UNIVERSITY OF SALERNO

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Ph.D. Course in Chemistry - XXXIV Cycle

Ph.D. Thesis in Chemistry

Exploring batch and flow catalytic reactions as valuable tools for safer and greener synthesis of APIs and their fluorine intermediates.

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LIST OF ABBREVIATIONS

aq.	aqueous
Ar	aryl
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bu	butyl
cat.	catalyst/s
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-Dimethylaminopyridine
DMP	Dimethylpyrazole
ee	enantiomeric excess
eq.	equivalent/s
h	hour(s)
Nu	nucleophile
p	*para*
PMB	*p*-Methoxybenzyl
p-TsOH	*p*-toluenesulfonic acid
rt	room temperature

t	*tert*
t-Bu	*t*-butyl
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene

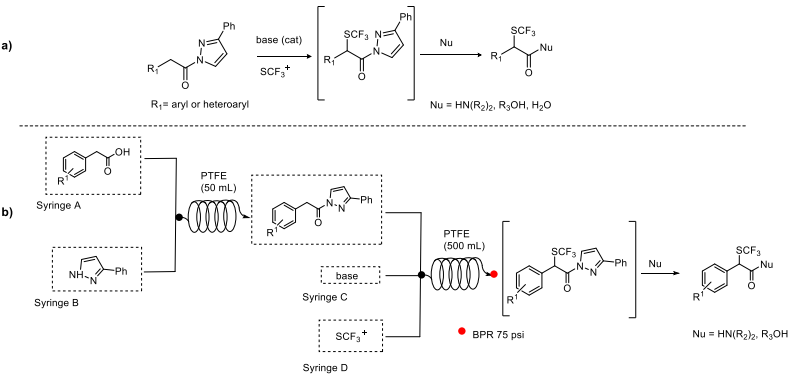
ABSTRACT

The trifluormethylthio (SCF_3) group assume a key role in the field of drug discovery thank to its unique properties. The high electron-withdrawing and lipophilic character made advantageous its incorporation in biologically active molecules. Different methods for the introduction of this group at the α-position of carbonyl compounds have been intensively investigated, achieving important results for ketones, aldehydes and 1,3-dicarbonyl compounds both under batch and flow conditions. However, few methods have been reported for the α-trifluoromethylthiolation of carboxylic acid derivatives.

In this industrial doctoral work, in collaboration with Laboratori Alchemia firstly a convenient metal-free and catalytic one-pot route for the introduction of SCF_3 group at α-position of carboxylic acid derivatives via *N*-acyl pyrazoles as surrogates was developed, amenable to mild conditions for enolate formation and simple transformation in one-pot fashion, into amides, esters, or carboxylic acids (Scheme Ia).

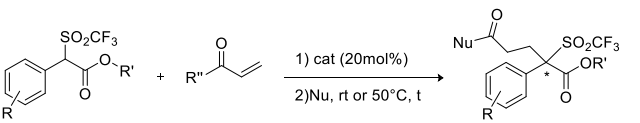
Furthermore, with the attempt to develop more convenient synthesis also suitable for industrial applications, a telescopic synthesis of the same products, starting directly from commercial sources by exploiting the flow chemistry technology, has been developed. With this strategy, the environmental footprint and the reaction time of the one-pot process are considerably reduced, minimizing the waste production and avoiding purification of the intermediates (Scheme

Ib).



Scheme I a) Organocatalytic one-pot α-trifluoromethylthiolation of carboxylic acid derivatives. b) Telescopic flow synthesis**.**

The last part of this doctoral thesis has been focused on the asymmetric organocatalytic synthesis of trifluoromethyl-substituted compounds bearing a quaternary stereocenter (Scheme II).



Scheme II Organocatalytic enantioselective one-pot Michael addition.

A first one-pot enantioselective organocatalytic Michael reaction to prepare highly enantioenriched triflones bearing a quaternary stereocenter has been developed, starting from easily enolizable aryl acetic triflone esters and acryloyl pyrazole. The one-pot methodology enables to obtain a variety of aryl-substituted triflones working under mild reaction conditions.

Finally, during the period spent in Laboratori Alchemia an intensive study on the *related substances* of Metaraminol, an API synthesized by Laboratori Alchemia through a new synthetic pathway, was

performed with the aim to identify these byproducts and allow to Laboratori Alchemia to declare the purity of Metaraminol.

1 Active pharmaceutical ingredients: an overview

1.1 Definition and general considerations

The World Health Organization (WHO) guidelines define the "*active pharmaceutical ingredient (API) a substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings."* [1]

Nowadays, there is an increased demand to provide new and more efficient drugs to treat the wide spectrum of known diseases including the emerging ones. The value of the global market for API is estimated at f $168.87 billion in 2019 and it is expected to grow rapidly in the next years to achieve a market value of US $285.5 billion by 2027.[2] Both in academia and in industrial field several efforts have been devoted by researchers to synthesize and screen the largest number of molecules with a potential activity.

Although the first discovery regarding the different behaviour of two enantiomeric forms of asparagine, today considered receptor-

[1] WHO Expert Committee on specifications for pharmaceutical preparations. Rev. Inst. Med. Trop. São Paulo **2008**, 50, 144–144.

[2] https://www.cphi-online.com/apis-active-pharmaceutical-ingredients-code007586.html

mediated biological activity, was made by Piutti in 1886,[3] until the 1987 around 90% of newly introduced drug were racemic.[4] The main reason why the enantioselective synthesis of active pharmaceutical ingredients have been developed only in the last decades of twenty century has to be found firstly in the complexity of these molecules, which in general contain different functional groups and stereocenters. Several advances in the study of asymmetric synthetic methods were needed for these technologies to become applicable to the production of chiral bioactive molecules. Thanks to the pioneering study in the organic synthesis reported by scientists like Woodward, Sheehan, and others, in the 1950s and 1960s, the necessary elements for the access to chiral APIs have been obtained.

Another relevant aspect, which cannot be disregarded, is the effect of the interaction between a racemic drug and biological systems such as proteins, nucleic acids, or cellular membranes. Biological matrices have well-defined three-dimensional structure and are able to interact with bioactive molecules in a single and precise way determining a stereospecific binding architecture. When an API may exist as two enantiomers, in general they do not interact in the same way, achieving different actions on biological system. Unfortunately, not more fifty years ago it was discovered that some drugs firstly given in racemic form caused dramatic effect. A classic example is

[3] A. Piutti, *Compt. Rend*., **1886**, 103, 134–138

[4] F. J. Leeper, P. Padmanabhan, G. W. Kirby, G. N. Sheldrake, *J. Chem. Soc. Chem. Commun.* **1987**, 505.

represented by Thalidomide that was prescribed as racemate for morning sickness, but while (R)-enantiomer has a therapeutic effect, (S)-Thalidomide has proved to be embryotoxic and teratogenic (Figure 1.1).[5]

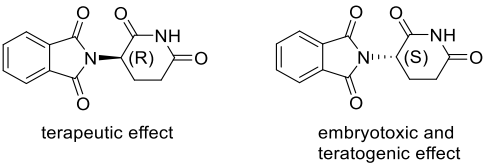


Figure 1.1 Thalidomide in two enantiomeric forms

[5] (a) G.-Q. Lin, J.-G. Zhang, J.-F. Cheng, in *Chiral Drugs* (Eds.: G.-Q. Lin, Q.-D. You, J.-F. Cheng), John Wiley & Sons, Inc., Hoboken, NJ, USA, **2011**, pp. 3–28. (b) A. J. Burke, C. S. Marques, N. J. Turner, G. J. Hermann, Eds., in *Act. Pharm. Ingred. Synth.*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2018**, pp. 1–30

1.2 Fluorine-containing APIs

Fluorine is the 13th most abundant element in Earth's crust by weight percent (0.054%),[6] nevertheless fluorine-containing compounds are very rarely found in the biosphere. Moreover, examples of biological processes in which fluorinate metabolites are involved are still unknown. On the other hand, since 1950s the introduction of fluorine containing motives on bioactive molecules has become an increasingly used practice. As a result, 9 of the 20 best-selling drugs in 2007 were found to be fluorine containing molecules. Among the best-selling drugs there is atorvastatin (Lipitor, US$13.3 billion sales), a molecule containing a single fluorine atom, used to lower cholesterol levels (LDL) (Figure 1.2). The introduction of fluorine atom(s) into the molecular skeleton of APIs has a dramatical effect in their physical, chemical, and biological properties due to the unique characteristics of fluorine. Fluorine is the most electronegative atom with van der Waals (vdW) radius of 1.35 Å (vdW radius of Hydrogen is 1.20 Å). Moreover, fluorine is able to give strong hydrogen bonding and polar interactions and the carbon-fluorine bond is a very strong bond.[7]

These properties have been found to significantly affect the biological

[6] N. Budisa, V. Kubyshkin, D. Schulze-Makuch, *Life* **2014**, *4*, 374–385

[7] (a) X.-L. Qiu, X. Yue, F.-L. Qing, in *Chiral Drugs* (Eds.: G.-Q. Lin, Q.-D. You, J.-F. Cheng), John Wiley & Sons, Inc., Hoboken, NJ, USA, **2011**, pp. 195–251. (b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Verlag GmbH & Co. KGaA, Weinheim, Germany, **2013**.

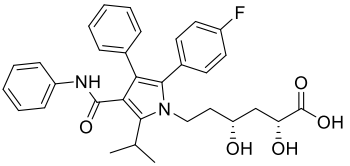


Figure 1.2 Lipitor

activity of fluorine containing compounds through:

- effect on pK_a
- lipophilic and electronic effects (π and σ)
- mimic and block effects

which are detailed in next paragraphs.

1.2.1 Effect on pKa

In the presence of fluorine atom(s) in organic compounds, an inductive effect is observed in neighbouring groups due to its high electronegativity. Accordingly, a significant increase of acidity in carboxylic acids and alcohols is determined. On the contrary, a decrease of basicity is observed in the case of amines (Table 1.1).

Table 1.1 pK_a and pK_b of organic compound in comparison with their fluorinated analogues

Acid	pK_a	Base	pK_b
CH_3COOH	4.76	$CH_3CH_2NH_2$	3.3
CH_2FCOOH	2.59	$FCH_2CH_2NH_2$	5.0
CF_3COOH	0.52	$F_3CCH_2NH_2$	8.1
CH_3CH_2OH	15.9	$C_6H_5NH_2$	9.4
CF_3CH_2OH	12.4	$C_6F_5NH_2$	14.36

As reported in the table 1.1, pK_a and pK_b values are closely related with the number of fluorine atom incorporated, observing stronger effect with more fluorine substitutions. In some cases, pK_a (pK_b) changes due the presence of fluorine atom, could have a beneficial effect on the bioactivity and on the stability of molecular drug. Concerning this point, it is important to mention the work reported by Morgenthaler in 2007, who developed a method based on experimental data to calculate the pK_a (pK_b) values of alkyl amines through the "σ-transmission effect" of fluorine.[8]

1.2.2 Lipophilic and electronic effects

Lipophilicity describes the ability of a molecule to dissolve in nonpolar media such as fats, oils and lipids or nonpolar solvents as hexane or toluene. The measure of this property is commonly indicated with the partition coefficient (P) between water and water-immiscible solvent generally *n*-octanol. LogP or π is calculated as the logarithm of the ratio of the concentration of neutral species in octanol divided by the concentration of neutral species in water (Equation 1.1).[9]

$$\pi = \log \frac{[neutral\ species]_{in\ octanol}}{[neutral\ species]_{in\ water}}$$

Equation 1.1 Definition of π (logP)

[8] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100–1115.

[9] A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525–616.

The ability of bioactive molecules to dissolve in nonpolar media, for instance phospholipidic membranes, is of crucial importance in drug discovery, because is associated with the molecular drugs efficiency to reach the target organs. The introduction of fluorine atom(s) or more in general fluorine-containing groups, especially on aromatic rings, generally increases the lipophilicity of bioactive molecules respect to their fluorine-free analogues (Table1.2).

Another important parameter useful to have a measure of the substituent influence on physiochemical properties of molecular drugs is the Hammet constant (σ).[10] The Hammet constant allows to quantify the effect that a specific functional group has on acidity or basicity of a site. It considers the distribution of partial charge of the bioactive molecule and its binding properties toward target systems (Table 1.2).

Table 1.2 Hammett constants and lipophilicity values of some fluorinated and non-fluorinated substituents.

Substituent X	σ	π	Substituent X	σ	π
CH_3	-0.17	+0.56	F	+0.06	+0.14
H	0	0	SCF_3	+0.48	+1.44
OCH_3	-0.27	-0.04	SO_2CF_3	+1.01	+0.55
OCF_3	+0.35	+1.04	SF_5	+0.68	+1.23

It is interesting to underline that in scaffolds with structure CF_3-Y-Ph (Y = O, S, SO_2), despite the presence of polar group (Y), an

[10] Corwin. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

extremely higher lipophilicity is observed for fluorinated compounds respect to their fluorine-free counterpart (CH_3-Y-Ph). The strong electron-withdrawing inductive effect of CF_3 group determines a decrease of the electron density of Y, reducing its ability to form hydrogen-bonds with water molecules and thus reducing its hydrophilicity. SCF_3, for example, is one of the most lipophilic groups ($\pi = + 1.48$) although it is a polar group ($\sigma = + 0.48$) (Table 1.2).

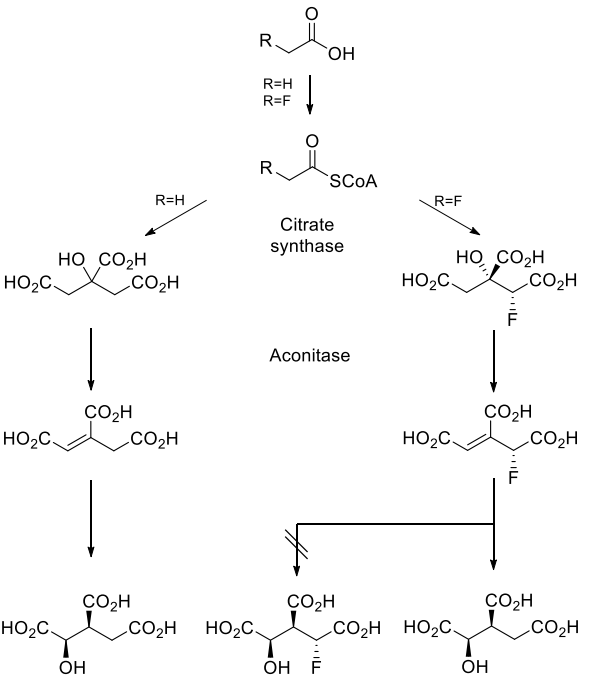
In general, all data regarding the properties of different functional groups can be used in mathematic quantitative structure–activity relationships (QSARs) methods for the design and structure optimization of new bioactive molecules and to predict the biologic and the physical-chemical properties or the environmental fate of molecular drug based by their chemical structure.[11]

1.2.3 Mimic and block effects

Considering the similar size of fluorine and hydrogen, hydrogen could be replaced by fluorine without a significant change in the spatial structure of bioactive molecules. Accordingly, in many cases the new molecules are recognized by several enzymes or microorganism similarly to the corresponding fluorine-free analogues, easily entering in the metabolic cycle. This event is defined as the “mimic effect” of fluorine for the hydrogen. Usually, the mimic effect occurs when one fluorine atom is introduced because

[11] S.-L. Li, M.-Y. He, H.-G. Du, *Int. J. Mol. Sci.* **2011**, *12*, 2982–2993.

the size of difluoromethyl or trifluoromethyl groups is bigger than methyl group. One of the most famous examples of "mimic effect" is given by fluoroacetic acid which takes part in the metabolic cycle of acetyl acid (Scheme 1.1).



Scheme 1.1 Metabolic cycle of acetyl acid and fluoroacetyl acid

As reported in the scheme 1.1, after the transformation of fluoroacetic acid and acetic acid into the corresponding acetyl-CoA, citrate synthase, converts both fluoracetyl-CoA and acetyl-CoA in their corresponding citric acids. In the same way, aconitase catalyses the following reaction of dehydration without differences for both substrates. Only in the last reaction hydroxylation step to obtain, in the normal metabolic cycle, the isocitric acid, (R)-fluoro-cisaconitic

acid is not recognized by the enzyme and therefore could not complete the normal metabolism cycle. On the contrary, in the last step of metabolic cycle the fluorinated compound undergoes hydroxylation-defluorination reaction leading to (R)-hydroxy-trans-aconitic acid.[12] Therefore, it is demonstrated that the fluorinated acetic acid easily enters in metabolic cycle of citric acid, thanks to "mimic effect". Nevertheless, the metabolic cycle is then blocked when the last substrate is not recognised by enzyme.

From another point of view, replacing hydrogen atom with fluorine could be exploited to obtain blocking agent for undesired metabolic pathway. One of the main degradative pathways for molecular drugs is the oxidative metabolism by the cytochrome P450 enzyme family. The oxidative process could significantly reduce the effectiveness of active pharmaceutical ingredients or, in some cases, could generate even toxic or mutagenic metabolites. One of the oxidative processes regards the hydroxylation of aliphatic compounds having substituents with labile hydrogen atoms and demethylations of aromatic methoxy groups or methylamines. For this reason, replacing hydrogen atom with fluorine represents a useful practice to prevent the deactivation of bioactive substance. An example of this effect is ezetimibe (brand name: Zetia, $1.40 billion sales in 2007) which is used as inhibitor of cholesterol absorption. The first design of this molecule included two phenyl rings bearing methoxy group at *para* position, a benzylic

[12] H. Lauble, M. C. Kennedy, M. H. Emptage, H. Beinert, C. D. Stout, *Proc. Natl. Acad. Sci.* **1996**, *93*, 13699–13703.

functionality, and a phenyl ring without substituents (Figure 1.3a). Subsequently, the strategic substitution of labile functional groups, including the replacement of hydrogen with fluorine, increases 50 times the activity of inhibitor in comparison with the conceptual starting compound (Figure 1.3).[13]

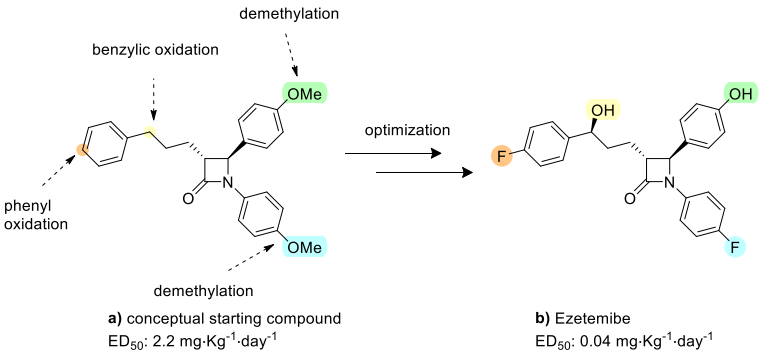


Figure 1.3 Strategic modification for synthesis of Ezetimibe, ED_{50} (effective dose) refers to reduction of liver cholesterol esters in hamsters.

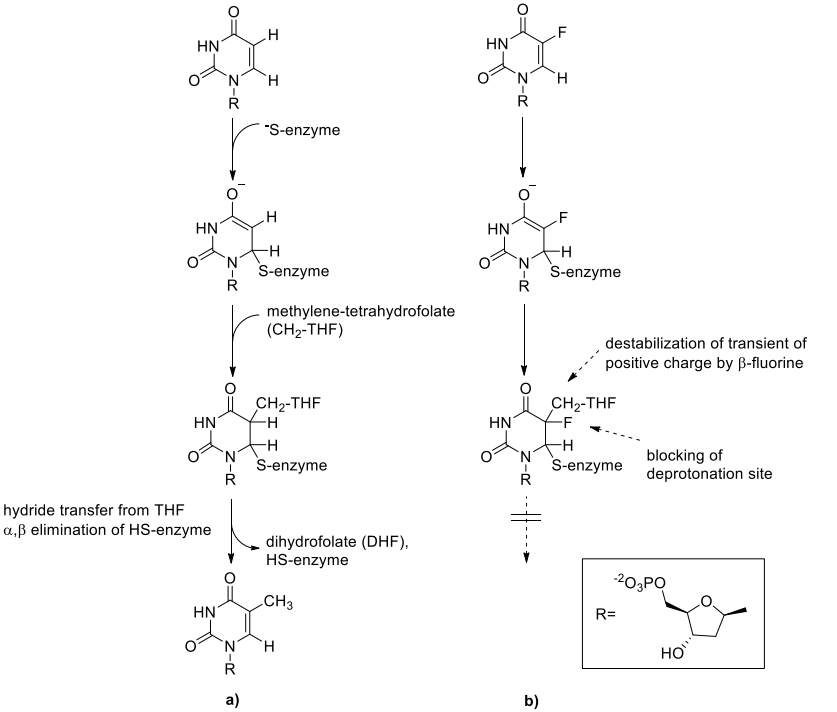
[13] S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis, N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.* **1998**, *41*, 973–980.

1.3 Mechanism of "suicide inhibition"

The mechanism of "suicide inhibition" is the main irreversible inhibition pathway that fluoropharmaceuticals can undergo. It involves the direct chemical reaction of fluorine-containing groups with the target organs[14] which takes place through the effects previously reported. The key to the efficiency of fluoropharmaceuticals lies in the similarity and, at the same time, the strong differences between fluorine and hydrogen. The mechanism of suicide inhibition can be explained considering the mode of action of 5-fluorouracil, a longstanding cytostatic agent (Scheme 1.2).[15] Initially, 5-fluorouracil is recognized by the enzyme entering in the process without modifications. After 1,4-addition by thiolic residue of the enzyme, 5-fluorouracil is covalently connected to coenzyme tetrahydropholate (THF) as the natural substrate (Scheme 1.2b). The crucial step of the process is the transfer of one hydride from THF coenzyme and the cleavage of covalent bond with the enzyme through α,β-elimination. In the natural pathway this step is favoured firstly in the hydride transfer by the partial positive charge on reactive centre, that in fluorine derivative does not occur.

[14] a) E. Wang, C. Walsh, *Biochemistry* **1978**, *17*, 1313–1321. b) R. B. Silverman, R. H. Abeles, *Biochemistry* **1976**, *15*, 4718–4723.

[15] D. C. Baker, T. H. Haskell, S. R. Putt, B. J. Sloan, *J. Med. Chem.* **1979**, *22*, 273–279.



Scheme 1.2 Mechanism of the "suicide inhibition" by 5-fluorouracil, a) pathway of natural substance b) pathway of inhibitor.

In addition, the separation of enzyme involves the deprotonation of uracil at position 5, that in the fluorine counterpart is blocked because fluorine could be exclusively eliminated as a fluoride anion. In this way, the enzyme partially elaborates the inhibitor that at the end of the process could not be expelled causing an irreversible deactivation of enzyme "suicide of enzyme".

1.4 Representative examples of biologic ingredient containing SO_nCF_3 (n= 0-2)

The fluorine is now considered the "second favourite heteroatom" after nitrogen for bioactive molecules.[16] Its incorporation in bioactive molecules is not limited to the single atom but especially in the most recent years, the introduction of SO_nCF_3 group is a topic of great interest.[17] The presence of these motives is a useful strategy to improve the oral bioavailability of molecular drugs. In this paragraph some representative examples of APIs containing the trifluormethylthio and trifluoromethylsulfonyl are reported (Figure 1.4).

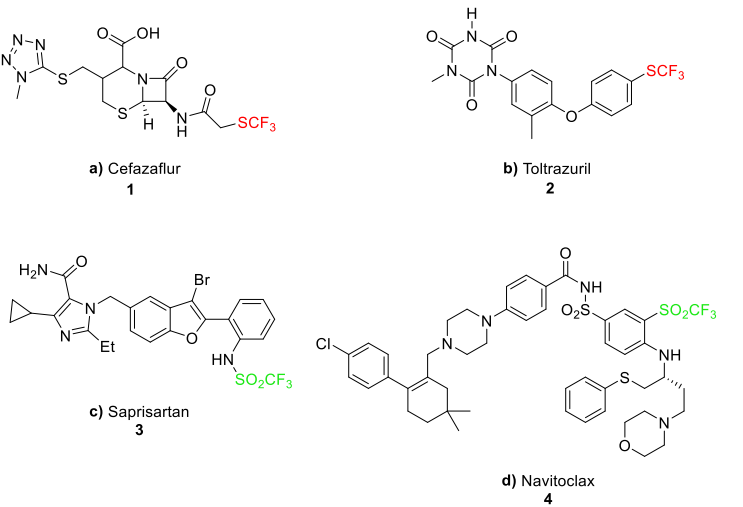


Figure 1.4 Active pharmaceutical ingredients bearing SO_nCF_3 (n= 0-2)

[16] F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, *2003*, 1559–1568
[17] G. A. Naclerio, N. S. Abutaleb, K. I. Onyedibe, M. N. Seleem, H. O. Sintim, *RSC Med. Chem.* **2020**, *11*, 102–110

Cefazaflur is an antibiotic having a trifluoromethylthio group at α-position of amide, belonging to the family of cephalosporins which was firstly synthesized in 1975 by SRVS Kids & Families (SK&F). This is one of the few examples where a SCF_3 group is installed on sp^3-C. The majority of cephalosporins commercially available endowed with interesting antibacterial activity has an acetamide group at 7-position bearing a phenyl ring or heterocycle. The study of SK&F had the aim to remove the aromatic functionalization and achieve cephalosporins containing simple acetamide at the same position.[18] After an extensive SAR (structure–activity relationship) study they discovered that the compound **1** (Figure 1.4a) is one of the most active against Gram-negative organism.[19]

Toltrazuril (Baycox®) **2** is a triazinetrione derivative used as anticoccidial agent bearing a trifluoromethylthio group (Figure 1.4b). It is widely used in chickens, turkeys, pigs, and cattle for the prevention and treatment of coccidiosis in oral administration. Biochemically it blocks the respiratory chain of mitochondria, the pyrimidine synthesis, the dihydrofolate reductase, and the dihydroorotate-cytochrome c reductase and disturbs the D1 protein of the photosystem II and EtCyp105. The toltrazuril sulfone (the oxidate form) represents the major metabolite. Recently also toltrazuril sulfone (Marquis®) was approved by Food and Drug Administration

[18] R. M. DeMarinis, J. C. Boehm, G. L. Dunn, J. R. E. Hoover, J. V. Uri, J. R. Guarini, L. Phillips, P. Actor, J. A. Weisbach, *J. Med. Chem.* **1977**, *20*, 30–35.
[19] F. Pertusati, M. Serpi, E. Pileggi, in *Fluor. Life Sci. Pharm. Med. Diagn. Agrochem.*, Elsevier, **2019**, pp. 141–180.

(FDA) to be used for the treatment of EPM. Toltrazuril sulfone is manufactured by Bayer Corporation, Agriculture Division, Shawnee Mission, KS, USA.[20]

Saprisartan, **3** synthesized in 1994 as a potent antihypertensive agent, presents a trifluoromethanesulfonamide group on phenyl ring that is essential for the absorption and oral bioavailability (Figure 1.4c).[21] The strategy for its development started from the molecule **5** (Figure 1.5) that was previously found to exhibit oral activity in the renal hypertensive rat.[22] The SAR (structure–activity relationship) of compound **5** guided the derivatization strategy, proving that the carboxylic acid in the imidazole ring, although important, is not crucial for high potency *in vitro.* For this reason, it was replaced by a neutral group, a secondary carboxamide.

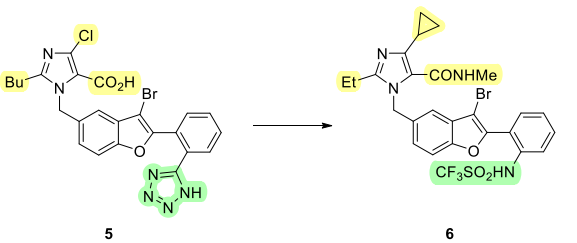


Figure 1.5 Development of Saprisartan

Moreover, to improve the oral bioavailability, different analogues

[20] a) A. Anadón, M. Martínez-Larrañaga, in *Encycl. Food Saf.*, Elsevier, **2014**, pp. 63–75. b) L. Dirikolu, W. Karpiesiuk, A. F. Lehner, C. Hughes, D. E. Granstrom, T. Tobin, *J. Vet. Pharmacol. Ther.* **2009**, *32*, 368–378.

[21] D. B. Judd, M. D. Dowle, D. Middlemiss, D. I. C. Scopes, B. C. Ross, T. I. Jack, M. Pass, E. Tranquillini, J. E. Hobson, *J. Med. Chem.* **1994**, *37*, 3108–3120.

[22] J. L. Cangiano, C. Rodríguez-Sargent, M. Martínez-Maldonado, *J. Pharmacol. Exp. Ther.* **1979**, *208*, 310–313.

were tested and the triflimide analogues were found to be better absorbed than a tetrazole. [21]

Novitoclax was developed by AbbVie in 2008 for the potential oral treatment of cancers such as lymphoid malignancies, small-cell lung cancer and solid tumours. The development of the Novitoclax started from the compound **7** which was found to bind a transmembrane protein *Bcl-xL* (B-cell lymphoma-extra-large) with an inhibition constant (Ki) of 36 nM. This property significantly decreases in the presence of serum, because of **7** affinity with human serum. To improve the selectivity toward *Bcl-xL*, the protein target, a modification in compound scaffold was accomplished achieving the molecules **8** which shows Ki 0.8 nM. The second structure **8** nevertheless binds the target less efficiently. To the aim of increase its efficiency a biphenyl group into piperazine ring moiety of **8** were added to access the compound **9** which shows better interaction into the binding pocket of the protein surface. ABT-737 (**9** in Figure 1.6) was proved to have a very interesting activity but suffers of very low aqueous solubility, poor absorption (permeability) and inadequate metabolic characteristics that make it poorly orally bioavailable. The substitution of nitro group on phenyl ring with the trifluoromethyl moiety increases the oral bioavailability but reduces the efficacy probably because of the less electron-withdrawing character of CF_3 group (**10** Figure 1.6).

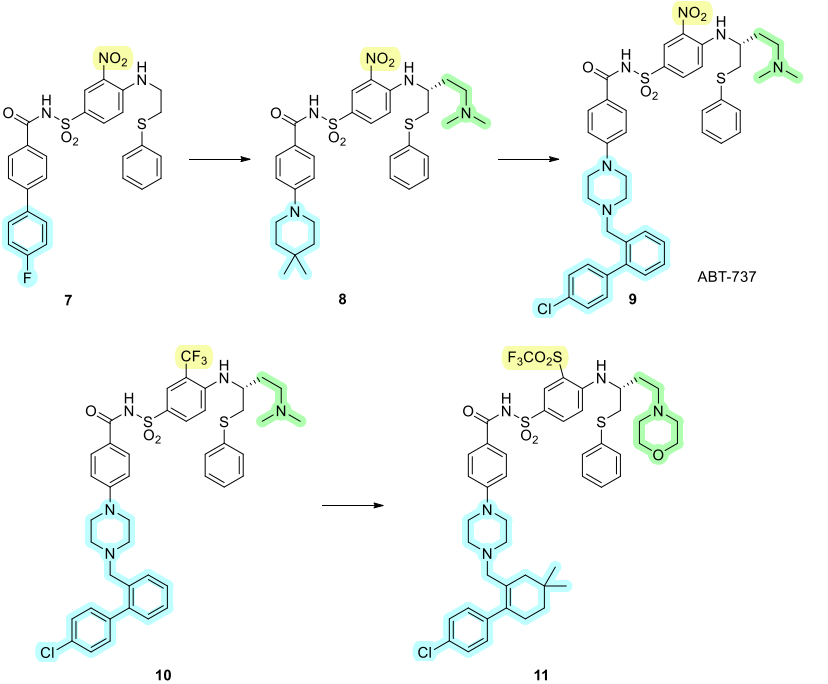


Figure 1.6 The development of the Novitoclax

To balance the efficacy and the oral bioavailability, considering that an electron-withdrawing group is needed, CF_3 moiety was replaced by a trifluoromethyl(sulfonyl) group achieving the desired properties in Novitoclax, **11**. Further optimization involved the replacement of the N,N-dimethylamino function by a morpholine ring, and one of the phenyls in the biphenyl fragment by a gem-dimethylcyclohexene group.[23]

[23] M. Bassetto, S. Ferla, F. Pertusati, *Future Med. Chem.* **2015**, *7*, 527–546

1.5 Direct method of trifluoromethylthiolation of carbonyl compounds

Recently, the interest for the trifluoromethylthio group is rapidly increasing among synthetic organic chemists.[24] Significant progresses in this area were achieved and many synthetic methods for the direct incorporation of this group at alpha position of carbonyl compounds were developed. The principal methods can be classified in:

- nucleophilic methods
- electrophilic methods
- radical methods

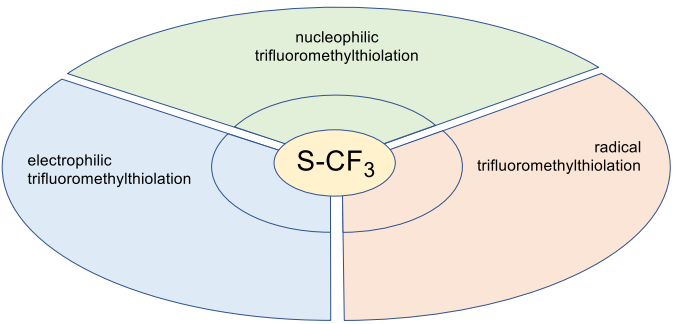
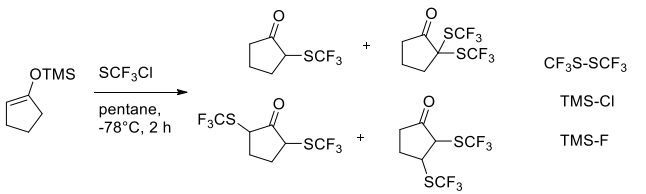


Figure 1.7 Trifluoromethylthiolating methods

[24] a) H. Ge, H. Liu, Q. Shen, in *Organofluor. Chem.* (Eds.: K. Szabó, N. Selander), Wiley, **2021**, pp. 99–172. b) L. Yan-mei, F. Jin-feng, H. Long-qiang, L. Wei-na, E. Vessally, *RSC Adv.* **2021**, *11*, 24474–24486. c) Y. Liang, D. Cahard, N. Shibata, in *Emerg. Fluorinated Motifs* (Eds.: D. Cahard, J. Ma), Wiley, **2020**, pp. 403–447. d) M. A. Hardy, H. Chachignon, D. Cahard, *Asian J. Org. Chem.* **2019**, *8*, 591–609. e) S. Rossi, A. Puglisi, L. Raimondi, M. Benaglia, *ChemCatChem* **2018**, *10*, 2717–2733. f) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764.

1.5.1 Radical methods

The trifluoromethylthiolation obtained starting from radical sources of SCF_3 is not the most efficient and useful method for the introduction of this group on carbonylic compounds. The main problem concerns the formation of several byproducts and the low control of the reaction parameters. The first example for the synthesis of α-trifluoromethylthio ketones was reported by Manuvalli in 2001 (Scheme 1.3).[25] The methodology employed cyclic trimethylsilyl enol ethers and SCF_3Cl as fluorine source. Unfortunately, the reaction shows poor selectivity and mono trifluoromethylthio ketones were obtained together with other byproducts in different ratio.



Scheme 1.3 Manuvalli's radical trifluoromethylthio protocol

Moreover, the toxicity of the trifluoromethansulphonate chloride makes this route not applicable in organic synthesis.

In the last few years other radical procedures for the incorporation of this motif, mediated by metallic trifluoromethylthio group, especially $AgSCF_3$, were developed by various research groups. Radical methodologies employing $AgSCF_3$ were applied on different

[25] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, H. D. Durst, *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, *177*, 1021–1031.

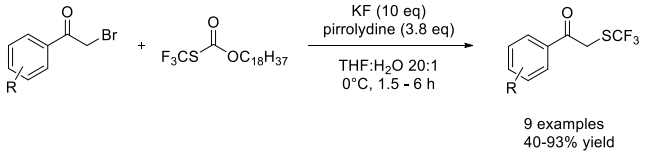
scaffolds from carbonyl compounds as quinones,[26] alkynes[27] and arylpropynones[28] obtaining in all these cases α-trifluoromethylthio ketones. More recently, the syntheses of trifluoromethylthiolated acetophenones involve oxidative processes starting from α,β-carboxylic acids and propionic acid.[29] Usually the radical $AgSCF_3$-mediated protocol needs an excess of trifluoromethylthiolating reagent in addition to radical initiator ($Fe(OAc)_2$ and Ag_2SO_4) and oxidating reagents ($K_2S_2O_8$ and $Na_2S_2O_8$) in over stoichiometric amount. For this reason, also considering the toxicity of reagents, catalytic and greenest approaches are desirable.

1.5.2 Nucleophilic methods

Nucleophilic trifluoromethylthiolation involves the reaction between an electrophilic substrate and SCF_3 anions. The most exploited electrophilic starting materials in nucleophilic procedures are α-halo ketones. However, in the last years new substrates have been investigated, as α-diazo esters with the aim to overcome the synthetic issues due to the intrinsic reactivity of halogen substituents. One of the first non-catalytic nucleophilic route, reported in 2013, involves the O-octadecyl-S-trifluoromethylthiocarbonate a cheap and stable

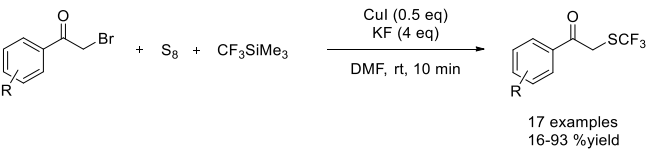
[26] C. Li, K. Zhang, X.-H. Xu, F.-L. Qing, *Tetrahedron Lett.* **2015**, *56*, 6273–6275.
[27] S. Pan, Y. Huang, F.-L. Qing, *Chem. - Asian J.* **2016**, *11*, 2854–2858.
[28] D.-P. Jin, P. Gao, D.-Q. Chen, S. Chen, J. Wang, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2016**, *18*, 3486–3489.
[29] a) M. Li, J. L. Petersen, J. M. Hoover, *Org. Lett.* **2017**, *19*, 638–641. b) Z.-F. Cheng, T.-T. Tao, Y.-S. Feng, W.-K. Tang, J. Xu, J.-J. Dai, H.-J. Xu, *J. Org. Chem.* **2018**, *83*, 499–504.

compound (Scheme 1.4). [30]



Scheme 1.4 Zard's nucleophilic metal-free trifluoromethylthiolation

Even though this is a nucleophilic metal-free procedure its applicability remains very limited due to the large amount of reagent required. In later years many other nucleophilic methodologies were disclosed, both included metallic or non-metallic SCF_3 sources. Interesting is the methodology developed by Ren and Zeng in 2015, a copper-catalysed trifluoromethylthiolation of both aromatic and aliphatic α-bromo ketones.[31] The process involved a sub-stoichiometric amount of CuI as catalyst and CF_3SiMe_3 and elemental sulfur as SCF_3 precursor (Scheme 1.5).



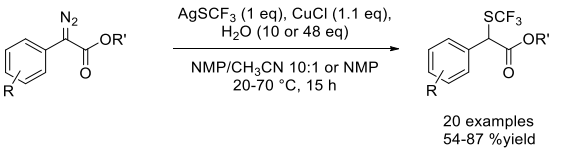
Scheme 1.5 Copper-catalysed trifluoromethylthiolation

This procedure differs from the previous copper-catalysed methodologies, because the presence of ligand for the catalytic action of copper is not needed. Moreover, the procedure can convert not only aromatic ketones but can be applied also to α-bromo

[30] S.-G. Li, S. Z. Zard, *Org. Lett.* **2013**, *15*, 5898–5901.
[31] J. Li, P. Wang, F.-F. Xie, X.-G. Yang, X.-N. Song, W.-D. Chen, J. Ren, B.-B. Zeng, *Eur. J. Org. Chem.* **2015**, *2015*, 3568–3571.

propiophenones and aliphatic starting material affording the desired products in moderate to good yields.

The α-diazo esters were employed firstly for the selective trifluoromethylthiolation of esters in 2014 by Hu and coworkers.[32] The methodology involves $CuSCF_3$ as active specie obtaining by the anion exchange between $AgSCF_3$ and the stoichiometric amount of CuCl. Moreover, the reaction requires water as promoter to guarantee high yield (Scheme 1.6).



Scheme 1.6 Trifluoromethylthiolation of α-diazo esters

The same reaction was developed independently by Wang[33] who reported a different approach for the reaction obtaining similar results. In Rueping methodology, developed in the same year, both mono-trifluoromethylthiolated and bis-trifluoromethylthiolated esters were achieved starting from α-diazo esters.[34]

1.5.3 Electrophilic methods

The electrophilic approach to the trifluoromethylthiolation of carbonylic compound is the most widespread strategy. Several

[32] M. Hu, J. Rong, W. Miao, C. Ni, Y. Han, J. Hu, *Org. Lett.* **2014**, *16*, 2030–2033.
[33] X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, *2014*, 3093–3096.
[34] Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.* **2014**, *50*, 6617.

electrophilic trifluoromethylthiolating agents progressively more sophisticated and endowed with higher efficiency have been developed in the years. To this regard a measure of SCF_3 cation-donating ability of these reagents was reported based by DFT calculation by Xue and Cheng (Figure 1.8).[35] The "trifluoromethylthiocation donating ability" (indicated with Tt^+DA) of many SCF_3 donating compounds represents a quantitative indicator of the aptitude of SCF_3 moiety of these reagents to be transferred to an organic molecule. Moreover, a correlation between the Tt^+DA and pKa of corresponding acids was proved to be a useful parameter to rationalize the chemistry of these reagents.

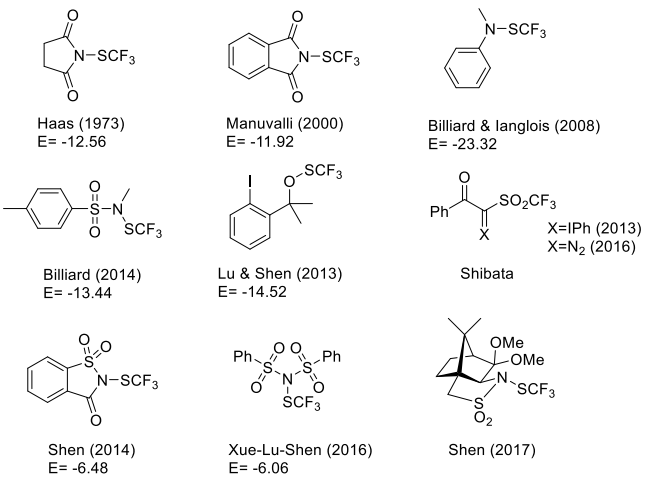
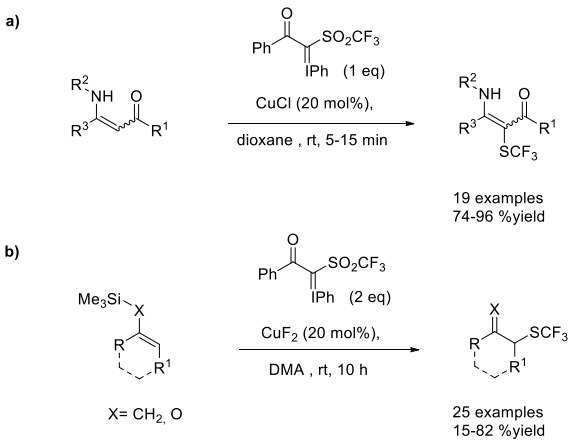


Figure 1.8 Electrophilic trifluoromethythiolating compounds, E (Electrophilicity parameters)

In recent years, the number of electrophilic trifluoromethylthiolation

[35] J. Zhang, J.-D. Yang, H. Zheng, X.-S. Xue, H. Mayr, J.-P. Cheng, *Angew. Chem. Int. Ed.* **2018**, *57*, 12690–12695.

reactions is constantly increasing involving the functionalization of ketones, esters, enamines, indoles, β-ketoesters and α-diazo esters. Also in this case, the presence of a metallic center can be useful to promote the α-functionalization. The main metal-based methods were disclosed by Shibata, that employing the trifluoromethanesulfonyl hypervalent iodonium ylide in the presence of copper catalyst (CuCl or CuF_2) achieved the synthesis of both β-enamino esters and β-enamino ketones in a very good results (Scheme 1.7a)[36] together with allylsilanes and trifluoromethylthiolated silyl enol ethers (Scheme 1.7b).[37]



Scheme 1.7 Trifluoromethanesulfonyl hypervalent iodonium ylide a) in the synthesis of trifluoromethylthiolated β-enamino esters and β-enamino ketones , b) in the synthesis of trifluoromethylthiolated allylsilanes and silyl enol ethers

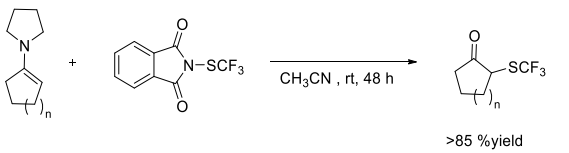
In the case of metal-free electrophilic trifluoromethylthiolation, the

[36] Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782–8785.

[37] S. Arimori, M. Takada, N. Shibata, *Org. Lett.* **2015**, *17*, 1063–1065.

first reagent employed was CF_3SCl, used in 1980 by Haas to achieve the synthesis of mono- and bis- trifluoromethylthiolated diethylmalonate.[38] Few years later, different methodologies exploited the same compound for the α-functionalization of ketones, cyclic β-diketones, β-keto acids and cyclohexanone esters. However due its toxicity newer and safer trifluoromethylthiolating reagents needed to be develop.

In 2000 Manuvalli reported the synthesis of N-(trifluoromethylthio)phthalimide that by reaction with enamines afforded α-functionalization of carbonyl compounds (Scheme 1.8).[39]

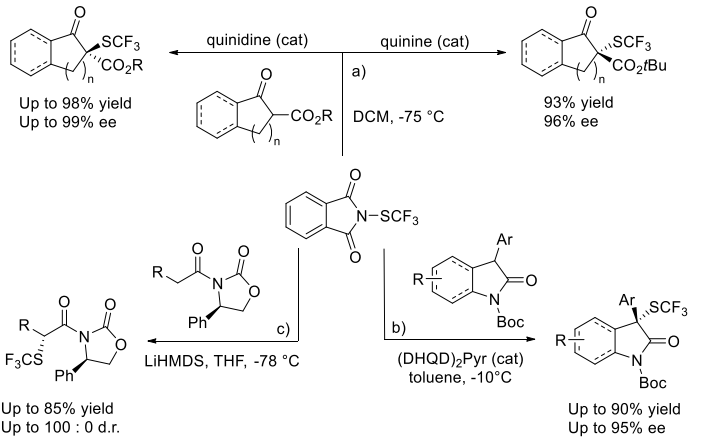


Scheme 1.8 Electrophilic trifluoromethylthiolation of ketone

Manuvalli reagent, a shelf-stable compound, is easily synthesised starting from $AgSCF_3$ and *N*-bromo phthalimide in only 3 h with excellent yield and nowadays is largely used as SCF_3 source in direct $C(sp_3)$–SCF_3 bond formation reactions also in asymmetric version. Since 2013, Rueping group disclosed firstly the enantioselective synthesis of trifluoromethylthio ketoesters employing quinidine and quinine as catalysts (Scheme 1.9a)[40] and one year later the

[38] M. Bauer, A. Haas, H. Muth, *J. Fluor. Chem.* **1980**, *16*, 129–136.
[39] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, d*Synth. Commun.* **2000**, *30*, 2847–2854.
[40] T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856–12859.

enantioselective cinchona alkaloid-catalysed trifluoromethylthiolation of oxindoles (Scheme 1.9b)[41] both with excellent results.



Scheme 1.9 Employment of N-trifluoromethylthiophtalimide as electrophilic reagent

DFT calculation have been carried out to better understand the activation mechanism of cinchona alkaloids catalyst. These studies showed that, among the three models proposed, the Wynberg ion pair-hydrogen bonding model is the most representative one. According to this model, a dual activation of N-(trifluoromethylthio)phthalimide by the indoxyl group of the catalyst and β-keto ester by the quinuclidine nitrogen is involved in the transition state (Figure 1.9).[42] The theorical calculations are in good agreement with experimental data, strongly supporting the proposed pathway.

[41] M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merkens, *Chem. Commun.* **2014**, *50*, 2508
[42] M. Li, X.-S. Xue, J.-P. Cheng, *ACS Catal.* **2017**, *7*, 7977–7986.

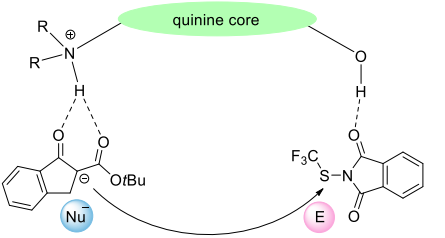


Figure 1.9 Wynberg ion pair hydrogen bonding model

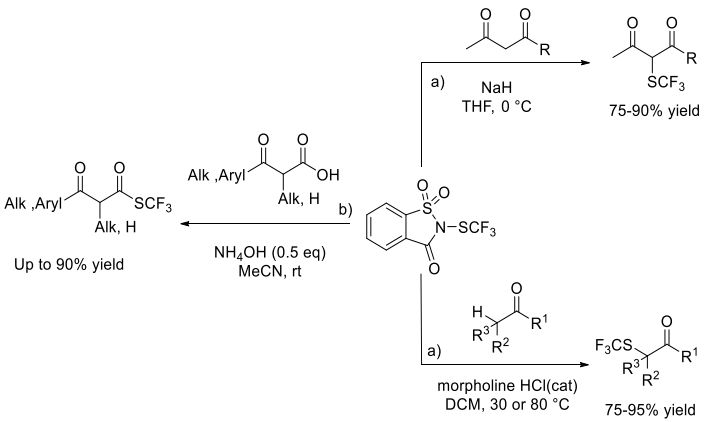
In the context of stereo-controlled reactions, another interesting methodology has been reported by Cahard in 2018. They described the diastereoselective electrophilic trifluoromethylthiolation of enolate, derived from Evans-type oxazolidinethione auxiliary, in the presence of a stoichiometric amount of a very strong base affording α-SCF_3 substituted carbonyl compounds with high relative stereo-control (Scheme 1.9c).[43] Although the achieved good results, the strictly controlled reaction conditions make the reaction not practical to be used.

Another interesting electrophilic trifluoromethylthiolating reagent is the N-(trifluoromethylthio)saccharin. It was synthesised for the first time in 2014 in Shen's group. This reagent shows a higher electrophilic power and reactivity in a broad substrate scope than the Manuvalli compound. The synthetic route reported by Shen to afford the desired compounds starting from saccharin involves a two-step process. After the synthesis of N-chlorosaccharin, obtained by treatment with tert-butyl hypochlorite, the second reaction step involved the anion exchange with $AgSCF_3$ to give the desired

[43] H. Chachignon, E. V. Kondrashov, D. Cahard, *Adv. Synth. Catal.* **2018**, *360*, 965–971.

products, with a high overall yield.[44] In the same work, to demonstrate the efficacy of N-(trifluoromethylthio)saccharin, the trifluoromethylthiolation of several nucleophiles was accomplished. In addition to carbonyl compounds (Scheme 1.10a), alcohols, amines, thiols and electron-rich arenes were successfully reacted under mild reaction conditions.

More recently, the same reagent was employed by Cahard and coworkers to carry out the decarboxylative trifluoromethylthiolation of β-ketocarboxylic acids in the presence of aqueous ammonium hydroxide (Scheme 1.10b). [45]

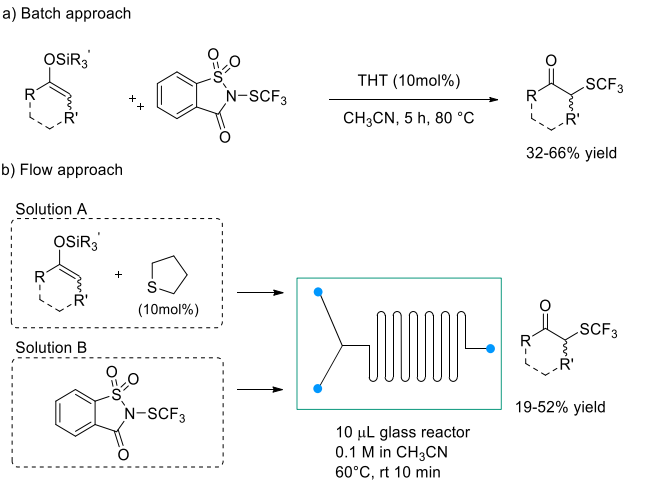


Scheme 1.10 Examples of electrophilic reactions using N-trifluoromethylthiosaccharin

With the growing development of flow technologies, the introduction of trifluoromethylthio group at α-position of silyl enol ethers was

[44] C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316–9320.
[45] H. Guyon, H. Chachignon, V. Tognetti, L. Joubert, D. Cahard, *Eur. J. Org. Chem.* **2018**, *2018*, 3756–3763.

realized under flow conditions for the first time by Benaglia group. As reported in the Scheme 1.11a the reaction performed under traditional batch conditions needs hard conditions and relatively long reaction time although achieving satisfactory yields.



Scheme 1.11 Flow-reaction for the synthesis of α-trifluoromethylthiolated ketones

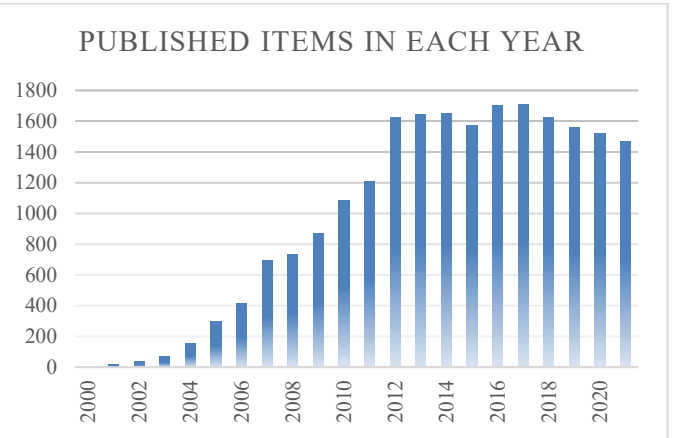
The flow chemistry approach, despite slightly lower yields, allows to work under milder reaction conditions in short reaction times, achieving higher productivity and higher space time yields (Scheme 1.11b).[46]

[46] S. S. Abubakar, M. Benaglia, S. Rossi, R. Annunziata, *Catal. Today* **2018**, *308*, 94–101

2 Organocatalysis

2.1 Definition and classification

The term “organocatalysis” refers to a branch of asymmetric catalysis that together with the other two main classes, bio- and metal-catalysis, represents the pillars of the synthetic chemistry. Considered the youngest area in asymmetric synthesis, has been and still is a fast-moving field. Since its birth at the end of 1990 the number of publications containing the term organocatalysis has increased markedly (Graphic 2.1), with more than 130 discrete reaction types that employed organocatalysts.[47]



Graphic 2.1 The number of publications on organocatalysis, obtained by searching ‘organocatalysis’ in Scifinder.

The catalysis in general offers the possibility to afford the target

[47] a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308. b) B. List, *Chem. Rev.* **2007**, *107*, 5413–5415.

products with excellent purity, in many cases this also implies an enantiomeric purity, that is an important added value especially in the field of pharmaceutical and agrochemicals. Moreover, the concept of "atom economy" in enantioselective catalytic transformation is surely guaranteed because the stoichiometric use of chiral auxiliary that must be introduced and removed can be avoid. Several significant advantages linked to the use of organocatalysts has allowed the widespread success which has been observed in the past decades. Organocatalysts are low molecular weight organic compound which, in catalytic ratio, are able to promote a chemical transformation. They are robust, inexpensive, readily available, and non-toxic. Thanks to their inertness to moisture and oxygen, very strictly reaction conditions (low temperatures, inert atmospheres and absolute solvents), in many cases, are not required. Moreover, the absence of transition metals makes the organocatalysis very attractive in those chemical areas where metal contamination is problematic, as pharmaceutical chemistry. Generally, chiral or achiral molecules are essentially composed by C, H, N, S, and P, but N- and P-based compounds are the most important and studied.

The organocatalysts can be classified in two different manners, according to the type of interaction between the catalyst and the substrate/s, in covalent catalysis or non-covalent catalysis. The covalent catalysis is referred to the formation of covalent bonds between the catalyst and reagent/s (with energies higher than 15 $kcal*mol^{-1}$), on the other hand non-covalent catalysis indicates that

the interactions involved between the catalyst and reagent/s are ion pairing, neutral host-guest interactions, acid-base associations, H-bonding (with energies usually lower than 4 kcal*mol^{-1}) (Figure 2.1).[48]

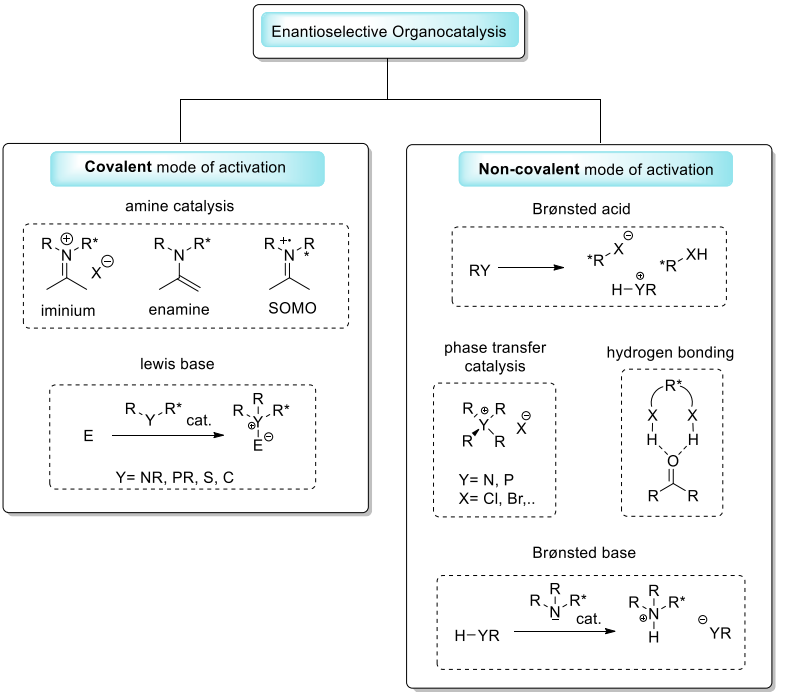


Figure 2.1 Classification of enantioselective organocatalysts

In the group of covalent catalysts are included aminocatalysts and carbenes, thioureas, squaramides, phosphoric acids and chiral bases such as cinchona alkaloid and phase-transfer catalysts belong to the

[48]a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**. b) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discov. Today* **2007**, *12*, 8–27.

second group.

Another subdivision considers the nature of the organocatalysts distinguishing Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids but it will not be discussed in this thesis.

2.2 Aminocatalysis: the leading covalent catalysis

As reported above, covalent catalysis includes mainly the aminocatalysis. The use of chiral secondary amines for the functionalization of aldehydes have represented in the "golden age of organocatalysis" an important breakthrough in asymmetric synthesis to the point that a large variety of functionalizations, as C-C, C-N, C-X (X= halogen), C-S and C-O bond-forming reactions, have been developed by exploiting this type of catalysis.

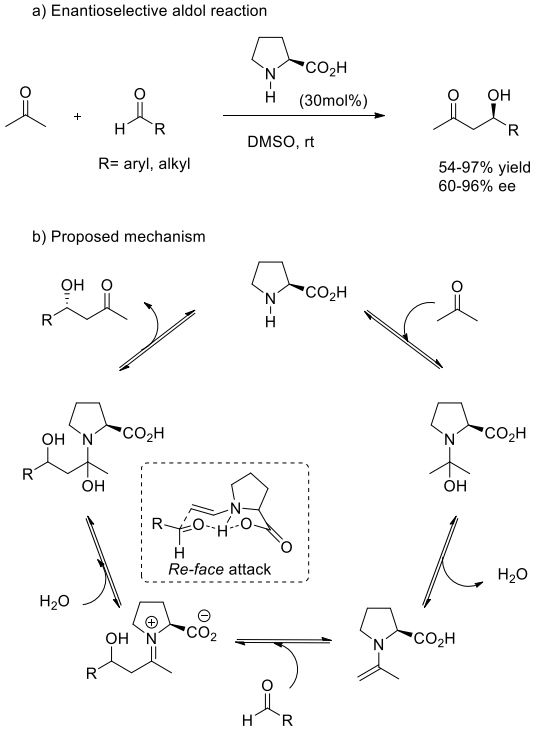
L-Proline certainly played a leading role in this context, named also as "simplest enzyme in the nature"[49] and "the universal catalyst"[50] thanks to its versatility and efficiency. Besides being one of the essential amino acids, it is a renewable compound and for this reason fully meets the principles of green chemistry.[51] Its catalytic and enantioselective activity in aldol reactions was discovered for the first time by List and coworkers in 2000, while they studied new enantioselective aldolase antibodies. In that period, they discovered that the aldolase antibody named "Aldolase Antibody 38C2" was able to catalyse aldol cyclodehydrations and afford enantioenriched cyclohexenones.[52] The same reaction was known to be catalysed also

[49] M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904–1905.
[50] J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
[51] B. S. Vachan, M. Karuppasamy, P. Vinoth, S. Vivek Kumar, S. Perumal, V. Sridharan, J. C. Menéndez, *Adv. Synth. Catal.* **2020**, *362*, 87–110.
[52] G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky, C. F. Barbas, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132.

by proline (Hajos–Parrish–Eder–Sauer–Wiechert reaction)[53], so List's group envisaged that the activation mechanism involved in each catalysis was the enamine mechanism. Based on these considerations, they disclosed the enantioselective aldol reaction of acetone with aromatic and alkyl aldehydes catalysed by L-Proline, achieving good results in terms of yields and enantiomeric excess (Scheme 2.1a).[54] In the same work, the authors proposed the catalytic pathway for the enantioselective aldol reaction. The first step provides the nucleophile attack of amino group to the ketones followed by the dehydration to give the enamine intermediate. At this point, the more reactive enamine (L-proline is in fact able to increase the HOMO energy, and thus the reactivity, of the nucleophile) reacts with the aldehyde to afford the iminium compound. In this phase, in addition to activation of the nucleophile by the amine moiety, the presence of the acid group is essential to achieve the stereocontrol in the transition state, where the aldehyde

exposes the *Re-face* to the enamine attack. The final addition of the water molecule leads to obtain the desired product and regeneration of the catalyst (Scheme 2.1b).

[53] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621., b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497.
[54] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.



Scheme 2.1 a) Enantioselective aldol reaction of acetone catalysed by L-Proline, b) proposed mechanism

Starting from the List's work and L-proline catalyst, numerous chemists devoted their efforts to the development of newer Proline-derived catalyst. MacMillan,[55] Hayashi[56] and Jørgensen[57] developed new methodologies based on L-proline. The modified catalysts present different characteristics in terms of acidity, steric hindrance, catalytic activity and stereocontrol ability (Figure 2.2). Precisely,

[55] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
[56] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.
[57] N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255.

because of these different characteristics, the proline-derived catalysts are divided in two main groups. On one hand, there are the catalysts that present a hydrogen-bond donor, able to exercise the enantiocontrol right through the hydrogen-bond formation with the electrophile, which is activated and correctly positioned. On the other hand, there are proline-derived catalysts characterised by the presence of a bulky moiety that allows the attack of the the electrophile selectively to one face of the enamine.

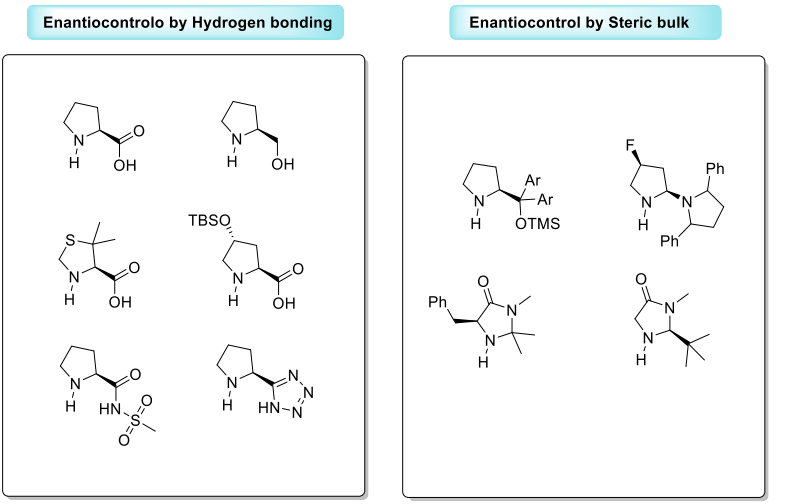


Figure 2.2 New organocatalysts derived from L-Proline

2.3 Bifunctional catalysts: example of non-covalent catalysis

In the field of non-covalent catalysis, an important role is certainly occupied by the bifunctional catalysts, obtained by the combination of a Brønsted acid and a Brønsted/Lewis basic centre. The unique characteristic of bifunctional catalyst makes them very appealing in asymmetric synthesis.[58] Indeed, the presence of two different functional groups ensures the cooperative and simultaneous activation of the pronucleophile, via deprotonation, and electrophile, via H-bonding interactions, according to the most general activation proposal (Figure 2.3).

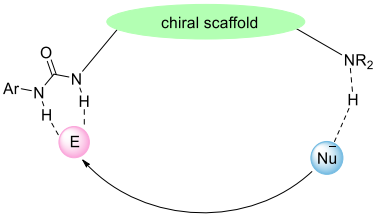


Figure 2.3 Dual activation of bifunctional organocatalysts

In addition, the organocatalyst thanks to the multipoint recognition is able to place the two reactants in a suitable spatial arrangement, allowing a faster and more selective conversion toward the products. The transition state that was generated shows well-organised geometry and rigidity assuring a stereocontrolled formation of the

[58] a) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *2010*, 1229–1279. b) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao, *Synlett* **2012**, *23*, 490–508. c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281. d) S. Gandhi, V. Sivadas, B. Baire, *Eur. J. Org. Chem.* **2021**, *2021*, 220–234.

new bonds. The simplest example of bifunctional organocatalysts is represented by Cinchona alkaloids. The tertiary quinuclidine nitrogen in quinine, quinidine, cinchonine and cinchonidine act as the basic group, while the hydroxyl group, namely a H-bond donor group, constitutes the Brønsted-acid moiety.

Another important class of organocatalysts consists of Brønsted base/H-bond donor organocatalysts, in which the basic center is represented by the tertiary amine group, such as Cinchona alkaloid-derived amines, and as hydrogen-bond donor group there are groups urea, thiourea, (thio)squaramide or sulphonamide, appropriately positioned on a chiral scaffold (Figure 2.4a).

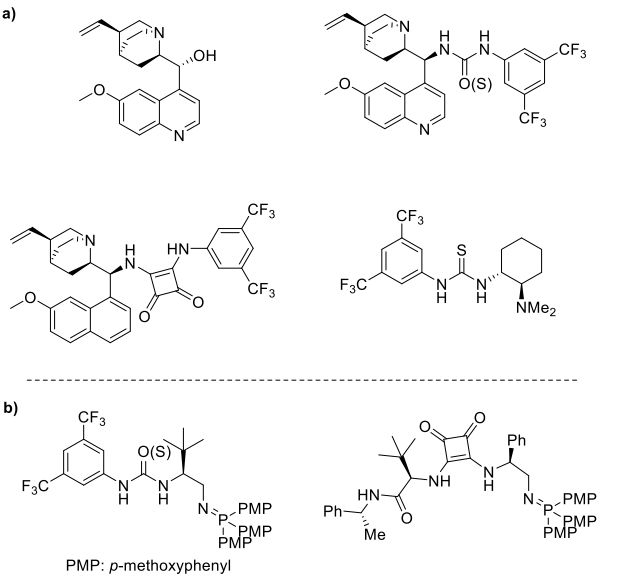


Figure 2.4 Representative examples of bifunctional organocatalysts

Although, these organocatalysts have a wide use in asymmetric synthesis, it is important to recognize that their employment is limited

to the intrinsic reactivity of reagents. Indeed, the tertiary chinuclidine amine is a relatively weak Brønsted base, in some cases unsuitable to deprotonate a pronucleophile. When necessary, more active catalysts must be considered, for example the powerful bifunctional iminophosphorane-based organocatalysts, which present an iminophosphorane with a higher deprotonative power (Figure 2.4b).

3 Ester/amide surrogates

3.1 General features

Ester/amide surrogates are a class of organic compounds that received great interest in recent years in the field of asymmetric catalysis. These molecules are often characterised by the presence in the acyclic position of a nitrogen-based heterocycle.[59] This template group is important as an activating moiety, becoming easier the functionalization of this carboxylic acid derivative with respect to the corresponding amide or ester, but the presence of the aza-heterocycle also affects the mode of interactions with the catalyst. Finally, the heterocycle can be replaced with a certain simplicity, enabling the back transformation to classical carboxylic acid derivatives (Figure 3.1).

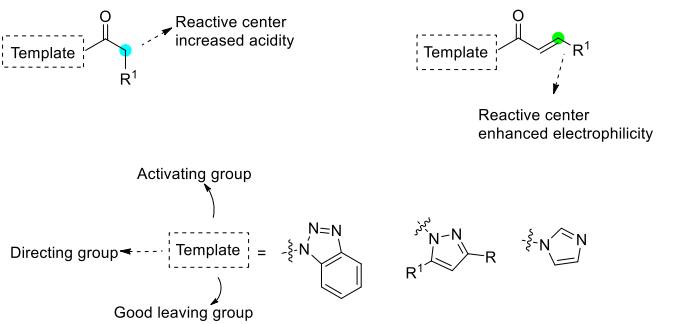


Figure 3.1 General scaffold of masked esters/amides

As mentioned above, the presence of the aza-heterocycle in ester

[59] a) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2015**, *115*, 9922–9980. b) D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. - Eur. J.* **2015**, *21*, 4494–4504.

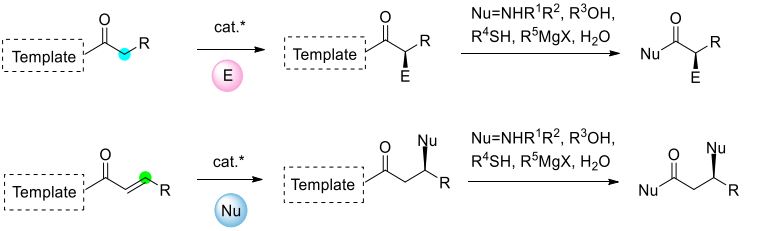
surrogates increase the reactivity in saturated carboxyl derivative, when they act as nucleophiles, increasing the α-acidity. On the other hand, in the corresponding α,β-unsaturated carboxyl compounds enhanced electrophilicity at the β position is observed due to lower LUMO energies computed for this type of electrophiles.[58a]

The principal limitation for the direct employment of the carboxylic acid derivatives, such as esters and amides as nucleophiles is surely their low reactivity explicated in the difficulty to generate the corresponding enolate by common organic bases, because of the moderate acidity at α position. On the contrary, when the "auxiliary group" is heteroaromatic an increased acidity is observed (about four orders of magnitude in the case of pyrazoleamides[60]) making possible the formation of C-C, C-X (X = S, N, Cl, Br..) bond under mild reaction conditions.

In addition, the heterocycle could act as by living group, making very interesting the employment of masked esters/amide to the synthesis of useful α-functionalised scaffolds.

As example, through typical addition-elimination step, using alcohols or amines as nucleophiles post-functionalizations give rise to the desired esters or amides (Scheme 3.1).

[60] C. Volpe, S. Meninno, A. Capobianco, G. Vigliotta, A. Lattanzi, *Adv. Synth. Catal.* **2019**, *361*, 1018–1022.



Scheme 3.1 General pathway of masked esters/amides and their post-functionalization

Various aza-heterocycles can be successfully employed in asymmetric catalysis either under metal- and organocatalytic conditions.[58]

3.2 Pyrazoleamides

Pyrazoleamides are likely the most studied ester surrogates in asymmetric catalysis. Pyrazoleamides were widely applied both as electrophiles and nucleophiles in asymmetric metal-, organic- and more recently photochemical catalysis.[61] They react under mild reaction conditions, being generally stable and simple to access through condensation reaction between the heterocycle and the corresponding carboxylic acid. As a general remark, the principal limitation is related to the use of simple aliphatic pyrazoleamides due to their poor reactivity, correlated to the low α-acidity. In the case of α,β-unsaturated ones, low reactivity at the β position is also observed, which imposes stoichiometric strong base use and harsch reaction conditions.[62]

The introduction of pyrazole moiety in the surrogate ester, was found to be useful in either metal-catalysed and organocatalyzed asymmetric processes not only to boost the reactivity but also to improve the stereocontrol of the processes.

3.2.1 Pyrazoleamides as electrophiles

As already mentioned, the pyrazoleamides demonstrated to be suitable starting materials in catalytic enantioselective reactions. The success of unsaturated acyl pyrazoles as electrophile is related to the lower LUMO energies compared with their esters or amides parents.

[61] S. Meninno, F. Franco, M. Benaglia, A. Lattanzi, *Adv. Synth. Catal.* **2021**, *363*, 3380–3410.
[62] C. E. Stivala, A. Zakarian, *J. Am. Chem. Soc.* **2011**, *133*, 11936–11939.

In general, the LUMO energy value of the electrophile depends on the electronwithdrawing character of its substituents. In the case of α,β-unsaturated pyrazoleamides, the higher electron withdrawing character of the acyl group results in a lower LUMO value of the corresponding derivative. As a results, the masked esters/amide bearing aromatic aza-heterocycles show the lowest energies and consequently are the most reactive compounds among those reported in Figure 3.2.

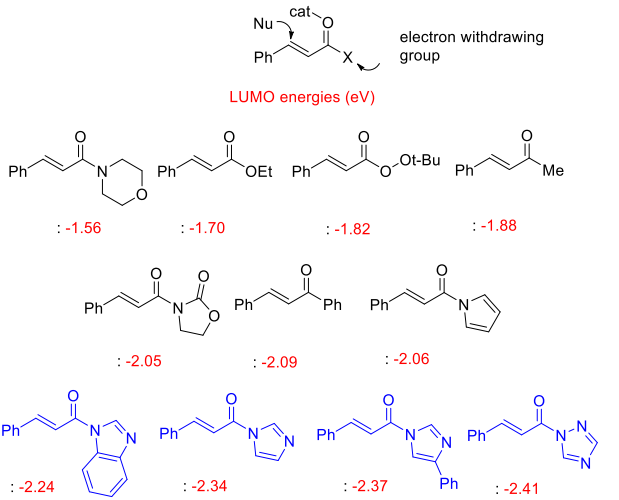
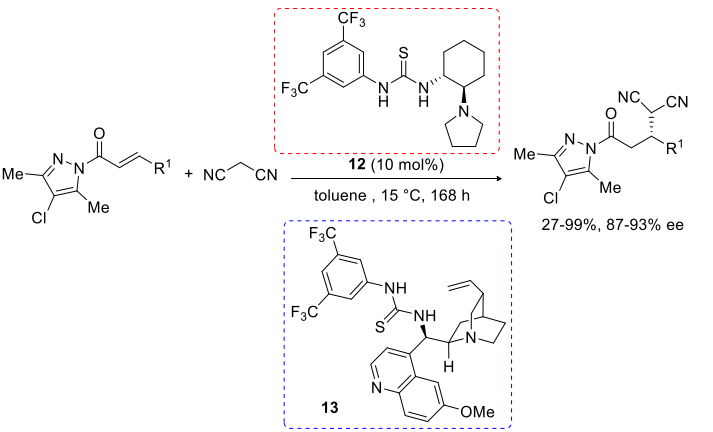


Figure 3.2 LUMO energies of representative carbonylic compounds and carboxylic acid derivatives

Another important feature of pyrazoleamides, mentioned above, is the ability of pyrazole moiety to establish a useful hydrogen-bonding network with the catalyst, thus achieving a rigid transition state. A nice example, that underlines this aspect has been reported by the Li

group in 2016.[63] The methodology conceptually takes up another work published by Kanemasa some year earlier, where the pyrazoleamides were applied in the same reaction under Ni-catalysis.[64]

In both methodologies, the Michael addition of malononitrile to aliphatic and aromatic α,β-unsaturated pyrazoleamides has been reported. The Li route involved the use of bifunctional thiourea **12** at 10 mol % loading, which afforded the products in good to high yields and enatioselectivities (Scheme 3.2), although the reactions were generally slow (168 h). A higher conversion, but a decrease of the enantioselectivity was observed when using the bifunctional organocatalyst **13**.



Scheme 3.2 Michael addition of malononitrile to α,β-unsaturated pyrazoleamides

[63] Y. Zheng, Y. Yao, L. Ye, Z. Shi, X. Li, Z. Zhao, X. Li, *Tetrahedron* **2016**, *72*, 973–978.
[64] K. Itoh, Y. Oderaotoshi, S. Kanemasa, *Tetrahedron Asymmetry* **2003**, *14*, 635–639.

The key role of the pyrazole moiety was demonstrated when using the α,β-unsaturated *N*-acylpyrrole as the reagent. Being the LUMO energies very close, a similar result in terms of yield and enantioselectivity was expected. However, in the case of *N*-acylpyrrole, the product was isolated with relatively poorer yield (77%) and lower enantioselectivity (88% ee), with respect to the use of α,β-unsaturated pyrazoleamide reagent (99% yield, 92% ee).

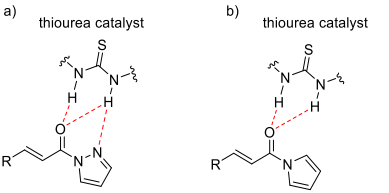


Figure 3.3 H-bonding of thiourea moiety with acylpyrazole and acylpyrrole

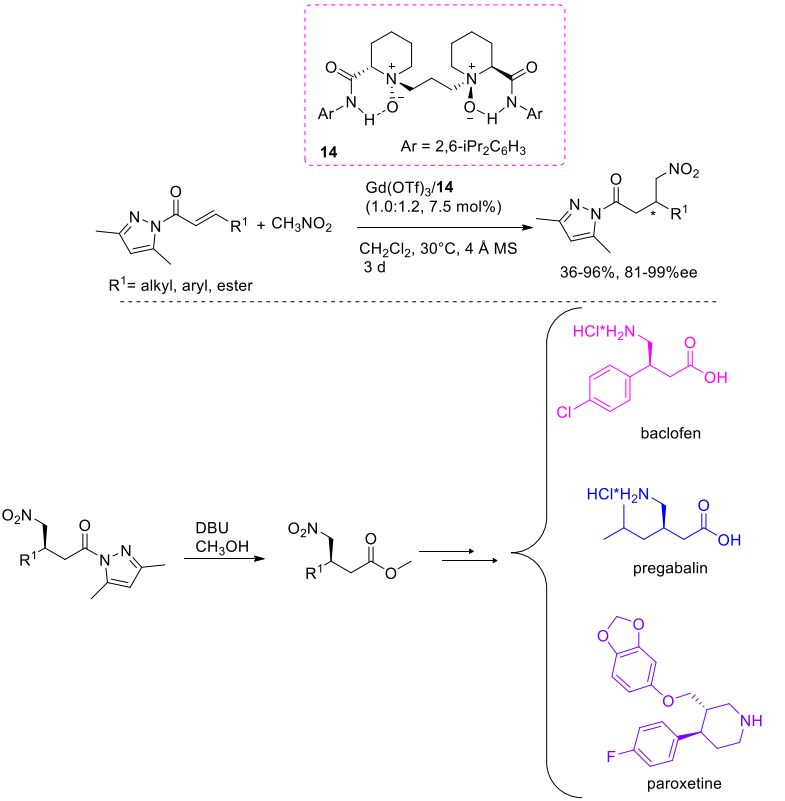
The different behaviour of *N*-acylpyrrole and *N*-acylpyrazole were explained suggesting a better hydrogen-bonding network displayed between the pyrazole unit and the thiourea group of the catalyst, which would account for higher level of enantioselectivity and reactivity (Figure 3.3).

Recently, many other investigations on α,β-unsaturated *N*-acylpyrazole were published. A very interesting metal-catalysed application of α,β-unsaturated *N*-acylpyrazole has been reported by Feng in 2015.[65] A highly enantioselective conjugate addition of nitroalkanes to α,β-unsaturated pyrazoleamides was catalysed by *N*,*N*'-dioxide/Gd(III) complex under mild conditions, using 7.5 mol

[65] Q. Yao, Z. Wang, Y. Zhang, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2015**, *80*, 5704–5712.

% loading of an *in situ* shaped catalyst (Scheme 3.3a).

The methodology proved to be of general scope, affording the γ–nitropyrazoleamides in high to excellent yields and enantioselectivity.

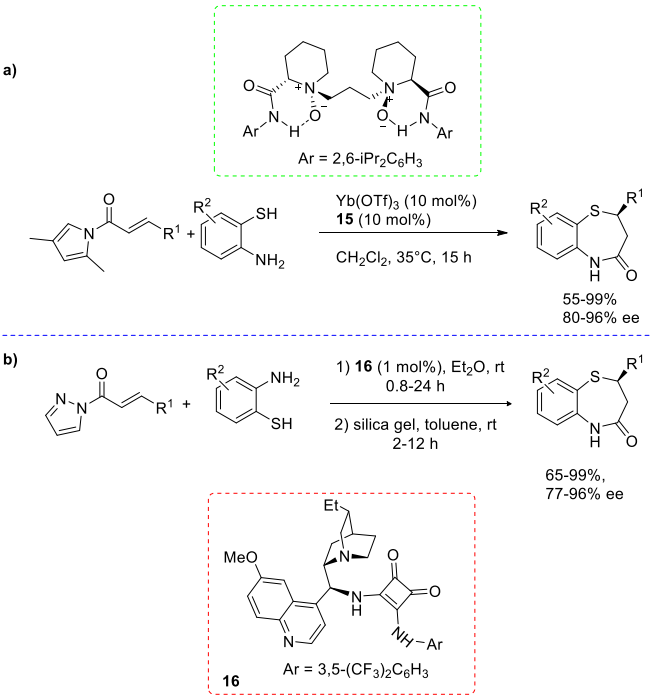


Scheme 3.3 Gd-catalyzed asymmetric addition of nitroalkanes to α,β-unsaturated pyrazolamides **(a)**, Optically active pyrazoleamide-based adducts useful for the synthesis of marketed pharmaceuticals **(b).**

In the Feng study, the displacement of pyrazole moiety by methanol allowed to obtain the corresponding optically active γ–nitroesters which are useful starting materials for the synthesis of some active

pharmacologically important ingredients as Pregabalin, Baclofen and Paroxetine (Scheme 3.3b).

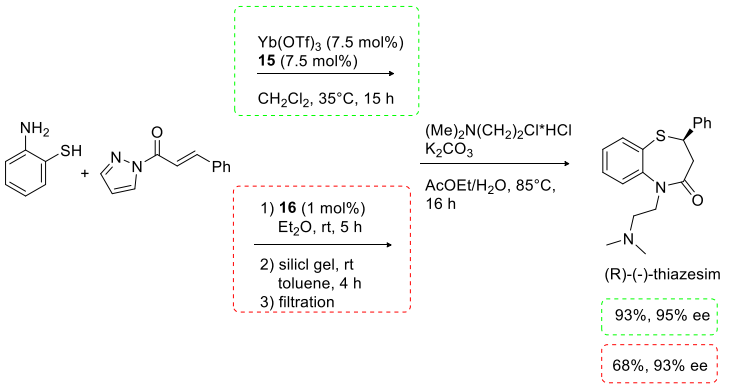
It is important to underline that many other nucleophiles were used in combination with this class of electrophilic pyrazoleamides. An example has been reported in the one-pot synthesis of NH-free 1,5-benzothiazepines starting from α,β-unsaturated pyrazoleamides and



Scheme 3.4 One-pot synthesis of NH-free 1,5-benzothiazepines metslcatalysed **(a)**, organocatalysed **(b)**

2-aminothiophenols disclosed simoultaneously by Feng's[66] and our research groups.[67] Feng developed a cascade sulfa-Michael/cyclization reaction catalysed by 10 mol% of a chiral Ytterbium complex (Scheme 3.4a), while our approach involved the employment of 1 mol% of a Cinchona alkaloid-derived squaramide **16** (Scheme 3.4b).

Both methodologies afforded, the benzothiazepine products in good to high yields an entantioselectivities. It is important consider that NH-unprotected products, are suitable for *N*-alkylation or acylation, to create libraries of compounds to test for biological activities.



Scheme 3.5 Multistep pathway of (R)-(-)-thiazesim

In both methodologies, through a multistep reaction concise synthesis of the antidepressant drug (R)-(−)-thiazesim has been illustrated, easily accessed in good overall yield and excellent enantiocontrol (Scheme 3.5).

[66] G. Wang, Y. Tang, Y. Zhang, X. Liu, L. Lin, X. Feng, *Chem. - Eur. J.* **2017**, *23*, 554–557.
[67] S. Meninno, C. Volpe, A. Lattanzi, *Chem. - Eur. J.* **2017**, *23*, 4547–4550.

3.2.2 Pyrazoleamides as nucleophiles

Introduced in asymmetric organocatalysis by Barbas in 2012,[68] pyrazoleamides bearing an active methylene have been exploited as pronucleophiles, thanks to easier enolization they can undergo (Figure 3.4).

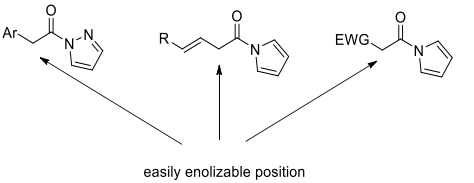
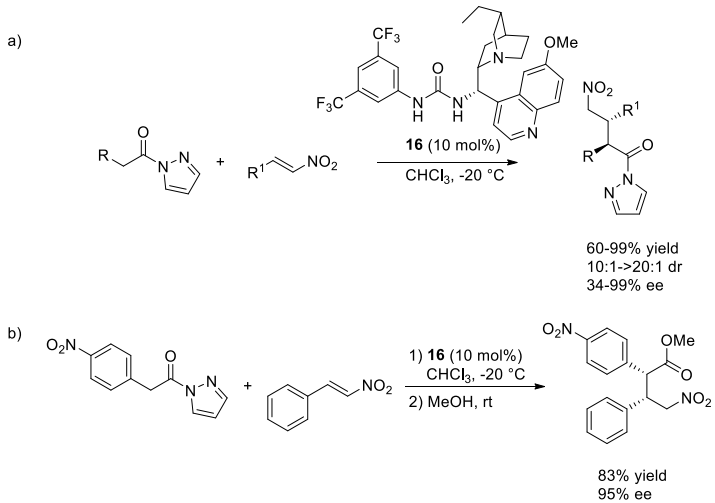


Figure 3.4 Easily enolizable acylpyrazoles

Indeed, the pyrazole moiety is able to increase the α-acidity in aryl acetic derived pyrazoleamides or β,γ-unsatured pyrazoleamides and those bearing an electronwithdrawing at α-position. In addition to the activating function, the pyrazole group once again performs a directing role thanks to the hydrogen-bonding network displayed with the catalyst (Figure 3.3).

[68] B. Tan, G. Hernández-Torres, C. F. Barbas, *Angew. Chem. Int. Ed.* **2012**, *51*, 5381–5385.



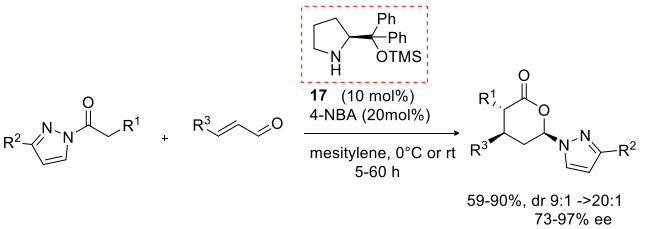
Scheme 3.6 Organocatalysed asymmetric Michael addition to nitrostyrenes **(a),** and successive derivatization **(b)**

In the Barbas' work, the aryl acetic derived pyrazoleamides were reacted in asymmetric Michael addition to nitrostyrenes catalysed by urea-containing cinchona-based catalyst **17** providing the adducts in excellent yields and ee values (Scheme 3.6a). The authors also reported a one-pot access to the corresponding ester products, achieving good overall yield and ee values (Scheme 3.6b).

After this example, a variety of methodologies involving the use of pyrazolamides as nucleophiles for the construction of C-C, C-X (X= S, Cl, F…) has been reported.61[61] In this section some representative examples are reported.

In 2015, the Singh group disclosed an interesting route to afford functionalised δ-lactones through a diastereo- and enantioselective Michael/cyclization cascade process, starting from pyrazoleamides as

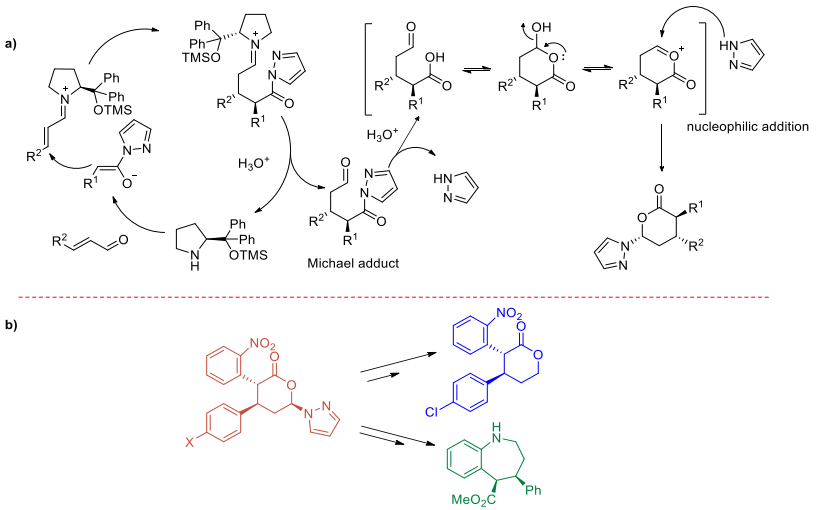
donor.[69] The reaction was fostered by Jørgensen-Hayashi catalyst **17** at 10 mol % loading, leading to the products in good to high yields high diastero- and enantioselectivities (Scheme 3.7).



Scheme 3.7 Diastereo- and enantioselective synthesis of functionalised δ-lactones

Mechanistic experiments showed that the pyrazole group acts in double. In the first catalytic cycle, the pyrazole was removed by the substitution of the water to afford the corresponding carboxylic acid. At this point, the lactonization was supported by the nucleophilic attack of the pyrazole (Scheme 3.8a).

[69] S. Agrawal, N. Molleti, V. K. Singh, *Chem. Commun.* **2015**, *51*, 9793–9796.

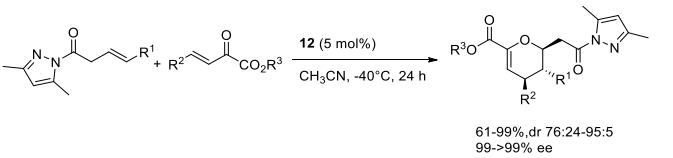


Scheme 3.8 Proposed mechanism for δ-lactones synthesis **(a)**, successive transformations **(b)**

In addition, the δ-lactone so obtained, can be manipulate, and without erosion of the enantioselectivity enabled to afford δ-lactones and benzazepines, scaffolds endowed with a wide range of biological activities (Scheme 3.8b).

Another interesting methodology illustrated the use of the β,γ-unsatured pyrazoleamides as nucleophiles in a formal inverse-electron-demand oxa-Diels-Alder reaction catalysed by amine-thiourea **12** at 5 mol % loading to achieve dihydropyrans bearing three vicinal chiral centers in good to high yield (61-99%) and with excellent enantioselectivity (99 to >99% ee). (Scheme 3.9).[70]

[70] J. Qin, Y. Zhang, C. Liu, J. Zhou, R. Zhan, W. Chen, H. Huang, *Org. Lett.* **2019**, *21*, 7337–7341.



Scheme 3.9 Enantioselective organocatalysed oxa-Diels-Alder reaction

The excellent regio- and stereoselective outcome was rationalised speculating a stepwise mechanism, in which the dienolate stabilised by H-bonding interactions with the ammonium ion moiety of the catalyst is supposed to attack the H-bonded acceptor, simultaneously oriented by the thiourea group. Furthermore, the aromatic stacking interaction is supposed to provide an additional effect in the transition state stabilization (Figure 3.5).

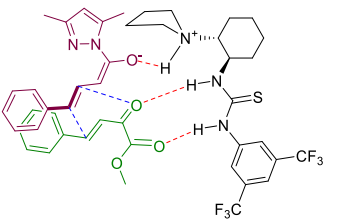
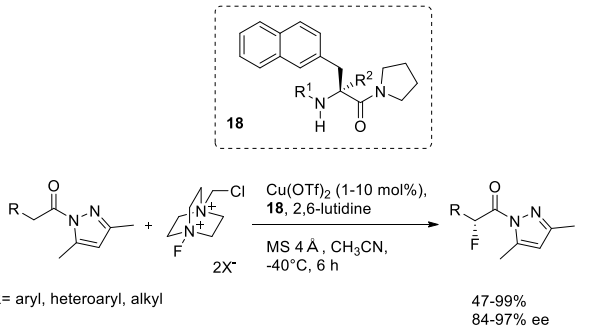


Figure 3.5 Suggested transition state model

As reported above, given the importance of fluorine atom in the bioactive molecules many efforts have been devoted to the design of new fluorinated compounds. So, Ishihara[71] in 2020 and Meggers[72] in 2021 developed two metal-catalysed methodologies for the enantioselective fluorine introduction at α-position of carboxylic acid derivatives, starting from *N*-acyl pyrazoles.

[71] K. Ishihara, K. Nishimura, K. Yamakawa, *Angew. Chem. Int. Ed.* **2020**, *59*, 17641–17647.
[72] Y. Grell, X. Xie, S. I. Ivlev, E. Meggers, *ACS Catal.* **2021**, *11*, 11396–11406.

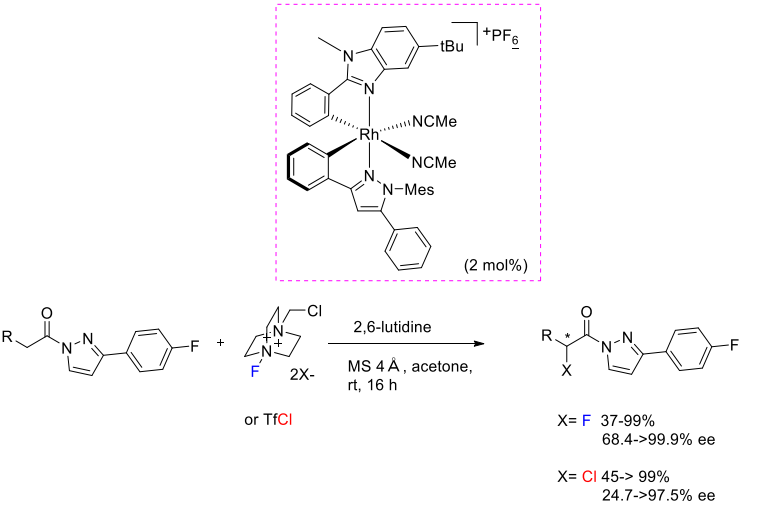
In the first work, the highly enantio- and site-selective reaction was catalysed by chiral *in situ* shaped π-Cu^{II} complex at 1-10 mol% loading (Scheme 3.10).



Scheme 3.10 Ishihara's method for the α-fluorination of *N*-acyl pyrazoles

The generality of the process was demonstrated affording a large number of fluorinated pyrazoleamides. The methodology indeed, works well both starting from the aryl acetic and aliphatic pyrazoleamides, achieving as unique product the α-fluorinated compounds. The reaction selectively proceeded when β,γ-or γ,δ-unsaturated carboxamides were used. Replacement of the pyrazole moiety has been successfully demonstrated leading to fluorinated esters, amides, aldehydes, and alcohols.

On the other hand, Meggers, disclosed the α-fluorination and α-chlorination of *N*-acylpyrazoles catalysed by non-C_2-symmetric and sterically demanding chiral-at-rhodium catalyst in high yields and enantioselectivity (Scheme 3.11).



Scheme 3.11 Meggers' method for the α-fluorination of *N*-acyl pyrazoles

The high enantiocontrol has been ascribed to the shielding of the *Si*-face of the coordinated enolate by π–π stacking interactions with the mesityl moiety of the pyrazole ligand. In this way, only the *Re*-face of the enolate is susceptible to electrophilic attack by the fluorinating reagent, thus supplying an almost perfect asymmetric induction (Figure 3.6).

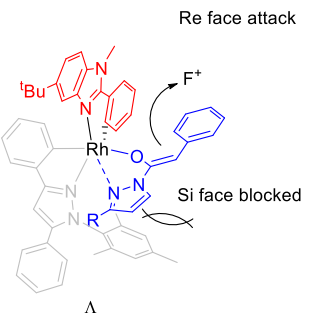


Figure 3.6 Proposed transition state model

4 Flow chemistry

4.1 Origin and benefits

The concept of continuous flow, initially used only in the field of petrochemical and bulk chemicals industries, was already known in the 1970s referring to high-performing, cost effective, safe, and atom-efficient chemical operations.[73] The term "flow chemistry" has been used in chemical synthesis only since 1990s and 2000s.[74] Although the fine-chemical industry is mainly based on batch or semi-batch reactors, the interest in continuous-flow processes, especially toward manufacturing of APIs, has appreciably increased over the years.[75] The flow technology refers to the use of channels or tubing to carry out a reaction in a continuous stream rather than in a flask. The peculiarity of this young technology regards the excellent heat and mass transfer, because of the high surface area to volume ratios and inherently small reactor volumes, that allows enhancing reactivity or in some cases enabling new reactions. On laboratory scale, a continuous flow process is run in microreactors, small-diameter devices that allow to perform the reaction in a confined space under rigorously controlled conditions (Figure 4.1). Due the small dimensions, all the reaction parameter as temperature, pressure, and

[73] *Energy Management and Effciency for the Process Industries.*, Wiley-AIChE, Place of Publication Not Identified, **2015**.
[74] S. Y. F. Wong Hawkes, M. J. V. Chapela, M. Montembault, *QSAR Comb. Sci.* **2005**, *24*, 712–721.
[75] a) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2–25. b) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728.

flow rate, are generally more easily set up and monitored compared to batch process, resulting in a more reproducible process. Moreover, in principle a continuous flow process could be easily scaled through three different approaches. To produce a large amount of compound it is possible running the reaction for a longer time (scaling-out). This is the easiest way to scale up a flow reaction by the continuous supply of reagents to increase the productivity. The other two approaches to scale up the process involve i) the use of multi reactors in parallel (numbering up), or ii) the use of a larger continuous reactor (scaling up).

Another important aspect to highlight is the safety issue. First, thanks to the high heat-exchange efficiency in microreactors, the generation of hot spots, temperature gradients, or accumulation of heat is suppressed. Moreover, the precise control of the temperature allows to avoid that uncontrolled reaction take place during the scale-up operations.

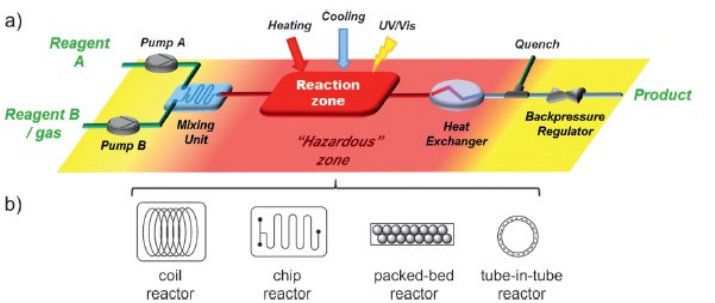


Figure 4.1 General flow set-up using microreactors

It becomes possible to carry out reactions involving even unstable or

hazardous reagents thanks to their easier handling in such systems compared with the flask chemistry. In fact, the presence of closed and pressurized system combined with small reactor volume and usually very low residence time guarantee the rapid transformation of toxic and hazardous reagents to give more stable compounds with a significant reduction of risks. Also, the managing of gas reactants is simplified because the volume of gas fraction in a pressurized liquid-filled system is significantly reduced thus decreasing the evaporation of low-boiling reagents or the formation of explosive gas mixtures. These peculiar and convenient features have led today to an increasing interest for the continuous flow process for the manufacturing of APIs or their intermediates.

Moreover, successful examples have been reported in which the continuous flow process has been combined to other technologies such as microwave irradiation, supported reagents or catalysts, photochemistry, inductive heating, electrochemistry, new solvent systems, 3D printing, or microreactor technology, thus leading to further improvements of the efficiency even obtaining fully automated systems.[76]

The continuous flow systems can be divided in four main typologies.[77]

[76] M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796–11893.

[77] T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329–332.

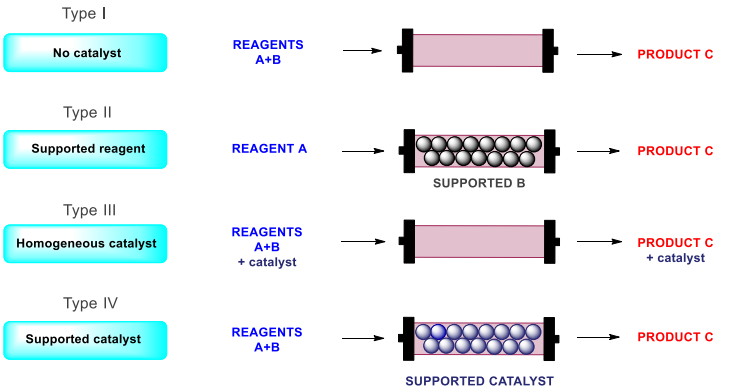


Figure 4.2 Principal reactor types

In the first two reactor types, I and II, the reaction works without a catalyst while in the type III and IV, a catalytic process is involved (Figure 4.2). The main difference between reactors I and II is in the supply of the reagents. In type I, both reagents are flowed into the tube, where the reaction occurs. At the end of the channel, the mixture is collected and in case there are any unreacted compounds, a further purification step is required. In type reactor II, one of the two substrates is supported in the tube. In this case, an excess of the reagent B is supported in the reactor, so the compound A is fully consumed, and the product is obtained pure. At the end, the reactor bearing the unreacted compound B must be changed.

As mentioned above, the reactor type III and IV involves the presence of catalyst. In type III the homogenous catalyst is pumped in the channel, so at the end it is necessary to separate the catalyst and possible byproducts. In type IV, the heterogenous catalyst is

supported and confined in the reactor, so when compound A completely reacts with B, in principle all the purification steps are avoided, and the catalyst could be recycled. In accordance with the "green sustainable chemistry"[78] the last two approaches, that exploit a catalytic system are better than type I and II. However, type IV is considered the most convenient in performing synthetic reactions because catalyst contamination is avoided in this system.

[78] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**

4.2 Batch vs flow reactions

Although thermodynamic and kinetic parameters of the reactions do not change in batch and in flow chemistry, these two processes show significant differences regarding important aspects of the reactions.

The first and more evident difference is in the extremely different apparatus (Figure 4.3). Traditional batch reactions involve many operations as reported in the figure 4.3a, starting from the flask set-up, quenching and further purification, including the employment of several glassware. Moreover, a high temperature reaction also needs a high boiling-point solvent, and in the case of volatile compound a refrigerating system.

In the typical flow set-up, many operations are included in the simple plant (Figure 4.3b). Indeed, at the end of the reactor is allocated the quenching module, which allows accurate control of the residence time.

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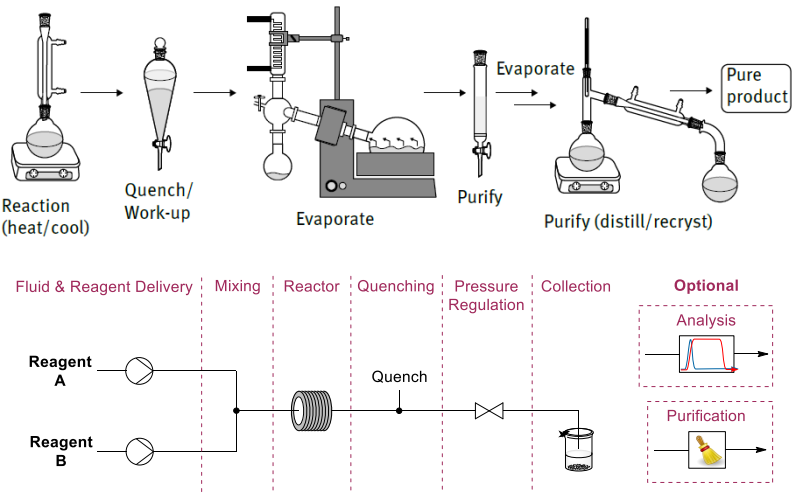


Figure 4.3 Typical operation in batch reaction **(a)**, and general flow set-up **(b)**

In addition, it is possible to increase the temperature of the reaction even when lower boiling-point solvents are used by easily applying a pressure regulation that avoid the solvent evaporation during the reaction. In some cases, especially by using type reactor IV (see paragraph 4.1), the products were obtained without further purification. On the contrary, many examples are reported in which the purification steps are included in the flow process.

Besides the differences regarding set-up and manual operations, there are significant conceptual distinctions between batch and flow reactions which will be discussed in the next paragraphs (Table 4.1).

Table 4.1 Difference between batch and flow set-up

	Batch	**Flow**
Stoichiometry	Concentration/ratio of the molar quantities	Concentration/ratio of the flow rates
Reaction time	Time spent under the defined conditions	Residence time spent in the reaction zone depending on the flow rate and reaction volume
Reaction progress	Time spent in the flask	Distance travelled in the channel
Steady state characteristics	It has a uniform concentration at each position within the flask at a particular moment	It has a steady but different concentration at each position throughout the length of the reactor

4.2.1 Reaction time

In batch chemistry, reaction time indicates the time in which the reaction mixture is at precise temperature value. On the other hand, in flow chemistry, time reaction indicates the residence time which is

the time spent by the reactant in reactor zone, the space between the reagent inlet and the position of the quencher inlet (Figure 4.4a).

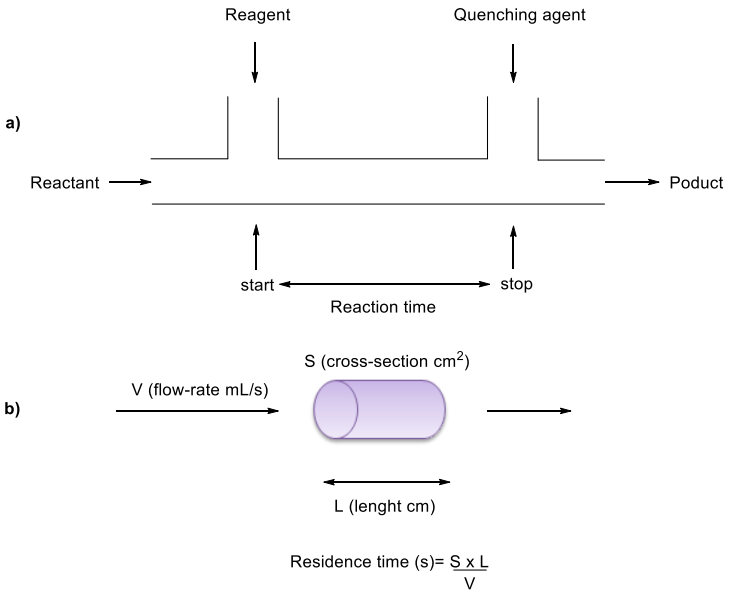


Figure 4.4 Evaluation of reaction time

It is calculated as the ratio between the reactor volume and the flow rate (Figure 4.4b).

4.2.2 Stoichiometry reaction and its outcome

The stoichiometry in continuous flow reaction is defined as the ratio between the concentration of the reagents and their flow rate. On the contrary, the stoichiometry for batch reaction is described by the concentration of the reactants and the ratio of their molar quantities.

By considering the concentration of reagents and products during the reaction time it is possible to recognize different important properties

of continuous flow process. In flask reaction, the concentration of reactants during the reaction is uniform in a flask at a precise time and exponentially decays during the reaction.

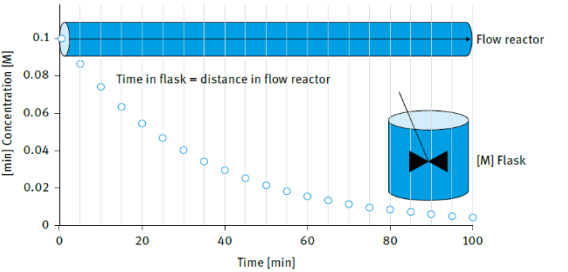


Figure 4.5 Exponential decays of reagent concentration

On the contrary, in flow reactor with a constant flow rate, the decay of the concentration depends exponentially on the distance along the tube (Figure 4.5). Essentially, the time in the batch reaction is equal to the distance in flow reactor.

In addition, the concentration of a reactant does not change with the progress of operation time in a particular point of the device. In this way, the reaction time in a flow reactor can be related to the space position inside of the reactor, thus making possible to set its value by adjusting the length of a flow reactor, and the flow rate.

4.2.3 Mixing of reactants

Both in a batch process and in the flow reactor the mixing of the reactants is the key parameter for achieving good results in term of yields. In the typical flask reactor, mass and heat transport is guaranteed by the mechanic or magnetic stirring. Generally, mixing step is on the timescale of seconds or longer and entails to

inhomogeneities, turbulence and chaotic mixing.

In the microreactor, thanks to the small dimension of the channel (diameter: 0.05–0.5 cm), the mixing of the reagents obtained through laminar flow is faster and allows an improved homogeneity. Due its high intensity mixing, that can only be achieved using inline mixers, the flow reactors are used in some fine chemical and pharmaceutical applications. This approach which exploits the enhanced mixing under flow conditions is commonly named as "flash chemistry".[79]

[79] J. Yoshida, Y. Takahashi, A. Nagaki, *Chem Commun* **2013**, *49*, 9896–9904.

4.3 Multi-step reactions

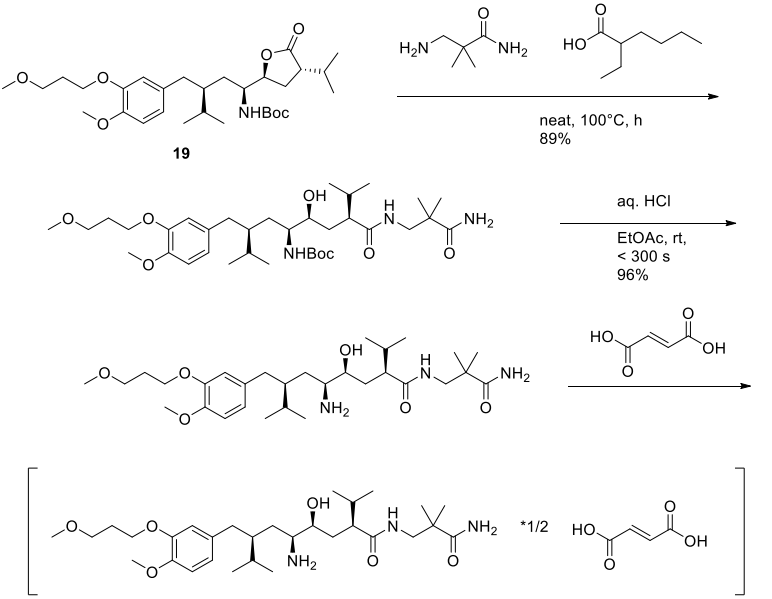
In general, under batch reactions, the multi-step transformations from starting material to the target product, involves a step-by-step process in which each synthetic step intermediate is isolated and purified to remove any byproducts that might interfere with the subsequent synthetic transformation.

Under flow reaction conditions, all these operations can be avoided and each intermediate is used in the follow transformation without furthermore purification. The maximization of this concept is expressed when a multi-step reaction is performed using automatized process.

The first integrated end-to-end plant was reported by researchers of the Novartis-MIT Center for Continuous Manufacturing in Cambridge, that developed the end-to-end continuous manufacturing of an API, aliskiren hemifumarate (Figure 4.6).[80]

Starting from the chemical intermediate **19**, all the reactions and chemical operations as, separations, crystallizations, drying, and formulation, were performed under flow conditions to obtain at the end of the process the final tablets.

[80] S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, B. L. Trout, *Angew. Chem. Int. Ed.* **2013**, *52*, 12359–12363.



Scheme 4.1 Reaction pathway for the synthesis of aliskiren hemifumarate

The synthetic process involved three reaction steps (Scheme 4.1). When carried out in batch, the isolation of each intermediate is needed to obtain the final product and the tablets are subsequently prepared. All the process, including purification steps, require 300 h and 21 operations.

By exploiting the continuous process, the process time is reduced to 48 h with only 14 operations. This result is even more significant when compared to industrial production, where the time reduction together with a decrease in the amount of solvents used represents a great economic advantage. In addition, reactor used has a volume of 0.8 L with a footprint of 2.4x7.3m^2 and working in continuous furnishes 0.8tons of API/years.

It is interesting to highlight that a reactor of about 7.7 L is required to synthesize the same amount of product in batch, making even more clear the volume difference between flow and batch process at commercially scale. In one year were placed on the market about 188 ton of aliskiren hemifumarate, obtained in a batch reactor of 1500 L. The same amount of API could be achieved using flow reactor of 136 L.

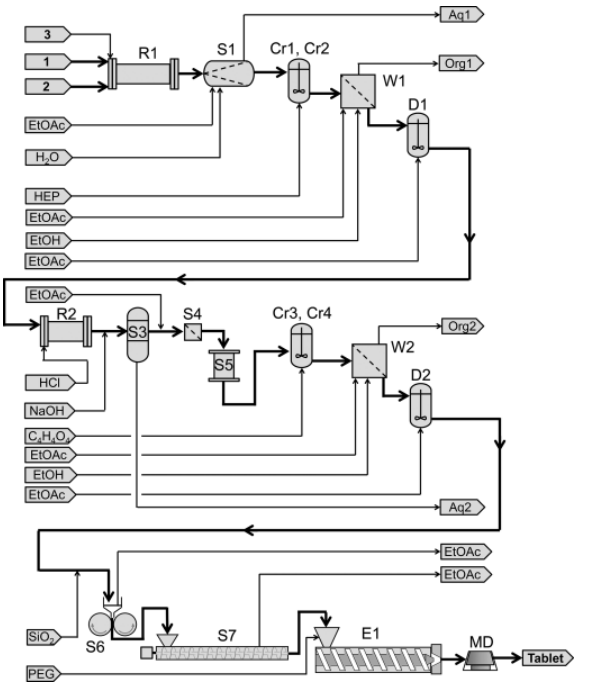
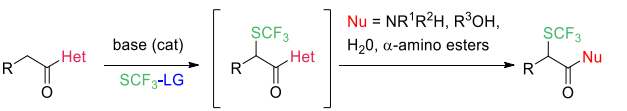


Figure 4.6 Continuo process of aliskiren hemifumarate synthesis

Research objectives

The main target of this industrial doctoral work in collaboration with Laboratori Alchemia s.r.l and University of Milano is the development of new mild and safer organocatalytic methodologies for the introduction of SCF_3 group into organic compounds useful in the pharmaceutical industry exploring batch and flow conditions.

Laboratori Alchemia is a pharmaceutical industry which deals with the synthesis of APIs from more than 60 years. Its research interests concern the application of new enabling technologies, as flow chemistry, able to provide high value intermediates with an improvement of the efficiency, greater reliability, safety and better sustainability. To learn the necessary skills to apply the flow chemistry in industrial process, a training period in the research group of Prof. Benaglia, a great expert of flow chemistry, has been undertaken. Given the pharmaceutical interest in the incorporation of the trifluoromethylthio group into bioactive molecules, the first goal of this work has been the development of an organocatalytic methodology for the formal incorporation of trifluoromethylthio group at the α-position of carboxylic acid derivatives, developing a one-pot methodology starting from pyrazoleamides.



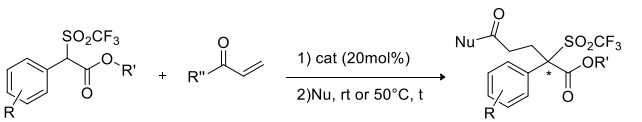
Indeed, the methodologies so far reported for this reaction are very

scarce, both using nucleophilic and electrophilic methods.

Initially, the reaction was studied under classical batch reaction conditions, including manipulations useful to prepare other difficult to obtain β-trifluoromethylthiolated alcohol and triflones.

In Milano the same reaction was approached under flow conditions and, during the period spent in Laboratori Alchemia, a strategy has been elaborated to overcome the limitations of the developed flow process, indicated by AIFA.

Then, in the last part of PhD at University of Salerno has been focused on the asymmetric organocatalytic synthesis of trifluoromethyl-substituted compounds bearing a quaternary sterocenter.



In this methodology triflones (-SO_2CF_3) have been used as pronucleophiles in the Michael reaction to access different products having a quaternary stereocenter suitable for the asymmetric synthesis of novel heterocycles.

5 Formal organocatalytic α-trifluoromethylthiolation of carboxylic acid derivatives under batch conditions via *N*-acyl pyrazoles

5.1 Background

The incorporation of fluorine atom(s) in bioactive molecules in the last decades has become one of the most attractive areas thanks to features this functional group is able to confer on a molecule in terms of unprecedented therapeutic profiles.[7] In this framework, a prominent place is occupied by trifluoromethylthio group that shows high lipophilicity (Hansch's hydrophobic parameter π=1.44) and strong electron withdrawing properties (Hammett constant: σ_m=0.40 and σ_p=0.50).[10,11] Pharmaceuticals, agrochemicals whose biological activity is strictly related to the presence of a SCF_3 residue in the molecular scaffold are known in the market (Figure 5.1). The academic and industrial interests in this appealing functionalization have led to the development of new methodologies to extend the scope of the trifluoromethylthiolated organic compounds. Historically, the metal catalysed formation of $C(sp^2)$–SCF_3 bond appeared as a first route.[24]

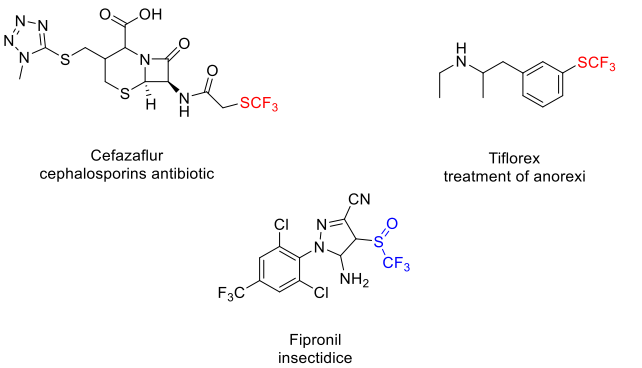


Figure 5.1 Bioactive molecules bearing SO_nCF_3 (n=0-1) groups

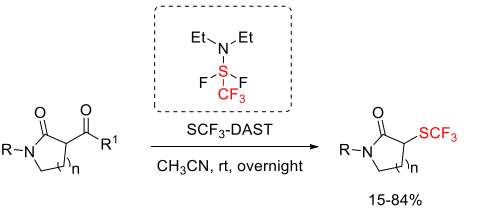
For the construction of C(sp^3)–SCF_3 bond, new achievements have been recently disclosed in the trifluoromethylthiolation of carbonyl compounds, with particular interest for ketones, silyl enol ethers and 1,3-dicarbonylic compounds. For the latters, enantioselective organocatalytic trifluoromethylthiolations have been developed, achieving the products in good yields and excellent stereo-control.[40,81]

The incorporation of the SCF_3 group at α-position of carbonyl compounds has been widely studied, whereas the number of protocols exploiting carboxylic acid derivatives are scarce, being a more challenging process. Scattered examples of functionalised esters have been reported, in which the desired products were usually prepared by using stoichiometric bases or metal catalysis under strictly controlled reaction conditions.[31-34]

A first example on the synthesis of trifluoromethylthiolated lactams,

[81] a) I. Saidalimu, S. Suzuki, T. Yoshioka, E. Tokunaga, N. Shibata, *Org. Lett.* **2016**, *18*, 6404–6407. b) Q.-H. Deng, C. Rettenmeier, H. Wadepohl, L. H. Gade, *Chem. - Eur. J.* **2014**, *20*, 93–97.

has been disclosed by Shibata in 2017. [82] A deacylative process is induced by SCF_3-DAST reagent, leading to the products in general good yields (Scheme 5.1).



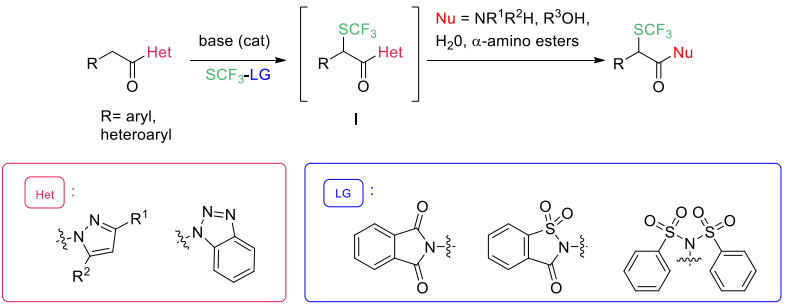
Scheme 5.1 Trifluoromethylthiolation of lactam

Considering the paucity of general procedures for the trifluoromethylthiolation of carboxylic acid derivatives and given the knowledge and background on the pyrazoleamides as pronucleophiles, we designed an efficient one-pot organocatalytic method for the formal trifluoromethylthiolation of these derivatives via *N*-acyl pyrazoles.

[82] I. Saidalimu, T. Yoshioka, Y. Liang, E. Tokunaga, N. Shibata, *Chem. Commun.* **2018**, *54*, 8761–8764.

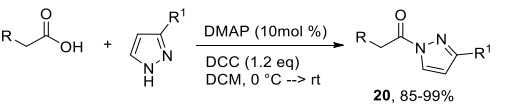
5.2 Results and discussion

We designed a one-pot base-promoted enolate generation of the corresponding *N*-acyl pyrazole, followed by the attack the trifluoromethylthio electrophilic reagent, to give the trifluoromethytlthiolated intermediate. The latter then would undergone acyl substitution by amines, alcohols, water and α-amino esters to afford the final products (Scheme 5.2).



Scheme 5.2 Formal one-pot trifluoromethylthiolation of carboxylic acid derivatives

We commenced our study by the synthesis of the pyrazoleamides **20** and SCF_3 electrophilic reagents **21**, through procedures already reported in the literature. Pyrazoleamides **20** were easily obtained by the DCC-mediated coupling reaction of carboxylic acid with the heterocycle promoted by DMAP (Scheme 5.3).[83]

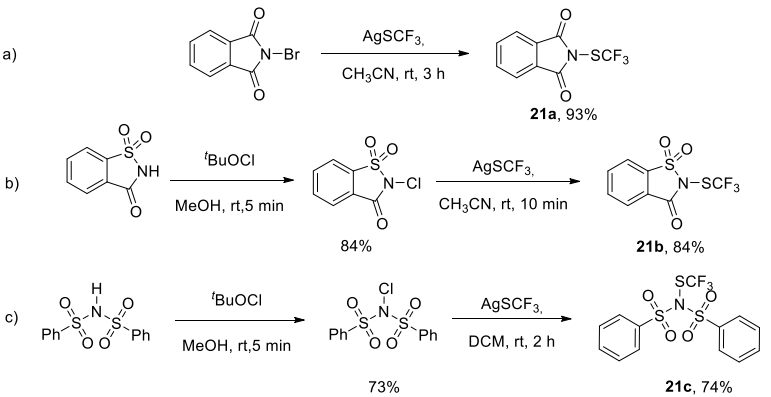


Scheme 5.3 Synthesis of *N*-acylpyrazoles

The electrophilic trifluoromethylthiolating reagents were obtained by

[83] J. Zhang, X. Liu, R. Wang, *Chem. - Eur. J.* **2014**, *20*, 4911–4915.

the reaction of the corresponding halogenide compound and silver(I) trifluomethanethiolate as reported in literature (Scheme 5.4). In the case of *N*-(trifluoromethylthio)phthalimide the simple reaction between *N*-bromophthalimide and silver(I) trifluomethanethiolate is sufficient for the synthesis of target molecule (Scheme 5.4a).[84] In the other two cases, the preparation of the halogenated precursor was achieved by treatment with the *tert*-butyl hypochlorite (Scheme 5.4b and c).[44,85]



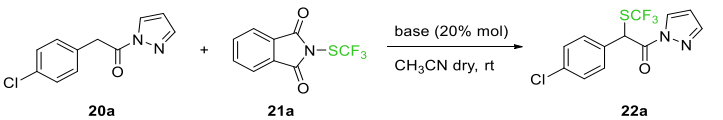
Scheme 5.4 Synthesis of electrophilic trifluoromethylthiolating reagents

Our investigation commenced reacting model compound **20a** with readily synthesized *N*-(trifluoromethylthio) phthalimide **21a** using 20 mol% of common bases in acetonitrile at room temperature (Table 5.1). Different bases have been tested; the tertiary amine, such as diisopropyl ethyl amine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane

[84] K. Kang, C. Xu, Q. Shen, *Org. Chem. Front.* **2014**, *1*, 294.
[85] P. Zhang, M. Li, X.-S. Xue, C. Xu, Q. Zhao, Y. Liu, H. Wang, Y. Guo, L. Lu, Q. Shen, *J. Org. Chem.* **2016**, *81*, 7486–7509.

(DABCO), afforded the product with moderate yields in a similar reaction time (Entries 1 and 2). *t*BuOK improved the conversion, providing the desired product in 60% conversion in only 30 min, although the presence of the bis-trifluoromethylthiolated compound was detected (Entry 3).

Table 5.1 Base screening in the synthesis of **22a**[a]



Entry	base	T (h)	Conv[b]. **22a** (%)
1	DIPEA	3	41
2	DABCO	4	30
3[c]	$^{t}BuO^{-}K^{+}$	0.5	60
4	KOH	4	30
5	Protone sponge (PS)	1	78
6	DBU	1.5	55
7[d]	TBD	1.5	65
8	PS	6	77
9[e]	PS	1	84

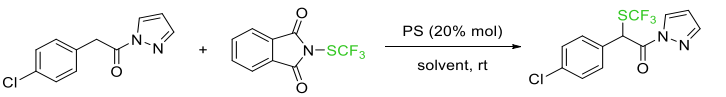
[a] Unless otherwise noted reactions were conducted with **20a** (0.1 mmol), **21a** (0.12 mmol), base (0.02 mmol), CH_3CN (0.2 M), under an N_2 atmosphere. [b] Determined by NMR spectroscopy of a crude reaction mixture using 1,3,5-trimethoxybenzene and α,α,α-trifluorotoluene as internal standards. [c] 10% of bis-trifluoromethylthiolated product was detected. [d] 6% of bis-trifluoromethylthiolated product was detected. [e] 0.1 mmol of PS was used.

The inorganic base KOH gives the same low yield of tertiary amines (Entry 4). Protone sponge (N,N,N',N'-tetramethyl-1,8-naphthalenediamine), supplied good conversion after a moderate reaction time (Entry 5).

Finally, stronger organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), did not furnish improved of yields and when employing TBD traces of the bis- trifluoromethylthiolated product was detected (Entries 6 and 7). Proton sponge (PS) was then further investigated. Only a slightly improved yield was observed when a stoichiometric amount of base was used (Entry 9), while longer reaction times did not affect the outcome of the reaction (Entry 8 vs Entry 5).

Optimization of the reaction conditions followed a solvent study. As reported in Table 5.2 a series of organic solvents was tested and the better results were achieved when acetonitrile and DMSO were employed (Entries 1 and 7). Although the conversions showed to be similar, acetonitrile was chosen being more manageable then DMSO.

Table 5.2 Solvent screening in the synthesis of **22a**[a]



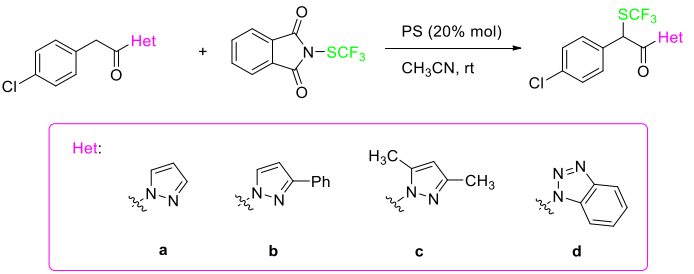
Entry	solvent	T (h)	Conv[b]. **22a** (%)
1	CH_3CN	6	75
2	CH_2Cl_2	6	10
3	toluene	6	16
4	MeO^tBu	6	31
5	AcOEt	6	21
6[c]	DMF	6	41
7[c]	DMSO	6	76

[a] Unless otherwise noted reactions were conducted with **20a** (0.1 mmol), **21a** (0.12 mmol), base (0.02 mmol), CH_3CN (0.2 M), under an N_2 atmosphere. [b] Determined by NMR spectroscopy of a crude reaction mixture using 1,3,5-trimethoxybenzene and α,α,α-trifluorotoluene as internal standards. [c] After reaction, the solvent was removed through aqueous extraction and the product was partially degraded.

Finally, the nature of the heterocycle in the model pyrazoleamide was investigated. According to the data reported in Table 5.3 3-phenyl pyrazole **b** was selected as the most effective reagent (Entry 2). When comparing the columns of conversion and isolated yield, some differences appear. This result can be explained considering that exposure to silica gel during chromatographic purification can lead to the cleavage of the pyrazole moiety. The cleavage is more or less significant according to the pyrazole substitution. Indeed, the compound bearing benzotriazole as acyl residue (Entry 4) was not recovered after chromatographic purification, due to the high stability

of the benzotriazole anion (pK_a= 9.3) which is easily cleaved.

Table 5.3 Heterocycle and concentration optimization in the synthesis of **22**[a]



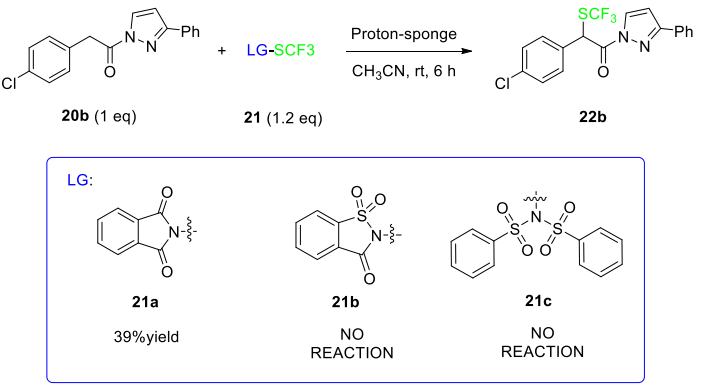
Entry	heterocycle	t (h)	Conv[b]. **22** (%)	Yield[c] 3 (%)
1	**a**	6	75	63
2	**b**	6	91	39
3	**c**	6	7	-
4	**d**	6	69	0

[a] Unless otherwise noted reactions were conducted with **20** (0.1 mmol), **21a** (0.12 mmol), **PS** (0.02 mmol), in anhydrous acetonitrile (0.5 mL) under nitrogen atmosphere. [b] Determined by ^{1}H-NMR and ^{19}F-NMR spectroscopy of crude reaction mixture using 1,3,5-trimethoxybenzene and α,α,α-trifluorotoluene as internal standard.[c] Yield of isolated product.

On the other hand, the pyrazole is a less effective leaving group (pK_a= 19.8), which allows us to isolate the final product after chromatography (Entries 1 and 2).

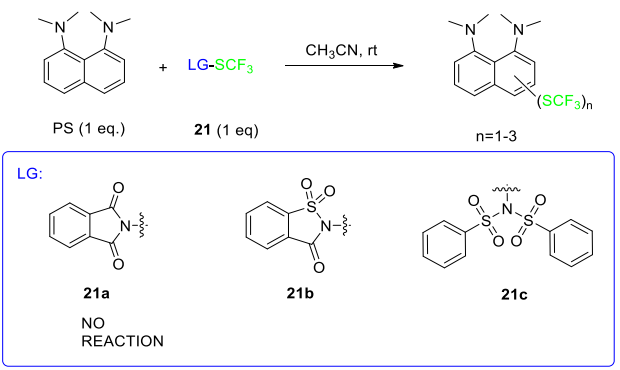
Other experiments were carried out to evaluate the most efficient electrophilic reagent for the reaction. Besides the *N*-(trifluoromethylthio) phthalimide, used in all the phase of optimization, other two electrophilic reagents, that are known to be

more electrophilic than the previous one, were tested (Scheme 5.5).[35] Surprisingly, in the reactions involving more reactive compounds **21b** and **21c** the desired product was not observed.



Scheme 5.5 Trifluoromethylthiolation using different electrophilic reagents

The direct reaction between PS and more electrophilic reagents **21b** and **21c** was demonstrated, which caused deactivation of the base,



Scheme 5.6 Reaction between PS and trifluoromethylthiolating agents

affording the mono- and the bis- trifluoromethylthiolated aromatic

compounds in agreement with results by Ozeryanskii (Scheme 5.6).[86] Confirmation of these side-reactions derived from the high-resolution mass spectrometry analysis (HRMS) of the crude reaction mixtures, which showed the presence of two main products reported in order of intensity of the corresponding molecular peaks (Figure 5.2).

a) The mono trifluoromethylthiolated proton-sponge A
   $[A+H]^+$ Found: m/z 315.1140, Calcd: m/z 315.1143
b) The bis trifluoromethylthiolated proton-sponge B
   $[B+H]^+$ Found: m/z 415.0736, Calcd: m/z 415.0737

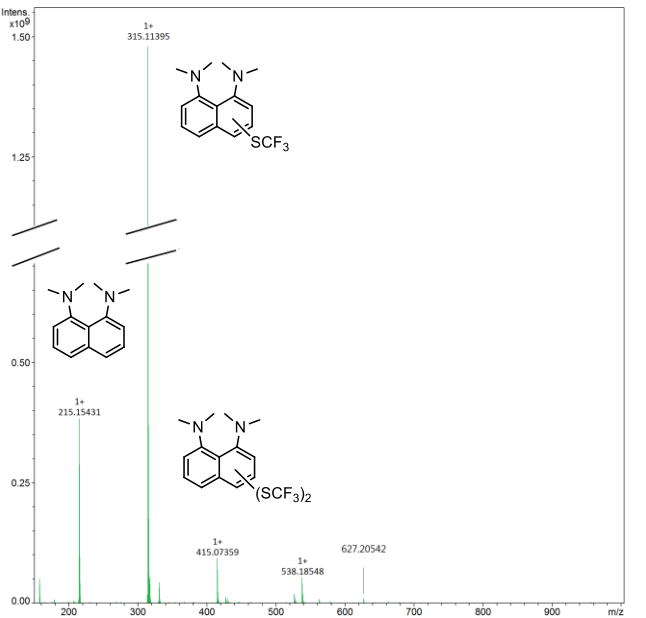


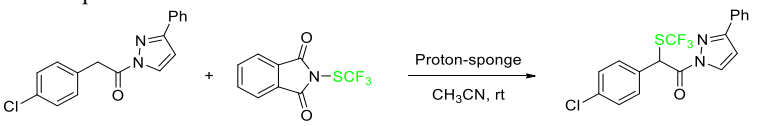
Figure 5.2 HRMS (ESI-FT ICR) analysis of the crude reaction mixture

[86] V. A. Ozeryanskii, A. F. Pozharskii, G. R. Milgizina, S. T. Howard, *J. Org. Chem.* **2000**, *65*, 7707–7709.

It is important to underline that in the case of *N*-(trifluoromethylthio) phthalimide, the formation of trifluoromethylthiolated-PS products of type A and B was not observed even at higher temperature.

Concentration, equivalents of base and temperature were then optimized (Table 5.4).

Table 5.4 Optimization of the reaction conditions

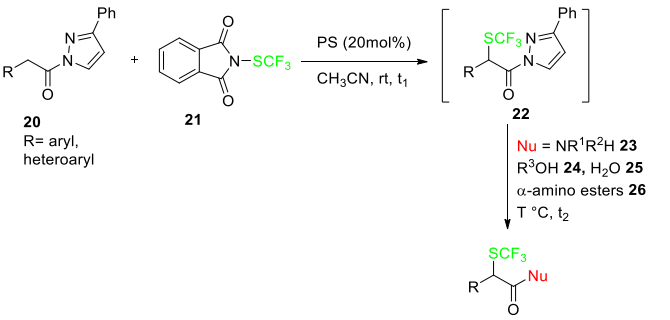


20b **21a** **22b**

Entry	C_1[M]	PS (eq)	t (h)	Conv[b]. **22b** (%)	Yield[c] **22b** (%)
1	0.2	0.2	6	91	39
2	0.2	0.1	6	45	-
3	0.5	0.2	6	60	-
4	0.15	0.2	6	78	-
5[d]	0.2	0.2	4.5	68	-

[a] Unless otherwise noted reactions were conducted with **20b** (0.1 mmol), **21a** (0.12 mmol), **PS** (20% mol) in anhydrous acetonitrile (0.5 mL) under nitrogen atmosphere. [b] Determined by ^{1}H-NMR and ^{19}F-NMR spectroscopy of crude reaction mixture using 1,3,5-trimethoxybenzene and α,α,α-trifluorotoluene as internal standard. [c] Yield of isolated product. [d] T= 45°C.

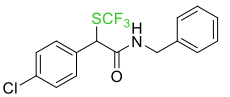
Under the optimized reaction conditions, (Table 5.4, Entry1), a one-pot approach was developed, in which the trifluoromethylthiolation step was followed by the addition of nucleophilic species such as amines, anilines, alcohols and water (Scheme 5.7).



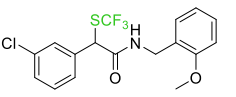
Scheme 5.7 One-pot synthesis of trifluoromethylthiolated carboxylic acid derivatives

Several aryl and hetoaryl *N*-acylpyrazoles **20** were investigated to explore the scope of the process in the synthesis of the α-trifluoromethylthiolated amides (Table 5.5). Acyl pyrazoles **20**, bearing *para*-, *meta*- and *ortho*-electron-withdrawing and donating groups in the benzene ring, were efficiently transformed in the α-trifluoromethylthiolated secondary amides (**23a-f**) after adding at the end of the first step simple or functionalized primary amines (1.3 eq) at room temperature. The addition of secondary amines needed higher temperature (50°C) to obtain tertiary α-trifluoromethylthiolated amides in very good yields (**23g-l**). The heteroaryl acyl pyrazoles as well as anilines are suitable compounds for the synthesis of the corresponding amides without yield erosion (**23m-p**). Finally, when an amino alcohol or a diamine were used to replace the pyrazole moiety, the selective formation of the secondary amide derivatives was observed (**23q-r**). However, aliphatic acyl pyrazoles did not give any product when reacted under usual conditions, probably due the reduced acidity of the α-hydrogen atoms.

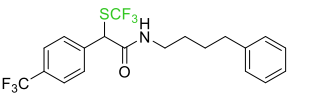
Table 5.5 Substrate scope for the one-pot synthesis of trifluoromethylthiolated amides



23a
t_1 6 h, t_2 2.5 h, 90%

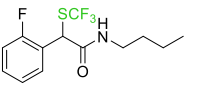


23b
t_1 3.5 h, t_2 1 h, 72%



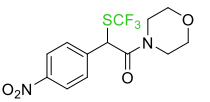
23c
t_1 1.5 h, t_2 3 h, 98%

23d
t_1 5 h, t_2 2 h, 74%



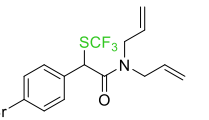
23e
t_1 5 h, t_2 3 h, 66%

23f
t_1 24 h, t_2 6 h, 75%

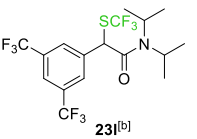


23g[b]
t_1 0.5 h, t_2 3 h, 93%

23h[b]
t_1 3 h, t_2 6 h, 98%

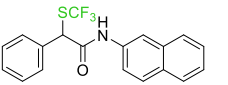


23i[b]
t_1 7 h, t_2 8 h, 72%

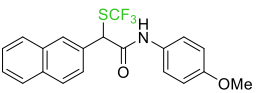


23l[b]
t_1 0.3 h, t_2 6 h, 73%

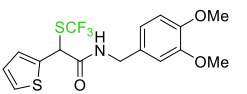
23m
t_1 3 h, t_2 5.5 h, 83%



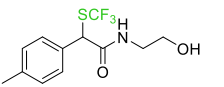
23n
t_1 20 h, t_2 48 h, 79%



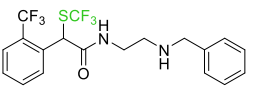
23o
t_1 5 h, t_2 5 h, 73%



23p
t_1 1 h, t_2 3 h, 72%



23q
t_1 24 h, t_2 3 h, 70%



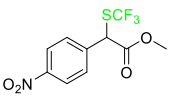
23r
t_1 4 h, t_2 2 h, 80%

[a] All reactions were carried out using **20b** (0.2 mmol), **21a** (0.24 mmol), PS (0.04 mmol), CH_3CN (0.2 M), under an N_2 atmosphere, at rt for t_1; then amine (0.26 mmol) was added, stirring maintained for t_2 at room temperature for compounds **23**. [b] Second reaction step was performed at 50 °C. Isolated yields of products are reported.

For the synthesis of the functionalized esters and carboxylic acids at the end of the first reaction step, CH_3CN was removed under reduced pressure. The esters were obtained adding the alcohol as solvent and 20mol% of DMAP (Table 5.6a). Final esters were rapidly formed performing the reaction at T=50°C and isolated in good yields, using both primary and secondary alcohols.

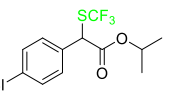
Table 5.6 Substrate scope for the one-pot synthesis of trifluoromethylthiolated esters

a)



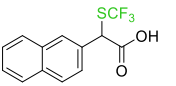
24a
t_1 0.5 h, t_2 1 h, 80%

24b
t_1 14 h, t_2 2 h, 78%

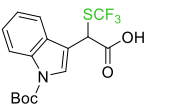


24c
t_1 14 h, t_2 4 h, 83%

b)



25a
t_1 7 h, t_2 16 h, 90%



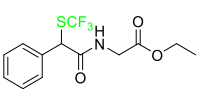
25b
t_1 8 h, t_2 16 h, 70%

[a] All reactions were carried out using **20b** (0.2 mmol), **21a** (0.24 mmol), PS (0.04 mmol), CH_3CN (0.2 M), under an N_2 atmosphere, at rt for t_1; after completion of the first step, acetonitrile was evaporated, DMAP (0.04 mmol) and anhydrous alcohol (2 mL) were added and the mixture stirred at 50 °C for compounds **24**. In the case of compounds **25**, after completion of the first step, acetonitrile was evaporated, LiOH (0.4 mmol) and THF/H_2O were added and the mixture stirred at rt. Isolated yields of products are reported.

To prepare the carboxylic acids, after the trifluoromethylthiolation step, hydrolysis was directly performed with LiOH in THF/H_2O at room temperature to afford the α-trifluoromethylthiolated acids in 90% and 70% yields, respectively (Table 5.6b).

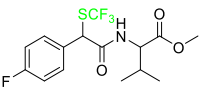
Interestingly, glycine ethyl ester and racemic α-amino acid ester hydrochloride salts are suitable reagents for the one-pot synthesis, under basic condition of highly functionalised α-trifluoromethylthiolated amides (Table 5.8). Thanks to this route, it was possible for the first time access the α-trifluoromethylthiolated amides in high yield as diastereosimeric mixture.

Table 5.7 Substrate scope for the one-pot synthesis of trifluoromethylthiolated functionalised amides from α-amino acid ester salts

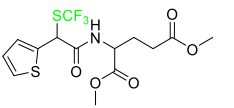


26a
t_1 20 h, t_2 3 h, 95%,

26b
t_1 3 h, t_2 3 h, 78%, 50/50



26c
t_1 5 h, t_2 3 h, 76%, 50/50



26d
t_1 1 h, t_2 4 h, 83%, 50/50

[a] All reactions were carried out using **20b** (0.2 mmol), **21a** (0.24 mmol), PS (0.04 mmol), CH_3CN (0.2 M), under an N_2 atmosphere, at rt for t_1; then α-amino ester hydrochloride (0.26 mmol) and triethylamine (0.26 mmol) were added and the mixture was stirred at rt. Isolated yields of products **26** are reported

To better understand the mechanism involved in the trifluoromethylthiolation step, some experiments were carried out. Indeed, the model reaction, reported in Table 5.4 was performed in the presence of radical scavenger 2,2,6,6-Tetramethylpiperidine 1-

oxyl (TEMPO 1 eq)[87]. At the end of the reaction, the product was obtained in 85% yield proving the absence of a radical process. Moreover, the same reaction was monitored by ^{19}F NMR in CD_3CN using α,α,α-trifluorotoluene as internal standard (Figure 5.3). Fast formation of the corresponding product peak at -41.0 ppm, was observed after one minute. The consumption of the trifluoromethylthiolating reagent was gradually observed by the decrease of the peak intensity at -49.9 ppm. After 2 hours, the formation of two new peaks at -46.6 ppm and -38.1 ppm, corresponding to $(SCF_3)_2$ and the bis-trifluoromethylthiolated product was observed, respectively.

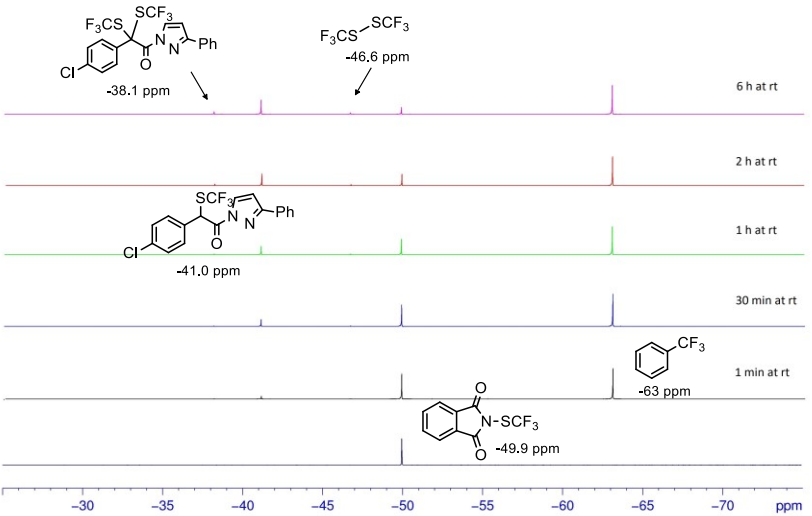


Figure 5.3 Trifluoromethylthiolation of *N*-acylpyrazoles monitored by ^{19}F NMR in CD_3CN

However, NMR spectra show that these products are formed in low

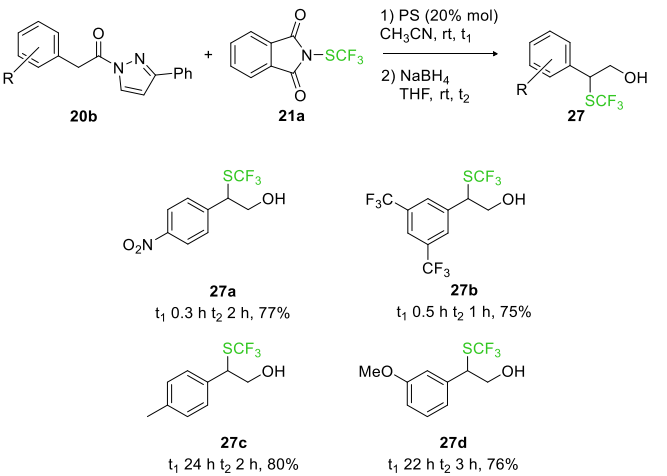
[87] See experimental section.

conversion, less than 5%, attesting that their formation is a negligible process.

All these data are in agreement with a mechanism, in which the acylpyrazole **20b** was firstly deprotonated by PS to give enolate that reacts with the trifluoromethylthiolating reagent **21a** to afford the product **22b**.

To furthermore expand the utility of our methodology, products **22b** were manipulated in order to achieve in a one-pot route to β-trifluoromethylthiolated alcohols under mild reaction conditions (Scheme 5.8). Similarly, to the synthesis of ester derivatives, at the end of the trifluoromethylthiolation step, the solvent was removed from the mixture reaction and the intermediate was subjected to smooth reduction by $NaBH_4$ in THF at room temperature to give primary alcohols in 75-80% yields. This sequence demonstrated to be a complementary route to prepare α-trifluoromethylthiolated alcohols.[85,88]

[88] L. Hu, M. Wu, H. Wan, J. Wang, G. Wang, H. Guo, S. Sun, *New J. Chem.* **2016**, *40*, 6550–6553.



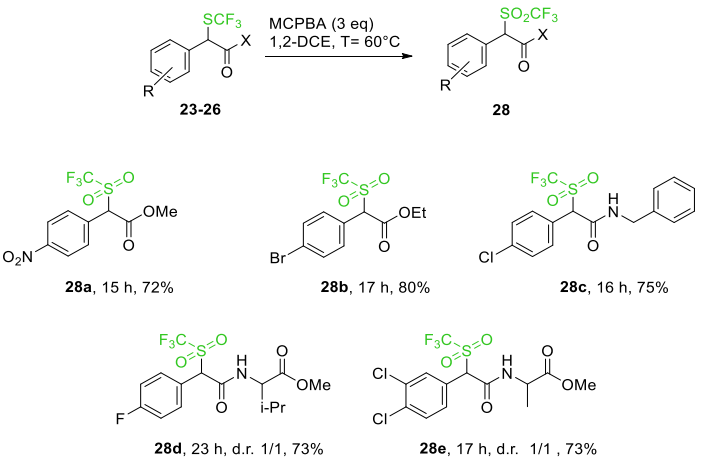
Scheme 5.8 One-pot synthesis of α-trifluoromethythiolated primary alcohols

As mentioned above, another important fluorine bearing functional group in bioactive compounds is the trifluoromethylsulfone, namely triflone (SO_2CF_3). Its introduction at α-position of carbonyl compounds is nowadays very rare.[89] More recently a procedure to prepare triflones has been disclosed by Shibata, using a trifluoromethanesulfonyl hypervalent iodonium ylide.[90] We found an alternative route to obtain the triflones via oxidation of the trifluoromethylthio group by *m*-chloroperbenzoic acid (MCPBA), a simple and easily available oxidant, working in 1,2-dichloroethane at T= 60°C (Scheme 5.9). Both esters, amides and highly functionalized amides were smoothly transformed in fairly good yields into the

[89] a) Z. Huang, Y.-D. Yang, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 1094–1097. b) F. Terrier, E. Kizilian, R. Goumont, N. Faucher, C. Wakselman, *J. Am. Chem. Soc.* **1998**, *120*, 9496–9503.

[90] Z. Huang, S. Jia, C. Wang, E. Tokunaga, Y. Sumii, N. Shibata, *J. Fluor. Chem.* **2017**, *198*, 61–66

corresponding triflones.



Scheme 5.9 Synthesis of triflones derivatives of compounds **23**,**24** and **26**

5.3 Conclusions

A first one-pot organocatalytic trifluoromethylthiolation of carboxylic acid derivatives *via* readily available *N*-acyl pyrazoles has been developed. This methodology, proceeds efficiently under mild reaction conditions, using catalytic loadings of a commercial base and the Munavalli reagent, followed by the addition of alcohols, amines, water and α-amino acid esters as the nucleophiles. In general, the α-trifluoromethylthiolated carboxylic acid derivatives starting from aryl and heteroaryl acetic acid derived pyrazoles were achieved in moderate to good yields. Mechanistic studies allowed to establish reagent **20** is deprotonated by PS to form the enolate, which would react with electrophilic compound **21a** to produce product **23**, excluding a radical process.

Straightforward elaboration of the products **23** to primary alcohols and more interesting to triflones opened the access to other useful classes of fluorine incorporating compounds, hitherto not readily available by previous methods.

6 Telescoped continuous flow synthesis of α-Trifluoromethylthiolated Esters and Amides via *N*-acyl pyrazoles

6.1 Background

Scientists' attention to pollution and waste disposal issues is considerably increasing in recent years. Among chemical industries, pharmaceutical industry has to face the problem of a higher production of waste. About 80% of waste derives from solvents.[91] For this reason, many efforts have been devoted to develop more convenient syntheses with lower environmental impact.

One of the most effective strategies to minimize the waste are "One-pot reactions" and "Telescoped processes", which allow to realize multiple transformations while avoiding the isolation of each intermediate of the sequence. The elimination of separation processes and purification of reaction intermediates allows to minimize chemical waste while saving time and simplifying several practical aspects. The "telescopic" and "one-pot" terms do not always describe the same type of process. In the one-pot process, unlike telescopic reaction, the reaction solvent, if necessary, could be removed by evaporation and replaced with another one. [92]

In this context, the continuous flow technology is providing to be a useful tool to carry out the telescoped synthesis of API offering a

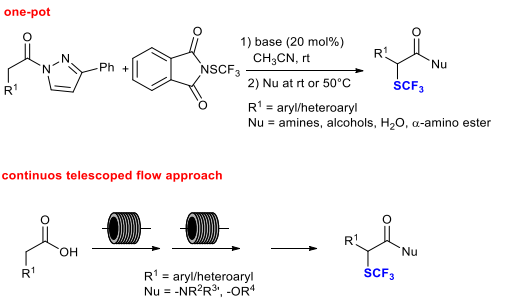
[91] M. C. F. C. B. Damião, R. Galaverna, A. P. Kozikowski, J. Eubanks, J. C. Pastre, *React. Chem. Eng.* **2017**, *2*, 896–907

[92] Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866–880.

variety of interesting opportunities.[91,93]

In our previous work we developed the α-trifluoromethylthiolation of carboxylic acid derivatives by using more reactive starting materials, *N*-acyl pyrazoles (Chapter 5).

We envisaged that the application of an alternative telescopic process, under flow reaction conditions, to obtain the same products starting directly from commercially available compounds could be highly practical and convenient. (Scheme 6.1).



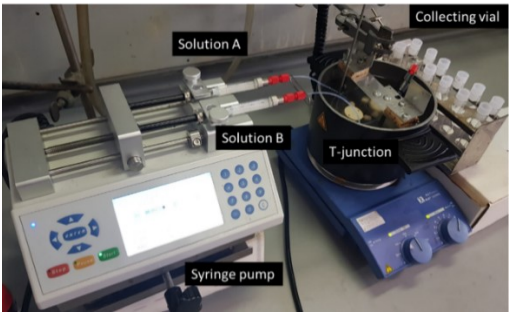
Scheme 6.1 Batch and flow approaches for the synthesis of α-trifluoromethylthiolated carboxylic acid derivatives

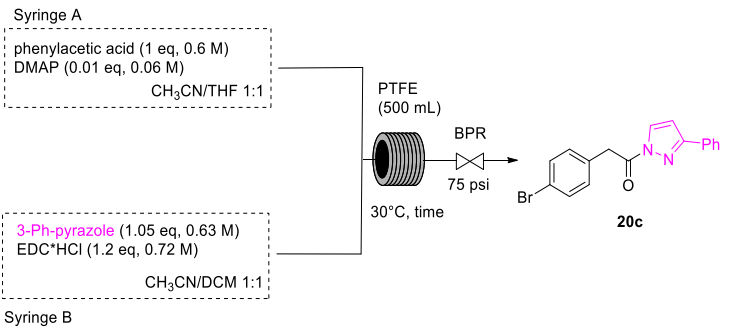
[93]a) Z. Fülöp, P. Szemesi, P. Bana, J. Éles, I. Greiner, *React. Chem. Eng.* **2020**, *5*, 1527–1555. b) S. A. May, *J. Flow Chem.* **2017**, *7*, 137–145.

6.2 Results and discussions

At the outset of our study, the synthesis of the *N*-acylpyrazole under flow conditions has been investigated. The flow methodology required a slight modification of used reactants with respect to the previously reported batch conditions (Scheme 5.3) to avoid the precipitation of byproducts. To this end, N,N'-dicyclohexylcarbodiimide (DCC) was thus replaced by N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC*HCl) whose urea byproduct is more soluble under the reaction mixture. This reaction step was carried out using a PTFE coil reactor (1.58 mm outer diameter, 0.78 mm inner diameter) coiled in a bundle and immersed in an oil bath heated to the desired temperature. A 2.5 mL SGE gastight syringe A, containing phenylacetic acid (1 mol/eq, 0.6 M solutions) and DMAP (0.1 mol/eq) and a syringe B, containing 3-phenylpyrazole (1.05 mol/eq, 0.63 M solution) and EDC*HCl (1.2 mol/eq), were connected by a PEEK tee junction to a 500 μL PTFE coil reactor. The device is ended by a 75 psi back-pressure regulator to avoid the evaporation of the reaction solvent (Table 6.1).

Table 6.1 Synthesis of *N*-acylpyrazoles under flow conditions[a]





Entry	Solvent	Flow rate (mL/min)	Residence time (min)	NMR yield[b] **20c** (%)
1	DCM	0.1	5	94
2	DCM	0.25	2	95
3	DCM	0.5	0,5	85
4	THF/CH_3CN/DCM	0.25	2	92
5[c]	THF/CH_3CN/DCM	0.25	2	93

[a] Reaction conditions: concentration of 0.1 M carboxylic acid. [b] Yield determined by ^{1}H-NMR analysis of crude reaction with 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction run at a concentration of 0.3 M carboxylic acid.

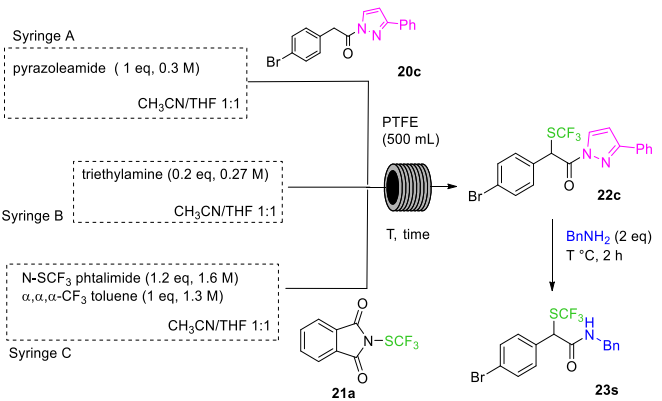
Initially, the reaction was performed in the same solvent and

conditions of the batch reaction achieving excellent results both with the residence time of 5 min and 2 min (Entries 1 and 2). A slight decrease of yield was observed when the residence time was furthermore reduced to 0.5 min (Entry 3). In order to simplify the subsequent steps in the continuous process, the reaction was carried out in different solvents and the THF/CH_3CN/DCM mixture was found to be the optimal, as it guarantees a good solubility of reagents and products without leading to a lowering of yields, so the compound **20c** was obtained in 92% yield in 2 min residence time (Entry 4). Finally, the concentration was increased to 0.3 M which is the optimal concentration value for the following reaction step in the telescopic process, in which the conditions required in the trifluoromethylthiolation step include a concentration of 0.2 M (Entry 5).

Subsequently, the investigation of the optimal parameters of residence time and temperature together with the optimal solvent and base to carry out the trifluoromethylthiolation step was performed.

The reactor consists of a 5 mL SGE gastight syringe, containing as a model substrate the 4-bromophenylacetic pyrazoleamide **20c** (3 mL of a 0.3 M solution in CH_3CN/THF 1:1, 1.0 eq) and two 1 mL SGE gastight syringes, containing respectively the base (0.27 M solution in CH_3CN/THF 1:1, 0.2 eq) and *N*-SCF_3 phthalimide **21a** (1.6 M solution in CH_3CN/THF 1:1, 1.2 eq) in addition to the α,α,α-CF_3 toluene as internal standard (1 eq).

Table 6.2 Optimization of in-flow amides' trifluoromethylthiolation[a]



Entry	Solvent	Flow rate (mL/min)	T (°C)	Residence time (min)	NMR yield[b] **23s**(%)
1	THF	PS	25	30	0
2	THF	PS	25	15	0
3	THF/CH_3CN (1:1)	PS	30	30	20
4	THF/CH_3CN (1:1)	PS	30	15	15
5	THF/CH_3CN (1:1)	TEA	30	30	61
6	THF/CH_3CN (1:1)	TEA	30	15	41
7	THF/CH_3CN (1:1)	TEA	45	15	52(51)
8[b]	THF/CH_3CN (1:1)	TEA	60	15	75(73)
9[c]	THF/CH_3CN (1:1)	TEA	90	15	50
10[d]	THF/CH_3CN (1:1)	TEA	45	15	83
11[e]	THF/CH_3CN (1:1)	TEA	45	15	85(83)

[a] Reaction conditions: 0.2 mol/eq of TEA was used. [b] Yield determined by ^{19}F NMR analysis of the crude reaction product with α,α,α-$CF_3C_6H_5$ as internal standard and in parentheses as yield after chromatographic purification. [c] A 20 psi BPR was applied to avoid the solvent evaporation. [d] 0.35 mol/eq of TEA. [e] 0.5 mol/eq of TEA.

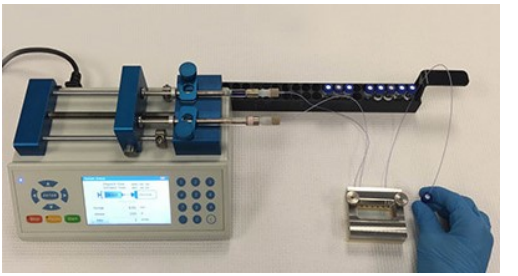
The reagents were mixed in a PEEK tee junction and pumped in the 500 μL PTFE coil reactor. The outcome of the reactor containing the trifluoromethylthiolated pyrazoleamide **22c** was collected in vial loaded with the benzylamine (2 eq), where it was stirred for further 2 h to afford *N*-benzyl amide **23s**. The yield was first evaluated by ^{19}F NMR and confirmed after chromatographic purification. In the preliminary experiments, the Protone-sponge (PS) was used being the election base in batch methodology, however low yields were observed due to solubility issues (Entries 1-4). To overcome this issue, triethylamine was tested as base using a mixture of THF/CH_3CN to guarantee the complete solubility of all the components thus improving the reaction outcomes (Entries 5-11). The reaction afforded the product **23s** in 61% NMR yield in 30 min residence time when TEA was used as catalyst in 20mol% loading (Entry 5). However, higher productivity was observed when the residence time was increased keeping the others parameter unchanged (Entry 6, productivity = 107.4 mg/h). Further experiments were carried out to optimize the amount of the catalytic base and the effect of the temperature on the reaction outcome. It was found that the yield increased at higher temperature, obtaining **23s** in 75% yield at T=60°C (Entry 8). Higher temperature values were found to have a deleterious effect on yield (Entry 9). By changing the base loading (35 mol% and 50 mol%, Entries 10 and 11 respectively) it was demonstrated that 50 mol% of base loading is necessary to reach higher yield of 85% (Entry 11), corresponding to a productivity =

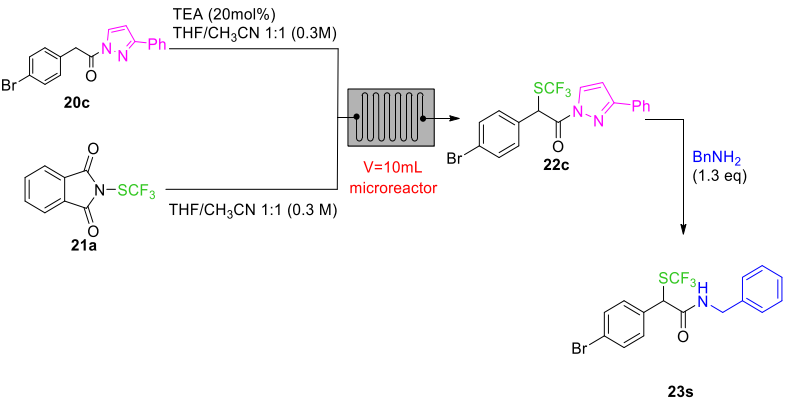
217.4 mg/h of the product **22c**. It is important to underline that performing the reaction sequence under batch reaction under the same experimental conditions (THF/CH_3CN (1:1), TEA) 66 mg of the product **22c** were obtained in 7h while the same amount of product was isolated in 20min by exploiting continuous flow reactor.

The methodology was also scaled up, performing the reaction in the same 0.5 mL PTFE reactor under the condition of Entry11 for a time of 10 h and achieving 2.02 g of product **23s**.

Moreover, a brief study of the trifluoromethylthiolation step by using a 10 μL glass microreactor was undertaken observing a similar behaviour respect to the temperature profile (Table 6.3). By working at the same reaction conditions with 20mol% of TEA in a mixture of CH_3CN/THF (1:1), the microfluidic reaction afforded better results in term of yield when carried out at 60°C, both with a residence time of 3.3 min (65%, P= 14.2 mg/h, Entry 2) and 1.3 min (50%, P= 28 mg/h, Entry 6).

Table 6.3 In microreactors flow amides' trifluoromethylthiolation[a]





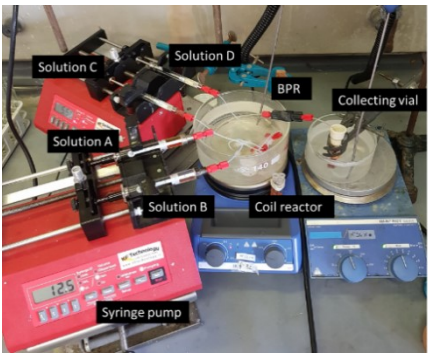
Entry	T (°C)	Flow rate (mL/min)	Residence time (min)	NMR yield[b] **23s** (%)
1	45	3	3.3	57
2	60	3	3.3	65
3	90	3	3.3	56
4	30	7.5	1.3	43
5	45	7.5	1.3	45
6	60	7.5	1.3	50
7	90	7.5	1.3	46

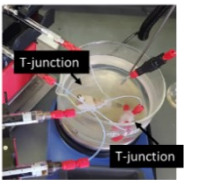
[a] Reaction conditions: 0,2 mol/eq TEA was used; [b] Yield determined by ^{19}F NMR analysis of crude reaction with α,α,α-$CF_3C_6H_5$ as internal standard

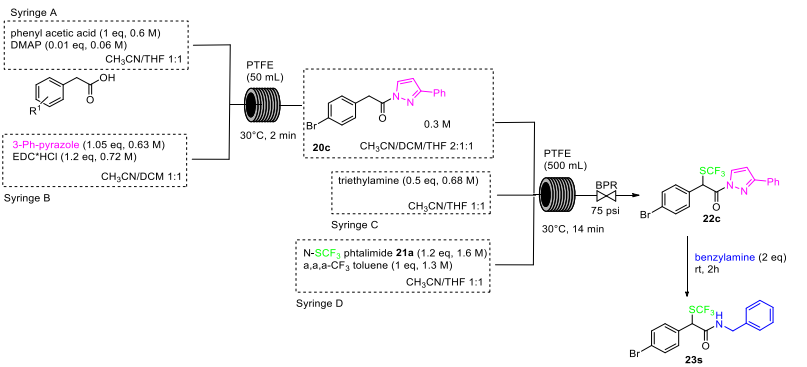
After the optimization of each single step, the telescopic process for the synthesis of α-trifluoromethylthio *N*-benzylamide was investigated (Table 6.4).

The first step was run in a 50 μL PTFE coil reactor (2 min residence time). The outcome was connected by a tee junction to two 2.5 mL SGE gastight syringes, containing TEA and *N*-SCF_3 phthalimide respectively, that were reacted at 30 °C in a second coil reactor (500 μL PTFE coil reactor, 15 min residence time). A 75 psi back pressure regulator was applied at the end of the reactor. After discharging the first volume, the reaction mixture was collected in a vial containing the amine (2 eq) and it was stirred for further 2 h to perform the last transformation. A further brief optimization study of the process was necessary to find the optimal conditions to perform the telescopic process. A little excess of *N*-SCF_3 phthalimide (1.5 eq) was used operating at 30 °C to obtain the highest yield of the product (70%, P = 183.4 mg/h, Entry 3).

Table 6.4 Telescoped Synthesis of α-trifluoromethylthio *N*-Benzylamide



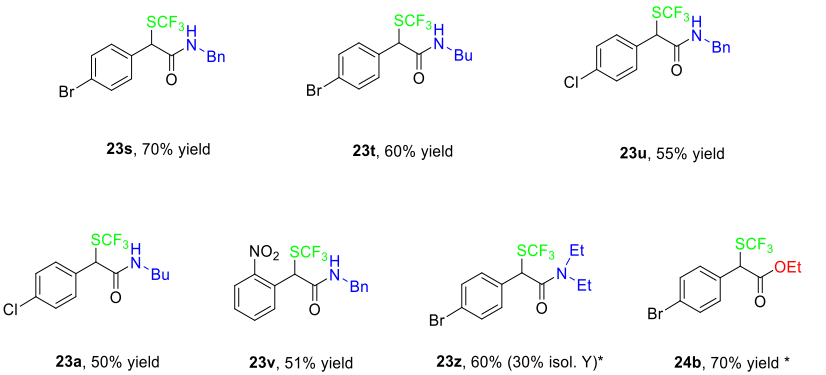




Entry	2 (eq)	base (eq)	T (°C)	NMR yield[b] **23s** (%)
1	1.2	0.2	30	30
2	1.2	0.5	30	58 (56)
3	1.5	0.5	30	72 (70)
4	1.5	0.45	60	65
5	1.5	0.5	60	55
6	1.5	0.35	60	52
7[b]	1.5	0.5	30	50 (48)

[a] Yield determined by ^{1}H NMR analysis of crude reaction with α,α,α-$CF_3C_6H_5$ as internal standard and confirmed as isolated yield after chromatographic purification; [b] Residence time second reactor 7 minutes

After defining the optimal set-up for the telescopic process for the model process, the protocol was applied to the multi-step synthesis of different amides and an ester which were isolated in overall good yields (Figure 6.1).



23s, 70% yield **23t**, 60% yield **23u**, 55% yield

23a, 50% yield **23v**, 51% yield **23z**, 60% (30% isol. Y)* **24b**, 70% yield *

* Reaction of pyrazolamide with Et_2NH and EtOH was performed at 50°C for 8 hours

Figure 6.1 Examples of amides and ester trifluoromethylthiolated

Both *N*-aliphatic and *N*-benzylic amides were isolated *in continuo* in good overall yields (50-70%) starting from different carboxylic acids. The *N,N*-dialkyl amide **23z** was obtained in lower yield probably due to higher steric hindrance of the amine, while the synthesis of the ester was achieved in satisfactory overall yield using 50 eq of alcohol. In both cases, higher temperature and longer reaction times were required.

6.3 Conclusions

The first multi-step catalytic synthesis of α-trifluoromethylthiolated esters and amides has been reported, starting exclusively from commercial and readily available reagents. Both micro- and meso-reactor were successfully exploited, achieving the synthesis of fluorinate derivatives in good overall yield in significantly short reaction time.

With a particular attention to the environmental impact, this methodology allows to avoid the isolation of the *N*-acyl pyrazole, thus avoiding the filtration to remove the produced precipitate and chromatography allowing a significant reduction of costs and amount of purification materials such as solvents and silica.

7 Asymmetric Michael addition of triflone-containing nucleophiles: enantioselective organocatalytic synthesis of quaternary stereocenters

7.1 Background

The construction of quaternary center in mild enantioselective catalytic reaction conditions represents, in modern organic synthesis, a highly challenging area of research.[94] The quaternary stereocenter is a fascinating molecular architecture, not only because is a recurring motive in bioactive compounds, but it is also difficult to racemize once it has been fabricated. The enantioselective organocatalytic Michael reaction starting from a methine active pronucleophile is one of the most reported strategies for the construction of quaternary stereocenters.[95] Several different nucleophiles were employed in the history of asymmetric Michael reaction as nitroalkanes[96], enolizable carbonyl compounds[97], oxazols[98] and many others.

An efficient nucleophile widely used for this reaction type is the

[94] a) W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin, H. Gong, *Chem. Soc. Rev.* **2021**, *50*, 4162–4184. b) T. S. Silva, F. Coelho, *Beilstein J. Org. Chem.* **2021**, *17*, 1565–1590. c) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181–191.d) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, *2013*, 2745–2759.

[95]a) E. Reyes, U. Uria, J. L. Vicario, L. Carrillo, in *Org. React.*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2016**, pp. 1–898. b) M. S. Manna, V. Kumar, S. Mukherjee, Chem Commun 2012, 48, 5193–5195.

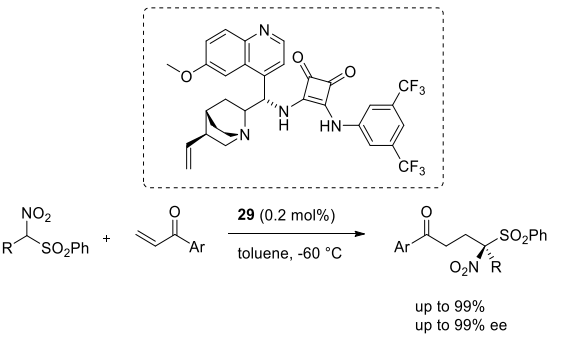
[96] M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233–8236.

[97] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559.

[98] S. Silva, B. T. Matsuo, R. C. da Silva, L. V. Pozzi, A. G. Correa, P. Rollin, J. Zukerman-Schpector, M. A. B. Ferreira, M. W. Paixão, *J. Org. Chem.* **2018**, *83*, 1701–1716.

sulfonyl group. The sulfonyl group shows strong inductive ability that makes it ideal for various types of organocatalysed reactions. In addition, further transformations of the sulfone moiety makes it a suitable group for the generation of a range of important products.[99]

An example of enantioselective organocatalytic of Michael addition of α-nitrosulfones as nucleophiles to α,β-unsatured ketones was reported by Namboothiri, in presence of the quinine-derived squaramide catalyst **29** at 0.2 mol% loading (Scheme 7.1). The conjugate addition smoothly proceeded, affording the products in excellent yield and enantioselectivity.[100]



Scheme 7.1 Enantioselelctive addition of sulphone to α,β-unsatured ketones

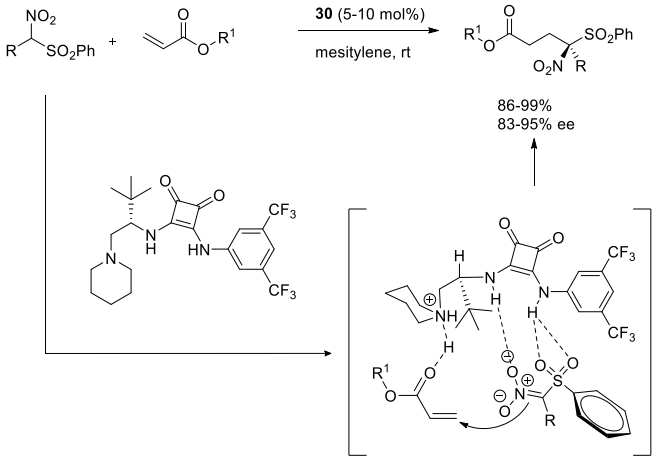
The same research group then extended the work to the synthesis of γ-tetrasubstituted γ-nitro-γ-sulfonyl esters, starting again from α-nitrosulfones (Scheme 7.2).[101] This methodology represents one of

[99] a) X. Liang, Y. Shen, *Asian J. Org. Chem.* **2022**, *11*, DOI 10.1002/ajoc.202100598. b) Y. Huang, J. Li, H. Chen, Z. He, Q. Zeng, *Chem. Rec.* **2021**, *21*, 1216–1239. c) C. Zhu, Y. Cai, H. Jiang, *Org. Chem. Front.* **2021**, *8*, 5574–5589. d) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixão, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 2668–2679.

[100] K. Bera, I. N. N. Namboothiri, *Chem. Commun.* **2013**, *49*, 10632.

[101] K. Bera, I. N. N. Namboothiri, *Org Biomol Chem* **2014**, *12*, 6425–6431.

the few examples of Michael addition to acrylates, affording the products in excellent yield and enantioselectivity. The high level of enantiocontrol has been explained considering a transition state model in which the squaramide scaffold interacts with sulfonyl and nitro groups via N-H-O hydrogen bonds.

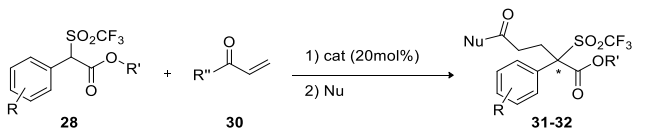


Scheme 7.2 Organocatalytic enantioselective addition of sulfone to α,β-unsatured esters

Although typical aryl substituted sulfonyl groups have been largely employed in organocatalysis, the counterpart reagents bearing the trifluoromethyl residue, namely triflone, have never been applied in this reaction type.

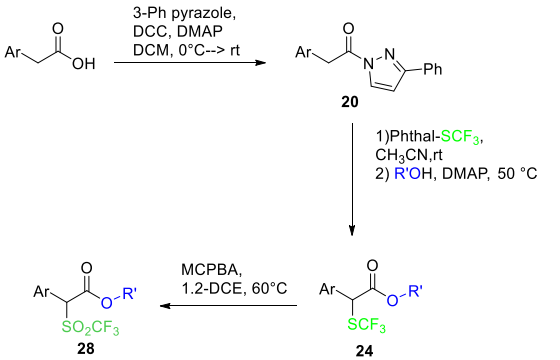
7.2 Results and discussions

In this PhD work, we developed a simple access to α-methylthiolated esters/amides, via the corresponding acylpyrazoleamides (Chapter 5). Moreover, the oxidation with MCPBA of the α-methylthiolated esters/amides opened the access to the corresponding triflones. This class of compounds, thanks to the presence of the highly electron-withdrawing triflone group might serve as suitable pronucleophiles to develop an asymmetric organocatalytic Michael reaction with α,β-unsaturated carboxylic acid surrogates (Scheme 7.3). The one-pot reaction catalysed by a bifunctional organocatalyst would have led to prepare a new class of highly functionalised triflones **31-32**, bearing a quaternary stereocenter.



Scheme 7.3 Organocatalytic enantioselective synthesis of triflones derivatives

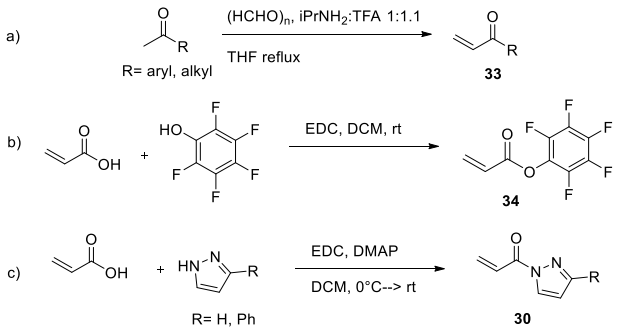
The synthesis of starting Michael acceptors was carried out according to previously reported procedures (see Scheme 7.5). Likewise, the functionalised triflones **28** were synthesized according to reactions reported in Scheme 7.4 (for more detail see the paragraph 5.2).



Scheme 7.4 Synthetic pathway to achieve starting material

A variety of Michael acceptors were initially checked in the process and synthesized according to literature procedures.[102] The α,β-unsatured ketones **33** were prepared by direct α-methylenation[102a] of aromatic ketones promoted by amine salt, diisopropylammonium trifluoroacetate, in THF as solvent with good yields (Scheme 7.5a). While both the acrylate derivatives were synthesized using EDC-coupling reactions. The pentafluorophenyl acrylates[102b] **34** and the acrylpyrazoles[102c] **30** were efficiently achieved in high yields starting from the acrylic acid and the corresponding aryl or heteroaryl groups under mild reaction conditions (Scheme 7.5b and c).

[102] a) A. Bugarin, K. D. Jones, B. T. Connell, *Chem. Commun.* **2010**, *46*, 1715. b) A. J. Pigott, R. J. Lepage, J. M. White, M. J. Coster, *Tetrahedron Lett.* **2014**, *55*, 6864–6867. c) C. Ye, S. Chen, F. Han, X. Xie, S. Ivlev, K. N. Houk, E. Meggers, *Angew. Chem. Int. Ed.* **2020**, *59*, 13552–13556.

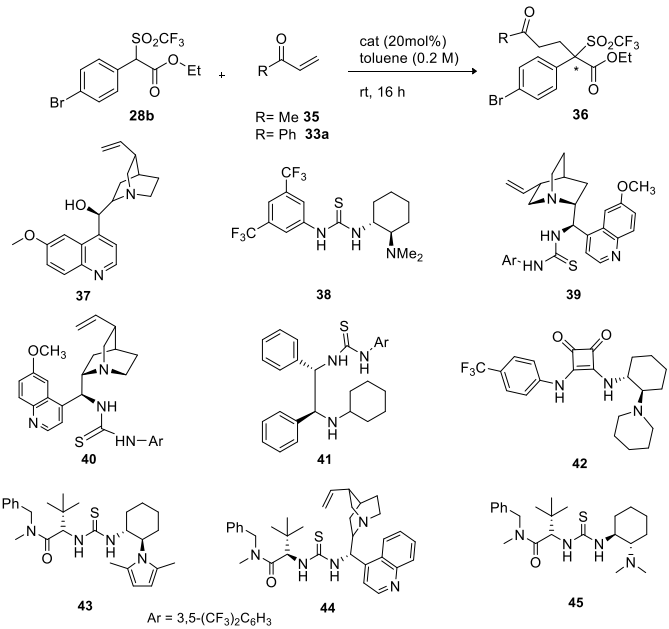


Scheme 7.5 Synthesis of Michael acceptors

Our investigation commenced reacting model compound **28b** with methyl vinyl ketone **35** using 20 mol% of common bifunctional organocatalysts in toluene at room temperature (Table 7.1). The reaction proceeded in reasonable reaction times to the expected product, attesting the feasibility of simple amino thiourea as promoters. However, the results were affected by the nature or scaffold of the organocatalyst used. The adduct **36** was isolated with the highest 55% ee (Entry 2), when using Takemoto catalyst **38**. Surprisingly, the Cinchona alkaloids derived thioureas proved to be much less effective (Entries 3 and 4). Then, phenyl vinyl ketone **33a** was reacted using Takemoto's catalyst achieving 67% ee (Entry 5).

Again, the squaramide compound **42** (Entry 7) as well as thiourea catalyst bearing the pyrrole moiety as basic group **43** (Entry 8) gave unsatisfactory results. The same outcome was observed when using more functionalized organocatalysts **44-45** (Entries 9-10).

Table 7.1 Organocatalysts screening in the Michael reaction of model **28b** with vinyl ketones **33-35** [a]

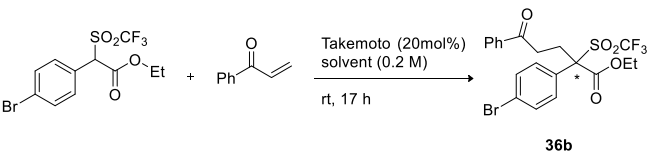


Entry	cat	Yield (%)	ee (%)[b]
1	**37**	82	20 (**36a**)
2	**38**	75	55
3	**39**	57	0
4	**40**	10	5
5	**38**	79	67 (**36b**)
6	**41**	44	37
7	**42**	23	0
8	**43**	13	-3
9	**44**	83	-14
10	**45**	<10	--

[a] Unless otherwise noted reactions were conducted with **28b** (0.1 mmol), **33** or **35a** (0.12 mmol), **catalyst** (0.02 mmol), in anhydrous toluene (0.5 mL) under nitrogen atmosphere. [b] Determined by chiral HPLC analysis on isolated product.

According to the data in the Table, Takemoto thiourea **38** was selected as the catalyst to further optimize the reaction with the aim to improve the enantioselectivity (Table 7.2). The reduction of the temperature to 0°C (Entry 1) had no effect on the enantioselectivity and a further decrement to -30 °C (Entry 2) had a slight improvement of the ee value (68% and 71% respectively). Dilution of the reaction mixture did not affect significantly the enantioselectivity (Entry 3). Other solvents such as dichloromethane, hexane, and trifluorotoluene were tested, but unsatisfactory ee values were observed (Entries 4-6).

Table 7.2 Base screening in the Michael reaction of model **28b** with **33a**[a]



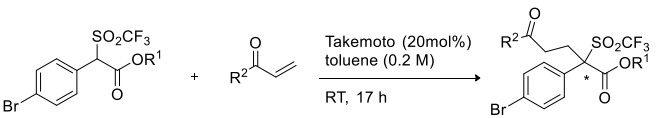
36b

Entry	solvent	Yield (%)	ee (%)[b]
1[c]	toluene	84	68
2[d]	toluene	71	71
3[e]	toluene	65	75
4	DCM	85	53
5	hexane	75	51
6	trifluorotoluene	86	56

[a] Unless otherwise noted reactions were conducted with **28b** (0.1 mmol), **33a** (0.12 mmol), **(R,R)-Takemoto catalyst** (0.02 mmol), in anhydrous solvent (0.5 mL) under nitrogen atmosphere. [b] Determined by chiral HPLC analysis on isolated product. [c] Reaction performed at 0°C. [d] Reaction performed at -30°C. [e] Reaction performed at -30°C and at C = 0.1 M.

With the aim to improve the stereochemical outcome of the reaction, Michael acceptors able to establish more rigid transition states were considered (Table 7.3). The introduction of more sterically hindered isopropyl alcohol in the esters moiety of nucleophilic compound negatively affected the enantioselectivity, with a decrease of the ee value (60% ee, Entry 1).

Table 7.3 Michael acceptors screening in the Michael reaction of model **28b**[a]



Entry	R^1	R^2	t (h)	Yield (%)	Ee (%)[b]
1	*i*Pr	Ph	17	76	63
2	Et	1-naphtyl	17	85	44
3	Et	$OCH(CF_3)_2$	25	<15	-
4	Et	OC_6F_5	20	-	-
5	Et	3-Ph-pyrazole	17	93	75
6[c]	Et	3-Ph-pyrazole	40	61	86
7	Et	pyrazole	17	32[d]	89
8[c]	Et	pyrazole	24	15[d]	94
9[e]	Et	pyrazole	24	96	94

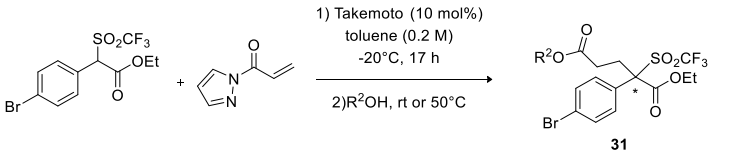
[a] Unless otherwise noted reactions were conducted with **28b** (0.1 mmol), **30** (0.12 mmol), **(R,R)-Takemoto catalyst** (0.02 mmol), in anhydrous toluene (0.5 mL) under nitrogen atmosphere. [b] Determined by chiral HPLC analysis on isolated product. [c] Reaction performed at -20°C. [d] The yield was affected by the degradation of products on silica gel, for further details see the experimental section. [e] Reaction performed at -20°C and in presence of 10 mol% of catalyst.

Concerning the electrophilic partner, when using more sterically hindered 1-naphthyl vinyl ketone (Entry 2), the desired adduct was isolated in low yield although with 71% ee. Additionally, activated esters by the presence of fluorine atoms were tested, but in both cases these compounds proved to be unreactive (Entries 3 and 4).

At this point, the pyrazole group, known to have high directing ability, was introduced in the acyl portion of the acceptor.[67]

When the unsaturated 3-Ph acyl pyrazole was reacted, an increased level of enantioselectivity both at room temperature (75% ee, Entry 5), and more significantly at -20 °C was achieved (86% ee, Entry 6). Finally, the simple acyl pyrazole derivative afforded the best enantiocontrol at -20°C (94% ee, Entry 8). Under these conditions it was also possible to reduce the amount of catalyst using to 10 mol%, without any loss of enantioselectivity (Entry 9). The final adduct showed to be sensitive to partial degradation, when running the silica gel chromatography (Entries 7 and 8). This prompted us further to develop a one-pot process to obtain enantioenriched diesters.

With the optimized reaction conditions in our hand, we decide to exploit once again the good leaving ability of the pyrazole moiety and prepare in a one-pot process directly chiral diesters (Scheme 7.6). Indeed, at the end of the first reaction step, the reaction was warmed to room temperature and the proper alcohol was added.



Scheme 7.6 Enantioselective one-pot synthesis of diesters compounds with a quaternary center

The optimized conditions were then applied to differently substituted reagents **28** and alcohols to explore the scope of the process (Figure 7.1).

The methodology proved to be effective with triflones bearing *para-, meta-* and *ortho-* substituted with electron-withdrawing and donating groups in the benzene ring (**31a-i**) achieving excellent yields and enantioselectivity (70-98%, 88-96% ee). When the *ortho*-position of the aromatic ring is occupied by a methyl group (**34l**), a significant drop in the yield was observed (40% yield after 4 days), achieving a high level of enantioselectivity (92% ee), probably due to the steric hindrance of methyl group close to the reactive site. Both longer chain primary and secondary alcohol could be employed in the methodology affording the corresponding esters in good yields and ee values (75-91%, 84-94% ee, **31m-q**). When alcohols other than methanol were added at the end of the first reaction step, the temperature should be increased to 50°C to achieve high yields. When using triflone bearing on aromatic ring a cyano group (**31m**), although the product was obtained in high yield a slight decrease of the enantiomeric excess was observed (84% ee). The products obtained from di-substituted aromatic triflones were isolated with

general good yields and high enantioselectivity (80-86%, 91-93% ee, **31p-q**).

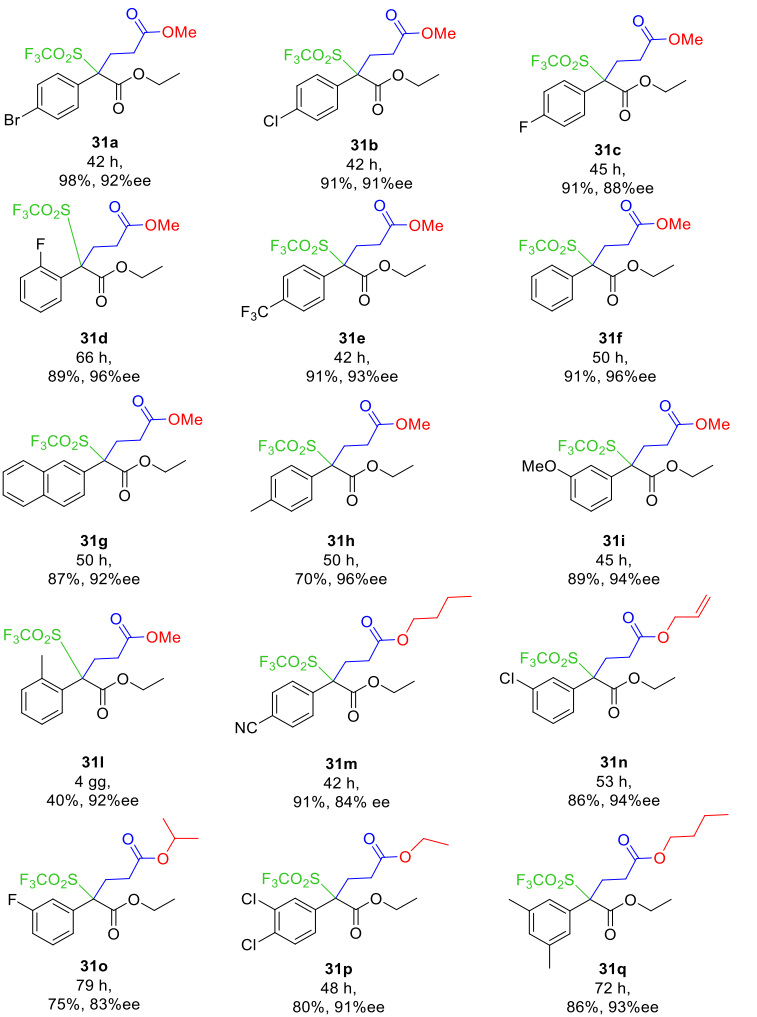
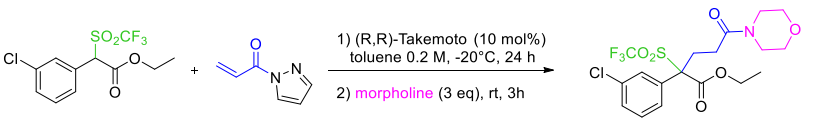


Figure 7.1 Substrate scope for the one-pot synthesis of diesters triflones

To demonstrate the versatility of our enantioselective one-pot route, at the end of the first reaction step amines were used as nucleophiles

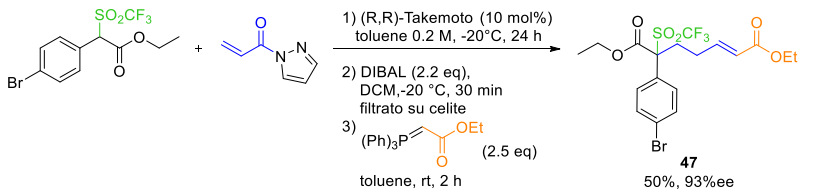
to replace the pyrazole moiety (Scheme 7.7). Pleasingly, the one-pot process using the morpholine afforded, under mild reaction conditions, the desired amide **32** with excellent yield and enantiomeric excess (92%, 91% ee).



Scheme 7.7 Enantioselective one-pot synthesis of amide

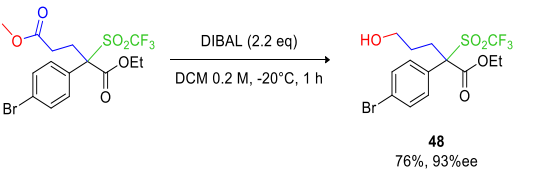
To probe the utility of the products, one-pot manipulation of the adduct **31** was coupled with a Horner-Emmons olefination.

At the end of the first reaction step, after removing toluene from the crude mixture, dichloromethane was added, and the selective reduction of the acyl pyrazole intermediate to aldehyde was carried out by DIBAL (2.2 eq) in a short reaction time. Filtration of the crude mixture on celite was required to remove side-products of the reducing agent. The aldehyde thus obtained, without furthermore purification, was used in the Horner-Emmons olefination with carbethoxymethylene)triphenylphosphorane to afford the final product **47** in good overall yield (50%) and excellent 93% ee (Scheme 7.8).



Scheme 7.8 One-pot synthesis of Horner-Emmons olefin.

Straightforward elaboration on the diesters compound **31** to alcohol **48** was performed working in dichloromethane and with DIBAL as mild reductive reagent in high yield and ee value (Scheme 7.9).



Scheme 7.9 Reduction of chiral diesters

7.3 Conclusions

A first one-pot enantioselective organocatalytic Michael reaction to prepare highly enantioenriched triflones bearing a quaternary stereocenter has been developed, starting from easily enolizable aryl acetic triflone esters and acryloyl pyrazole. The methodology, that proceeds under mild reaction conditions, is catalysed by the readily available Takemoto thiourea catalyst.

The one-pot methodology enables to obtain a variety of aryl-substituted triflones working under mild reaction conditions.

The final products can be transformed via selective reduction followed by Horner-Emmons olefination into highly functionalised alkenes or reduced to fluorine-containing alcohols.

8 Synthetic approach to the identification of product's impurities in industrial company

8.1 Background: principles of drug discovery

In the last two centuries, medicinal chemistry has made great breakthroughs in the discovery and development of novel drugs. Patients' average life has become longer, and diseases or conditions that some time ago were considered incurable today can be treated by new therapeutic agents.

However, the research for the development of new drugs is in general very long and expensive. It has been estimated that for placing on the market a new drug, it is necessary analyse more than 10000 candidate compounds, not mentioning the number of preclinical and clinical studies required. In 2011, it was reported that, due complexity of the drug discovery research, all the process to produce a new drug needs a time equal to 12-15 years and a cost of about $1.75bilion.[103]

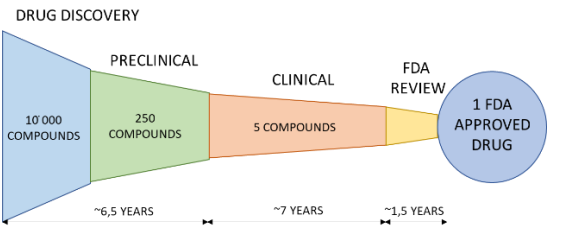


Figure 8.1 Drug discovery & development timeline

To exemplify the complicated process, it can be divided in two major

[103] S. M. Paul, D. S. Mytelka, C. T. Dunwiddie, C. C. Persinger, B. H. Munos, S. R. Lindborg, A. L. Schacht, *Nat. Rev. Drug Discov.* **2010**, *9*, 203–214.

stages, drug discovery and drug development. The first step includes all the studies and experimentation required for the identification of the biological target for the precise studied disease, followed by the evaluation of drug candidates showing possible relevant activity. The main phases of drug discovery are the target discovery, the lead discovery, and the lead optimization. Drug development starts from good candidates, which have been identified in the previous stage, and consists in submitting them to a series of tests before to bring the drug on the market. The main phases in the drug development include the preclinical development, the clinical development and at the end the regulatory approval (Figure 8.2). [104]

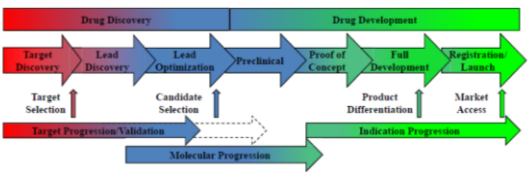


Figure 8.2 Major stages of drug discovery and development

Although the entire drug supply chain has to be in general respected, is it not required that each pharmaceutical industry has to follow the entire trial (from API identification, production, formulation of final drug, its packaging).

[104] a) B. E. Blass, in *Basic Princ. Drug Discov. Dev.*, Elsevier, **2015**, pp. 1–34. b) R. B. Silverman, M. W. Holladay, *The Organic Chemistry of Drug Design and Drug Action*, Elsevier/AP, Academic Press, Is An Imprint Of Elsevier, Amsterdam; Boston, **2014**. c) S. C. Gad, Ed., *Pharmaceutical Manufacturing Handbook: Production and Processes*, Wiley-Interscience, Hoboken, N.J, **2008**.

8.1.1 Regulatory agencies and Good Manufacturing Practise

In the US, the regulatory authority that controls the drugs sales is the FDA (food and drug administration) but each State has its own regulatory institution. In Europe is the EMA (European Medicines Agency) while in Italy drugs market is regulated by AIFA (Agenzia italiana del farmaco). GMP (Good Manufacturing Practice) certificate is one of the tools used by regulatory institutions to ensure quality of the active ingredients and of the commercialized drugs. GMP includes a set of rules describing methods, equipment, tools and production management to ensure appropriate quality standards. GMPs are applied to all phases of the production of API (or drug), from production operation and quality control to storage and packaging.[105] The chemical companies are obliged to prepare the documentation describing all the activities performed in the supply chain and about the control quality analysis (Chemical Manufacturing, entry 1 the Table 8.1). This documentation has to be submitted to regulatory institutions in the form of the ASMF (Active substance master file).

[105]ICH Q7 Good manufacturing practice for active pharmaceutical ingredients

Table 8.1 Application of GMP guidelines

Type of Manufacturing	Application of this guidance to steps (shown in gray) used in this type of manufacturing				
Chemical Manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establish-ment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establish-ment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements

ASMF contains detailed scientific information and is divided in two main parts, namely the Applicant's Part (AP) and the Restricted Part (RP). The AP contains non-confidential information that have to be disclosed also to the applicant, meaning as example the Pharma company that want to buy the active ingredient. On the contrary, the RP regards the confidential information that must be shared only with the authority as manufacturing method (reaction conditions, temperature, validation, and evaluation data of critical steps) and quality control during the manufacture of the active substance.[106]

[106] Guideline on Active Substance Master File Procedure

8.2 Synthesis of Metaraminol in Laboratori Alchemia

Laboratori Alchemia S.r.l is a chemical medium-small company that works in the synthesis of high qualitive active ingredients from more than 60 years. Laboratori Alchemia holds the GMP certificate released by Italian authority and provides its products to pharmaceutical industries which are part of European and non-European markets such as Russian, Japanese, South Korean, North and South African, Canadian, South American and Australian market. Laboratori Alchemia has deposited several process patents. The most recent patent, deposited in 2016, describes the synthetic pathway developed for the synthesis of Metaraminol bi-L tartrate (Figure 8.3).[107]

The metaraminol is a potent sympathomimetic amine, able to increase both systolic and diastolic blood pressure which is used for the treatment of the acute hypotensive state.[108]

[107] Davide Brenna, Marchesi Andrea, Mihali Voichita, *PROCESS FOR THE PREPARATION OF METARAMINOL*, **n.d**

[108]a) https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/009509s026lbl.pdf b) V. R. Kee, *Crit. Care Nurse* **2003**, *23*, 79–82.

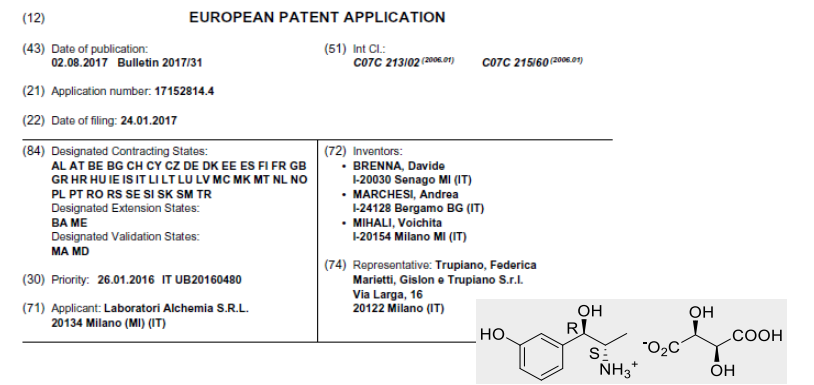


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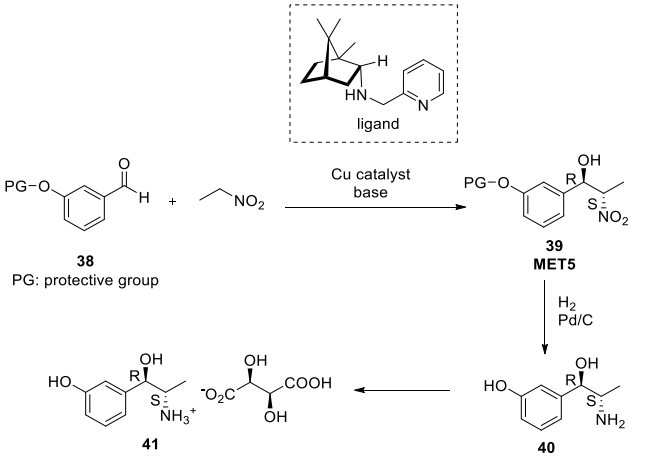
Figure 8.3 European patent application for Metaraminol synthesis

The reaction pathway, reported in the scheme 8.1 involves three reaction steps. The first step is the stereoselective Henry reaction of benzaldehyde bearing protected hydroxylic group and nitroethane catalyzed by a copper complex. The crude intermediate was directly reduced by using hydrogen and palladium on carbon. At the end the addition of L-tartaric acid gives the target compound (Scheme 8.1).



Scheme 8.1 General synthetic pathway of Metaraminol

As mentioned above, for the synthesis of new API it is necessary to submit the ASMF to the authority. In the submission of ASMF of the Metaraminol, AIFA questioned the specific - *related substances* - of the intermediate *MET5* **39**.

The letter cites: *"The limits for related substances in the specification for the intermediate MET5 should be tightened. In addition, any single impurity found above 0,20% should be expressed as single known impurity with its own acceptance criterion. The limit for any unknown single impurity should be not more than 0.20%."*

8.3 Results and discussion

The *related substances* are known or unknown by-products detected during the control quality analysis. MET5 HPLC profile shows four principal impurities (Figure 8.4). The purity parameters required in the synthesis of API have to be applied to the final compound but also to its intermediate. Table 8.2 shows that the amount of any unknown impurity is less than 1%.

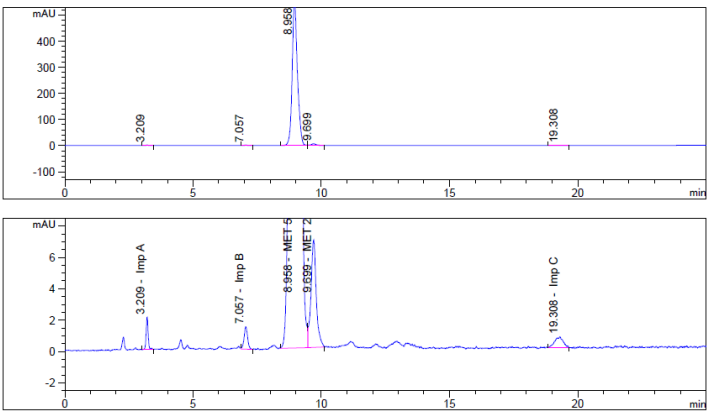


Figure 8.4 HPLC chromatogram of one batch of MET5. Chromatographic conditions: H_3PO_4 0.1% in H_2O/CH_3CN 45:55

Imp A, Imp B and Imp C (rt= 3.209, 7.057, 19.308 respectively) are unknown (Table 8.2). On the contrary, impurity with rt =9.699 min is the only one known impurity and corresponds to the starting material of the Henry reaction **38** (benzaldehyde protected).

Table 8.2 HPLC data of recursive impurities

Es	Name	retention time (min)[a]	area %
1	Imp A	3,209	0,732
2	Imp B	7,057	0,553
3	**39** (MET5)	8,958	97,049
4	**38**	9,699	1,227
5	Imp C	19,308	0,339

[a] Retention time evaluated in Inverse phase HPLC. Chromatographic conditions: H_3PO_4 0.1% in H_2O/CH_3CN 45:55

To satisfy the purity standards imposed by AIFA, two strategic approaches have been chosen:

- The identification of the major unknown recurring impurities of the analysed intermediate
- The reduction of the amount of the unknown impurities through new synthetic pathway

Although the reduction of the byproducts would be the preferred approach, it involves an update of the ASMF that is not an easy or fast process. Due to these considerations, it was selected the first approach.

In order to identify the impurities, the HPLC chromatograms of different batch of MET5 were examined by analyzing the UV profiles obtained with variable wavelength revelator (DAD). In the next paragraph, each single impurity will be investigated.

8.3.3 Impurity A

About impurity A, some interesting consideration led to the speculation of its chemical nature.

The HPLC chromatogram gives an important information about the polarity of Imp A. Indeed, considering that HPLC was in inverse phase for the analysis, it is possible to claim that Imp A is more polar than the target compound MET5 (Figure 8.4).

In addition, the comparison of the UV profile of the unknown compound and the MET5 shows a certain similarity with a slight shift of maximum absorbance for Imp A respect to the MET5 (Figure 8.5).

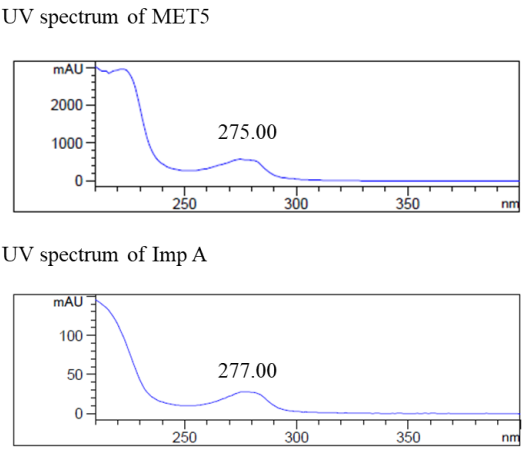
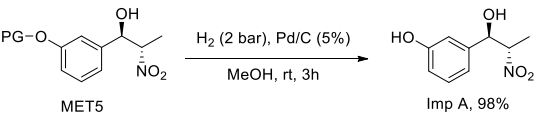


Figure 8.5 UV profile of **39** vs Imp A

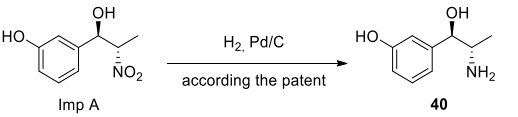
It is therefore reasonable to assume that impurity A is the deprotected MET5 which could be obtained during the acid work up. To confirm our hypothesis, it was necessary to synthesize this compound. The synthesis of the impurity started from MET5 through a mild hydrogenation on Palladium on charcoal to carry out the

deprotonation of the hydroxyl group, without reducing the nitro group (Scheme 8.2).



Scheme 8.2 Controlled hydrogenative reaction of compound **39**

The isolated product was characterized by NMR spectroscopy and mass spectrometry. The external analysis, performed at University of Milano, confirmed the hypothesized structure and allowed to demonstrate that Imp A does not affect the purity of Metaraminol. In fact, by treating Imp A under controlled hydrogenative reaction conditions, it can be converted in the same product Metaraminol like MET5 (Scheme 8.3).



Scheme 8.3 Synthetic pathway to achieve compound **40** from Imp A

8.3.2 Impurity C

Based on the same considerations illustrated above on the retention time, it is possible to assume that Impurity C is an apolar compound (Figure 8.4). In this case UV profile does not give any useful information (Figure 8.6).

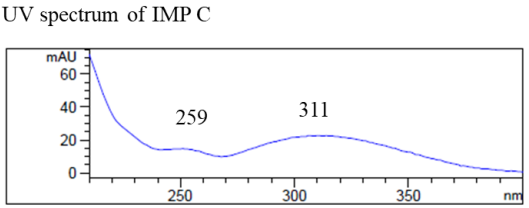
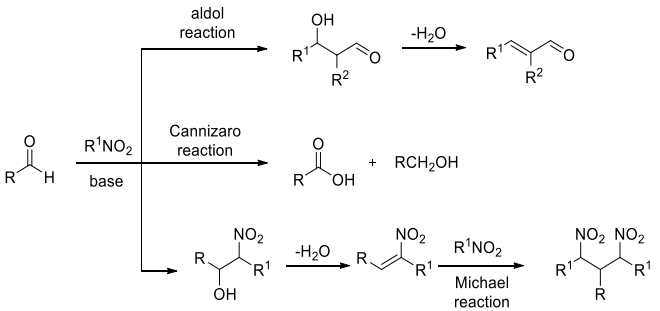


Figure 8.6 UV profile of Imp C

Recently Bez disclosed a new version of the Henry reaction[109] and in this work all the most common side products of the reaction were analysed (Scheme 8.4).



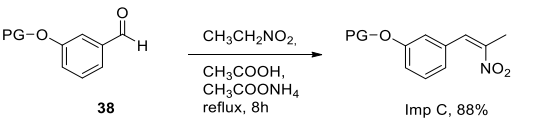
Scheme 8.4 Plausible side products in Henry reaction

Aldol reaction in our case cannot take place because there are not enolyzable carbonylic compounds, and considering the polarity of the impurity C, also the potential Cannizaro reaction could be excluded. One of the most common side-products of Henry reaction is nitrostyrene.

The synthesis of nitrostyrene was carried out according to literature performing the reaction between the protected benzaldehyde and

[109] P. P. Bora, G. Bez, *Eur. J. Org. Chem.* **2013**, *2013*, 2922–2929.

nitroethane in the presence of acetic acid buffer (Scheme 8.5).[110] The isolated compound is comparable with impurity C, so it was characterized by NMR spectroscopy and mass spectrometry.



Scheme 8.5 Synthesis of nitrostyrene from **38**

Surprisingly, the reaction did not afford only nitrostyrene but also impurity B was obtained in very small amount.

8.3.3 Impurity B

Clarifying the chemical structure of the impurity B was a very challenging task. The UV profile of Imp B was very similar to the starting material, the protected benzaldehyde **38** (Figure 8.6). This analogy was explained only hypothesizing that Imp B could have the same level of unsaturation of benzaldehyde.

[110] G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4235–4238.

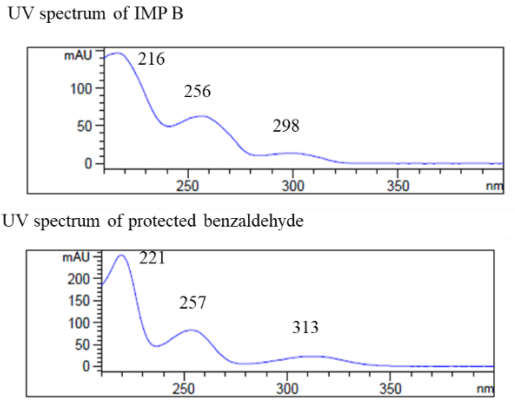
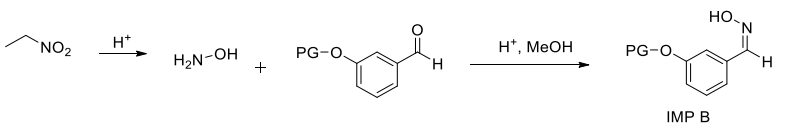


Figure 8.7 UV profiles of **38** vs Imp B

Considering that Imp B was obtained in very low yield in the rection for the nitrostyrene synthesis, after an intensive bibliography research, it was hypothesised that Imp B could be an oxime derivative.

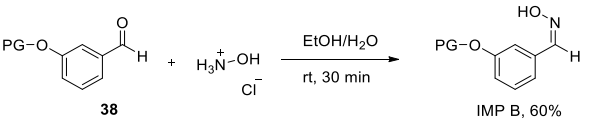
The oxime, although in very small amount, probably is formed in the Henry reaction step from nitroethane, which under acid conditions, could be converted in the corresponding hydroxylamine that in turn reacts with benzaldehyde to give the oxime (Scheme 8.6).



Scheme 8.6 Plausible pathway for synthesis of imp B

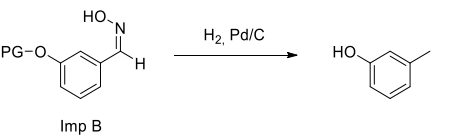
The reaction between hydroxylamine hydrochloride and protected benzaldehyde was then carried out according to literature

procedure[111] and the product was isolated and characterized (Scheme 8.7).



Scheme 8.7 Synthesis of Imp B from **38**

Also for impurity B it was analysed the chemical pathway of the impurity during the successive hydrogenative step. Supported by literature data and experimental analysis, it was demonstrated that Impurity B is transformed into *m*-cresol by reductive reaction. The chemically labile oxime moiety is rapidly reduced, and the protecting group is easily cleaved through high-pressure hydrogenation. In addition, under these reaction conditions even the primary amine functional group is cleaved from the benzyl moiety, [112] leading to ammonia and m-cresol product, which is not a genotoxic compound, and can be easily removed from the final product Metaraminol by methanol washing (Scheme 8.8).



Scheme 8.8 Plausible pathway in reduction of Imp B

[111] E.-C. Wang, K.-S. Huang, H.-M. Chen, C.-C. Wu, G.-J. Lin, *J. Chin. Chem. Soc.* **2004**, *51*, 619–627.
[112] L. McMillan, L. F. Gilpin, J. Baker, C. Brennan, A. Hall, D. T. Lundie, D. Lennon, *J. Mol. Catal. Chem.* **2016**, *411*, 239–246.

8.4 Conclusions

In conclusion, in this work the main recurring impurities in the synthesis of an intermediate of the process to obtain Metaraminol, have been identified, synthesized and characterized. These studies allow Laboratori Alchemia to declare that the final API produced is free from the studied impurities and their plausible derivatives.

At the end in response to the AIFA deficiency Laboratori Alchemia affirms: *In accordance with the results for related substances of intermediate MET 5 obtained in the Technical and Validation batches, which guaranteed the expected quality of the final Drug Substance, we propose a Related Substances total impurities specification parameter of not more than 5.0% and a single unknown impurity specification parameter of not more than 0.50%* (Table 8.3).

Table 8.3 Specification parameter before and after impurities analysis

Related substances specifications (HPLC) Initial ASMF package	Related substances specification (HPLC) Proposed ASMF package
Single impurity: not more than 2.0 %	Impurity A: not more than 2.0%
Total impurities: not more than 5.0 %	Impurity B: not more than 2.0%
	Impurity C: not more than 2.0%
	MET 2: not more than 2.0%
	Any other impurity: not more than 0.50%

It is important to mention that AIFA has considered satisfactory the additional provided documentation thus approving the subsequent

commercialization of Metaraminol.

9 Experimental section

9.1 General experimental conditions

General methods and material

All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Anhydrous THF, toluene, m-xylene, and methanol were purchased from Aldrich and used as received; all other solvents were dried over molecular sieves. Molecular sieves (Aldrich Molecular Sieves, 4 Å, 1.6 mm pellets) were activated under vacuum at 200 °C overnight. Reactions were monitored using thin layer chromatography (TLC) on Macherey–Nagel precoated silica gel plates (0.25 mm) and visualized by UV light, potassium permanganate and cerium sulfate staining solutions. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). 1H NMR and 13C NMR spectra were recorded on a Bruker Avance III HD 600, Bruker Avance-400, Bruker Avance-300 or Bruker Avance-250 spectrometer in CDCl3 or CD3OD as solvents at room temperature. Chemical shifts for protons are reported using residual solvent protons (1H NMR: δ = 7.26 ppm for CDCl3, δ = 3.31 ppm for CD3OD) as internal standard. Carbon spectra were referenced to the shift of the 13C signal of CDCl3 (δ = 77.0 ppm) or CD3OD (δ = 49.0 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s – singlet; d – doublet; t – triplet; q – quartet; dd – double doublet; m – multiplet; bs – broad signal. Optical rotation of compounds was performed on a

Jasco P-2000 digital polarimeter using a WI (tungsten– halogen) lamp (λ = 589 nm). High resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively shielded superconducting magnet. The samples were ionized in the positive ion mode using a MALDI ionization source. Melting points were measured with a Stuart Model SMP 30 melting point apparatus and are uncorrected. Petrol ether (PE) refers to light petroleum ether (boiling point 40-60 °C).

9.2 Formal organocatalytic α-trifluoromethylthiolation of carboxylic acid derivatives under batch conditions via N-acyl pyrazoles

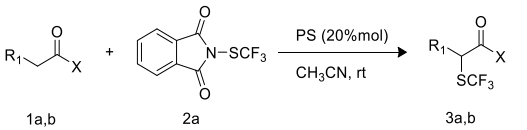
Experimental procedures and compounds characterization

All starting materials (unless otherwise noted) were purchased from Aldrich and used as received.

N-bromophtalimide, N-chlorosuccinimide, dibenzesulfonamide and silver(I)trfluoromethanethiolate were purchased from TCI and used as received. Proton-sponge was purchased from Sigma Aldrich and used as received. N-SCF_3 reagents **21a-c** are known compounds, they were prepared according to

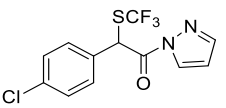
literature.[113] The pyrazolamides **20** were prepared by using general procedures reported in literature.[114]

General procedure for the synthesis of products 22a and 22b



In an oven-dried vial N-acylpyrazole **20a** or **20b** (0.2 mmol), N-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) and anhydrous acetonitrile (1 mL) were introduced. To this solution PS (0.04 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred at rt and monitored by TLC. After completion, the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products 3a and 3b in 39-63% yield. A partial decomposition of products 3a and 3b was observed on silica gel, thus determining slightly lower yield values compared to the estimated NMR conversion values.

2-(4-chlorophenyl)-1-(1H-pyrazol-1-yl)-2-((trifluoromethyl)thio)ethanone (22a)



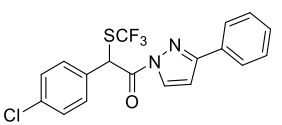
Colorless oil, 40.4 mg, 63% yield. FTIRν_{max}(KBr)/cm^{-1}:3464, 1641, 1386, 1113, 757. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, 1H,

[113] [a] Kang, K.; Xu, C.; Shen, Q. *Org. Chem. Front.* **2014**, *1*, 294-297, [b] Q. Lefebvre, E. Fava, P. Nikolaienko,M. Rueping, *Chem. Commun.*, **2014**, 50, 6617 [c] P. Zhang, M. Li, X. Xue, C. Xu, Q. Zhao, Y. Liu, H. Wang, Y. Guo, L. Lu, Q. Shen, *J. Org. Chem.*, **2016**, 81, 7486−7509

[114] J. Zhang, X. Liu, R. Wang *Chem. Eur. J.* **2014**, *20*, 4911.

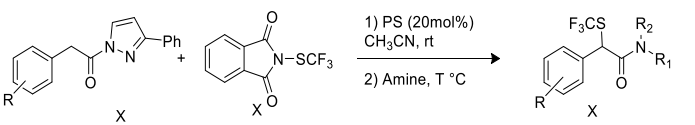
J = 2.9 Hz), 7.73 (d, 1H, *J* = 1.3Hz), 7.52 (d, 2H, *J* = 8.6 Hz), 7.33 (d, 2H, *J* = 8.6), 6.56 (s, 1H), 6.48 (dd, 1H, *J* = 2.9 Hz, *J* = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 145.0, 135.2, 132.3, 130.1, 129.8 (q $^1J_{CF}$ = 307.5 Hz), 129.4, 129.1, 111.2, 49.1. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -40.8. HRMS (MALDI-FT ICR) exact mass $[M+H]^+$ calculated for $C_{12}H_8ClF_3N_2OS$: 320,9998, found: 320.9915.

2-(4-chlorophenyl)-1-(3-phenyl-1H-pyrazol-1-yl)-2-((trifluoromethyl)thio)ethenone (22b)



Colorless oil, 30.9 mg, 39% yield. FTIRν_{max}(KBr)/cm^{-1}:3460, 1699, 1661, 1652, 1558, 1505, 1114, 758. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, 1H, *J* = 2.8 Hz), 7.86 (d, 2H, *J* = 6.5 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 7.51-7.45 (m, 3H), 7.35 (d, 2H, *J* = 8.5 Hz), 6.81 (d, 1H, *J* = 2.8 Hz), 6.63 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 156.4, 135.2, 132.6, 131.0, 130.3, 130.1, 129.9 (q $^1J_{CF}$ = 307.6 Hz), 129.7, 129.3, 128.9, 126.4, 109.1, 49.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -40.7. HRMS (MALDI-FT ICR) exact mass $[M+H]^+$ calculated for $C_{18}H_{12}ClF_3N_2OS$: 397.0311 found: 397.0348.

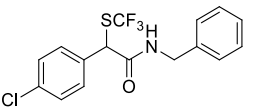
General procedure for one-pot synthesis of α-SCF_3 amides



In an oven-dried vial, under nitrogen atmosphere, PS (0.02 mmol) was added to a mixture of *N*-acylpyrazole **20** (0.2 mmol) and *N*-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) in anhydrous

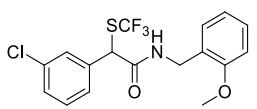
acetonitrile (1 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the first step, the opportune amine (0.26 mmol) was added and the mixture was stirred for the time and at the temperature reported in Table 5.5. After completion, the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 70/30) to afford products **23a-q** in 64-98% yield.

N-benzyl-2-(4-chlorophenyl)-2-((trifluoromethyl)thio)acetamide (23a)



White solid, 64.7 mg, 90% yield. mp 127.8-129.1 °C. FTIRν_{max}(KBr)/cm^{-1}: 3460, 1649, 1560, 1491, 1154, 1115, 697. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.29 (m, 5H), 7.31 (d, 2H, J = 7.2 Hz), 7.17 (d, 2H, J = 7.2 Hz), 6.51 (bs, 1H), 5.01 (s, 1H), 4.45 (dd, 1H, J = 14.8 Hz, J = 5.8 Hz), 4.37 (dd, 1H, J = 14.8 Hz, J = 5.8Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.1, 137.0, 135.1, 133.8, 129.7 (q, $^{1}J_{CF}$ = 308.3 Hz), 129.4 (2H), 128.8, 127.9, 127.7, 52.9, 44.3. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -40.6. HRMS (MALDI-FT ICR) exact mass $[M+H]^+$ calculated for $C_{16}H_{13}ClF_3NOS$: 360.0358, found: 360.0427

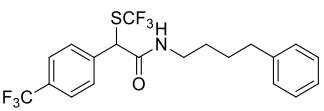
2-(3-chlorophenyl)-N-(2-methoxybenzyl)-2-((trifluoromethyl)thio)acetamide (23b)



White solid, 56.1 mg, 72% yield. **mp** 97.0-98.8 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3450, 3304, 1652, 1558, 1495, 1464, 1246, 1155, 1115, 1030, 755. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.38 (s, 1H), 7.31-7.26 (m,

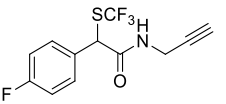
4H), 7.19 (d, 1H, J = 7.5 Hz), 6.90 (t, 1H, J = 7.5 Hz), 6.86 (d, 1H, J = 8.3 Hz), 6.70 (bs, 1H), 4.96 (s, 1H), 4.46 (dd, 1H, J = 14.3 Hz, J = 5.8 Hz), 4.41 (dd, 1H, J = 14.3 Hz, J = 5.8 Hz), 3.78 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.5, 157.4, 137.5, 134.9, 134.3, 130.3, 129.9, 129.7 (q, $^1J_{CF}$ = 309.7 Hz), 129.3, 129.1, 128.2, 126.4, 124.9, 120.7, 110.3, 55.1, 53.1, 40.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.7. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{17}H_{15}ClF_3NO_2S$: 390.0464, found: 390.0424.

N-(4-phenylbutyl)-2-(4-(trifluoromethyl)phenyl)-2-((trifluoromethyl)thio)acetamide (23c)



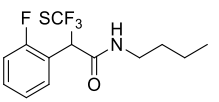
White solid, 85.3 mg, 98% yield. **mp** 86.6-88.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}: 3460, 1654, 1326, 1169, 1112, 1064. **^{1}H NMR** ($CDCl_3$, 300 MHz): 7.63 (d, 2H, J = 8.2 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.30-7.25 (m, 2H), 7.20 (dt, 1H, J = 7.2 Hz, J = 1.5 Hz), 7.12 (dd, 2H, J = 7.2 Hz, J = 1.5 Hz), 6.04 (bs, 1H), 4.99, (s, 1H), 3.30 (q, 2H, J = 6.5 Hz), 2.60 (t, 2H, J = 7.3 Hz), 1.62-1.53 (m, 4H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 166.7, 141.8, 139.5, 131.2 (q, $^2J_{CF}$ = 32.7 Hz), 129.7 (q, J_{CF} = 307.9 Hz), 128.5, 128.4, 128.3, 126.2 (q, $^2J_{CF}$ = 3.3 Hz), 125.9, 122.7 (q, $^1J_{CF}$ = 272.6 Hz), 53.0, 40.2, 35.3, 28.8, 28.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.6, -62.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{20}H_{19}F_6NOS$: 436.1092, found: 436.1054.

2-(4-fluorophenyl)-N-(prop-2-yn-1-yl)-2-((trifluoromethyl)thio)acetamide (23d)



White solid, 42.0 mg, 74% yield. **mp** 117.8-118.7 °C. **FTIR**ν_{max}(KBr)/cm^{-1}: 3460, 2032, 1646, 1508, 1231, 1112. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.39 (dd, 2H, J = 8.6 Hz, J = 5.0 Hz), 7.07 (dd, 2H, J = 8.6 Hz), 6.31 (bs, 1H), 5.01 (s, 1H), 4.13 (ddd, 1H, J =17.6 Hz, J = 5.4 Hz, J = 2.6 Hz), 4.08 (ddd, 1H, J =17.6 Hz, J = 5.4 Hz, J = 2.6 Hz), 2.25 (dd, 1H, ^1J =^{2}J= 2.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.2, 162.9 (d, $^1J_{CF}$ = 248.0 Hz), 130.6, 130.0 (d, $^3J_{CF}$ = 8.4 Hz), 129.6 (q, $^1J_{CF}$ = 308.7 Hz), 116.4 (d, $^2J_{CF}$ = 21.8 Hz), 78.2, 72.4, 52.4, 30.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.7, -111.7. **HRMS (MALDI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{12}H_9F_4NOS$: 314.0233 found: 314.0237.

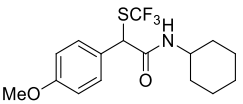
N-butyl-2-(2-fluorophenyl)-2-((trifluoromethyl)thio)acetamide (23e)



White solid, 40.8 mg, 66% yield. **mp** 58.8-59.5 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3299, 3086, 2962, 2936, 2876, 1652, 1558, 1491, 1456, 1244, 1152, 1116. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.52 (t, 1H, J = 7.4 Hz), 7.37-7.30 (m, 1H), 7.19-7.09 (m, 2H), 6.19 (bs, 1H), 5.28 (s, 1H), 3.27 (ddd, 2H, J = J = J =7.2 Hz), 1.48 (quint, 2H, J = 7.2 Hz), 1.29 (sextet, 2H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 166.7, 159.7 (d, $^1J_{CF}$ = 248.3 Hz), 130.7 (d, $^3J_{CF}$ = 8.5 Hz), 129.9 (q, $^1J_{CF}$ = 309.0 Hz), 129.7 (d, $^4J_{CF}$ = 1.9 Hz), 125.0 (d, $^3J_{CF}$ = 3.5 Hz), 123.2 (d, $^2J_{CF}$ = 13.7 Hz), 115.7 (d, $^2J_{CF}$ = 25.4 Hz), 46.3, 40.1, 31.2, 19.8, 13.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -41.1, -117.3. **HRMS**

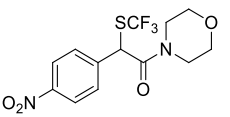
(MALDI-FT ICR) exact mass $[M+H]^+$ calculated for $C_{13}H_{15}F_4NOS$: 310.0810, found: 310.0856.

N-cyclohexyl-2-(4-methoxyphenyl)-2-((trifluoromethyl)thio)acetamide (23f)



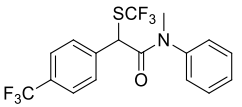
Pale yellow solid, 52.1 mg, 75% yield. **mp** 141.0-143.3 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3469, 2934, 2856, 1648, 1449, 1255, 1114, 526. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.31 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.02 (bs, 1H), 4.97 (s, 1H), 3.80 (s, 3H), 1.89-1.09 (m, 11 H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 166.8, 159.9, 129.8 (q,^{1} J_{CF} = 308.6 Hz), 129.3, 127.0, 114.5, 55.3, 53.2, 49.0, 32.8, 32.5, 25.3, 24.7, 24.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.7. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{16}H_{20}F_3NO_2S$: 348.1235, found: 348.1239.

1-morpholino-2-(4-nitrophenyl)-2-((trifluoromethyl)thio)ethenone (23g)



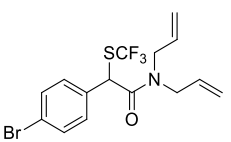
Brown solid, 65.2 mg, 93% yield. **mp** 147.8-153.9 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3453, 2365, 1645, 1524, 1445, 1349, 1113. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.25 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4Hz), 5.43 (s, 1H), 3.70-3.52 (m, 6H), 3.35-3.26 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.2, 148.0, 143.3, 130.2 (q, $^1J_{CF}$ = 309.6 Hz), 129.1, 124.4, 66.4, 65.9, 51.1, 46.6, 43.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.1. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{13}H_{13}F_3N_2O_4S$: 351.0548, found: 351.0593.

N-methyl-N-phenyl-2-(4-(trifluoromethyl)phenyl)-2-((trifluoromethyl)thio)acetamide (23h)



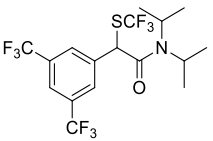
Yellow oil, 53.5 mg, 68% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3455, 1558, 1496, 1386, 1325, 1173, 1110, 1068, 1020. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.51 (d, 2H, J = 8.1 Hz), 7.44 (bs, 3H), 7.23 (d, 2H, J = 8.1 Hz), 7.03 (bs, 2H), 5.08 (s, 1H), 3.28 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.3, 142.2, 139.9, 130.7 (q, $^{2}J_{CF}$ = 32.8 Hz), 130.1 (q, $^{1}J_{CF}$ = 308.3 Hz), 130.0, 129.0, 128.7, 127.4, 125.6 (q, $^{3}J_{CF}$ = 3.3 Hz), 123.8 (q, $^{1}J_{CF}$ = 272.5 Hz), 50.3, 38.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.9, -62.7. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{17}H_{13}F_6NOS$: 394.0622, found: 394.0694.

N,N-diallyl-2-(4-bromophenyl)-2-((trifluoromethyl)thio)acetamide (23i)



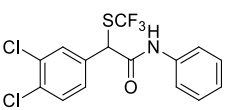
Colorless oil, 56.2 mg, 72% yield. **FTIR**ν_{max}(KBr)/cm^{-1}: 3464, 1645, 1555, 1398, 1210, 1115, 544. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J = 8.3 Hz), 7.65 (d, 2H, J = 8.3 Hz), 5.87-5.81 (m, 1H), 5.73-7.66 (m, 1H), 5.31-5.13 (m, 5H), 4.13 (d, 2H, J = 6.0 Hz), 3.80 (d, 2H, J = 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 189.9, 166.4, 132.4, 132.0, 131.6, 131.1, 130.2 (q $^{1}J_{CF}$ = 310.8 Hz), 130.2, 119.4, 118.8, 49.4, 46.1, 29.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.4. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{15}H_{15}BrF_3NOS$: 394.0010, found: 394.0025.

2-(3,5-bis(trifluoromethyl)phenyl)-N,N-diisopropyl-2-((trifluoromethyl)thio)acetamide (23l)



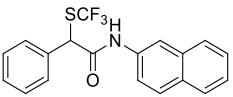
White solid, 66.5 mg, 73% yield. **mp** 82.3-84.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3406, 3049, 2370, 1653, 1558, 1505, 1117. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.89 (s, 2H), 7.86 (s, 1H), 5.52 (s, 1H), 3.86 (sept, 1H, J = 6.6 Hz), 3.36 (sept, 1H, J = 6.7 Hz), 1.44 (d, 3H, J = 6.7 Hz), 1.28 (d, 3H, J = 6.7 Hz), 1.26 (d, 3H, J = 6.6 Hz), 0.61 (d, 3H, J = 6.6 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.9, 140.4, 132.5 (q, $^{2}J_{CF}$ = 33.5 Hz), 130.4 (q, $^{1}J_{CF}$ = 308.9 Hz), 128.3, 122.8 (q, $^{1}J_{CF}$ = 273.1 Hz), 122.4 (q, $^{3}J_{CF}$ = 3.6 Hz), 53.7, 50.2, 47.0, 20.8, 20.3, 19.6, 19.2. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.1, -63.0. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{17}H_{18}F_9NOS$: 456.0965, found: 456.0986.

2-(3,4-dichlorophenyl)-N-phenyl-2-((trifluoromethyl)thio)acetamide (23m)



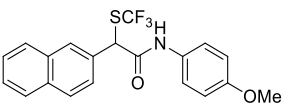
Yellow solid, 63.1 mg, 83% yield. **mp** 109.8-111.5 °C. **FTIR**ν_{max}(KBr)/cm^{-1}: 3450, 1654, 1560, 1500, 1446, 1111, 756. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.81 (bs, 1H), 7.58 (d, 1H, J = 1.4 Hz), 7.47 (m, 3H), 7.34 (t, 3H, J = 7.6 Hz), 7.17 (t, 1H, J = 7.4 Hz), 5.07 (s,1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 164.8, 136.4, 135.0, 133.7, 133.5, 131.2, 130.1, 129.6 (q, $^{1}J_{CF}$ = 308.6 Hz), 129.2, 127.4, 125.6, 120.3, 53.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.4. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{15}H_{10}Cl_2F_3NO$: 379.9812, found: 379.9853.

N-(naphthalen-2-yl)-2-phenyl-2-((trifluoromethyl)thio)acetamide (23n)



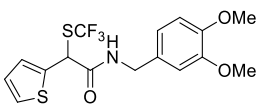
Brown solid, 57.1 mg, 79% yield. **mp** 151.2-153.3 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3460, 1652, 1508, 1152, 1113, 767, 696. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.19 (bs, 1H), 7.91 (m, 2H), 7.75 (d, 1H, J = 8.3 Hz), 7.60 (d, 2H, J = 7.0 Hz), 7.53-7.48 (m, 7H), 5.39 (s,1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.0, 134.7, 134.2, 133.6, 131.0, 129.8 (q, $^{1}J_{CF}$ = 307.3 Hz), 129.4, 129.3, 128.9, 128.2, 127.7, 127.5, 126.7, 125.5, 119.7, 117.4, 54.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.6. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{19}H_{14}F_3NOS$: 362.0748, found: 362.0712.

N-(4-methoxyphenyl)-2-(naphthalen-2-yl)-2-((trifluoromethyl)thio)acetamide (23o)



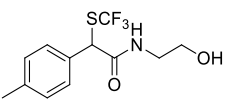
White solid, 57.1 mg, 73% yield. **mp** 164.2-165.7 °C **FTIR**ν_{max}(KBr)/cm^{-1}:3489, 2057, 1637, 1512, 1249, 1155, 1108, 714, 478. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.91-7.83 (m, 4H), 7.68 (bs, 1H), 7.59-7.52 (m, 3H), 7.35 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 5.35 (s, 1H), 3.77 (s, 3H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.5, 157.1, 133.3, 133.2, 132.2, 129.8, 129.8 (q, $^{1}J_{CF}$ = 307.1 Hz), 129.6, 128.1, 127.8, 127.7, 127.1, 126.9, 125.1, 122.1, 114.2, 55.5, 54.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.5. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{20}H_{16}F_3NO_2S$: 392.0854, found: 392.0813.

N-(3,4-dimethoxybenzyl)-2-(thiophen-2-yl)-2-((trifluoromethyl)thio)acetamide (23p)



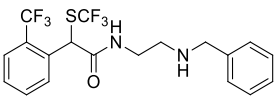
Brown solid, 56.4 mg, 72% yield. **mp** 113.1-115.3 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3043, 1735, 1701, 1685, 1654, 1648, 1560, 1541, 1518, 1459, 1267, 1114. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33 (d, 1H, , J = 4.5 Hz), 7.12 (d, 1H, , J = 2.9 Hz), 6.97 (t, 1H, , J = 4.5 Hz), 6.78 (m, 2H), 6.74 (s, 1H), 6.39 (bs, 1H), 5.34 (s, 1H), 4.43 (d, 2H, J = 5.7 Hz), 3.86 (s, 3H), 3.91 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 166.9, 149.2, 148.6, 136.6, 129.7, 129.6 (q,$^{1}J_{CF}$ = 308.5 Hz), 127.9, 127.4, 127.2, 120.1, 111.1, 110.8, 55.9, 55.7, 48.9, 44.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.9. **HRMS (MALDI-FT ICR)** exact mass $[M+K]^+$ calculated for $C_{16}H_{16}F_3NO_3S_2$: 430.0155, found: 430.0161.

N-(2-hydroxyethyl)-2-(p-tolyl)-2-((trifluoromethyl)thio)acetamide (23q)



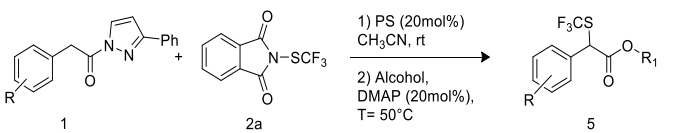
Pink solid, 41.1 mg, 70% yield. **mp** 89.0-91.6 °C **FTIR**ν_{max}(KBr)/cm^{-1}:3440, 2927, 1652, 1558, 1512, 1456, 1464, 1246, 1155, 1115, 1030. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.29 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H; J = 8.0 Hz), 6.58 (bs, 1H), 5.01 (s, 1H), 3.70 (m, 2H), 3.49-3.38 (m, 2H), 2.34 (s, 3H), 2.19 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.7, 139.1, 132.0, 129.9, 129.8. (q, $^{1}J_{CF}$ = 308.6 Hz), 127.9, 61.7, 53.4, 42.7, 21.2. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{12}H_{14}F_3NO_2S$: 294.0697, found: 294.0658.

N-(2-(benzylamino)ethyl)-2-(2-(trifluoromethyl)phenyl)-2-((trifluoromethyl)thio)acetamide (23r)



Dark red oil, 69.8 mg, 80% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3445, 1670, 1519, 1454, 1315, 1154, 1123, 1061, 1038. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.90 (d, 1H, J = 7.7 Hz), 7.68 (d, 1H, J = 7.7 Hz), 7.59 (t, 1H, J = 7.7 Hz), 7.45 (t, 1H, J = 7.7 Hz), 7.34-7.23 (m, 5H), 6.65 (bs, 1H), 5.38 (s, 1H), 3.72 (s, 2H), 3.39-3.32 (m, 1H), 3.29-3.21 (m, 1H), 2.80 (bs, 1H), 2.76-2.71 (m, 2H) **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 167.7, 140.9, 135.8, 133.7, 131.6, 130.7 (q, $^{1}J_{CF}$ = 307.4 Hz), 129.7, 129.4, 128.9, 128.5 (q, J_{CF} = 29.9 Hz), 128.1, 127.0 (q, J_{CF} = 5.5 Hz), 125.1 (q, J_{CF} = 275.1 Hz), 54.3, 49.7, 48.1, 40.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -41.1, -57.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{19}H_{18}F_6N_2OS$: 437.1044, found: 437.1027.

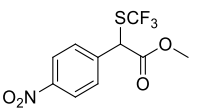
General procedure for one-pot synthesis of α-trifluoromethylthio esters



In an oven-dried vial, under nitrogen atmosphere, **PS** (0.02 mmol) was added to a mixture of *N*-acylpyrazole **20** (0.2 mmol) and *N*-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) in anhydrous acetonitrile (1 mL). The reaction mixture was stirred at room

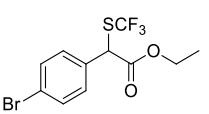
temperature and monitored by TLC. After completion of the first step, acetonitrile was evaporated and DMAP (0.04 mmol) and anhydrous alcohol (2 mL) were added and the mixture was stirred at 50°C for the time reported in Table 5.6 in the paragraph 5.2. After completion, the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 80/20) to afford products **24a-c** in 78-83% yield.

Methyl 2-(4-nitrophenyl)-2-((trifluoromethyl)thio)acetate (24a)



Pale yellow solid, 47.2 mg, 80% yield. **mp** 60.2-61.7 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3460, 1652, 1549, 1508, 1152, 1113, 767, 696, 419. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.25 (d, 2H, J = 8.7 Hz), 7.66 (d, 2H, J = 8.7 Hz), 5.15 (s, 1H), 3.79, (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 168.1, 148.2, 141.4, 129.4 (q,$^{1}J_{CF}$ = 308.6 Hz), 129.3, 124.3, 53.9, 50.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{10}H_8F_3NO_4S$: 296.0126, found: 296.0173.

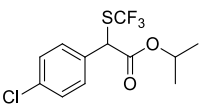
Ethyl 2-(4-bromophenyl)-2-((trifluoromethyl)thio)acetate (24b)



Yellow oil, 53.5 mg, 78% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3454, 2986, 1654, 1489, 1299, 1274, 1157, 1113, 1013, 757, 508. **^{1}H NMR** ($CDCl_3$, 300 MHz):7.51 (d, 2H, J = 8.3 Hz), 7.33 (d, 2H, J = 8.3 Hz), 4.9, (s, 1H), 4.25 (dq, 1H, J = 15.8 Hz, J = 7.1 Hz), 4.19 (dq, 1H, J = 15.8 Hz, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 168.4, 133.3, 132.2, 129.8, 129.6 (q,$^{1}J_{CF}$ = 306.9 Hz), 123.3, 62.8, 50.9, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.4. **HRMS**

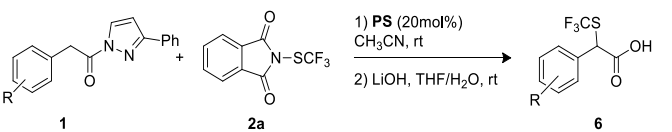
(MALDI-FT ICR) exact mass $[M+Na]^+$ calculated for $C_{11}H_{10}BrF_3O_2S$: 366.9409, found: 366.9407.

Isopropyl 2-(4-chlorophenyl)-2-((trifluoromethyl)thio)acetate (24c)



Brown oil, 51.9 mg, 83% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3440, 2987, 1733, 1652, 1493, 1377, 1280, 1116, 1098, 1016, 767. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.39 (d, 2H, J = 8.6 Hz), 7.34 (d, 2H, J = 8.6 Hz), 5.04 (sept, 1H, J = 6.3 Hz), 4.97 (s, 1H), 1.26 (d, 3H, J = 6.3 Hz), 1.17 (d, 3H, J = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 168.0, 135.1, 132.8, 129.7 (q,$^1J_{CF}$ = 308.3 Hz), 129.5, 129.3, 70.8, 51.1, 21.4, 21.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.9. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{12}H_{12}ClF_3O_2S$: 313.0199, found: 313.0146.

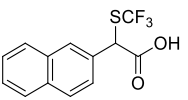
General procedure for one-pot synthesis of α-trifluoromethylthio acids



In an oven-dried vial, under nitrogen atmosphere, **PS** (0.02 mmol) was added to a mixture of *N*-acylpyrazole **20** (0.2 mmol) and *N*-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) in anhydrous acetonitrile (1 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the first

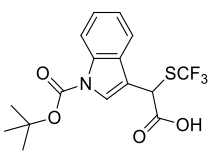
step, acetonitrile was evaporated and LiOH·H_2O (0.4 mmol) and THF/H_2O (2:1, 1.5 mL) were added. The mixture was stirred for 16 h at room temperature. After completion, LiOH was quenched with acetic acid, then the reaction mixture was diluted with H_2O and the aqueous phase was extracted with EtOAc (x3). The organic layers were dried over Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10 + 1% of acetic acid) to afford product **25a** and **25b** in 70-90% yield.

2-(naphthalen-2-yl)-2-((trifluoromethyl)thio)acetic acid (25a)



White solid, 51.5 mg, 90% yield. **mp** 103.0-105.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3460, 2925, 2852, 1719, 1273, 1159, 1110, 811, 748, 482. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ, 8.49 (bs, 1H), 7.91 (s, 1H), 7.87-7.82 (m 3H), 7.54-7.51 (m, 3H), 5.25 (s, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.7, 134.2, 133.1, 130.5, 129.6 (q,$^1J_{CF}$ = 307.8 Hz), 129.3, 128.1, 127.9, 127.7, 127.1, 126.8, 125.0, 51.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.7. **HRMS (MALDI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{26}H_{18}F_6O_4S_2$: 595.0448, found: 595.0450

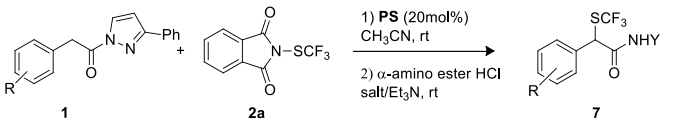
2-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)-2-((trifluoromethyl)thio)acetic acid (25b)



Pale yellow solid, 52.5 mg, 70% yield. **mp** 129.0-131.2°C. **FTIR**ν_{max}(KBr)/cm^{-1}:3450, 2915, 2851, 1705, 1265, 1139, 1110, 821, 750. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ, 9.0 (bs, 1H), 8.16

(d, 1H, *J* = 7.8 Hz), 7.78 (s, 1H), 7.68 (d, 1H, *J* = 7.4 Hz), 7.38 (dd, 1H, *J* = 7.1 Hz, *J* = 7.8 Hz), 7.31 (dd, 1H, *J* = 7.1 Hz, *J* = 7.4 Hz), 5.35 (s, 1H), 1.67 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.3, 149.2, 135.5, 129.6 (q, $^1J_{CF}$ = 308.8 Hz), 127.6, 125.7, 125.3, 123.2, 119.1, 115.6, 111.6, 84.7, 43.1, 28.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -41.0. **HRMS (MALDI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{32}H_{32}F_6N_2O_8S_2$: 773.1397, found: 773.1460.

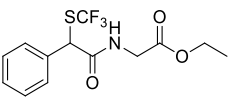
General procedure for one-pot synthesis of functionalized α-SCF_3 amides



1 **2a** **7**

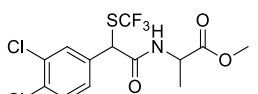
In an oven-dried vial *N*-acylpyrazole **20** (0.2 mmol), *N*-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) and anhydrous acetonitrile (1 mL) were introduced. Under nitrogen atmosphere, **PS** (0.02 mmol) was added to this solution. The reaction mixture was stirred at room temperature for the time indicated in Table 3 and monitored by TLC. After completion, α-amino ester hydrochloride (0.26 mmol) and triethylamine (0.26 mmol) were added and the mixture was stirred at room temperature for 2 hours. After completion, the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/diethyl ether 100/0 to 70/30) to afford products **26a-d** in 76-95% yield.

Ethyl 2-(2-phenyl-2-((trifluoromethyl)thio)acetamido)acetate (26a)



White solid, 61.0 mg, 95% yield. **mp** 90.7-93.9 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3304, 3216, 1750, 1661, 1539, 1377, 1307, 1201, 1163, 1112, 1053, 1023, 713. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.44-7.34 (m, 5H), 6.70 (bs, 1H), 5.09 (s, 1H), 4.20 (q, 2H, J = 7.1 Hz), 4.09 (dd, 1H, J = 18.3 Hz, J = 5.2 Hz), 3.98 (dd, 1H, J = 18.3 Hz, J = 5.2 Hz), 1.26 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.2, 167.8, 134.3, 129.8 (q,$^{1}J_{CF}$ = 309.4 Hz), 129.2, 129.1, 128.2, 61.8, 53.3, 41.9, 14.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for: $C_{13}H_{14}F_3NO_3S$: 322.0646, found: 322.0617.

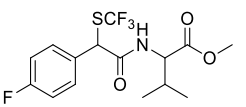
Methyl 2-(2-(3,4-dichlorophenyl)-2-((trifluoromethyl)thio)acetamido)propanoate (26b)



White solid, 60.9 mg, 78% yield. **mp** 75.5-79.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3309, 2959, 1747, 1658, 1543, 1484, 1455, 1397, 1353, 1219, 1154, 1113, 767. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (diastereoisomers A+B) 7.55 (m,1H+1H, J = 2.6 Hz) , 7.47 (s, 1H), 7.45 (s, 1H), 7.30 (m, 1H, J = 2.6 Hz), 7.28 (m, 1H, J = 2.6 Hz), 6.73 (d, 1H, J = 5.6 Hz), 6.62 (d, 1H, J = 5.6 Hz), 4.96 (s, 1H), 4.92 (s, 1H), 4.60 (q, 1H, J = 7.2 Hz), overlapped with 4.55 (q, 1H, J = 7.1 Hz), 3.78 (s, 3H), 3.74 (s, 3H), 1.45 (d, 3H, J = 7.2 Hz), 1.40 (d, 3H,

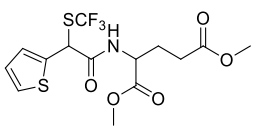
J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ (diastereoisomers A+B) 172.7, 172.6, 166.2, 166.1, 135.0, 133.5, 133.4, 133.3, 131.2, 131.1, 130.1, 129.6 (q,$^1J_{CF}$ = 308.5 Hz), 127.4, 52.8, 52.7, 52.0, 48.9, 48.7, 18.1, 17.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.6. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{13}H_{12}Cl_2F_3NO_3S$: 389.9867, found: 389.9821.

Methyl 2-(2-(4-fluorophenyl)-2-((trifluoromethyl)thio)acetamido)-3-methylbutanoate (26c)



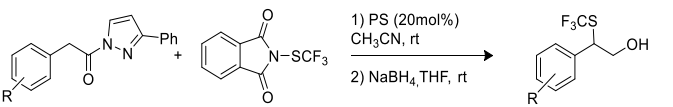
White solid, 55.8 mg, 76% yield. **mp** 75.5-79.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3836, 3676, 3600, 3525, 2957, 1748, 1650, 1558, 1509, 1227, 1114, 669. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (diastereoisomers A+B) 7.44-7.39 (m, 2H+2H), 7.09-7.04 (m, 2H+2H), 6.63 (bs, 1H+1H), 5.08 (s, 1H), 5.04 (s, 1H), 4.56 (q, 1H, J = 4.3 Hz) overlapped with 4.52 (q, 1H, J = 4.3 Hz), 3.75 (s, 3H), 3.71 (s, 3H), 2.17 (sept, 1H+1H, J = 6.6 Hz), 0.92 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.6 Hz), 0.83 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ (diastereoisomers A+B) 171.9, 171.7, 167.5, 167.3, 162.8 (d,$^1J_{CF}$ = 249.6 Hz), 131.8, 131.2 (d, $^4J_{CF}$ = 2.9 Hz), 130.7 (d, $^4J_{CF}$ = 2.9 Hz), 129.9 (d, $^3J_{CF}$ = 8.4 Hz), 129.7 (q, $^1J_{CF}$ = 308.6 Hz), 129.6 (q, $^1J_{CF}$ = 308.6 Hz), 116.3 (d, $^2J_{CF}$ = 21.8 Hz), 116.2 (d, $^2J_{CF}$ = 21.8 Hz), 57.7, 57.6, 52.9, 52.5, 52.4, 52.3, 31.8, 31.2, 18.7, 17.7, 17.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.6, -40.7, -111.9. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{15}H_{17}F_4NO_3S$: 368.0865, found: 368.0842.

Dimethyl 2-(2-(thiophen-2-yl)-2-((trifluoromethyl)thio)acetamido)malonate (26d)



Colorless oil, 61.6 mg, 83% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3348, 1734, 1675, 1457, 1441, 1115, 1110. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ (diastereoisomers A+B) 7.34 (d, 2H, J = 5.2 Hz), 7.18 (d, 1H, J = 3.4 Hz), 7.15 (1, 2H, J = 3.5 Hz), 7.01-6.97 (m, 4H), 5.35 (s, 1H), 5.32 (s, 1H), 4.65-4.58 (m, 2H), 2.76 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 2.46-2.19 (m, 6H), 2.11-1.99 (m, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): (diastereoisomers A+B) δ 173.3, 173.2, 171.5, 171.4, 167.1, 167.0, 136.2, 136.0, 129.5 (q,$^{1}J_{CF}$ = 308.6 Hz), 128.1, 127.5, 127.2, 127.2, 52.7, 52.44, 52.42, 51.9, 48.6, 29.8, 29.7, 26.8, 26.7.**^{19}F NMR** ($CDCl_3$, 376 MHz): δ -40.9, -41.0. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{12}H_{12}F_3NO_5S_2$: 400.0042, found: 400.0028.

General procedure for one-pot synthesis of β-trifluoromethylthio alcohols

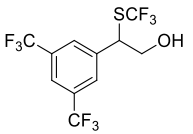


1 2a 8

In an oven-dried vial, under nitrogen atmosphere, **PS** (0.02 mmol) was added to a mixture of *N*-acylpyrazole **20** (0.2 mmol) and *N*-(trifluoromethylthio)phthalimide **21a** (0.24 mmol) in anhydrous acetonitrile (1 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After completion acetonitrile

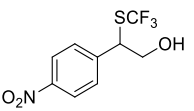
was replaced with THF (1 mL) and $NaBH_4$ (0.2 mmol) was added. The mixture was stirred at room temperature for the time reported in Scheme 2 in the paper. After completion, $NaBH_4$ was quenched with water and the aqueous phase was extracted with EtOAc (x3). The organic layers were dried over Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 70/30) to afford products **27a-d** in 75-80% yield.

2-(3,5-bis(trifluoromethyl)phenyl)-2-((trifluoromethyl)thio)ethanol (27a)



Colorless oil, 57.9 mg, 75% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3435, 3221, 1959, 1774, 1754, 1634, 1328, 1308, 1280, 1175, 1139, 1054, 1037, 926. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.86 (s, 3H), 4.57 (t, 1H, *J* = 5.9 Hz), 4.11 (dd, 1H, *J* =11.4 Hz, *J* = 5.8 Hz), 4.07 (dd, 1H, *J* =11.4 Hz, *J* =5.8 Hz), 1.96 (bs, 1H). **^{13}C NMR** $CDCl_3$, 150 MHz): *δ* 140.9, 132.3 (q, $^2J_{CF}$ = 34.1 Hz), 130.1 (q, $^1J_{CF}$ = 308.0 Hz), 128.3, 123.0 (q, $^1J_{CF}$ = 272.1 Hz), 122.4 (q, $^3J_{CF}$ = 3.6 Hz), 65.2, 50.4.**^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -39.7, -62.9. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{11}H_7F_9OS$: 359.0074, found: 359.0029.

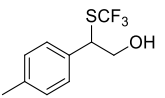
2-(4-nitrophenyl)-2-((trifluoromethyl)thio)ethanol (27b)



Colorless oil, 45.5 mg, 77% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3435, 2929, 1773, 1726, 1608, 1592, 1350, 1163, 1124, 1066, 862. **^{1}H**

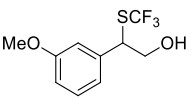
NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, 2H, J = 8.4 Hz), 7.58 (d, 2H, J = 8.4 Hz), 4.55 (t, 1H, J = 5.9 Hz), 4.07 (m, 2H), 1.98 (dd, 1H, $J = J$ = 5.9 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 147.7, 145.3, 130.1 (q,$^1J_{CF}$ = 307.7 Hz), 129.0, 128.0, 124.1, 65.2, 50.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -39.7. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_9H_8F_3NO_3S$: 268.0177, found: 268.0138.

2-(p-tolyl)-2-((trifluoromethyl)thio)ethanol (27c)



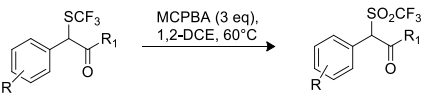
Brown oil, 42.3 mg, 80% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3455, 2924, 1645, 1515, 1112, 756. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.24 (d, 2H, J =8.7 Hz), 7.21 (d, 2H, J =8.7 Hz), 4.44 (t, 1H, J =6.6 Hz), 4.00 (d, 2H, J =6.6 Hz), 2.35 (s, 3H), 1.78 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 138.4, 134.1, 130.4 (q,$^1J_{CF}$ = 307.4 Hz), 129.8, 127.7, 65.7, 50.9, 21.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -39.6. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{10}H_{11}F_3OS$: 237.0483, found: 237.0416.

2-(3-methoxyphenyl)-2-((trifluoromethyl)thio)ethanol (27d)



Brown oil, 42.6 mg, 76% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3416, 2924, 1602, 1587, 1493, 1438, 1264, 1148, 1112, 1051, 757, 700. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.29 (t, 1H, J = 7.9 Hz), 6.93 (d, 1H, J = 7.9 Hz), 6.87 (m, 2H), 4.42 (t, 1H, J = 6.4 Hz), 4.01 (m, 2H), 3.82 (s, 3H), 1.86 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 161.0, 139.7, 131.3 (q,$^1J_{CF}$ = 305.9 Hz), 131.2, 120.9, 114.8, 114.7, 66.7, 56.3, 52.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -39.7. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{10}H_{11}F_3O_2S$: 253.0432, found: 253.0498.

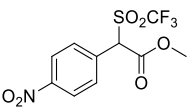
General procedure for oxidation of α-trifluoromethylthio derivates



4-7 9

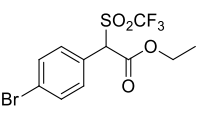
In an oven-dried vial α-trifluoromethylthio derivate **23-26** (0.2 mmol), MCPBA (0.6 mmol) and anhydrous 1,2-dichlorethane (1 mL) were introduced. The reaction mixture was stirred at 60°C for 16 hours as reported in Scheme 5.9 in the paragraph 5.2. After completion of the reaction, PPh_3 (0.2 mmol) was added and the mixture was stirred for 30 min and then extracted with EtOAc and washed with $NaHCO_3$ (x3) and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 70/30) to afford products **28a-e** in 72-85% yield.

Methyl 2-(4-nitrophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28a)



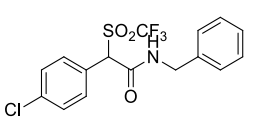
Yellow solid, 47.1 mg, 72% yield. **mp** 200.6-204.6 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3435, 2950, 2919, 2850, 1752, 1654, 1529, 1376, 1352, 1209, 1114. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.32 (d, 2H, J = 8.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 5.43 (s, 1H), 3.92 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 161.8, 149.4, 131.9, 130.9, 124.2, 119.6 (q,$^1J_{CF}$ = 327.8 Hz), 69.2, 54.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.4. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{10}H_8F_3NO_6S$: 328.0024, found: 328.0059.

Ethyl 2-(4-bromophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28b)



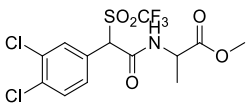
White solid, 63.8 mg, 80% yield. **mp** 60.2-61.7 °C. **FTIR** ν_{max}(KBr)/cm^{-1}:3328, 1747, 1658, 1540, 1484, 1455, 1397, 1353, 1219, 1163, 1113, 757. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, J = 8.5 Hz), 7.49 (d, 2H, J = 8.5 Hz), 5.26 (s, 1H), 4.37 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.31 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.2, 132.6, 132.2, 125.7, 124.6, 119.6 (q,$^{1}J_{CF}$ = 329.9 Hz), 69.6, 63.9, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.4. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{11}H_{10}BrF_3O_4S$: 374.9435, found: 374.9416.

N-benzyl-2-(4-chlorophenyl)-2-((trifluoromethyl)sulfonyl)acetamide (28c)



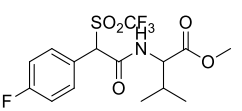
White solid, 58.8 mg, 75% yield. **mp** 162.8-164.1 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3462, 2960, 2376, 2045, 1652, 1558, 1539, 1504, 1373, 1215, 1129, 701. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.52 (d, 2H, J =8.4 Hz), 7.42 (d, 2H, J = 8.4 Hz), 7.35-7.30 (m, 3H), 7.24 (d, 2H, J = 7.7 Hz), 6.72 (bs, 1H), 5.21 (s, 1H), 4.54 (dd, 1H, J = 14.7 Hz, J = 5.3 Hz), 4.46 (dd, 1H, J =14.7 Hz, J = 5.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.0, 137.3, 136.4, 131.8, 129.6, 128.9, 128.1, 127.8, 123.4, 119.6 (q,$^{1}J_{CF}$ = 330.0 Hz), 70.4, 44.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.1. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{16}H_{13}ClF_3NO_3S$: 392.0257, found: 392.0249.

Methyl 2-(2-(3,4-dichlorophenyl)-2-((trifluoromethyl)sulfonyl)acetamido)propanoate (28d)



Pale yellow oil, 65.9 mg, 78% yield. **FTIR**ν_{max}(KBr)/cm^{-1}:3343, 2956, 2921, 2850, 1743, 1674, 1538, 1471, 1375, 1213, 1116. **^{1}H NMR** ($CDCl_3$, 300 MHz): (diastereoisomers A+B) δ 7.73 (s, 1H+1H), 7.56-7.46 (m, 2H+2H), 7.28 (bs, 1H), 7.13 (bs, 1H), 5.32 (s, 1H) overlapped with 5.30 (s, 1H), 4.63 (q, 1H+1H, J = 7.2 Hz), 3.79 (s, 3H), 3.76 (s, 3H), 1.48 (d, 3H, J = 7.2 Hz), 1.43 (d, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): (diastereoisomers A+B) δ 172.5, 172.4, 159.4, 159.3, 135.7, 135.6, 133.7, 133.5, 132.45, 132.39, 131.2, 131.1, 129.8, 129.7, 124.8, 124.7, 121.6 (q,$^1J_{CF}$ = 331.7 Hz), 69.4, 69.3, 52.93, 52.90, 49.2, 49.1, 17.9, 17.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -72.9, -73.2. **HRMS (MALDI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{13}H_{12}Cl_2F_3NO_5S$: 443.9658, found: 443.9669.

Methyl 2-(2-(4-fluorophenyl)-2-((trifluoromethyl)sulfonyl)acetamido)-3-methylbutanoate (28e)



White solid, 58.3 mg, 73% yield. **mp** 100.9-102.4 °C. **FTIR**ν_{max}(KBr)/cm^{-1}:3343, 2970, 1747, 1668, 1607, 1539, 1509, 1440, 1373, 1211, 1116. **^{1}H NMR** ($CDCl_3$, 300 MHz): (diasetereoisomers A+B) δ 7.65-7.57 (m, 2H+2H), 7.20-7.10 (m, 2H+2H), 7.03 (d, 1H, J =8.4 Hz), 6.94 (d, 1H, J =7.8 Hz), 5.29 (s, 1H+1H), 4.63-4.58 (m, 1H+1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.25 (sept, 1H+1H, J =6.4 Hz),

0.99 (d, 3H, *J* =6.4 Hz), 0.94 (d, 3H, *J* =6.4 Hz), 0.93 (d, 3H, *J* =6.4 Hz), 0.89 (d, 3H, *J* =6.4 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): (diastereoisomers A+B) δ 171.6, 171.4, 164.2 (d, $^1J_{CF}$ = 252.4 Hz), 164.1 (d, $^1J_{CF}$ = 252.3 Hz), 160.6, 159.8, 132.8 (d, $^3J_{CF}$ = 8.7 Hz), 132.6 (d,$^3J_{CF}$ = 8.7 Hz), 120.7 (d,$^4J_{CF}$ = 2.9 Hz), 120.6 (d,$^4J_{CF}$ = 2.6 Hz), 119.7 (q,$^1J_{CF}$ = 329.8 Hz), 119.6 (q,$^1J_{CF}$ = 329.9 Hz), 116.7 (d,$^2J_{CF}$ = 22.4 Hz), 116.4 (d,$^2J_{CF}$ = 22.4 Hz), 70.2, 70.1, 58.1, 57.9, 52.5, 31.5, 31.1, 18.8, 17.5, 17.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -73.2, -73.5, -109.3, -109.8. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{15}H_{17}F_4NO_5S$: 400.0764, found: 400.0725.

9.3 Telescoped continuous flow synthesis of α Trifluoromethylthiolated Esters and Amides via N-acyl pyrazoles

Experimental procedures and compounds characterization

All starting materials (unless otherwise noted) were purchased from Aldrich and TCI used as received. N-SCF3 phthalimide **21a** and the pyrazolamides **20** were prepared by using general procedures reported in literature.

Synthesis of N-Benzyl α-Trifluoromethylthioamide (23s) under Batch Conditions.

In an oven-dried vial, under nitrogen atmosphere, TEA (5.6 μL 0.04 mmol, 0.2 eq) was added to a mixture of N-acylpyrazole **20** (0.2 mmol, 1 eq) and N-(trifluoromethylthio)phthalimide **21a** (59.3 mg,

0.24 mmol, 1.2 eq) in a mixture of anhydrous CH3CN and THF (1:1, 1 mL). The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the first step, N-benzylamine (0.26 mmol, 1.3 e) was added, and the mixture was stirred for 2 h at room temperature. After completion, the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 80/20) to afford products **23s** in 70% yield.

General Flow Reactor Setup

The coil reactor was realized by using PTFE tubing (1.58 mm outer diameter, 0.78 mm inner diameter) coiled in a bundle and immersed in an oil bath heated to the desired temperature. Reagent solutions were mixed using a PEEK T-mixer. The end of tubing chain connected to a 75 psi back-pressure regulator, and the outlet stream was collected in vial.

In-Flow Synthesis of Acyl Pyrazole (20c)

Syringe A: 2.5 mL SGE gastight syringe containing 4-Br-phenylacetic acid (2 mL of a 0.6 M solution in CH_3CN/THF 1:1, 0.4 mmol, 1.0 eq) and DMAP (0.06 M solution CH_3CN/THF 1:1, 0.04 mmol, 0.1 eq) and Syringe B: 2.5 mL SGE gastight syringe containing 3 phenylpyrazole (2 mL of a 0.63 M solution in CH_3CN/DCM 1:1, 0.42 mmol, 1.05 eq) and EDC·HCl (0.72 M solution in CH_3CN/DCM 1:1, 0.48 mmol, 1.2 eq), were connected by

a PEEK tee junction to a 500 μL PTFE coil reactor. Both syringes fed the solution at 125 μL/min giving a residence time of 2 min. The system was pressurized at 75 PSI by applying a PEEK black pressure regulator. The outcome of the reactor was collected in a vial, and the solvent was evaporated. After the first five volumes were discarded, steady-state conditions were reached. The yield of product was evaluated by ^{1}H NMR, using 1,3,5- trimethoxybenzene as an internal standard (0.33 eq), and was reported as an average value calculated on three separately collected reactor volumes.

In-Flow Synthesis of N-Benzyl α-Trifluoromethylthioamide (23s)

Syringe A: 5 mL SGE gastight syringe containing pyrazoleamide **20** (3 mL of a 0.3 M solution in CH_3CN/THF 1:1, 0.9 mmol), Syringe B: 1 mL SGE gastight syringes containing TEA (0.68 M solution in CH_3CN/THF 1:1, 0.68 mmol), and Syringe C: 1 mL SGE gastight syringes containing N-SCF_3 phtalimide **21a** (1.6 M solution in CH_3CN/THF 1:1, 1.6 mmol) and α,α,α-CF_3 toluene as an internal standard (1.3 M solution in CH_3CN/THF 1:1, 1.3 mmol) were connected by a PEEK tee junction to a 500 μL PTFE coil reactor. Syringe A fed the solution at 25 μL/min, while both syringes B and C fed the solution at 5.5 μL/min, giving a residence time of 14 min and a molar ratio in the reactor of pyrazoleamide (1 mol/eq), TEA (0.5 mol/eq), *N*-SCF_3 phtalimide (1.2 mol/eq), and α,α,α-CF_3 toluene (1 eq). The outcome of the reactor was collected in a vial containing benzylamine (0.2 mmol, 2 eq), where it was stirred for further 2 h.

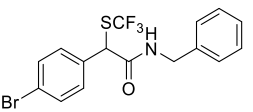
The reaction mixture was dissolved in $CDCl_3$ (without removing reaction solvent to avoid the evaporation of the internal standard) and subjected to ^{19}F NMR, to evaluate the NMR yield of the product. After discarding the first reaction volume, steady-state conditions were reached. The yield was reported as an average value calculated on three separately collected reactor volumes. Reactor volumes were reunited and purified by column chromatography.

Telescoped Synthesis of α-Trifluoromethylthioamides (23s-z)

Syringe A: 5 mL SGE gastight syringe containing the appropriate phenylacetic acid (0.6 M solution in CH_3CN/THF 1:1, 1.8 mmol, 1 eq) and DMAP (0.06 M solution CH_3CN/THF 1:1, 0.18 mmol 0.1 eq) and Syringe B: 5 mL SGE gastight syringe, containing 3-phenylpyrazole (0.63 M solution in CH_3CN/DCM 1:1, 1.89 mmol, 1.05 eq) and EDC·HCl (0.72 M solution in CH_3CN/DCM 1:1, 2.16 mmol, 1.2 eq) were connected by a PEEK tee junction to a 50 μL PTFE coil reactor. Both syringes fed the solution at 12.5 μL/min giving a residence time of 2 min. The outcome of the reactor was connected by another tee junction to two 2.5 mL SGE gastight syringes: Syringe C containing TEA (0.68 M solution in CH_3CN/THF 1:1, 1.70 mmol) and Syringe D containing N-SCF_3 phtalimide **21a** (2 M solution in CH_3CN/THF 1:1, 5.11 mmol) and α,α,α-CF_3 toluene as an internal standard (1.3 M solution in CH_3CN/THF 1:1, 3.25 mmol). Both the syringes C and D fed the solution at 5.5 μL/min, giving an overall residence time of 36 min and a molar ratio in the reactor of

pyrazoleamide (1 mol/eq), TEA (0.5 mol/eq), N-SCF_3 phtalimide (1.5 mol/eq), and α,α,α-CF_3 toluene (1 eq). The system was pressurized at 75 PSI by applying a PEEK black pressure regulator. To avoid the precipitation of the N-SCF_3 reagent, syringe D was kept at 35 °C. After discarding the first volume, the outcome of the reactor was collected in a vial containing the proper amine (0.2 mmol, 2 eq), and the mixture was stirred for further 2 h at the temperature reported in Figure 6.1 in paragraph 6.2. The reaction mixture was dissolved in $CDCl_3$ (without removing the reaction solvent to avoid the evaporation of the internal standard) and subjected to ^{19}F NMR, to evaluate the yield of the product. The ^{19}F NMR experiments were recorded with d1 = 5 s to obtain a quantitative analysis. The yield was evaluated by the integral ratio between the signal of SCF_3 group of the product (∼−40 ppm) and the signal of the CF_3 group of the internal standard (−63 ppm). The NMR yield was reported as an average value calculated on three separately collected reactor volumes. Reactor volumes were reunited and purified by column chromatography.

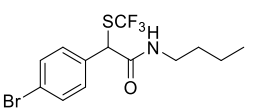
N-Benzyl-2-(4-bromophenyl)-2-((trifluoromethyl)thio)acetamide (23s)



The compound was purified by flash silica gel column chromatography (hexane/ethyl acetate 100/0 to 80/20). White solid, 85.7 mg, 70% yield. **mp** 130.5−131.4 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.53 (d, 2H, J = 8.3 Hz), 7.35−7.28 (m, 5H), 7.22 (d, 2H, J = 7.5 Hz), 6.26 (br,

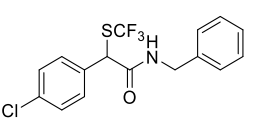
1H), 4.99 (s, 1H), 4.52 (dd, 1H, J = 14.7 Hz, J = 5.7 Hz), 443 (dd, 1H, J = 14.7 Hz, J = 5.7 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 167.1, 137.0, 134.4, 132.4, 129.7, 129.7 (q, $^1J_{CF}$= 308.3 Hz), 128.8, 127.9, 127.7, 123.3, 53.0, 44.4. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ −40.6. **HRMS (ESI-FT ICR)** exact mass $[M + Na]^+$ calculated for $C_{16}H_{13}BrF_3NOSNa$: 425.9751, found: 425.9759.

N-Butyl-2-(4-bromophenyl)-2-((trifluoromethyl)thio)acetamide (23t)



White solid, 66.2 mg, 60% yield **mp** 85.6−87.0 °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.52 (d, 2H, J = 8.3 Hz), 7.30 (d, 2H, J = 8.3 Hz), 6.08 (br, 1H), 4.96 (s, 1H), 3.29 (ddd, 2H, J = J = J ≈ 7.0 Hz), 1.49 (quint, 2H, J = 7.3 Hz), 1.31 (sext, 2H, J = 7.4 Hz), 0.92 (t, 3H, J = 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): δ 167.0, 134.5, 132.3, 129.74 (q, $^1J_{CF}$ = 308.4 Hz), 129.7, 123.1, 52.9, 40.0, 31.2, 19.9, 13.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −40.6. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{13}H_{16}BrF_3NOS$: 370.0083, found: 370.0094.

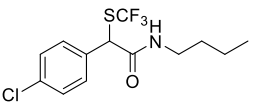
N-Benzyl-2-(4-chlorophenyl)-2-((trifluoromethyl)thio)acetamide (23u)



White solid, 57.8 mg, 55% yield. **mp** 127.8−129.1 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.33−7.29 (m, 5H), 7.31 (d, 2H, J = 7.2 Hz), 7.17 (d, 2H, J = 7.2 Hz), 6.51 (br, 1H), 5.01 (s, 1H), 4.45 (dd, 1H, J = 14.8 Hz, J = 5.8 Hz), 4.37 (dd, 1H, J = 14.8 Hz, J = 5.8 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 167.1, 137.0, 135.1, 133.8, 129.7 (q, $^1J_{CF}$

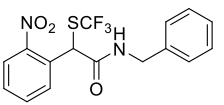
= 308.3 Hz), 129.4 (2C), 128.8, 127.9, 127.7, 52.9, 44.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −40.6. **HRMS (MALDI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{16}H_{14}ClF_3NOS$: 360.0437, found: 360.0431.

N-Butyl-2-(4-chlorophenyl)-2-((trifluoromethyl)thio)acetamide (23a)



White solid, 49.4 mg, 50% yield **mp** 72.7−73.7 °C **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.36 (m, 4H), 6.24 (br, 1H), 4.99 (s, 1H), 3.28 (ddd, 2H, J = J = J ≈ 7.0 Hz), 1.48 (quint, 2H, J = 7.4 Hz), 1.30 (sext, 2H, J = 7.4 Hz), 0.9 (t, 3H, J = 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 167.2, 135.0, 134.0, 129.80 (q, $^1J_{CF}$ = 308.2 Hz), 129.4, 129.3, 52.9, 40.1, 31.2, 19.9, 13.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −40.7. **HRMS (ESI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{13}H_{16}ClF_3NOS$: 326.0588, found: 326.0574.

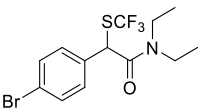
N-Benzyl-2-(2-nitrophenyl)-2-((trifluoromethyl)thio)acetamide (23v)



Colorless oil, 57.2 mg, 51% yield **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07 (d, 1H, J = 1.4 Hz), 7.76−7.68 (m, 2H), 7.55 (t, 1H, J = 7.7 Hz), 7.35−7.22 (m, 5H), 7.00 (br, 1H), 5.45 (s, 1H), 4.54 (dd, 1H, J = 14.9 Hz, J = 5.9 Hz), 4.41 (dd, 1H, J = 14.9 Hz, J = 5.7 Hz). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 166.1, 147.5, 137.2, 134.5, 132.8, 132.2, 130.3 (q, $^1J_{CF}$ = 308.4 Hz), 129.9, 128.9, 127.9, 127.7, 125.4, 49.7, 44.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −41.5. **HRMS (MALDI-FT ICR)** exact

mass $[M+Na]^+$ calculated for $C_{16}H_{13}F_3N_2O_3SNa$: 393.0497, found: 393.0472.

N,N-Diethyl-2-(4-bromophenyl)-2-((trifluoromethyl)thio)-acetamide (23z)

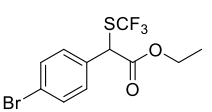


Pale yellow oil, 33.6 mg, 30% yield. °C. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 5.28 (s, 1H), 3.41 (m, 1H), 3.31 (m, 2H), 3.21 (m, 1H), 1.08 (t, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.5, 135.7, 132.3, 130.6 (q, $^1J_{CF}$ = 308.1 Hz), 129.8, 122.9, 51.9, 42.5, 41.0, 14.0, 12.5. **^{19}F NMR** (CDCl3, 376 MHz): δ −40.4. **HRMS (ESI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{13}H_{15}BrF_3NOS$ 370.0083, found 370.0087.

Telescoped Synthesis of Ethyl 2-(4-Bromophenyl)-2-((trifluoromethyl)thio)acetate (24b)

Syringe A: 5 mL SGE gastight syringe containing 4-Br-phenylacetic acid (0.6 M solution in CH_3CN/THF 1:1, 1.8 mmol, 1.0 eq) and DMAP (0.06 M solution CH_3CN/THF 1:1, 0.18 mmol, 0.1 eq) and Syringe B: 5 mL SGE gastight syringe containing 3-phenylpyrazole (0.63 M solution in CH_3CN/DCM 1:1, 1.89 mmol, 1.05 eq) and EDC·HCl (0.72 M solution in CH_3CN/DCM 1:1, 2.16 mmol, 1.2 eq) were connected by a PEEK tee junction to a 50 µL PTFE coil reactor. Both syringes fed the solution at 12.5 µL/min giving a residence time of 2 min. The outcome of the reactor was connected by another tee

junction to two 2.5 mL SGE gastight syringes: Syringe C containing TEA (0.68 M solution in CH_3CN/THF 1:1, 1.70 mmol) and Syringe D containing N-SCF_3 phtalimide **21** (2 M solution in CH_3CN/THF 1:1, 5.11 mmol) and α,α,α-CF3 toluene as an internal standard (1.3 M solution in CH_3CN/THF 1:1, 3.25 mmol). Both syringes C and D fed the solution at 5.5 μL/min, giving an overall residence time of 36 min and a molar ratio in the reactor of pyrazoleamide (1 mol/eq), TEA (0.5 mol/eq), N-SCF_3 phtalimide (1.5 mol/eq), and α,α,α-CF_3 toluene (1 eq). The system was pressurized at 75 PSI by applying a PEEK black pressure regulator. To avoid the precipitation of the N-SCF_3 reagent, syringe D was kept at 35 °C. The outcome of the reactor was collected in a vial containing ethanol (5 mmol, 50 eq) and DMAP (1.3 mg, 0.01 mmol, 0.1 eq), and the mixture was stirred for a further 8 h at 50 °C. The reaction mixture was dissolved in $CDCl_3$ (without removing the reaction solvent to avoid the evaporation of the internal standard) and subjected to ^{19}F NMR to evaluate the yield of the product. The ^{19}F NMR experiments were recorded with d1 = 5 s to obtain a quantitative analysis. The yield was evaluated by the integral ratio between the signal of SCF_3 group of the product (∼−40 ppm) and the signal of the CF_3 group of the internal standard (−63 ppm). The NMR yield was reported as an average value calculated on three separately collected reactor volumes. Reactor volumes were reunited and purified by column chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10).

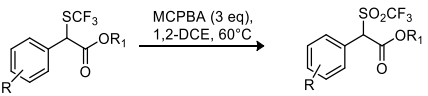


Pale yellow oil, 72.8 mg, 70% yield. **^{1}H NMR**

($CDCl_3$, 300 MHz):7.51 (d, 2H, J = 8.3 Hz), 7.33 (d, 2H, J = 8.3 Hz), 5.00 (s, 1H), 4.25 (dq, 1H, J = 15.8 Hz, J = 7.1 Hz), 4.19 (dq, 1H, J = 15.8 Hz, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 168.4, 133.3, 132.2, 129.8, 129.6 (q, 1JCF = 306.9 Hz), 123.3, 62.8, 50.9, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ −41.0. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{11}H_{10}BrF_3O_2SNa$ 466.9752, found 466.9736.

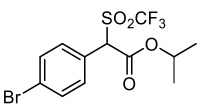
9.4 Asymmetric Michael addition of triflone-containing nucleophiles: enantioselective organocatalytic synthesis of quaternary stereocenters

General synthesis of α-trifluoromethylsulfonyl esters



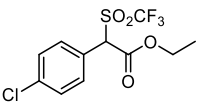
In an oven-dried vial *α*-trifluoromethylthio derivate **24** (0.5 mmol), MCPBA (336.2 mg, 1.5 mmol) and anhydrous 1,2-dichlorethane (2.5 mL) were introduced. The reaction mixture was stirred at 60°C for 16 hours as reported in Scheme **5.9** in the chapter **5**. After completion of the reaction, PPh_3 (131.1 mg 0.5 mmol) was added and the mixture was stirred for 30 min and then extracted with EtOAc and washed with $NaHCO_3$ (x3) and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **28** in 72-85% yields.

Isopropyl 2-(4-bromophenyl)-2 ((trifluoromethyl)sulfonyl)acetate (28f)



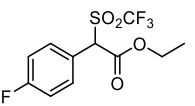
White solid, 155.7 mg, 80% yield. **mp** 39.7-40.5 °C. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.60 (d, 2H, J = 8.6 Hz), 7.49 (d, 2H, J = 8.6 Hz), 5.22 (s, 1H), 5.16 (sept, 1H, J = 6.4 Hz), 1.34 (d, 3H, J = 6.4 Hz), 1.29 (d, 3H, J = 6.4 Hz). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 161.5, 132.3, 125.8, 123.1, 124.6, 119.9 (q,$^{1}J_{CF}$ = 329.9 Hz), 72.6, 70.0, 21.6, 21.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.4.

Ethyl 2-(4-chlorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28g)



Colourless oil, 129.0 mg, 78% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.57 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 5.31 (s, 1H), 4.37 (dq, 1H, J = 13.4 Hz, J = 7.2 Hz), 4.30 (dq, 1H, J = 13.4 Hz, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.1, 137.5, 132.1, 129.7, 123.0, 119.9 (q,$^{1}J_{CF}$ = 330.6 Hz), 69.7, 64.0, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -73.5.

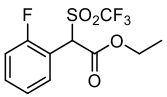
Ethyl 2-(4-fluorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28h)



Colourless oil, 102.1 mg, 65% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.57 (d, 2H, J = 8.6 Hz), 7.44 (d, 2H, J = 8.6 Hz), 5.31 (s, 1H), 4.37 (dq, 1H, J = 13.4 Hz, J = 7.2 Hz), 4.30 (dq, 1H, J = 13.4 Hz, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): δ 164.4 (d,^{1} J_{CF} =

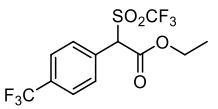
252.2 Hz), 162.2, 132.9 (d,$^3J_{CF}$ = 8.8 Hz), 120.3 (d,$^4J_{CF}$ = 3.1 Hz), 119.9 (q,$^1J_{CF}$ = 330.3 Hz), 116.6 (d,$^2J_{CF}$ = 22.1 Hz), 69.9, 64.0, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -73.5.

Ethyl 2-(2-fluorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28i)



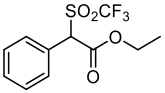
Colourless oil, 94.3 mg, 60% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.92 (t, 1H, J = 7.4 Hz), 7.50 (ddd, 1H, J = 7.1 Hz, J = 1.3 Hz), 7.29 (d, 1H, J = 7.1 Hz), 7.19 (t, 1H, J = 8.6 Hz), 5.84 (s, 1H), 4.38 (dq, 1H, 1H, J = 14.2 Hz, J = 7.2 Hz), 4.38 (dq, 1H, 1H, J = 14.2 Hz, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): δ 161.9, 160.9 (d,$^1J_{CF}$ = 251.1 Hz), 132.9 (d,$^3J_{CF}$ = 8.7 Hz), 131.6, 125.2, 119.8 (q,$^1J_{CF}$ = 330.0 Hz), 116.0 (d,$^2J_{CF}$ = 22.0 Hz), 112.6 (d,$^2J_{CF}$ = 13.6 Hz), 64.0, 62.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -74.5, -116.6.

Ethyl 2-(4-(trifluoromethyl)phenyl)-2-((trifluoromethyl)sulfonyl)acetate (28l)



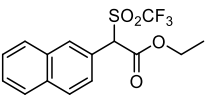
White solid, 149.3 mg, 82% yield. **mp** 46.2-47.4. °C **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.78 (d, 2H, J = 8.6 Hz), 7.73 (d, 2H, J = 8.6 Hz), 7.29 (d, 1H, J = 7.1 Hz), 5.36 (s, 1H), 4.38 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.34 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 161.8, 133.1 (q,$^2J_{CF}$ = 33.0 Hz), 131.3, 128.5, 126.3 (q,$^3J_{CF}$ = 3.5 Hz), 123.6 (q,$^1J_{CF}$ = 272.8 Hz), 119.8 (q,$^1J_{CF}$ = 329.6 Hz), 69.8, 64.2, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.1, -73.5.

Ethyl 2-phenyl-2-((trifluoromethyl)sulfonyl)acetate (28m)



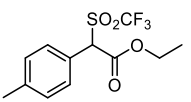
White solid, 111.1 mg, 75% yield. **mp** 49.5-50.1. °C. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.62 (dd, 2H, J = 7.6 Hz, J = 1.6 Hz), 7.51-7.43 (m, 3H), 5.31 (s, 1H), 4.36 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.32 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.4, 130.9, 130.8, 129.4, 124.5, 119.9 (q,$^{1}J_{CF}$ = 329.9 Hz), 70.5, 63.8, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -73.6.

Ethyl 2-(naphthalen-2-yl)-2-((trifluoromethyl)sulfonyl)acetate (28n)



White solid, 142.0 mg, 82% yield. **mp** 96.0-98.7. °C **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11 (d, 1H, J = 1.5 Hz), 7.95-7.87 (m, 3H), 7.68 (dd, 1H, J = 8.6 Hz, J = 1.9 Hz), 7.61-7.54 (m, 2H), 5.48 (s, 1H), 4.38 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.34 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.5, 134.1, 133.1, 131.4, 129.3, 128.6, 127.9, 127.1, 126.7, 121.7, 120.0 (q,$^{1}J_{CF}$ = 329.5 Hz), 70.6, 63.8, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.5.

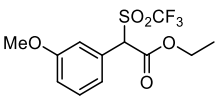
Ethyl 2-(p-tolyl)-2-((trifluoromethyl)sulfonyl)acetate (28o)



White solid, 105.5 mg, 68% yield. **mp** 49.9-50.7. °C **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.49 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 5.28 (s, 1H), 4.34 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.31 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 2.39 (s, 3H), 1.32 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75

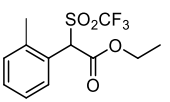
MHz): δ 162.5, 141.3, 130.7, 130.1, 121.4, 119.9 (q,$^1J_{CF}$ = 330.1 Hz), 70.3, 63.7, 21.4, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -73.6.

Ethyl 2-(3-methoxyphenyl)-2-((trifluoromethyl)sulfonyl)acetate (28p)



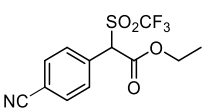
Colourless oil, 119.1 mg, 73% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36 (t, 1H, J = 7.9 Hz), 7.18 (s, 1h), 7.15 (d, 1H, J = 7.7 Hz), 7.03 (d, 1H, J = 8.0 Hz), 5.28 (s, 1H), 4.35 (dq, 1H, J = 14.0 Hz, J = 7.1 Hz), 4.31 (dq, 1H, J = 14.0 Hz, J = 7.1 Hz), 3.82 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.3, 160.2, 130.3, 125.6, 123.1, 119.9 (q,$^1J_{CF}$ = 329.8 Hz), 116.7, 116.1, 70.3, 63.8, 55.5, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.7.

Ethyl 2-(o-tolyl)-2-((trifluoromethyl)sulfonyl)acetate (28q)



Colourless oil, 100.8 mg, 65% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.85 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz), 7.40-7.28 (m, 3H), 5.66 (s, 1H), 4.34 (dq, 1H, J = 14.3 Hz, J = 7.1 Hz), 4.29 (dq, 1H, J = 14.3 Hz, J = 7.1 Hz), 2.46 (s, 3H), 1.31 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.8, 138.6, 131.4, 130.8, 130.3, 127.1, 122.9, 120.0 (q,$^1J_{CF}$ = 330.1 Hz), 65.6, 63.7, 19.8, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -74.4.

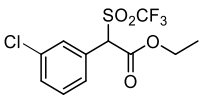
Ethyl 2-(4-cyanophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28r)



Colourless oil, 133.3 mg, 83% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.76 (s, 4H), 5.37 (s, 1H), 4.37 (dq, 1H, J = 14.3 Hz, J = 7.1 Hz), 4.33 (dq,

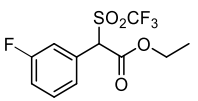
1H, *J* = 14.3 Hz, *J* = 7.1 Hz), 1.33 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): *δ* 162.8, 138.6, 131.4, 130.8, 130.3, 127.1, 122.9, 120.0 (q,$^1J_{CF}$ = 330.1 Hz), 65.6, 63.7, 19.8, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -73.3.

Ethyl 2-(3-chlorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28s)



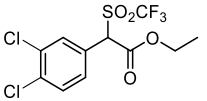
Colourless oil, 127.0 mg, 77% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): *δ* 7.63 (t, 1H, *J* = 1.7 Hz), 7.50 (td, 2H, *J* = 7.9 Hz, *J* = 1.7 Hz), 7.40 (t, 1H, *J* = 7.9 Hz), 5.26 (s, 1H), 4.36 (dq, 1H, *J* = 14.3 Hz, *J* = 7.2 Hz), 4.32 (dq, 1H, *J* = 14.3 Hz, *J* = 7.2 Hz), 1.34 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): *δ* 161.9, 135.4, 131.2, 130.8, 130.5, 129.0, 126.3, 119.9 (q,$^1J_{CF}$ = 330.1 Hz), 69.7, 64.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -73.3.

Ethyl 2-(3-fluorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28t)



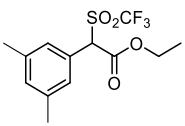
Colourless oil, 128.8 mg, 82% yield. **^{1}H NMR** ($CDCl_3$, 300 MHz): *δ* 7.48-7.35 (m, 3H), 7.50 (td, 2H, *J* = 7.9 Hz, *J* = 1.7 Hz), 7.21 (tt, 1H, *J* = 8.3 Hz, *J* = 1.3 Hz,), 5.30 (s, 1H), 4.36 (dqd, 1H, *J* = 14.4 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz), 4.33 (dqd, 1H, *J* = 14.4 Hz, *J* = 7.2 Hz, *J* = 1.0 Hz), 1.33 (dt, 3H, *J* = 7.2 Hz, *J* = 1.0 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): *δ* 162.8 (d,$^1J_{CF}$ = 247.5 Hz), 161.9, 130.9 (d,$^1J_{CF}$ = 7.5 Hz), 126.8, 126.5 (d,$^1J_{CF}$ = 8.3 Hz), 119.9 (q,$^1J_{CF}$ = 330.1 Hz), 118.1, 118.1 (d,$^1J_{CF}$ = 44.6 Hz), 69.8, 64.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -73.5, -110.5.

Ethyl 2-(3,4-dichlorophenyl)-2-((trifluoromethyl)sulfonyl)acetate (28u)



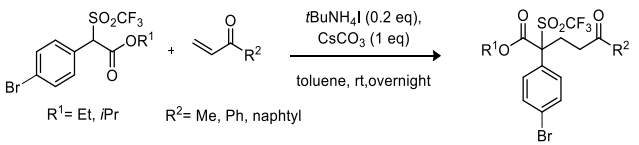
Colourless oil, 129.6 mg, 71% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.73 (d, 1H, J = 2.1 Hz), 7.55 (d, 1H, J = 8.4 Hz), 7.49 (dd, 1H, J = 8.4 Hz, J = 2.1 Hz), 5.25 (s, 1H), 4.37 (dq, 1H, J = 14.3 Hz, J = 7.2 Hz), 4.33 (dq, 1H, J = 14.4 Hz, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.7, 135.9, 133.8, 132.6, 131.3, 130.0, 124.4, 119.8 (q,$^1J_{CF}$ = 330.1 Hz), 69.1, 64.3, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.4.

Ethyl 2-(3,5-dimethylphenyl)-2-((trifluoromethyl)sulfonyl)acetate (28v)



Colourless oil, 129.7 mg, 80% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.21 (s, 2H), 7.12 (s, 1H), 5.23 (s, 1H), 4.35 (dq, 1H, J = 14.2 Hz, J = 7.2 Hz), 4.30 (dq, 1H, J = 14.2 Hz, J = 7.2 Hz), 2.35 (s, 6H), 1.33 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 162.6, 139.2, 132.7, 128.4, 124.0, 119.9 (q,$^1J_{CF}$ = 329.9 Hz), 70.3, 63.6, 21.3, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -73.6.

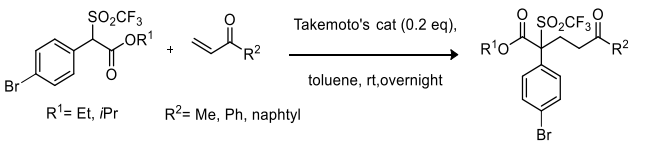
General procedure for racemic Michael reaction of vinyl ketones



In an oven-dried vial α-trifluoromethylsulfonyl esters **28** (0.1 mmol)

and vinyl ketone (0.12 mmol), or (0.25 mmol, 21 μL) in the case of methyl vinyl ketone, and anhydrous toluene (0.5 mL) were introduced. To this solution *t*BuNH$_4$I (0.02 mmol, 7.39 mg) and $CsCO_3$ (0.1 mmol, 32.6 mg) were added under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 19 h. After completion of the reaction, HCl 1N to quench the reaction and the mixture was extracted with diethyl ether (x3). The organic layers were dehydrated with Na_2SO_4, and the solvent was evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **36a-d** in 25-56% yield.

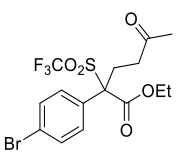
General procedure for enantioselective Michael reaction of vinyl ketones



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol) and vinyl ketone (0.12 mmol), or (0.25 mmol, 21 μL) in the case of methyl vinyl ketone, and anhydrous toluene (0.5 mL) were introduced. To this solution (R,R)-Takemoto's catalyst (0.02 mmol, 8,26 mg) was added under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 17 h. After completion of the reaction the solvent was evaporated and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0

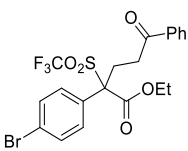
to 90/10) to afford products **36a-d** in 75-85% yield.

Ethyl 2-(4-bromophenyl)-5-oxo-2-((trifluoromethyl)sulfonyl)hexanoate (36a)



Colourless oil, 33.4 mg, 75% yield (55% ee). $[\alpha]_D^{23}$ = +10.61 (*c* 0.89, CHCl3).**^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.58 (d, 2H, *J* = 8.9 Hz), 7.34 (d, 2H, *J* = 8.9 Hz), 7.40 (t, 1H, *J* = 7.9 Hz), 4.44 (dq, 2H, *J* = 7.2 Hz, *J* = 1.6 Hz), 2.92 (dd, 2H, *J* = 8.0 Hz, *J* = 6.8 Hz), 2.79 (ddd, 1H, *J* = 18.0 Hz, *J* = 8.0 Hz, *J* = 6.8 Hz), 2.41 (ddd, 1H, *J* = 18.0 Hz, *J* = 8.0 Hz, *J* = 6.8 Hz), 2.11 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 205.3, 165.7, 132.3, 131.2, 127.8, 125.3, 120.7 (q,$^1J_{CF}$ = 334.5 Hz), 82.5, 64.1, 38.6, 26.5, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.2. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{15}H_{16}BrF_3O_5SNa$ 466.9752, found 466.9798. **HPLC** analysis with Chiralpak AD-H column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 10.6 min, major enantiomer tR = 12.5 min.

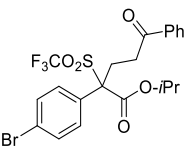
Ethyl 2-(4-bromophenyl)-5-oxo-5-phenyl-2-((trifluoromethyl)sulfonyl)pentanoate (36b)



Colourless oil, 40.1 mg, 79% yield (67% ee). $[\alpha]_D^{16}$ = +1.84 (*c* 0.58, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.88 (dd, 2H, *J* = 8.3 Hz, *J* = 1.2 Hz), 7.60-7.54 (m, 3H), 7.47-7.38 (m, 4H), 4.45 (q, 2H, *J* = 7.2 Hz), 3.37 (ddd, 2H, *J* = 17.3 Hz, *J* = 9.2 Hz, *J* = 6.2 Hz), 3.11 (m, 2H), 2.93 (ddd, 1H, *J* = 17.4 Hz, *J* = 8.9 Hz, *J* = 5.3 Hz), 1.37 (t, 3H, *J* = 7.2

Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 197.1, 165.7, 136.3, 133.7, 132.4, 131.3, 128.9, 128.1, 127.9, 125.4, 120.8 (q,$^1J_{CF}$ = 333.3 Hz), 82.8, 64.1, 33.9, 27.1, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{20}H_{18}BrF_3O_5SNa$ 528.9903, found 528.9898. **HPLC** analysis with Chiralpak AD-H column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 14.6 min, major enantiomer tR = 17.3 min.

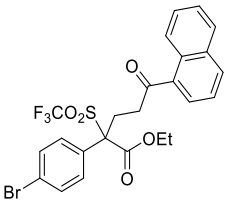
Isopropyl 2-(4-bromophenyl)-5-oxo-5-phenyl-2-((trifluoromethyl)sulfonyl)pentanoate (36c)



Colourless oil, 39.6 mg, 76% yield (63% ee). **$[\alpha]_D^{17}$** = +1.59 (*c* 0.53, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.89 (dd, 2H, *J* = 8.4 Hz, *J* = 1.2 Hz), 7.58 (dd, H, *J* = 8.7 Hz, *J* = 1.6 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.45 (t, 2H, *J* = 7.5 Hz), 7.40 (dd, 2H, *J* = 8.7 Hz, *J* = 1.6 Hz), 5.32 (quint, 1H, *J* = 6.1 Hz), 3.38 (ddd, 1H, *J* = 17.5 Hz, *J* = 9.5 Hz, *J* = 5.3 Hz), 3.11 (m, 2H), 2.93 (ddd, 1H, *J* = 17.5 Hz, *J* = 9.5 Hz, *J* = 5.7 Hz), 1.37 (t, 3H, *J* = 6.0 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 197.1, 165.2, 136.2, 133.7, 132.3, 131.2, 128.9, 128.1, 128.0, 125.3, 120.7 (q,$^1J_{CF}$ = 336.3 Hz), 82.6, 72.9, 33.9, 27.1, 21.6, 21.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -66.9. **HRMS_(ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{21}H_{20}BrF_3O_5SNa$ 543.0059, found 543.0043. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 11.5 min, major enantiomer tR = 13.7 min.

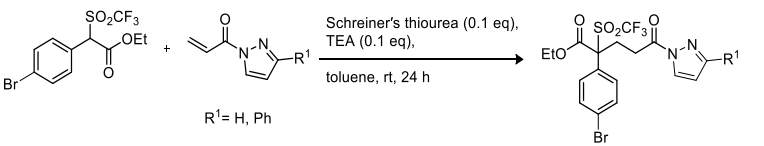
Ethyl 2-(4-bromophenyl)-5-(naphthalen-1-yl)-5-oxo-2-

((trifluoromethyl)sulfonyl)pentanoate (36d)



Colourless oil, 49.1 mg, 85% yield (44% ee). **[α]$_D^{14}$** = +0.67 (*c* 0.29, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.59 (d, 1H, *J* = 8.5 Hz), 7.99 (d, 1H, *J* = 8.3 Hz), 7.87 (d, 1H, *J* = 8.3 Hz), 7.76 (d, 1H, *J* = 7.2 Hz), 7.63-7.53 (m, 4H), 7.48-7.42 (m, 3H), 4.46 (q, 2H, *J* = 7.2 Hz), 3.45 (ddd, 1H, *J* = 17.6 Hz, *J* = 8.2 Hz, *J* = 6.7 Hz), 3.20 (m, 2H), 3.01 (ddd, 1H, *J* = 17.6 Hz, *J* = 8.2 Hz, *J* = 5.9 Hz), 1.38 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 200.9, 165.7, 134.9, 134.1, 133.4, 132.4, 131.3, 130.2, 128.7, 128.4, 128.0, 127.8, 126.7, 125.7, 125.4, 124.4, 120.8 (q,$^1J_{CF}$ = 334.1 Hz), 82.8, 64.1, 37.1, 27.3, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{24}H_{20}BrF_3O_5SNa$ 579.0065, found 579.0047. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 26.4 min, major enantiomer tR = 16.4 min.

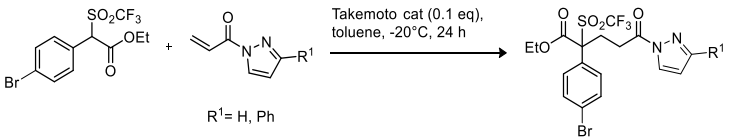
General procedure for racemic Michael reaction of a,b-unsaturated pyrazoleamides



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole **30** (0.15 mmol) and anhydrous toluene (0.5

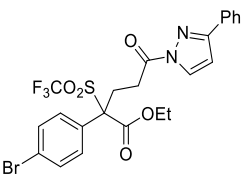
mL) were introduced. To this solution Schreiner′s Thiourea Catalyst (0.01 mmol, 5.00 mg) and triethylamine (0.01 mmol, 1.5 μL) were added under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 24 h and monitored by TLC. After completion of the reaction the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford **46a-b** in 70-93% yield.

General procedure for enantioselective Michael reaction of α,β-unsaturated pyrazoleamides



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole (0.15 mmol) and anhydrous toluene (0.5 mL) were introduced. The reaction mixture was cooled at -20°C and after the temperature was reached the Takemoto catalyst (0.01 mmol, 4.13 mg) was added, in the same temperature condition. The reaction mixture was stirred at -20°C for 24 h and monitored by TLC. After completion of the reaction the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **46a-b** in 93-96% yield.

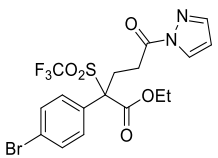
Ethyl 2-(4-bromophenyl)-5-oxo-5-(3-phenyl-1H-pyrazol-1-yl)-2 ((trifluoromethyl)sulfonyl)pentanoate (46a)



Colourless oil, 53.3 mg, 93% yield (86% ee).

[α]$_D$^{14} = -25.1 (*c* 0.47, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.25 (d, 1H, *J* = 2.9 Hz), 7.82 (dd, 2H, *J* = 7.8 Hz, *J* = 1.5 Hz), 7.60 (d, 2H, *J* = 8.7 Hz), 7.49-7.38 (m, 5H), 6.78 (d, 1H, *J* = 2.9 Hz), 4.49 (dq, 2H, *J* = 7.1 Hz, *J* = 1.5 Hz), 3.53-3.42 (m, 1H), 3.28-3.16 (m, 3H), 1.40 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 170.1, 165.4, 156.0, 132.4, 131.6, 131.5, 129.7, 129.5, 128.9, 127.2, 126.5, 125.5, 120.8 (q,$^1J_{CF}$ = 333.5 Hz), 108.0, 82.7, 64.2, 29.9, 27.4, 13.9. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -67.0. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{23}H_{20}BrF_3N_2O_5SNa$ 595.0126, found 595.0118. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 26.4 min, major enantiomer tR = 16.4 min.

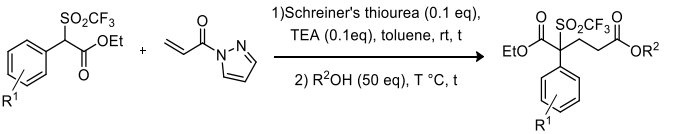
Ethyl 2-(4-bromophenyl)-5-oxo-5-(1H-pyrazol-1-yl)-2-((trifluoromethyl)sulfonyl)pentanoate (46b)



Colourless oil, 47.7 mg, 96% yield (94% ee). **[α]$_D$**^{21} = +6.62 (*c* 0.64, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.22 (s, 1H), 7.67 (s, 1H), 7.59 (d, 1H, *J* = 8.5 Hz), 7.43 (d, 1H, *J* = 8.5 Hz), 6.44 (s, 1H), 4.46 (q, 2H, *J* = 7.2 Hz), 3.54-3.39 (m, 1H), 3.17-3.05 (m, 3H), 1.38 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 170.2, 165.4, 144.5, 132.4, 131.3, 128.5, 127.2, 125.5, 120.8 (q,$^1J_{CF}$ = 334.1 Hz), 110.1, 82.6, 64.2, 29.9, 27.2, 13.8. **^{19}F NMR** ($CDCl_3$, 282 MHz): δ -67.0. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{17}H_{16}BrF_3N_2O_5SNa$ 518.9813, found 518.9801. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-

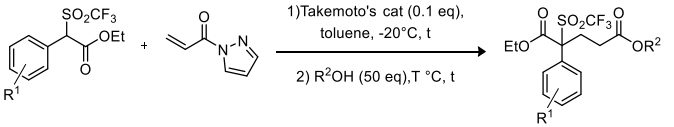
propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 11.5 min, major enantiomer tR = 15.7 min.

General procedure for racemic Michael reaction and esterification



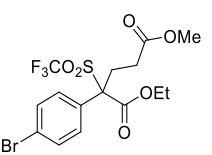
In an oven-dried vial α-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole (0.15 mmol) and anhydrous toluene (0.5 mL) were introduced. To this solution Schreiner′s Thiourea Catalyst (0.01 mmol, 5.00 mg) and triethylamine (0.01 mmol, 1.5 μL) were added under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 24 h and monitored by TLC. After completion of the first step, anhydrous alcohol (5 mmol) was added and the mixture was stirred for the time and at the temperature reported in Figure **7.1** and monitored by TLC. After completion of the reaction the solvent was evaporated, and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **31a-q** in 70-93% yield.

General procedure for enantioselective Michael reaction and esterification



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole (0.15 mmol) and anhydrous toluene (0.5 mL) were introduced. The reaction mixture was cooled at -20°C and after the temperature was reached the Takemoto catalyst was added (0.01 mmol, 4.13 mg), in the same temperature condition. The reaction mixture was stirred at -20°C for 24 h and monitored by TLC, as reported in the Figure **7.1**. After completion of the first step, anhydrous alcohol (5 mmol) was added and the mixture was stirred for the time and at the temperature reported in Figure **7.1** and monitored by TLC. After completion of the reaction the solvent was evaporated and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **31a-q** in 40->99% yield.

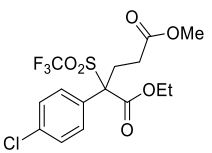
1-Ethyl 5-methyl 2-(4-bromophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31a)



Colourless oil, 45.7 mg, 91% yield (92% ee). **$[\alpha]_D^{14}$** = +16.85 (*c* 0.47, CHCl3). **^{1}H NMR** ($CDCl_3$, 250 MHz): *δ* 7.58 (d, 2H, *J* = 8.9 Hz), 7.34 (d, 2H, *J* = 8.9 Hz), 4.45 (q, 2H, *J* = 7.2 Hz), 3.64 (s, 3H), 3.01-2.94 (m, 2H), 2.60 (ddd, 1H, *J* = 16.7 Hz, *J* = 9.6 Hz, *J* = 6.6 Hz), 2.28 (ddd, 1H, *J* = 16.7 Hz, *J* = 9.6 Hz, *J* = 6.6 Hz), 1.38 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): *δ* 172.0, 165.4,

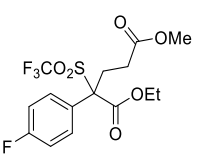
132.3, 131.1, 127.4, 125.4, 120.7 (q,$^1J_{CF}$ = 334.1 Hz), 82.4, 64.1, 52.2, 29.5, 27.9, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{15}H_{16}BrF_3O_6SNa$ 482.9695, found 482.9697. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 8.6 min, major enantiomer tR = 10.3 min.

1-Ethyl 5-methyl 2-(4-chlorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31b)



Colourless oil, 42.0 mg, 91% yield (92% ee). **$[\alpha]_D^{15}$** = +25.02 (*c* 0.62, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.43 (s, 4H), 4.45 (dq, 2H, *J* = 7.1 Hz, *J* = 1.9 Hz), 3.68 (s, 3H), 3.01-2.95 (m, 2H), 2.61 (ddd, 1H, *J* = 16.8 Hz, *J* = 10.3 Hz, *J* = 6.6 Hz), 2.29 (ddd, 1H, *J* = 16.8 Hz, *J* = 10.1 Hz, *J* = 5.7 Hz), 1.39 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.0, 165.4, 137.1, 131.1, 129.4, 126.9, 120.8 (q,$^1J_{CF}$ = 333.1 Hz), 82.3, 64.1, 52.2, 29.6, 28.0, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{15}H_{16}ClF_3O_6SNa$ 439.0200, found 439.0191. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 7.9 min, major enantiomer tR = 9.5 min.

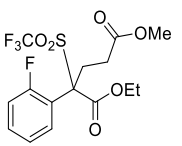
1-Ethyl 5-methyl 2-(4-fluorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31c)



Colourless oil, 36.4 mg, 91% yield (82% ee). **$[\alpha]_D^{15}$** = +17.1 (*c* 0.39, CHCl3). **^{1}H NMR** ($CDCl_3$, 600

MHz): δ 7.50 (m, 2H), 7.14 (t, 2H, J = 8.5 Hz), 4.45 (q, 2H, J = 7.2 Hz), 3.03-2.95 (m, 2H), 2.61 (ddd, 1H, J = 16.8 Hz, J = 10.4 Hz, J = 6.2 Hz), 2.31 (ddd, 1H, J = 16.8 Hz, J = 10.5 Hz, J = 5.4 Hz), 1.398 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 172.0, 165.6, 163.8 (d,^{1} J_{CF} = 251.9 Hz), 131.9 (d,^{3} J_{CF} = 8.7 Hz), 124.0 (d,^{4} J_{CF} = 3.5 Hz), 120.8 (q,$^1J_{CF}$ = 333.8 Hz), 116.3 (d,^{2} J_{CF} = 22.2 Hz), 82.3, 64.1, 52.2, 29.6, 28.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.3, -109.3. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{15}H_{16}F_4O_6SNa$ 423.0496, found 423.0494. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 7.7 min, major enantiomer tR = 9.5 min.

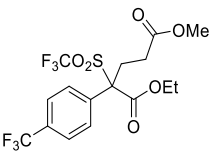
1-Ethyl 5-methyl 2-(2-fluorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31d)



Colourless oil, 35.6 mg, 89% yield (96% ee). **$[\alpha]_D^{14}$** = -2.92 (*c* 0.49, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.59 (t, 1H, J = 7.7 Hz), 7.48 (q, 1H, J = 8.2 Hz), 7.27 (t, 1H, J = 7.7 Hz), 7.13 (q, 1H, J = 8.3 Hz), 4.40 (q, 2H, J = 7.1 Hz), 3.68 (s, 3H), 3.04-2.99 (m, 2H), 2.71 (ddd, 1H, J = 16.8 Hz, J = 9.3 Hz, J = 6.0 Hz), 2.40 (ddd, 1H, J = 16.8 Hz, J = 9.3 Hz, J = 6.0 Hz), 1.35 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): δ 172.1, 165.6, 161.4 (d,^{1} J_{CF} = 252.6 Hz), 132.9 (d,^{3} J_{CF} = 8.5 Hz), 130.7 124.9 (d,^{4} J_{CF} = 3.1 Hz), 120.8 (q,$^1J_{CF}$ = 334.0 Hz), 117.2 (d,^{2} J_{CF} = 23.9 Hz), 117.1, 79.5, 63.9, 52.2, 29.4, 28.0, 13.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.5, -105.6. **HRMS (ESI-FT ICR)** exact

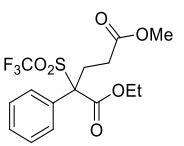
mass $[M+Na]^+$ calculated for $C_{15}H_{16}F_4O_6SNa$ 423.0496, found 423.0494. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 7.1 min, major enantiomer tR = 7.6 min.

1-Ethyl 5-methyl 2-(4-(trifluoromethyl)phenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31e)



Colourless oil, 41.0 mg, 91% yield (93% ee). **$[\alpha]_D^{17}$** = +20.32 (*c* 0.52, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.71 (d, 2H, *J* = 8.5 Hz), 7.64 (d, 2H, *J* = 8.5 Hz), 4.48 (dq, 2H, *J* = 7.1 Hz, *J* = 3.0 Hz), 3.68 (s, 3H), 3.08-2.95 (m, 2H), 2.63 (ddd, 1H, *J* = 16.7 Hz, *J* = 10.1 Hz, *J* = 6.3 Hz), 2.28 (ddd, 1H, *J* = 16.7 Hz, *J* = 10.1 Hz, *J* = 5.2 Hz), 1.41 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.2, 165.8, 130.5, 129.4, 129.1, 128.5, 120.7 (q, $^1J_{CF}$ = 334.1 Hz), 83.0, 63.9, 52.1, 29.7, 28.2, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.2, -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{16}H_{16}F_6O_6SNa$ 473.0464, found 473.0477. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 5.9 min, major enantiomer tR = 7.6 min.

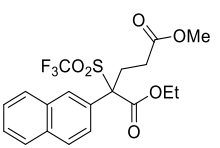
1-Ethyl 5-methyl 2-phenyl-2-((trifluoromethyl)sulfonyl)pentanedioate (31f)



Colourless oil, 34.8 mg, 91% yield (96% ee). **$[\alpha]_D^{17}$** = +26.45 (*c* 0.54, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50-7.44 (m, 5H), 4.46 (dq, 2H, *J* = 7.1

Hz, *J* = 1.9 Hz), 3.68 (s, 3H), 3.00 (t, 2H, *J* = 8.0 Hz), 2.65 (ddd, 1H, *J* = 16.8 Hz, *J* = 9.3 Hz, *J* = 7.3 Hz), 2.40 (ddd, 1H, *J* = 16.7 Hz, *J* = 9.1 Hz, *J* = 6.3 Hz), 1.40 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): *δ* 172.1, 165.6, 161.4 (d,$^{1}J_{CF}$ = 252.6 Hz), 132.9 (d,$^{3}J_{CF}$ = 8.5 Hz), 130.7 124.9 (d,$^{4}J_{CF}$ = 3.1 Hz), 120.8 (q,$^{1}J_{CF}$ = 334.0 Hz), 117.2 (d,$^{2}J_{CF}$ = 23.9 Hz), 117.1, 79.5, 63.9, 52.2, 29.4, 28.0, 13.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -67.3. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{15}H_{17}F_3O_6SNa$ 405.0590, found 405.0602. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 7.0 min, major enantiomer tR = 7.4 min.

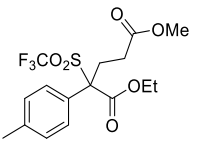
1-Ethyl 5-methyl 2-(naphthalen-2-yl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31g)



Colourless oil, 37.6 mg, 87% yield (92% ee). **$[\alpha]_D^{17}$** = +25.53 (*c* 0.58, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): *δ* 7.96-7.85 (3, 4H), 7.61-7.52 (m, 3H), 4.51 (dq, 2H, *J* = 7.2 Hz, *J* = 2.0 Hz), 3.66 (s, 3H), 3.15-3.09 (m, 2H), 2.70 (ddd, 1H, *J* = 16.7 Hz, *J* = 9.5 Hz, *J* = 7.3 Hz), 2.35 (ddd, 1H, *J* = 16.7 Hz, *J* = 9.5 Hz, *J* = 6.7 Hz), 1.43 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): *δ* 172.2, 165.9, 133.7, 132.7, 129.9, 129.0, 128.8, 128.1, 127.7, 127.1, 125.7, 125.6, 120.8 (q,$^{1}J_{CF}$ = 334.1 Hz), 83.2, 63.9, 52.1, 29.7, 28.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): *δ* -67.2. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{19}H_{19}F_3O_6SNa$ 455.0747, found 455.0739. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-

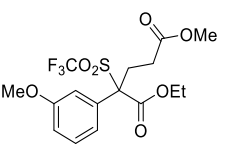
propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 10.3 min, major enantiomer tR = 11.3 min.

1-Ethyl 5-methyl 2-(p-tolyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31h)



Colourless oil, 27.7 mg, 70% yield (96% ee). **$[\alpha]_D^{15}$** = +23.12 (*c* 0.49, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.36 (d, 2H, *J* = 8.1 Hz), 7.24 (d, 2H, *J* = 8.0 Hz), 4.45 (q, 2H, *J* = 7.1 Hz), 3.67 (s, 3H), 2.98 (t, 2H, *J* = 8.0 Hz), 2.63 (dt, 1H, *J* = 16.8 Hz, *J* = 8.0 Hz), 2.38 (s, 3H), 2.32 (dt, 1H, *J* = 16.8 Hz, *J* = 8.0 Hz), 1.39 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 62.5 MHz): δ 172.3, 165.9, 140.9, 129.8, 129.4, 125.2, 120.8 (q,$^1J_{CF}$ = 333.6 Hz), 83.0, 63.8, 52.1, 29.7, 28.0, 21.3, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.3. **HRMS (ESI-FT ICR)** exact mass $[M+K]^+$ calculated for $C_{16}H_{19}F_3O_6SK$ 435.0486, found 435.0477. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 6.2 min, major enantiomer tR = 6.8 min.

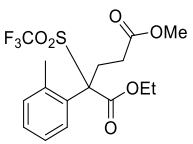
1-Ethyl 5-methyl 2-(3-methoxyphenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31i)



Colourless oil, 36.7 mg, 89% yield (94% ee). **$[\alpha]_D^{15}$** = +24.12 (*c* 0.49, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.34 (t, 1H, *J* = 8.3 Hz), 7.04-7.02 (m, 2H), 6.97 (dd, 1H, *J* = 8.3 Hz, *J* =2.3 Hz), 4.45 (dq, 2H, *J* = 7.1 Hz, *J* = 2.8 Hz), 3.81 (s, 3H), 3.67 (s, 3H), 2.96 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 2.67 (ddd, 1H, *J* = 16.8 Hz, *J* = 9.3 Hz, *J* = 7.3

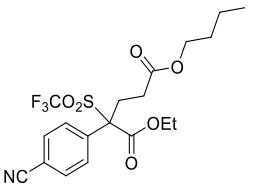
Hz), 2.38 (s, 3H), 2.32 (dt, 1H, J = 16.8 Hz, J = 9.2 Hz, J = 6.3 Hz), 1.39 (t, 3H, J = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.3, 165.7, 159.9, 130.1, 130.0, 121.4, 120.8 (q,$^1J_{CF}$ = 334.3 Hz), 115.7, 115.5, 82.9, 63.8, 55.5, 52.1, 29.7, 28.4, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.2. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{16}H_{19}F_3O_7SNa$ 435.0696, found 435.0481. **HPLC** analysis with Chiralpak IC column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 11.2 min, major enantiomer tR = 12.2 min.

1-Ethyl 5-methyl 2-(o-tolyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31l)



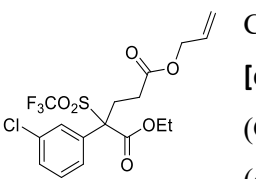
Colourless oil, 15.9 mg, 40% yield (92% ee). **$[\alpha]_D^{16}$** = -21.90 (c 0.60, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.46 (d, 1H, J = 7.7 Hz), 7.36 (d, 1H, J = 7.5 Hz), 7.30 (t, 2H, , J = 7.5 Hz), 4.40 (q, 2H, J = 7.2 Hz), 3.69 (s, 3H), 2.98 (t, 2H, J = 8.0 Hz), 3.17 (ddd, 1H, J = 15.0 Hz , J = 9.5 Hz , J = 5.3 Hz), 3.00 (ddd, 1H, J = 15.1 Hz , J = 9.3 Hz , J = 6.4 Hz), 2.57 (ddd, 1H, J = 15.8 Hz, J = 9.3 Hz, J = 6.3 Hz), 2.52 (ddd, 1H, J = 15.3 Hz, J = 9.4 Hz, J = 5.6 Hz), 2.38 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.3, 166.7, 141.2, 133.6, 130.7, 130.5, 126.4, 125.7, 121.1 (q,$^1J_{CF}$ = 334.0 Hz), 82.8, 63.9, 52.2, 29.5, 28.6, 21.8, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.4. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{16}H_{19}F_3O_6SNa$ 419.0747, found 419.0740. **HPLC** analysis with Chiralpak AD column, 95:5 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 8.3 min, major enantiomer tR = 8.8 min.

5-butyl 1-ethyl 2-(4-cyanophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31m)



Colourless oil, 40.9 mg, 91% yield (84% ee). **$[\alpha]_D^{16}$** = +19.75 (*c* 0.61, CHCl3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.75 (d, 2H, *J* = 8.8 Hz), 7.65 (d, 2H, *J* = 8.8 Hz), 4.48 (q, 2H, *J* = 7.2 Hz), 4.41 (dt, 2H, *J* = 6.8 Hz , *J* = 2.9 Hz), 3.03 (ddd, 1H, *J* = 16.3 Hz, *J* = 10.5 Hz, *J* = 6.3 Hz), 2.98 (ddd, 1H, *J* = 15.3 Hz, *J* = 10.4 Hz, *J* = 5.9 Hz), 2.59 (ddd, 1H, *J* = 16.7 Hz, *J* = 10.6 Hz, *J* = 6.1 Hz), 2.25 (ddd, 1H, *J* = 16.4 Hz, *J* = 10.3 Hz, *J* = 4.8 Hz), 1.59 (quint, 2H, *J* = 6.9 Hz), 1.41 (t, 3H, *J* = 7.2 Hz), 1.36 (quint, 2H, *J* = 7.5 Hz), 0.92 (t, 3H, *J* = 7.5 Hz). **^{13}C NMR** ($CDCl_3$, 150 MHz): δ 171.4, 164.9, 133.7, 132.6, 130.5, 120.7 (q, $^1J_{CF}$ = 333.8 Hz), 117.7, 114.6, 82.2, 65.2, 64.4, 30.7, 29.6, 27.9, 19.2, 13.9, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.0. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{19}H_{22}F_3NO_6SNa$ 472.1012, found 472.1009 **HPLC** analysis with Chiralpak ASH column, 95:5 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 14.7 min, major enantiomer tR = 16.1 min.

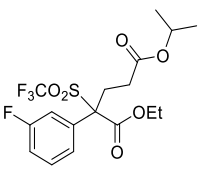
5-Allyl 1-ethyl 2-(3-chlorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31n)



Colourless oil, 38.1 mg, 86% yield (94% ee). **$[\alpha]_D^{17}$** = +17.78 (*c* 0.60, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.48-7.38 (m, 4H), 5.89 (ddd, 1H, *J* = 16.3 Hz *J* = 11.6 Hz *J* = 5.9 Hz),

5.30 (dd, 1H, *J* = 17.1 Hz *J* = 1.2 Hz), 5.24 (dd, 1H, *J* = 10.5 Hz *J* = 1.2 Hz), 4.58 (d, 2H, *J* = 5.8 Hz), 4.47 (dq, 2H, *J* = 7.2 Hz, *J* = 1.9 Hz), 3.05-2.90 (m, 2H), 2.67 (ddd, 1H, *J* = 16.8 Hz, *J* = 10.3 Hz, *J* = 6.3 Hz), 2.32 (ddd, 1H, *J* = 16.6 Hz *J* = 10.1 Hz *J* = 5.9 Hz), 1.40 (t, 3H, *J* = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.2, 1652, 135.2, 131.8, 130.8, 130.6, 130.3, 129.6, 127.5, 120.9 (q,$^1J_{CF}$ = 333.8 Hz), 118.9, 82.2, 65.9, 64.2, 29.7, 28.1, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{17}H_{18}ClF_3O_6SNa$ 465.0357, found 465.0409. **HPLC** analysis with Chiralpak ODH column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 5.4 min, major enantiomer tR = 5.9 min.

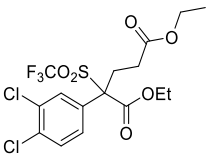
1-Ethyl 5-isopropyl 2-(3-fluorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31o)



Colourless oil, 32.1 mg, 75% yield (85% ee). **$[\alpha]_D^{17}$** = +16.56 (*c* 0.47, CHCl3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.43 (dt, 1H, *J* = 8.1 Hz, *J* = 6.0 Hz), 7.29 (dd, 1H, *J* = 8.0 Hz, *J* = 1.2 Hz), 7.25 (dt, 1H, *J* = 10.1 Hz *J* = 2.1 Hz), 7.17 (td, 1H, *J* = 8.1 Hz *J* = 2.1 Hz), 5.00 (sept, 1H, *J* = 6.3 Hz), 4.47 (dq, 2H, *J* = 7.2 Hz, *J* =3.6 Hz), 2.98 ddd(s, 1H, *J* = 16.3 Hz *J* = 10.4 Hz *J* = 5.9 Hz), 2.95 (ddd, 1H, *J* = 14.7 Hz, *J* =10.6 Hz *J* = 4.9 Hz), 2.59 (ddd, 1H, *J* = 16.7 Hz, *J* = 10.7 Hz, *J* = 5.9 Hz), 2.25 (ddd, 1H, *J* = 16.4 Hz *J* = 10.4 Hz *J* = 4.9 Hz), 1.40 (t, 3H, *J* = 7.2 Hz), 1.23 (d, 3H, *J* = 6.3 Hz), 1.21 (d,3H, *J* = 6.3 Hz). **^{13}C NMR** ($CDCl_3$, 120 MHz): δ 171.9, 165.3, 162.7 (d,$^1J_{CF}$ =

248.1 Hz), 131.1 (d,$^{3}J_{CF}$ = 7.6 Hz), 130.6 (d,$^{3}J_{CF}$ = 8.2 Hz), 125.2 (d,$^{4}J_{CF}$ = 2.4 Hz), 120.7 (q,$^{1}J_{CF}$ = 334.1 Hz), 117.7 (d,$^{2}J_{CF}$ = 20.9 Hz), 116.9 (d,$^{2}J_{CF}$ = 24.4 Hz), 82.4, 68.7, 64.1, 30.1, 28.2, 21.9 (2H), 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.2, -110.4. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{17}H_{20}F_4O_6SNa$ 451.0809, found 451.0859. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 4.5 min, major enantiomer tR = 5.1 min.

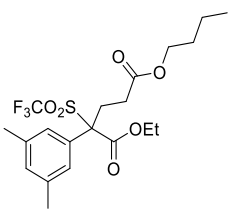
Diethyl 2-(3,4-dichlorophenyl)-2-((trifluoromethyl)sulfonyl)pentanedioate (31p)



Colourless oil, 37.2 mg, 80% yield (91% ee). **$[\alpha]_D^{17}$** = +21.81 (*c* 0.48, CHCl3). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.59 (d, 2H, *J* = 2.2 Hz), 7.53 (d, 2H, *J* = 8.6 Hz), 7.36 (dd, 1H, *J* = 8.6 Hz, *J* = 2.2 Hz), 4.46 (dq, 2H, *J* = 7.1 Hz, *J* = 3.5 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.04-2.88 (m, 2H), 2.58 (ddd, 1H, *J* = 16.7 Hz, *J* = 10.3 Hz, *J* = 6.1 Hz), 2.28 (ddd, 1H, *J* = 16.6 Hz, *J* = 10.0 Hz, *J* = 5.0 Hz), 1.40 (t, 3H, *J* = 7.1 Hz), 1.25 (t, 3H, *J* = 7.3 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 171.4, 165.0, 135.4, 133.6, 131.6, 131.1, 128.8, 128.6, 120.7 (q,$^{1}J_{CF}$ = 333.3 Hz), 81.8, 64.3, 61.3, 29.7, 27.9, 14.3, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.0. **HRMS (ESI-FT ICR)** exact mass $[M+H]^+$ calculated for $C_{16}H_{17}Cl_2F_3O_6S$ 465.0148, found 465.0404. **HPLC** analysis with Chiralpak AD column, 95:5 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 6.6 min, major enantiomer tR = 7.4 min.

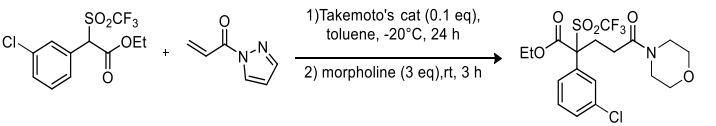
5-Butyl 1-ethyl 2-(3,5-dimethylphenyl)-2-

((trifluoromethyl)sulfonyl)pentanedioate (31q)



Colourless oil, 38.9 mg, 86% yield (93% ee). $[\alpha]_D^{16}$ = +23.38 (*c* 0.54, CHCl3). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.07 (s, 1H), 7.05 (s, 2H), 4.45 (q, 2H, *J* = 7.1 Hz), 4.07 (t, 2H, *J* = 6.7 Hz), 2.96 (t, 2H, *J* = 7.8 Hz), 2.71-2.60 (m, 1H), 2.33 (s, 6H), 2.40-2.25 (m, 1H), 1.58 (sixt, 2H, *J* = 7.6 Hz), 1.42-1.32 (m, 5H), 0.92 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.0, 166.0, 138.7, 132.2, 128.3, 126.9, 120.8 (q, $^1J_{CF}$ = 334.3 Hz), 83.1, 65.0, 63.7, 30.7, 29.9, 28.2, 21.6, 19.2, 13.9, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.2. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{20}H_{27}F_3O_6SNa$ 475.1373, found 475.1367. **HPLC** analysis with Chiralpak AD column, 90:10 n-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer tR = 3.9 min, major enantiomer tR = 4.8 min.

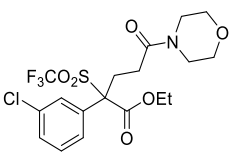
General procedure for enantioselective Michael reaction and amidation



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole (0.15 mmol) and anhydrous toluene (0.5 mL) were introduced. The reaction mixture was cooled at -20°C and after the temperature was reached the Takemoto catalyst was added

(0.01 mmol, 4.13 mg), in the same temperature condition. The reaction mixture was stirred at -20°C for 24 h and monitored by TLC, as reported in the Scheme **7.7**. After completion of the first step, morpholine (0.3 mmol, 26 μL) was added and the mixture was stirred for 3 hours and at room temperature and monitored by TLC. After completion of the reaction the solvent was evaporated and the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 90/10) to afford products **32** in 92% yield.

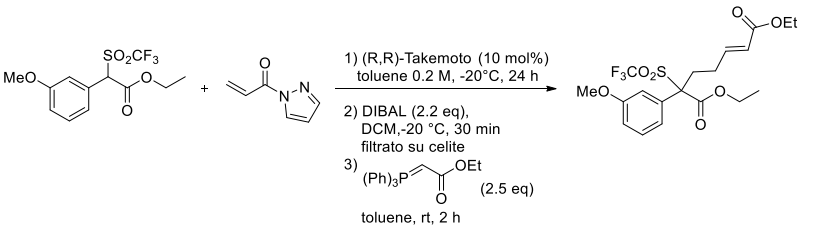
Ethyl 2-(3-chlorophenyl)-5-morpholino-5-oxo-2-((trifluoromethyl)sulfonyl)pentanoate (32)



Colourless oil, 42.9 mg, 92% yield (91% ee). **$[\alpha]_D^{16}$** = -7.59 (*c* 0.54, CHCl3). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.47 (t, 1H, *J* = 1.8 Hz), 7.44 (dt, 1H, *J* = 7.5 Hz *J* = 1.9 Hz), 7.40 (dt, 1H, *J* = 8.1 Hz *J* = 7 .7 Hz), 7.38 (t, 1H, *J* = 7.6 Hz), 4.46 (dq, 2H, *J* = 7.1 Hz, *J* = 3.5 Hz), 3.65-3.57 (m, 6H), 3.39-3.32 (m, 2H), 3.04 (ddd, 1H, *J* = 15.3 Hz, *J* = 10.8 Hz, *J* = 4.7 Hz), 2.99 (ddd, 1H, *J* = 15.2 Hz, *J* = 10.4 Hz *J* = 5.4 Hz), 2.67 (ddd, 1H, *J* = 16.3 Hz, *J* = 10.8 Hz, *J* = 5.6 Hz), 2.24 (ddd, 1H, *J* = 15.7 Hz, *J* = 10.3 Hz, *J* = 4.8 Hz), 1.39 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 120 MHz): δ 169.9, 165.5, 135.1, 131.0, 130.7, 130.2, 129.5, 127.5, 120.7 (q, $^1J_{CF}$ = 334.2 Hz), 82.5, 66.9, 66.5, 64.1, 45.7, 42.2, 28.8, 28.3, 13.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.1. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{18}H_{21}ClF_3NO_6SNa$ 494.0622, found 494.0638. **HPLC** analysis with Chiralpak IC column, 90:10 n-

hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 12.1 min, major enantiomer tR = 13.7 min.

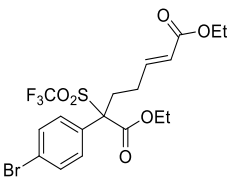
General procedure for enantioselective one-pot Horner-Emmons olefination



In an oven-dried vial *α*-trifluoromethylsulfonyl esters **28** (0.1 mmol), the proper acrylpyrazole (0.15 mmol) and anhydrous toluene (0.5 mL) were introduced. The reaction mixture was cooled at -20°C and after the temperature was reached the Takemoto catalyst was added (0.01 mmol, 4.13 mg), in the same temperature condition. The reaction mixture was stirred at -20°C for 24 h and monitored by TLC, as reported in the Scheme **7.8**. After completion of the first step, the solvent was evaporated and the reaction mixture was dissolved in CH_2Cl_2 (0.5 mL). The mixture was cooled at -20°C and DIBAL 1.0 M in toluene (2.2 eq, 220 μL) was added dropwise in 15 minutes. After the DIBAL addition, the reaction was stirred at the same temperature for 30 minutes and monitored by TLC. After completion of the reaction the reaction was quenched with MeOH (1.0 mL), the mixture was filtered on celite pad, and the solvent was evaporated. The crude mixture was dissolved in toluene and

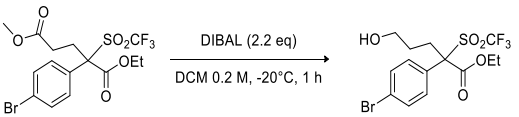
(carbethoxymethylene)triphenylphosphorane (2.5 eq, 87.1 mg) was added. The reaction was stirred for 2 hours at room temperature and when the reaction was finished the product was purified by flash chromatography (eluent: hexane/ethyl acetate , 100/0 to 90/10) to afford products **47** in 50% yield.

Diethyl (E)-6-(4-bromophenyl)-6-((trifluoromethyl)sulfonyl)hept-2-enedioate (47)



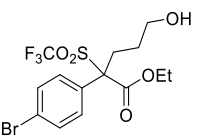
Colourless oil, 25.1 mg, 50% yield (93% ee). $[\alpha]_D^{17}$ = +23.63 (*c* 0.32, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, *J* = 8.7 Hz), 7.36 (d, 2H, *J* = 8.7 Hz), 6.87 (dt, 1H, *J* = 15.7 Hz, *J* = 6.8 Hz), 5.83 (d, 1H, *J* = 15.7 Hz), 4.46 (dq, 2H, *J* = 7.2, Hz *J* = 4.7 Hz), 4.41 (q, 2H, *J* = 7.1 Hz), 2.80 (ddd, 1H, *J* = 16.3 Hz, *J* = 11.3 Hz, *J* = 5.1 Hz), 2.67 (ddd. 1H, *J* = 15.9 Hz, *J* = 11.4 Hz, *J* = 4.4 Hz), 2.47-2.38 (m, 1H), 2.20-2.11 (m, 1H), 1.40 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 166.2, 165.2, 145.4, 132.3, 131.1, 127.6, 125.3, 123.0, 120.7 (q, $^1J_{CF}$ = 332.7 Hz), 82.6, 64.1, 60.6, 31.3, 27.4, 14.4, 13.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.2. **HRMS (ESI-FT ICR)** exact mass $[M+Na]^+$ calculated for $C_{18}H_{20}BrF_3O_6SNa$ 523.0008, found 523.0035. **HPLC** analysis with Chiralpak IC column, 90:10 n-hexane:2-propanol, 1 mL/min, 254-220 nm; minor enantiomer tR = 9.9 min, major enantiomer tR = 7.9 min.

General procedure for reduction of chiral diesters



In an oven-dried vial chiral trifluoromethylsulfonyl diesters **31** (0.1 mmol) was dissolved in anhydrous CH_2Cl_2 (0.5 mL) and cooled at -20°C. To this mixture, DIBAL 1.0 M in toluene (2.2 eq, 220 μL) was added dropwise in 15 minutes, and the reaction was stirred at the same temperature for 1 hour and monitored by TLC. After completion of the reaction, the mixture was quenched with MeOH (1 mL) was stirred at room temperature for 15 minutes. The crude mixture was then filtered on celite pad, and after the solvent was evaporated. The crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate 100/0 to 80/20) to afford products **48** in 76% yield.

Ethyl 2-(4-bromophenyl)-5-hydroxy-2-((trifluoromethyl)sulfonyl)pentanoate (48)



Colourless oil, 32.9 mg, 76% yield (93% ee). $[\alpha]_D^{14}$ = +5.59 (*c* 0.59, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.57 (d, 2H, *J* = 8.8 Hz), 7.41 (d, 2H, *J* = 8.8 Hz), 4.45 (dq, 2H, *J* = 7.2 Hz, *J* = 3.5 Hz), 3.74-3.66 (m, 2H), 2.76-2.74 (m, 2H), 1.74-1.67 (m, 1H), 1.58-1.52 (m, 2H), 2.40-2.25 (m, 1H), 1.39 (t, 3H, *J* = 7.1 Hz). **^{13}C NMR** ($CDCl_3$, 120 MHz): δ 165.6, 132.1, 131.6, 127.7, 125.1, 120.8 (q,$^1J_{CF}$ = 334.1 Hz), 83.1, 63.9, 62.0, 29.4, 27.8, 14.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -67.5.

HRMS (ESI-FT ICR) exact mass $[M+H]^+$ calculated for $C_{14}H_{17}BrF_3O_5S$ 432.9927, found 432.9903. **HPLC** analysis with Chiralpak IE3 column, 90:10 n-hexane:2-propanol, 0.8 mL/min, 220 nm; minor enantiomer tR = 10.1 min, major enantiomer tR = 12.3 min.

The work contained within this thesis is partially described in the following publications:

"Formal a-trifluoromethylthiolation of carboxylic acid derivatives via N-acyl pyrazoles"
F. Franco, S. Meninno, M. Benaglia and A. Lattanzi, *Chem. Commun*., 2020, 56, 3073

"*Continuous Flow Synthesis of α-Trifluoromethylthiolated Esters and Amides from Carboxylic Acids: a Telescoped Approach*"
F. Franco, S. Meninno, A. Lattanzi, A. Puglisi, M. Benaglia, *J. Org. Chem.,* 2021, 20, 14207–14212

Pyrazoleamides in Catalytic Asymmetric Reactions: Recent Advances
S. Meninno, F. Franco, M. Benaglia, and A. Lattanzi, *Adv. Synth. Catal*., 2021, 363, 3380– 3410

"*First catalytic entry to enantioenriched triflones featuring a quaternary stereocenter*"
F. Franco, S. Meninno, J. Overgaard, S. Rossi, M. Benaglia and A. Lattanzi, *Org. Lett.,* submitte