chem.*, **2009**, *7*, 2286–2296.

In the ψ[CH(CF_3)NH]-peptidomimetics the carbonyl group is replaced by the $CHCF_3$ group, its isoster (Figure 5).

Figure 5

The stereogenic trifluoroethylamine[94] function is a conceptually new peptide bond surrogate that has recently found the first validation in drug discovery thanks to the highly potent and metabolically stable Cathepsin Kinhibitor Odanacatib, that is now in Phase III clinical trials for the therapy of postmenopausal osteoporosis.[95]

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[94] Sani, M.; Volonterio, A.; Zanda, M. *Med. Chem.* **2007**, *2*, 1693–1700.

[95] a) Black, W. C.; Bayly, C. I.; Davies, D. E.; Desmarais, S.; Falgueyret, J.-P.; Léger, S.; Li, C. S.; Massé, F.; McKay, D. J.; Palmer, J. T.; Percival, M. D.; Robichaud, J.; Tsou, N.; Zamboni, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741–4744; b) Li, C. S.; Deschenes, D.; Desmarais, S.; Falgueyret, J.-P.; Gauthier, J. Y.; Kimmel, D. B.; Léger, S.; Massé, F.; McGrath, M. E.; McKay, D. J.; Percival, M. D.; Riendeau, D.; Rodan, S. B.; Thérien, M.; Truong, V.-L.; Wesolowski, G.; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1985–1989; c) Black, W. C.; Percival, M. D. *ChemBioChem* **2006**, *7*, 1525–1535; d) Gauthier, J. Y.; Chauret, N.; Cromlish, W.; Desmarais, S.; Duong, L. T.; Falgueyret, J.-P.; Kimmel, D. B.; Lamontagne, S.; Léger, S.; LeRiche, T.; Sing Li, C.; Massé, F.; McKay, D. J.; Nicoll-Griffith, D. A.; Oballa, R. M.; Palmer, J. T.; Percival, M. D.; Riendeau, D.; Robichaud, J.; Rodan, G. A.; Rodan, S. B.; Seto, C.; Thérien, M.; Truong, V.-L.; Venuti, M. C.; Wesolowski, G.; Young, R. N; Zamboni, R.; Black, W. C. *Bioorg. Med. Chem. Lett.* **2008**,

This peptide-bond replacement has peculiar properties. First of all, the sp^3 N atom of the trifluoroethylamine function has little Lewis basicity and is a bad hydrogen bond acceptor: the electron-withdrawing CF_3 group is responsible for the neutralization of the amine function making the NH moiety poorly basic. Moreover, the trifluoroethylamine NH moiety is a good hydrogen-bond donor, thanks to the increased acidity due to the presence of the α-CF_3 group. On the contrary, the CF_3 group is a weak hydrogen bond acceptor,[96] therefore the trifluoroethylamine function is an effective peptide bond replacement only when the C=O of the original ligand's amide/peptide-bond is not involved in essential hydrogen-bond with the receptor. The trifluoroethylamine unit presents an sp^3 tetrahedral configuration which can contribute to the optimization of the geometry and spatial orientations of the interactions between the original planar amide/peptide moiety and the receptor. In addition, there is substantial evidence that the trifluoroethylamine unit has a high metabolic stability.

18, 923–928; e) O'Shea, P. D.; Chen, C.; Gauvreau, D.; Gosselin, F.; Hughes, G.; Nadeau, C.; Volante, R. P. *J. Org. Chem.* **2009**, *74*, 1605−1610.

[96] Dunitz, J. D.; Taylor, R. *Chem. Eur. J.*, **1997**, *3*, 89–98.

RESULTS AND DISCUSSION

Chapter 5

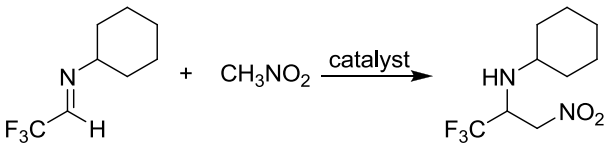
Reactivity of nitro alkanes

5.1 *Preliminary studies*

All tested fluorinated (*E*)-aldimines were synthesised by the reported solvent-free condensation reaction between trifluoroacetaldehyde ethyl hemiacetal and various amines[10] and used without further purification.

With the aim of fixing the optimal reaction conditions (*E*)-*N*-(2,2,2-trifluoroethylidene)cyclohexanamine (**1a**) and nitromethane (**2a**) were chosen as suitable starting materials and the different reaction conditions reported in Table 1 were considered.

Table 1.



1a **2a** **3a**

Entry	Catalyst	Solvent	Molar ratios **1a**:**2a**:catalyst	Time (h)	Yield[a] (%)
1	-	-	1:5:0	24	-
2	KF	*i*-PrOH	1:5:0.4	24	-

3	KF[b]	*i*-PrOH	1:5:0.4	24	-
4	KF	-	1:5:0.4	24	-
5	Et_3N	THF	1:5:1	24	-
6	Et_3N[b]	THF	1:5:1	24	-
7	Et_3N	-	1:5:1	24	-
8	$(CO_2H)_2$	-	1:5:0.5	24	-
9	$ZrCl_4$	-	1:5:1	2	65[c]
10	$ZrCl_4$	-	1:5:1.3	2	trace
11	$ZrCl_4$	-	1:5:0.5	2	87[c]
12	$ZrCl_4$	-	1:2.5:0.5	2	50
13	$ZrCl_4$	-	1:5:0.25	2	20
14	$ZrCl_4$	-	1:5:0.25	18	20

[a] By ^1H NMR spectra on the crude mixtures. [b] Performed at 70 °C. [c] After purification on silica gel.

At first, the aza-Henry reaction was attempted without added base, to test if the same imine could generate *in situ* the nitronate, acting as both base and substrate,[97] but no reaction occurred and both reagents were quantitatively recovered (entry 1). Then, different inorganic or organic bases in polar protic[98] (entries 2 and 3) or aprotic solvents (entries 5 and 6) were added to promote the formation of a nucleophilic species, but once again both aldimine **1a** and nitromethane **2a** were quantitatively recovered in all cases. Therefore, to promote the

[97] 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. 21 and Barani, M.; Fioravanti, S.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 3829−3834.

[98] Hubner, J.; Liebscher, J.; Patzel, M. *Tetrahedron* **2002**, *58*, 10485−10500. To the best of our knowledge only one paper reported a base catalyzed aza-Henry reaction performed on fluorinated α,β-unsatured ketimines: Zhang, F.; Liu, Z-J.; Liu J-T. *Org. Biomol. Chem.* **2011**, *9*, 3625−3628.

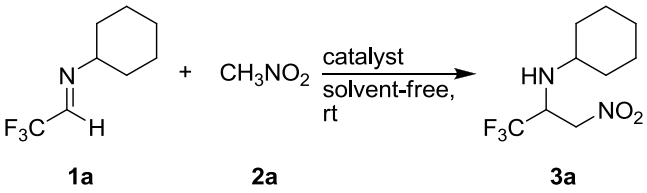
aza-Henry condensation, an acid catalysis was considered hoping to increase the electrophilicity of **1a**. While an organic protic catalyst (entry 8) did not lead to the formation of products, the use of $ZrCl_4$, chosen as suitable Lewis acid catalyst on the basis of our previous results,[29] finally lead to the expected *N*-(1,1,1-trifluoro-3-nitropropan-2-yl)cyclohexanamine (**3a**), working under solvent-free reaction conditions (entries 9 and 10).

In order to optimise the $ZrCl_4$-catalysed aza-Henry reaction, different molar ratios between catalyst and reagents were considered, the optimal reactions condition resulting those reported in entry 11 of Table 1.

Then, to understand the specific role of $ZrCl_4$, other different Lewis acids were tested as catalysts. However, as reported in Table 2, neither the use of $AlCl_3$, BF_3•Et_2O, (entries 1 and 2) nor the use of Cu(I), Cu(II), and Ti(IV) (entries 3-5), employed in similar condensation reactions,[99] led to the expected product, except in trace (entry 5).

[99] a) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227−230; b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992−2995.

Table 2.



1a **2a** **3a**

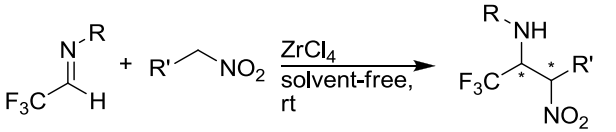
Entry	Catalyst	Molar ratios **1a**:**2a**:catalyst	Time (h)	Yield[a] (%)
1	$AlCl_3$	1:5:0.5	24	-
2	BF_3•Et_2O	1:5:0.5	24	-
3	CuCl	1:5:0.5	24	-
4	$CuCl_2$	1:5:0.5	24	-
5	$TiCl_4$	1:5:0.5	24	trace

[a] By ^{1}H NMR spectra on the crude mixtures.

Therefore, the $ZrCl_4$-catalyzed aza-Henry reaction has been extended to different trifluoromethyl (*E*)-aldimines and nitro alkanes.

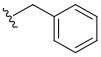
As detected by ^{1}H NMR spectra performed on the crude mixtures, quantitative conversions were found in all cases and the obtained β-nitro α-trifluoromethyl amines were purified on silica gel. The results are reported in Table 3.

Table 3.



1a-d **2a-c** **3a-j**

syn/*anti* = 30/70

Entry	**1**	R	**2**	R'	**3**	Time h	Yield[a] %
1			**a**	H	**a**	2	87
2	**a**		**b**	Me	**b**	18	82
3			**c**	Et	**c**	24	79
4			**a**	H	**d**	2	84
5	**b**		**b**	Me	**e**	18	80
6			**c**	Et	**f**	24	75
7	**c**		**a**	H	**g**	2	86
8			**b**	Me	**h**	18	77
9	**d**		**a**	H	**i**	2	83
10			**b**	Me	**j**	18	78

[a] After purification on silica gel.

As shown in Table 3, the aza-Henry reaction outcome seems to be independent from the cyclic or linear structure of R groups, while it was deeply influenced by the nature of the used nitro compound, showing to suffer from steric hindrance. In fact, moving from nitromethane (entries 1, 4, 7 and 9) to nitroethane (entries 2, 5, 8 and 10) and 1-nitropropane (entries 3 and 6) the reactions needed more time to occur and the corresponding β-nitro amines were obtained progressively in lower yields. Moreover, when the reaction was performed with 2-nitropropane no condensation was observed and both reagents were quantitatively recovered.

On the contrary, the stereochemical reaction outcome was not influenced by the used nitro alkane, being in all cases

the *anti* isomer[100] the major product in a 30/70 diastereomeric ratio, as determined by ^{1}H NMR analysis performed on the crude mixtures.

In order to improve the diastereoselectivity, an aza-Henry reaction was performed on **1a** by changing the reaction temperature (−20 °C, 0 °C and 70 °C), but in all cases no change in diastereomeric ratios were observed.

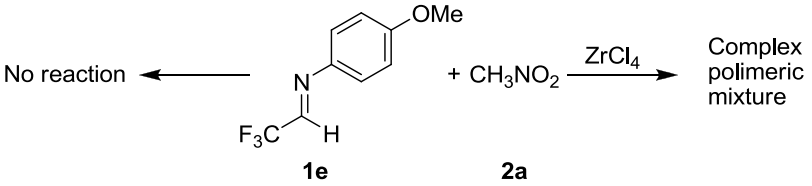
Except for **3c** and **3f**, the *syn*/*anti* isomers were obtained as pure compounds after separation by flash chromatography on silica gel.

The collected data have shown the strong influence of the fluorine atoms on the imine reactivity in the reaction. Contrary to what one might expect and to what reported in the literature, in the aza-Henry reaction the inductive electron-withdrawing effect of the CF_3 group seems to be strong enough to decrease both carbon electrophilicity and nitrogen basicity of the C=N double bond.

To attempt to modulate this strong CF_3 effect on the imine reactivity, the aromatic *p*-methoxyphenyl (PMP) protecting group was introduced on the imine nitrogen, hoping

[100] The *syn*/*anti* nomenclature is used according to Masamune convention: a) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S *Angew. Chem. Int. Ed.* **1980**, *19*, 557−558; b) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521−5523.

that the electron-donating mesomeric effect of the methoxy group on the aromatic ring could increase the nitrogen basicity. However, no products were observed without catalyst, probably because the nitronate species was not generated. On the contrary, in the presence of $ZrCl_4$ an exothermic reaction occurred leading to a complex polymeric mixture (Scheme 37).



1e **2a**

Scheme 37

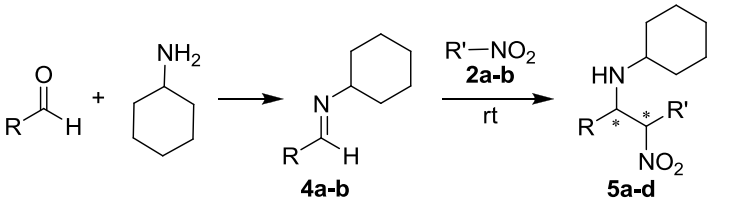
These results are in agreement with the strong inductive electron-withdrawing effect of the CF_3 group and its remarkable influence on the fluorinated molecule reactivity.

In order to confirm this, the reactivity of analogous unfluorinated imines (*E*)-**4a**,**b** towards nitro alkanes **2a**,**b** was studied.

Imines **4** were synthesized by a direct equimolar condensation reaction between suitable aldehydes and cyclohexylamine, under solvent-free conditions. The imines were obtained as only *E* isomers and used without further purification.

The aza-Henry reaction on unfluorinated imines were tested both in the presence and in the absence of the catalyst. While the use of $ZrCl_4$ led to exothermic reactions with probable complete polymerizations of the starting materials, the condensations performed without catalyst and solvent gave the expected unfluorinated β-nitro amines **5a-d** in good yields. The results are reported in Table 4.

Table 4.



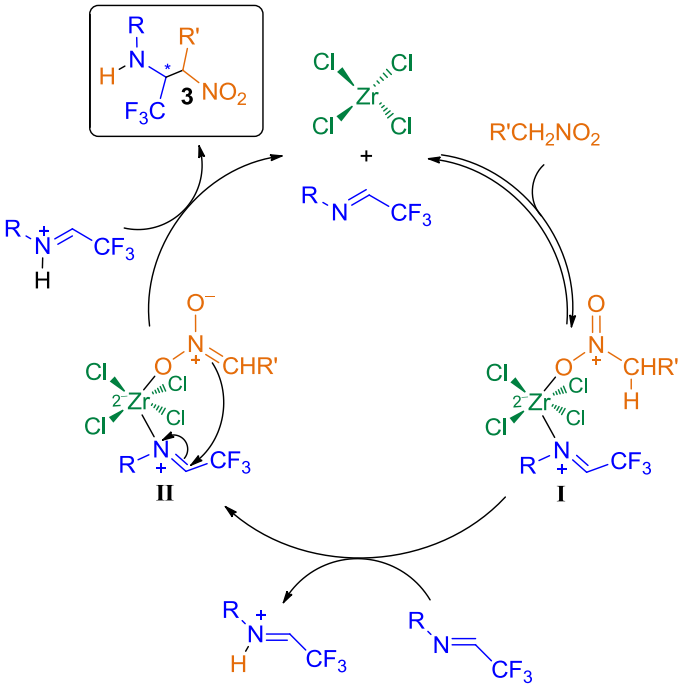
Entry	**2**	R'	**4**	R	**5**	Time (h)	Yield[a] (%)
1	**a**	H	**a**	Me	**a**	3	95
2	**b**	Me	**a**	Me	**b**	18	90
3	**a**	H	**b**	*i*-Bu	**c**	3	90
4	**b**	Me	**b**	*i*-Bu	**d**	18	89

[a] After fast filtration through a plug filled with silica gel.

Working with unfluorinated substrates (*E*)-**4a**,**b**, while no differences in the stereochemical outcome were observed, the reaction pathway is completely different and still interesting. Probably, the same imines act as both substrates and bases, generating *in situ* the nitronate and activating

themself by self-protonation, showing a remarkable difference of reactivity with the respect to analogous fluorinated compounds, thus confirming the noteworthy effect of the trifluoromethyl group on the reactivity of compounds in which is present.

Considering the collected data, a catalytic cycle to explain the $ZrCl_4$-catalyzed aza-Henry reaction pathway performed on trifluoromethyl (*E*)-aldimines can be proposed (Scheme 38).



Scheme 38

Zr(IV) coordinates both the imino nitrogen and the nitro alkane oxygen (**I**), similarly to what proposed in the literature for the Cu^{2+},[81,101] determining an increase of acidity of the nitro compound, that can be then deprotonated by a second molecule of trifluoromethyl aldimine. Finally, a favoured intramolecular nucleophilic attack (**II**) followed by protonation, brings to the formation of fluorinated β-nitro amines **3**.

The weak coordination on the nitro group oxygen has proved to be crucial, in fact when the reaction was performed using 2-nitroethanol or its benzyl derivate, as nitro compound, no addiction occurred. Probably the alcohol oxygen coordinates to the zirconium centre instead of the nitro oxygen, precluding an efficient generation of the nucleophilic nitronate.

5.2 *Stereochemical studies*

In order to achieve an asymmetric synthesis of the desired β-nitro amines, it was considered the use of a Lewis acid bearing chiral ligands.

Since zirconium was found to be the only metal capable of catalysing the aza-Henry reaction (Table 2), it was necessary

[101] Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc. Perkin Trans. 2* **1997**, 1183−1185

to maintain it as the catalytic active metal centre. In the literature a Zr/BINOL (1/2) Lewis acid, prepared *in situ* starting from zirconium-(IV) *tert*-butoxide [Zr(O*t*-Bu)$_4$], was reported as an efficient catalyst in Mannich type reactions of silyl enol ethers with aldimines[102] or in addition reactions of glycine-derived silicon enolate to aldehydes.[103]

At first a test reaction was performed using the commercially available Zr(O*t*-Bu)$_4$ as catalyst in place of the corresponding tetrachloride, but no reaction was observed. Probably the presence of the *t*-Bu electron-donating group on the oxygen atoms bound to the zirconium centre made it unable to promote the proposed mechanism and the reactants were quantitatively recovered. Nevertheless, the chiral catalysts were prepared, hoping that the introduction of the naphthyl residues on the oxygen atoms could overcome the expected electronic factors which probably cause the low activity of the catalyst.

Two different BINOL chiral ligands were tested (Figure 6), being reported in the cited articles[102] their different catalytic activity both in the resulting yields and stereoselectivity.

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[102] a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154; b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186.

[103] Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi S. *J. Am. Chem. Soc.* **2004**, *126*, 9192−9193.

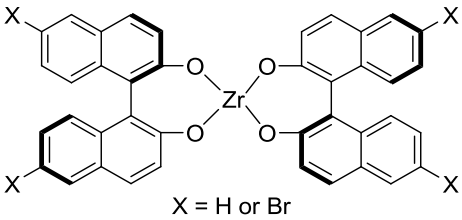


Figure 6

Unfortunately both the catalysts failed in catalysing the aza-Henry addition and the reagents were quantitatively recovered in all cases.

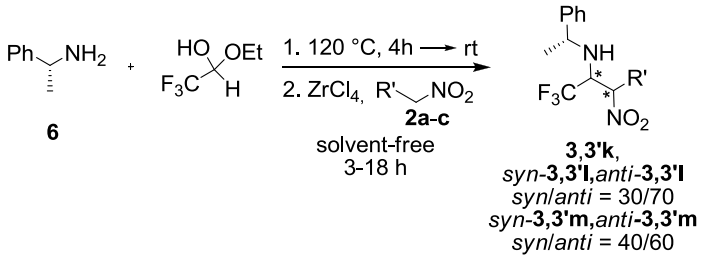
Considering the observed $ZrCl_4$ unique properties and analysing the proposed catalytic cycle (Scheme 38), it is evident that the actual active species are the intermediates **I** and **II**, in which the imine is bound to the metal Zr centre. Therefore, to achieve asymmetric reactions at low cost and with a higher atom economy, it was considered the possibility of generating *in situ* the chiral catalytic complex by using, as chiral ligand, directly an optical active trifluoromethyl imine, substrate of the desired reaction.

Chiral (*R*)-1-phenylethylamine (**6**) was considered as suitable starting primary amine due to the presence of the benzyl group, easily removable under mild hydrogenolytic conditions. Since the imine synthesis was performed under

solvent-free conditions as well as the aza-Henry addition, a one-pot reaction was attempted.

Thus, trifluoroacetaldehyde ethyl hemiacetal was added in equimolar ratio to the commercial amine **6**, heating to 120 °C and the reaction was followed by ^{19}F NMR spectroscopy (4 h). After bringing the reaction to room temperature, $ZrCl_4$ (50 % M) and the appropriate nitro alkane **2a-c** (5 equiv) were added directly in the same vessel. The aza-Henry reactions were followed by ^{19}F NMR spectroscopy and the results are reported in Table 5.

Table 5.



Entry	**2**	R'	T (h)	Products	Yield[a] (%)	dr[b]
1	**a**	H	3	**3**,**3'k**	80	80:20
2	**b**	Me	18	*syn*-**3**,**3'l**	24	72:28
				anti-**3**,**3'l**	52	72:28
3	**c**	Et	18	*syn*-**3**,**3'm**	24	67:33
				anti-**3**,**3'm**	48	67:33

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

In all cases, a complete disappearance of the not isolated imine CF_3 signal was observed by ^{19}F NMR spectra and the expected β-nitro α-trifluoromethyl amines were obtained in satisfactory yields after flash chromatography on silica gel. In hope of enhancing the stereoselective outcome, the reactions were repeated by varying the temperature (0 and – 20 °C), but no significant changes in the diastereomeric ratios (dr) were determined by the ^{19}F NMR analysis performed on the crude mixtures.

As reported in Table 6, using nitromethane **2a** a moderate diastereomeric ratio was observed (entry 1) and, when the aza-Henry reactions were performed employing nitro alkanes **2b** or **2c** (entries 2 and 3), all the four possible diastereomers were obtained, although in different ratios (Figure 7).

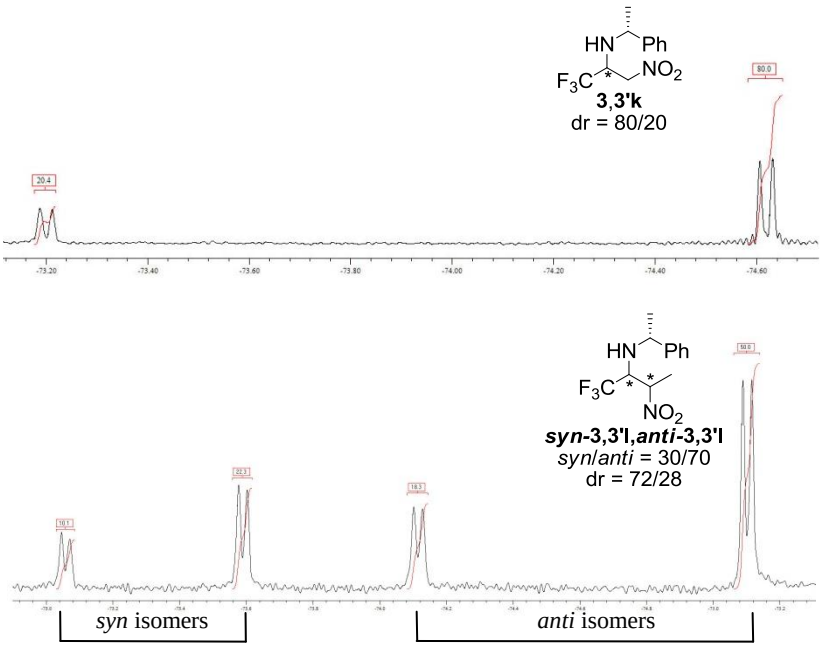


Figure 7

Fortunately, the diastereomers could be separated between them by flash chromatography on silica gel to obtain diastereomerically pure compounds.

In order to univocally assign the chirality of the new formed stereocentres, 2D NOESY ^{1}H NMR spectra (Figure 8) were acquired on the purified **3k** (**A**) and **3'k** (**B**)

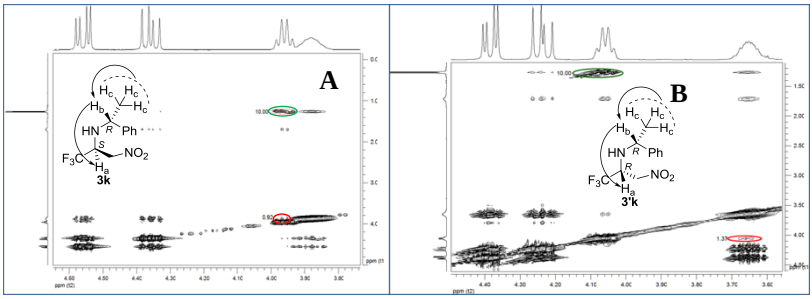


Figure 8

These experiments permit to determine interproton distances through the measure of cross peak volumes and thus molecular geometry.[104] In fact, as reported,[105] starting from a reference cross peak whose interproton distance is known, it is possible to calculate the distances between other protons according to the following equation:

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

[104] a) Aliev, A. E.; Mia, Z. A.; Busson, M. J. M.; Fitzmaurice, R. J.; Caddick S. *J. Org. Chem.* **2012**, *77*, 6290–6295; b) Falk, M.; Burton, I. W.; Hu, T.; Walter, J. A.; Wright, J. L. C. *Tetrahedron* **2001**, *57*, 8659−8665; c) Silvi, M.; Renzi, P.; Rosato, D.; Margarita, C.; Vecchioni, A.; Bordacchini, I.; Morra, D.; Nicolosi, A.; Cari, R.; Sciubba, F.; Scarpino Schietroma, D. M.; Bella, M. *Chem. Eur. J.* **2013**, *19*, 9973−9978; d) Carroccia, L.; Delfini, M.; Fioravanti, S.; Pellacani, L.; Sciubba, F. *J.Org. Chem.* **2012**, *77*, 2069−2073; e) Aresu, E., Fioravanti, S.; Gasbarri, S.; Pellacani, L.; Sciubba, F. *RSC Adv.* **2013**, *3*, 13470−13476; f) Aresu, E., Fioravanti, S.; Pellacani, L.; Sciubba, F.; Trulli, L. *New J. Chem.* **2013**, *37*, 4125–4129.

[105] Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546–4553.

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.

Considering that the chiral centre on the amine residue is always in *R* configuration, the interproton distance between H_b and the protons H_c in both **3k** and **3'k** can be considered as a fixed value and employed as a ruler to determine the distance between H_a and H_b. On the basis of the optimised geometries of both diastereomers, 2.66 Å was found as the medium value of the interproton distance (d_R) between H_b and the protons H_c and the corresponding volume V_R was set at 10 arbitrary units (au). Therefore, the volumes relative to the cross peaks between H_a and H_b (V_X) were found to be 0.92 au for **3a** and 1.37 au for **3'a**, and the corresponding interproton distances (3.96 Å and 3.70 Å respectively, with a confidence level of ~3%)[106] were calculated. Thus, comparing the collected data, the absolute configurations of the new chiral centres, *S* for **3k** and *R* for **3'k**, were univocally assigned (Figure 9).

[106] Jones, C. R.; Butts, C. P.; Harvey, J. N. *Beilstein J. Org. Chem.* **2011**, *7*, 145–150.

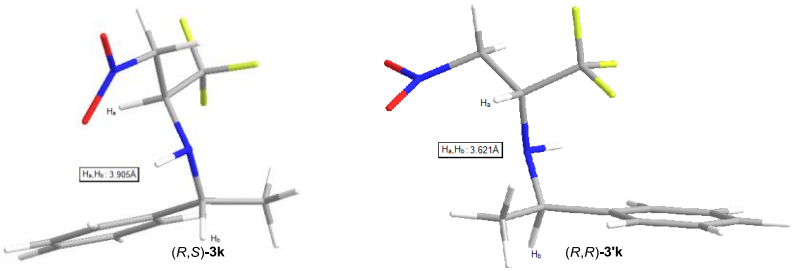
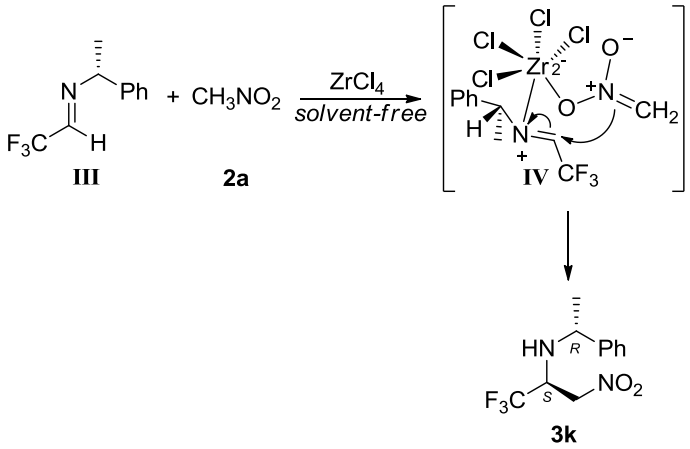


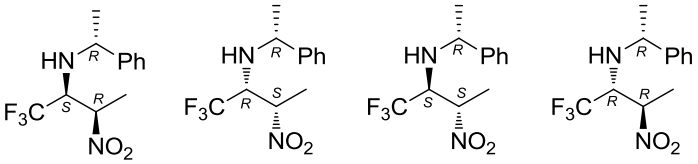
Figure 9

Considering the previous supposed mechanism (Scheme 38), the data showed that the nucleophilic attack takes place preferentially on the less hindered *Si* face of the not isolated intermediate trifluoromethyl (*E*,*R*)-imine **III**, probably following the mechanism reported in Scheme 39 for the synthesis of the major isomer (*R*,*S*)-**3k**, which involves the formation *in situ* of the chiral metallic intermediate **IV**.



Scheme 39

Finally, 2D NOESY ^{1}H NMR spectra were performed also on the *syn*-**3,3'l** and *anti*-**3,3'l** and the absolute configurations of all new chiral centres of diastereomerically pure β-nitro α-trifluoromethyl amines were assigned (Figure 10).



syn-**3l** *syn*-**3'l** *anti*-**3l** *major* *anti*-**3'l**

syn/*anti* = 3/7; *syn*-**3l**/*syn*-**3'l**/*anti*-**3l**/*anti*-**3'l** = 2/1/5/2

Figure 10

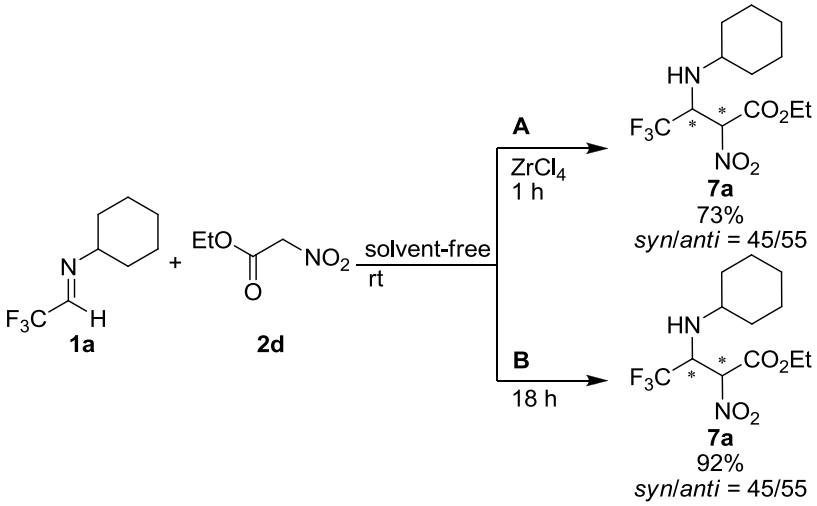
Chapter 6

Reactivity of ethyl nitroacetate

6.1 *Preliminary studies*

The ethyl nitroacetate reactivity in the aza-Henry addition was tested using (*E*)-*N*-(2,2,2-trifluoroethylidene)cyclohexanamine (**1a**) as suitable substrate.

Following the procedure previously reported in this thesis, a first experiment was performed in the presence of $ZrCl_4$ as catalyst. Compounds **7a** were obtained in only 1 h of stirring and in good yields (Scheme 40, pathway A), but it was observed concurrent polymerization reactions. Therefore, considering the acidity of the nitroacetate methylene protons, the aza-Henry reaction was attempted in the absence of catalyst: the addition gave, even if in longer times (18 h), the expected β-amino α-nitro esters in very high yields and purity, without side reactions (Scheme 40, pathway B).

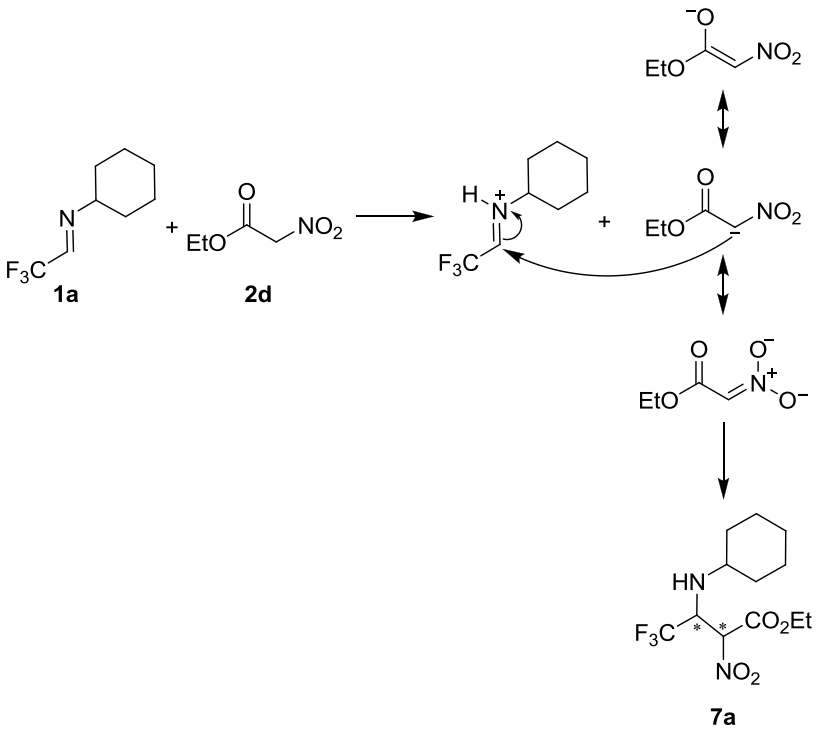


Scheme 40

The yield satisfactorily increased when no catalyst was employed and, more importantly, no difference in the *syn*/*anti* ratio was observed performing the addition under the two different reaction conditions (catalyst/without catalyst), suggesting that the $ZrCl_4$ influenced only the reaction rate but no its *syn*/*anti* selectivity outcome. The obtained *syn*/*anti* ratio was probably due to the lower steric hindrance of the CO_2Et group with the respect to those of the alkyl residues present in the other reported nitro alkanes.[107]

[107] Even when nitro alkanes **2b,c** were used it can be assumed that the *syn*/*anti* selectivity outcomes was independent from the presence of the catalyst, while they were due only to the steric hindrance of the nitro compounds. Unfortunately this hypothesis cannot be demonstrated since the cited reactions occurred only on the presence of $ZrCl_4$.

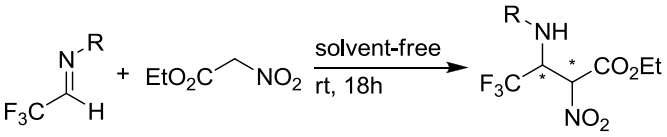
It is notable to stress that the aza-Henry addition performed following pathway B of Scheme 40 can be considered a good example of green chemistry. In fact, the reaction took place at room temperature, with no or very low environmental impact since no solvent or catalyst were used, no work-up was needed and it proceeded with total atom economy by a mechanism proposed in Scheme 41.



Scheme 41

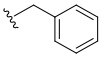
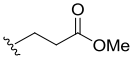
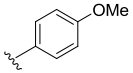
The optimal green aza-Henry reaction conditions has been extended to different trifluoromethyl (*E*)-aldimines **1b-f**, to obtain the corresponding *syn*/*anti* trifluoromethyl β-amino α-nitro esters **7b-f**. The results are reported in Table 6.

Table 6



1a-f **2d** **7a-f**

syn/*anti* = 45/55

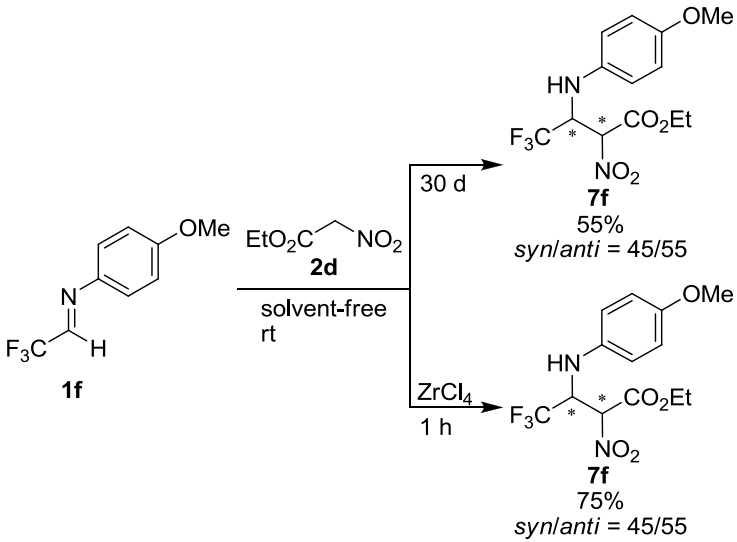
Entry	**1**	R	**7**	Yield[a] (%)
1	**a**		**a**	92
2	**b**		**b**	88
3	**c**		**c**	87
4	**d**		**d**	80
5	**e**		**e**	95
6	**f**		**f**	55[b]

[a] After fast filtration through a plug filled with celite, keeping the reaction mixtures stirring for 1h. [b] After fast filtration through a plug filled with celite, keeping the reaction mixtures stirring for 30 d.

The desired compounds were obtained in high yields and very high chemical purity for all the tested substrates

except for the imine **1f** (entry 6). When the PMP protected trifluoromethyl imine was considered, the addition reaction took place only after 30 d and even in low yields, because of the different basicity/electrofilicity of this aromatic imine from that of alkyl ones.

Therefore, to obtain the desired β-amino α-nitro esters **7f** in higher yields and shorter times, the aza-Henry addition between **1f** and **2d** was repeated in the presence of $ZrCl_4$ (Scheme 42).



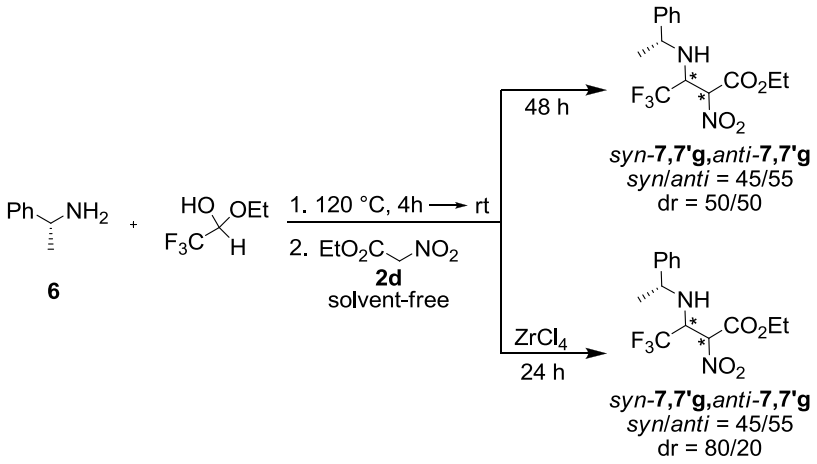
Scheme 42

Finally, the *syn*/*anti* compounds **7f** were obtained in 1 h in 75% yield and in very high chemical purity, confirming, as

reported in Scheme 42, that $ZrCl_4$ influenced only the addition rate but not the reaction stereoselectivity

6.2 *Stereochemical studies*

Starting from the results obtained using the chiral imine derived from (*R*)-1-phenylethylamine (§ **5.2**), the same optically pure substrate was considered in a one-pot aza-Henry reaction with ethyl nitroacetate both in the presence and in the absence of catalyst (Scheme 43).



Scheme 43

All diastereomeric ratios were determined by ^{1}H and ^{19}F NMR spectra analyses performed on the crude mixtures. As

expected, while no difference in the *syn*/*anti* diastereomeric ratio was observed in the presence or in the absence of $ZrCl_4$, the diastereoselectivity of the attack is deeply influenced by the catalyst (dr 45/55 *vs* 80/20), showing the crucial role of $ZrCl_4$ on the facial selectivity of the attack.

In fact, the chiral resident centre on the substrate seems to influence the diastereoselective attack on the prochiral face *Si* or *Re* only when the imine nitrogen was coordinated to the zirconium centre, availing the hypothesis of the formation of a chiral complex intermediate able to control the reaction selectivity.

Unfortunately, all attempts to separate and purify the obtained diastereomers failed: when tried a flash chromatography on silica gel, the *syn*/*anti* major products **7** were completely lost, while by HPLC analyses no separations were achieved even when using chiral solid phases.[108]

Continuing our stereochemical studies, it was considered the possibility to gain a new asymmetric aza-Henry reaction using an added chiral catalyst, in order to compare also the eventual difference in the diastereoselective outcomes between the two methods. In fact, considering the greater

[108] Chiral HPLC analyses were performed using a CHIRALPAK# IA column, a 0.9 ml/min flow and hexane/2-propanol = 86/14.

reactivity of ethyl nitroacetate compared to the other nitro alkanes, the two different Zr/BINOL catalysts reported in Figure 6 were tested in the aza-Henry reactions. As suitable testing substrates were chosen imines **1b** and **1f**, since they presented two protecting groups easily to remove through two different classical procedures.[109] The asymmetric Zr/BINOL-catalysed additions were attempted on the imine **1b**: the mixtures were followed by ^{1}H NMR analyses but no reaction occurred during 5 h, as observed also when the same addition was performed without catalyst. Therefore the reaction mixtures were kept stirring overnight, obtaining the corresponding addition products. Unfortunately, as showed by the HPLC analyses performed by a chiral solid phases, the desired products were obtained as racemic mixtures using both Zr/BINOL catalyst. This stereochemical outcome could derive either from a Zr/BINOL non asymmetric catalysis or, more probably, from the already described uncatalysed green aza-Henry additions (Table 6).

[109] a) For benzyl hydrogenolysis see: Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2143−2153; b) For the PMP CAM-catalysed deprotection see: Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862−1891.

Then, to avoid the possible uncatalysed addition, the imine **1f**, which reacted only during 30 d in the absence of zirconium, was considered.

However, once again, after 1.5 h no reaction occurred, contrary to what happened in the analogous $ZrCl_4$-catalysed reaction. Consequently, the reaction mixtures were kept stirring and monitored by ^1H NMR analyses, at first every 2h and then every 72 h. Only after 30 d the disappearance of starting materials were achieved and the desired products were obtained in yields similar to those gained in the absence of any catalyst.

These results suggested that, once again, the presence of the aromatic groups on the oxygen atoms bound to the Zirconium centre inhibited its catalytic activity, confirming what it was already assumed when the Zr/BINOL catalysts were tested starting from nitromethane (§ **5.2**)

6.3 *Reactivity of ethyl nitroacetate towards optical active trifluoromethyl aldimines deriving from L-α-amino esters*

Trifluoromethyl aldimines deriving from L-α-amino esters were considered as very interesting substrate for the

asymmetric aza-Henry reaction, because of the potential chemical transformations of obtained molecules.

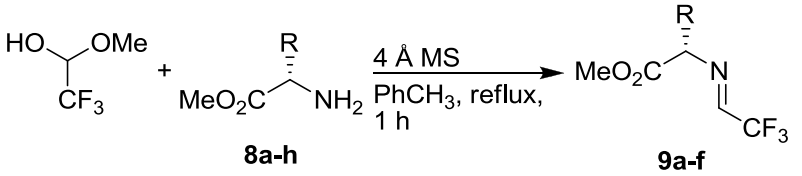
6.3.a Synthesis of trifluoromethyl aldimines deriving from L-α-amino esters

Following the reaction conditions reported in the literature,[110] the desired products were obtained in 2 h but not in satisfactory yields (up to 50%). Moreover all attempts to obtain the desired imines by our reported solvent-free method[10] failed for all the tested commercially available L-α-amino esters. Therefore a new methodology involving the use of 4 Å molecular sieves as dehydrating agents was successfully developed. The reaction proceeded in only 1 h, using toluene at reflux as solvent and a 1.5/1 molar ratio between the commercial trifluoromethyl methyl emiacetal and the considered α-amino esters **8a-f**, leading in good yields to the corresponding trifluoromethyl imines **9a-f**, which were used

[110]In the literature it was reported only one synthesis to obtain the trifluoromethyl imines of interest and only two α-amino esters: valine and methionine were employed: Gulevich, A. V.;. Shevchenko, N. E;. Balenkova,E. S; Röschenthaler, G-V.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 11706−11712. The proposed condensation reactions were performed using PTSA as catalyst and the Dean-Stark trap to promote the dehydration step.

without any further purification. The results are reported in Table 7.

Table 7



8a-h **9a-f**

Entry	**8**	R	**9**	Yields[a] (%)
1	**a**	$CH(CH_3)_2$	**a**	75
2	**b**	$CH(CH_3)CH_2CH_3$	**b**	72
3	**c**	$CH_2CH(CH_3)_2$	**c**	74
4	**d**	$CH_2CH_2SCH_3$	**d**	70
5	**e**	CH_2Ph	**e**	73
6	**f**	$CH(O\textit{t}\text{-}Bu)CH_3$	**f**	74
7	**g**	H		-
8	**h**	CH_3		-

[a] Determined after fast filtration through a plug filled with celite

Unfortunately it was not possible to obtain the desired imines starting from both glycine and alanine methyl esters, in any conditions (under solvent-free or classical conditions or in

the presence of 4Å Ms) even modifying reagent ratios, reaction temperatures and times.

Probably these two amino esters failed because of the low nucleophilicity of the amine group, which is affected by the absence of a strong electron-donating group on the chiral α-carbon, able to counter the carboxylic electron-withdrawing effect.

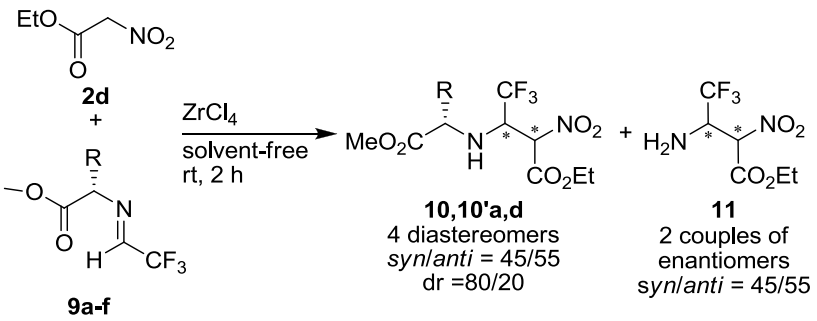
6.3.b Aza-Henry reaction between ethyl nitroacetate and trifluoromethyl aldimines deriving from L-α-amino esters

The obtained imines **9a-f** were considered in the asymmetric aza-Henry reaction with ethyl nitroacetate using $ZrCl_4$ as catalyst (50% mol), a **9**/**2d** = 1.3/1 molar ratio, in the absence of solvent and at room temperature. The reactions were monitored by ^1H NMR analyses, following the nitroacetate methylene protons signal disappearance.

Surprisingly, the NMR analyses performed on the crude mixtures showed the formation of six different compounds. Studying the crude mixtures ^1H and ^{13}C NMR spectra, it was possible to identify the four *syn*/*anti*-**10**,**10'a-d** diastereomers and to hypothesise for the unexpected other two compounds the structure **11**, in which interestingly the α-amino ester

$RCHCO_2Me$ groups were lost, achieving the primary amine functions. The results are reported in Table 8.

Table 8



Entry	**9**	R	Conversion of **10,10′** (%)[a]		Conversion of **11** (%)[a]
1	**a**	$CH(CH_3)_2$	**a**	55	45
2	**b**	$CH(CH_3)CH_2CH_3$	**b**	50	50
3	**c**	$CH_2CH(CH_3)_2$	**c**	trace	>90
4	**d**	$CH_2CH_2SCH_3$	**d**	trace	>90
5	**e**	CH_2Ph	**e**	-	99
6	**f**	CH(O*t*-Bu)CH_3	**f**	-	>95

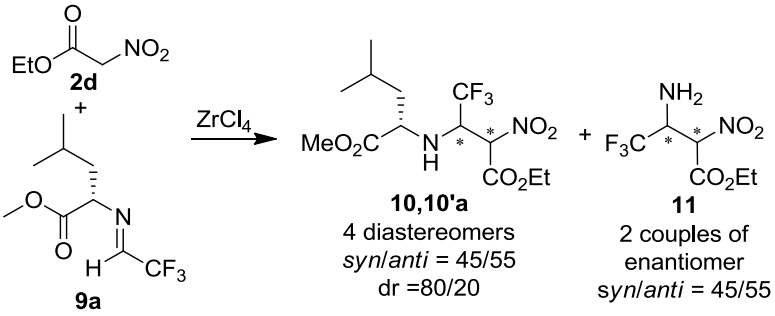
[a] Conversions determined by ^1H and ^{19}F NMR spectra performed on the crude mixtures

As reported in Table 8, the relative **10**,**10'**/**11** formation ratio seems to depend on the structure of R groups: when phenylalanine or *O*-*t*-Bu-threonine methyl esters were used, only **11** were obtained, being not present at all the expected

10,**10'e** diastereomers. Thanks to these results, the structure of **11** was univocally confirmed.

In order to limit and/or avoid the formation of the primary amine products, the reactions were performed on imine **9a** varying temperatures and molar ratios between catalyst and starting compounds, but no notably difference was observed in any case (Table 9).

Table 9

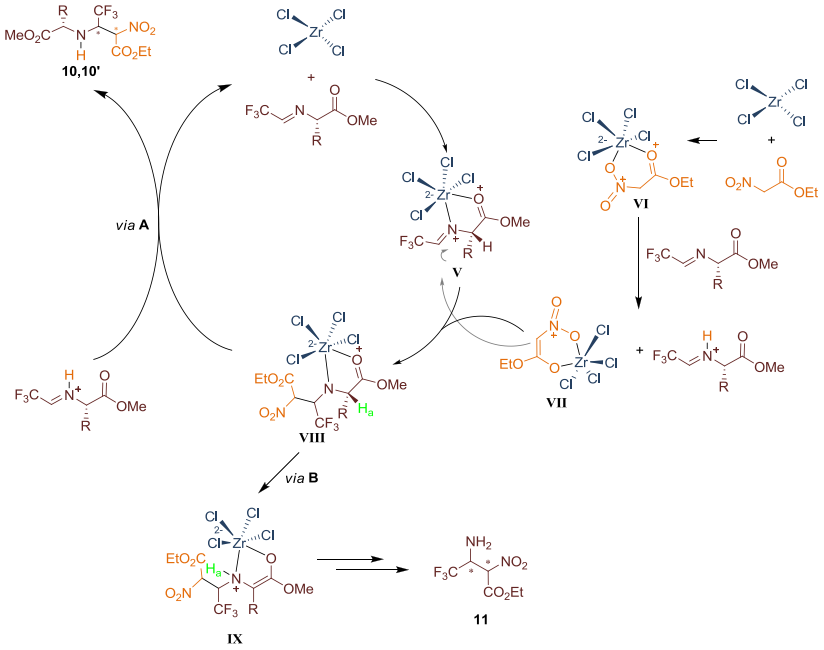


Entry	$ZrCl_4$/**9a**/**2d**	Time	T (° C)	**10,10′a** (%)[a]	**11** (%)[a]
1	0.5/1.3/1	2 h	25	trace	45
2	0.5/1.3/1	6 h	0	trace	50
3	0.5/1.3/1	2 d	–20	trace	>95
4	0.5/1.3/2	3 h	25	10	99
5	0.3/1.3/1	3 h	25	10	>95

[a] Conversions determined by ^1H and ^{19}F NMR spectra performed on the crude mixtures.

Furthermore, working without the catalyst, the reaction does not take place, highlighting the different reactivity of imines **9** from that of imines **1** derived from primary alkyl amines.

Starting from the collected data, two different pathways can occur in the formation of compounds **10**,**10'** and **11** (Scheme 44).



Scheme 44

Probably both the imines and ethyl nitroacetate coordinate $ZrCl_4$, forming the cyclic complexes **V** and **VI**. As a

consequence, the aza-Henry reaction can occur only through an intermolecular attack which leads to the key tetrahedral intermediate **VIII**. Depending on the R group, which influences the H_a proton acidity by its inductive effect, this last intermediate undergoes or an intermolecular deprotonation, giving the desired products **10**,**10′** and restoring the cycle (via A), or an intramolecular deprotonation with formation of **IX** (via B), which leads to the primary amines **11**.

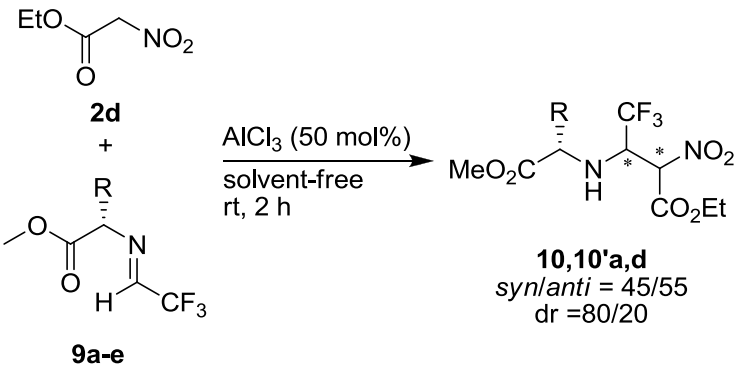
This hypothesis seems to be confirmed by the increase of **11** *vs* **10**,**10′** related to enhancement of H_a proton acidity: the presence of a benzyl group or of hetero atom in the chain (imines **9e**,**f** see Table 8, entries 5and 6) changes the course of the reaction towards the formation of only **11** (via B, Scheme 44).

To avoid or limit the formation of **11**, the use of a different catalyst was considered. No information was achieved using Cu (I or II), because no reaction occurred; unfortunately, also using the monodentate boron no reaction was observed, as already happened starting from nitro alkanes.

On the contrary, compounds **10**,**10'a-d** bearing the α-amino ester functions were obtained in high yields and

satisfactory diastereoselectivity[111] when $AlCl_3$ was used as catalyst (Table 10).

Table 10



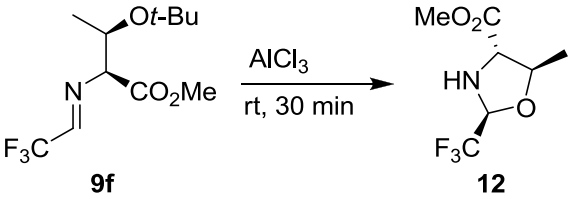
Entry	**9**	R	**10,10′**	**Yield** (%)
1	**a**	$CH(CH_3)_2$	**a**	80
2	**b**	$CH(CH_3)CH_2CH_3$	**b**	75
3	**c**	$CH_2CH(CH_3)_2$	**c**	72
4	**d**	$CH_2CH_2SCH_3$	**d**	70
5	**e**	CH_2Ph		-

Once again, using the imine **9e** (entry 5), the desired compounds were not achieved and compounds **11** were the

[111] In order to improve the diastereomeric ratio the reactions were performed at different temperature, but no changes occurred.

only products of the reaction, confirming the influence of the acidity of the chiral proton of the L-α-amino ester residue.

The very interesting and singular reactivity of imine **9f** deserves a separate discussion. Under the reaction conditions, instead of occurring the expected aza-Henry addition, the imine **9f** itself underwent an intramolecular oxygen nucleophilic attack on the iminic carbon, forming a new interesting 5-membered heterocyclic compound **12** (Scheme 45).



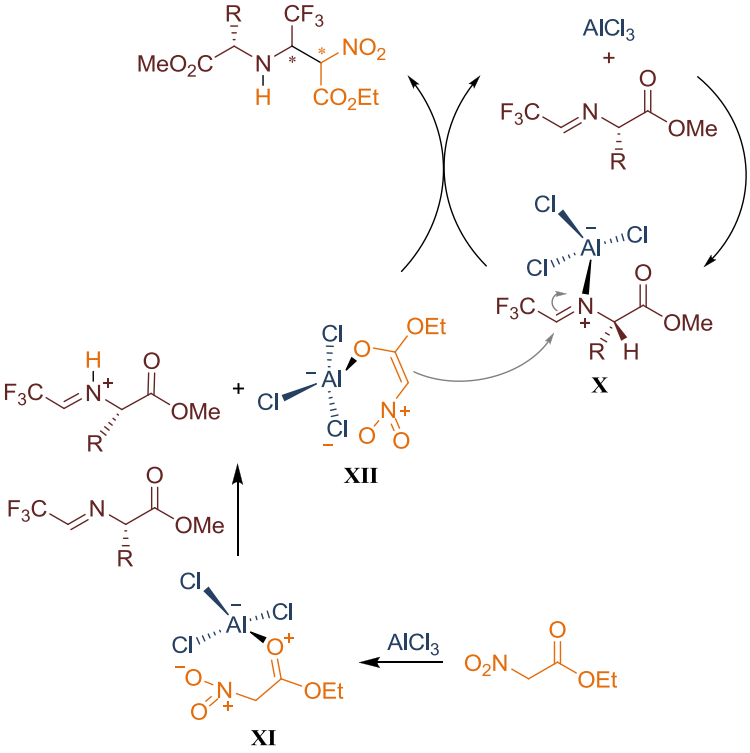
9f **12**

Scheme 45

A quantitative conversion was achieved in only 30 min; in addition the new product was obtained with high chemical and stereochemical purity, being present only one of the two possible diastereomers. The absolute configuration of the new formed chiral centre was determined through the method reported in § **5.2** by the comparison of energy minimization studies and 2D NMR NOESY analyses performed on the isolated product.

In order to explore this particular reactivity, the reaction was repeated in the absence of ethyl nitroacetate both in the presence or in the absence of $AlCl_3$. While in the first case no reaction occurred and the imine was completely recovered, in the second one compound **12** was quantitatively formed, the catalyst having clearly a fundamental role in the electrophile activation on the observed intramolecular cyclization reaction.

Concerning the $AlCl_3$ catalysed aza-Henry reactions (Table 10, entries 1-4), a possible pathways to explain the successfully formation of only compounds **10**,**10'** can be hypothesised (Scheme 46).



Scheme 46

It involves the imine and the nitro compound coordination to the catalyst to form the intermediates **X** and **XI**, respectively. After the generation of the nucleophilic species **XII** an intermolecular attack followed by deprotonation gave the desired products restoring the catalytic cycle

Unfortunately, after 12 h, it was observed the complete isomerization of the obtained diastereomers, with resultant loss

of reaction diastereoselectivity. As a consequence, it was not possible to purify and separate the obtained diastereoisomers, even by HPLC.

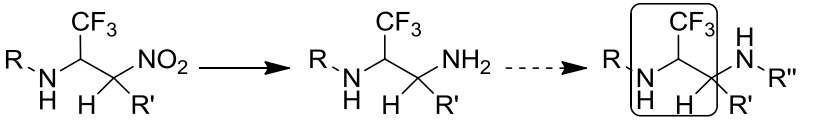
To overcome this problem and obtain the interesting trifluoromethyl diamino diesters as optically pure compounds, the crude mixtures were directly considered in the following nitro group reduction reaction.

Chapter 7

Synthetic elaboration of obtained compounds: nitro group reduction reaction

The presence of two nitrogen atoms in different oxidation state in the obtained compounds allows to perform chemoselective transformations on those two moieties.

In particular the attention was focused on the nitro group reduction reaction(Scheme 47), which lead to remarkable vicinal diamine, in which the new formed primary amine group represents a molecular growing site.



Scheme 47

Even more interesting, if R and R" are the amino acid residues or opportune *N*-protecting groups, it is possible to obtain a small backbone of ψ[CH(CF_3)NH]-

peptidomimetics[93,94]in which the carbonyl group is replaced by the its isoster $CHCF_3$ group.

7.1 *Preliminary studies and chemoselective nitro group reduction*

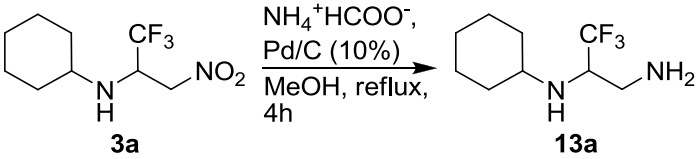
At first, modifying a reported procedure for the nitro group reduction reaction,[112] it was attempted to obtain the vicinal primary diamine by treating the β-nitro amine **3d** with anhydrous ammonium formate (5 equivalents) in the presence of 10% Pd/C (95 mg/1mmol of **3d**), under an inert atmosphere (Ar), using anhydrous MeOH as solvent at reflux for 4 h.Unfortunately, the desired compound was not achieved and the ^{1}H NMR spectra of the crude mixture were very difficult to understand.

Whereas the benzylic residue can be removed under the used hydrogenolitic conditions, it can be assumed that the desired primary amine, probably formed, then decomposes rapidly because of its instability.

However, as it is not possible to exclude an influence of the CF_3 group on the reaction outcome, the nitro group

[112]Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608−5609.

reduction reaction was repeated (Scheme 48) starting from the β-nitro amine **3a**, which was chosen as an appropriate substrate, bearing a not removable alkyl group on the nitrogen amine.



Scheme 48

The reaction gave the expected *N*-alkyl substituted diamine **13a**, confirming that the problem observed starting from **3d** was the reaction chemoselectivity.

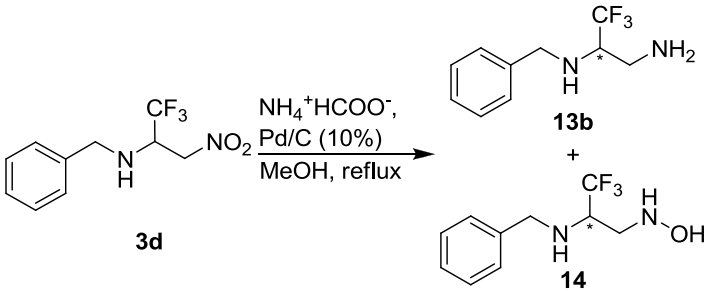
Consequently, some different reported NO_2 reduction reactions not involving hydrogenolitic conditions were tested on **3a** and **3d**. However neither the use of SmI_2 in THF/MeOH at room temperature[113] nor $ZrCl_4/NaBH_4$ reducing mixture in anhydrous THF at reflux[114] nor indium at room temperature in the presence of both an aqueous solution of HCl[115] or NH_4Cl in

[113]Kend, A. S.; Mendoza, J.S.*Tetrahedron Lett.***1991**,*32*, 1699−1702.
[114]PurushothamaChray, K.; Raja Ram, S.; Iyengar, D. S. *Synlett***2000**, 683−685.
[115]Jung Gyu, L.; Kyung, I. C.; Hun, Y. K.; Youseung, K.; Yonghan, K.; Yong S. C. *Synthesis***2001**, 81−84.

ethanol[116] gave the desired products and in all cases the substrates were quantitatively recovered.

Since the nitro group reduction was achieved only using classical reaction (ammonium formate in the presence of Pd/C), chemoselective hydrogenolitic conditions had to be developed. Therefore, different **3d**/ammonium formate molar ratios and reaction times were tested to obtain the synthesis of *N*-benzyl protected amine **13b**. The results are reported in Table 11.

Table 11



Entry	**3d**/NH_4^+-OOCH	Time (h)	Yields[a] (%)	**13b**/**14**[b]
1	1/2	1.5	40	1/1
2		5	46	1/0.5
3		24	50	1/0.5
4	1/3	1.5	48	1/0.5
5		5	52	1/0.3

[116]Pitts, R. M.; Harrison, R. J.; Moody, J. C. J. *Chem. Soc., Perkin Trans. 1* **2001**, 955−977.

6		24	58	1/0.3
7	1/5	1.5	70	1/0

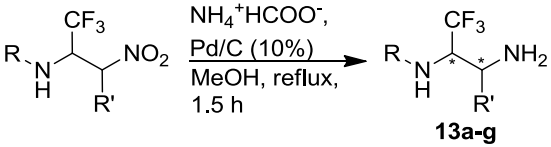
[a] Determined after a fast filtration through a plug filled with celite; [b]Determined by ^{1}H spectra performed on the crude mixtures.

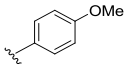
The reactions, performed with 1/2 (entries 1-3) and 1/3 (entries 3-6) molar ratios, were followed every 30 min by ^{1}H and ^{19}F NMR analyses. After 1.5 h the formation of both primary amine and hydroxylamine, well-known intermediate in the reduction reaction, was observed but longer reaction times did not change the ratio between the two products. Consequently, after 24h the ammonium formate (up to 10 equiv) was added to the reaction mixtures, but the hydroxylamine **14** was still present, even keeping the reaction stirring up to 48 h.

Finally, using directly a molar ratio **3d**/$NH_4^{+-}OOCH$= 1/5 and keeping the mixture stirring for 1.5 h (entry 7), we succeeded in obtaining **13b** as the unique product in satisfactory yields.

The optimized chemoselective nitro group reduction conditions were extended to other trifluoromethyl β-nitro amines (Table 12).

Table 12



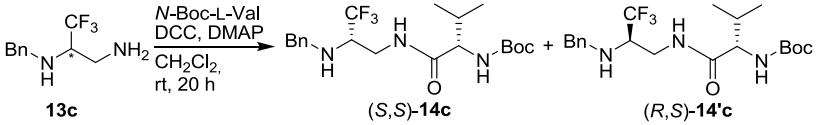
Entry	**13**	R	R'	*Syn*/*anti*	Yield[a] (%)
1	**a**		H	-	70
2	**b**		CO_2Et	45/55	83
3	**c**		H	-	65
4	**d**		CO_2Et	45/55	74
5	**e**		CO_2Et	45/55	81
6	**f**		H	-	81
7	**f′**		H	-	80
8	**g**,**g′**[b]		CO_2Et	45/55	83

[a] After flash chromatography on silica gel; [b]dr = 80/20

As reported in Table 12, the vicinal diamines **13a**-**g** were obtained in good yields, with the same *syn*/*anti* and diasteromeric ratios of the corresponding starting β-nitro amines. All the *syn*/*anti* diamines were purified by flash chromatography on silica gel, obtaining either racemic mixtures (compounds **13a**-**e**), or optically pure compounds (**13f**,**f′** and **13g**,**g′**).

7.2 Synthesis of ψ[CH(CF$_3$)NH]-peptidomimetics

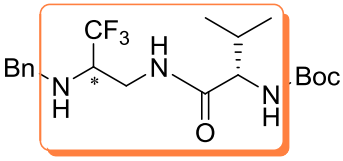
Interested in a molecular growing, a racemic resolution by a DCC coupling reaction with *N*-Boc-L-Valine was performed on racemic vicinal diamines **13c** (Scheme 49), following the classical conditions.[117]



Scheme 49

The coupling reaction gave in high yields the corresponding diastereomers **14**,**14'c**, which were successfully separated by flash chromatography on silica gel.

Thanks to the benzyl protecting group presence, interesting ψ[CH(CF$_3$)NH]-peptidomimetics were thus obtained (Figure 11).



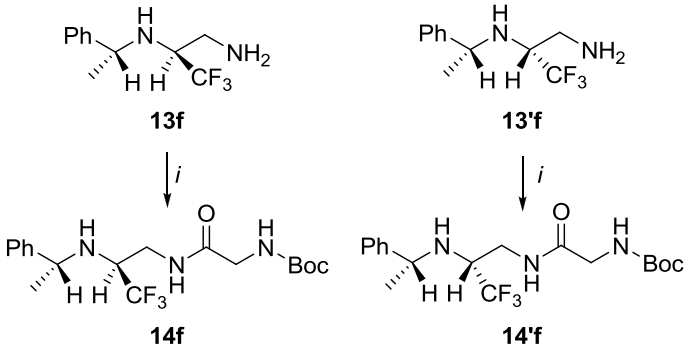
(*S*,*S*)-**14c** and (*R*,*S*)-**14'c**

Figure 11

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

The absolute configurations of the new chiral centre were determined by NOESY experiments, following the above reported methodology (§**5.2**) and choosing like distance ruler the one between the proton on *N*-Boc-protected and the proton on the L-Valine chiral centre.

The synthetic procedure was extended to the valuable optically pure β-nitro α-trifluoromethyl amines **13f** and **13'f** (Scheme 50).

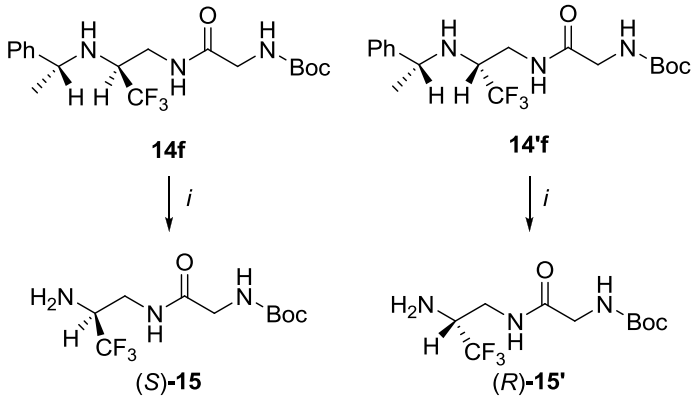


Reagents and conditions: *i: N*-Boc-Gly, DCC, DMAP (10 %M), CH_2Cl_2, rt, 24 h

Scheme 50

The presence of two different *N*-protecting groups on compounds **14**,**14′c** and **14**,**14′f** permits to choose the further site of growth and molecular diversification. In fact, a

hydrogenolysis reaction[118] allows removing the benzyl group (Scheme 51) while an acidic hydrolysis leads to remove the Boc group.



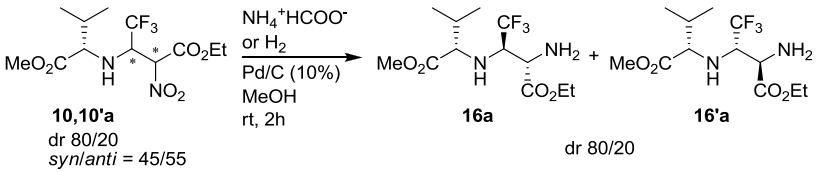
Scheme 51

The hydrogenolysis reaction lead to the corresponding (*S*)-**15** and (*R*)-**15'**, chiral CF_3-modified dipeptides, in which the presence of a primary amine function can allow a further molecular growth.

[118]Grishina, G. V.;Luk'yanenko, E. R.;Borisenko, A. A. *Russ. J. Org. Chem.* **2005**, *41*, 807–810.

7.3 *Nitro group reduction of β-nitro amine α-amino esters functionalised 10,10'a-c*

The reaction was at first tested on nitro compound **10**,**10'a**. The nitro group reduction reaction was tested using MeOH as solvent and 10 % Pd/C as catalyst and two different hydrogen sources: ammonium formate and H_2 at atmospheric pressure. The first one required high temperature (MeOH at reflux), while the second one proceeded at room temperature (Scheme 52). The reactions were followed by ^{1}H NMR analyses, which showed the substrate disappearance after 2 h in both cases. However the reaction performed with H_2 required lower temperature, easier work-up and gave the desired products in higher yields.

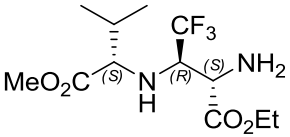


Scheme 52

Surprisingly in both crude mixtures only the two *anti* isomer amines were obtained, as determined by 2D NMR analyses. They were obtained with the same dr of the starting

compounds and then separated by flash chromatography on silica gel.

By the comparison of energy minimization studies and 2D NMR analyses of the isolated products (§ **5.2**) it was possible to establish that the major isomer was **16a** (Figure 12).



16a

Figure 12

Starting from the stereochemical obtained data, it was possible to suppose that the nucleophilic intermolecular attack of the aza-Henry reaction occurs preferentially on the less hindered *Si* face of the chiral metallic complex **XIII** (Figure 13).

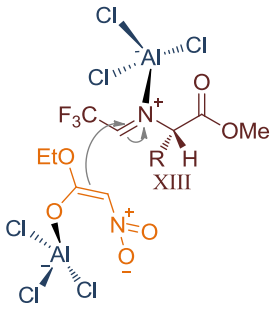
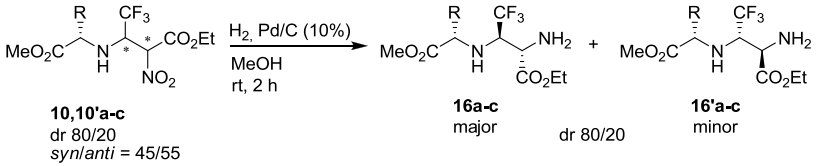


Figure 13

The nitro group reductions were repeated starting from **10**,**10'a-c** and in all cases only the two reduced *anti* isomers were obtained (Table 13).

Table 13



Entry	R	**16**	Yield[a] (%)	**16'**	Yield[a] (%)
1	$CH(CH_3)_2$	**a**	36	**a**	9
2	$CH(CH_3)CH_2CH_3$	**b**	37	**b**	9
3	$CH_2CH(CH_3)_2$	**c**	31	**c**	8

[a] After flash chromatography on silica gel.

It is important to remark that the obtained ψ[$CH(CF_3)NH$]-peptidomimetics present a second chiral α-amino acidic centre, which makes more fascinating the peptidomimetic backbones, also permitting further interesting molecular diversifications. In addition to the free NH_2 moiety, the presence of the two carboxylic groups could permit, after ester group removal, either a C-terminal molecular growing or to fix the peptidomimetics to a solid matrix.

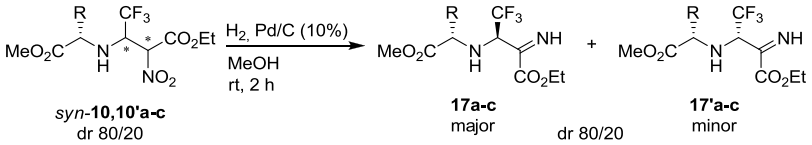
Considering the reduction reaction outcome, it can be hypothesised that the obtained *anti* amine derived from the corresponding starting *anti* β-nitro amines.

Therefore, we turned our attention to the unexpected absence of the reduced *syn* isomers. At first, bearing in mind that compounds **10**,**10'** could isomerise, it was hypothesised that a fast isomerisation of the *syn* isomers into the *anti* ones could occur even before the reduction reaction. To avoid this hypothesis the reduction reaction were performed as soon as the starting nitro compounds were obtained as a crude mixture, but again, only the *anti* isomers were observed. Then, it was supposed an isomerization of the *syn* isomers into the *anti* ones during the reduction reaction; but after flash chromatography on silica gel, the purified compounds yields suggested to discard this hypothesis.

Indeed, analysing more deeply the NMR spectra of the crude mixtures and of all the different purified compounds,the formation of two new unexpected conjugated imines was supposed. The hypothesised structures were univocally identified analysing the monodimensional ^{1}H, ^{13}C and the bidimensional (COSY, NOESY and HSQC) NMR spectra performed on the purified compounds.

Considering the collected data, the new, highly functionalised conjugated imines **17**,**17′a-c** should result only by the *syn* nitro compounds **10**,**10′a-c** during the Pd-catalysed hydrogenation reaction (Table 14).

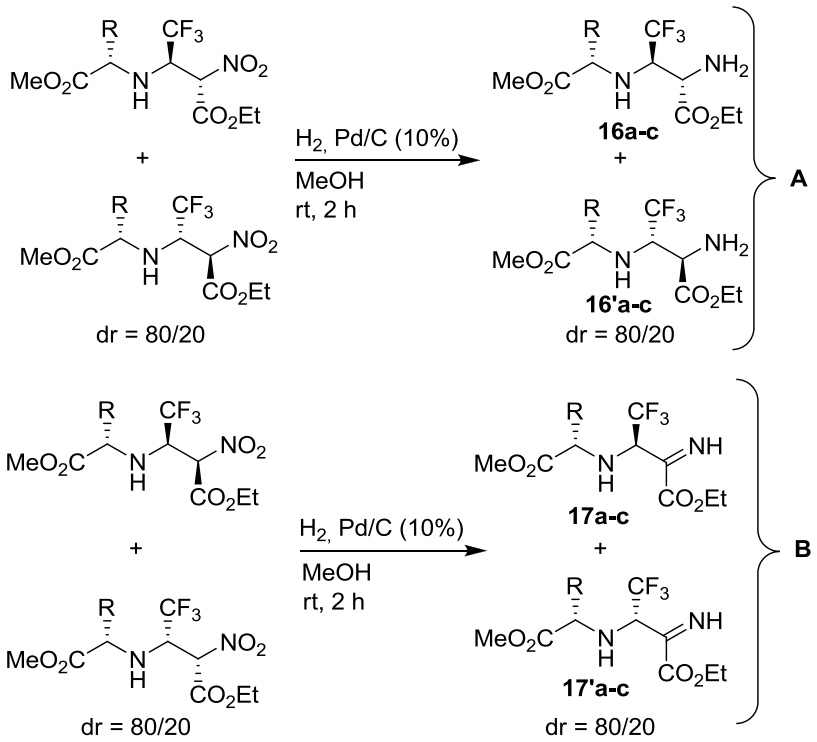
Table 14



Entry	R	**17**	Yield[a] (%)	**17'**	Yield[a] (%)
1	$CH(CH_3)_2$	**a**	29	**a**	7
2	$CH(CH_3)CH_2CH_3$	**b**	30	**b**	8
3	$CH_2CH(CH_3)_2$	**c**	25	**c**	6

[a] After flash chromatography on silica gel.

Probably, the geometry of the starting compounds and/or the intermediates coupled with the use of a solid catalyst are responsible for the two different reaction pathways observed between the *anti* (Scheme 53, pathway **A**) and the *syn* (Scheme 53, pathway **B**) isomers.



Scheme 53

Probably, the new highly functionalised imines derived from a palladium-catalysed *syn* β-elimination of the corresponding not isolated hydroxylamines, well-known intermediates in the nitro group reduction reaction.

Chapter 8

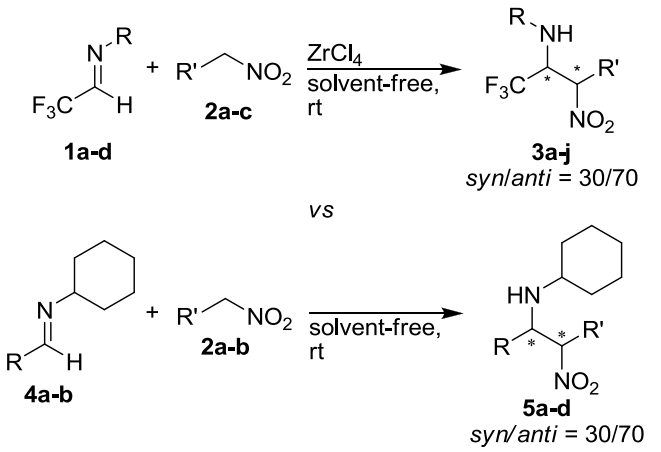
Conclusions

In this thesis studies on the trifluoromethyl (*E*)-aldimines reactivity towards different nitro compounds in the aza-Henry reaction were reported.

As previously described, it is well documented in the literature the deep influence of the CF_3 moiety in physical and chemical properties of compounds in which it is present. Whereas it is well documented as the trifluoromethyl group, thanks to its strong inductive electron-withdrawing effect, makes an electrophile site more reactive towards nucleophilic addition. Therefore, the reactivity of fluorinated aldimines towards simple nitro alkanes was compared to that of unfluorinated analogues.

It was found that the CF_3 moiety presence greatly affects the addition reaction of nitro compounds, but contrary to what expected, and probably just as a consequence of its strong inductive electron-withdrawing effect, it depresses both nitrogen basicity and carbon electrophilicity of imine C=N. In fact, while the trifluoromethyl imines reacted only in the

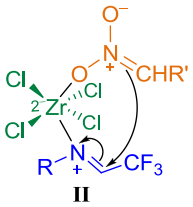
presence of $ZrCl_4$, as an efficient catalyst, the analogous unfluorinated imines did not need any catalysis (Scheme 54).



Scheme 54

As reported in Scheme 54, the reaction diastereoselectivity seems to be independent from the presence or the absence of both CF_3 and the catalyst, being probably due only to the R′ steric hindrance.

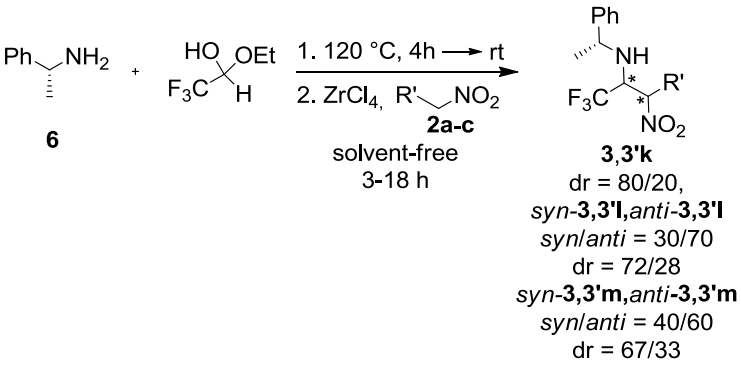
A possible mechanism for the aza-Henry reaction was proposed (§**5.1**) and it involves an intramolecular nucleophilic attack of the nitronate to the imine, both coordinated to the Zr centre in the key intermediate **II** (Figure 14)



II

Figure 14

The diastereoselective reaction outcome was tested at first attempting an asymmetric aza-Henry addition using a chiral metallic complex. Failing all attempts to obtain a selective attack using added chiral catalysts, we succeeded in developing a new asymmetric aza-Henry reaction at low costs and higher atom economy. In fact, starting from the proposed mechanism, we successfully considered the possibility to use a suitable optically active fluorinated imine as appropriate substrate to generate *in situ* the chiral organocatalytic complex responsible of the facial attack selectivity (Scheme 55).



Scheme 55

The obtained diastereomers were separated by flash chromatography and the absolute configurations of the new formed chiral centres were determined by comparison of energy minimization studies and 2D NOESY NMR analyses of isolated products.

The stereochemical outcome showed that the nucleophilic attack occurs preferentially on the less hindered *Si* face of the starting imine, involving the *in situ* formation of the following intermediate **IV** in the synthesis of the major isomer (Figure 15).

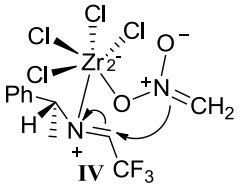
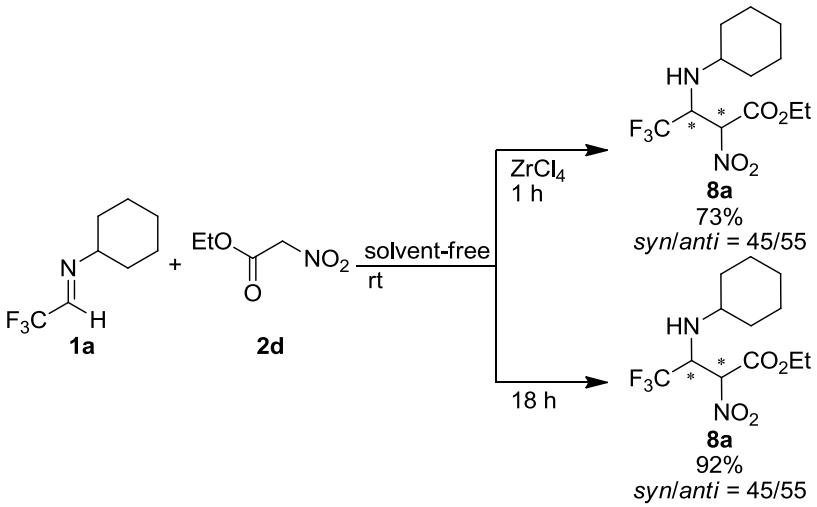


Figure 15

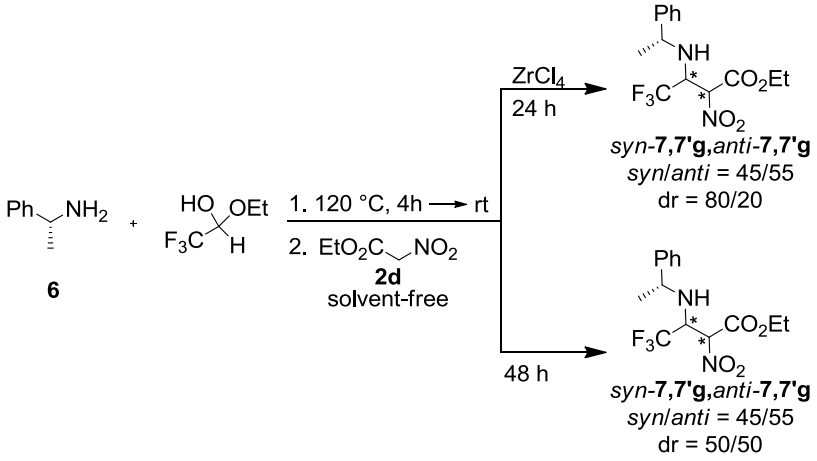
The aza-Henry reaction was then studied using ethyl nitroacetate as an interesting functionalised nitro compound, suitable nucleophilic precursor, in order to test if the presence of a second EWG could modify the reaction pathway and/or its diastereomeric outcome.

The acidity of nitroacetate methylene protons permitted to perform the aza-Henry reactions either in the presence or in the absence of the catalyst, allowing to study, for the first time, the role of $ZrCl_4$. Comparing the reaction outcome of the new green uncatalysed aza-Henry with that of the catalysed one, it was evident that the $ZrCl_4$ presence has no influence on the *syn*/*anti* stereochemical reaction outcome, while it affects only the reaction rate (Scheme 56).



Scheme 56

The particular reactivity of ethyl nitroacetate allowed us to better understand the catalyst role in the reported asymmetric aza-Henry reactions, testing them both in the presence and in the absence of $ZrCl_4$. While a 80/20 dr was obtained in the first case, a 50/50 dr was achieved performing the reaction without the catalyst, demonstrating the crucial role of $ZrCl_4$ in the *in situ* formation of the chiral complex, which is fundamental in the stereochemical reaction induction.

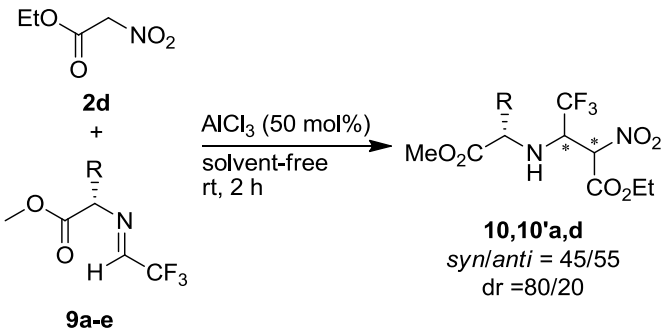


Scheme 57

The asymmetric reaction was then tested using, as remarkable starting materials, trifluoromethyl (*E*)-aldimines **10** deriving from L-α-amino esters, obtained through a new synthetic methodology (§***6.3.a***).

Surprisingly, while in the absence of any catalyst, the reaction did not take place, probably because the presence of the ester EWG on the nitrogen atom depresses the imine reactivity, in the presence of $ZrCl_4$ the reactions gave unexpected primary amines in addition to the desired compounds (§***6.3.b***).

Therefore, the addition reaction conditions must be modified and $AlCl_3$ was found as an optimal catalyst instead of $ZrCl_4$ (Scheme 58).

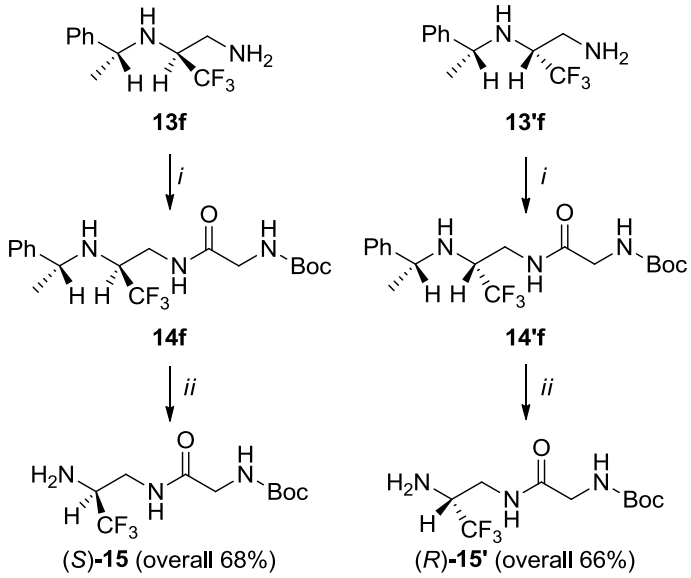


Scheme 58

The reaction gave the desired highly functionalized compounds, which were considered for further synthetic elaboration.

Among all the possible β-nitro amine transformations, the nitro group reduction reaction was investigated, optimizing chemoselective reduction conditions, to obtain interesting primary amines.

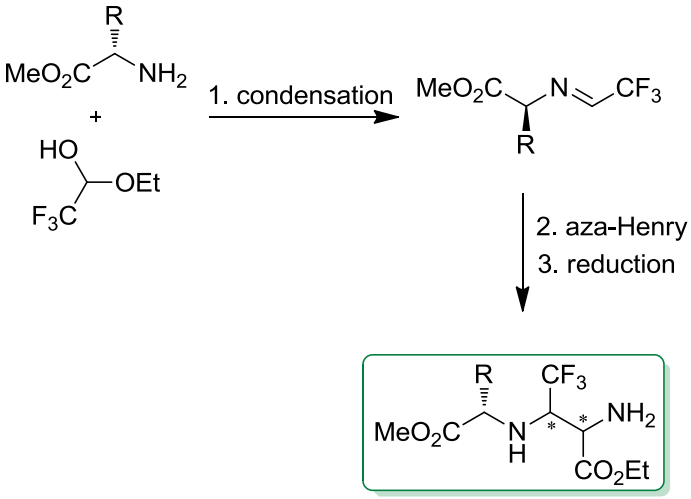
Starting from which, new ψ[CH(CF_3)NH]-peptidomimetics were obtained by a DCC coupling reaction followed by the benzyl group hydrogenolysis (Scheme 59).



Reagents and conditions: *i: N*-Boc-Gly, DCC, DMAP (10 %M), CH_2Cl_2, rt, 24 h; *ii:* H_2, Pd/C (10 %M), anhydrous MeOH, rt, 24 h

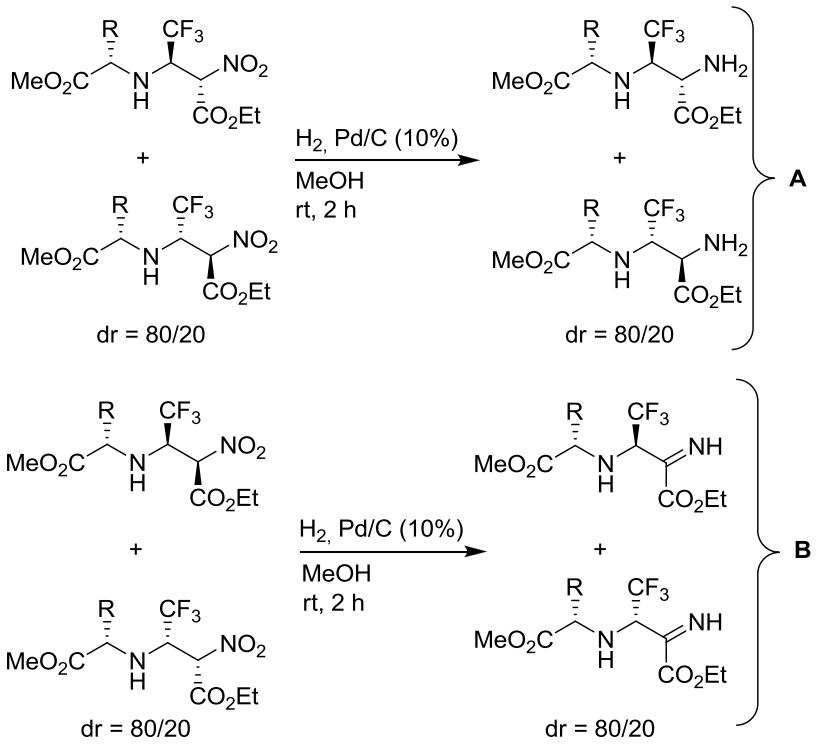
Scheme 59

The new synthetic reported procedure, performed using α-amino esters as starting materials, permits to obtain ψ[$CH(CF_3)NH$]-peptidomimetics in only three steps (Scheme 60).



Scheme 60

Moreover, a particular and unexpected reactivity of α-amino ester functionalized β-nitro amines was observed performing the Pd-catalysed nitro group reaction. In fact, depending on the geometry of the starting compounds and probably thanks to the use of a solid catalyst, the reduction reactions proceeded in two different way. While starting from the *anti* nitro isomers the expected corresponding amines were obtained (Scheme 61, pathway **A**), the same reduction reactions on the *syn* nitro isomers gave new stable conjugated imines (Scheme 61, pathway **B**), probably deriving from a palladium-catalysed *syn* β-elimination of the not isolated hydroxylamine intermediates.



Scheme 61

In all cases, the obtained compounds were separated by flash chromatography on silica gel and the absolute configurations of the new formed chiral centres were univocally assigned, allowing the identification of the preferred attack site in the previous $AlCl_3$-catalysed aza-Henry reactions.

In conclusion, in this thesis the particular reactivity of different nitro compounds in aza-Henry reactions on trifluoromethyl imines has been studied.

The CF_3 group influences both the carbon electrophilicity and imine nitrogen basicity. This has required the study of new synthetic strategies to obtain the addition reactions. Therefore, new solvent-free green synthetic strategies have been developed which did not require the use of any catalyst or involved the use of the eco-friendly $ZrCl_4$ as catalyst, to achieve new remarkable highly functionalised compounds.

The differently functionalised trifluoromethyl nitrogen-containing compounds, obtained by the reported aza-Henry reactions, can be regarded as versatile building blocks for the synthesis of more complex compounds, which could be useful for many different applications in organic, bioorganic, pharmaceuticals and medicine chemistry

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 cm^{-1}.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 300 and 400 MHz, respectively on a Varian-Mercury 300 instrument and on a Bruker 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.

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.

Chapter 9

Reactivity of nitro alkanes

9.1 ***General procedure for the synthesis of β-nitro α-trifluoromethyl amines*** **3a-j**: To a mixture of trifluoromethyl (*E*)-aldimine **1a-d** (1 mmol) and nitro compound **2a-c** (5 mmol), $ZrCl_4$ (0.5 mmol) was added. The reactions were performed under solvent-free conditions and stirred at room temperature (2-24 h). Then, after addition of water (5 mL), the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The crude mixtures were purified by flash chromatography on silica gel. β-Nitro α-trifluoromethyl amines **3d**,**e**[119]

***N*-(1,1,1-Trifluoro-3-nitropropan-2-yl)cyclohexanamine** (**3a**). Yellow-brown oil. Yield 87% (0.209 g). Purified by fast filtration through plug filled with silica gel using AcOEt as

[119] Korotaev, V. Yu.; Barkov, A. Yu.; Kodess, M. I.; Kutyashev, I. B.; Slepukhin, P. A.; Zapevalov, A. Ya. *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 1886−1898

eluent. ν_{max} cm^{-1} 3355, 1567. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.61 (dd, *J*=12.6, 4.2 Hz, 1H), 4.35 (dd, *J*=12.6, 9.4 Hz, 1H), 4.14-4.01 (m, 1H), 2.71-2.63 (m, 1H), 1.89-1.48 (m, 5H), 1.35-0.99 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.2 (q, *J* = 284.5 Hz), 75.3, 55.7 (q, *J* = 29.1 Hz), 54.8, 34.1, 32.8, 25.9, 24.7, 24.4. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{16}F_3N_2O_2$ 241.1164, found 241.1161.

***N*-(1,1,1-Trifluoro-3-nitrobutan-2-yl)cyclohexanamine** (*syn*-**3b**). Pale yellow oil. Yield 24% (0.061 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3365; 1558. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.69-4.60 (m, 1H), 3.74-3.64 (m, 1H), 2.69-2.61 (m, 1H), 1.82-1.54 (m, 6H), 1.63 (dd, *J* = 6.8, 1.4 Hz, 3H), 1.27-1.08 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.62 (q, *J* = 285.4 Hz), 83.7, 59.7 (q, *J* = 28.1 Hz), 55.3, 34.2, 32.8, 25.9, 24.8, 24.4, 16.4. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{10}H_{18}F_3N_2O_2$ 255.1320, found 255.1326.

***N*-(1,1,1-Trifluoro-3-nitrobutan-2-yl)cyclohexanamine** (*anti*-**3b**). Pale yellow oil. Yield 58% (0.147 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3365; 1558. ^{1}H NMR ($CDCl_3$, 300 MHz) δ:

4.75-4.65(m, 1H), 4.14 (m, J = 7.5, 4.3 Hz, 1H), 2.69-2.54 (m, 1H), 1.86-1.63 (m, 6H), 1.55 (dd, J = 6.8, 0.7 Hz, 3H), 1.35-1.07 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.2 (q, J = 285.4 Hz), 81.2, 58.9 (q, J = 27.9 Hz), 55.1, 34.1, 32.9, 25.8, 24.7, 24.3, 12.8. HRMS: m/z $[M + H]^+$ calcd. for $C_{10}H_{18}F_3N_2O_2$ 255.1320, found 255.1322.

***N*-(1,1,1-Trifluoro-3-nitropentan-2-yl)cyclohexanamine** (*syn*,*anti*-**3c**). Pale yellow oil. Yield 79% (0.212 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3373; 1558. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.58-4.42 (m, 2H), 3.92-3.80 (m, 1H, major isomer), 3.66-3.50 (m, 1H, minor isomer), 2.66-2.60 (m, 2H), 2.18-1.95 (m, 4H), 1.88-1.50 (m, 12H), 1.36-1.04 (m, 10H), 0.99 (t, J = 7.4 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.2 (q, J = 285.1 Hz, 2C), 90.1 (minor isomer), 88.7 (major isomer), 59.2 (q, J = 28.1 Hz, major), 58.9 (q, J = 28.1 Hz, minor), 55.6 (major), 55.3 (minor), 34.3 (minor), 34.2 (major), 33.2 (major), 32.8 (minor), 25.9 (2C), 24.8 (2C), 24.5 (major), 24.4 (minor), 22.5 (2C), 10.5 (2C). HRMS: m/z $[M + H]^+$ calcd. for $C_{11}H_{20}F_3N_2O_2$ 269.1477, found 269.1475.

***N*-Benzyl-1,1,1-trifluoro-3-nitropentan-2-amine** (*syn*,*anti*-**3f**). Pale yellow oil. Yield 75% (0.207 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3368; 1560. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.29 (m, 10H), 4.66-4.60 (m, 1H, minor isomer), 4.59-4.52 (m, 1H, major isomer), 4.15-3.99 (m, 3H), 3.90-3.80 (m, 2H), 3.59-3.49 (m, 1H, minor), 2.19-2.03 (m, 6H), 1.00 (t, *J* = 7.3Hz, 3H, major), 0.96 (t, *J* = 7.4Hz, 3H, minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (minor isomer), 138.4 (major isomer), 128.6 (2C, major), 128.5 (2C, minor), 128.4 (2C, minor), 128.3 (2C, major), 127.7 (major), 127.6 (minor), 125.4 (q, *J* = 285.9 Hz, 2C), 89.1 (minor), 88.0 (major), 60.8 (q, *J* = 28.0 Hz, major), 60.4 (q, *J* = 28.0 Hz, minor), 52.7 (major), 52.2 (minor), 22.2 (2C), 10.3 (major), 10.2 (minor). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{16}F_3N_2O_2$ 277.1164, found 277.1172.

***N*-(1,1,1-Trifluoro-3-nitropropan-2-yl)cyclopentanamine** (**3g**). Yellow-brown oil. Yield 86% (0.194 g). Purified by fast filtration through plug filled with silica gel using AcOEt as eluent. ν_{max} cm^{-1} 3365; 1556. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.60 (dd, *J* = 12.7, 4.2 Hz, 1H), 4.36 (dd, *J* = 12.7, 9.4 Hz, 1H), 4.07-3.94 (m, 1H), 3.39-3.31 (m, 1H), 1.86-1.25 (m, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.1 (q, *J* = 284.8 Hz), 74.8, 57.6,

56.9 (q, *J* = 29.0 Hz), 33.8, 32.4, 23.4, 23.3,HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_8H_{13}F_3N_2NaO_2$ 249.0827, found 249.0828.

***N*-[2-Nitro-1-(trifluoromethyl)propyl]cyclopentanamine** (*syn*-**3h**). Yellow oil. Yield 21% (0.051 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3370; 1556. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74-4.67 (m, 1H), 3.66-3.56 (m, 1H), 3.36-3.27 (m, 1H), 1.85-1.59(m, 4H), 1.64 (dd, *J* = 6.8, 1.3 Hz, 3H), 1.58-1.48 (m, 2H), 1.33-1.20 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.4 (q, *J* = 185.8 Hz), 83.3, 60.9 (q, *J* = 27.8 Hz), 58.1, 34.0, 32.2, 23.3 (2C), 12.5.HRMS: *m*/*z* [M + H]$^+$ calcd. for $C_9H_{16}F_3N_2O_2$ 241.1164, found 241.1169.

***N*-[2-Nitro-1-(trifluoromethyl)propyl]cyclopentanamine** (*anti*-**3h**). Yellow oil. Yield 56% (0.135 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3370; 1556. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.73-4.61 (m, 1H), 4.14-4.05 (m, 1H), 3.36-3.27 (m, 1H), 1.85-1.63(m, 4H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.58-1.46 (m, 2H), 1.36-1.18 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.4 (q, *J* = 185.8 Hz), 81.0, 60.2 (q, *J* = 27.8 Hz), 58.1, 33.9, 32.4, 23.4, 23.2,

12.5.HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{16}F_3N_2O_2$ 241.1164, found 241.1169.

***N*-(1,1,1-Trifluoro-3-nitropropan-2-yl)pentan-1-amine** (**3i**) Yellow-brown oil. Yield 83% (0.190 g). Purified by fast filtration through plug filled with silica gel using AcOEt as eluent. ν_{max} cm^{-1} 3368; 1569. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.59 (dd, *J* = 13.0, 4.2 Hz, 1H), 4.41 (dd, *J* = 13.0, 9.4 Hz, 1H), 4.01-3.89 (m, 1H), 2.89-2.81 (m, 1H), 2.69-2.60 (m, 1H), 1.50-1.21 (m, 7H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.08 (q, *J* = 285.0 Hz), 74.2, 58.4 (q, *J* = 29.2 Hz), 47.8, 29.8, 28.9, 22.3, 13.8. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_8H_{16}F_3N_2O_2$ 229.1146, found 229.1148; *m*/*z* $[M + Na]^+$ calcd. for $C_8H_{15}F_3N_2NaO_2$ 251.0983, found 251.0975.

***N*-(1,1,1-Trifluoro-3-nitrobutan-2-yl)pentan-1-amine** (*syn*-**3j**). Yellow oil. Yield 20% (0.048 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3368; 1558. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.75-4.66 (m, 1H), 3.62-3.52 (m, 1H), 2.92-2.83 (m, 1H), 2.64-2.55 (m, 1H), 1.65 (dd, *J* = 6.8, 1.3 Hz, 3H), 1.79-1.14 (m, 7H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.5 (q, *J* = 285.6 Hz), 83.1, 62.6 (q, *J* = 28.0 Hz), 48.5, 30.0, 28.9,

22.4, 16.4, 12.7. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{18}F_3N_2O_2$ 243.1320, found 243.1324.

***N*-(1,1,1-Trifluoro-3-nitrobutan-2-yl)pentan-1-amine** (*anti*-**3j**). Yellow oil. Yield 58% (0.140 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 98:2). ν_{max} cm^{-1} 3368; 1558. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.74-4.62 (m, 1H), 4.09-4.00 (m, 1H), 2.94-2.84 (m, 1H), 2.64-2.56 (m, 1H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.78-1.12 (m, 7H), 0.90 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.4 (q, *J* = 285.5 Hz), 80.9, 61.8 (q, *J* = 28.0 Hz), 49.1, 30.0, 28.9, 22.4, 16.4, 13.9. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{18}F_3N_2O_2$ 243.1320, found 243.1328.

9.2 ***General procedure for the synthesis of (E)-aldimines*** **4a,b.** Equimolar amounts (5 mmol) of aldehyde and cyclohexylamine were reacted under solvent free conditions. The reaction mixtures were stirred at room temperature for 15 min, then CH_2Cl_2 (3 mL) and anhydrous sodium sulfate were added and the mixtures were filtered off. The organic solvent was evaporated under vacuum to give the expected aldimines which were used without further purification. **5a**

[120] and **5b**[4121] are known compounds

9.3 ***General procedure for the synthesis of β-nitro amines*** **5a-d**: (*E*)-Aldimines **4a-b** (1 mmol) were stirred at room temperature (3-18 h) with a five-fold excess of nitro compound, under solvent-free conditions. After removal of excess nitro compound under vacuum, the crude mixtures were purified through plug filled with silica gel using AcOEt as eluent

***N*-(1-Nitropropan-2-yl)cyclohexanamine** (**5a**). Yellow-brown oil. Yield 95% (0.177 g). ν_{max} cm^{-1} 3355; 1568. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.38-4.27 (m, 1H), 3.56-3.46 (m, 1H), 2.55-2.46 (m, 1H), 1.86-1.55 (m. 7H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.33-0.99 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 79.8, 53.9, 51.8, 34.2, 33.7, 26.0, 24.8, 24.7, 17.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{19}N_2O_2$ 187.1447, found 187.1445.

***N*-(3-Nitrobutan-2-yl)cyclohexanamine** (**5b**). Yellow-brown oil. Yield 90% (0.181 g). ν_{max} cm^{-1} 3368; 1555. ^1H NMR (300

[120] Lalonde, J. J.; Bergbreiter, D. E. ; Newcomb, M. *J. Org. Chem.* **1986**, *51*, 1369−1372.
[121] Braddock, D. C.; Hii, K. K.; Brown, J. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1720−1723.

MHz, $CDCl_3$) δ: 4.53-4.37 (m, 2H), 3.28-3.14 (m, 2H), 2.38-2.25 (m, 2H), 1.49 (d, *J* = 6.7 Hz, 3H, minor isomer), 1.45 (d, *J* = 6.7 Hz, 3H, major isomer), 1.79-1.43 (m, 12H), 1.07 (d, *J* = 6.5 Hz, 3H, minor), 1.06 (d, *J* = 6.5 Hz, 3H, major), 1.26-0.95 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 87.7 (major isomer), 86.4 (minor isomer), 53.8 (major), 53.7 (minor), 53.0 (2C), 34.0 (major), 33.8 (minor), 33.4 (minor), 33.2 (major), 25.7 (2C), 24.6 (major), 24.5 (2C, minor), 24.3 (major), 17.2 (minor), 16.6 (major), 14.5 (major), 14.4 (minor). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{10}H_{21}N_2O_2$ 201.1603, found 201.1609.

***N*-(4-Methyl-1-nitropentan-2-yl)cyclohexanamine** (**5c**). Yellow-brown oil. Yield 90% (0.205 g). ν_{max} cm^{-1} 3363; 1556. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.38-4.26 (m, 2H), 3.39-3.30 (m, 1H), 2.42-2.51 (m, 1H), 1.51-1.88 (m, 7H), 0.98-1.38 (m, 7H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 79.8, 53.9, 51.8, 42.9, 34.2, 33.7, 25.9, 24.8 (2C), 24.7, 22.8, 22.2. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{25}N_2O_2$ 229.1916, found 229.1999.

***N*-(5-Methyl-2-nitrohexan-3-yl)cyclohexanamine** (**5d**). Yellow-brown oil. Yield 89% (0.217 g). ν_{max} cm^{-1} 3368; 1555. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.58-4.49 (m, 2H), 3.21-3.11

(m, 2H), 2.96-2.81 (m, 2H), 2.45-2.34 (m, 2H), 2.12-2.05 (m, 4H), 1.79-1.50 (m, 12H), 1.42 (d, *J* = 6.7, 3H, minor isomer), 1.41 (d, *J* = 6.7, 3H, major isomer), 1.27-1.06 (m, 10H), 0.94-0.88 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 85.7 (minor isomer), 84.7 (major isomer), 56.1 (major), 56.0 (minor), 54.4 (minor), 54.1 (major), 41.5 (major), 40.2 (minor), 34.4 (2C, major), 34.2 (2C, minor), 25.9 (2C), 24.8 (2C, major), 24.7 (2C, minor), 24.6 (minor), 24.4 (major), 23.0 (major), 22.7 (minor), 22.3 (major), 22.1 (minor), 13.4 (major), 13.1 (minor). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{27}N_2O_2$ 243.2073, found 243.2065.

9.4 ***Stereochemical studies: general procedure for One-pot synthesis of β-nitro α-trifluoromethyl amines 3,3'k-m:*** A stirred equimolar solution (1 mmol) of trifluoroacetaldehyde ethyl hemiacetal (90% aq. solution, 160 mg) and (*R*)-1-phenylethylamine **6** (122 mg) was heated at 120 °C under solvent-free conditions in a flask fitted with a calcium chloride tube. After 4 h the reaction mixture was cooled to room temperature and $ZrCl_4$ (0.5 mmol, 116 mg) and nitro compound **2a-c** (5 mmol) were added under stirring. The reactions were followed by ^{1}H and ^{19}F NMR (3-18 h, see Table 5). Then, after

addition of water (5 mL), the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The crude mixtures were purified by flash chromatography on silica gel.

(2*S*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]propan-2-amine (**3k**). Yellow pale oil (64%, 168 mg). ν_{max} cm^{-1} 3328, 1570 cm^{-1}- $[\alpha]_D^{25}$ –79.0 (*c* = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.39 (m, 5H), 4.65 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.45 (dd, *J* = 12.8, 7.8 Hz, 1H), 4.05 (q, *J* = 6.4 Hz, 1H), 3.91–4.02 (m, 1H), 1.79 (br, 1H), 1.36 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 128.6 (2C), 127.7, 126.6 (2C), 124.9 (q, *J* = 283.4 Hz), 73.9, 56.03 (q, *J* = 28.6 Hz), 55.5, 23.22. ^{19}F NMR (282 MHz, $CDCl_3$) δ –77.3 (d, *J* = 7.0 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{11}H_{14}F_3N_2O_2$ 263.1007, found 263.1011; *m*/*z* $[M+Na]^+$ calcd for $C_{11}H_{13}F_3N_2NaO_2$ 285.0827, found 285.0834.

(2*R*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]propan-2-amine (**3'k**)

Yellow pale oil (16%, 42 mg). $[\alpha]_D^{25}$ –15.3 (*c* = 3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.38 (m, 5H), 4.44 (dd, *J* =

12.6, 4.3, 1H), 4.29 (dd, *J* = 12.6, 9.3, 1H), 4.11 (q, *J* = 6.4, 1H), 3.59–3.80 (m, 1H), 1.77 (br, 1H), 1.32 (d, *J* = 6.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 128.7 (2C), 127.9, 127.0 (2C), 125.3 (q, *J* = 286.2 Hz), 74.7, 55.9, 55.2 (q, *J* = 28.8 Hz), 24.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ –75.9 (d, *J* = 6.6 Hz). HRMS: *m/z* $[M + H]^+$ calcd. for $C_{11}H_{14}F_3N_2O_2$ 263.1007, found 263.1002; *m/z* $[M+Na]^+$calcd for $C_{11}H_{13}F_3N_2NaO_2$ 285.0827, found 285.0821.

Synthesis of *syn,anti*-**3,3'l.** Yield: 76% (210 mg). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 92:8). ν_{max} cm^{-1} 3990, 1550 cm^{-1}. **(2*S*,3*R*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]butan-2-amine** (*syn*-**3l**). Yellow oil (17%, 46 mg). $[\alpha]_D^{25}$ –8.8 (*c* = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.28 (m, 5H), 4.55–4.45 (m, 1H), 3.89 (q, *J* = 6.3 Hz, 1H), 3.65–3.78 (m, 1H), 1.74 (br, 1H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 128.6 (2C), 127.7, 127.1 (2C), 124.3 (q, *J* = 284.9 Hz), 80.4, 58.4 (q, *J* = 27.6 Hz), 55.9, 22.7, 12.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.6 (d, *J* = 6.9 Hz). HRMS: *m/z* $[M + H]^+$ calcd. for $C_{12}H_{16}F_3N_2O_2$ 277.1164, found 277.1159; *m/z* $[M+Na]^+$calcd for $C_{12}H_{15}F_3N_2NaO_2$ 299.0983, found 299.0978.

(2*S*,3*S*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]butan-2-amine (*anti*-**3l**). Yellow oil (37%, 105 mg). $[\alpha]_D^{25}$ –7.8 (*c* = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.28 (m, 5H), 4.58–4.67 (m, 1H), 4.12–4.01 (m, 1H), 3.90 (q, *J* = 6.3 Hz, 1H), 1.89 (br, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 128.6 (2C), 127.7 (2C), 126.7, 124.8 (q, *J* = 284.1 Hz), 80.6, 58.7 (q, *J* = 28.3 Hz), 55.8, 22.8, 12.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ –75.10 (d, *J* = 7.4 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{16}F_3N_2O_2$ 277.1164, found 277.1168; *m*/*z* $[M+Na]^+$ calcd for $C_{12}H_{15}F_3N_2NaO_2$ 299.0983, found 299.0977.

(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]butan-2-amine (*syn*-**3'l**)

Yellow oil (7%, 21 mg). $[\alpha]_D^{25}$ –16.4 (*c* = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.17 (m, 5H), 4.50–4.59 (m, 1H), 3.89 (q, *J* = 6.4 Hz, 1H), 3.11–3.26 (m, 1H), 1.57 (br, 1H), 1.42 (d, *J* = 7.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 127.8 (2C), 127.3 (2C), 126.5, 124.3 (q, *J* = 284.9 Hz), 82.2, 59.6 (q, *J* = 28.5 Hz), 56.1, 22.7, 16.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.1 (d, *J* = 6.7 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{16}F_3N_2O_2$ 277.1164, found 277.1171;

m/*z* $[M+Na]^+$ calcd for $C_{12}H_{15}F_3N_2NaO_2$ 299.0983, found 299.0986.

(2*R*,3*R*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]butan-2-amine (*anti*-**3'l**). Yellow oil (15%, 38 mg). $[\alpha]_D^{25}$ –8.0 (*c* = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.30 (m, 5H), 4.63–4.74 (m, 1H), 3.98 (q, *J* = 6.4 Hz, 1H), 4.67–4.58 (m, 1H), 1.75 (br, 1H), 1.60 (d, *J* = 8.0 Hz, 3H), 1.24 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 128.6 (2C), 127.7, 126.7 (2C), 124.6 (q, *J* = 284.5 Hz), 82.9, 59.3 (q, *J* = 28.4 Hz), 56.1, 22.7, 16.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.1 (d, *J* = 7.1 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{16}F_3N_2O_2$ 277.1164, found 277.1165; *m*/*z* $[M+Na]^+$ calcd for $C_{12}H_{15}F_3N_2NaO_2$ 299.0983, found 299.0984.

Synthesis of *syn*,*anti*- **3**,**3'm**. Yield: 72% (210 mg). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 92:8). ν_{max} cm^{-1} 3350, 1560 cm^{-1}. **(2*S*,3*R*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]pentan-2-am*ine*** ***(syn*-3m)**. Yellow oil (16%, 44 mg). $[\alpha]_D^{25}$ –14.5 (*c* = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.37 (m, 5H), 4.38–4.43 (m, 1H), 4.05 (q, *J* = 6.4, 1H), 3.56–3.62 (m, 1H), 1.95–2.07 (m, 2H), 1.56 (br, 1H), 1.37 (d, *J* = 6.5, 3H), 0.93 (t,

J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 128.7 (2C), 127.2 (2C), 126.5, 124.3 (q, *J* = 284.7 Hz), 88.5, 58.6 (q, *J* = 28.4 Hz), 55.9, 24.6, 24.2, 10.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ –75.7 (d, *J* = 7.4 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ 291.1132, found 291.1137.

(2*S*,3*S*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]pentan-2-amine (*anti*-**3m**). Yellow oil (32%, 90 mg). $[\alpha]_D^{25}$ –9.8 (*c* = 4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.35 (m, 5H), 4.52–4.57 (m, 1H), 4.05 (q, *J* = 6.4, 1H), 3.79–3.89 (m, 1H), 1.92–2.05 (m, 2H), 1.69 (br, 1H), 1.34 (d, *J* = 6.5, 3H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 128.7 (2C), 127.7, 126.8 (2C), 124.5 (q, *J* = 284.4 Hz), 88.0, 59.0 (q, *J* = 28.2 Hz), 56.1, 23.0, 22.8, 10.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ –75.7 (d, *J* = 7.4 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ 291.1132, found 291.1125.

(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]pentan-2-amine (*syn*-**3'm**). Yellow oil (8%, 25 mg). $[\alpha]_D^{25}$ +17.1 (*c* = 4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.30 (m, 5H), 4.38–4.41 (m, 1H), 4.05 (q, *J* = 6.4 Hz, 1H), 3.05–3.15 (m, 1H), 1.57–1.67 (m, 2H), 1.48 (br, 1H), 1.30

(d, J = 6.5 Hz, 3H), 0.74 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 128.6 (2C), 127.8, 127.5 (2C), 124.3 (q, J = 284.6 Hz), 88.5, 58.0 (q, J = 27.8 Hz), 55.8, 24.7, 24.2, 10.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ –73.6 (d, J = 6.9 Hz). HRMS: m/z $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ 291.1132, found 291.1128.

(2*R*,3*R*)-1,1,1-Trifluoro-3-nitro-*N*-[(1*R*)-1-phenylethyl]pentan-2-amine (*anti*-**3′m**).Yellow oil (16%, 50 mg). $[\alpha]_D^{25}$ –13.6 (c = 4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.37 (m, 5H), 4.57–4.62 (m, 1H), 4.10 (q, J = 6.4, 1H), 3.56–3.64 (m, 1H), 2.12–2.25 (m, 2H), 1.70 (br, 1H), 1.32 (d, J = 6.6, 3H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 128.3 (2C), 127.8, 126.8 (2C), 124.9 (q, J = 284.2 Hz), 90.1, 59.4 (q, J = 28.6 Hz), 56.3, 22.0, 21.8, 10.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ –74.7 (d, J = 6.8 Hz). HRMS: m/z $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ $[M+H]^+$: 291.1132, found 291.1139.

Chapter 10

Reactivity of ethyl nitroacetate

10.1 ***General procedure for the synthesis of trifluoromethyl β-amino α-nitro esters*** **7a-e*:*** A mixture of (*E*)-trifluoromethyl aldimine **1a-f** (1.1 mmol) and ethyl nitroacetate **2d** (1 mmol), were kept stirring overnight under solvent-free conditions at room temperature. The obtained crude mixtures were recovered and used without any further purification in the subsequent reaction.

Ethyl 3-(cyclohexylamino)-4,4,4-trifluoro-2-nitrobutanoate (*syn*, *anti*-**7a**): Yellow-brown oil. Yield 95% (0.295g). ν_{max} cm^{-1} 3371; 1755; 1571. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.36 (d, *J*=5.9Hz, 1H, *anti* isomer), 5.22 (d, *J*=6.8, 1H, *syn* isomer), 4.52 – 3.95 (m, 6H), 2.71 – 2.65 (m, 2H), 1.99 (d, *J*=11.5 Hz, 1H), 1.92 – 1.49 (m, 9H), 1.33 (t, *J*=7.2 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H), 1.26 – 0.87 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7 (2C), 24.2 (2C), 24.4 (2C), 25.7 (2C), 32.4, 32.6, 33.9 (2C), 54.7, 55.0, 57.2 (q, *J* = 29.5 Hz), 57.5 (q, *J* = 29.4 Hz), 63.3, 63.8, 86.1, 87.0,124.7 (q, *J* = 286.0 Hz), 124.8 (q, *J* = 285.2

Hz), 161.7, 162.0. HRMS: *m/z* $[M + H]^+$ calcd. for $C_{12}H_{20}F_3N_2O_4$ 313.1370, found 313.1378.

Ethyl 3-(benzylamino)-4,4,4-trifluoro-2-nitrobutanoate (*syn*, *anti*-**7b**): Yellow oil. Yield 95% (0.305g). ν_{max} cm^{-1} 3381; 1754; 1574. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.24 (m, 10H), 5.46 (d, *J*=5.5 Hz, 1H, *anti* isomer), 5.31 (d, *J*=6.4 Hz, 1H, *syn* isomer), 4.34 (q, *J*=7.1 Hz, 4H), 4.17 – 4.02 (m, 3H), 3.99 – 3.83 (m, 3H), 2.56 (br, 1H), 2.26 (br, 1H), 1.32 (t, *J*=7.2 Hz, 3H), 1.28 (t, *J*=7.1Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.7, 161.6, 138.2, 138.1, 128.7 (2C), 128.5 (2C), 128.4 (2C), 128.2, 128.1, 127.6, 127.5, 124.8 (q, *J*=285.9 Hz), 124.7 (q, *J*=286.7 Hz), 86.6, 85.4, 63.7, 63.4, 59.5 (q, *J*=29.5 Hz), 59.3 (q, *J*=29.5 Hz), 52.3, 52.2, 13.6 (2C). HRMS: *m/z* $[M + H]^+$ calcd. for $C_{13}H_{16}F_3N_2O_4$ 321.1057, found 321.1053.

Ethyl 3-(cyclopentylamino)-4,4,4-trifluoro-2-nitrobutanoate (*syn*, *anti*-**7c**): Yellow-brown oil. Yield 90% (0.265g). ν_{max} cm^{-1} 3380; 1743; 1565. ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.35 (d, *J*=5.6 Hz, 1H, *anti* isomer), 5.19 (d, *J*=6.8 Hz, 1H, *syn* isomer), 4.26 (q, *J*=7.2, 4H), 4.18 – 4.00 (m, 2H), 3.51 – 3.38 (m, 1H), 3.38 – 3.26 (m, 2H), 2.09 (d, *J*=11.2, 1H), 1.97 – 1.41 (m, 16H), 1.28 (t, *J*=7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.9,

161.7, 124.9 (q, *J*=285.7 Hz), 124.7 (q, *J*=286.6 Hz), 86.8, 85.9, 63.6, 63.2, 58.9 (q, *J*=29.3 Hz), 57.8 (q, *J*=26.3 Hz), 52.2 (2C), 33.9, 33.8, 30.8 (2C), 23.8, 23.3 (2C), 23.2, 13.6 (2C). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{11}H_{18}F_3N_2O_4$ 299.1213, found 299.1216.

Ethyl 4,4,4-trifluoro-2-nitro-3-(pentylamino)butanoate (*syn*, *anti*-**7d**): Yellow-brown oil. Yield 80% (0.238g). ν_{max} cm^{-1} 3373; 1755; 1553. ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.36 (d, *J*=6.0 Hz, 1H, *anti* isomer), 5.21 (d, *J*=6.8 Hz, 1H, *syn* isomer), 4.31 (q, *J*=7.1 Hz, 2H, *anti*), 4.30 (q, *J*=7.1, 2H, *syn*), 4.19 – 4.09 (m, 1H, *anti*), 4.08 – 3.99 (m, 1H, *syn*), 2.92 – 2.81 (m, 3H), 2.72 – 2.53 (m, 2H), 1.94 (br, 1H), 1.72 – 1.48 (m, 4H), 1.48 – 1.35 (m, 4H), 1.34 – 1.19 (m, 10H), 0.86 (t, *J*=6.7, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.9, 161.6, 124.9 (q, *J*=285.7), 124.7 (q, *J*=286.3 Hz), 86.8, 85.8, 63.6, 63.3, 60.7 (q, *J*=29.3 Hz), 60.3 (q, *J*=28.0 Hz), 48.9, 48.8, 29.9 (2C), 28.9 (2C), 22.3(2C), 13.8(2C), 13.7 (2C). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{11}H_{20}F_3N_2O_4$ 301.1370, found 301.1368.

Ethyl 4,4,4-trifluoro-3-[(3-methoxy-3-oxopropyl)amino]-2-nitrobutanoate (*syn*, *anti*-**7e**): Yellow-brown oil. Yield 95% (0.302g). ν_{max} cm^{-1} 3364; 1743; 1684; 1571. ^1H NMR ($CDCl_3$,

300 MHz) δ: 5.34 (d, *J*=6.3 Hz, 1H, *anti* isomer), 5.22 (d, *J*=6.6 Hz, 1H, *syn* isomer), 4.31 (q, *J*=7.1 Hz, 2H, *anti*), 4.30 (d, *J*=7.1 Hz, 2H, *syn*), 4.18 – 3.97 (m, 2H), 3.66 (s, *J*=4.2 Hz, 6H), 3.31 – 3.14 (m, 4H), 3.00 – 2.81 (m, 4H), 2.74 (br, 1H), 2.27 (br, 1H), 1.30 (t, *J*=7.2, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.4, 171.9, 161.7, 161.5, 124.6 (q, *J*=285.4 Hz), 124.5 (q, *J*=286.1 Hz), 86.7, 85.5, 63.8, 63.4, 60.8 (q, *J*=29.7 Hz), 60.5 (q, *J*=29.7 Hz), 51.6 (2C), 44.4 (2C), 35.1, 35.0, 13.7 (2C). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{10}H_{16}F_3N_2O_6$ 317.0955, found 317.0954.

10.2 *$ZrCl_4$-catalysed synthesis of* *syn*, *anti*-7f. To a mixture of trifluoromethyl (*E*)-aldimine **1f** (1.1 mmol) and ethyl nitroacetate (1 mmol), $ZrCl_4$ (0.5 mmol) was added. The reaction was performed under solvent-free conditions and stirred at room temperature (1.5-24 h). Then, after addition of water (5 mL), the crude mixture was extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The obtained crude mixture were used without any further purification in the subsequent nitro reduction reaction. **Ethyl 4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]-2-nitrobutanoate** (*syn*, *anti*-**7f**):

Brown oil. Yield 80% (0.269 g). ν_{max} cm^{-1} 3364; 1758; 1563. ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.85 – 6.69 (m, 8H), 5.60 (d, *J*=4.4 Hz, 1H, *anti* isomer), 5.38 (d, *J*=5.9 Hz, 1H, *syn* isomer), 5.14 – 5.00 (m, 1H), 4.88 – 4.70 (m, 1H), 4.60 (d, *J*=11.1 Hz, 2H), 4.37 – 4.12 (m, 4H), 3.75 (s, 6H), 1.26 (t, *J*=7.2 Hz, 3H, *syn*), 1.17 (t, *J*=7.2 Hz, 3H, *anti*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.6, 161.4, 154.2, 154.1, 138.5, 138.2, 124.0 (d, *J*=284.7 Hz), 123.83 (q, *J*=285.3 Hz), 116.6 (2C), 116.3 (2C), 114.9 (2C), 114.8(2C), 85.4, 84.3, 64.2, 63.8, 58.7 (q, *J*=31.2 Hz), 58.3 (q, *J*=31.0, Hz), 55.5 (2C), 13.6 (2C). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{16}F_3N_2O_5$ 337.1006, found 337.1008.

10.3 ***Stereochemical studies: one-pot synthesis of*** *syn*, *anti*-**7,7′g**. A stirred equimolar solution (1 mmol) of trifluoroacetaldehyde ethyl hemiacetal (90% aq. solution, 160 mg) and (*R*)-1-phenylethylamine **6** (122 mg) was heated at 120 °C under solvent-free conditions in a flask fitted with a calcium chloride tube. After 4 h the reaction mixture was cooled to room temperature and $ZrCl_4$ (0.5 mmol, 116 mg) and nitro compound **2d** (1 mmol) were added under stirring. After 24 h 5 ml of water were added, the crude mixture was extracted three times with Et_2O. The collected organic layers were dried over

anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The crude mixtures was used without any further purification in the subsequent nitro reduction reaction. **Ethyl 4,4,4-trifluoro-2-nitro-3-{[(1*R*)-1-phenylethyl]amino}butanoate** (*syn*, *anti*-**7,7′g**)**.** Yellow oil. Yield 85% (0.284 g). ν_{max} cm^{-1} 3378; 1748; 1554. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.19 (m, 20H), 5.42 (d, *J*=4.9 Hz, 1H, *anti* major isomer), 5.34 (d, *J*=4.6 Hz, 1H, *anti* minor isomer), 5.28 (d, *J*=5.7 Hz, 1H, *syn* major isomer), 5.15 (d, *J*=5.6 Hz, 1H, *syn* minor isomer), 4.45 – 4.26 (m, 8H), 4.23 – 3.94 (m, 7H), 3.82 – 3.74 (m, 1H), 2.27 (br, 4H), 1.40 – 1.28 (m, 21H), 1.20 (t, *J*=7.1 Hz, 3H, *anti* minor isomer). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (2C), 161.6 (2C), 143.9, 143.6, 142.5, 142.2, 128.8 (2C), 128.6 (4C), 128.4 (2C), 127.8 (2C), 127.7 (2C), 127.3 (2C), 127.1 (2C), 126.7, 126.6 (3C), 124.7 (q, *J*=247.5 Hz, 2C), 124.6 (q, *J*=252.2 Hz, 2C), 86.4, 86.0, 85.3 (2C), 63.9, 63.7, 63.5, 63.3, 57.5 (q, *J*=29.8 Hz, 2C), 57.4 (q, *J*=29.5 Hz, 2C), 55.9, 55.7 (2C), 55.6, 24.8, 24.7, 23.1 (2C), 13.70 (2C), 13.6 (2C). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{18}F_3N_2O_4$ 335.1213, found 335.1217.

10.4 *General procedure for the synthesis of trifluoromethyl (E)-aldimines functionalised with α-amino esters* 9a-f

A solution of 1 mmol of α-amino ester and 1.5 mmol of trifluoroacetaldehyde ethyl hemiacetal in anhydrous toluene (5 ml) is added under Ar into a round-bottom flask containing previously activated 4 Å molecular sieves (3 g). The reaction is stirred at reflux for 1 h. The crude mixture is filtered on filter paper. After solvent removal, the product is obtained and used without any purification. Compounds **9a**,**d** were already reported in the literature [110]

Methyl (2*S*,3*S*)-3-methyl-2-{[(1*E*)-2,2,2-trifluoroethylidene]amino}pentanoate (**9b**)**.** Yellow orange oil, 74% (0.166 g). ν_{max} cm^{-1} 1738, 1686. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.81 − 0.91 (m, 6 H), 1.02 − 1.50 (m, 2 H), 2.01 − 2.15 (m, 1 H), 3.72 (s, 3 H), 3.84 (d, *J* = 6.5 Hz, 1 H), 7.62 (q, *J* = 3.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 10.9, 15.4, 24.8, 37.9, 52.1, 76.7, 118.4 (q, *J* = 275.1 Hz), 151.6 (q, *J* = 38.5 Hz), 170.3. ^{19}F NMR ($CDCl_3$ 282 MHz) δ: -71.5 (d, *J*=3.0 Hz). HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{14}F_3NNaO_2$ $(M + Na)^+$: 248.0874, found 248.0871.

Methyl (2S)-4-methyl-2-{[(1E)-2,2,2-trifluoroethylidene]amino}pentanoate (**9c**)**.** Yellow orange oil, 72% (0.161 g). ν_{max} 1736, 1686. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.89 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.44 − 1.55 (m, 1 H), 1.81 (t, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H), 4.16 (t, *J* = 7.2 Hz, 1 H), 7.66 − 7.70 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 21.3, 22.7, 24.3, 41.4, 52.4, 69.5, 118.5 (q, *J* = 275.1 Hz), 151.4 (q, *J* = 38.6 Hz), 170.7. ^{19}F NMR ($CDCl_3$ 282 MHz) δ: -71.46 (d, *J* = 3.3 Hz). HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{14}F_3NNaO_2$ 248.0874, found 248.0878.

Methyl (2*S*)-3-phenyl-2-{[(1*E*)-2,2,2-trifluoroethylidene]amino}propanoate (**9e**)**.** Yellow orange oil, 73% (0.190 g). ν_{max} cm^{-1} 1737, 1683. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.03 − 3.40 (m, 2 H), 3.79 (s, 3 H), 4.12 − 4.17 (m, 1 H), 7.09 − 7.33 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 38.6, 52.3, 72.8, 118.1 (q, *J* = 275.4 Hz), 127.0, 128.4, 129.4, 135.6, 152.0 (q, *J* = 38.5 Hz), 174.2. ^{19}F NMR ($CDCl_3$ 282 MHz) δ: -71.4 (d, *J* = 3.0 Hz). HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{12}F_3NNaO_2$: 282.0718; found: 282.0725.

Methyl (2*S*,3*R*)-3-*tert*-butoxy-2-{[(1*E*)-2,2,2-trifluoroethylidene]amino}butanoate (**9f**)**.** Yellow oil, 74%

(0.120 g). ν_{max} cm^{-1} 1735, 1690. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (q, *J*=6.7 Hz, 1H), 4.08 (dq, *J*=8.1 Hz, 6.1 Hz, 1H), 3.82 (d, *J*=8.1 Hz, 1H), 3.77 (s, 3H), 1.21 (d, *J*=6.1, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.5, 152.8 (q, *J*=38.5 Hz), 120.4 (q, *J*=282.4 Hz), 78.2, 74.7, 67.3, 52.4, 28.6 (3C), 20.5. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -71.6 (d, *J*=3.1 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{11}H_{19}F_3NO_3$ 370.1312, found 370.1311.

10.5 ***General procedure for $AlCl_3$-catalysed aza-Henry reactions between trifluoromethyl aldimines derived from α-amino esters and ethyl nitroacetate. Synthesis of*** **10,10′a-d** and **11.** To a mixture of trifluoromethyl (*E*)-aldimine **9a-d** (1.3 mmol) and ethyl nitroacetate (1 mmol), $AlCl_3$ (0.5 mmol) was added. The reactions were performed under solvent-free conditions and stirred at room temperature during 2 h. Then, after addition of water (5 mL), the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The obtained crude mixtures were used without any further purification in the subsequent nitro reduction reaction.

Ethyl 4,4,4-trifluoro-3-{[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}-2-nitrobutanoate (***syn***, ***anti*-10,10′a**). Yellow-brown oil. Yield 80% (0.276 g). ν_{max} cm^{-1} 3373; 1743; 1573. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.46 (d, *J*=4.3 Hz, 1H, *anti* major isomer), 5.35 (d, *J*=6.4 Hz, 1H, *anti* minor isomer), 5.28 (d, *J*=4.9 Hz, 1H, *syn* major isomer), 5.24 (d, *J*=6.2 Hz, 1H, *syn* minor isomer), 4.42 – 4.19 (m, 10H), 4.14 – 3.98 (m, 2H), 3.72 (s, 6H, minor isomers), 3.70 (s, 6H, major isomers), 3.33 – 3.23 (m, 2H, major isomers), 3.22 – 3.14 (m, 1H, minor isomer), 3.14 – 3.06 (m, 1H, minor isomer), 2.79 (br, 2H), 2.66 (br, 2H), 2.05 – 1.91 (m, 2H, major isomers), 1.91 – 1.78 (m, 2H, minor isomers), 1.34 (t, *J*=7.2 Hz, 6H, minor isomers), 1.33 (t, *J*=7.2 Hz, 6H, major isomers), 0.95 (d, *J*=6.8 Hz, 12H, major isomers), 0.91 (d, *J*=3.2 Hz, 6H, minor isomers), 0.88 (d, *J*=3.2 Hz, 6H, minor isomers). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8 (2C), 173.7 (2C), 161.8 (major isomer), 161.7 (major) , 161.6 (minor isomer), 161.4 (minor), 124.21 (q, *J*=284.4 Hz, 4C), 86.9 (minor), 85.7 (2C), 84.8 (major), 67.4 (2C), 67.0 (minor), 66.9 (minor), 66.8 (major), 64.0 (minor), 63.8 (minor), 63.7 (major), 63.4 (major), 61.1 (q, *J*=29.8 Hz, minor), 60.95 (q, *J*=29.8 Hz, minor), 60.2 (q, *J*=30.1 Hz, major), 60.18 (q, *J*=30.2 Hz, major), 51.8 (minor), 51.7 (2C), 51.6 (major), 32.62 (minor, 2C), 32.1 (major), 31.9 (major), 18.9 (2C), 18.8 (2C), 17.7

(minor), 17.6 (2C, major), 17.5 (minor), 13.8 (minor), 13.7 (minor), 13.60 (2C, major). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -72.5 (d, *J*=6.8 Hz, minor isomer), -73.5 (d, *J*=6.6 Hz, minor), -73.6 (d, *J*=6.8 Hz, major isomer), -74.0 (d, *J*=7.0, major). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{20}F_3N_2O_6$ 345.1268, found 345.1265.

Methyl (2*S*,3*S*)-2-{[3-ethoxy-2-nitro-3-oxo-1-(trifluoromethyl)propyl]amino}-3-methylpentanoate (*syn*, *anti*-10,10′b). Yellow-brown oil. Yield 75% (0.276 g). ν_{max} cm^{-1} 3385; 1756; 1568. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.46 (d, *J*=4.3 Hz, 1H, *anti* major isomer), 5.34 (d, *J*=6.4 Hz, 1H, *anti* minor isomer), 5.29 (d, *J*=4.9, 1H, *syn* major isomer), 5.24 (d, *J*=6.3, 1H, *syn* minor isomer), 4.42 – 4.29 (m, 8H), 4.29 – 4.18 (m, 2H), 4.12 – 3.99 (m, 2H), 3.72 (s, 6H, minor isomers), 3.70 (s, 6H, major isomers), 3.41 – 3.33 (m, 2H), 3.28 – 3.17 (m, 2H), 2.82 – 2.72 (m, 2H), 2.71 – 2.59 (m, 2H), 1.80 – 1.67 (m, 2H), 1.67 – 1.53 (m, 2H), 1.52 – 1.38 (m, 4H), 1.37 – 1.29 (m, 12H), 1.25 – 1.05 (m, 4H), 0.96 – 0.78 (m, 24H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.0 (4C), 161.9 (major isomer), 161.8 (2C, minor isomers), 161.7 (major), 124.17 (q, *J*=287.3 Hz, 4C), 86.8 (minor), 86.6 (minor), 85.6 (major), 84.6 (major), 66.2 (minor), 66.0 (minor), 65.8 (2C, major isomers), 64.1 (major),

64.0 (minor), 63.8 (major), 63.5 (minor), 61.0 (q, *J*=29.9 Hz, minor), 60.4 (q, *J*=29.7, minor), 60.0 (q, *J*=30.2, Hz, major), 59,9 (q, *J*=30.3 Hz, major), 51.9 (minor), 51.8 (3C), 39.4 (2C, minor isomers), 38.9 (major), 38.6 (major), 24.7 (2C, major isomers), 24.6 (minor), 24.5 (minor), 15.4 (2C, major isomers), 15.2 (2C, minor isomers), 13.8 (2C), 13.7 (minor), 13.6 (major), 11.4 (2C, major isomers), 11.3 (2C, minor isomers). ^{19}F NMR (282 MHz, $CDCl_3$) δ: -72.5 (d, *J*=6.7 Hz, minor isomer), -73.4 (d, *J*=6.3 Hz, minor), -73.5 (d, *J*=6.4 Hz, major isomer), -74.0 (d, *J*=6.7 Hz, major). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_6$ 359.1424, found 359.1427.

Methyl (2*S*)-2-{[3-ethoxy-2-nitro-3-oxo-1-(trifluoromethyl)propyl]amino}-4-methylpentanoate (*syn*, *anti*-10,10′c). Yellow-brown oil. Yield 72% (0.258 g). ν_{max} cm^{-1} 3365;1758; 1555. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.44 (d, *J*=4.5 Hz, 1H, *anti* major isomer), 5.35 (d, *J*=6.2 Hz, 1H, *anti* minor isomer), 5.28 (d, *J*=5.0 Hz, 1H, *syn* major isomer), 5.23 (d, *J*=6.1 Hz, 1H, *syn* minor isomer), 4.37 – 4.21 (m, 8H), 4.15 – 3.98 (m, 4H), 3.68 (s, 6H, minor isomers), 3.67 (s, 6H, major isomers), 3.56 – 3.47 (m, 2H), 3.41 – 3.26 (m, 2H), 2.70 – 2.59 (m, 2H), 2.57 – 2.42 (m, 2H), 1.77 – 1.20 (m, 24H), 0.91 – 0.80 (m, 24H). ^{13}C NMR ($CDCl_3$,75 MHz) δ: 174.4 (4C), 162.4

(4C), 125.1 (q, *J*=285.1 Hz, 2C), 123.91 (q, *J*=283.7 Hz, 2C), 86.7 (minor isomer), 85.9 (2C), 84.6 (major isomer), 62.3 (major), 62.2 (minor), 61.7 (major), 61.5 (minor), 59.3 (2C, major isomers),59.0 (d, *J*=27.3 Hz, 2C, minor isomers), 57.9 (2C, minor isomers) 58.8 (q, *J*=28.4 Hz, 2C, major isomers),53.0 (minor), 51.9 (minor), 51.8 (2C, major isomers), 43.8 (2C, major isomers), 41.6 (2C, minor isomers), 24.6 (minor), 24.5 (2C), 24.4 (major), 22.7 (4C), 22.0 (minor), 21.9 (minor), 21.8 (2C, major isomers), 13.8 (4C). ^{19}F NMR (282 MHz, $CDCl_3$) δ = 72.5 (d, *J*=7.2 Hz, minor isomer), -73.3 (d, *J*=6.8 Hz, minor), -73.4 (d, *J*=7.2 Hz, major isomer), -73.7(d, *J*=7.0 Hz, major). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_6$ 359.1424, found 359.1422.

Ethy l 4,4,4-trifluoro-3-{[(1*S*)-1-(methoxycarbonyl)-3-(methylthio)propyl]amino}-2-nitrobutanoate (***syn***, ***anti*-10,10′d).** Brown oil. Yield 70% (0.265 g). ν_{max} cm^{-1} 3395; 1765; 1568. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.41 (d, *J*=4.4 Hz, 1H, *anti* major isomer), 5.29 (d, *J*=6.4 Hz, 1H, *anti* minor isomer), 5.24 (d, *J*=4.8 Hz, 1H, *syn* major isomer), 5.19 (d, *J*=5.8 Hz, 1H, *syn* minor isomer), 4.35 – 4.17 (m, 8H), 4.11 – 3.96 (m, 4H), 3.68 (s, 6H, minor isomers), 3.66 (s, 3H, major), 3.65 (s, 3H, major), 3.62 – 3.49 (m, 4H), 2.91 – 2.66 (m, 4H),

2.60 – 2.46 (m, 4H, minor isomers), 2.42 (t, *J*=7.0 Hz, 4H, major isomers), 2.06 – 1.98 (m, 12H), 1.98 – 1.62 (m, 8H), 1.33 – 1.21 (m, 12H). ^{13}C NMR ($CDCl_3$,75 MHz) δ: 174.9 (2C, minor isomers), 173.9 (2C, major isomers), 161.8 (2C), 161.6 (2C), 124.6 (q, *J*=286.2 Hz, 2C), 124.5 (q, *J*=286.4 Hz, 2C), 87.1 (minor), 85.9 (2C), 84.9 (major),67.6 (major), 67.2 (major), 67.1 (minor), 67.0 (minor), 64.2 (minor), 64.0 (major), 63.8 (minor), 63.6 (major), 61.3 (q, *J*=29.8 Hz, 2C), 61.1 (q, *J*=29.8 Hz, 2C), 52.6 (major), 52.1 (minor), 51.9 (minor), 51.8 (major), 32.3 (minor), 32.1 (minor), 31.2 (2C, major isomers), 30.2 (minor), 30.1 (minor), 29.9 (2C, major isomers), 15.3 (minor), 15.1 (minor), 15.0 (2C, major isomers), 13.9 (2C), 13.8 (2C). ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: -72.1 (d, *J*=6.8 Hz, minor), -73.1 (d, *J*=6.6 Hz, minor), -73.2 (d, *J*=6.8 Hz, major), -73.6 (d, *J*=7.0 Hz, major). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{20}F_3N_2O_6S$ 377.0989, found 377.0991.

Ethyl 3-amino-4,4,4-trifluoro-2-nitrobutanoate (***syn***, ***anti*-11**)**.** Yellow oil. Yield 75% (0.258 g). ν_{max} cm^{-1} 3396; 3343; 1755; 1555. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.40 (d, *J*=5.7 Hz, 1H, *anti* isomer), 5.30 (d, *J*=4.5 Hz, 1H, *syn* isomer), 5.25 – 4.95 (m, 1H), 4.91 – 4.81 (m, 1H), 4.41 – 4.30 (m, 4H), 3.75 – 3.69 (m, 4H), 1.36 – 1.29 (m, 6H). ^{13}C NMR ($CDCl_3$,75 MHz)

δ: 162.2, 161.9, 122.8 (q, *J*=282.5 Hz), 122.7 (q, *J*=282.7 Hz), 85.7, 83.9, 70.0 (q, *J*=33.3 Hz), 69.6 (q, *J*=33.5 Hz), 64.4, 64.3, 13.7, 13.6. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: -76.9 (d, *J*=6.2 Hz), -77.3 (d, *J*=6.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_6H_8F_3N_2O_4$ 229.0431, found 229.0436.

10.6. ***Synthesis of*** **12.** A mixture of imine **9f** (1 mmol) and $AlCl_3$ (0,5 mmol) was stirred during 30 min at room temperature. Then 5 mL of water were added and the crude mixtures were extracted three times with Et_2O. The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The obtained crude was filtrated through a plug filled with celite. **Methyl (2*S*,4*S*,5*R*)-5-methyl-2-(trifluoromethyl)-1,3-oxazolidine-4-carboxylate** (**12**)**.** Yellow oil. Yield 65% (0.139 g). ν_{max} cm^{-1} 3396; 1774; 1587. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.04 (q, *J*=5.3 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.81 (s, 3H), 3.57 (d, *J*=8.5 Hz, 1H), 2.32 (br, 1H), 1.45 (d, *J*=6.0, 3H). ^{13}C NMR ($CDCl_3$,75 MHz) δ: 170.3, 123.0 (q, *J*=282.0 Hz), 87.4 (q, *J*=34.3 Hz), 78.7, 64.7, 52.4, 18.1. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: -82.4 (d, *J*=5.3 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_7H_{11}F_3NO_3$ 214.0686, found 214.0688.

Chapter 11

Nitro group reduction reaction

11.1 ***General procedure for the chemoselective nitro group reduction reaction***. To a solution of the appropriate β-nitro amine (1 equiv) in anhydrous MeOH, under an inert atmosphere (Ar), anhydrous ammonium formate (5 equiv) and Pd/C 10% (95 mg/1 mmol of nitro compound) were added. The reaction mixture was kept at reflux for 1.5 h and then filtered off to remove the catalyst. The solvent was evaporated under vacuum and 5 mL of water were added; the mixture was extracted three times with Et_2O. The collected organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum.

(2*R*)-N^2-cyclohexyl-3,3,3-trifluoropropane-1,2-diamine (13a). Pale yellow oil. Yield 70% (0.147 g). Purified by fast filtration through plug filled with silica gel using AcOEt as eluent. ν_{max} cm^{-1} 3378; 3190. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.04 − 3.16 (m, 1H,), 2.95 (dd, *J* = 4.1 Hz, 13.0 Hz, 1H), 2.60 − 2.74 (m, 2H), 0.97-1.91 (m, 13H). ^{13}C NMR ($CDCl_3$,75

MHz) δ: 126.9 (q, *J* = 284.5 Hz), 58.6 (q, *J* = 26.0 Hz), 54.9, 40.9 (q, *J* = 2.6 Hz), 34.3, 33.4, 26.0, 24.8, 24.6. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_9H_{18}F_3N_2$ 211.1422 found 211.1427.

Ethyl 2-amino-3-(cyclohexylamino)-4,4,4-trifluorobutanoate (*anti*-13b. Pale yellow oil. Yield 43% (0.115 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). ν_{max} cm^{-1} 3380; 3302; 1730. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.21 (q, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 2.3 Hz, 1H), 3.71 (dq, *J* = 2.3 Hz, 7.9 Hz, 1H), 2.50 – 2.59 (m, 1H), 1.51 – 1.87 (m, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.89 – 1.21 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 126.3 (q, *J* = 285.5 Hz), 61.7, 57.8 (q, *J* = 26.3 Hz), 54.3, 53.5 (q, *J* = 2.0 Hz), 34.0, 33.1, 25.9, 24.6, 24.4, 14.1. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{22}F_3N_2O_2$ 283.1628, found 283.1630.

Ethyl 2-amino-3-(cyclohexylamino)-4,4,4-trifluorobutanoate (***syn*-13b**)**.** Pale yellow oil. Yield 40% (0.113 g). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). ν_{max} cm^{-1} 3385; 3314; 1745. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.16 – 4.26 (m, 2H), 3.56 – 3.64 (m, 2H), 2.56 – 2.65 (m, 1H), 1.56 – 1.85 (m, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.07 – 1.23 (m, 4H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ: 172.8, 125.91 (q, *J* = 284.7 Hz), 61.4, 58.7 (q, *J* = 26.5 Hz), 54.6, 54.5, 33.7, 33.5, 25.9, 24.6, 24.5, 14.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{22}F_3N_2O_2$ 283.1628, found 283.1623.

***N*^{2}-Benzyl-3,3,3-trifluoropropane-1,2-diamine (13c).** Pale yellow oil. Yield 65% (0.142 g) Purified by fast filtration through plug filled with silica gel using AcOEt as eluent. ν_{max} cm^{-1} 3491; 3393. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 5H), 3.96 (dd, *J* = 62.6, 13.1 Hz, 2H), 3.11-2.92 (m, 1H), 2.97 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.74 (dd, *J* = 13.0, 8.1 Hz, 1H), 1.83 (br, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.4, 128.4 (2C), 128.1 (2C), 127.2, 126.6 (q, *J* = 284.5 Hz), 60.2 (q, *J* = 26.0 Hz), 51.7, 40.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{10}H_{14}F_3N_2$ 219.1109, found 219.1105.

Ethyl 2-amino-3-(benzylamino)-4,4,4-trifluorobutanoate (*anti*-13d). Pale yellow oil. Yield 38% (0.105 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3376; 3308; 1753. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.11 (m, 5H), 4.14 (q, *J*= 7.1 Hz, 2H), 4.10 (d, *J*=1.5 Hz, 1H), 3.96 – 3.78 (m, 3H), 2.43 (br, 3H) 1.24 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 138.9,

129.7, 128.5 (2C), 128.1, 127.7, 122.3 (q, *J*=286.6 Hz), 65.1 (q, *J*=30.9 Hz), 61.8, 61.0, 55.7, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -75.8 (d, *J*=6.9 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ 291.1315, found 291.1318.

Ethyl 2-amino-3-(benzylamino)-4,4,4-trifluorobutanoate – (*syn*-13d). Pale yellow oil. Yield 36% (0.099 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3388; 3315; 1755. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.26 (m, 5H), 4.19 (ddd, *J*=14.2 Hz, 7.1 Hz, 2.2 Hz, 2H), 3.95 (dd, *J*=30.3 Hz, 13.3 Hz, 2H), 3.70 (d, *J*=3.9 Hz, 1H), 3.61 – 3.48 (m, 1H), 2.05 (br, 3H), 1.26 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.1, 139.2, 128.4 (2C), 128.2 (2C), 127.3, 124.00 (q, *J*=281.7 Hz), 61.5, 60.9 (q, *J*=25.8 Hz), 54.0, 51.7, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (d, *J*=7.6 Hz).HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_2$ 291.1315, found 291.1313.

Ethyl 2-amino-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butanoate (*anti*-13e). Pale yellow oil. Yield 42% (0.103 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3376; 3357; 1736. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 – 6.72

(m, 2H), 6.70 – 6.64 (m, 2H), 4.59 (d, *J*=7.5, 1H), 4.42 – 4.37 (m, 1H), 4.13 (s, 1H), 4.04 (q, *J*=7.1, 2H), 3.73 (s, 3H), 2.18 (br, 2H), 1.08 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ:171.0, 153.2, 140.1, 125.66 (q, *J*=284.6 Hz), 116.0 (2C), 114.7 (2C), 62.1, 58.4 (q, *J*=28.4 Hz), 55.7, 52.7, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -73.4 (d, *J*=7.4 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_3$ 307.1264, found 307.1267.

Ethyl 2-amino-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butanoate (***syn*-13e**)**.** Pale yellow oil. Yield 39% (0.096 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3396; 3343; 1755. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.83 – 6.77 (m, 2H), 6.76 – 6.69 (m, 2H), 4.48 (d, *J*=8.8 Hz, 1H), 4.36 – 4.16 (m, 3H), 3.74 (m, 4H), 2.24 (br, 2H), 1.29 (t, *J*=7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.3, 153.4, 139.4, 125.32 (q, *J*=284.3 Hz), 116.1 (2C), 115.0 (2C), 61.8, 59.0 (q, *J*=27.7 Hz), 55.6, 54.0, 14.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -71.2 (d, *J*=7.3 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{18}F_3N_2O_3$ 307.1264, found 307.1261.

(2*S*)-3,3,3-Trifluoro-N^2-[(1*R*)-1-phenylethyl]propane-1,2-diamine (**13f**)**.** Yellow oil. Yield: 81% (188 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +12.7 (*c* = 5, $CHCl_3$). ν_{max} cm^{-1} 3488, 3395cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.4 Hz, 3H), 1.89 (br, 3H), 2.76 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.87–3.03 (m, 2H), 3.97 (q, *J* = 6.4 Hz, 1H), 7.17–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 39.4, 55.2, 57.9 (q, *J* = 26.1 Hz), 126.2 (q, *J* = 284.3 Hz), 126.7 (2C), 127.3, 128.5 (2C), 144.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ –76.4 (d, *J* = 7.7 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{11}H_{16}F_3N_2$ 233.1266, found 233.1272.

(2*R*)-3,3,3-Trifluoro-N^2-[(1*R*)-1-phenylethyl]propane-1,2-diamine (**13′f**)**.**Yellow oil. Yield: 80% (186 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +14.2 (*c* = 4.5, $CHCl_3$). ν_{max} cm^{-1} 3488, 3395 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 4.09 (q, *J* = 6.3 Hz, 1H), 2.68–2.85 (m, 2H), 2.59 (dd, *J* = 12.3, 7.5 Hz, 1H), 1.57 (br, 3H), 1.36 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 128.5 (2C), 127.4, 127.0 (2C), 126.4 (q, *J* = 284.6 Hz), 58.2 (q, *J* = 25.7 Hz), 56.2, 40.9, 24.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ –76.1 (d, *J* = 6.5 Hz). HRMS:

m/*z* $[M + H]^+$ calcd. for $C_{11}H_{16}F_3N_2$ $[M+H]^+$: 233.1266, found 233.1258.

Ethyl (2*R*,3*S*)-2-amino-4,4,4-trifluoro-3-{[(1*R*)-1-phenylethyl]amino}butanoate (***anti*-13g**)**.** Pale yellow oil. Yield 37% (0.096 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3388; 3346; 1772. $[\alpha]_D^{25}$ 29.7 (c = 3.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.26 (m, 5H), 4.20 (q, *J*=7.2 Hz, 2H), 4.04 (q, *J*=6.4 Hz, 1H), 4.01 (d, *J*=4.1 Hz, 1H), 3.62 – 3.52 (m, 1H), 2.04 (br, 3H), 1.36 (d, *J*=6.4 Hz, 3H), 1.24 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.3, 144.2, 128.6 (2C), 127.5, 126.8 (2C), 125.3 (q, *J*=283.9 Hz), 63.5, 61.7, 56.5 (q, *J*=28.0 Hz), 55.6, 23.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ = -71.8 (d, *J*=8.0 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{20}F_3N_2O_2$ 305.1471, found 305.1476.

Ethyl (2*S*,3*S*)-2-amino-4,4,4-trifluoro-3-{[(1*R*)-1-phenylethyl]amino}butanoate (***syn*-13g**)**.** Pale yellow oil. Yield 30% (0.077 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3375; 3338; 1762. $[\alpha]_D^{25}$ 21.4 (c = 1.4, $CHCl_3$).^1H NMR (400 MHz, $CDCl_3$) δ: 7.47 – 7.28 (m, 5H), 4.32 – 4.21 (m, 2H), 4.13

(q, *J*=6.5 Hz, 1H), 3.82 (d, *J*=3.1, 1H), 3.34 – 3.43 (m, 1H), 3.11 (br, 3H), 1.41 (d, *J*=6.5, 3H), 1.33 (t, *J*=7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.1, 143.2, 128.7 (2C), 127.7, 127.1 (2C), 125.7 (q, *J*=287.8 Hz), 64.2, 61.6, 55.8, 55.7(q, *J*=27.7 Hz), 24.9, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -70.8 (d, *J*=7.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{20}F_3N_2O_2$ 305.1471, found 305.1472.

Ethyl (2*S*,3*R*)-2-amino-4,4,4-trifluoro-3-{[(1*R*)-1-phenylethyl]amino}butanoate (***anti*-13′g**). Pale yellow oil. Yield 9% (0.025 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3366; 3335; 1743. $[\alpha]_D^{25}$ 26.8 (c = 3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.21 (m, 5H), 4.19 (q, *J*=7.1 Hz, 2H), 4.04 (q, *J*=6.8 Hz, 1H), 3.96 (d, *J*=3.4 Hz, 1H), 3.67 (m, 1H), 2.04 (br, 3H), 1.31 – 1.23 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.2, 144.2, 128.5(2C), 127.1 (2C), 126.7, 123.9 (q, *J*=285.0 Hz), 63.6, 62.1, 56.7 (q, *J*=27.5 Hz), 55.6, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -72.3 (d, *J*=7.8 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{20}F_3N_2O_2$ 305.1471, found 305.1478.

Ethyl (2*R*,3*R*)-2-amino-4,4,4-trifluoro-3-{[(1*R*)-1-phenylethyl]amino}butanoate (***syn*-13′g**). Pale yellow oil.

Yield 7% (0.018 g). Separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25). ν_{max} cm^{-1} 3365; 3342; 1758. $[\alpha]_D^{25}$ 31.3 (c = 6, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.28 (m, 5H), 4.29 (q, *J*=7.1 Hz, 2H), 4.08 (q, *J*=6.5 Hz, 1H), 3.78 (d, *J*=4.1 Hz, 1H), 3.38 – 3.33 (m, 1H), 2.63 (br, 3H), 1.34 (d, *J*=6.4 Hz, 3H), 1.26 (t, *J*=7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.2, 143.5, 128.5 (2C), 127.4, 127.1 (2C), 123.9 (q, *J*=281.4 Hz), 63.6, 62.0, 56.7 (q, *J*=27.3), 55.8, 24.8, 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -70. 6 (d, *J*=7.3 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{20}F_3N_2O_2$ 305.1471, found 305.1478.

11.2 ***Coupling reactions: general procedure*****.** To a solution of diamines **13c** or **13f** or**13′f**, (0.5 mmol) in 10 mL of CH_2Cl_2 equimolar amounts of *N*-Boc protected α-amino acid, *N*,*N*'-dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP, 10% M) 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.

tert*-Butyl [(2*S*)-1-{[(2*S*)-2-(benzylamino)-3,3,3-trifluoropropyl]amino}-3-methyl-1-oxobutan-2-yl]carbamate** [(S*,*S*)-14c**]**.** White viscous oil. Yield: 42% (105 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ –14.1 (*c* = 3, $CHCl_3$). ν_{max} cm^{-1} 3440, 3342, 1708, 1670. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.33 (m, 5H), 6.29 (br, 1H), 4.96 (br, 1H), 3.63–4.00 (m, 6H), 3.04–3.18 (m, 1H), 2.01 (br, 1H), 1.36 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 172.0, 139.1, 128.6 (2C), 128.2 (2C), 127.4, 125.6 (q, *J* = 284.1 Hz), 82.3, 60.1, 57.1–59.0 (q, *J* = 26.7 Hz), 51.5, 37.5, 30.6, 28.2 (3C), 19.3 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ –76.6 (d, *J* = 5.0 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{31}F_3N_3O_3$ $[M+H]^+$ 418.2239, found 418.2243; *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{30}F_3N_3NaO_3$ 440.2137, found 440.2129.

***tert*-Butyl [(2*S*)-1-{[(2*R*)-2-(benzylamino)-3,3,3-trifluoropropyl]amino}-3-methyl-1-oxobutan-2-yl]carbamate [(*R*,*S*)-14'c].** White viscous oil. Yield: 44% (110 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ –10.5 (*c* = 4, $CHCl_3$). ν_{max} cm^{-1} 3440, 3343, 1710, 1671. ^1H NMR (300 MHz, $CDCl_3$) δ

7.15–7.33 (m, 5H), 6.31 (br, 1H), 4.89 (br, 1H), 3.64–3.98 (m, 6H), 3.02–3.19 (m, 1H), 2.13 (br, 1H), 1.38 (s, 9H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.8, 139.1, 128.6 (2C), 128.4 (2C), 127.5, 125.8 (q, *J* = 284.3 Hz), 80.1, 60.0, 57.7 (q, *J* = 26.9 Hz), 51.4, 37.6, 30.4, 28.3 (3C), 19.3 (2C). ^{19}F NMR (282 MHz, $CDCl_3$) δ –76.7 (d, *J* = 5.3 Hz).). HRMS: *m*/*z* $[M + H]^+$calcd for $C_{20}H_{31}F_3N_3O_3$ 418.2239, found 418.2242; *m*/*z* $[M+Na]^+$calcd for $C_{20}H_{30}F_3N_3NaO_3$ 440.2137, found 440.2131.

***tert*-Butyl (2-oxo-2-{(2*S*)-3,3,3-trifluoro-2-[(1*R*)-1-phenylethylamino]propylamino}ethyl) carbamate [(*R*,*S*)-14f].** White viscous oil. Yield: 91% (212 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +10.4 (*c* = 3, $CHCl_3$). ν_{max} cm^{-1} 3450, 3342, 1708, 1667. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.31 (m, 5H), 6.64 (br, 1H), 5.29 (br, 1H), 3.96–4.02 (m, 2H), 3.66–3.86 (m, 4H), 1.86 (br, 1H), 1.85 (s, 9H), 1.26 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 156.1, 144.4, 128.5 (2C), 127.3, 126.8 (2C), 126.5 (q, *J* = 284.6 Hz), 80.4, 56.0 (q, *J* = 26.8 Hz), 55.3, 44.5, 28.2 (3C), 24.7, 24.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ –77.0 (d, *J* = 7.8 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd for

$C_{18}H_{27}F_3N_3O_3$ 390.2005, found 390.1997; *m/z* $[M+Na]^+$calcd for $C_{18}H_{26}F_3N_3NaO_3$ 412.1824, found 412.1831.

tert*-Butyl (2-oxo-2-{(2*R*)-3,3,3-trifluoro-2-[(1*R*)-1-phenylethylamino]propylamino}ethyl) carbamate** [(R,R)*-14'f].** White viscous oil. Yield: 89% (208 mg). Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). $[\alpha]_D^{25}$ +8.9 (*c* = 3, $CHCl_3$). ν_{max} cm^{-1} 3457, 3352, 1728, 1668. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41– 7.17 (m, 5H), 6.46 (br, 1H), 5.13 (br, 1H), 3.96–4.12 (m, 2H), 3.50–3.77 (m, 4H), 1.89 (br, 1H), 1.45 (s, 9H), 1.33 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 156.0, 144.1, 128.7 (2C), 127.6, 126.9 (2C), 126.8 (q, *J* = 284.5 Hz), 80.3, 60.3, 56.4 (q, *J* = 26.9 Hz), 44.2, 28.2 (3C), 24.9, 24.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ –77.2 (d, *J* = 5.6 Hz). HRMS: *m/z* $[M + H]^+$calcd for $C_{18}H_{27}F_3N_3O_3$ 390.2005, found 390.1999; *m/z* $[M+Na]^+$calcd for $C_{18}H_{26}F_3N_3NaO_3$ 412.1824, found 412.1819.

11.3 *Synthesis of N-Boc-protected CF_3-modified dipeptides* (*S*)-15 *and* (*R*)-15'. In a two-neck flask trifluoromethyl dipeptides (*R*,*S*)-**14** and (*R*,*R*)-**14'** (0.4 mmol) were dissolved in 5 mL of anhydrous MeOH and 60 mg of 10% Pd/C were

added. The reaction mixtures were hydrogenated under atmospheric pressure at room temperature for 24 h after which the crude mixtures were filtered off to remove the catalyst and the solvent was removed by evaporation at reduced pressure.

***tert*-Butyl (2-{[(2*S*)-2-amino-3,3,3-trifluoropropyl]amino}-2-oxoethyl)carbamate [(*S*)-15].** Pale yellow oil. Yield: 95% (150 mg). $[\alpha]_D^{25}$ –5.5 (*c* = 3.5, $CHCl_3$). ν_{max} cm^{-1} 3390, 3342, 1708, 1667. ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (br, 2H), 5.13 (br, 2H), 4.05–4.30 (m, 1H), 3.75–3.85 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 156.8, 124.8 (q, *J* = 283.7 Hz), 80.3, 53.6 (q, *J* = 27 Hz), 41.0, 33.6, 28.1 (3C). ^{19}F NMR (282 MHz, $CDCl_3$) δ –76.3 (d, *J* = 3.9 Hz). HRMS: *m*/*z* [M + H]$^+$calcd for $C_{10}H_{18}F_3N_3O_3$ 286.1300, found 286.1305; *m*/*z* [M+Na]$^+$calcd for $C_{10}H_{18}F_3N_3NaO_3$ 308.1198, found 308.1205.

***tert*-Butyl (2-{[(2*R*)-2-amino-3,3,3-trifluoropropyl]amino}-2-oxoethyl) carbamate [(*R*)-15'].** Pale yellow oil. Yield: 93% (141 mg). $[\alpha]_D^{25}$ +5.5 (*c* = 3, $CHCl_3$).

11.4 ***General procedure for the nitro group reduction reaction of compounds*** **10**,**10′a-c.** In a two-neck flask the crude mixtures of trifluoromethyl β-amino α-nitro esters **10**,**10′a-c** were dissolved in 5 mL of anhydrous MeOH and 10 % Pd/C (120 mg/mmol of nitro compound) were added. The reaction mixtures were hydrogenated under atmospheric pressure at room temperature for 2 h after which the crude mixtures were filtered off to remove the catalyst and the solvent was removed by evaporation at reduced pressure. The obtained compounds were separated by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 75:25)..

Ethyl (2*S*,3*R*)-2-amino-4,4,4-trifluoro-3-{[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}butanoate (**16a**)**.** Pale yellow oil. Yield 36% (0.090 g). $[\alpha]_D^{25}$ -6.5 (c = 7, $CHCl_3$). ν_{max} cm^{-1} 3545; 3391; 1733. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.26 (q, *J*=7.1, 2H), 4.02 (d, *J*=3.5 Hz, 1H), 3.75 (s, 3H), 3.61 – 3.54 (m, 1H), 3.30 (d, *J*=5.0 Hz, 1H), 3.06 (d, *J*=5.3 Hz, 3H), 2.10 – 2.01 (m, 1H), 1.30 (t, *J*=7.1 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H), 0.90 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 169.5, 125.9 (q, *J*=285.9 Hz), 66.9, 64.5, 61.9, 58.7 (q, *J*=28.1 Hz), 51.6, 32.6, 19.3, 17.8, 14.0. ^{19}F

NMR ($CDCl_3$, 282 MHz) δ: -72.75 (d, *J*=7.7 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{21}F_3N_2O_4$ 314.1453, found 314.1454.

Ethyl (2*R*,3*S*)-2-amino-4,4,4-trifluoro-3-{[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}butanoate (**16′a**)**.** Pale yellow oil. Yield 9% (0.025 g). $[\alpha]_D^{25}$ 6.8 (c = 7, $CHCl_3$). ν_{max} cm^{-1} 3498; 3357; 1754. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.25 (q, *J*= 7.1 Hz, 2H), 3.93 (d, *J*=4.6 Hz, 1H), 3.71 (s, 3H), 3.62 – 3.53 (m, 4H), 2.08 – 1.99 (m, 1H), 1.30 (t, *J*=7.1, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.2, 169.7, 124.0 (q, *J*=284.4 Hz), 66.6, 64.1, 61.7, 59.6 (q, *J*=28.0 Hz), 51.8, 32.7, 19.2, 17.7, 14.0. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.10 (d, *J*=8.1 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{21}F_3N_2O_4$ 314.1453, found 314.1450.

Methyl (2*S*,3*S*)-2-{[(1*R*,2*S*)-2-amino-3-ethoxy-3-oxo-1-(trifluoromethyl)propyl]amino}-3-methylpentanoate (**16b**)**.** Pale yellow oil. Yield 37% (0.092 g). $[\alpha]_D^{25}$ -5.25 (c = 2, $CHCl_3$). ν_{max} cm^{-1} 3432; 3321; 1748. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.24 (qd, *J*=7.1 Hz, 2.5 Hz, 2H), 3.96 (d, *J*=3.5 Hz, 1H), 3.73 (s, 3H), 3.56 – 3.46 (m, 1H), 3.34 (d, *J*=5.0 Hz, 1H), 1.73 (br, 3H), 1.52 – 1.43 (m, 1H), 1.28 (t, *J*=7.1 Hz, 3H), 1.24

– 1.13 (m, 2H), 0.93 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.9, 169.6, 123.8 (q, *J*=281.8 Hz), 66.9, 63.3, 62.2, 58.5 (q, *J*=28.7 Hz), 51.5, 38.2, 24.9, 15.7, 13.9, 11.4. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.8 (d, *J*=7.8). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{24}F_3N_2O_4$ 329.1683, found 329.1688.

Methyl (2*S*,3*S*)-2-{[(1*S*,2*R*)-2-amino-3-ethoxy-3-oxo-1-(trifluoromethyl)propyl]amino}-3-methylpentanoate (16′b). Pale yellow oil. Yield 9% (0.022 g). $[\alpha]_D^{25}$ 4.8 (c = 7, $CHCl_3$). ν_{max} cm^{-1} 3432; 3321; 1748. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.23 (q, *J*=7.2 Hz, 2H), 3.90 (d, *J*=4.6 Hz, 1H), 3.69 (s, 3H), 3.60 – 3.50 (m, 1H), 3.19 (d, *J*=5.6 Hz, 1H), 1.65 (br, 2H), 1.52 – 1.40 (m, 2H), 1.28 (t, *J*=7.2 Hz, 3H), 1.22 – 1.08 (m, 2H), 0.88 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.2, 169.7, 125.2 (q, *J*=286.0 Hz), 65.5, 63.8, 61.7, 59.3 (q, *J*=28.3 Hz), 51.6, 39.5, 24.7, 15.4, 13.8, 11.3. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.2 (d, *J*=7.5 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{24}F_3N_2O_4$ 329.1683, found 329.1685.

Methyl (2*S*)-2-{[(1*R*,2*S*)-2-amino-3-ethoxy-3-oxo-1-(trifluoromethyl)propyl]amino}-4-methylpentanoate (16c). Pale yellow oil. Yield 31% (0.073 g). $[\alpha]_D^{25}$ -8.8 (c = 3,

$CHCl_3$). ν_{max} cm^{-1} 3482; 3331; 1762. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.24 (qd, *J*=7.0 Hz, 1.8 Hz, 2H), 3.99 (d, *J*=3.6 Hz, 1H), 3.74 (s, 3H), 3.58 – 3.50 (m, 2H), 1.87 – 1.66 (m, 2H), 1.56 – 1.42 (m, 4H), 1.29 (t, *J*=7.1, 3H), 0.92 (d, *J*=6.6 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.2, 168.7, 124.9 (q, *J*=290.9 Hz), 63.3, 62.1, 59.3, 58.6 (q, *J*=29.7 Hz), 52.0, 43.8, 24.5, 22.7, 22.0, 13.8. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.6 (d, *J*=8.0 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{24}F_3N_2O_4$ 329.1683, found 329.1681.

Methyl (2*S*)-2-{[(1*S*,2*R*)-2-amino-3-ethoxy-3-oxo-1-(trifluoromethyl)propyl]amino}-4-methylpentanoate (16′b). Pale yellow oil. Yield 8% (0.019 g). $[\alpha]_D^{25}$ 5.7 (c = 8, $CHCl_3$). ν_{max} cm^{-1} 3530; 3344; 1746. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.25 (qd, *J*=7.1 Hz, 1.7 Hz, 2H), 3.97 (d, *J*=4.3 Hz, 1H), 3.71 (s, 3H), 3.68 – 3.63 (m, 1H), 3.41 – 3.35 (m, 1H), 1.80 – 1.70 (m, 1H), 1.54 – 1.40 (m, 3H), 1.36 – 1.23 (m, 5H), 0.93 (d, *J*=6.3 Hz, 3H), 0.91 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.2, 169.1, 125.0 (q, *J*=285.6 Hz), 63.5, 61.9, 59.3, 58.7 (q, *J*=29.0 Hz), 51.9, 43.8, 24.5, 22.8, 21.9, 13.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -71.9 (d, *J*=8.1 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{24}F_3N_2O_4$ 329.1683, found 329.1684.

Ethyl (3*R*)-4,4,4-trifluoro-2-imino-3-{[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}butanoate (17a). Pale yellow oil. Yield 29% (0.074 g). $[\alpha]_D^{25}$ -34.8 (c = 16, $CHCl_3$). ν_{max} cm^{-1} 3545; 3388; 1734; 1684. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.83 – 4.70 (m, 1H), 4.35 (q, *J*=7.1 Hz, 2H), 3.62 (s, 3H), 3.07 (d, *J*=5.4 Hz, 1H), 2.67 (br, 2H), 2.01 – 1.91 (m, 1H), 1.36 (t, *J*=7.1 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.9, 162.2, 145.6, 123.8 (q, *J*=281.7 Hz), 67.8, 62.3, 55.9 (q, *J*=32.8 Hz), 51.6, 31.8, 19.1, 17.9, 13.9. ^{19}F NMR ($CDCl_3$, 282 MHz,) δ: -72.06 (d, *J*=8.5). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{19}F_3N_2O_4$ 312.1297, found 312.1293.

Ethyl (3*S*)-4,4,4-trifluoro-2-imino-3-{[(1*S*)-1-(methoxycarbonyl)-2-methylpropyl]amino}butanoate (17′a). Pale yellow oil. Yield 7% (0.006 g). $[\alpha]_D^{25}$ -5.5 (c = 6, $CHCl_3$). ν_{max} cm^{-1} 3545; 3388; 1734; 1684. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.86 (q, *J*=7.8 Hz, 1H), 4.34 (q, *J*=7.1 Hz, 2H), 3.73 (s, 3H), 3.13 (d, *J*=6.0 Hz, 1H), 2.54 (br, 2H), 2.01 – 1.92 (m, 1H), 1.36 (t, *J*=7.1 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.7, 162.0, 145.2, 124.0 (q, *J*=284.3 Hz), 66.1, 62.4, 55.3 (q, *J*=31.9 Hz), 51.8, 31.6, 19.0, 18.0, 13.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -71.53 (d, *J*=7.8

Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{12}H_{19}F_3N_2O_4$ 312.1297, found 312.1295.

Methyl (2*S*,3*S*)-2-{[(1*R*)-3-ethoxy-2-imino-3-oxo-1-(trifluoromethyl)propyl]amino}-3-methylpentanoate (17b). Pale yellow oil. Yield 30% (0.074 g). $[\alpha]_D^{25}$ -51.3 (c = 3, $CHCl_3$). ν_{max} cm^{-1} 3556; 3395; 1762; 1679. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.82 – 4.69 (m, 1H), 4.35 (q, *J*=7.1 Hz, 2H), 3.61 (s, 3H), 3.13 (br, 2H), 1.72 (br, 2H), 1.59 – 1.43 (m, 1H), 1.36 (t, *J*=7.1 Hz, 3H), 1.25 – 1.13 (m, 1H), 0.90 – 0.86 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.0, 162.0, 145.6, 125.4 (q, *J*=283.6 Hz), 65.8, 61.8, 55.9 (q, *J*=32.3 Hz), 52.0, 38.5, 24.7, 15.6, 13.9, 11.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.1 (d, *J*=8.4 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_4$ 327.1526, found 327.1523.

Methyl (2*S*,3*S*)-2-{[(1*S*)-3-ethoxy-2-imino-3-oxo-1-(trifluoromethyl)propyl]amino}-3-methylpentanoate (17′b). Pale yellow oil. Yield 8% (0.020 g). $[\alpha]_D^{25}$ -6.3 (c = 2, $CHCl_3$). ν_{max} cm^{-1} 3449; 3388; 1757; 1682. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.85 (q, *J*=7.8 Hz, 1H), 4.30 (q, *J*= 7.1 Hz, 2H), 3.70 (s, 3H), 3.15 (d, *J*=5.7 Hz, 1H), 1.75 – 1.58 (m, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 1.21 – 1.13 (m, 2H), 0.86 – 0.83 (m, 6H). ^{13}C NMR (101

MHz, $CDCl_3$) δ: 173.6, 162.1, 145.2, 124.0 (q, *J*=284.4 Hz), 65.0, 62.2, 55.0 (q, *J*=32.1 Hz), 51.6, 38.2, 24.9, 15.3, 13.8, 11.2. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -71.1 (d, *J*=7.6). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_4$ 327.1526, found 327.1527.

Methyl (2S)-2-{[(1R)-3-ethoxy-2-imino-3-oxo-1-(trifluoromethyl)propyl]amino}-4-methylpentanoate (17c). Pale yellow oil. Yield 25% (0.059 g). $[\alpha]_D^{25}$ -54.7 (c = 8, $CHCl_3$). ν_{max} cm^{-1} 3449; 3385; 1758; 1687. ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.8 (q, *J*=7.8 Hz, 1H), 4.35 (q *J*= 7.1 Hz, 2H), 3.61 (s, 3H), 3.37 (t, *J*=7.2 Hz, 1H), 1.88 – 1.75 (m, 2H), 1.56 – 1.43 (m, 3H), 1.37 (t, *J*=7.1 Hz, 3H), 0.92 (d, *J*=6.5, 3H), 0.91 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.6, 162.3, 145.6, 124.0 (q, *J*=285.5 Hz), 62.6, 58.1, 54.2 (q, *J*=31.7 Hz), 52.2, 41.8, 24.6, 23.0, 22.0, 14.1. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -72.2 (d, *J*=8.2 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_4$ 327.1526, found 327.1528.

Methyl (2*S*)-2-{[(1*S*)-3-ethoxy-2-imino-3-oxo-1-(trifluoromethyl)propyl]amino}-4-methylpentanoate (17′c). Pale yellow oil. Yield 6% (0.014 g). $[\alpha]_D^{25}$ -4.7 (c = 5, $CHCl_3$). ν_{max} cm^{-1} 3478; 3352; 1764; 1689. ^1H NMR ($CDCl_3$, 400 MHz)

δ: 4.93 (q, *J*=8.0 Hz, 1H), 4.34 (q, *J*=7.1 Hz, 2H), 3.70 (s, 3H), 3.43 – 3.37 (m, 1H), 1.78 – 1.63 (m, 2H), 1.59 – 1.44 (m, 3H), 1.36 (t, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.5 Hz, 3H), 0.87 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 162.1, 145.4, 123.8 (q, *J*=283.2 Hz), 62.4, 57.9, 54.0 (q, *J*=32.2 Hz), 51.9, 41.6, 24.5, 22.8, 21.8, 13.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ: -71.3 (d, *J*=7.6 Hz). HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{13}H_{22}F_3N_2O_4$ 327.1526, found 327.1526.