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# Valorization of versatile fluoroacrylates in Michael addition

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Normandie Université

## THESE

Pour obtenir le diplôme de doctorat

Spécialité Chimie Organique

Préparée au sein de l'INSA de Rouen

### Valorization of versatile fluoroacrylates in Michael addition

Présentée et soutenue par  
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## Abstract

On one hand, due to the unique properties of the fluorine atom, organofluorinated compounds play an important role in various fields including drug development, crop protection, and material science. On the other hand, Michael addition reaction (MAR) has been widely used in contemporary synthesis to access multifarious functionalized products owing to its significant atom economy for the diastereo- and enantioselective bond formation. The combination of MAR and fluorine chemistry to afford organofluorinated compounds through the building-block strategy appears as an attractive strategy, but little attention has been paid in this area (see Chapter 1). Therefore, in my Ph.D. thesis, we mainly focused on the synthesis of organofluorinated compounds by organocatalytic MAR to  $\alpha$ -fluorinated  $\alpha,\beta$ -unsaturated carbonyl substrates.

In the first part of this thesis (Chapter 2), we described a sulfa-Michael addition to polysubstituted  $\alpha$ -fluoroacrylates in both non-enantioselective and enantioselective versions. Furthermore, two fluorinated analogues of Diltiazem and Tiazesim were successfully synthesized. In the second part of this thesis (Chapter 3), we developed a highly diastereoselective phospho-Michael addition to  $\alpha$ -trifluoromethylacrylates for the first time, and this method was also applied to  $\alpha$ -fluoromethylacrylates. In the last part of this thesis (Chapter 4), we discussed the various reactions attempted to enlarge the scope of Michael addition reaction with our  $\alpha$ -fluorinated Michael acceptors including fluorinated ester, ketone, and aldehyde.



## Résumé

Les composés organofluorés, en raison des propriétés uniques de l'atome de fluor, sont largement utilisés dans divers domaines comme les matériaux, la chimie pharmaceutique ou encore l'agrochimie. Parmi les modes d'obtention de ces molécules fluorées, la Réaction d'Addition de Michael (RAM) a été très peu utilisée alors qu'elle apparaît comme une stratégie très intéressante pour accéder à de nouveaux motifs fluorés d'intérêt. En effet, la RAM est connue depuis longtemps comme une voie d'accès dia- et énantio-sélective à de multiples composés polyfonctionnalisés. Néanmoins, cette réaction a été très peu appliquée aux accepteurs de Michael fluorés (voir chapitre 1 bibliographique). Dans cette thèse, nous avons donc développé de nouvelles méthodologies de synthèse pour construire de manière diastéréosélective (voire énantiosélective) des produits fluorés originaux par réaction d'addition de Michael organocatalysée. Différents nucléophiles ont été utilisés en addition conjuguée sur des dérivés carbonyles  $\alpha$ -fluorés  $\alpha,\beta$ -insaturés et plus particulièrement sur les acrylates  $\alpha$ -fluorés.

Dans la première partie de cette thèse (chapitre 2), nous avons développé une réaction d'addition de Michael de thiophenols (sulfa-Michael addition) sur des acrylates fluorés polysubstitués dans des versions racémiques et énantiosélectives. De plus, deux analogues fluorés du Diltiazem et du Tiazesim, des biomolécules d'intérêt pharmaceutique, ont été synthétisés avec succès. Dans la deuxième partie de cette thèse (chapitre 3), nous avons pour la première fois mis au point une addition de Michael hautement diastéréosélective d'oxyde de phosphine (phospha-Michael addition) sur des trifluorométhylacrylates polyfonctionnalisés; cette méthode a également été appliquée à des fluorométhylacrylates polyfonctionnalisés. Dans la dernière partie de cette thèse (chapitre 4), nous présentons d'autres réactions d'addition de Michael que nous avons étudié avec nos accepteurs fluorés incluant des esters, cétones et aldéhydes  $\alpha$ -fluorés,  $\alpha,\beta$ -insaturés.



## Abbreviations and Acronyms

Ac	acetyl
aq	aqueous
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
<i>de</i>	diastereomeric excess
DIPA	diisopropylamine
DIPEA	N,N-diisopropylethylamine
DMP	Dess-Martin periodinane
<i>dr</i>	diastereoisomeric ratio
<i>ee</i>	enantiomeric excess
Equiv	equivalent
<i>er</i>	enantiomeric ratio
Et	ethyl
ETFE	poly(1,1,2,2-tetrafluorobutane-1,4-diyl)
EWG	electron-withdrawing group
h	hour
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
<i>i</i> Bu	isobutyl
Int	intermediate
IPA	isopropyl alcohol
<i>i</i> Pr	isopropyl
IR	infrared
<i>J</i>	spin-spin coupling constant
LCMS	liquid chromatography-mass spectrometry

Abbreviations and Acronyms

LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M.P.	melting point
Me	methyl
MS	molecular sieves
MTBE	methyl <i>tert</i> -butyl ether
MWI	microwave irradiation
<sup>n</sup> Bu	normal butyl
NMR	nuclear magnetic resonance
<sup>n</sup> Pr	normal propyl
Ns	nosyl
Nu	nucleophile
PG	protecting group
Ph	phenyl
PTFE	polytetrafluoroethylene
( <i>R</i> )-H <sub>8</sub> -BINOL	( <i>R</i> )-(+)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol
rt	room temperature
( <i>S</i> )-BINAP	( <i>S</i> )-(-)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine)
<sup>s</sup> Bu	secondary butyl
T	temperature
TBAF	tetra- <i>n</i> -butylammonium fluoride
<sup>t</sup> Bu	tertiary butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine

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# Chapter 1

## General Introduction



# 1. General Introduction

## 1.1 Introduction of organofluorine chemistry

Fluorine is a chemical element with the symbol F and atomic number 9. It is the 13<sup>th</sup> most abundant element in earth's crust and the 24<sup>th</sup> most abundant element in the universe.<sup>1</sup> The inorganic minerals CaF<sub>2</sub> and Na<sub>3</sub>AlF<sub>6</sub> are the main sources of fluorine in nature, whereas the organic fluorine-containing compounds are rare (less than 20).<sup>2</sup> As the second smallest and the most electronegative element of the periodic table (**Table 1**),<sup>3</sup> fluorine atom generally exhibits unique properties and effects in organofluorine compounds.<sup>4</sup>

**Table 1** A comparison of atomic properties

Property	X				
	H	N	O	F	Cl
Bond length C-X (Å)	1.09	1.47	1.43	1.35	1.77
Bond dissociation energy C-X (kcal mol <sup>-1</sup> )	98.8	69.7	84.0	105.4	78.5
Electronegativity (Pauling scale)	2.20	3.04	3.44	3.98	3.16
Van der Waals radius (Å)	1.20	1.55	1.52	1.47	1.75
Atom polarizability, $\alpha$ (10 <sup>-24</sup> cm <sup>3</sup> )	0.667	1.100	0.802	0.557	2.180

### 1.1.1 Mimic effect

Fluorine atom has a van der Waals radius that is only larger than hydrogen atom and very close to oxygen atom ( $r_{\text{H}} = 1.20 \text{ \AA}$ ,  $r_{\text{O}} = 1.52 \text{ \AA}$ ,  $r_{\text{F}} = 1.47 \text{ \AA}$ ). Thus, it is possible to replace hydrogen or oxygen with fluorine retaining the original spatial structure of a molecule. However, because of the highest electronegativity of fluorine among all the elements, this replacement often implies a great change for the electronic environment of the new fluorinated molecule.

<sup>1</sup> Cameron, A. G. W. *Space Sci. Rev.* **1973**, *15*, 121-146.

<sup>2</sup> Harper, D. B.; O'Hagan, D. *Nat. Prod. Rep.* **1994**, *11*, 123-133.

<sup>3</sup> (a) Sen, K. D.; Jorgensen, C. K. *Electronegativity in Structure and Bonding*, Vol. 66 (Springer-Verlag, New York, 1987). (b) Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*, Springer US, Boston, MA, **1994**.

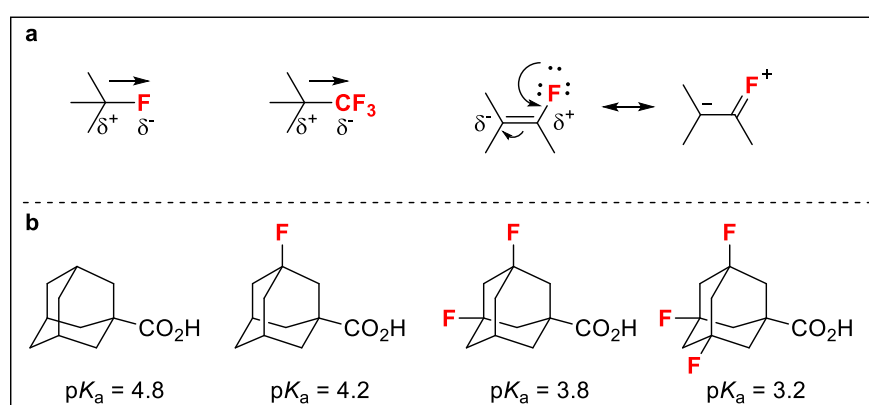
<sup>4</sup> (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308-319. (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1-16.

### 1.1.2 Blocking effect in metabolic transformation

Owing to the high energy of the C-F bond (bond dissociation energy = 105.4 kcal mol<sup>-1</sup>), the introduction of a fluorine atom or a fluorinated moiety in a defined position of a biomolecule, known to be highly sensitive to metabolism, usually allows developing an obvious resistance in metabolic transformations. In this way, the oxidative metabolism of fluorinated compounds can be selectively prevented, thus increasing their metabolic stability.

### 1.1.3 Electronic effect

The C-F bond is the strongest C-heteroatom bond and one of the strongest single bonds in chemistry. This bond is very short, highly polarized with the fluorine atom having a partial negative charge. So, the inductive electronic effect of fluorine makes implies an electron-withdrawing property in general, but sometimes fluorine could exhibit electron-donating characteristic in resonance structure by mesomeric effect (**Figure 1, a**). Besides, the lone pairs of fluorine could serve as a weak hydrogen bond acceptor. Additionally, due to the strong electron-withdrawing effect of fluorine, the fluorinated substituent remarkably enhances the acidity of vicinal acidic moieties in organic molecules (**Figure 1, b**).



**Figure 1** Electronic effects of fluorine

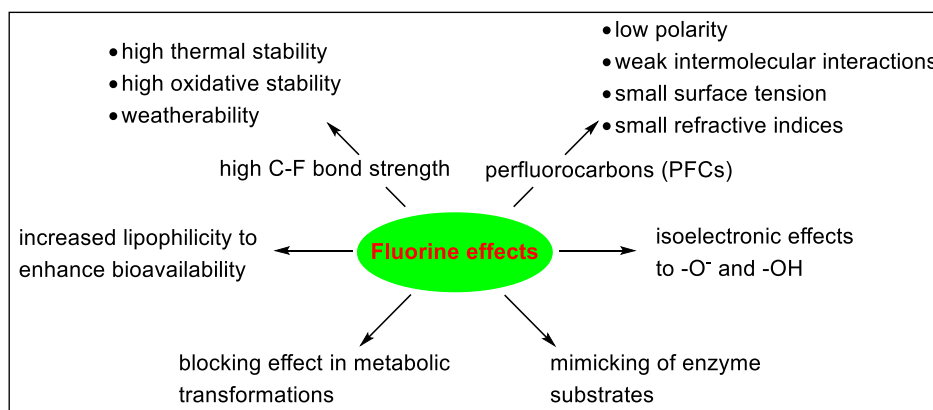
### 1.1.4 Some other physical effects

The low polarizability of the fluorine atom directly affects the intermolecular force and influences macrophysical properties of organofluorine compounds, such as

boiling point, lipophilicity, surface tension, and so on. Generally, the organofluorine compound has a lower boiling point and a weaker surface tension compared to its non-fluorinated analogue. Introducing fluorine or fluorinated moiety into a molecule will change its lipophilicity. Usually, the introduction of F or CF<sub>3</sub> on a sp<sup>2</sup> carbon will increase the molecular lipophilicity of a molecule whereas their introduction on a sp<sup>3</sup> carbon will do the opposite.

### 1.1.5 Applications of organofluorinated compounds

By virtue of the unique properties of fluorine atom (**Figure 2**)<sup>5</sup>, organofluorinated compounds are widely used in various fields including material science, pharmaceutical, and agrochemical industries.<sup>6</sup>



**Figure 2** Fluorine effects in biologically active agents and materials

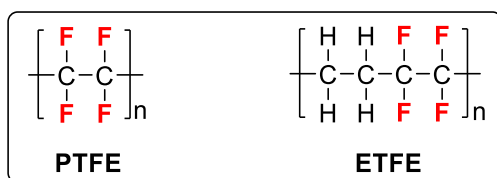
Indeed, since the advent of Freon (CCl<sub>2</sub>F<sub>2</sub>) in the early 1930s, organofluorine chemistry has been developed vigorously, fluorinated compounds are present in almost every aspect of human daily life. In material, for example, perfluorobutane (C<sub>4</sub>F<sub>10</sub>) is used as an extinguishing agent. PTFE (Teflon) and ETFE (**Figure 3**) are two very important polymer materials with excellent physical and chemical properties: PTFE is widely used in various applications requiring acid, alkali,

<sup>5</sup> Shimizu, M.; Hiyama, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231.

<sup>6</sup> (a) Dolbier, W. R. *Organofluorine Compounds: Chemistry and Applications* ACS Publications, **2000**; (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, **2004**; (c) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and medicinal chemistry of fluorine*; John Wiley & Sons, **2008**; (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330; (e) Uneyama, K. *Organofluorine chemistry*; John Wiley & Sons, **2008**; (f) Smith, D. W.; Iacono, S. T.; Iyer, S. S. *Handbook of fluoropolymer science and technology*; John Wiley & Sons, **2014**.

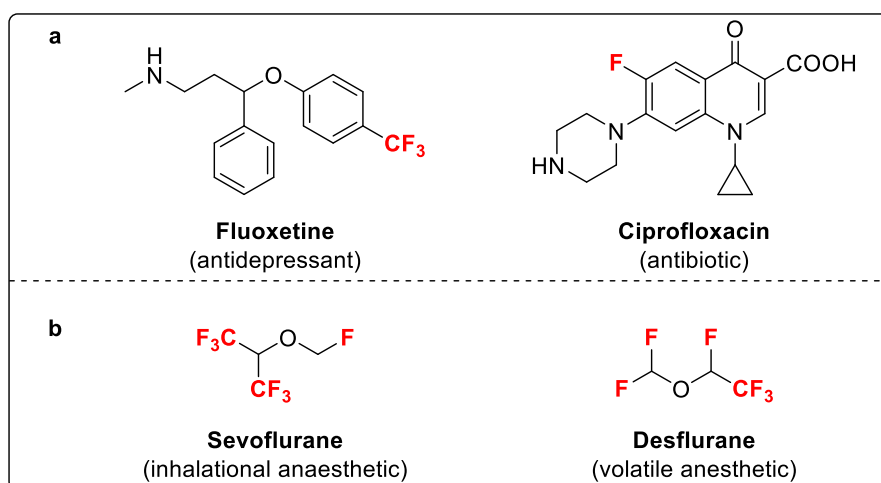


and organic solvents, like making non-stick pans and dry transformers. Also due to its soft texture, PTFE is often used as a coating; ETFE has a high melting temperature and excellent electrical, chemical, and high-energy radiation resistance properties. Thus, it has been used in many famous buildings and designs, like the National Space Centre in the UK, the football stadium called Allianz Arena in Germany, and so on.



**Figure 3** The molecular structure of PTFE and ETFE

In medicine, it has been reported that about 20% of commercial pharmaceuticals containing at least one fluorine atom (**Figure 4, a**),<sup>7</sup> for example, an important pharmaceutical application is the use of fluorinated compounds as anesthetics such as sevoflurane or desflurane (**Figure 4, b**). In agrochemical industries, about 30% of agrochemicals contain fluorine (**Figure 5**). Similar to fluorinated pharmaceuticals, fluorine substitutions in agrochemicals can increase their biological stay time, the membrane crossing as well as their molecular recognition.<sup>8</sup>



**Figure 4** Structure of some fluorinated pharmaceutical agents

<sup>7</sup> Inoue, M.; Sumii, Y.; Shibata, N. *ACS Omega* **2020**, *5*, 10633-10640.

<sup>8</sup> Theodoridis, G. *Advances in fluorine science* **2006**, *2*, 121-175.

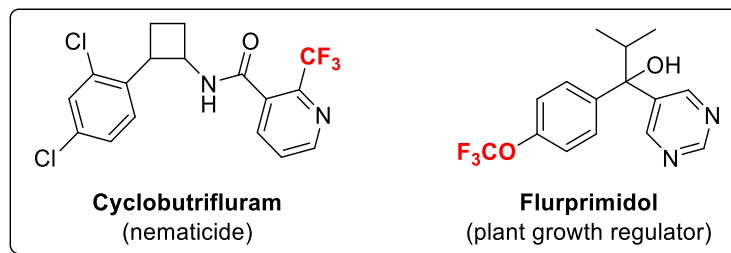


Figure 5 Structure of some fluorinated agrochemicals

## 1.2 Access to organofluorinated compounds

There are two major strategies to introduce fluorine atom(s) or fluorinated moieties into an organic molecule (Figure 6)<sup>5,9</sup>: a) the direct introduction of one or several fluorine atom(s) into organic molecules by fluorination, using nucleophilic, electrophilic, or radical fluorinating reagents.<sup>10</sup> b) the use and the transformation of already fluorinated building-block. This method starts from fluorine-containing raw materials, converts functional groups and form C-C or C-heteroatom bonds to access more complex fluorinated molecules.<sup>11</sup> As the organofluorinated compounds draw more and more attention, it is still worthwhile to explore mild and efficient methods to access new fluorinated scaffolds. Among them, Michael addition reaction appears as a relevant tool to design new organofluorinated products and enlarge their structural diversity.

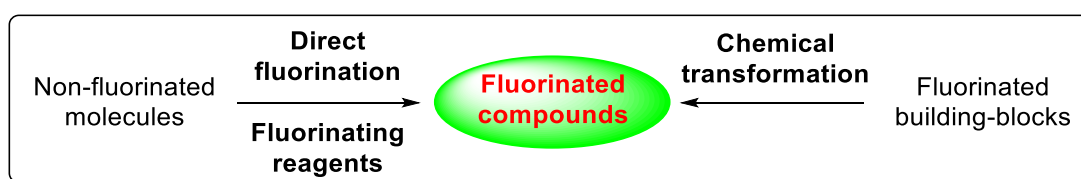


Figure 6 Strategies to access fluorinated compounds

## 1.3 A brief introduction of Michael addition reaction

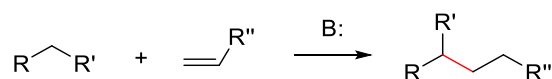
Michael addition reaction was originally defined by Arthur Michael in the late 1880s,

<sup>9</sup> Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264.

<sup>10</sup> Champagne, P. A.; Desroches, J.; Hamel, J. D.; Vandamme, M.; Paquin, J. F. *Chem. Rev.* **2015**, *115*, 9073-9174.

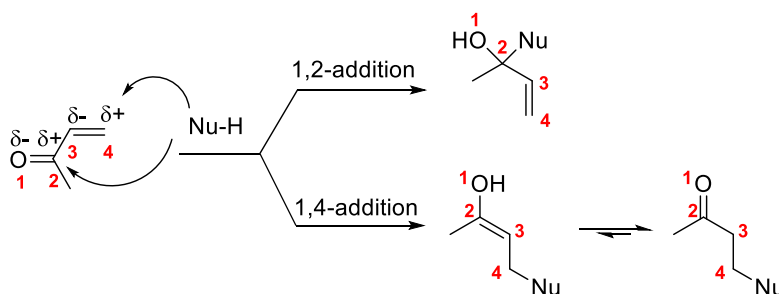
<sup>11</sup> (a) Percy, J. M. *Organofluorine Chemistry* **1997**, 131-195. (b) Konev, A. S.; Khlebnikov, A. F. *Collect. Czech. Chem. Commun.* **2008**, *73*, 1553-1611.

thus called Michael addition or Michael addition reaction (MAR).<sup>12</sup> Basically, MAR is the nucleophilic addition of a carbanion or another nucleophile to an  $\alpha,\beta$ -unsaturated carbonyl compound containing an electron-withdrawing group (EWG).<sup>13</sup> It is one of the most useful methods for mild formation of the C-C bond. A typical MAR is shown in **Scheme 1**, the R and R' on the nucleophile (Michael donor) are EWGs such as acyl group and nitrile. These EWGs make the methylene hydrogen acidic, thus, in the presence of a base (B), it is easy to convert into a stable and reactive carbanion. Commonly, the alkene (Michael acceptor) activated by the presence of an EWG group (R'') reacts with a nucleophile, to form the corresponding adduct.



**Scheme 1** General process of MAR

More usually, MAR is also called “1,4-addition” to  $\alpha,\beta$ -unsaturated carbonyl compounds. However, “1,2-addition” can also be observed competitively (**Scheme 2**).<sup>14</sup>



**Scheme 2** The competition between 1,2- and 1,4-addition

Since its discovery, MAR has received much attention from organic chemists, the use of different Michael donors allows to enlarge the scope of the reaction and to exceed the only formation of C-C bond by the constructions of C-N, C-S, C-O, C-P, and other C-X bonds. These derived aza-,<sup>15</sup> sulfa-,<sup>16</sup> oxa-,<sup>17</sup> phospho-<sup>18</sup> Michael addition

<sup>12</sup> (a) Michael, A. *J. Prakt. Chem.* **1887**, 35, 349-356. (b) Michael, A. *J. Prakt. Chem.* **1894**, 49, 20-25.

<sup>13</sup> (a) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; Mcloughlin, J. I. In *Organic Reactions* **2004**, 315-552. (b) Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Progress in Polymer Science* **2006**, 31, 487-531.

<sup>14</sup> Poon, T.; Mundy, B. P.; Shattuck, T. W. *J. Chem. Educ.* **2002**, 79, 264-267.

<sup>15</sup> (a) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, 15, 11058-11076. (b) Krishna, P. R.; Sreeshailam, A.;

reactions are also known as hetero-Michael addition reactions. Due to its significant atom economy for diastereoselective and enantioselective bond formation in asymmetric synthesis, MARs are widely used alone or in tandem with other reactions in contemporary organic synthesis to afford various functionalized products starting from the inexpensive and simple starting materials. In the following paragraph, we will concentrate only on fluorinated Michael acceptors, which are the core of my Ph.D. work, and their various uses in MAR reported to date.

## 1.4 Fluorinated Michael acceptors

Considering the power of MAR emerged in organic synthesis as well as the importance of fluorine-containing molecules, the combination of both fields, MAR and fluorine chemistry, to synthesize fluorinated compounds through the building-block strategy, appears as an appealing strategy, but little attention has been paid in this area.<sup>19</sup> In most reported MARs to access fluorine-containing compounds, the fluorine or fluorinated moieties are located in Michael donors.<sup>20</sup> Although the examples of using the fluorinated substrates as Michael acceptors is far less than as Michael donors, this approach to access the fluorinated compounds is evolving. In the past years, many conjugated fluorinated compounds have been synthesized by simple and efficient methods, like fluorinated  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>21</sup>, fluorinated nitroalkenes<sup>22</sup> and fluorinated  $\alpha,\beta$ -unsaturated

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Srinivas, R. *Tetrahedron*. **2009**, *65*, 9657-9672. (c) Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem*. **2012**, *4*, 917-925.

<sup>16</sup> (a) Enders, D.; Lüttgen, K.; Narine, A. *Synthesis* **2007**, *2007*, 959-980. (b) Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N. *Chem. Mater.* **2013**, *26*, 724-744. (c) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807-8864. (d) Wadhwa, P.; Kharbanda, A.; Sharma, A. *Asian J. Org. Chem.* **2018**, *7*, 634-661.

<sup>17</sup> (a) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41*, 988-999. (b) Wang, Y.; Du, D.-M. *Org. Chem. Front.* **2020**, *7*, 3266-3283.

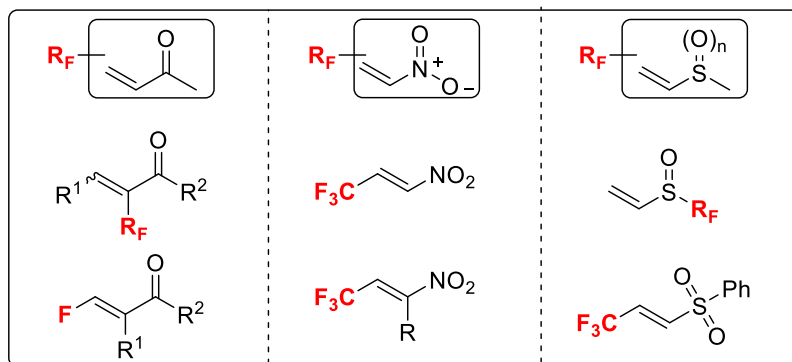
<sup>18</sup> (a) Enders, D.; Saint-Dizier, A.; Lannou, M. I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29-49. (b) Rulev, A. Y. *RSC Adv.* **2014**, *4*, 26002-26012.

<sup>19</sup> Valero, G.; Companyo, X.; Rios, R. *Chem. Eur. J.* **2011**, *17*, 2018-2037.

<sup>20</sup> For the selected examples on fluorinated Michael donors, see: (a) Prakash, G. K.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4090-4094. (b) Kwiatkowski, J.; Lu, Y. *Chem. Commun.* **2014**, *50*, 9313-9316. (c) Sung, H. J.; Mang, J. Y.; Kim, D. Y. *J. Fluorine Chem.* **2015**, *178*, 40-46. (d) Chen, D.-Y.; Song, S.; Chen, L.-Y.; Ren, X.; Li, Y. *Tetrahedron Lett.* **2021**, *68*.

<sup>21</sup> (a) Rousee, K.; Bouillon, J. P.; Couve-Bonnaire, S.; Pannecoucke, X. *Org. Lett.* **2016**, *18*, 540-543. (b) Lemonnier,

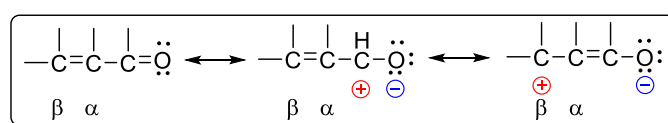
sulfoxide/sulfone<sup>23</sup> (**Figure 7**), these types of molecules could serve as the Michael acceptors. The progress of fluorinated substrates as Michael acceptors in MARs is summarized below.



**Figure 7** Selected examples of conjugated fluorinated compounds

### 1.4.1 Fluorinated $\alpha,\beta$ -unsaturated carbonyl Michael acceptors

$\alpha,\beta$ -unsaturated carbonyl compounds refer to organic compounds with the general structure  $R^1-C^\beta=C^\alpha-(R^2C=O)$ . The conjugation of the double bond to the carbonyl group could transfer the electrophilic property of the carbonyl carbon to the  $\beta$ -carbon of the double bond, a resonance description of this transfer is shown in **Figure 8**. The corresponding fluorinated  $\alpha,\beta$ -unsaturated carbonyl Michael acceptors can be classified by the different fluorinated moieties like F,  $CF_3$ ,  $CHF_2$ , perfluoro and so on.



**Figure 8** The electrophilic character transfer of  $\alpha,\beta$ -unsaturated carbonyls

#### 1.4.1.1 F-containing Michael acceptors

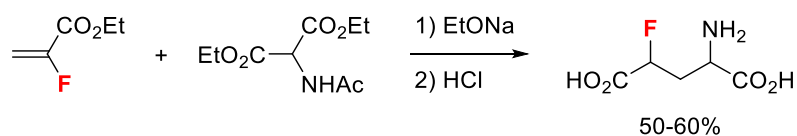
The use of alkyl  $\alpha$ -fluoroacrylates as Michael acceptors for the synthesis of relevant

G.; Zoute, L.; Dupas, G.; Quirion, J. C.; Jubault, P. *J. Org. Chem.* **2009**, *74*, 4124-4131. (c) Lim, C. H.; Kim, S. H.; Lee, H. J.; Kim, H. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2013**, *34*, 993-996. (d) Xiao, P.; Schlinquer, C.; Pannecoucke, X.; Bouillon, J. P.; Couve-Bonnaire, S. *J. Org. Chem.* **2019**, *84*, 2072-2082. (e) O'Connor, T. J.; Toste, F. D. *ACS Catal.* **2018**, *8*, 5947-5951.

<sup>22</sup> (a) Schechter, H.; Ley, D. E.; Roberson, E. B., *J. Am. Chem. Soc.* **1956**, *78*, 4984-4991. (b) Gao, J. R.; Wu, H.; Xiang, B.; Yu, W. B.; Han, L.; Jia, Y. X. *J. Am. Chem. Soc.* **2013**, *135*, 2983-2986.

<sup>23</sup> (a) Sokolenko, L.; Maletina, I.; Yagupolskii, L.; Yagupolskii, Y. *Synlett.* **2010**, *2010*, 2075-2078. (b) Xiang, Y.; Li, Y.; Kuang, Y.; Wu, J. *Adv. Synth. Catal.* **2017**, *359*, 2605-2609.

$\gamma$ -fluoroglutamic acid can be traced back to the 60s. In 1960, Hudlický used the ethyl 2-fluoroacrylate as Michael acceptor in the presence of EtONa and diethyl *N*-acetylamalonate as a nucleophile. Hydrolysis of the corresponding Michael adduct gave the desired  $\gamma$ -fluoroglutamic acid in 50-60% yield (**Scheme 3**).<sup>24</sup> In 1988, Tsushima and co-workers reported the same reaction in 70% yield.<sup>25</sup>



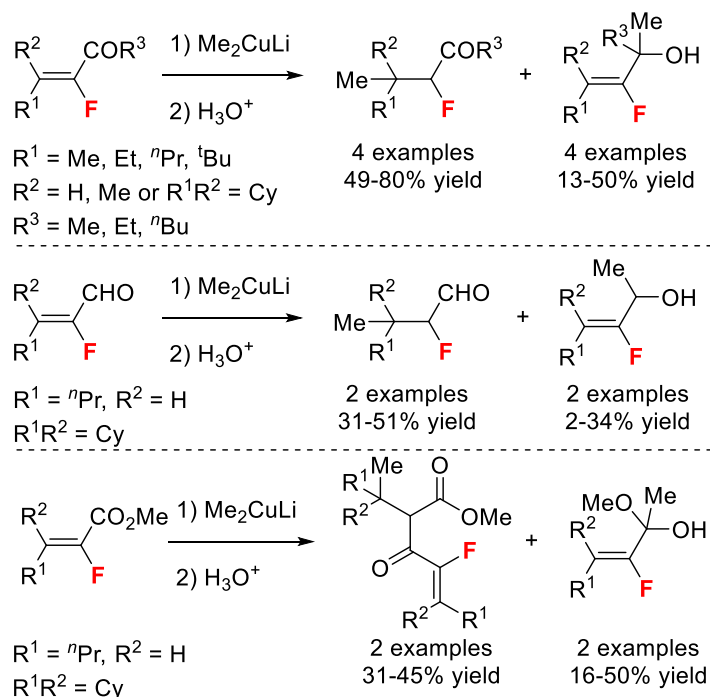
**Scheme 3** The synthesis of  $\gamma$ -fluoroglutamic acid

The  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ketone and aldehyde also could be applied to MARs. In an early report, Normant and co-workers studied the addition of lithium dimethylcuprate to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl compounds (**Scheme 4**).<sup>26</sup> The use of these fluorinated Michael acceptors with cuprates could form both 1,2- and 1,4-adducts, the ratio of 1,2- and 1,4-adducts being affected by the steric hindrance at  $\beta$ -position of the Michael acceptor. Surprisingly, in the case of fluorinated ester ( $R^1R^2 = \text{Cy}$  and  $R^1 = \text{}^n\text{Pr}$ ,  $R^2 = \text{H}$ ), the enolate from 1,4-addition immediately underwent a Claisen reaction to form a dimeric product with loss of the fluorine atom instead of forming the desired 1,4-adduct.

<sup>24</sup> Hudlický, M. *Tetrahedron Lett.* **1960**, *1*, 21-22.

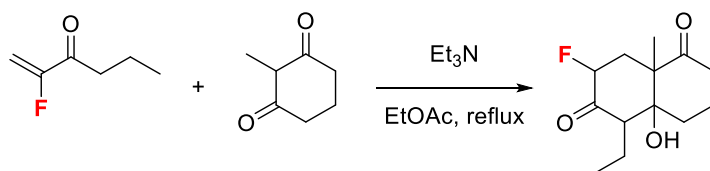
<sup>25</sup> Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N.; Shiratori, O.; Higaki, J.; Hirata, M. *Tetrahedron* **1988**, *44*, 5375-5387.

<sup>26</sup> Chuit, C.; Sauvêtre, R.; Masure, D.; Normant, J. F. *Tetrahedron* **1979**, *35*, 2645-2653.



**Scheme 4** Addition of  $\text{Me}_2\text{CuLi}$  to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated Michael acceptors

In 1981, Elkik and co-workers described the reaction between the 2-fluorohex-1-en-3-one and the 2-methylcyclohexane-1,3-dione. The new fluorinated cyclic product was formed by the Michael addition and a subsequent aldol reaction, but there was no characterization offered for this product (**Scheme 5**).<sup>27</sup>

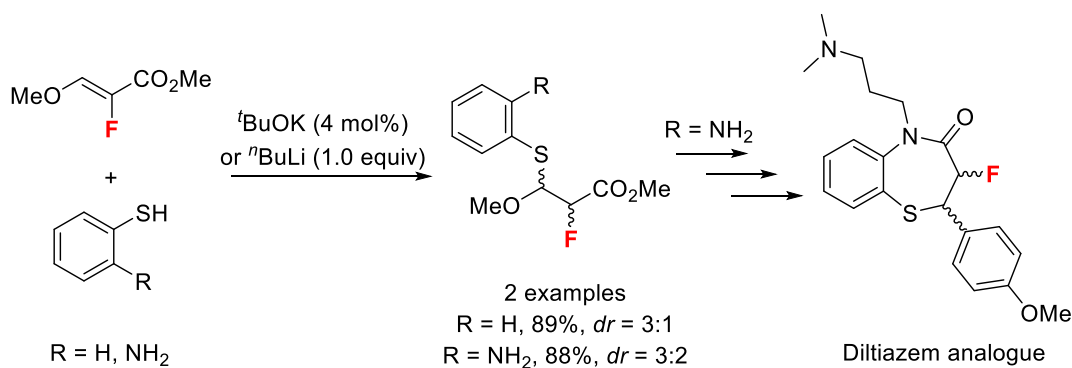


**Scheme 5** 2-fluorohex-1-en-3-one as the Michael acceptor

In 1996, Schlosser and co-workers described a sulfa-Michael addition on 2-fluoro-3-methoxyacrylate, a specially designed Michael acceptor. In the presence of  $^t\text{BuOK}$  or  $^n\text{BuLi}$ , the sulfa-Michael adducts were obtained as a mixture of diastereoisomers in good yields with moderate diastereoselectivities. The adduct of 2-aminothiophenol could be further used in the synthesis of fluorinated analogue related to Diltiazem (**Scheme 6**).<sup>28</sup>

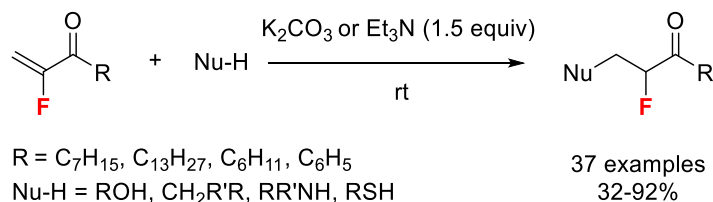
<sup>27</sup> Elkik, E.; Dahan, R.; Parlier, A. *Bull. Soc. Chim. Fr.* **1981**, 9, 1353-1360.

<sup>28</sup> Shi, G. Q.; Qian, W.; Schlosser, M. *Tetrahedron* **1996**, 52, 4403-4410.



**Scheme 6** The addition of thiophenols to 2-fluoro-3-methoxyacrylate

More recently, Haufe and co-workers investigated the Michael addition of various nucleophiles (carbon, nitrogen, sulfur, and oxygen) to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ketones and observed their behavior in the formation of C-C and C-heteroatom bonds (**Scheme 7**).<sup>29</sup> In the constructions of C-C, C-N, and C-S bond, all the selected fluorinated ketones were successfully converted into the desired  $\beta$ -substituted- $\alpha$ -fluoro ketones which could be separated in moderate to good yields. The formation of C-O bond was possible with MeOH or EtOH. The use of other bulky alcohols or starting from fluorinated ketones with Cy or Ph substituent, led to complex inseparable product mixtures.

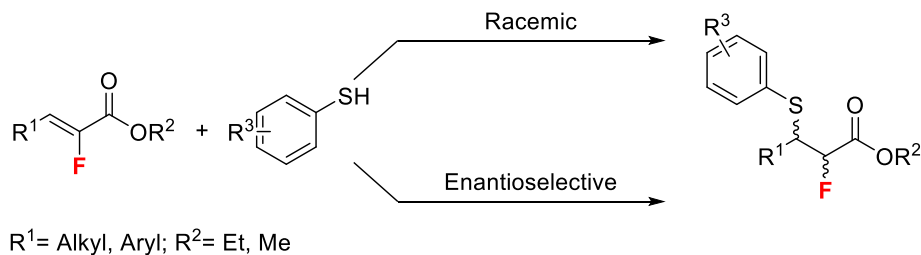


**Scheme 7** The addition of nucleophiles to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ketones

We can notice that very few MAR have been developed with  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl derivatives and even less with  $\beta$ -substituted  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl derivatives whereas the latter could give two adjacent stereogenic centers. During my Ph.D., I studied a sulfa-Michael addition reaction of aryl thiols to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters both in non-enantioselective and enantioselective versions (**Scheme 8**). This reaction will be discussed in more detail in the next chapter.

<sup>29</sup> Ramb, D. C.; Lerchen, A.; Beutel, B.; Fustero, S.; Haufe, G. *Eur. J. Org. Chem.* **2016**, *2016*, 1751-1759.

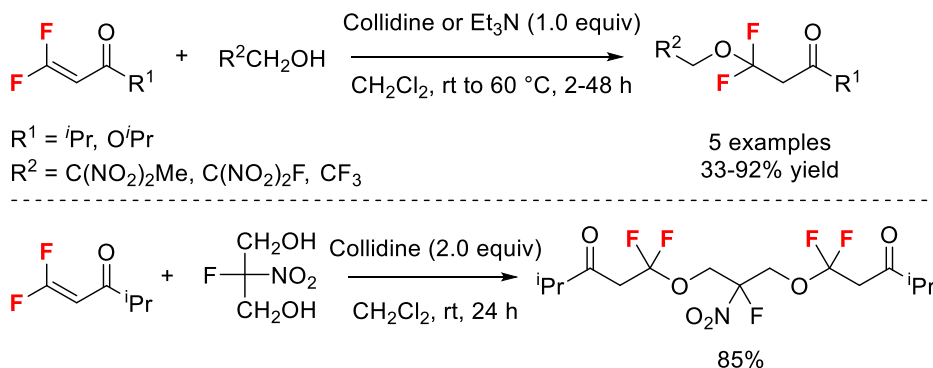




**Scheme 8** The addition of aryl thiols to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

### 1.4.1.2 F<sub>2</sub>-containing Michael acceptors

In 1990, Archibald and co-workers described an oxa-Michael addition of  $\beta$ -nitroalcohols to  $\beta,\beta$ -difluoroacrylates or  $\beta,\beta$ -difluorovinyl ketones.<sup>30</sup> The electronegatively substituted alcohols generally affording the corresponding fluoro nitro ethers in moderate to high yields. Moreover, when the glycol, 2-fluoro-2-nitro-1,3-propanediol was used, a bis-adduct was obtained in 85% yield (**Scheme 9**).



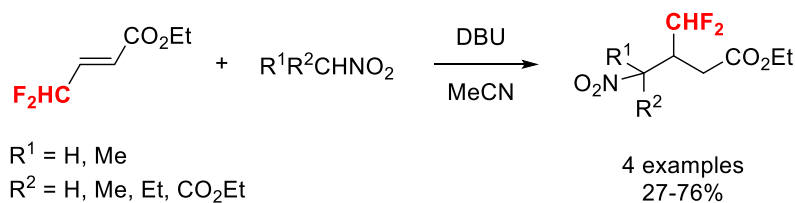
**Scheme 9** The addition of  $\beta$ -nitroalcohols to  $\beta,\beta$ -difluoroolefins

### 1.4.1.3 CHF<sub>2</sub>-containing Michael acceptors

There were very few reports of MAR specific with CHF<sub>2</sub>-containing Michael acceptors. Normally, the CHF<sub>2</sub>-containing Michael acceptor comes up as a single substrate in the method which was developed for other fluorinated Michael acceptors. To our knowledge, only one example of MAR with CHF<sub>2</sub>-containing Michael acceptor has been reported in 2005 by Kitazume and co-workers. They employed a  $\beta$ -CHF<sub>2</sub>-acrylate as a Michael acceptor for the synthesis of difluoromethylated materials

<sup>30</sup> Archibald, T. G.; Baum, K. *J. Org. Chem.* **1990**, *55*, 3562-3565.

using a microreactor.<sup>31</sup> In the presence of DBU, the 3-CHF<sub>2</sub>-acrylate with nitroalkanes proceeded smoothly to afford the corresponding 1,4-adducts in the microreactor without any detectable formation of polymeric products (**Scheme 10**).



**Scheme 10** The addition of nitroalkanes to ethyl (*E*)-4,4-difluorobut-2-enoate

#### 1.4.1.4 CF<sub>3</sub>-containing Michael acceptors

MAR involving CF<sub>3</sub>-containing Michael acceptors is the most developed in the literature. This part has been divided by class of Michael acceptors beginning with the derivatives I studied during my Ph.D., acrylate derivatives.

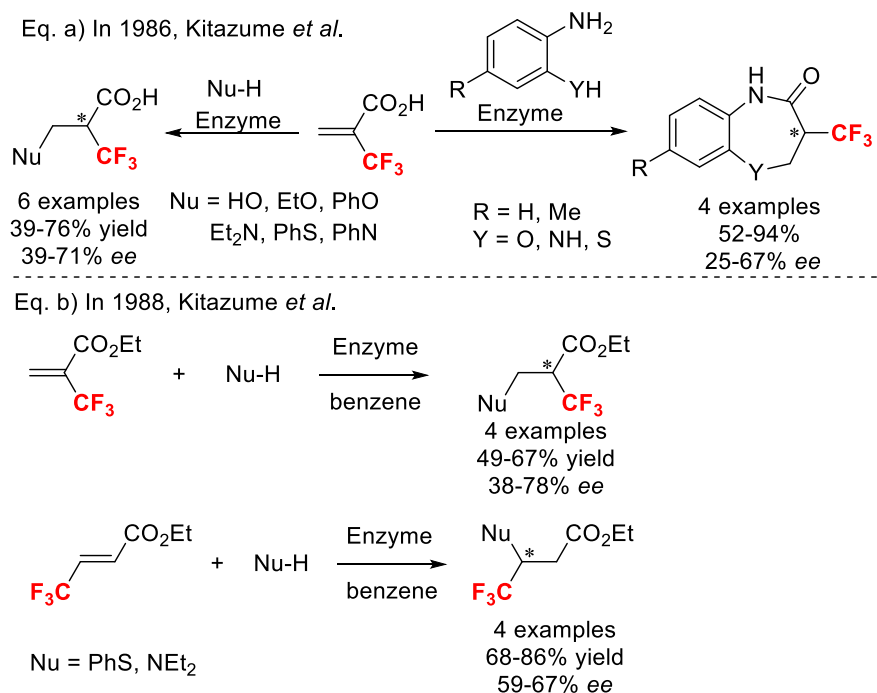
##### 1.4.1.4.a CF<sub>3</sub>-containing acrylic acid and acrylates

In 1986, Kitazume and co-workers reported enzyme-catalyzed enantioselective conjugate additions of a series of nucleophiles to commercially available 2-(trifluoromethyl)acrylic acid.<sup>32</sup> Various nucleophiles such as water, ethanol, phenol, thiophenol, and amines were applied in this reaction, giving the corresponding 1,4-adducts in moderate yields and enantioselectivities. From *o*-substituted anilines, a chiral Michael addition reaction followed by a condensation reaction allowed the formation of the optically active heterocycles in good yields and moderate enantioselectivities (**Scheme 11**, Eq. a). Two years later, the  $\alpha$ - and  $\beta$ -CF<sub>3</sub>-acrylates were also employed to give optically active trifluoromethylated compounds via the biocatalytic reaction of enzymes (**Scheme 11**, Eq. b).<sup>33</sup>

<sup>31</sup> Kawai, K.; Ebata, T.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 956-961.

<sup>32</sup> Kitazume, T.; Ikeya, T.; Murata, K. *Journal of the Chemical Society, Chemical Communications* **1986**, 1331-1333.

<sup>33</sup> Kitazume, T.; Murata, K.; Kokusho, Y.; Iwasaki, S. *J. Fluorine Chem.* **1988**, *39*, 75-86.

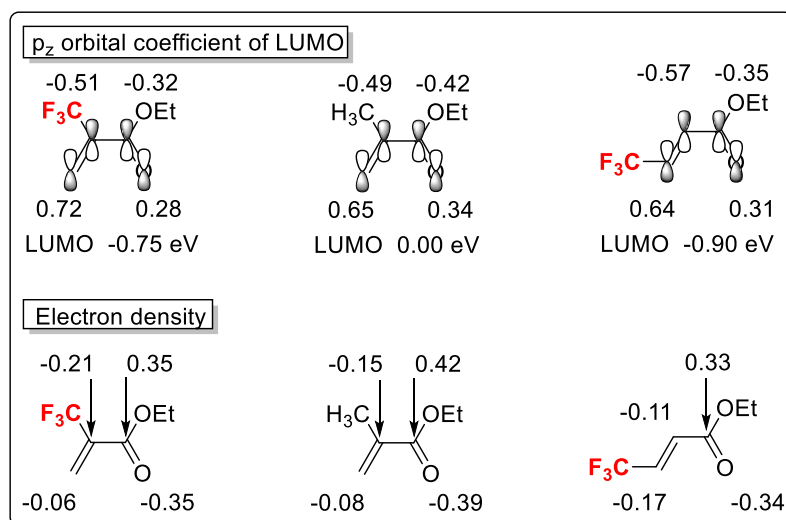


**Scheme 11** Biocatalytic Michael addition to  $\alpha$ -CF<sub>3</sub>-acrylic acid and  $\alpha$ -/ $\beta$ -CF<sub>3</sub>-acrylates

Since 1984, the Michael addition reactions of lithium enolates as a tool for the diastereoselective construction of a new C-C bond came into chemists' view.<sup>34</sup> The comparison of the  $p_z$  orbital coefficient of LUMO and the electron density between the CF<sub>3</sub>-acrylates and their nonfluorinated congeners showed similar characteristics at the  $\beta$ -position (**Figure 9**).<sup>35</sup> Nevertheless, the electron-withdrawing trifluoromethyl moiety lowered the LUMO energy levels which should increase the reactivity of the CF<sub>3</sub>-acrylates compared to non-fluorinated ones. The MAR strategy has thus been used to access CF<sub>3</sub>-containing compounds by the addition of lithium enolates to CF<sub>3</sub>-acrylates.

<sup>34</sup> (a) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661-5664. (b) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132-157. (c) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157-172.

<sup>35</sup> Yamazaki, T.; Hiraoka, S.; Kitazume, T. *J. Org. Chem.* **1994**, *59*, 5100-5103.

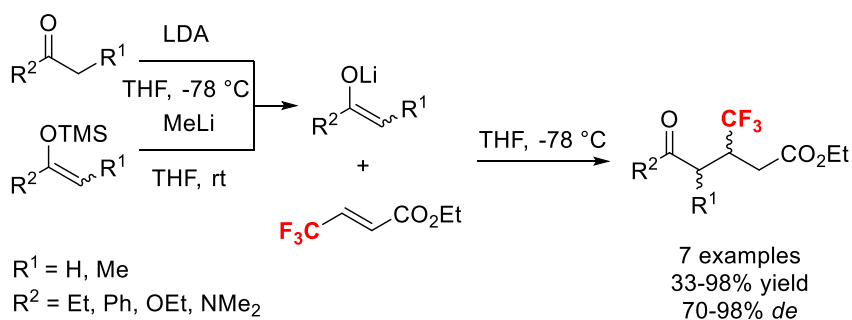


**Figure 9** The  $p_z$  orbital coefficient of LUMO and electron density of  $\text{CF}_3$ -acrylates

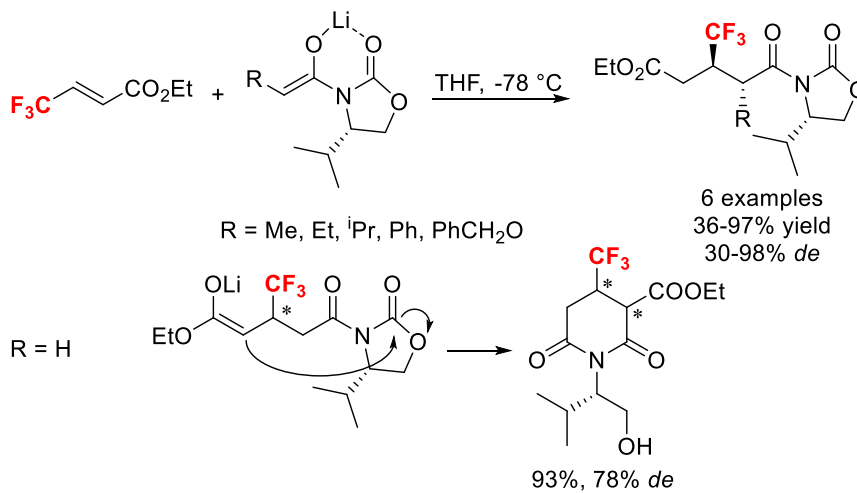
In 1991, Yamazaki and co-workers reported the MARs of lithium enolates to (*E*)- $\beta$ - $\text{CF}_3$ -acrylate, these reactions were found to proceed smoothly in moderate to excellent yields as well as with high diastereoselectivities (**Scheme 12**, Eq. a).<sup>36</sup> The same year, they described the addition of lithium enolates derived from chiral acylated oxazolidinones to the same Michael acceptor. Enantiomerically pure adducts were obtained in good to excellent yields with a high level of diastereoselectivity (**Scheme 12**, Eq. b).<sup>37</sup> There was a special case when  $R = \text{H}$ , which furnished the cyclic product possibly via a nucleophilic attack of the resulting ester enolate to the carbonyl moiety of oxazolidinone ring.

<sup>36</sup> Yamazaki, T.; Haga, J.; Kitazume, T.; Nakamura, S. *Chem. Lett.* **1991**, *20*, 2171-2174.

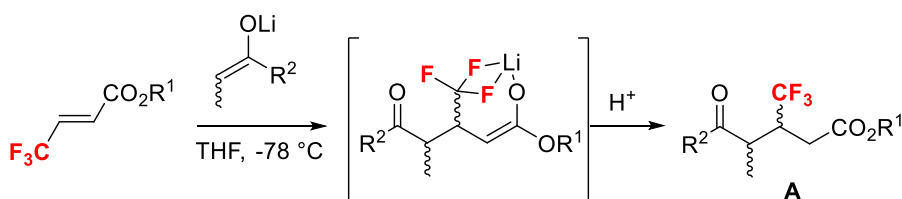
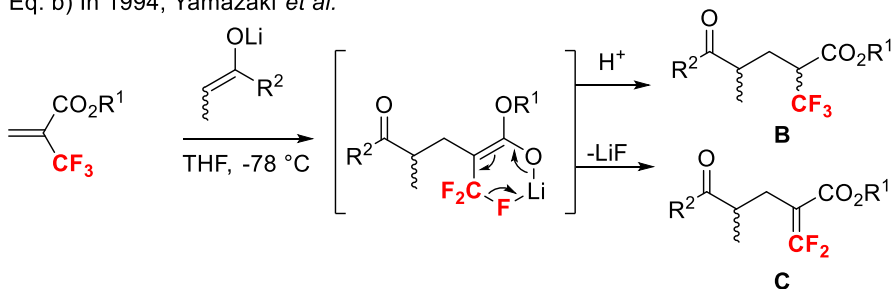
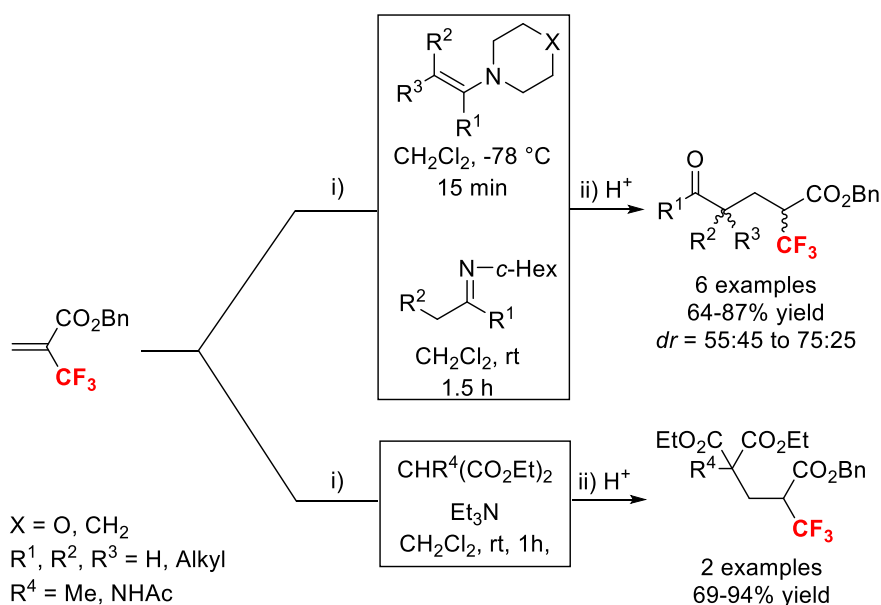
<sup>37</sup> Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, *20*, 2175-2178.

Eq. a) In 1991, Yamazaki *et al.*

$R^1 = H, Me$   
 $R^2 = Et, Ph, OEt, NMe_2$

Eq. b) In 1991, Yamazaki *et al.***Scheme 12** The addition of enolates to (*E*)- $\beta$ - $CF_3$ -acrylates

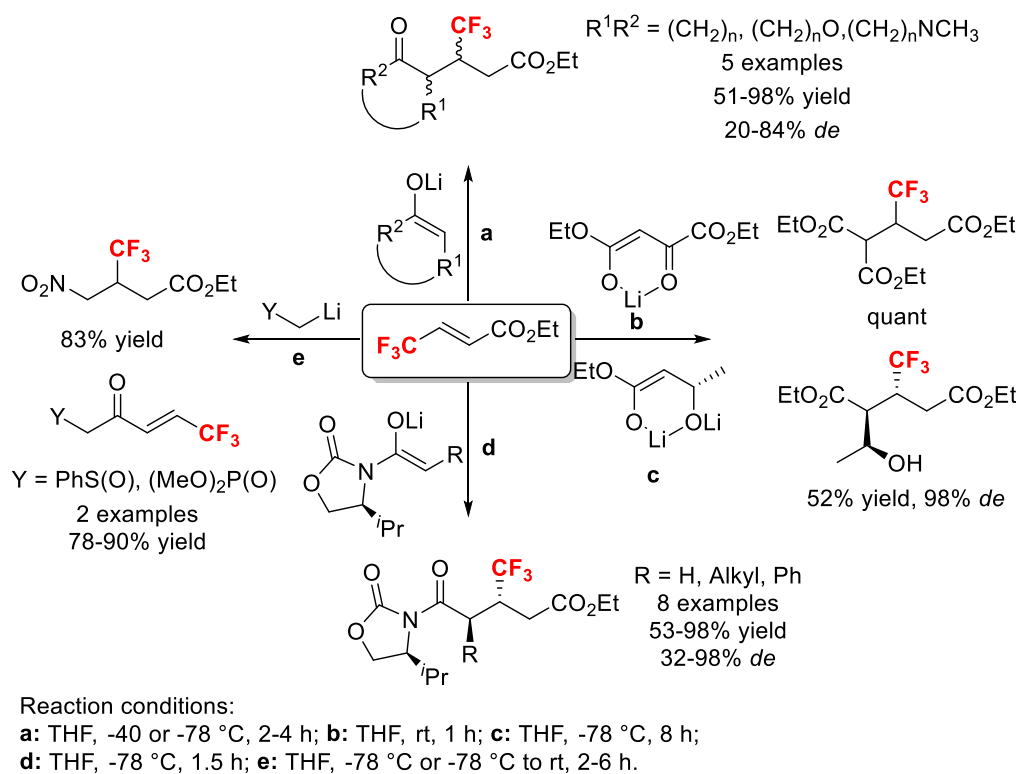
For MAR of various types of lithium enolates to (*E*)- $\beta$ - $CF_3$ -acrylate, the intramolecular Li-F interaction with both fluorine atoms played an important role to stabilize the intermediate and allowed the Michael addition reaction to occur (**Scheme 13**, Eq. a).<sup>36</sup> In 1994, the same authors proposed that the formation of Michael adducts of lithium enolates from  $\alpha$ - $CF_3$ -acrylates may go through a similar six-membered intermediate. Nevertheless, instead of the expected 1,4-adduct (**B**), only polymerized products, coming from the polymerization of substrates and/or byproduct (**C**), obtained from the LiF elimination (**Scheme 13**, Eq. b), occurred from metallic enolates. Taking into account the high reactivity of such  $\alpha$ - $CF_3$ -acrylates, the authors suggested that the employment of much weaker nonmetallic nucleophiles could limit or avoid the polymerization reaction as well as the formation of defluorinated byproducts (**C**). In this context, they described the MAR of enamines, imines, and active methylenes to benzyl- $\alpha$ - $CF_3$ -acrylate (**Scheme 14**).<sup>35</sup>

Eq. a) In 1991, Yamazaki *et al.*Eq. b) In 1994, Yamazaki *et al.***Scheme 13** The possible formations of Michael adducts of lithium enolates from CF<sub>3</sub>-acrylates**Scheme 14** Addition of nucleophiles to benzyl α-CF<sub>3</sub>-acrylate

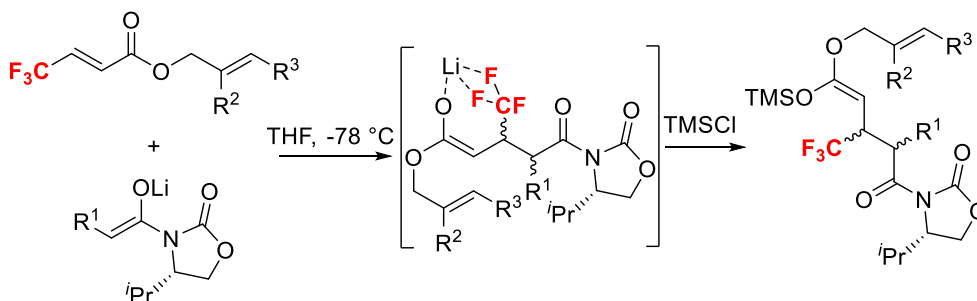
One year later, building on their previous work, Yamazaki and co-workers extended the range of lithium donors, employing some cyclic enolates, enolates derived from β-carbonyl, β-hydroxyl ester, acyloxazolidinones and the lithium donor with anion-stabilizing functionalities to react with the ethyl (*E*)-β-CF<sub>3</sub>-acrylate (**Scheme 15**).<sup>38</sup> Interestingly, In their subsequent work on sequential Michael addition-Ireland Claisen reactions, the key intermediates of lithium enolate Michael addition reaction

<sup>38</sup> Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363-4374.

were trapped with TMSCl (**Scheme 16**).<sup>39</sup>



**Scheme 15** The addition of lithium donors to (*E*)- $\beta$ -CF<sub>3</sub>-acrylate

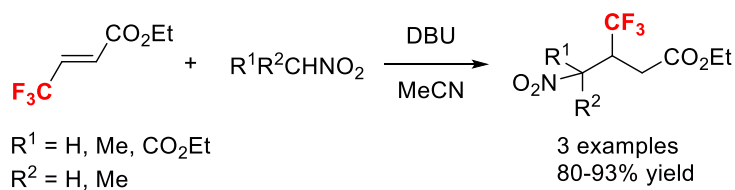


**Scheme 16** The key intermediates were trapped with TMSCl

In 2003, Kitazume and co-workers employed a  $\beta$ -CF<sub>3</sub>-acrylate as a Michael acceptor for the synthesis of trifluoromethylated materials using a microreactor (**Scheme 17**).<sup>40</sup> Compared to the additions to  $\beta$ -CHF<sub>2</sub>-acrylate in the microreactor (see **Scheme 10**), better NMR yields were obtained.

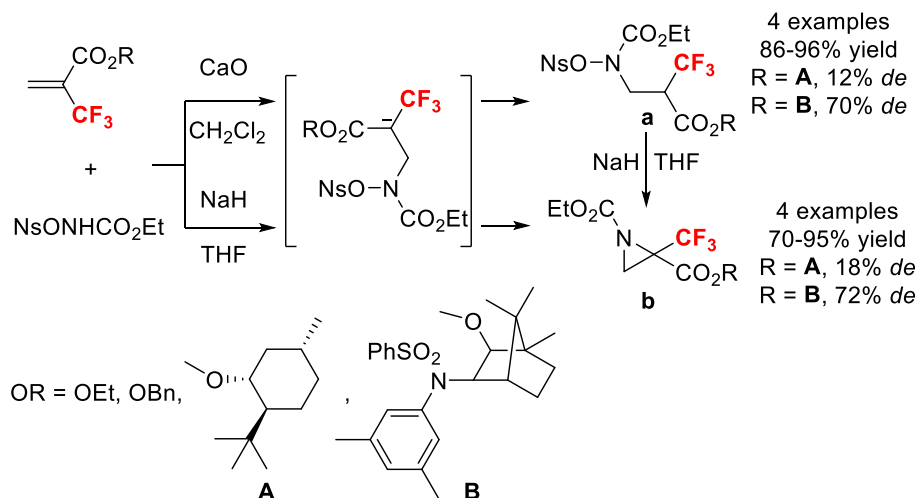
<sup>39</sup> Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140-8141.

<sup>40</sup> Miyake, N.; Kitazume, T. *J. Fluorine Chem.* **2003**, *122*, 243-246.



**Scheme 17** The addition of nitroalkanes to (*E*)- $\beta$ -CF<sub>3</sub>-acrylate in the microreactor

In 2004, Pellacani and co-workers reported an aza-Michael Addition of nosyloxycarbamates to four  $\alpha$ -trifluoromethylacrylates, including both containing chiral auxiliary.<sup>41</sup> The use of different bases led to two products: A weaker base as CaO led to the  $\beta$ -amino ester (**a**) by immediate protonation, whereas with the NaH, the absence of water might favor the ring closure reaction forming the aziridine (**b**). The equip of (-)-8-phenylmenthol (**A**) to the  $\alpha$ -CF<sub>3</sub>-acrylate induced a low diastereoselectivity, gave 12% and 18% of *de* to  $\beta$ -amino ester (**a**) and aziridine (**b**) respectively, better results were obtained by using the bulkier Helmchen's auxiliary (**B**), giving 70% and 72% of *de* respectively (**Scheme 18**).



**Scheme 18** The addition of nosyloxycarbamates to  $\alpha$ -CF<sub>3</sub>-acrylate

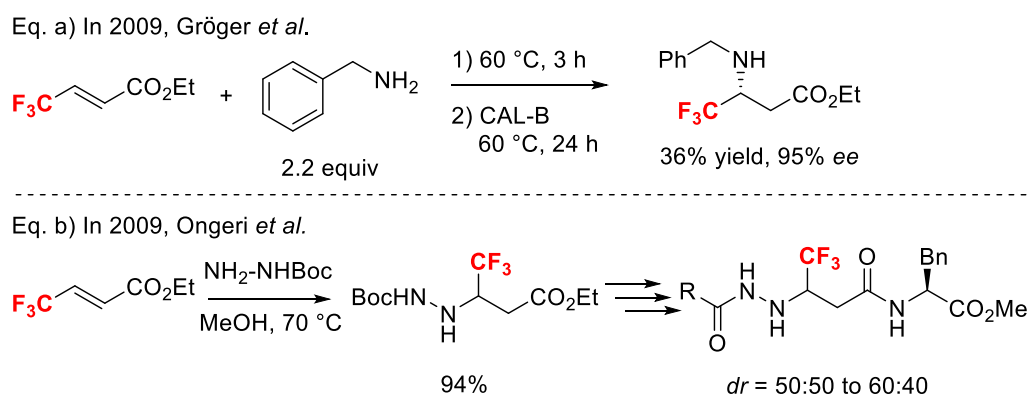
Gröger and co-workers described a one-pot process to synthesize the short-chain aliphatic  $\beta$ -amino acid esters in 2009.<sup>42</sup> The desired chiral amino acid ester was obtained in a two-step, one-pot process. Firstly, a non-enantioselective aza-Michael addition of benzylamine to enoates occurred to form the 1,4-adduct. Then, an

<sup>41</sup> Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197-200.

<sup>42</sup> Gröger, H.; Weiß, M. *Synlett* **2009**, *2009*, 1251-1254.

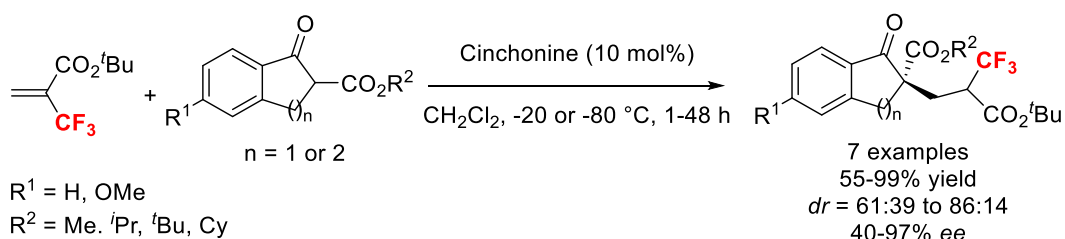


addition of a lipase allowed to catalyze an enantioselective aminolysis reaction. (*E*)- $\beta$ -CF<sub>3</sub>-acrylate was used in this approach to give the  $\beta$ -CF<sub>3</sub>- $\beta$ -amino acid ester in 36% yield with high enantioselectivity (**Scheme 19**, Eq. a). The same year, Ongerri and co-workers selected the same ethyl (*E*)- $\beta$ -CF<sub>3</sub>-acrylate as Michael acceptor to react with Boc-protected carbazate, giving an interesting  $\beta$ -trifluoromethyl- $\beta$ -hydrazino ester scaffold used to design various inhibitors of rabbit (20S) proteasome (**Scheme 19**, Eq. b).<sup>43</sup>



**Scheme 19** The addition of benzylamine and Boc-protected carbazate to (*E*)- $\beta$ -CF<sub>3</sub>-acrylate

The same year, Shibata and co-workers constructed nonadjacent quaternary stereocenters by the organocatalyzed Michael addition of cyclic  $\beta$ -ketoesters to *tert*-butyl  $\alpha$ -trifluoromethylacrylate.<sup>44</sup> Several commercially available cinchona alkaloids were tested and among them, cinchonine, gave the best results, furnishing the corresponding adducts in moderate to excellent yields as well as in moderate to very good diastereo- and enantioselectivities (**Scheme 20**).

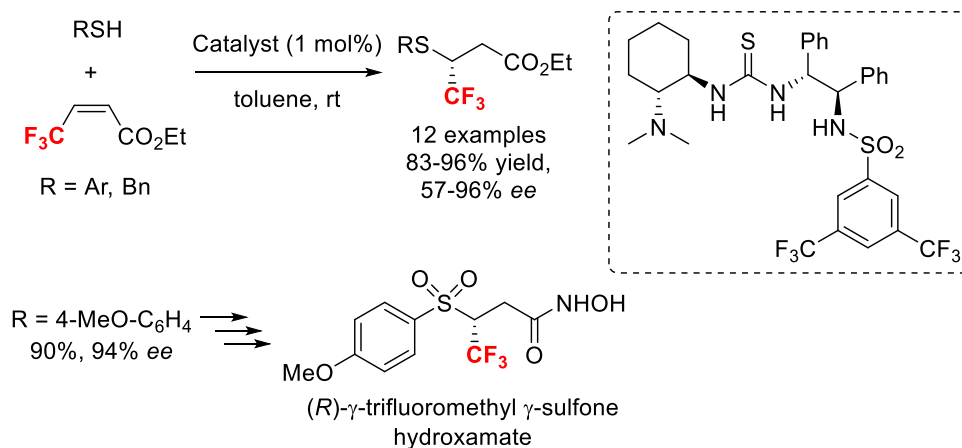


**Scheme 20** The addition of  $\beta$ -ketoesters to  $\alpha$ -CF<sub>3</sub>-acrylate

<sup>43</sup> Formicola, L.; Marechal, X.; Basse, N.; Bouvier-Durand, M.; Bonnet-Delpon, D.; Milcent, T.; Reboud-Ravaux, M.; Ongerri, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 83-86.

<sup>44</sup> Ogawa, S.; Yasui, H.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Chem. Lett.* **2009**, *38*, 1006-1007.

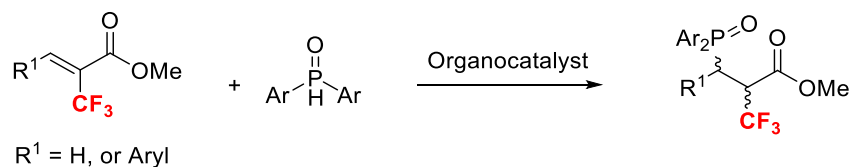
Two years later, Wang and co-workers developed a highly efficient asymmetric sulfa-Michael addition of thiols to (*Z*)-ethyl 4,4,4-trifluorocrotonate under the catalysis of a bifunctional amine-thiourea, furnishing the corresponding 1,4-adducts in high yields and excellent enantioselectivities. The subsequent transformation led to the convenient preparation of (*R*)- $\gamma$ -trifluoromethyl  $\gamma$ -sulfone hydroxamate which is the key intermediate of the potent inhibitor of MMP-3 (**Scheme 21**).<sup>45</sup>



**Scheme 21** The addition of thiols to (*Z*)-ethyl 4,4,4-trifluorocrotonate

The trifluoromethyl acrylic acid derivatives are easily accessible and have been used in Michael addition as presented in this section. Nevertheless, we can point out that most of the reactions have been done on unsubstituted  $\alpha$ - or  $\beta$ - trifluoromethyl acrylates whereas two adjacent stereogenic centers could be obtained directly from  $\alpha,\beta$ -disubstituted trifluoromethyl acrylate. Moreover, most of the reactions led to the formation of C-C bond, with few examples of C-N or C-S bond formation. To our knowledge, there is no example of C-P bond formation with this kind of substrates so far. During my Ph.D., we developed a phospho-Michael addition on trifluoromethyl acrylic acid derivatives, and the results will be presented in Chapter 3 (**Scheme 22**). Hereafter, we will continue to describe the different MAR with other CF<sub>3</sub>-containing Michael acceptors.

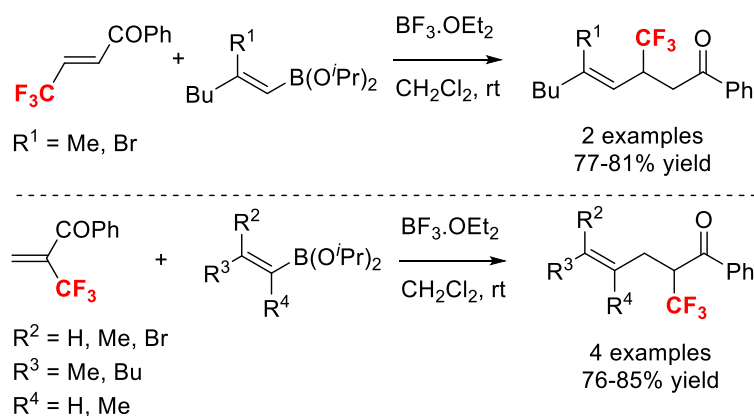
<sup>45</sup> Dong, X. Q.; Fang, X.; Wang, C. J. *Org. Lett.* **2011**, *13*, 4426-4429.



**Scheme 22** The phospha-Michael addition on  $\alpha$ -trifluoromethyl acrylates

#### 1.4.1.4.b $\text{CF}_3$ -containing enones

Trifluoromethyl- $\alpha,\beta$ -unsaturated ketone is a very important building block<sup>46</sup> used in MARs for the synthesis of fluorinated molecules. In 1993, Hara and Suzuki described a method for 1,4-addition of organoborane compounds to both  $\alpha$ - and  $\beta$ - $\text{CF}_3$ -enones, obtaining the desired  $\gamma,\delta$ -unsaturated ketones in good yields (**Scheme 23**).<sup>47</sup>



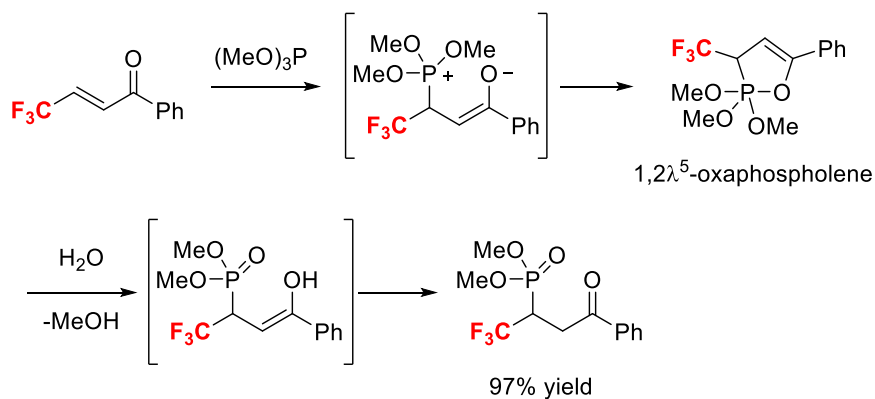
**Scheme 23** The addition of organoboranes to  $\alpha$ - and  $\beta$ - $\text{CF}_3$ -enones

In 2000, an example of using  $\beta$ - $\text{CF}_3$ -enone as a Michael acceptor for the C-P formation was reported by Röschenthaler and co-workers.<sup>48</sup> The authors synthesized  $\gamma$ -ketophosphonate by the reaction between  $\beta$ - $\text{CF}_3$ -enone and trimethyl phosphite. A [4+1] cycloaddition reaction, where the initial attack of phosphorus occurred at the  $\beta$ -position of the enone followed by ring closure, produced 1,2 $\lambda^5$ -oxaphospholene as a single product which upon hydrolysis furnished  $\gamma$ -ketophosphonate (**Scheme 24**).

<sup>46</sup> (a) Nenajdenko, V. G.; Balenkova, E. S. *ARKIVOC* **2011**, 2011, 246-328. (b) Sanz-Marco, A. *Synlett* **2015**, 26, 271-272. (c) Chaudhary, B.; Kulkarni, N.; Saiyed, N.; Chaurasia, M.; Desai, S.; Potkule, S.; Sharma, S. *Adv. Synth. Catal.* **2020**, 362, 4794-4819.

<sup>47</sup> Takada, E. I.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1993**, 34, 7067-7070.

<sup>48</sup> Ratner, V. G.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2000**, 102, 73-77.



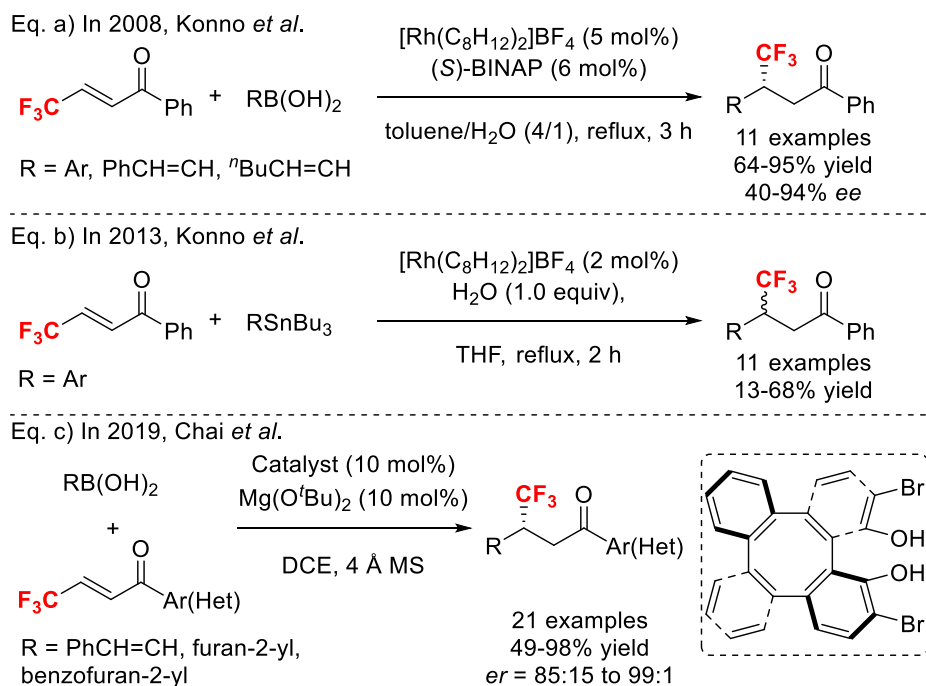
**Scheme 24** The addition of trimethyl phosphite to  $\beta$ -CF<sub>3</sub>-enone

In 2008, a rhodium-catalyzed Michael addition reaction of arylboronic acids to trifluoromethylated- $\alpha,\beta$ -unsaturated ketones has been reported by Konno and co-workers. The adducts were obtained in good to excellent yields as well as the enantioselectivities (**Scheme 25**, Eq. a).<sup>49</sup> Some other CF<sub>3</sub>-containing Michael acceptors such as acrylate, acrylamide, nitroalkene, sulfone, and phosphonate were also employed, albeit showing less reactivity and enantioselectivity. Later, the addition of arylstannanes was described by the same research group. Unlike the previous work, these reactions occurred without ligand, and the authors did not provide the enantioselectivity (**Scheme 25**, Eq. b).<sup>50</sup> More recently, a transition metal-free asymmetric addition reaction of (*E*)-styrylboronic acids to  $\beta$ -CF<sub>3</sub>-enones was described by Chai and co-workers in 2019.<sup>51</sup> The reaction was carried out in the presence of a chiral organocatalyst, Mg(O<sup>*t*</sup>Bu)<sub>2</sub> and 4 Å molecular sieves as additives. The adducts were obtained in moderate to high yields with excellent enantiomeric ratios (up to 99:1) (**Scheme 25**, Eq. c).

<sup>49</sup> Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, *49*, 2106-2110.

<sup>50</sup> Morigaki, A.; Tanaka, T.; Miyabe, T.; Ishihara, T.; Konno, T. *Org. Biomol. Chem.* **2013**, *11*, 586-595.

<sup>51</sup> Chai, G. L.; Sun, A. Q.; Zhai, D.; Wang, J.; Deng, W. Q.; Wong, H. N. C.; Chang, J. *Org. Lett.* **2019**, *21*, 5040-5045.

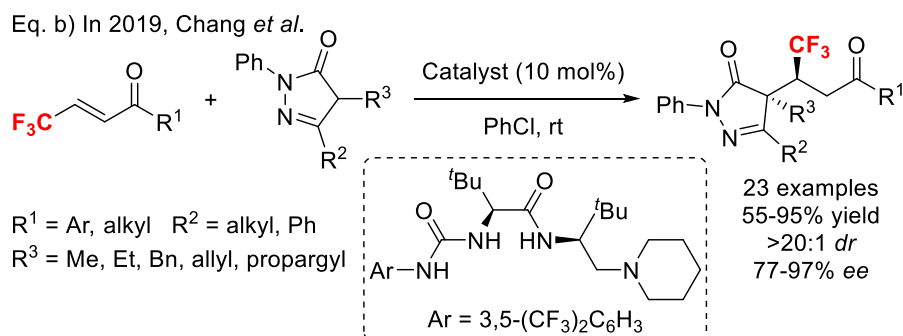
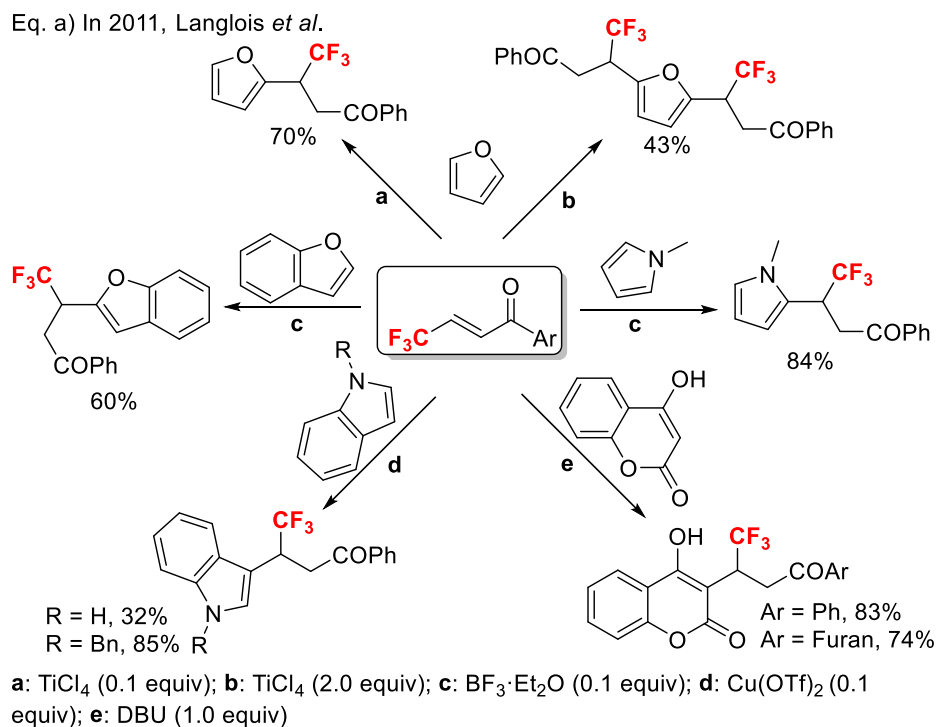


**Scheme 25** The addition of boronic acids/arylstannanes to  $\beta$ -CF<sub>3</sub>-enones

In 2011, Langlois and co-workers reported a Michael addition reaction of various electron-rich N- and O-containing heterocycles such as furans, benzofurans, pyrroles, and indoles to  $\beta$ -CF<sub>3</sub>-enones affording the heterocycle products bearing a CF<sub>3</sub> group (**Scheme 26**, Eq. a).<sup>52</sup> They used different Lewis acid catalysts involving TiCl<sub>4</sub>, BF<sub>3</sub>·Et<sub>2</sub>O and Cu(OTf)<sub>2</sub> with the different types of Michael donors to favor the reaction. In the addition of furan, the use of 2 equivalents of TiCl<sub>4</sub> and  $\beta$ -CF<sub>3</sub>-enone could form the bis-adduct. For furan, benzofuran, and pyrrole, the addition occurred at C2 position whereas it occurred at C3 position with indoles. Also, with the similar  $\beta$ -CF<sub>3</sub>-enones Michael acceptors, the organocatalytic asymmetric addition of pyrazol-5-ones was described by Zhu and Chang in 2019.<sup>53</sup> A urea-amide-tertiary amine organocatalyst was used and the asymmetric addition took place at the C3 position of pyrazolone and at the  $\beta$ -position of the enone, generating two adjacent chiral centers. The desired products were obtained in good yields and enantio- as well as diastereoselectivities (**Scheme 26**, Eq. b).

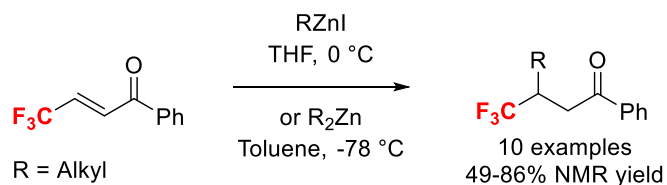
<sup>52</sup> Leuger, J.; Blond, G.; Billard, T.; Haufe, G.; Langlois, B. R. *J. Fluorine Chem.* **2011**, *132*, 799-803.

<sup>53</sup> Xu, X.; He, Y.; Zhou, J.; Li, X.; Zhu, B.; Chang, J. *J. Org. Chem.* **2020**, *85*, 574-584.



**Scheme 26** The addition of electron-rich heterocycles to  $\beta\text{-CF}_3$ -enones

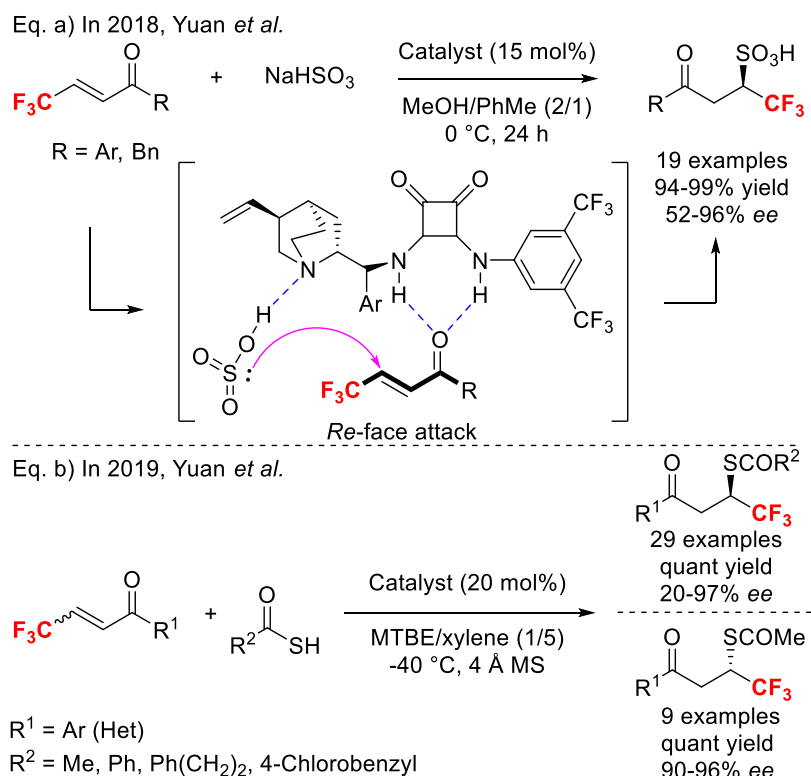
In 2012, Konno and co-workers reported a 1,4-conjugate addition of organozinc reagents to  $\beta\text{-CF}_3$ -enone which gave the corresponding alkylated 1,4-adducts in moderate yields without using either transition metals or Lewis acids (**Scheme 27**).<sup>54</sup> With  $\text{Et}_2\text{Zn}$ , some other  $\text{CF}_3$ -containing Michael acceptors such as phosphate, sulfone and a  $\text{CHF}_2$ -containing enone were applied, giving moderate to good isolated yields.



**Scheme 27** The addition of organozinc reagents to  $\beta\text{-CF}_3$ -enone

<sup>54</sup> Konno, T.; Morigaki, A.; Miyabe, T.; Tsukade, K.; Arimitsu, S.; Ishihara, T. *Synthesis* **2012**, *45*, 101-105.

$\beta$ -CF<sub>3</sub>-enones were also employed in sulfa-Michael addition reactions, to construct the stereogenic carbon center bearing a sulfur atom and a CF<sub>3</sub> group. In 2018, Yuan and co-workers described an asymmetric sulfa-Michael addition of NaHSO<sub>3</sub> to  $\beta$ -CF<sub>3</sub>-enones for the preparation of optically active CF<sub>3</sub>-containing sulfonic acids.<sup>55</sup> A plausible transition state showed a dual hydrogen-bonding interaction between the N-H of cinchona alkaloid-derived squaramide and the carbonyl oxygen atom thus enhancing the electrophilicity of the  $\beta$ -position. Then, the addition of the activated bisulfate occurred from the *Re*-face to give the 1,4-adducts in (*R*)-configuration (**Scheme 28**, Eq. a). One year later, they used the same organocatalyst with thiocarboxylic acids as the sulfur-sources, to give the desired 1,4-adducts in quantitative yields and good to high enantioselectivities. In addition, the developed method could also be applied to (*Z*)-  $\beta$ -CF<sub>3</sub>-enones offering the corresponding adducts in (*S*)-configuration (**Scheme 28**, Eq. b).<sup>56</sup>



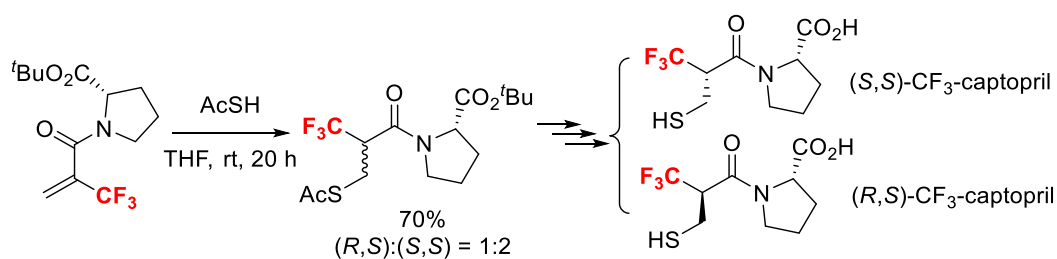
**Scheme 28** Sulfa-Michael addition of  $\beta$ -CF<sub>3</sub>-enones

<sup>55</sup> Hu, W. F.; Zhao, J. Q.; Chen, Y. Z.; Zhang, X. M.; Xu, X. Y.; Yuan, W. C. *J. Org. Chem.* **2018**, *83*, 5771-5777.

<sup>56</sup> Hu, W. F.; Zhao, J. Q.; Chen, X. Z.; Zhou, M. Q.; Zhang, X. M.; Xu, X. Y.; Yuan, W. C. *Tetrahedron* **2019**, *75*, 2206-2214.

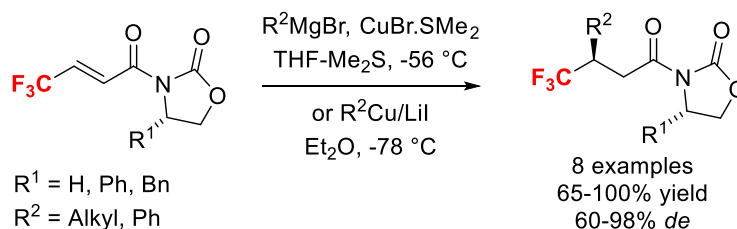
1.4.1.4.c CF<sub>3</sub>-containing acrylamides

Trifluoromethylated acrylamides Michael acceptors also caught the attention of chemists and especially for the asymmetric synthesis. Indeed, in 1991, Ojima and co-workers described the preparation of fluorinated captopril analogues by conjugate addition of thiolacetic acid to a chiral  $\alpha$ -CF<sub>3</sub>-acrylamide Michael acceptor (**Scheme 29**).<sup>57</sup> The diastereomeric adducts were obtained with a ratio of 1:2 (*R,S*:*S,S*) and were separated by medium pressure liquid chromatography. Then, subsequent reactions (removal of *tert*-butyl and thioacetyl groups) gave (*R,S*)- and (*S,S*)-trifluoromethyl captoprils.



**Scheme 29** The addition of thiolacetic to  $\alpha$ -CF<sub>3</sub>-acrylamide

In 1996, Yamazaki and co-workers also employed the chiral  $\beta$ -CF<sub>3</sub>-acrylamides as Michael acceptors with a series of organocopper reagents. The optically active molecules bearing a CF<sub>3</sub> group at the chiral center were obtained in good yields and high levels of diastereoselectivity (**Scheme 30**).<sup>58</sup> The stereochemical results of the reaction showed that organocopper approached the  $\beta$ -position of the Michael acceptor from the less hindered *Si*-face of alkene moiety.



**Scheme 30** Addition of organocopper to chiral  $\beta$ -CF<sub>3</sub>-acrylamides

The use of peptides in drug development is limited due to their rapid degradation

<sup>57</sup> Ojima, I.; Jameison, F. A. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 581-584.

<sup>58</sup> Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1999**, *97*, 91-96.



and poor bioavailability.<sup>59</sup> The modification of peptide backbone appeared as an attractive strategy to overcome these disadvantages. The group of Fustero and Zanda described a methodology for the synthesis of partially modified retro  $\Psi$ [NHCH<sub>2</sub>]-peptides containing a chemically stable and stereo-defined trifluoroalanine unit. The key reaction was a stereo-controlled aza-Michael addition of  $\alpha$ -amino ester to  $\alpha$ -CF<sub>3</sub>-acrylamides (**Scheme 31**).<sup>60</sup> They also developed the stereo-controlled solid<sup>61</sup> and fluorous-phase<sup>62</sup> syntheses of partially modified retropeptides by using Wang resin-supported Michael acceptors (**Figure 10, A**) and <sup>F</sup>TMSE tagged Michael acceptors (**Figure 10, B**) respectively. A mechanistic study showed that this type of reaction is a two-step process. Firstly, the amide enol intermediate was generated by the initial aza-Michael addition of  $\alpha$ -amino esters to  $\alpha$ -CF<sub>3</sub>-acrylamide acceptors; then, an intramolecular hydrogen transfer stereoselectively occurred to give the final products.<sup>63</sup> The highly efficient aza-Michael addition of different amines to  $\alpha$ -CF<sub>3</sub>-acrylamide acceptors can afford other families of peptidomimetics: dipeptides, tripeptides, and structures containing a urea moiety or two units of  $\alpha$ -CF<sub>3</sub>- $\beta^2$ -alanine. With the help of X-ray analysis and NMR techniques, Fustero and co-workers studied the conformation of some newly synthesized peptidomimetics, the results showed a  $\beta$ -turn-like conformation for these structures both in the solid-state and in solution.<sup>64</sup>

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<sup>59</sup> (a) Loffet, A. *J. Pept. Sci.* **2002**, *8*, 1-7. (b) Lau, J. L.; Dunn, M. K. *Bioorg. Med. Chem.* **2018**, *26*, 2700-2707. (c) Brian Chia, C. S. *Int. J. Pept. Res. Ther.* **2021**, *27*, 1397-1418.

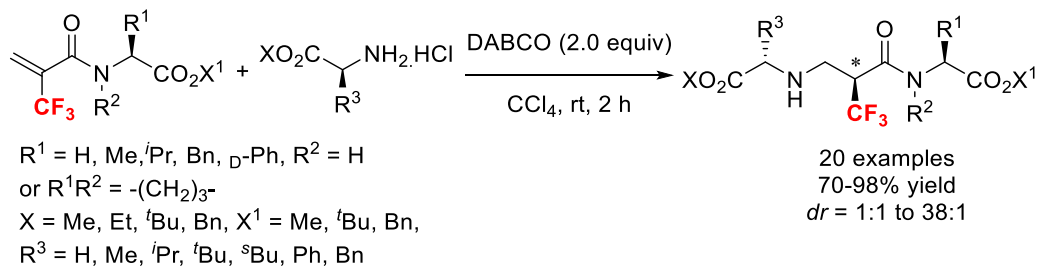
<sup>60</sup> Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2060-2063.

<sup>61</sup> Volonterio, A.; Chiva, G.; Fustero, S.; Piera, J.; Sanchez Rosello, M.; Sani, M.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 7019-7022.

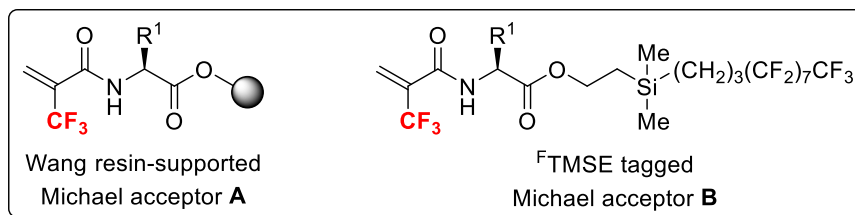
<sup>62</sup> Fustero, S.; Garcia Sancho, A.; Chiva, G.; Sanz-Cervera, J. F.; del Pozo, C.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 3299-3302.

<sup>63</sup> Fustero, S.; Chiva, G.; Piera, J.; Volonterio, A.; Zanda, M.; Gonzalez, J.; Ramallal, A. M. *Chem. Eur. J.* **2007**, *13*, 8530-8542.

<sup>64</sup> Fustero, S.; Chiva, G.; Piera, J.; Sanz-Cervera, J. F.; Volonterio, A.; Zanda, M.; Ramirez de Arellano, C. *J. Org. Chem.* **2009**, *74*, 3122-3132.



**Scheme 31** The addition of  $\alpha$ -amino ester to  $\alpha$ -CF<sub>3</sub>-acrylamides



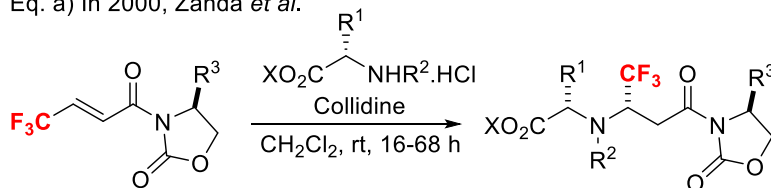
**Figure 10** Structures of two Michael acceptors

Like the  $\alpha$ -CF<sub>3</sub>-acrylamides, the modification of the peptide backbone could also start from the  $\beta$ -CF<sub>3</sub>-acrylamides. In 2000, Zanda and co-workers exploited the asymmetric conjugate additions of chiral  $\alpha$ -amino esters to  $\beta$ -CF<sub>3</sub>-acrylamide acceptors. Several partially modified  $\Psi$  [NHCH(CF<sub>3</sub>)] retropeptides were prepared as possible mimics of the usual  $\Psi$  (NHCO) retropeptides.<sup>65</sup> These retropeptides containing a  $\Psi$  [NHCH(CF<sub>3</sub>)] unit were produced in nearly quantitative yields and moderate to good diastereoselectivities, the latter being with the bulkiness of  $\gamma$ -amino ester side-chain R<sup>1</sup> (**Scheme 32**, Eq. a). Subsequently, a solid-phase synthesis of the partially modified retro- $\Psi$  [NHCH(CF<sub>3</sub>)] peptides was also developed with the reaction between resin-bound  $\alpha$ -amino hydroxamate (derived from Wang resin) and the same  $\beta$ -CF<sub>3</sub>-acrylamide Michael acceptor. Almost no diastereocontrol was obtained in this case (**Scheme 32**, Eq. b).<sup>66</sup> Later, this strategy was applied to the design of a novel matrix metalloprotease (MMP) inhibitor (**Figure 11**).<sup>67</sup>

<sup>65</sup> Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827-1830.

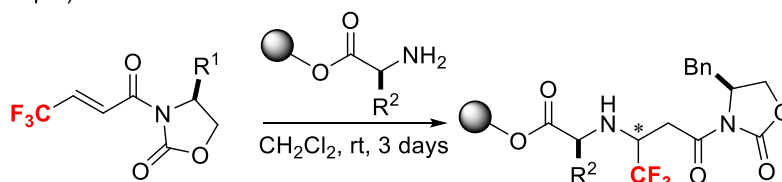
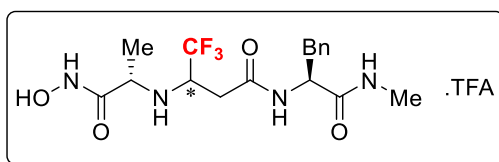
<sup>66</sup> (a) Volonterio, A.; Bravo, P.; Moussier, N.; Zanda, M. *Tetrahedron Lett.* **2000**, *41*, 6517-6521. (b) Volonterio, A.; Bravo, P.; Zanda, M. *Tetrahedron Lett.* **2001**, *42*, 3141-3144.

<sup>67</sup> Volonterio, A.; Bellosta, S.; Bravo, P.; Canavesi, M.; Corradi, E.; Meille, Stefano V.; Monetti, M.; Moussier, N.; Zanda, M. *Eur. J. Org. Chem.* **2002**, *2002*, 428-438.

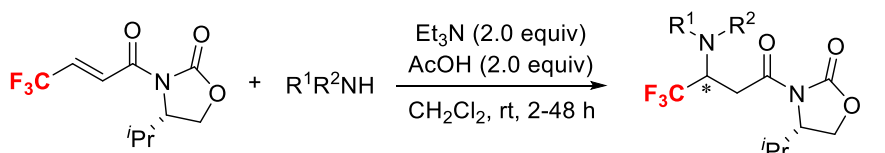
Eq. a) In 2000, Zanda *et al.*R<sup>1</sup> = H, Me, *i*Pr, *i*Bu; R<sup>2</sup> = Hor R<sup>1</sup>R<sup>2</sup> = (CH<sub>2</sub>)<sub>3</sub>R<sup>3</sup> = *i*Pr, Bn; X = Me, Et, Bn

10 examples

78-98% yield

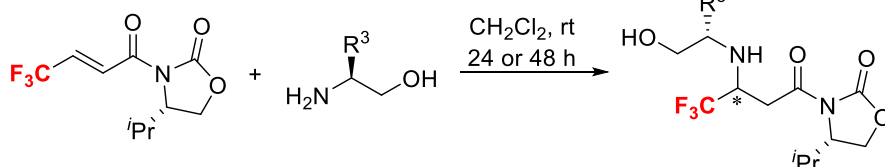
29-78% *de*Eq. b) In 2000 and 2001 Zanda *et al.***Scheme 32** The addition of  $\alpha$ -amino esters to  $\beta$ -CF<sub>3</sub>-acrylamide acceptor**Figure 11** Structure of (MMP) inhibitor

Zanda and co-workers also reported the addition of amines and amino alcohols to the chiral  $\beta$ -CF<sub>3</sub>-acrylamide in 2007.<sup>68</sup> The reactions occurred in good to excellent yields, but with a low diastereocontrol. (**Scheme 33**).

R<sup>1</sup> = Me, Cy, Bn, PhR<sup>2</sup> = H, Me

4 examples

67-90% yield

*dr* = 1:1 to 1.7:1R<sup>3</sup> = *i*Pr, Bn, Ph

3 examples

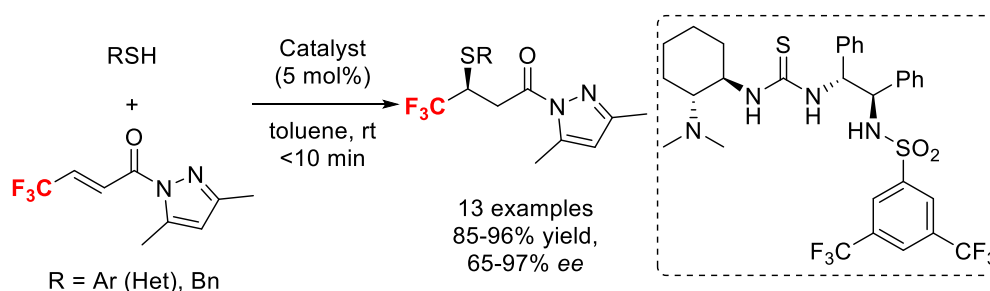
72-95% yield

*dr* = 1.3:1 to 1.5:1**Scheme 33** The addition of amines and amino alcohols to  $\beta$ -CF<sub>3</sub>-acrylamide

In 2012, Wang and co-workers reported an efficient sulfa-Michael addition on the  $\beta$ -

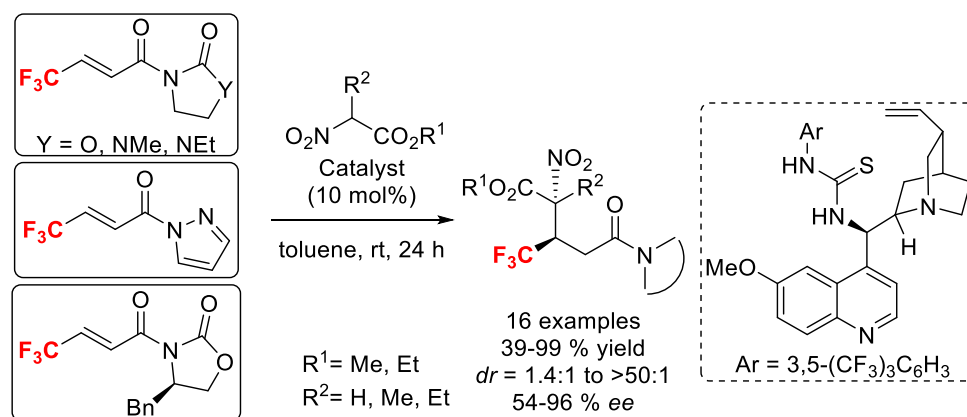
<sup>68</sup> Molteni, M.; Volonterio, A.; Fossati, G.; Lazzari, P.; Zanda, M. *Tetrahedron Lett.* **2007**, *48*, 589-593.

CF<sub>3</sub>-acrylamide to access the chiral CF<sub>3</sub>-building blocks. Excellent yields and good to excellent enantioselectivities of products were obtained in a very short time with a low catalyst loading (**Scheme 34**).<sup>69</sup> Another feature of this protocol is that all the products are solid due to the incorporation of pyrazole moiety, and could be easily obtained in enantioenriched form by simple crystallization of the crude.



**Scheme 34** The addition of thiols to  $\beta$ -CF<sub>3</sub>-acrylamide

In 2013, an enantioselective organocatalytic Michael addition of nitroalkanes to  $\beta$ -CF<sub>3</sub> acrylamides was described by Lu and co-workers.<sup>70</sup> Different  $\beta$ -CF<sub>3</sub>-acrylamides were chosen as the Michael acceptors, under the catalysis of Cinchona-alkaloid-thiourea, affording the corresponding adducts in moderate to excellent yields, diastereoselectivities, and enantioselectivities (**Scheme 35**).



**Scheme 35** The addition of nitroalkanes to  $\beta$ -CF<sub>3</sub>-acrylamide

### 1.4.1.5 Perfluorinated Michael acceptors

In 1994, Portella and coworkers reported a reaction using a  $\beta$ -perfluorinated  $\alpha$ -fluoro,  $\beta$ -fluoro-unsaturated ketone to prepare heterocycles by reaction with bis-

<sup>69</sup> Dong, X. Q.; Fang, X.; Tao, H. Y.; Zhou, X.; Wang, C. J. *Adv. Synth. Catal.* **2012**, 354, 1141-1147.

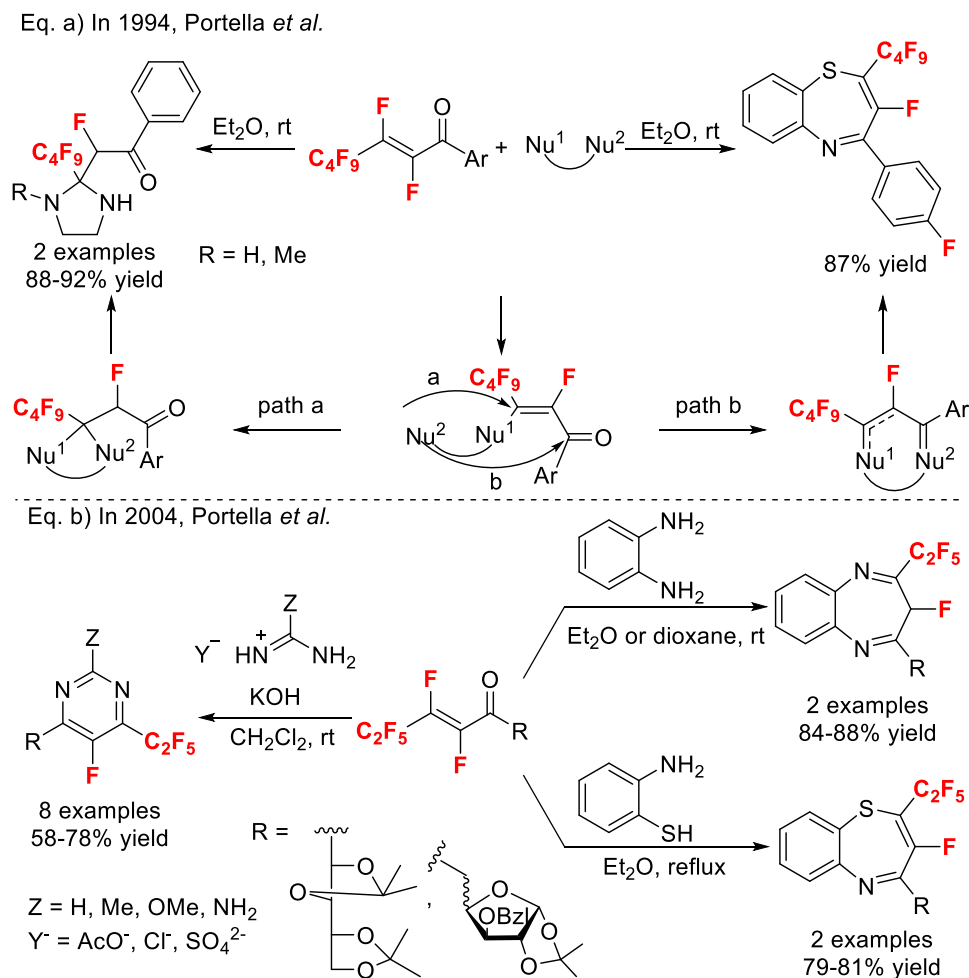
<sup>70</sup> Wen, L.; Yin, L.; Shen, Q.; Lu, L. *ACS Catal.* **2013**, 3, 502-506.

nucleophiles.<sup>71</sup> For this type of Michael acceptor, the bis-nucleophiles initial attack occurred at the  $\beta$ -carbon atom of the ketone with the formation of a carbanion at the  $\alpha$ -position, subsequently followed by the elimination of the fluoride ion present at the  $\beta$ -position. Then the intramolecular nucleophilic cyclization can take place in two directions, at the  $\beta$ -carbon (path a: Michael-type addition) or at the carbonyl carbon atom (path b: condensation). The use of a more rigid bis-nucleophile will inhibit the formation of the Michael-type product (path a) and favor the formation of condensation product (path b) (**Scheme 36**, Eq. a). This regioselectivity of cyclization has also been observed later when they reported the use of constrained nucleophiles, such as *o*-phenylenediamine, 2-amino-thiophenol or amidinium salts (**Scheme 36**, Eq. b).<sup>72</sup>

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<sup>71</sup> Dondy, B.; Doussot, P.; Iznaden, M.; Muzard, M.; Portella, C. *Tetrahedron Lett.* **1994**, *35*, 4357-4360.

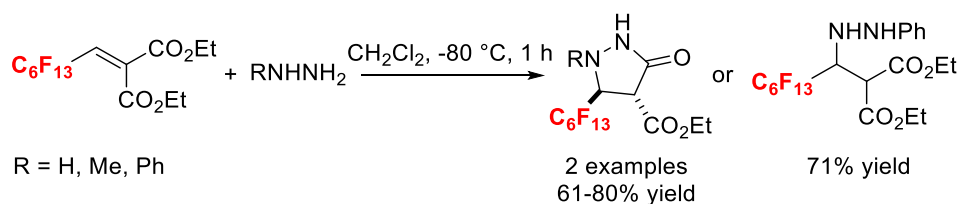
<sup>72</sup> Chanteau, F.; Didier, B.; Dondy, B.; Doussot, P.; Plantier-Royon, R.; Portella, C. *Eur. J. Org. Chem.* **2004**, *2004*, 1444-1454.



**Scheme 36** The addition of bis-nucleophiles to  $\alpha,\beta$ -difluoro- $\beta$ -perfluorinated ketones

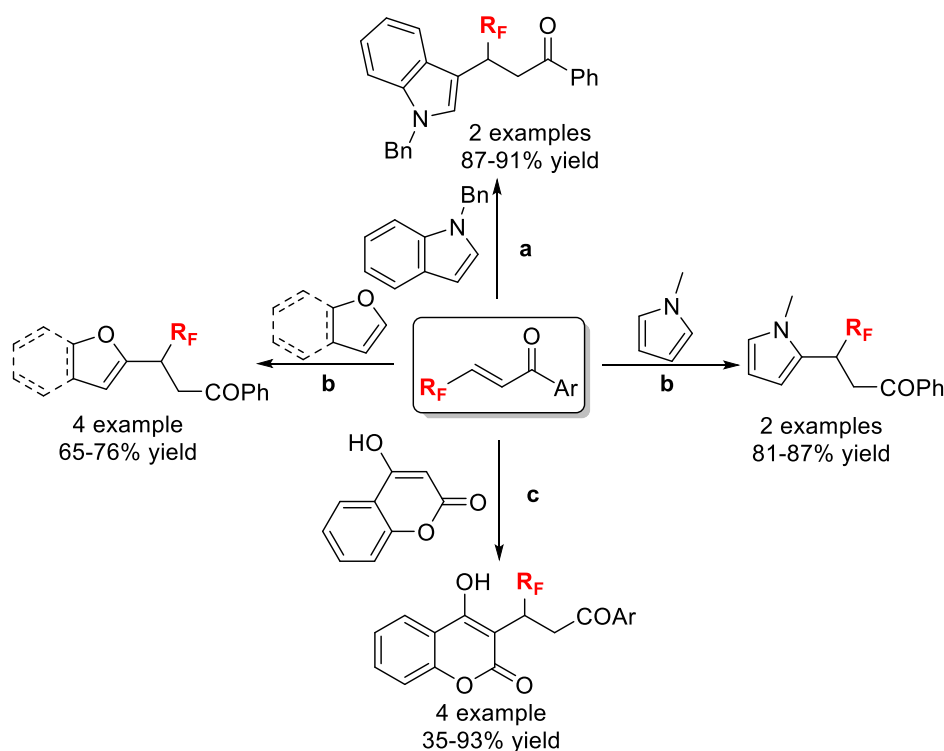
In 2011, Yamazaki and co-workers described the addition of hydrazines to  $\beta$ -perfluorinated methylene malonate.<sup>73</sup> This type of substrate was expected to be an excellent Michael acceptor due to three EWG substituents installed on the ethylene unit. The conjugate addition of hydrazine was very quick in CH<sub>2</sub>Cl<sub>2</sub>. The normal 1,4-adduct and the product of intramolecular cyclization after the initial 1,4-addition were obtained depending on the nature of hydrazines. The use of less nucleophilic phenylhydrazine only producing Michael adduct (**Scheme 37**).

<sup>73</sup> Aoki, S.; Kawasaki-Takasuka, T.; Yamazaki, T. *Tetrahedron* **2011**, *67*, 4845-4851.



**Scheme 37** The addition of hydrazines to  $\beta$ -perfluorinated dicarbonyl Michael acceptor

In the work described by Langlois and co-workers in 2011 that we already discussed, the Michael addition of various electron-rich O- and N- containing heterocycles has already been done to  $\beta$ -CF<sub>2</sub>Cl and  $\beta$ -C<sub>2</sub>F<sub>5</sub> enone.<sup>52</sup> The corresponding adducts have been obtained in moderate to good yields (**Scheme 38**).

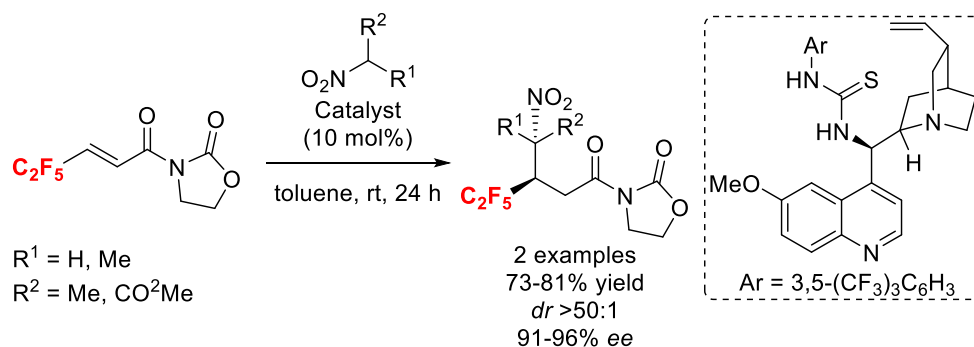


$R_F = \text{CF}_2\text{Cl}, \text{C}_2\text{F}_5$

a: Cu(OTf)<sub>2</sub> (0.1 equiv); b: BF<sub>3</sub>·Et<sub>2</sub>O (0.1 equiv), c: DBU (1.0 equiv)

**Scheme 38** The addition of electron-rich heterocycles to  $\beta$ -perfluorinated enones

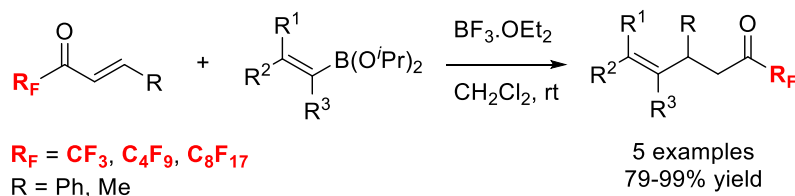
Similarly, in the Michael addition to  $\beta$ -CF<sub>3</sub>-acrylamide reported by Lu in 2013 (see **Scheme 35**), the  $\beta$ -C<sub>2</sub>F<sub>5</sub>-acrylamide could also serve as a good Michael acceptor. Under the optimized conditions, the adducts were obtained as good as those from  $\beta$ -CF<sub>3</sub>-acrylamide, *i.e.* in good yields with high diastereo- and enantioselectivities (**Scheme 39**).<sup>70</sup>



**Scheme 39** The adducts obtained from  $\beta$ - $\text{C}_2\text{F}_5$ -acrylamides

#### 1.4.1.6 Other Fluorinated $\alpha,\beta$ -unsaturated carbonyl Michael acceptors

Another type of fluorinated  $\alpha,\beta$ -unsaturated carbonyl compound where the fluorinated moieties were located in carbonyl group, instead of in the  $\alpha$ - or  $\beta$ -position of the alkene, was also used in Michael addition reaction. As early as 1993, in the work of Suzuki and co-workers, the addition of alkenyldiisopropoxyboranes to these substrates could occur smoothly, and the desired products were obtained in good yields without the formation of 1,2-adducts (**Scheme 40**).<sup>47</sup>

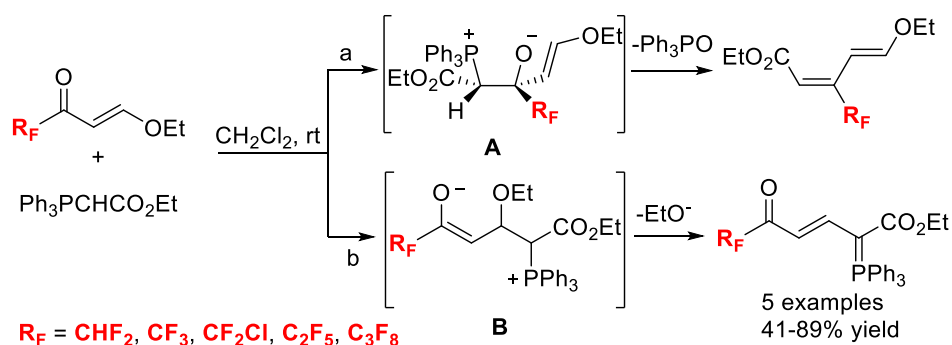


**Scheme 40** The addition of boranes

In 2007, Kondratov and co-workers reported the reaction between the ethyl triphenylphosphoranylidenacetate ( $\text{Ph}_3\text{PCHCO}_2\text{Et}$ ) and  $\beta$ -alkoxyvinyl polyfluoroalkyl ketones (fluorinated  $\beta$ -ketoaldehyde derivatives). The reaction offered a mixture of two products, which can be easily separated, in high overall yields.<sup>74</sup> Surprisingly, the unusual major process is an initial ylide addition to  $\beta$ -carbon (intermediate B), instead of ylide addition to carbonyl moiety (intermediate A) of the enone, with the subsequent  $\text{EtO}^-$  elimination to form Michael adducts (**Scheme 41**). Worthy of note that the increase of  $R_F$  group bulkiness favored the formation of the Michael adduct.

<sup>74</sup> Kondratov, I. S.; Gerus, I. I.; Furmanova, M. V.; Vdovenko, S. I.; Kukhar, V. P. *Tetrahedron* **2007**, *63*, 7246-7255.



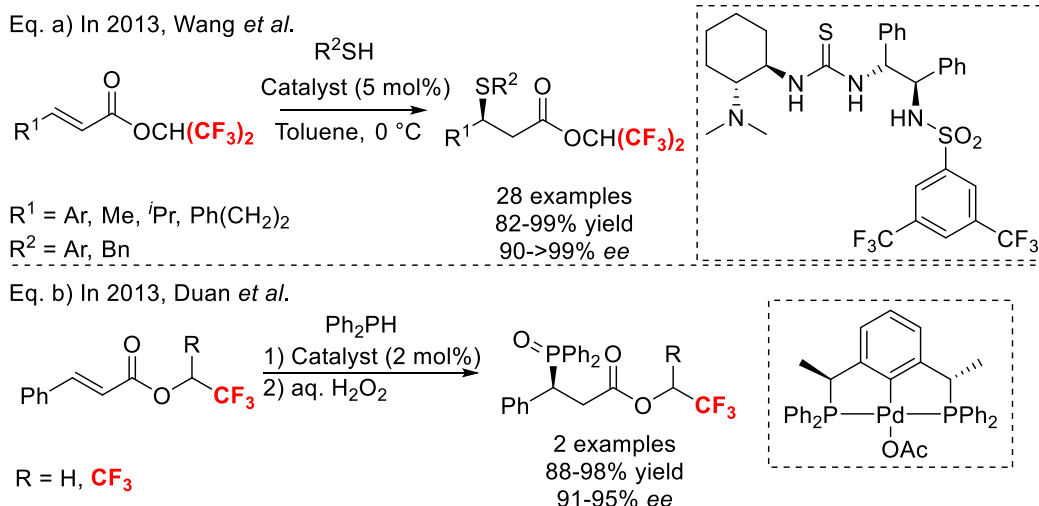


**Scheme 41** The addition of  $\text{Ph}_3\text{PCHCO}_2\text{Et}$  to fluorinated  $\beta$ -ketoaldehyde derivatives

In 2013, an organocatalytic asymmetric sulfa-Michael addition reaction on hexafluoroisopropyl  $\alpha,\beta$ -unsaturated esters has been developed by Wang and co-workers. Introducing the two- $\text{CF}_3$  group on the ester moiety is crucial to increase the electrophilicity of  $\alpha,\beta$ -unsaturated ester as Michael acceptor as well as to hinder the carbonyl moiety. The catalytic system performed well over a broad substrate scope with excellent yields and enantioselectivities (**Scheme 42**, Eq. a).<sup>75</sup> In the same year, Duan and co-workers described an asymmetric phospho-Michael addition reaction of diphenylphosphine to the similar substrates.<sup>76</sup> Under the catalysis of a chiral palladium complex catalyst, the reaction of 2,2,2-trifluoroethyl cinnamate furnished the adduct with good yield and enantioselectivity. More electrophilic Michael acceptor 1,1,1,3,3,3-hexafluoroisopropyl cinnamate gave better yield and enantioselectivity (**Scheme 42**, Eq. b).

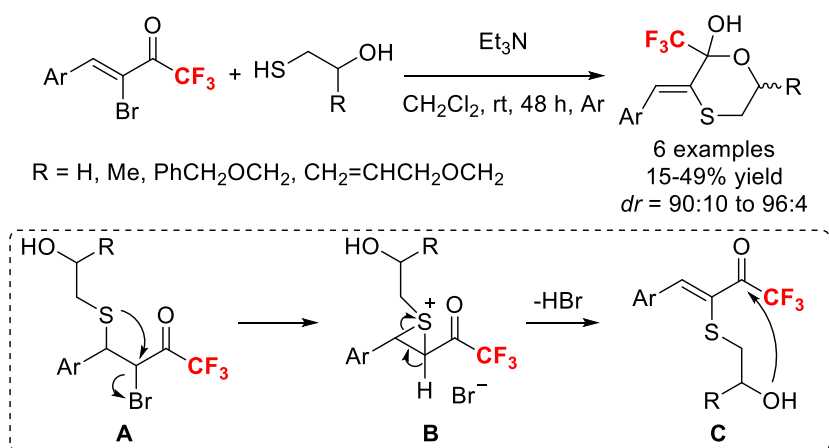
<sup>75</sup> Fang, X.; Li, J.; Wang, C. J. *Org. Lett.* **2013**, *15*, 3448-3451.

<sup>76</sup> Du, D.; Lin, Z. Q.; Lu, J. Z.; Li, C.; Duan, W. L. *Asian J. Org. Chem.* **2013**, *2*, 392-394.



**Scheme 42** The addition of thiols to hexafluoroisopropyl  $\alpha,\beta$ -unsaturated esters

In 2018, a protocol for the synthesis of *O, S*-containing heterocycles has been reported. The desired products were obtained by the sequentially sulfa-Michael addition and heterocyclization starting from the  $\beta$ -fluorinated  $\alpha$ -bromo enones (**Scheme 43**).<sup>77</sup> A proposed mechanism showed that the initial step of this reaction sequence was a sulfa-Michael addition to give **A**, which easily underwent intramolecular nucleophilic substitution to give sulfonium intermediate **B**. Then, the intermediate **B** underwent deprotonation and ring-opening to give the intermediate **C** which could form the desired heterocycle product by an intramolecular acetalization (**Scheme 43**).



**Scheme 43** The addition of  $\beta$ -Mercaptoalcohols to fluorinated  $\alpha$ -bromo enones

<sup>77</sup> Obijalska, E.; Pawelec, M.; Mlostoń, G.; Capperucci, A.; Tanini, D.; Heimgartner, H. *Eur. J. Org. Chem.* **2018**, 2018, 3716-3723.

## 1.4.2 Fluorinated nitroalkene Michael acceptors

The fluorinated nitroalkene represents a highly reactive, easily handled fluorinated building block, which is very promising in the synthesis of functionalized organofluorinated compounds.<sup>78</sup> The (*E*)-3,3,3-trifluoro-1-nitropropene is the most common substrate having a structure of a double bond bearing both CF<sub>3</sub>- and NO<sub>2</sub>-groups with (*E*)-configuration. The fluorinated nitroalkenes have been used in Diels-Alder,<sup>79</sup> 1,3-dipolar,<sup>80</sup> Friedel-Crafts<sup>81</sup> reactions. There were also some reports, discussed hereafter, using this substrate as Michael acceptor.

In 2003 and 2009, Zanda and co-workers described the modification of the peptide backbone with a stereogenic [CH(CF<sub>3</sub>)NH] unit.<sup>82</sup> The key step was an aza-Michael reaction between (*E*)-3,3,3-trifluoro-1-nitropropene and a series of chiral  $\alpha$ -amino acid esters delivering two diastereoisomers which could be separated in pure form by flash chromatography. The stereoselectivity was strongly dependent on several experimental parameters, like the solvent, the bulkiness of the nucleophile, and the base (**Scheme 44**, Eq. a). Later, Zanda and co-workers also synthesized new peptide mimics featuring [CH(R<sub>F</sub>)NH] units as peptide-bond surrogates, with different degrees of fluorination.<sup>83</sup> The diastereoselectivity of this process was more influenced by the electronegativity, rather than by the bulkiness of R<sub>F</sub> group of the fluorinated nitroalkenes (**Scheme 44**, Eq. b). A possible transition state for the formation of the major diastereomers was proposed (**Figure 12**). The (*E*)-nitroalkenes reacted from *Re* face of the  $\alpha$ -amino acid ester and a dual hydrogen bonding exists between the upward hydrogen of amino group with carbonyl oxygen

<sup>78</sup> (a) Korotaev, V. Y.; Kutyashev, I. B.; Sosnovskikh, V. Y. *Heteroat. Chem.* **2005**, *16*, 492-496. (b) Massolo, E.; Benaglia, M.; Orlandi, M.; Rossi, S.; Celentano, G. *Chem. Eur. J.* **2015**, *21*, 3589-3595. (c) Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia, F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2015**, *17*, 3826-3829. (d) Zhu, Y.; Li, B.; Wang, C.; Dong, Z.; Zhong, X.; Wang, K.; Yan, W.; Wang, R. *Org. Biomol. Chem.* **2017**, *15*, 4544-4547.

<sup>79</sup> Klenz, O.; Evers, R.; Miethchen, R.; Michalik, M. *J. Fluorine Chem.* **1997**, *81*, 205-210.

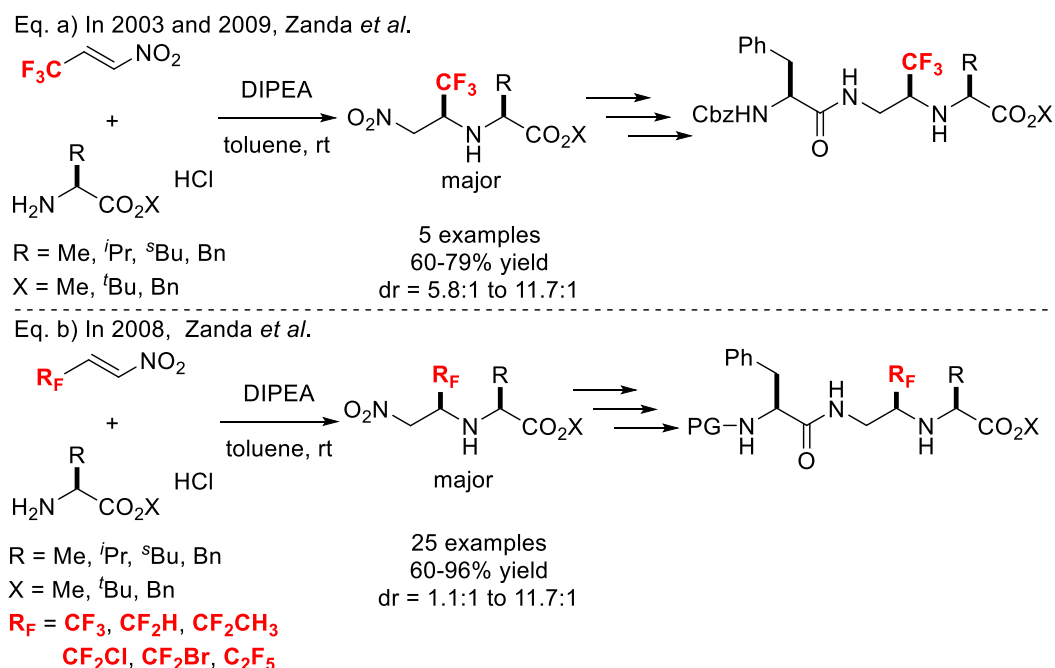
<sup>80</sup> Tanaka, K.; Mori, T.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 263-268.

<sup>81</sup> Iwata, S.; Ishiguro, Y.; Utsugi, M.; Mitsuhashi, K.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2432-2435.

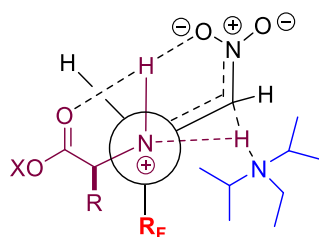
<sup>82</sup> (a) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887-3890. (b) Molteni, M.; Bellucci, M. C.; Bigotti, S.; Mazzini, S.; Volonterio, A.; Zanda, M. *Org. Biomol. Chem.* **2009**, *7*, 2286-2296.

<sup>83</sup> (a) Bigotti, S.; Meille, S. V.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2008**, *129*, 767-774. (b) Zanda, M.; Volonterio, A.; Bigotti, S. *Synlett* **2008**, *2008*, 958-962.

and the nitro oxygen respectively, transferring the hydrogen from the amino group to the  $\alpha$ -position of nitroalkene with the assistance of the DIPEA.



**Scheme 44** The addition of chiral  $\alpha$ -amino acid esters to fluorinated nitroalkenes



**Figure 12** The possible transition state leading to the major diastereomers

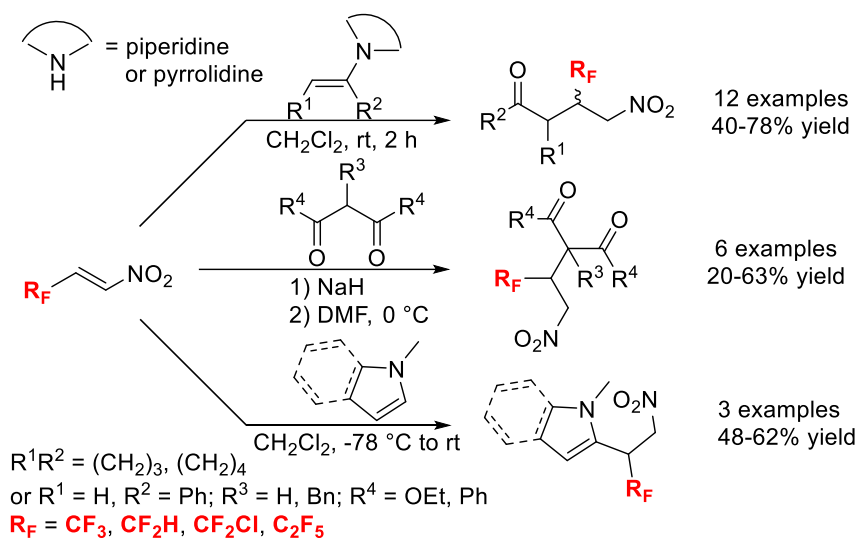
Then, the same authors reported Michael addition reactions of ketone-derived enamines, methylene active compounds, and methylated pyrroles/indoles to (*E*)-fluorinated nitroalkenes, providing the corresponding adducts in moderate to good yields (**Scheme 45**, Eq. a).<sup>84</sup> In 2014, Liu and co-workers also investigated a Michael addition reaction of 1,3-dicarbonyl compounds to similar substrates.<sup>85</sup> The cinchona alkaloid catalytic system showed high efficiency with a broad scope substrate and the desired products were generally obtained in good to high yields, high diastereo-

<sup>84</sup> (a) Molteni, M.; Zanda, M. *Lett. Org. Chem.* **2005**, *2*, 566-568. (b) Molteni, M.; Consonni, R.; Giovenzana, T.; Malpezzi, L.; Zanda, M. *J. Fluorine Chem.* **2006**, *127*, 901-908.

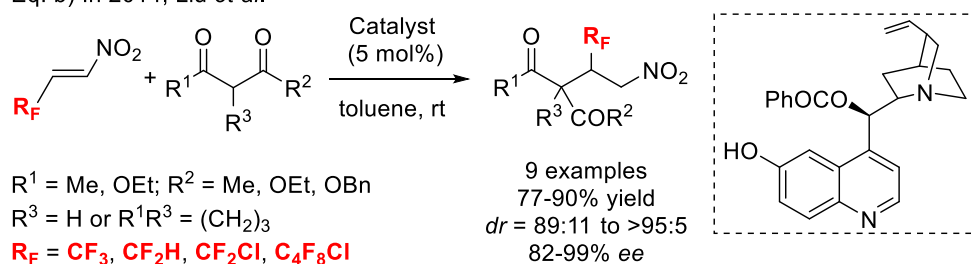
<sup>85</sup> Zhao, Y.; Wang, X. J.; Lin, Y.; Cai, C. X.; Liu, J. T. *Tetrahedron* **2014**, *70*, 2523-2528.

and enantioselectivities under mild conditions (**Scheme 45**, Eq. b).

Eq. a) In 2005 and 2006, Zanda *et al.*



Eq. b) In 2014, Liu *et al.*

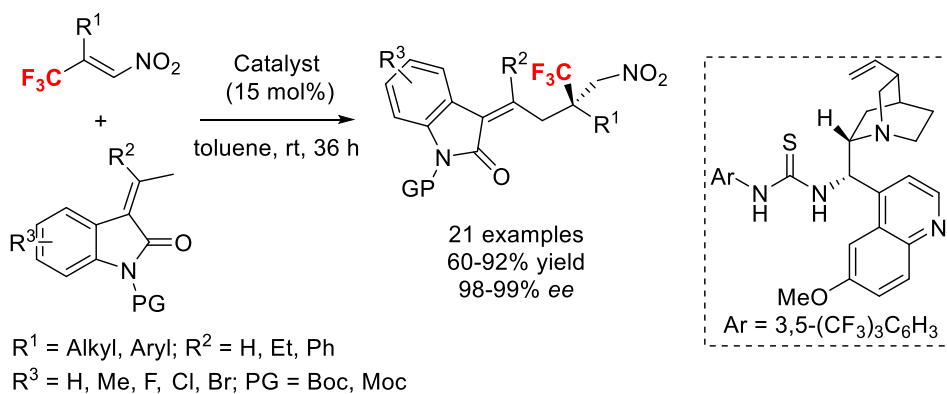
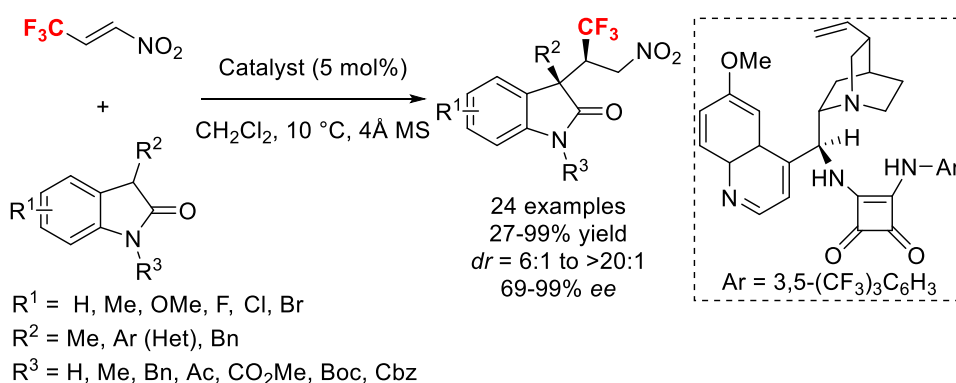


**Scheme 45** The addition of C-nucleophiles to (*E*)-3- $\text{R}_F$ -1-nitropropenes

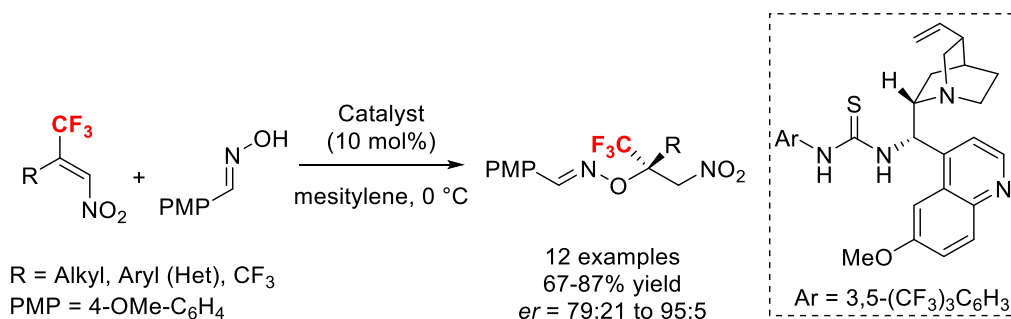
In 2014, a highly enantioselective Michael addition of oxindole derivatives to fluorinated nitroalkenes has been described by Wang and co-workers.<sup>86</sup> A series of biologically important chiral oxindoles, bearing a  $\text{CF}_3$  group at the newly formed quaternary chiral center, were obtained in good yields with excellent enantioselectivities (**Scheme 46**, Eq. a). The same year, Shi and co-workers described a similar Michael addition between 3-substituted oxindoles and trifluoromethylated nitroolefins catalyzed by a quinine-derived squaramide. The corresponding adducts bore a trifluoromethylated chiral carbon center and an adjacent quaternary stereocenter at the C3 position of the oxindoles (**Scheme 46**, Eq. b).<sup>87</sup>

<sup>86</sup> Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394-1397.

<sup>87</sup> Zhao, M. X.; Ji, F. H.; Zhao, X. L.; Han, Z. Z.; Shi, M. *Eur. J. Org. Chem.* **2014**, *2014*, 644-653.

Eq. a) In 2014, Wang *et al.*Eq. b) In 2014, Shi *et al.***Scheme 46** The addition of oxindoles to trifluoromethylated nitroolefins

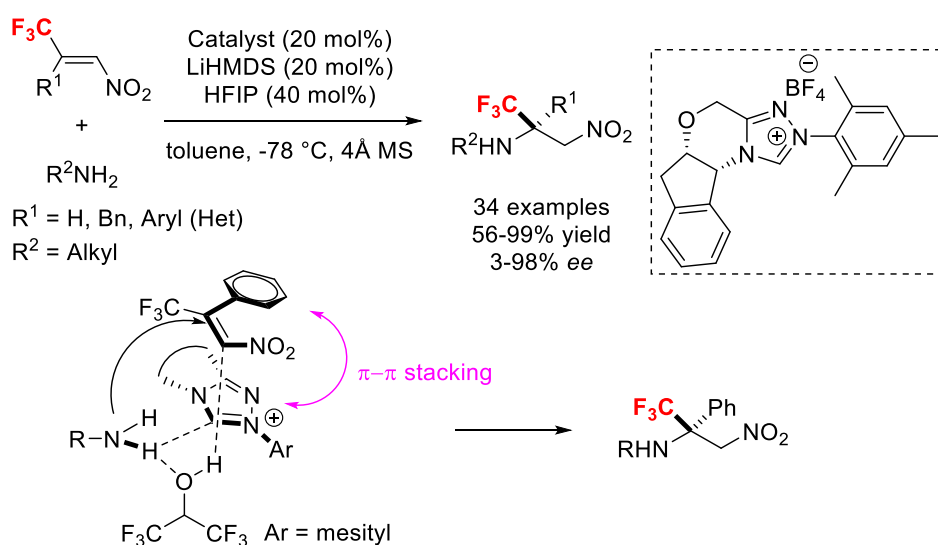
Some additional reactions of other nucleophiles to trifluoromethylated nitroolefins have also been reported. For example, in 2014, Xiao and co-workers developed a cinchona alkaloid-based thiourea catalyzed oxa-Michael addition of oximes to  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes.<sup>88</sup> A variety of oxime ethers with a trifluoromethylated chiral center were obtained in good yields and high enantioselectivities (**Scheme 47**).

**Scheme 47** The addition of oximes to  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes

In 2015, a chiral *N*-heterocyclic carbene (NHC) promoted aza-Michael reaction

<sup>88</sup> Liu, F. L.; Chen, J. R.; Feng, B.; Hu, X. Q.; Ye, L. H.; Lu, L. Q.; Xiao, W. J. *Org. Biomol. Chem.* **2014**, *12*, 1057-1060.

between primary alkyl amines and  $\beta$ -CF<sub>3</sub>- $\beta$ -aryl nitroalkenes has been developed (**Scheme 48**).<sup>89</sup> In this reaction, a dual role of the *NHC* was proposed: the alkyl amines cannot be deprotonated by *NHC* due to their high  $pK_a$  values, thus enhancing the nucleophilicity of N atom through the concurrent H-bonding between amines with *NHC* and HFIP. Meanwhile, a weak  $\pi$ - $\pi$  interaction between the  $\beta$ -aryl substituent and positively charged *NHC* heterocycle was suggested by linear free-energy relationship (LFER) study, which might be an explanation for the poor enantioselectivities when  $R^1 = \text{H}$  or Bn.



**Scheme 48** The addition of primary alkyl amines to  $\beta$ -CF<sub>3</sub>- $\beta$ -aryl nitroalkenes

### 1.4.3 Fluorinated sulfoxide and sulfone Michael acceptors

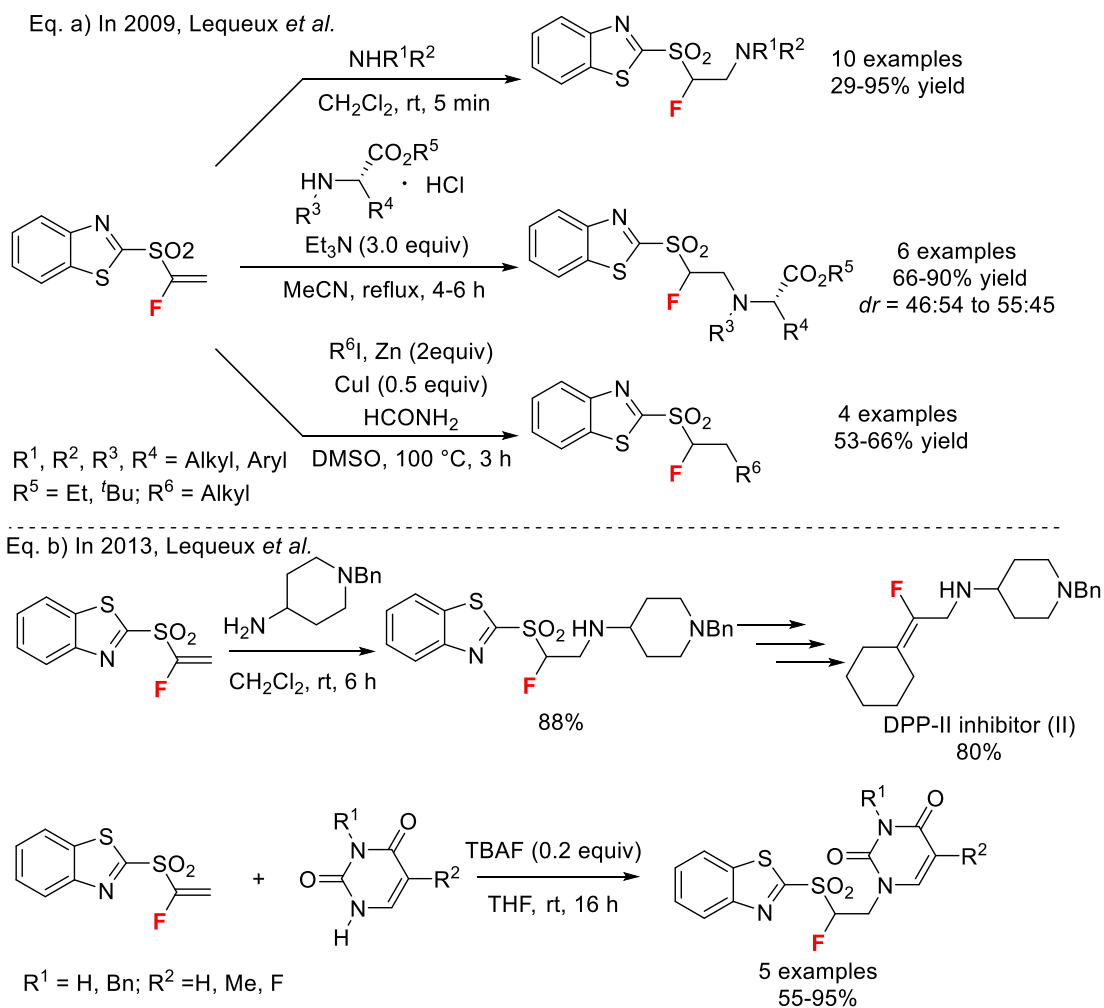
Because of the strong inductive electron-withdrawing effect of the sulfonyl or sulfinyl, a double bond with such moieties could be considered as a suitable Michael acceptor.<sup>90</sup> Meanwhile, some fluorinated Michael acceptors containing the sulfoxide or sulfone group have been investigated, providing a straightforward route to many building blocks bearing both the sulfur atom and a fluorinated moiety.

In 2009, Lequeux and co-workers described the synthesis of a fluorovinyl sulfone by elimination or HWE reactions. This fluorovinyl sulfone could be functionalized by the

<sup>89</sup> Wang, L.; Chen, J.; Huang, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 15414-15418.

<sup>90</sup> (a) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399-7400. (b) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793-814.

aza-Michael addition reaction of aliphatic, aromatic amines, and amino acid alkyl esters. Additionally, some fluoroalkylsulfones were prepared from alkyl iodides in the presence of Zn/CuI (**Scheme 49**, Eq. a).<sup>91</sup> In another report, the same authors described an aza-Michael addition reaction of 1-benzylpiperidin-4-amine to fluorovinylsulfone to prepare DPP-II inhibitor (II), they also investigated the conjugate addition of nucleic bases onto this fluorovinylsulfone (**Scheme 49**, Eq. b).<sup>92</sup>



**Scheme 49** The addition of nucleophiles to fluorovinylsulfone

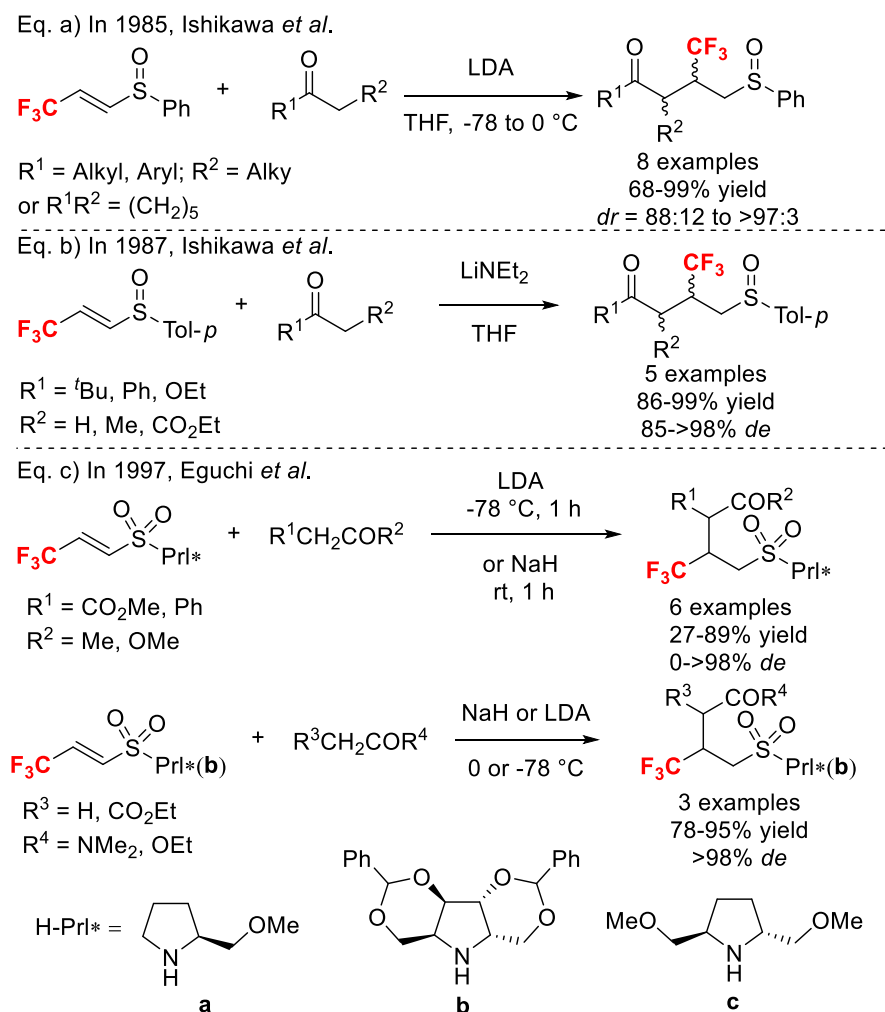
In early reports from Ichikawa and co-workers,  $\beta$ -trifluoromethyl vinyl sulfoxide has been treated with a variety of lithium enolates and produced the corresponding adducts in high yields with excellent diastereoselectivities (**Scheme 50**, Eq. a and

<sup>91</sup> Calata, C.; Pfund, E.; Lequeux, T. *J. Org. Chem.* **2009**, *74*, 9399-9405.

<sup>92</sup> Prunier, A.; Calata, C.; Legros, J.; Maddaluno, J.; Pfund, E.; Lequeux, T. *J. Org. Chem.* **2013**, *78*, 8083-8097.



b).<sup>93</sup> Then, in 1997, Eguchi and co-workers reported a similar addition of enolates to chiral  $\beta$ -trifluoromethyl vinyl sulfonamides.<sup>94</sup> The corresponding products were obtained in moderate diastereoselectivities except for the one obtained with tetrasubstituted bulky pyrrolidine sulfonamide (**b**) (>98% *de*). Based on these results, the reaction of some other enolates with chiral sulfonamide **b** was performed and all the products were obtained in good to high yields with excellent diastereoselectivities (**Scheme 50**, Eq. c).



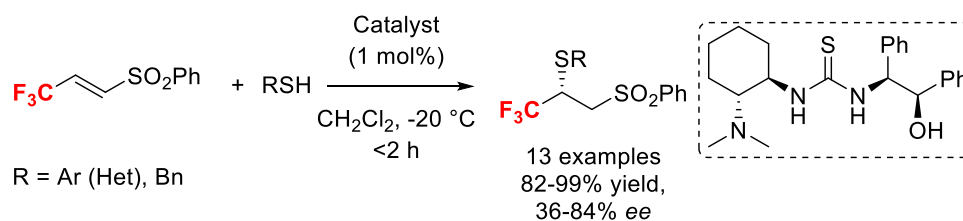
**Scheme 50** The addition of enolates to fluorinated sulfone derivatives

Furthermore, in 2013, Wang and co-workers reported the first asymmetric sulfa-Michael addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone. This

<sup>93</sup> (a) Yamazaki, T.; Ishikawa, N. *Chem. Lett.* **1985**, *14*, 889-892. (b) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *Journal of the Chemical Society, Chemical Communications* **1987**, 1340-1342.

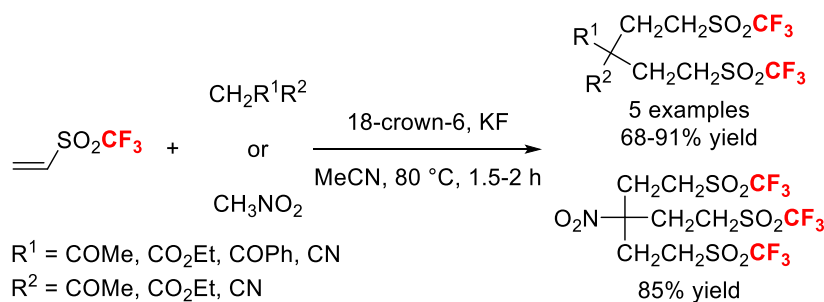
<sup>94</sup> Tsuge, H.; Takumi, K.; Nagai, T.; Okano, T.; Eguchi, S.; Kimoto, H. *Tetrahedron* **1997**, *53*, 823-838.

reaction proceeded with 1 mol% of bifunctional amine-thiourea catalyst in a short time. The desired sulfa-Michael adducts, bearing a CF<sub>3</sub>-group and a sulfur atom at the chiral center, were obtained in high yields and moderate to good enantioselectivities (**Scheme 51**).<sup>95</sup>



**Scheme 51** The addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone

There were also some examples of fluorinated sulfoxides/sulfones where the fluorinated moiety was beared by the sulfur atom. In 1982, Popov and co-workers reported the Michael addition of organic compounds with active methylene derivatives (malonates,  $\beta$ -diketones, nitromethane *et al.*) to trifluoromethyl vinyl sulfone.<sup>96</sup> Due to the powerful electronegative inductive effect of the CF<sub>3</sub>SO<sub>2</sub>, the nucleophiles occurred double addition or triple addition in the presence of KF and 18-crown-6-ether, furnished the corresponding products in good yields (**Scheme 52**).



**Scheme 52** The double or triple addition to trifluoromethyl vinyl sulfone

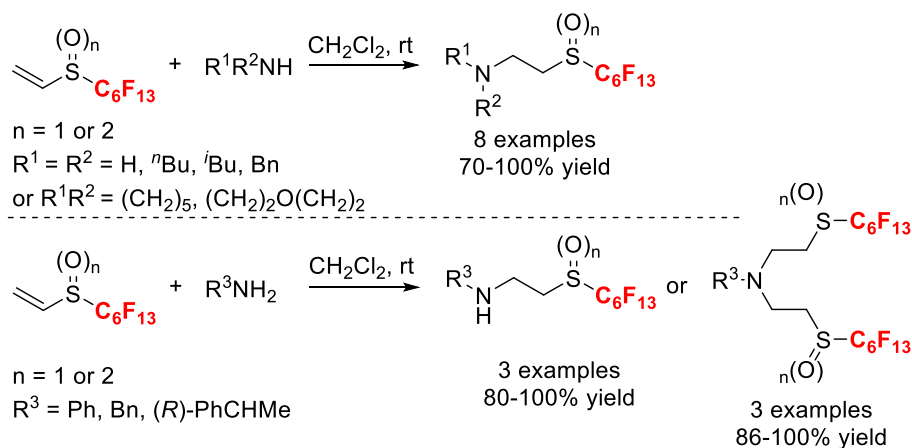
More recently, in the Michael addition of amines to perfluoroalkylated sulfoxides and sulfones developed by Magnier and co-workers, some examples of double addition were also described.<sup>97</sup> The secondary amines only occurred mono addition, affording the corresponding product in good to high yields. When the primary

<sup>95</sup> Fang, X.; Dong, X. Q.; Liu, Y. Y.; Wang, C. J. *Tetrahedron Lett.* **2013**, *54*, 4509-4511.

<sup>96</sup> Haas, A.; Popov, V. J. *Fluorine Chem.* **1982**, *20*, 99-105.

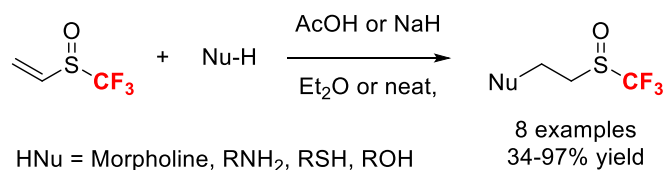
<sup>97</sup> Magnier-Bouvier, C.; Blazewski, J. C.; Larpent, C.; Magnier, E. *Tetrahedron Lett.* **2006**, *47*, 9121-9124.

amines were used as the nucleophile, there were some different results. Poor nucleophilic aniline only produced monoadduct regardless of the equivalent of Michael acceptor, whereas more nucleophilic benzyl amine and (*R*)-1-phenylethan-1-amine produced bis-adducts when the reaction was carried out with an excess of perfluoroalkylated sulfoxide and sulfone (**Scheme 53**).



**Scheme 53** The addition of amines to perfluoroalkylated sulfoxides and sulfones

In 2010, Sokolenko and co-workers reported a novel efficient approach to synthesize trifluoromethyl vinyl sulfoxide from 2-mercaptoethanol and trifluoromethyl iodide. Furthermore, the Michael addition of different nucleophiles (*S*-, *O*-, *N*-) was demonstrated, providing a series of compounds containing the (trifluoromethylsulfinyl)ethyl moiety in moderate to good yields (**Scheme 54**).<sup>98</sup>

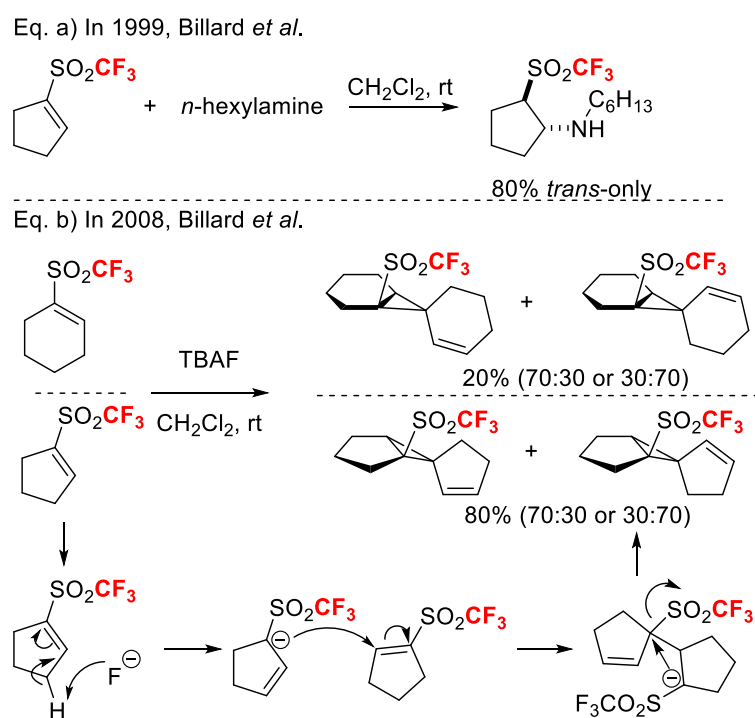


**Scheme 54** The addition of different nucleophiles to trifluoromethyl vinyl sulfoxide

The carbocycles bearing a trifluoromethyl sulfone are also constituted potentially valuable building blocks for further syntheses. In 1999, Billard and co-workers reported a Michael addition of *n*-hexylamine to a pentacyclic trifluoromethyl vinylsulfone, which occurred in a completely diastereoselective fashion and affording

<sup>98</sup> Sokolenko, L.; Maletina, I.; Yagupolskii, L.; Yagupolskii, Y. *Synlett* **2010**, 2010, 2075-2078.

only the *trans*-adduct (**Scheme 55**, Eq. a).<sup>99</sup> Then, this kind of substrates has been further studied in 2008 by the same group. Surprisingly, instead of the expected  $\beta$ -fluoro-adduct, two inseparable diastereoisomers in a 70 :30 ratio were obtained in good yield when the substrate was reacted in the presence of TBAF. The same reaction occurred starting from hexacyclic trifluoromethyl sulfone, albeit in a low yield. Owing to the fact that the  $-\text{SO}_2\text{CF}_3$  is a strong EWG as well as a good leaving group and the fluoride anion can behave as a base, a feasible mechanism was proposed (**Scheme 55**, Eq. b).<sup>100</sup>



**Scheme 55** The addition to cyclic trifluoromethyl sulfones

## 1.5 Objectives

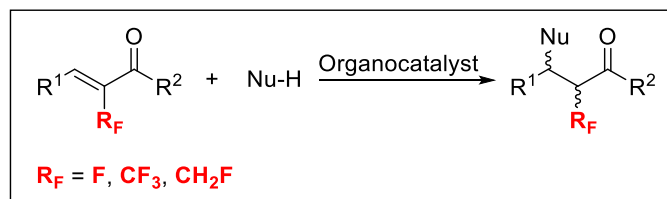
In summary, some fluorinated substrates were used as Michael acceptors and showed a great potential to access more complex fluorinated compounds from simple and readily available starting materials.

In my Ph.D. thesis, we aimed at developing new methodologies for the construction of highly diastereoselective (enantioselective) fluorinated compounds by the

<sup>99</sup> Billard, T.; Langlois, B. R. *Tetrahedron* **1999**, *55*, 8065-8074.

<sup>100</sup> Billard, T.; Langlois, B. R.; Essers, M.; Haufe, G. *Collect. Czech. Chem. Commun.* **2008**, *73*, 1814-1824.

organocatalytic Michael addition of different nucleophiles to  $\alpha$ -fluorinated  $\alpha,\beta$ -unsaturated carbonyl substrates (**Scheme 56**).



**Scheme 56** General objectives

In the following second chapter, we will describe the sulfa-Michael addition to polysubstituted  $\alpha$ -fluoroacrylates. The latter is easily accessible and only very few Michael addition has been developed with it. In the third chapter, we will present the first phospho-Michael addition on  $\alpha$ -trifluoromethylacrylates. Finally, our last chapter will present the various reactions attempted to enlarge the scope of Michael addition reactions with our  $\alpha$ -fluorinated Michael acceptors.

# Chapter 2

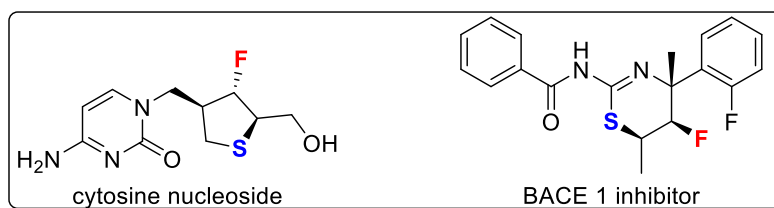
## Sulfa-Michael Addition of Thiophenols to $\alpha$ -Fluoro- $\alpha,\beta$ -Unsaturated Esters



## 2. Sulfa-Michael addition (SMA) of thiophenols to $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

### 2.1 State of the art

Sulfur-containing compounds are widely found in natural and non-natural biologically active products, as well as pharmaceutically important drugs.<sup>101</sup> Meanwhile, as mentioned at the beginning of the thesis, the incorporation of one or several fluorine atoms into an organic molecular structure can modulate lipophilicity, metabolic stability, and acidity, for instance,<sup>4</sup> which are very important properties in drug design.<sup>6d</sup> Thus, with the goal of designing potential new drugs, introducing fluorine atom or fluorinated moiety into sulfur-containing compounds might be feasible. As expected, numerous biologically active compounds contain both a sulfur atom and a fluorine atom (**Figure 13**).<sup>102</sup> Therefore, the development of simple and convenient strategies for the incorporation of both a sulfur atom and a fluorine atom into molecules is highly valuable. Among the various approaches to access the C-S bond, the sulfa-Michael addition (SMA) reaction represents a typical and convenient method. Similar to all other Michael addition reactions, the SMA reaction has the potential to construct two adjacent stereogenic carbon centers in one synthetic step, with an appropriate acceptor under suitable conditions.



**Figure 13** Biologically active compounds containing a sulfur atom and a fluorine atom at two

<sup>101</sup> (a) Nudelman, A. *Chemistry of Optically Active Sulfur Compounds*, Gordon and Breach, New York, **1984**. (b) Damani, L. A. *Sulphur-Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry and Toxicology: Metabolism and Pharmacokinetics of Sulphur-Containing Drugs*, Horwood, E. **1989**. (c) Moran, K. L.; Gutteridge, M. C. J.; Quinlan, J. G. *Curr. Med. Chem.* **2001**, *8*, 763-772. (d) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160-187. (e) Chatgililoglu, C.; Asmus, K. D. *Sulfur-centered reactive intermediates in chemistry and biology*, Springer Science & Business Media, **2013**.

<sup>102</sup> (a) Kim, K. R.; Moon, H. R.; Park, A. Y.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem.* **2007**, *15*, 227-234. (b) Isou, Y.; Anan, K.; Kusakabe, K. I.; Gijssen, H.; Bischoff, F. WO Patent 2017061534, **2017**



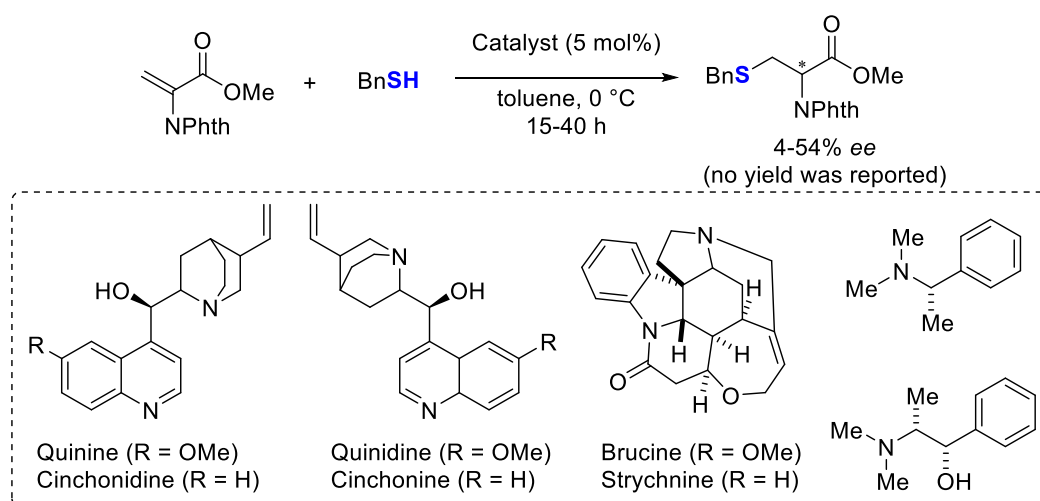
adjacent stereogenic carbons

### 2.1.1 Organocatalytic asymmetric SMA reactions on non-fluorinated $\alpha,\beta$ -unsaturated carbonyl substrates

SMA reaction on non-fluorinated substrates has made a great progress, a variety of catalytic systems to construct C-S bonds with high enantioselectivity and catalytic efficiency were established involving catalysis by chiral metal complex, organic molecules, enzymes, supramolecular structures, and polymeric compounds.<sup>16</sup> Some selected examples of organocatalytic asymmetric SMA reaction on  $\alpha,\beta$ -unsaturated carbonyl substrates were summarized in this section, classified by different chiral catalysts involving alkaloid-, proline- and urea-based catalysts.

#### 2.1.1.1 Alkaloid-based catalysts

In 1977, Pracejus and co-workers studied an enantioselective SMA reaction of benzylthiol with  $\alpha$ -phthalimidomethacrylate.<sup>103</sup> In the screening of chiral catalysts, the targeting cysteine derivatives were obtained in low to moderate enantioselectivities, among the different chiral catalysts, the cinchona alkaloids provided the best enantioselectivity. Worth mentioning that no yield was reported for these reactions (**Scheme 57**).



**Scheme 57** SMA reaction catalyzed by alkaloid-based catalysts

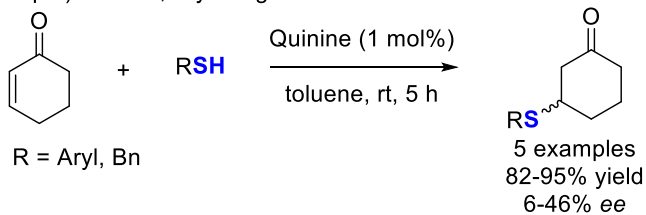
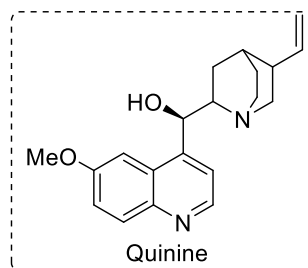
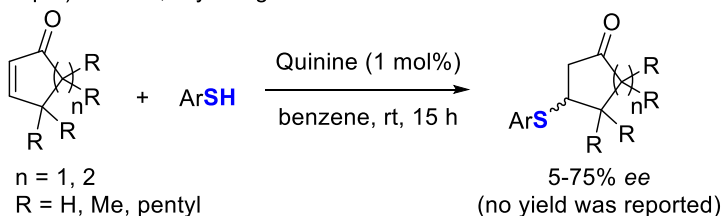
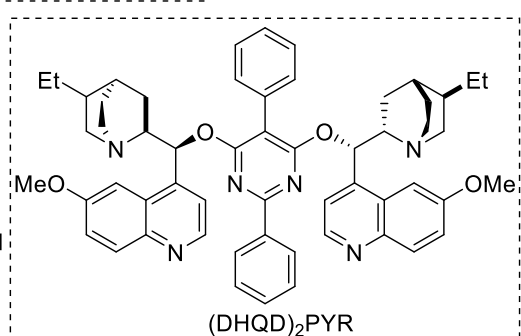
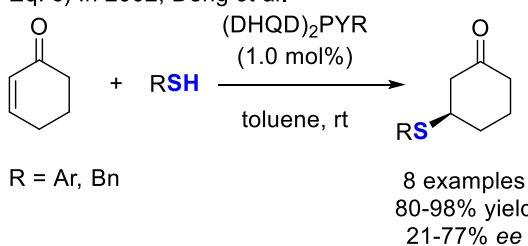
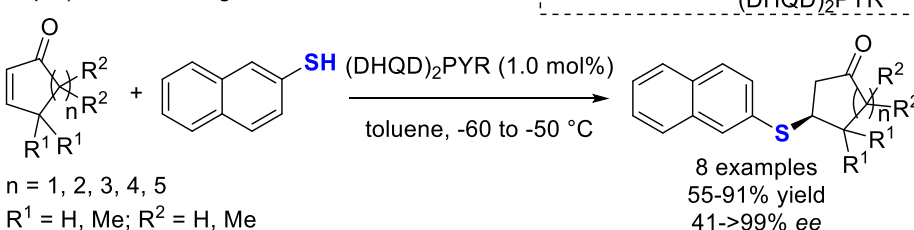
<sup>103</sup> Pracejus, H.; Wilcke, F. W.; Hanemann, K. J. *Prakt. Chem.* **1977**, 319, 219-229.

In the same year, Wynberg and co-workers exploited the catalytic potential of natural cinchona alkaloids for enantioselective SMAs of aromatic thiols to cyclic enones for the first time.<sup>104</sup> Quinine at a low catalyst loading (1 mol%) promoted the SMA of thiols to various cyclic enones, providing  $\beta$ -thioketones with good to excellent yields albeit with low to moderate enantioselectivities (**Scheme 58**, Eq. a). Under the optimized reaction conditions, the authors found that various thiophenols could be added to five- and six-membered enones (**Scheme 58**, Eq. b). To date, (DHQD)<sub>2</sub>PYR which is a dimer of cinchona derivatives with a pyrimidine core, was found to be more effective than natural cinchona alkaloids as the chiral catalyst for asymmetric SMA reactions. In 2002, Deng and co-workers described a highly enantioselective SMA of thiols to cyclic enones under the catalysis of (DHQD)<sub>2</sub>PYR.<sup>105</sup> At room temperature, they studied the addition of different thiols (e.g. thiophenol, *o*-, *m*-, and *p*-substituted thiophenol, benzyl thiol, and 2-thionaphthol) to cyclohexenone, the sulfa-Michael adducts were given in good to excellent yields with low to moderate *ee* values (**Scheme 58**, Eq. c). With 2-thionaphthol which afforded the best enantioselectivity at room temperature, five- to nine-membered cyclic  $\alpha,\beta$ -unsaturated ketones were employed as Michael acceptor and furnished the desired products with moderate to excellent yields and enantioselectivities (**Scheme 58**, Eq. d).

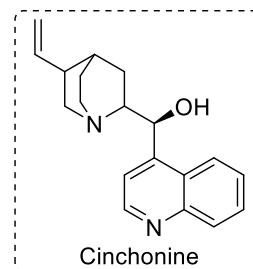
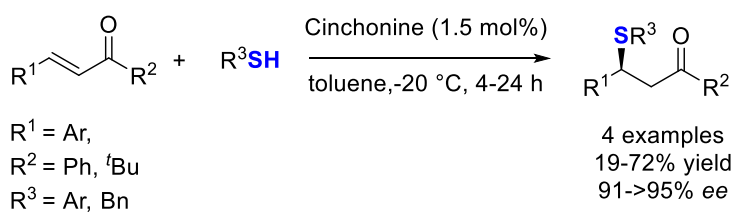
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<sup>104</sup> Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2181-2182.

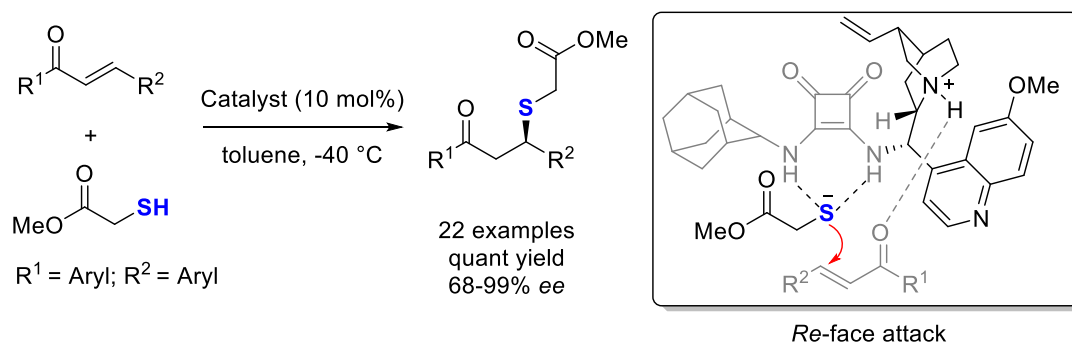
<sup>105</sup> McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed.* **2002**, *114*, 348-350.

Eq. a) In 1977, Wynberg *et al.*Eq. b) In 1977, Wynberg *et al.*Eq. c) In 2002, Deng *et al.*Eq. d) In 2002, Deng *et al.***Scheme 58** SMA reactions catalyzed by quinine and (DHQD)<sub>2</sub>PYR

In 2005, Skarzewski and co-workers investigated the SMA reaction of thiols to acyclic  $\alpha,\beta$ -unsaturated ketones.<sup>106</sup> In the presence of cinchonine as the catalyst, the sulfa-Michael adducts were obtained in moderate to good yields and excellent enantioselectivities (**Scheme 59**).

**Scheme 59** SMA reaction catalyzed by cinchonine<sup>106</sup> Zielinska-Błajet, M.; Kowalczyk, R.; Skarzewski, J. *Tetrahedron* **2005**, *61*, 5235-5240.

More recently, Tanyeli and co-workers reported a highly enantioselective SMA reaction of methyl thioglycolate to *trans*-chalcones, in the presence of quinine derived 2-adamantyl squaramide organocatalyst, the corresponding adducts were obtained in quantitative yields and moderate to excellent enantioselectivities. They proposed a transition state model to explain the control of the enantioselectivity. The methyl thioglycolate was activated by the two hydrogens on squaramide via hydrogen bonding, the chalcone was activated and stabilized by quinuclidine ion. Then, the nucleophilic attack occurred from the *Re* face of the complex, giving the (*R*)- product (**Scheme 60**).<sup>107</sup>



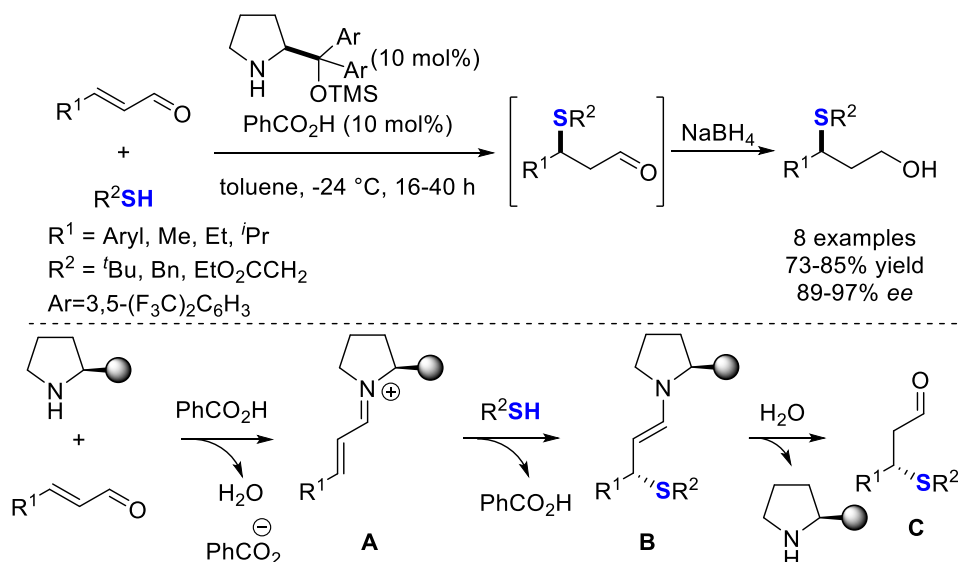
**Scheme 60** SMA reaction catalyzed by quinine derivative

### 2.1.1.2 Proline-based catalysts

In 2005, Jørgensen and co-workers reported a highly enantioselective SMA reaction on  $\alpha,\beta$ -unsaturated aldehydes under the catalysis of trimethylsilyl (TMS) protected prolinol catalyst.<sup>108</sup> The alcohol products were obtained after a subsequent reduction of the sulfa-Michael adducts in good yields with excellent enantioselectivities. The  $\alpha,\beta$ -unsaturated aldehyde was activated by this proline-based catalyst via the formation of a reactive iminium ion intermediate **A**. Then, the sulfur nucleophile attacked the  $\beta$ -carbon from *si*-face, achieving the enantioselective control and forming the enamine **B**, after hydrolysis, giving the corresponding enantiomer **C** (**Scheme 61**).

<sup>107</sup> Hasilcioğulları, D.; Tanyeli, C. *Tetrahedron Lett.* **2018**, *59*, 1414-1416.

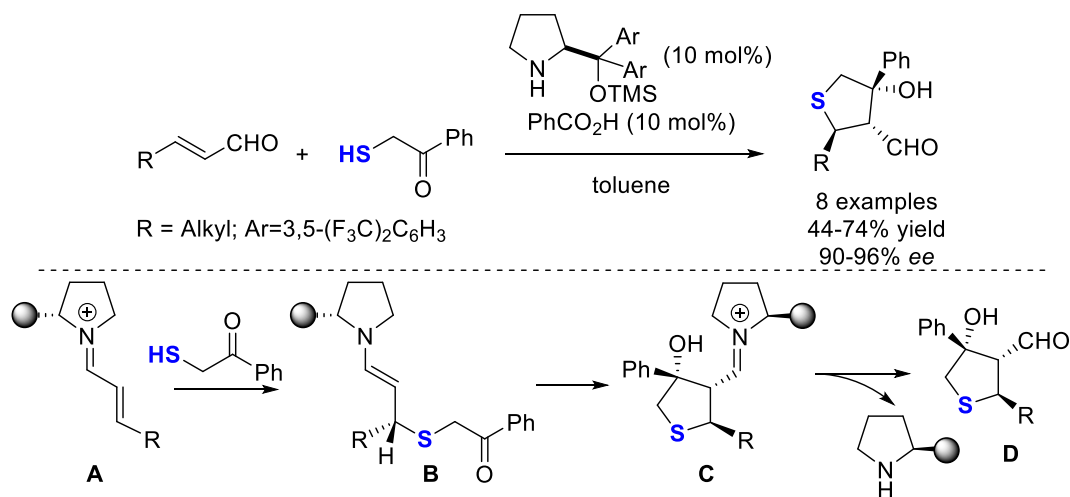
<sup>108</sup> Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710-15711.



**Scheme 61** SMA catalyzed by the proline-based catalyst

Later on, they developed a tandem sulfa-Michael/aldol reaction leading to tetrahydrothiophenes with the same proline-based catalyst.<sup>109</sup> The reaction of various  $\alpha,\beta$ -unsaturated aldehydes with 2-thioacetophenone was found to give the tetrahydrothiophenes in moderate to good yields and excellent enantioselectivities. This reaction can be considered as a two-step process: Firstly, the iminium ion **A** was formed between the proline-based catalyst and the  $\alpha,\beta$ -unsaturated aldehyde, the SMA reaction of thiol to the iminium **A** generated sulfa-Michael adduct **B** which underwent an intramolecular aldol reaction to form the intermediate **C**, then hydrolysis of **C** providing the desired tetrahydrothiophene **D** (**Scheme 62**).

<sup>109</sup> Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986-14991.



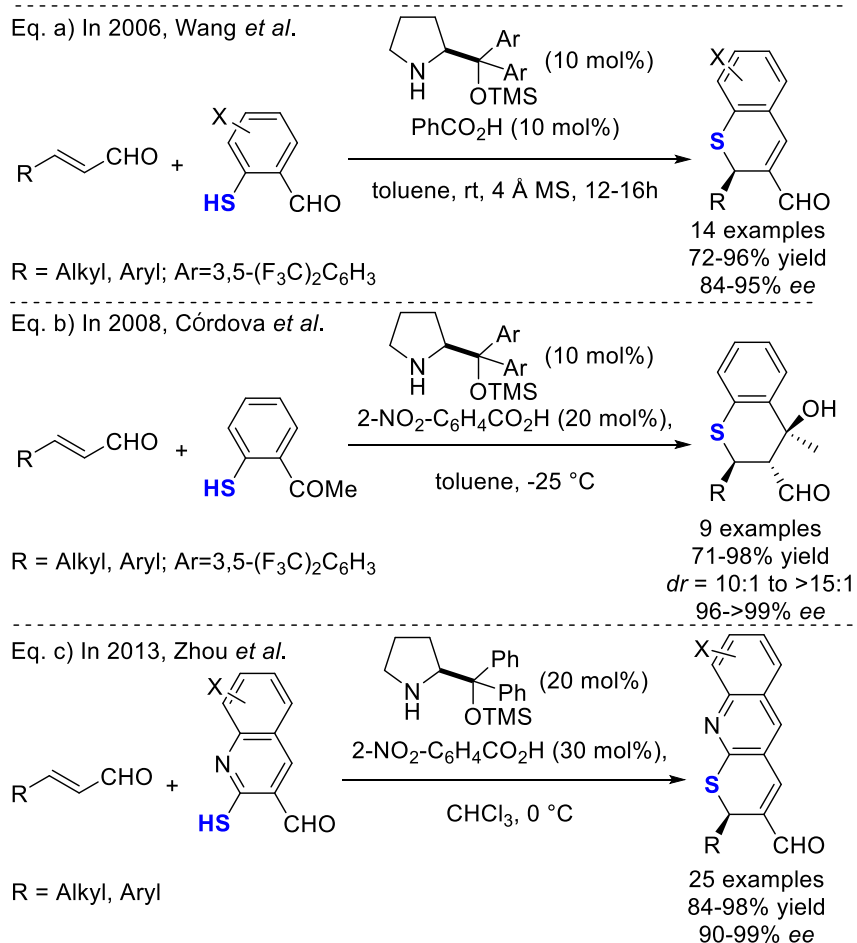
**Scheme 62** Sulfa-Michael/aldol reaction catalyzed by the proline-based catalyst

This kind of sulfa-Michael/aldol reaction between  $\alpha,\beta$ -unsaturated aldehydes and carbonyl-containing thiols has also been reported by other groups. The same year, Wang and co-workers developed an organocatalytic method to prepare chiral thiochromenes from  $\alpha,\beta$ -unsaturated aldehydes and thiosalicylaldehydes using a tandem sulfa-Michael/intramolecular aldol reaction.<sup>110</sup> The same TMS-protected prolinol catalyst showed high catalytic efficiency and enantioselectivity in the model reaction. After extensive optimization of reaction conditions, the best results were obtained by performing the reaction in toluene in the presence of benzoic acid and molecular sieves (**Scheme 63**, Eq. a). In 2008, Córdova and co-workers developed a domino sulfa-Michael/aldol reaction of 2-mercaptoacetophenone and  $\alpha,\beta$ -unsaturated aldehydes promoted by the same catalyst in the presence of 2-nitrobenzoic acid as an additive.<sup>111</sup> A series of thiochromanes bearing three stereogenic centers with one tetrasubstituted carbon were obtained after a subsequent intramolecular aldol reaction. Good to high yields, excellent enantioselectivities and good diastereocontrol were observed for various enals (**Scheme 63**, Eq. b). Then, Zhou and co-workers described an efficient sulfa-Michael/aldol reaction of 2-mercaptoquinoline-3-carbaldehydes with enals catalyzed by a similar proline-based catalyst. A series of pharmaceutically useful

<sup>110</sup> Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354-10355.

<sup>111</sup> Zhao, G. L.; Vesely, J.; Rios, R.; Ibrahim, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 237-242.

enantioenriched 2*H*-thiopyrano[2,3-*b*]-quinoline derivatives was obtained in good to high yields and high enantioselectivities (**Scheme 63**, Eq. c).<sup>112</sup>

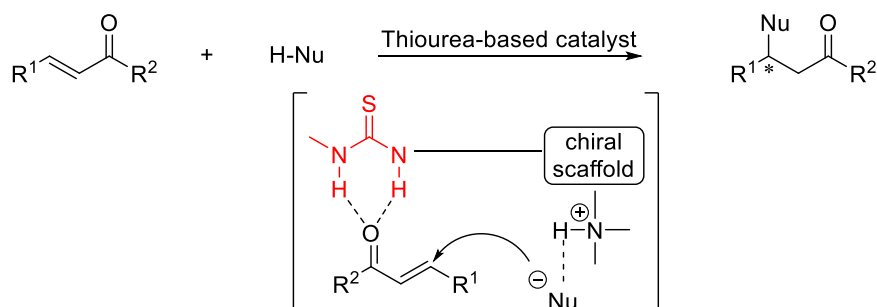


**Scheme 63** Sulfa-Michael/aldol reaction catalyzed by the proline-based catalyst

### 2.1.1.3 Thiourea-based catalysts

The thiourea-based catalysts contain two sites to activate the  $\alpha,\beta$ -unsaturated carbonyl Michael acceptor, through the cooperative activation of their two functionalities, the transition state can be specifically controlled and give the product in good yield with high stereocontrol (**Scheme 64**). This type of catalyst has also been widely used in asymmetric SMA reactions.

<sup>112</sup> Wu, L.; Wang, Y.; Song, H.; Tang, L.; Zhou, Z.; Tang, C. *Chem. Asian J.* **2013**, *8*, 2204-2210.



**Scheme 64** General transition state of thiourea-based catalyst reaction.

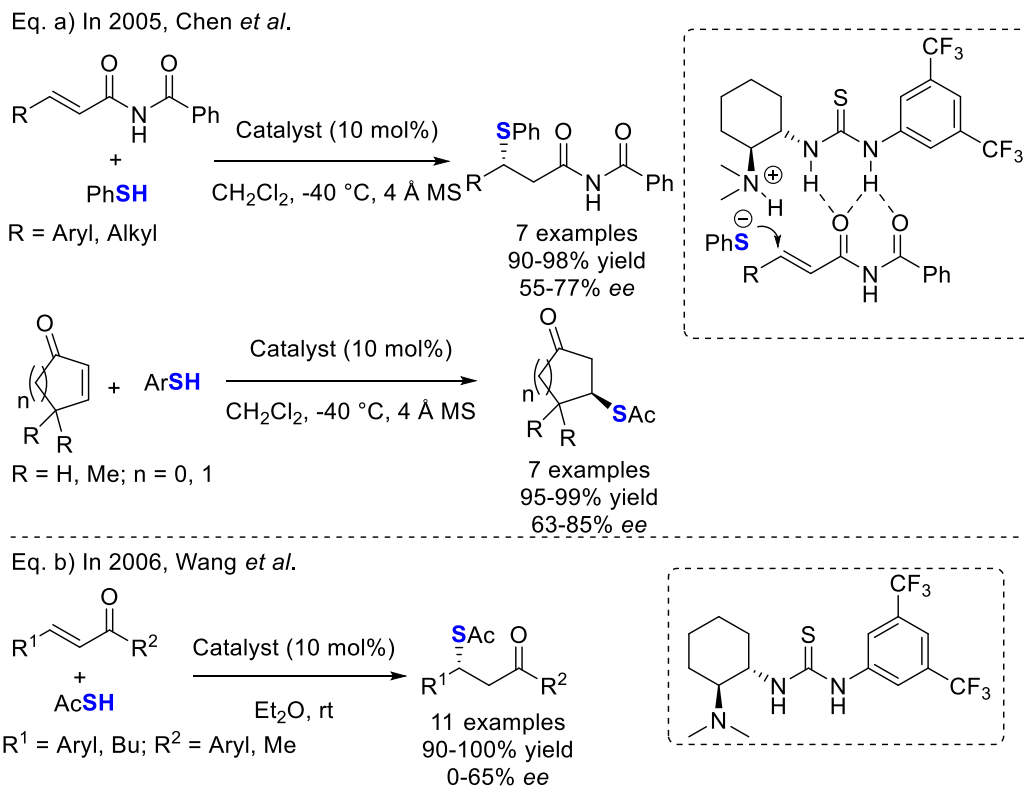
In 2005, Chen and co-workers have used Takemoto's catalyst<sup>113</sup> in the asymmetric SMA on unsaturated imides. The corresponding adducts were obtained in excellent yields and moderate to good enantioselectivities. Based on the obtained (*R*)-products, a possible transition state was suggested. The imide was activated by the dual hydrogen-bonding interactions between its two carbonyls and the thiourea moiety. The sulfur nucleophile activated by tertiary amine had a *Si*-face attack on the complex. This catalytic system was also found to be efficient for promoting the SMA of thiophenols to cyclic enones (**Scheme 65**, Eq. a).<sup>114</sup> Later, with the same catalyst, Wang and co-workers have also performed the SMA reaction of thioacetic acid to  $\alpha,\beta$ -unsaturated ketones.<sup>115</sup> The reactions proceeded smoothly at room temperature, affording the products in excellent yields whereas with poor enantioselectivities (**Scheme 65**, Eq. b).

<sup>113</sup> Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.

<sup>114</sup> Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett* **2005**, *2005*, 603-606.

<sup>115</sup> Li, H.; Zu, L.; Wang, J.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 3145-3148.





**Scheme 65** SMA catalyzed by bifunctional thiourea catalyst

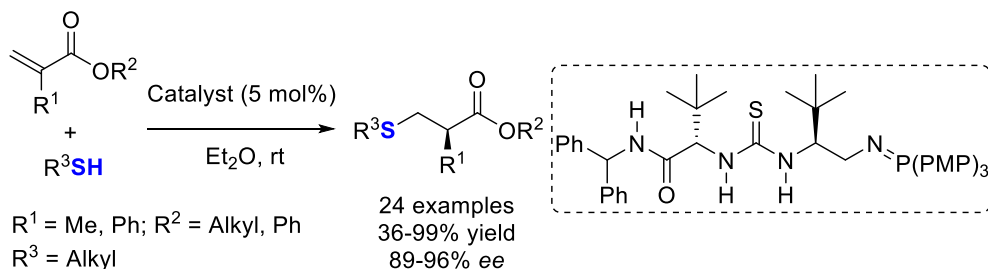
Bifunctional iminophosphorane catalysts (BIMP) were firstly designed and used in nitro-Mannich reactions and conjugate addition reactions.<sup>116</sup> More recently, these catalysts were found to be highly efficient and selective in asymmetric SMA reactions. In 2015, Dixon and co-workers described a highly enantioselective SMA of aliphatic thiols to  $\alpha$ -substituted acrylates catalyzed by a BIMP under mild conditions.<sup>117</sup> The aliphatic thiols could be deprotonated by the BIMP catalyst due to its high basicity from the iminophosphorane moiety, meanwhile, the original chiral thiourea structure can activate the unreactive acrylates and achieve the enantioselective control. As a consequence, the sulfa-Michael adducts were obtained in excellent yields and enantioselectivities and could be scaled up to a gram-scale with a catalyst loading as low as 0.05 mol% (**Scheme 66**, Eq. a). Inspired by these results, they also studied the asymmetric SMA of alkyl thiols to  $\beta$ -substituted acrylates catalyzed by

<sup>116</sup> (a) Nunez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348-16351. (b) Goldys, A. M.; Nunez, M. G.; Dixon, D. J. *Org. Lett.* **2014**, *16*, 6294-6297.

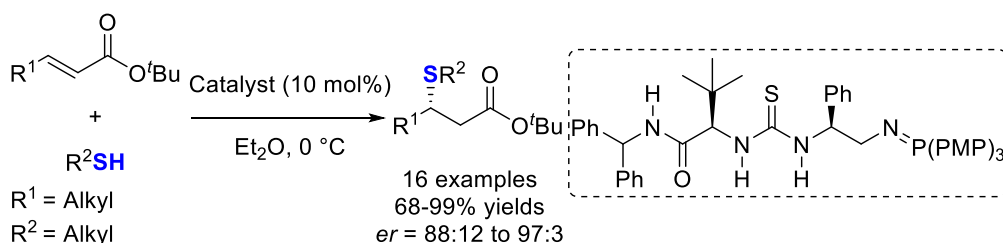
<sup>117</sup> Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992-15995.

the BIMP catalyst.<sup>118</sup> In this case, the corresponding sulfa-Michael adducts were also obtained in excellent yields and enantioselectivities and the reaction was efficient even using a low 1 mol% catalyst loading (**Scheme 66**, Eq. b).

Eq. a) In 2015, Dixon *et al.*



Eq. b) In 2017, Dixon *et al.*



**Scheme 66** SMA catalyzed by BIMP catalyst

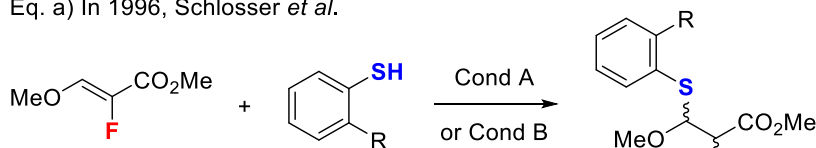
## 2.1.2 SMA reaction on $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl substrates

Compared to non-fluorinated  $\alpha,\beta$ -unsaturated carbonyl substrates, the use of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl compounds as Michael acceptors in SMA reaction has not been developed. To our knowledge, only two examples have been reported so far and both are described in a non-enantioselective fashion. Indeed, in 1996, Schlosser and co-workers reported two examples of 1,4-addition of thiophenols on 2-fluoro-3-methoxyacrylate. In the presence of  $t\text{BuOK}$  or  $n\text{BuLi}$ , the corresponding 1,4-adducts were obtained as a mixture of diastereoisomers in 3:1 to 3:2 ratios and in high yields (**Scheme 67**, Eq. a).<sup>28</sup> In 2016, Haufe and co-workers investigated the Michael addition of different nucleophiles (*C*-, *N*-, *S*-, and *O*- nucleophiles) to the functionalization of *gem*- $\alpha$ -fluorinated ketones. In the addition of sulfur-nucleophiles,

<sup>118</sup> Yang, J.; Farley, A. J. M.; Dixon, D. J. *Chem. Sci.* **2017**, *8*, 606-610.

both 4-methylthiophenol, boc-cysteine methyl ester, and benzothiazole-thiol were tested, whereas only the first two sulfur nucleophiles could react, giving the products in moderate to good yields. In all cases of Boc-cysteine methyl ester, the 1,4-adducts were detected by  $^{19}\text{F}$  NMR with diastereomeric ratio 1:1 (**Scheme 67**, Eq. b).<sup>29</sup>

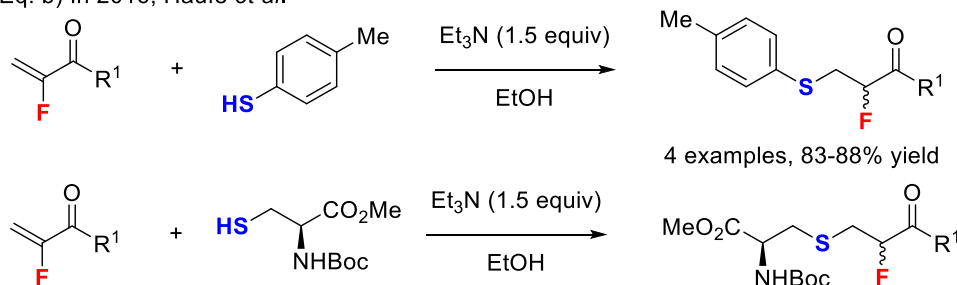
Eq. a) In 1996, Schlosser *et al.*



R = H, Conditions A:  $t\text{BuOK}$  (4 mol%),  $\text{Et}_2\text{O}$ , rt, 89% *dr* = 3:1

R =  $\text{NH}_2$ , Conditions B:  $n\text{BuLi}$  (1 equiv), THF, rt, 88% *dr* = 3:2

Eq. b) In 2016, Haufe *et al.*



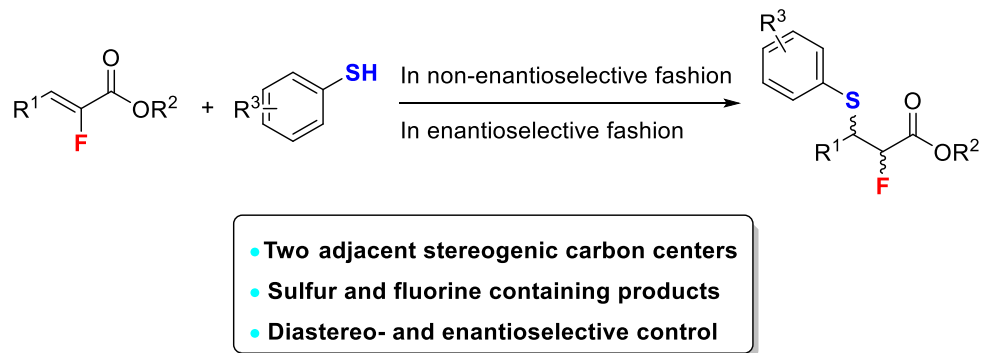
$\text{R}^1 = \text{C}_7\text{H}_{15}, \text{C}_{13}\text{H}_{27}, \text{C}_6\text{H}_{11}, \text{C}_6\text{H}_5$

**Scheme 67** SMA reaction on  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl substrates

## 2.2 Objectives

As all mentioned above, the asymmetric SMA reaction has indeed made great progress. However, the asymmetric SMA reaction on  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl substrates remains a challenge and no attempt has been made to our knowledge.

In this context, we aimed at developing new methodologies of organocatalytic SMA of thiols to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl substrates in both non-enantioselective and, for the first time, in enantioselective versions (**Scheme 68**).

Scheme 68 SMA of thiophenols to  $\alpha$ -fluoroacrylates

## 2.3 Non-enantioselective version

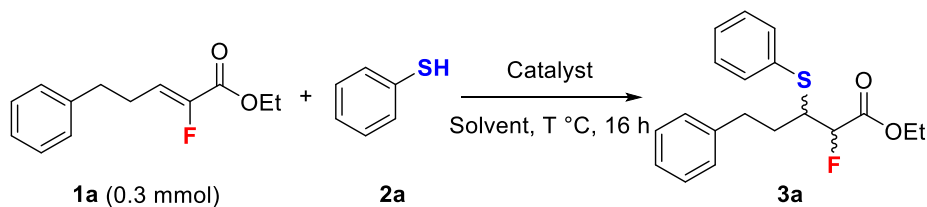
The first investigations were carried out in non-enantioselective conditions. To begin with the SMA reaction of thiophenols to  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carbonyl substrates, the (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (**1a**) was chosen as the Michael acceptor and the thiophenol (**2a**) as the nucleophile in a model reaction. It is worth to mention whatever precaution is taken, during the SMA reactions, the oxidation of thiophenols always occurred as a side-reaction, making difficult the purification of 1,4-adducts. So, to minimize the production of disulfide by-products, all the following reactions were performed in degassed solvents under argon.

### 2.3.1 Optimization of the reaction conditions

Herein, we discussed several parameters which have been tested with the model SMA reaction, including the equivalent of **2a**, the nature of catalyst, the catalyst loading, the solvent, and the temperature (**Table 2**).

In the first attempts, Lewis acids were used as a catalyst in  $\text{CH}_2\text{Cl}_2$ . The use of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  and  $\text{Me}_2\text{AlCl}_3$  to a full recovery of **1a**, even in the refluxing  $\text{CH}_2\text{Cl}_2$  (**Table 2**, entries 1-2). Considering that the SMA reactions have been generally carried out under basic conditions<sup>16</sup> and **2a** has a low pKa value, a weak base  $\text{Et}_3\text{N}$  was used as the catalyst. When  $\text{Et}_3\text{N}$  was employed in  $\text{CH}_2\text{Cl}_2$ , traces of 1,4-adducts (**3a**) were observed in  $^{19}\text{F}$  NMR (-195.7 ppm, dd,  $J = 48.0, 22.6$  Hz; -197.0 ppm, dd,  $J = 48.0, 28.2$  Hz), and there is no actual improvement of conversion when the reaction mixture was heated to reflux (**Table 2**, entry 3). In order to perform the reaction at a higher

temperature, another solvent was tested. To our surprise, the use of MeCN showed an obvious improvement for the conversion even at room temperature (**Table 2**, entry 4). Heating the reaction to reflux, 75% conversion and 73:27 *dr* were obtained. Nevertheless, **3a** was isolated in only 37% yield due to difficulties to separate **3a** from the remaining starting material and disulfide byproduct (**Table 2**, entry 5). The reaction did not occur in the absence of base or when PhSNa was used instead of the combination of two reactants base/PhSH (**Table 2**, entries 6-7). Increasing the amount of **2a** led to 84% isolated yield of **3a** (**Table 2**, entry 8). The amount of Et<sub>3</sub>N could be reduced to 0.1 equivalent giving a similar yield and *dr* (**Table 2**, entry 9). We finally found this reaction could be performed in neat **2a**, and the use of 5 equivalent of **2a** could give a full conversion of **1a** and **3a** was isolated in 89% yield as a mixture of two diastereoisomers in a 76:24 ratio (**Table 2**, entries 10-12). Some other tertiary amines were tested, the use of DIPEA and DBU slightly improved the *dr* ratio with lower yields whereas the use of DABCO gave a lower yield with a similar *dr* ratio (**Table 2**, entries 13-15).

**Table 2** Optimization of non-enantioselective SMA reaction

Entry	Equiv of PhSH	Catalyst (Equiv)	Solvent	T (°C)	Conversion <sup>b</sup> (Yield) <sup>c</sup> %	<i>Dr</i> <sup>d</sup>
1	1.1	BF <sub>3</sub> ·Et <sub>2</sub> O (1.5)	CH <sub>2</sub> Cl <sub>2</sub>	rt or 45	0	-
2	1.1	Me <sub>2</sub> AlCl <sub>3</sub> (1.5)	CH <sub>2</sub> Cl <sub>2</sub>	rt or 45	0	-
3	1.1	Et <sub>3</sub> N (0.14)	CH <sub>2</sub> Cl <sub>2</sub>	rt or 45	Trace	-
4	1.1	Et <sub>3</sub> N (0.14)	MeCN	rt	50	-
5	1.1	Et <sub>3</sub> N (0.14)	MeCN	80	75 (37)	73:27
6	1.1	-	MeCN	80	0	-
7	PhSNa (2.0)	-	MeCN	80	0	-
8	2	Et <sub>3</sub> N (0.14)	MeCN	80	98 (84)	77:23
9	2	Et <sub>3</sub> N (0.10)	MeCN	80	94 (81)	76:24
10	3	Et <sub>3</sub> N (0.10)	-	80	91 (77)	74:26

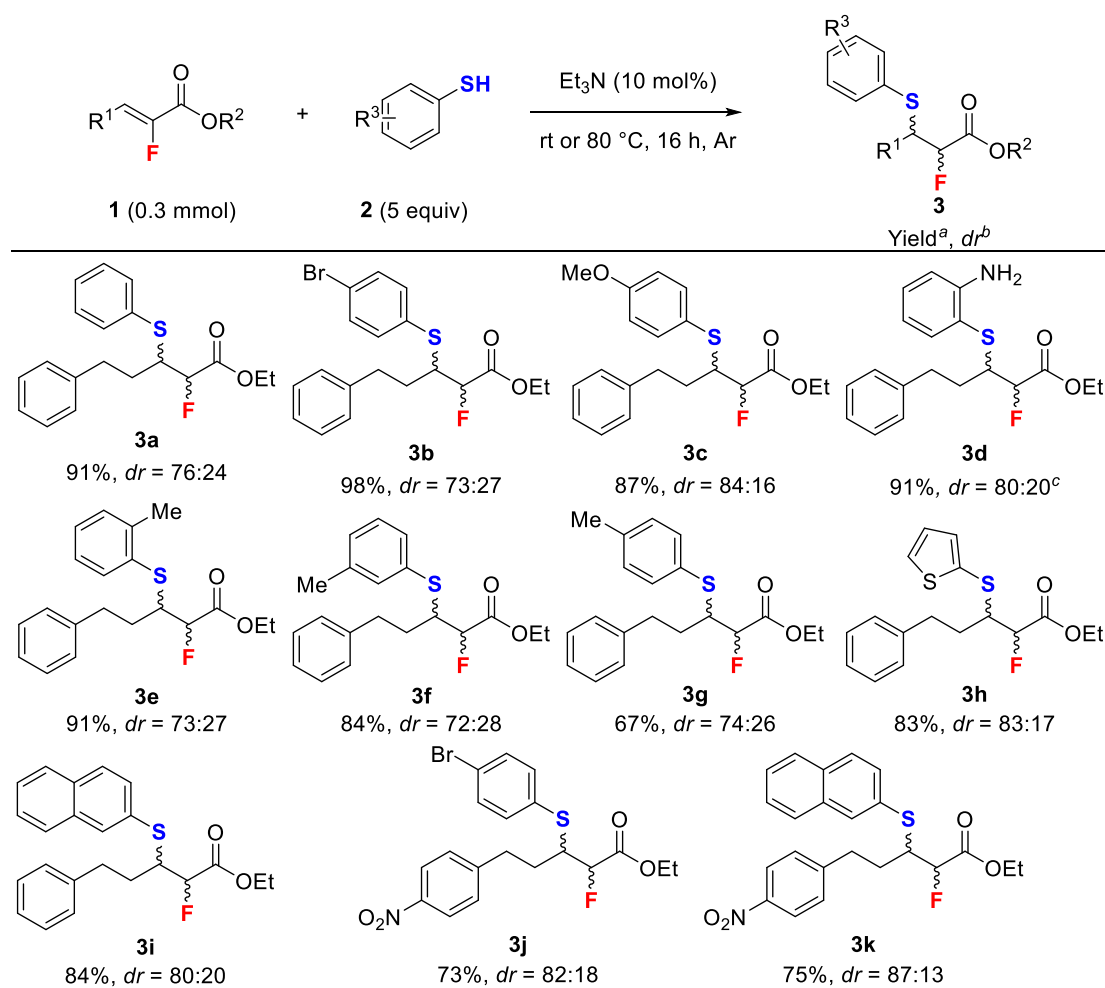
11	5	Et <sub>3</sub> N (0.10)	-	80	100 (89)	76:24
12	10	Et <sub>3</sub> N (0.10)	-	80	100 (91)	77:23
13	5	DIPEA (0.10)	-	80	82 (68)	88:12
14	5	DBU (0.10)	-	80	61 (37)	82:18
15	5	DABCO (0.10)	-	80	100 (81)	77:23

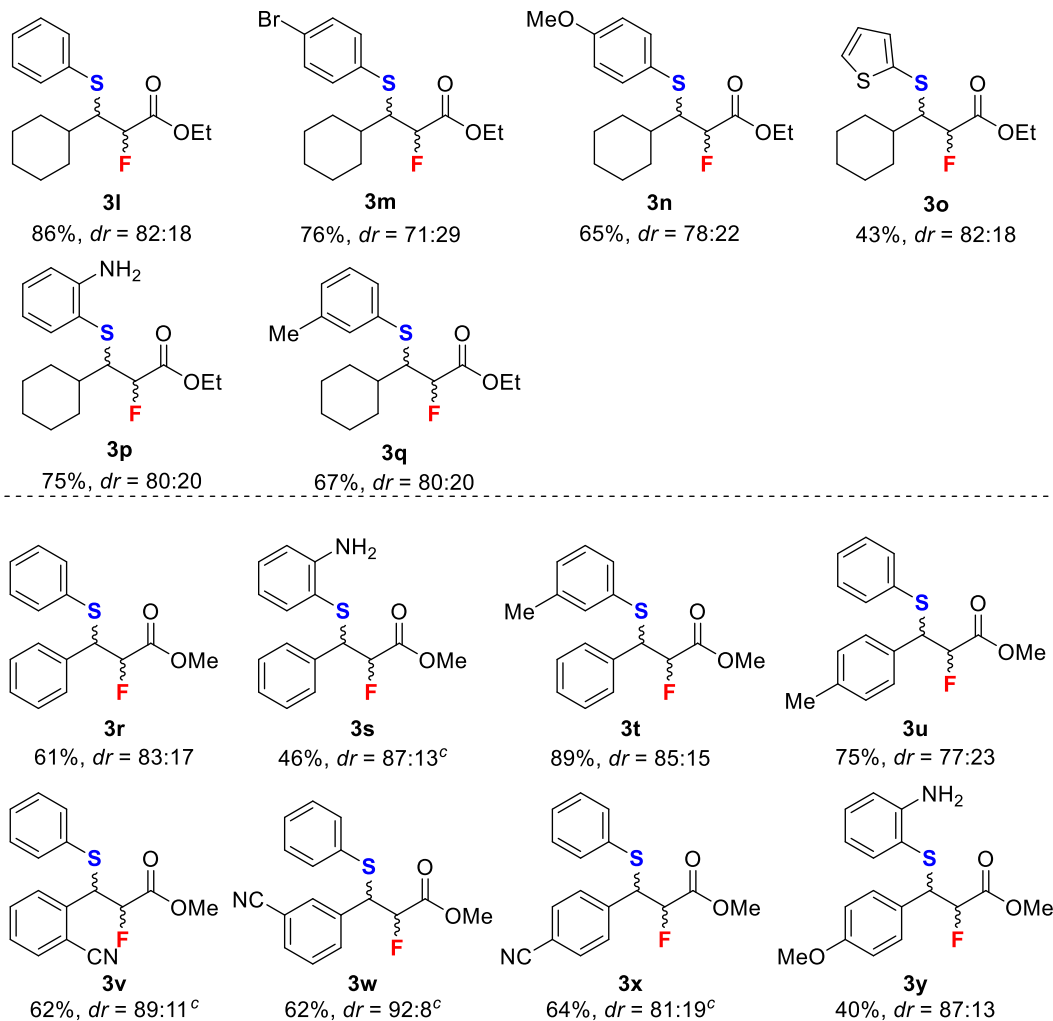
<sup>a</sup>Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.33-3.0 mmol, 1.1-10 equiv), catalyst (0.10-1.5 equiv), degassed solvent (0.5 mL or neat), room temperature or refluxing, 16 h, under argon. <sup>b</sup>Determined by the <sup>19</sup>F NMR of the reaction mixture. <sup>c</sup>Isolated yield of the diastereoisomers mixture (**3a**). <sup>d</sup>Determined by the <sup>19</sup>F NMR of the reaction crude

### 2.3.2 Substrates scope of the reaction

With the optimized conditions in hand, we started the investigation of the scope on SMA reaction of various thiols to some  $\alpha$ -fluoroacrylates under non-enantioselective conditions (**Table 3**).

**Table 3** Substrate scope in the non-enantioselective process





<sup>a</sup>Isolated yield of diastereoisomers. <sup>b</sup>Determined by <sup>19</sup>F NMR of the reaction crude. <sup>c</sup>Reaction performed at room temperature.

Under the reaction conditions, this SMA reaction showed good tolerance with both  $\alpha$ -fluoroacrylates and aryl thiols. With the (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (**1a**), thiophenol could bear some common substituents, such as bromo, methoxy, amino, and methyl, and successfully provided the desired products in good to excellent yields with good diastereoselectivities (**3b-g**). Thiophenol with a methyl group substituted at the *ortho*-, *meta*-, and *para*-position furnished the desired products in similar diastereoselectivities, but higher yields were obtained when the methyl at *ortho*- and *meta*-position (**3e-g**). The aryl thiol could be extended to 2-thiophenethiol and 2-naphthalenethiol giving the 1,4-adducts in the good yields and moderate diastereoselectivities (**2h-i**). Additions of 4-bromothiophenol and 2-naphthalenethiol to a fluorinated Michael acceptor bearing a nitro-aryl substituent

occurred also in good yields and moderate diastereoselectivities (**3j-k**). Cyclohexyl  $\alpha$ -fluoroacrylates were also tested, giving moderate to good yields and moderate diastereoselectivities (**3l-q**). At the end, we studied this SMA addition on different aryl  $\alpha$ -fluoroacrylates, which generally afforded the 1,4-adducts with similar diastereoselectivities but in lower yields compared to alkyl  $\alpha$ -fluoroacrylates.  $\alpha$ -Fluorocinnamates bearing a cyano group at the *ortho*-, *meta*-, and *para*-positions of the arene moiety were tested and showed no significant substituent effects (**3v-x**). To be briefly summarized in the non-enantioselective process, the sulfa-Michael adducts were obtained in moderate to excellent yields (40-98%) with the ratio of two diastereoisomers from 71:29 to 92:8. The substituent in thiols or fluoroacrylates did not show significant effects on the yield or diastereoselectivity. The fair yields of products **3o** (43%), **3s** (46%), **3y** (40%) were due to the purification issues between the desired products and disulfide by-products. The major diastereoisomer in *syn*-configuration was confirmed by X-ray analysis of the crystals obtained from **3k** (Figure 14).

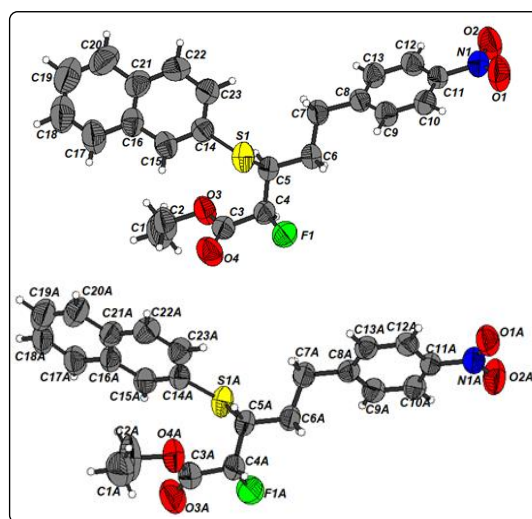


Figure 14 X-ray of major diastereoisomer of **3k**

## 2.4 Enantioselective version

After completing the substrates scope under non-enantioselective conditions, we turned our attention to the development of the corresponding asymmetric SMA



reactions.

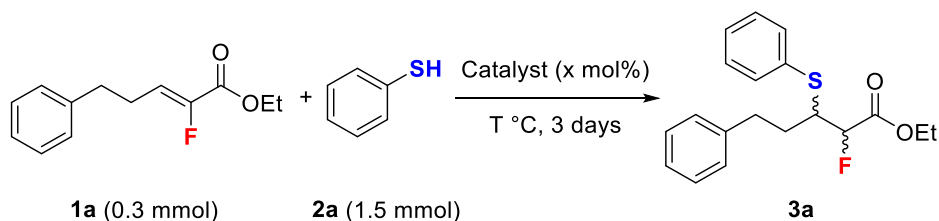
### 2.4.1 Optimization of the reaction conditions

Based on the previous optimizations, all the following reactions were performed in neat thiophenol (**2a**). Hereafter we explored the effects of temperature and different chiral organocatalysts including cinchona alkaloids, bis-cinchona alkaloids, urea derivatives, and chiral amines (**Table 4**). All the structures of catalysts were shown in the following **Scheme 69**.

We started the investigation with cinchona alkaloids (**I-III**) which have proven to be effective bases for the asymmetric SMA of thiols to non-fluorinated substrates<sup>103-104, 106</sup> (**Table 4**, entries 1-3). Whereas the conversions and diastereoselectivities were pretty good, we were disappointed to see that the best *ee* was only 15% (**Table 4**, entry 1). Using the quinidine (**II**) led to the same kind of results with a reverse *ee* as low as 13% (**Table 4**, entry 2). Surprisingly, the use of the cinchonine (**III**) led to racemic 1,4-adducts (**Table 4**, entry 3). Increasing the catalyst loading to 20 mol% did not have a positive effect on the *ee* values (**Table 4**, entries 4-5). However, when bis-cinchona alkaloids (DHQ)<sub>2</sub>PYR, (DHQ)<sub>2</sub>AQN, and (DHQD)<sub>2</sub>PHAL (**IV**, **VI**, and **VII**) were used, comparable results in terms of *dr* with full conversions and better *ee* values were obtained (**Table 4**, entries 6, 9-10). Lowering the catalyst loading to 5 mol% decreased both conversion and *ee* value (**Table 4**, entry 7). The use of (DHQD)<sub>2</sub>PYR (**V**) afforded the expected product **3a** with 72% *ee* but with only 63% conversion (**Table 4**, entry 8). We also tested the thiourea derivatives (**VIII** and **IX**), which showed high selectivity in SMA reactions,<sup>114-115</sup> but no better results were observed (**Table 4**, entries 11-12). The use of chiral amines (**X** and **XI**) only provided racemic products (**Table 4**, entries 13-14). In comprehensive consideration of conversion, *dr* and *ee* value, (DHQ)<sub>2</sub>PYR (**IV**) was selected as it gave the best results: 100% conversion, 89:11 *dr*, 68% *ee* (**Table 4**, entry 4). On the basis of choosing (DHQ)<sub>2</sub>PYR (**IV**) as the catalyst, we studied the influence of temperature. The reaction performed at 80 °C was complete after 16 h but gave only 37% *ee* (**Table 4**, entry 17). Decreasing the

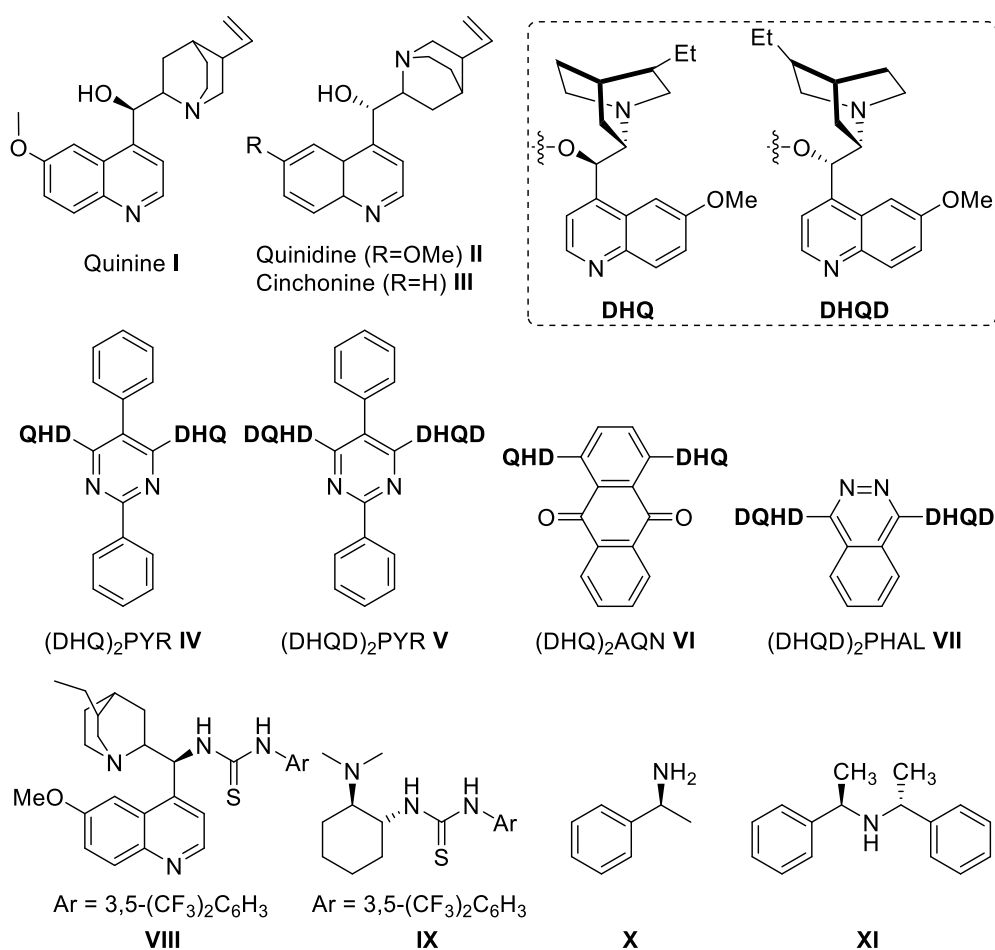
temperature allowed the obtention of better *ee* values but lower conversions (**Table 4**, entries 15-16). Extended the reaction time to 5 days provided the full conversion with 71% *ee* (**Table 4**, entry 18).

**Table 4** Screening of chiral catalysts and temperature for the asymmetric SMA



Entry	Catalyst	x (mol%)	T (°C)	Conversion <sup>b</sup> (Yield) <sup>c</sup> %	<i>Dr</i> <sup>d</sup>	<i>Ee</i> (%) <sup>e</sup>
1	Quinine I	10	rt	90	83:17	15
2	Quinidine II	10	rt	85	85:15	-13
3	Cinchonine III	10	rt	98	86:14	0
4	Quinine I	20	rt	96	80:20	15
5	Quinidine II	20	rt	87	83:17	-11
6	(DHQ) <sub>2</sub> PYR IV	10	rt	100	89:11	68
7	(DHQ) <sub>2</sub> PYR IV	5	rt	98	87:13	60
8	(DHQD) <sub>2</sub> PYR V	10	rt	63	88:12	-72
9	(DHQ) <sub>2</sub> AQN VI	10	rt	100	85:15	51
10	(DHQD) <sub>2</sub> PHAL VII	10	rt	100	92:8	-53
11	VIII	10	rt	60	60:40	50
12	IX	10	rt	69	61:39	22
13	X	10	rt	88	72:28	0
14	XI	10	rt	72	84:16	0
15	(DHQ) <sub>2</sub> PYR IV	10	-20	42	81:19	73
16	(DHQ) <sub>2</sub> PYR IV	10	0	89 (73)	85:15	70
17	(DHQ) <sub>2</sub> PYR IV	10	80	100 (91)	85:15	37
18	(DHQ) <sub>2</sub> PYR IV	10	0	100 (82)	84:16	71

<sup>a</sup>Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (1.5 mmol, 5 equiv), catalyst (0.05-0.20 equiv), the given temperature, under argon, 3 days. <sup>b</sup>Determined by the <sup>19</sup>F NMR of the reaction mixture. <sup>c</sup>Isolated yield of the diastereoisomers mixture (**3a**). <sup>d</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>e</sup>Determined for the major diastereoisomer by HPLC. <sup>f</sup>Reaction time = 16 h. <sup>g</sup>Reaction time = 5 days.



Scheme 69 Structures of chiral catalysts

In order to further improve the enantioselectivity, we also investigated the influence of different solvents on this model reaction at room temperature for 3 days (**Table 5**). Various solvents were tested including Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, MeCN, toluene, and MeOH (**Table 5**, entries 1-5). Et<sub>2</sub>O and toluene gave relatively good *ee* values, 60% and 64% respectively (**Table 5**, entry 1, 4). Accordingly, two other solvents MTBE and *m*-xylene were tested, both of them furnished excellent *dr* but unfortunately gave lower conversions and *ee* values (**Table 5**, entries 6-7). Carrying out the reaction in neat thiophenol still provided the best results in terms of conversion, *dr* and *ee* value (**Table 5**, entry 8).

**Table 5** Influence of solvents

Entry	Solvent (0.5 mL)	Conversion (%) <sup>b</sup>	<i>Dr</i> <sup>c</sup>	<i>Ee</i> <sup>d</sup>
1	Et <sub>2</sub> O	76	88:12	60
2	CH <sub>2</sub> Cl <sub>2</sub>	32	85:15	48
3	MeCN	47	91:9	49
4	Toluene	58	85:15	64
5	MeOH	62	83:17	36
6	MTBE	62	96:4	56
7	<i>m</i> -Xylene	18	97:3	59
8	-	100	89:11	68

<sup>a</sup>Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (1.5 mmol, 5 equiv), (DHQ)<sub>2</sub>PYR (0.03 mmol, 10 mol%), solvent (0.5 mL), room temperature, 3 days, under argon. <sup>b</sup>Determined by the <sup>19</sup>F NMR of the reaction mixture.

<sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Determined for the major diastereoisomer by HPLC.

In addition, some further studies on this reaction have been explored concerning the nature of the ester group of the Michael acceptor. The use of bulkier esters such as *iso*-propyl and *tert*-butyl than methyl or ethyl group slightly increased the *dr* but led to lower yields and *ee* values (**Table 6**).

**Table 6** Effects of the ester group

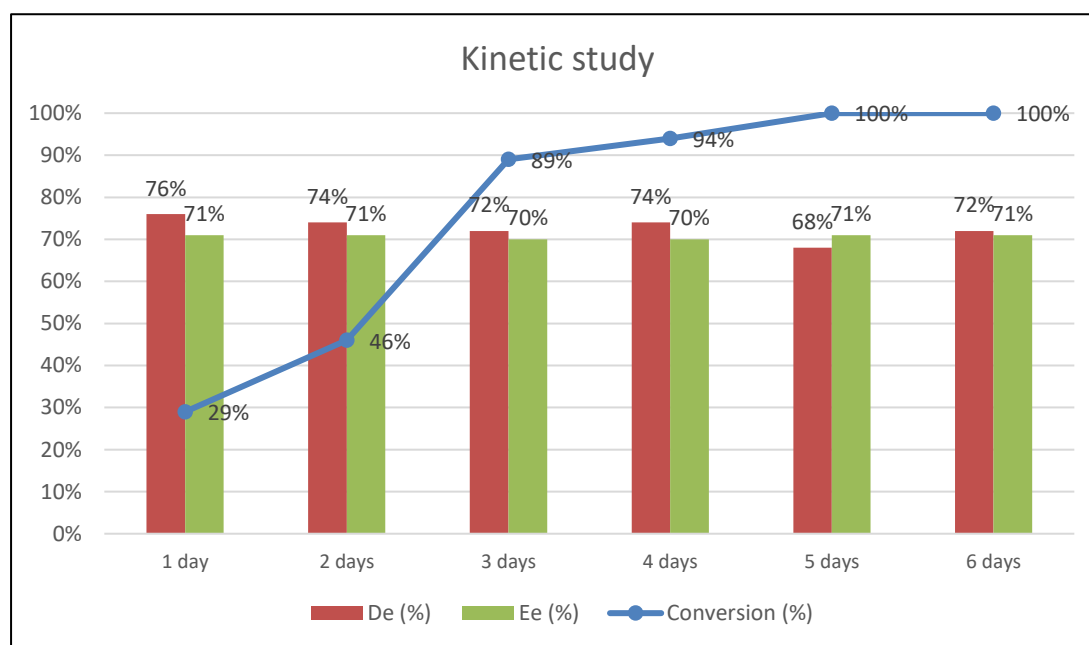
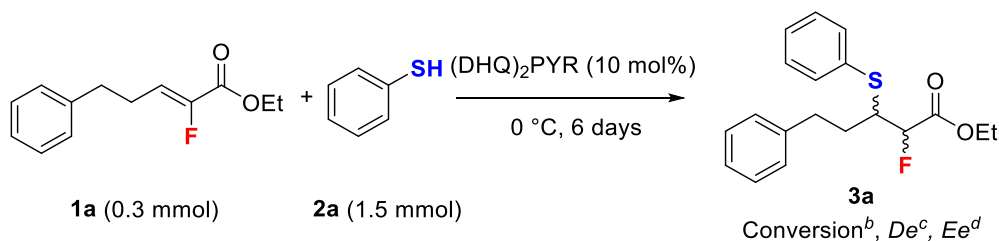
Entry	R	isolated yield (%) <sup>b</sup>	<i>Dr</i> <sup>c</sup>	<i>Ee</i> (%) <sup>d</sup>
1	Me	75	86:14	49
2	Et	82	84:16	71
3	<i>i</i> Pr	41	95:5	43
4	<i>t</i> Bu	19	92:8	55

<sup>a</sup>Reaction conditions: **1a'** (0.3 mmol, 1.0 equiv), **2a** (1.5 mmol, 5 equiv), (DHQ)<sub>2</sub>PYR (0.03 mmol, 10 mol%), 0 °C, 5

days, under argon. <sup>b</sup>Isolated yield of the diastereoisomers mixture (**3a'**). <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Determined for the major diastereoisomer by HPLC.

A kinetic study showed that during the reaction, the ratio of the two diastereoisomers stays the same as well as the *ee* value of the major diastereoisomer (**Table 7**).

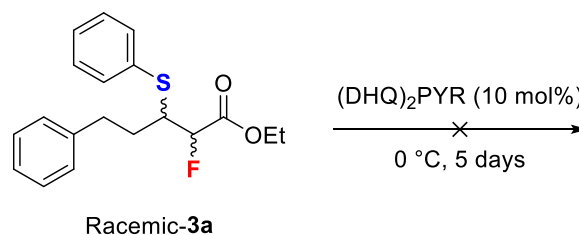
**Table 7** kinetic study



<sup>a</sup>Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (1.5 mmol, 5 equiv), (DHQ)<sub>2</sub>PYR (0.03 mmol, 10 mol%), 0 °C, 6 days, under argon. <sup>b</sup>Determined by the <sup>19</sup>F NMR of the reaction mixture. <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Determined for the major diastereoisomer by HPLC.

The stability of **3a** in the catalytic system proved that no *retro*-Michael addition occurred (**Table 8**).

**Table 8** Stability of products



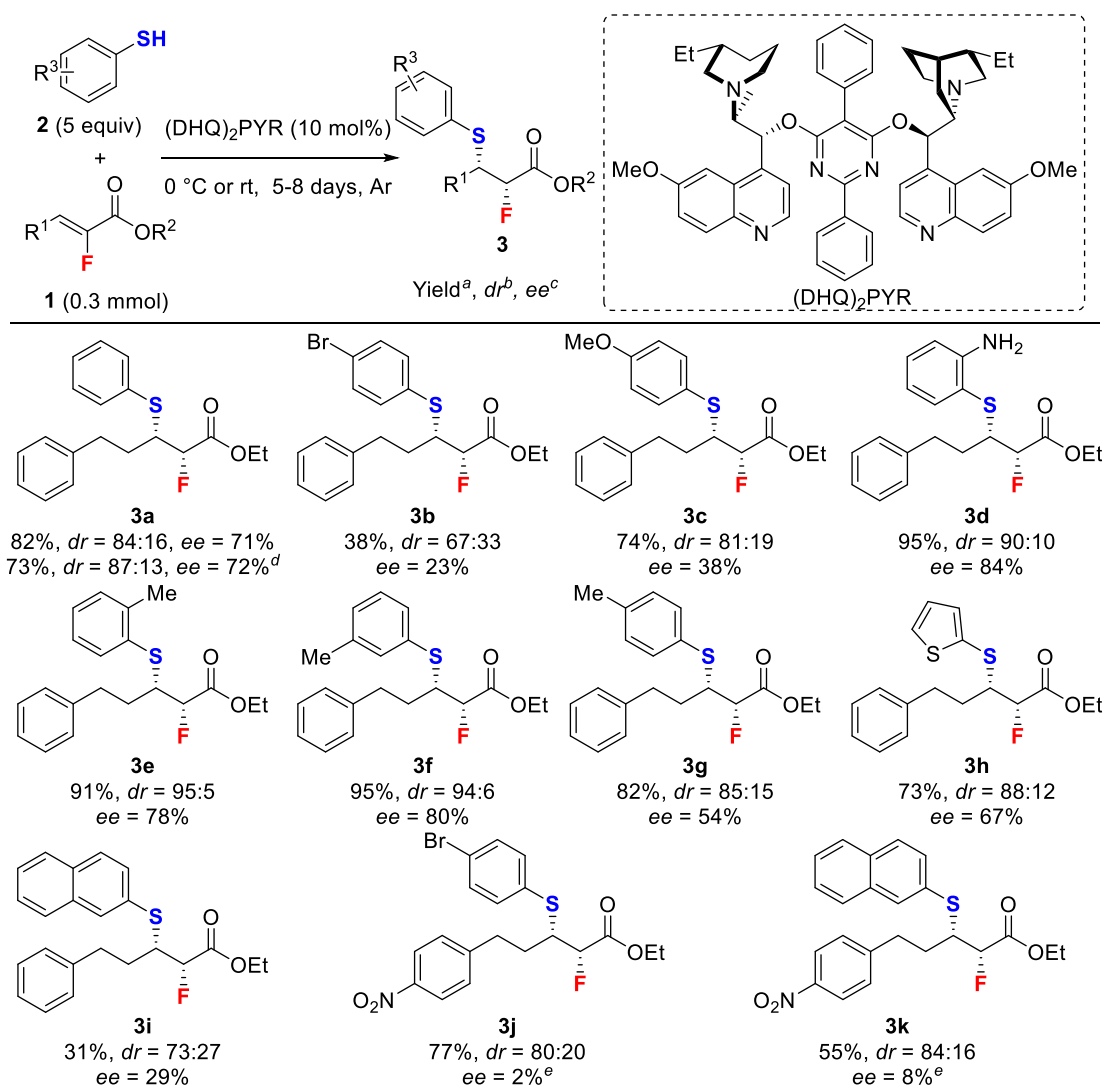
	1 day	2 days	3 days	4 days	5 days
$^{19}\text{F}$ NMR <sup>b</sup>	S.M.	S.M.	S.M.	S.M.	S.M.
<i>Ee</i> (%) <sup>c</sup>	0	0	0	0	0

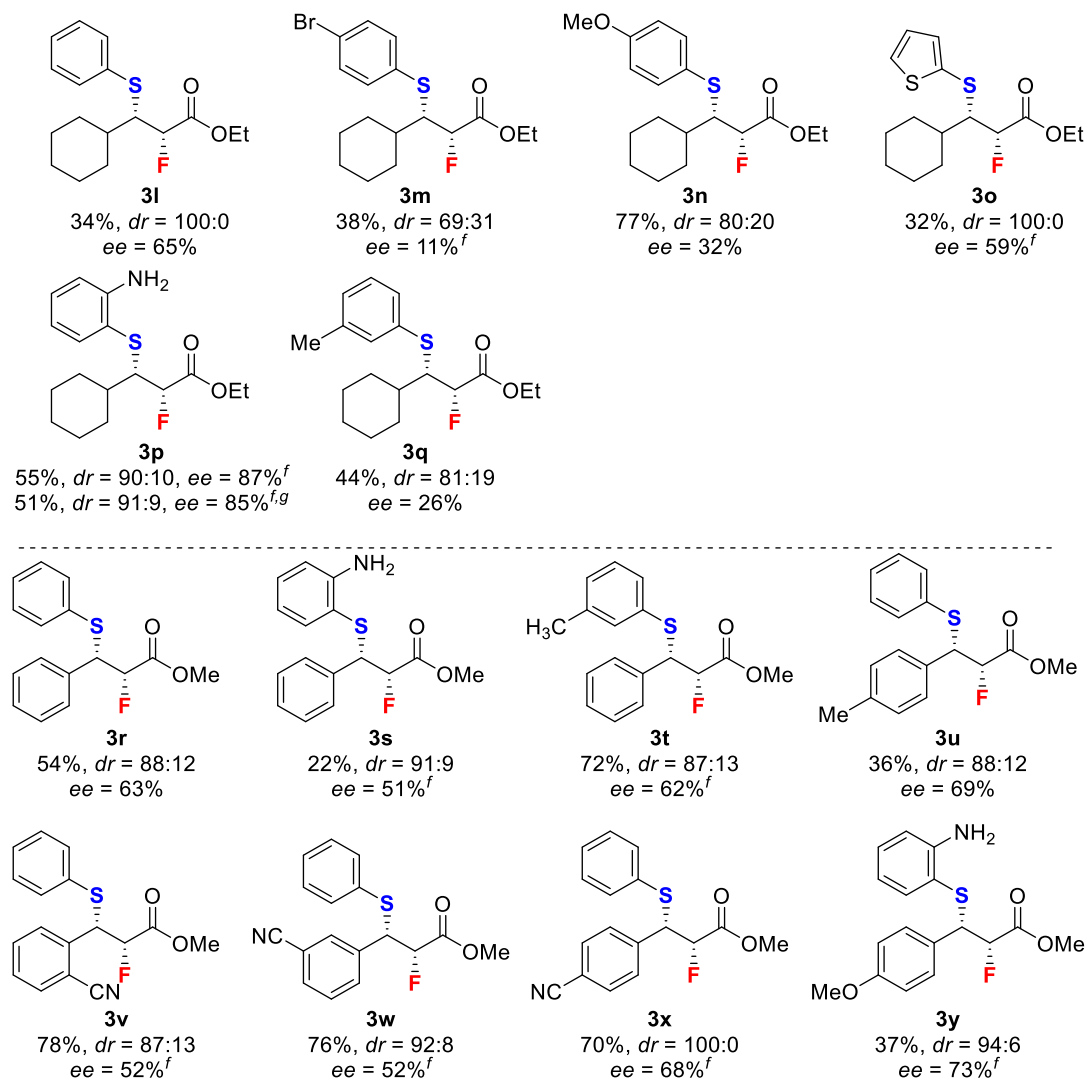
<sup>a</sup>Reaction conditions: Racemic-**3a** (0.2 mmol, 1.0 equiv), **2a** (1.0 mmol, 5 equiv), (DHQ)<sub>2</sub>PYR (0.02 mmol, 10 mol%), 0 °C, 5 days, under argon. <sup>b</sup>S.M. = starting material, only **3a** were detected in  $^{19}\text{F}$  NMR. <sup>c</sup>Determined for **3a** by HPLC.

## 2.4.2 Substrates scope of the reaction

After having the optimized conditions for the enantioselective process, we investigated the scope on SMA reaction of various thiols to  $\alpha$ -fluoroacrylates (**Table 9**).

**Table 9** Substrate scope of the reaction



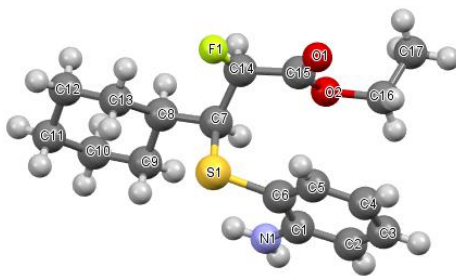


<sup>a</sup>Isolated yield of diastereoisomers. <sup>b</sup>Determined by <sup>19</sup>F NMR of the reaction crude. <sup>c</sup>Determined for the major diastereoisomer by HPLC. <sup>d</sup>Reaction performed on 1.5 mmol scale of **1a**. <sup>e</sup>Toluene as a solvent. <sup>f</sup>Reaction performed at room temperature. <sup>g</sup>Reaction performed on 1.0 mmol scale of **1c**

In the asymmetric process, with the (*Z*)-ethyl 2-fluoro-5-phenylpent-2-enoate (**1a**), aryl thiols substituted with a halogen (**3b**) and some common electron-donating groups like methoxy (**3c**), amino- (**3d**), and methyl (at *ortho*-, *meta*- and *para*-positions) (**3e-g**) groups were suitable substrates and the desired products were obtained in moderate to excellent yields (38-95%), *dr* (67:33 to 95:5) and moderate to good *ee* values (23-84%). Thiophenol with a substituent at the *ortho*- or the *meta*-position offered good results in both yields, *dr* and *ee* values (**3d-f**). However, thiophenol with a substituent in *para*-position, **3b** (*p*-Br), **3c** (*p*-OMe), and **3g** (*p*-Me), gave relatively low *ee* values, 23%, 38%, and 54% respectively. 2-Thiophenethiol and 2-naphthalenethiol furnished the products in moderate *dr*, but higher yield and *ee*

value were obtained by the 2-thiophenethiol (**3h-i**). Additions of 4-bromothiophenol and 2-naphthalenethiol to a fluorinated Michael acceptor bearing a nitro substituent (**1b**) occurred in moderate yields and *dr* but without enantioselectivities (**3j-k**). Cyclohexyl  $\alpha$ -fluoroacrylate (**1c**) was also used, the corresponding adducts were given in fair yields (34-77%), moderate to excellent *dr* (69:31 to 100:0) and moderate to good *ee* values (26-87%) (**3l-q**). The use of thiophenol and thiophene-2-thiol led to the formation of a single diastereoisomer (**3l**, **3o**). The product **3p** was obtained in the best enantiomeric excess 87%, and its X-ray crystal revealed that two stereogenic centers are both in *S* absolute configurations (**Figure 15**). Then, we studied the asymmetric SMA reaction on some aryl  $\alpha$ -fluoroacrylates (**1d-i**). Generally, aryl  $\alpha$ -fluoroacrylates have lower reactivity compared to alkyl  $\alpha$ -fluoroacrylates as a higher temperature was required and lower yields were obtained for the 1,4-adducts (22-78%). However, they did not show much difference in the diastereoselectivity (87:13 to 100:0) and enantioselectivity (51-73%).  $\alpha$ -Fluorocinnamates bearing a cyano group at the *ortho*-, *meta*-, and *para*-position of arene moiety gave the desired products in similar results showing no significant substituent effects (**3v-x**). The asymmetric SMA reaction could be easily scaled up under the optimized conditions. The reaction of **1a** on a larger scale (1.5 mmol) succeeded in producing the desired products **3a** in 73% isolated yield, 87:13 *dr* and 72% *ee* value for the major diastereoisomer giving the same results that in 0.3 mmol scale (82% yield, 84:16 *dr*, 71% *ee*). The reaction of **1c** on 1.0 mmol scale produced **3p** in 51% isolated yield, 91:9 *dr* and 85% *ee* value for the major diastereoisomer which is quite equivalent to the results obtained in 0.3 mmol scale (55% yield, 90:10 *dr*, 87% *ee*).





C7 and C14 are both in S absolute configuration

**Figure 15** X-ray of the major enantiomer of **3p**

Throughout all the products, we could notice that the low enantioselectivities (2-38% *ee*) were generally obtained with *para*-substituted aryl thiols and 2-naphthalenethiol (**3b**, **3c**, **3i**, **3j**, **3k**, **3m**, **3n**). This might be due to the *para*-substituent or the bulky naphthalen-2-yl hindering the approach of the aryl thiols in the catalyst “pocket”. The mechanism of bis-cinchona alkaloids derivatives catalyzed Michael addition reaction<sup>105,119</sup> is still not clear, essentially because of the lack of hydrogen-donor sites of these catalysts which generally exist in natural cinchona alkaloids and thiourea-based catalysts. Referring to the X-ray of (DHQ)<sub>2</sub>PYR (**Figure 16**)<sup>120</sup>, hereafter, we proposed a transition state model to explain the low *ee* values obtained for *para*-substituted aryl thiols and 2-naphthalenethiol in our SMA reaction (**Figure 17**). We hypothesized that the thiophenolate enter into the pocket-like of the catalyst after deprotonation by the tertiary amine. Checking the X-ray of (DHQ)<sub>2</sub>PYR, we could find that the inward phenyl of pyrimidine is not a planar and could imply steric hindrance for the entered thiophenolate. This might explain why we obtained very low *ee* values with *para*-substituted thiol and 2-naphthalenethiol whereas relatively higher *ee* values were obtained with *meta*- and *ortho*-substituted thiols. Then, the  $\alpha$ -fluoroacrylate came from the *si*-face to minimize the steric interaction and allowed the conjugate addition.

<sup>119</sup> (a) Fang, X.; Dong, X.-Q.; Wang, C.-J. *Tetrahedron Lett.* **2014**, *55*, 5660-5662. (b) Calter, M. A.; Korotkov, A. *Org. Lett.* **2015**, *17*, 1385-1388. (c) Auriá-Luna, F.; Marqués-López, E.; Gimeno, M. C.; Heiran, R.; Mohammadi, S.; Herrera, R. P. *J. Org. Chem.* **2017**, *82*, 5516-5523.

<sup>120</sup> Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4157-4161.

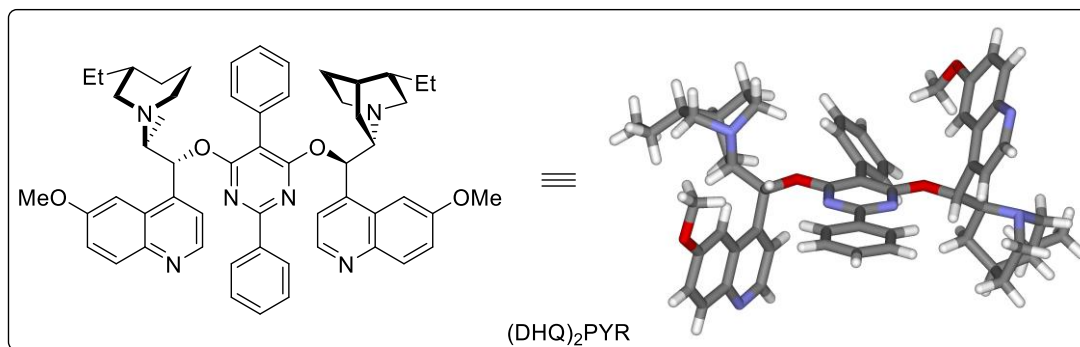
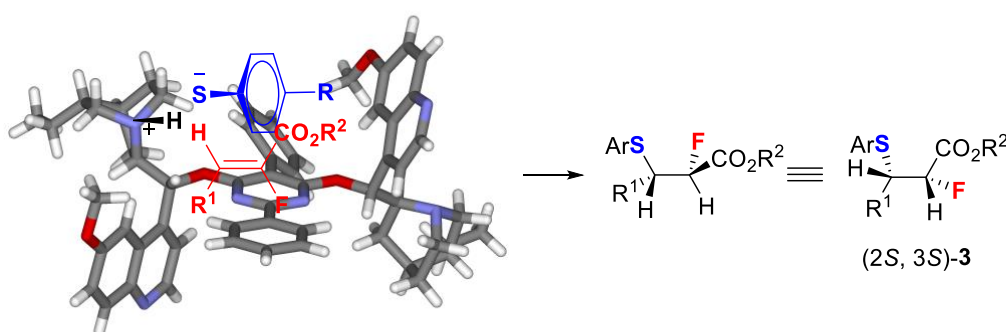
Figure 16 X-ray of (DHQ)<sub>2</sub>PYR

Figure 17 Transition state model

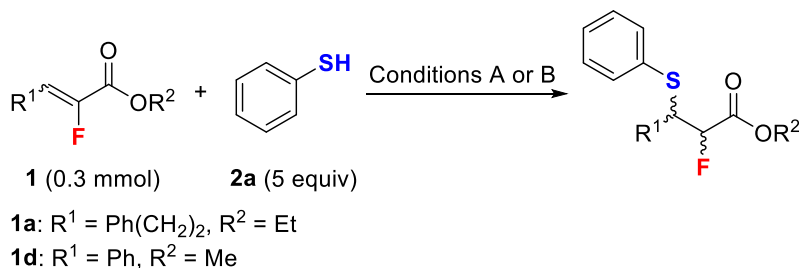
## 2.5 Influence of the double bond geometry

As the reaction scope was all explored with (*Z*)- $\alpha$ -fluoroacrylates. To get insight into the influence of double bond geometry on this reaction, substrates (*E*)-**1a** and (*E*)-**1d** have been synthesized and used in the SMA reaction (**Table 10**). The results showed that the replacement of (*Z*)-substrates by corresponding (*E*)-isomers gave similar yields and enantiomeric excess for the major diastereoisomer but with reversed diastereoisomer ratios. It has to be noted that for the reaction of (*E*)-**1d**, the starting material contained a small amount of (*Z*)-**1d** (*E/Z* = 90/10), explaining the lower *dr* obtained (**Table 10**, entries 6 and 8). All these results point out the face attack does not vary with the geometry of the double bond. Ninomiya and co-workers reported the same observations when they studied the SMA reaction between thiophenol and  $\alpha,\beta$ -trisubstituted acrylates in the presence of a catalytic amount of base, and a concerted process was proposed to explain their results.<sup>121</sup> In our case, we may have

<sup>121</sup> Miyata, O.; Shinada, T.; Naito, T.; Ninomiya, I. *Chem. Pharm. Bull.* **1989**, *39*, 3158-3160.

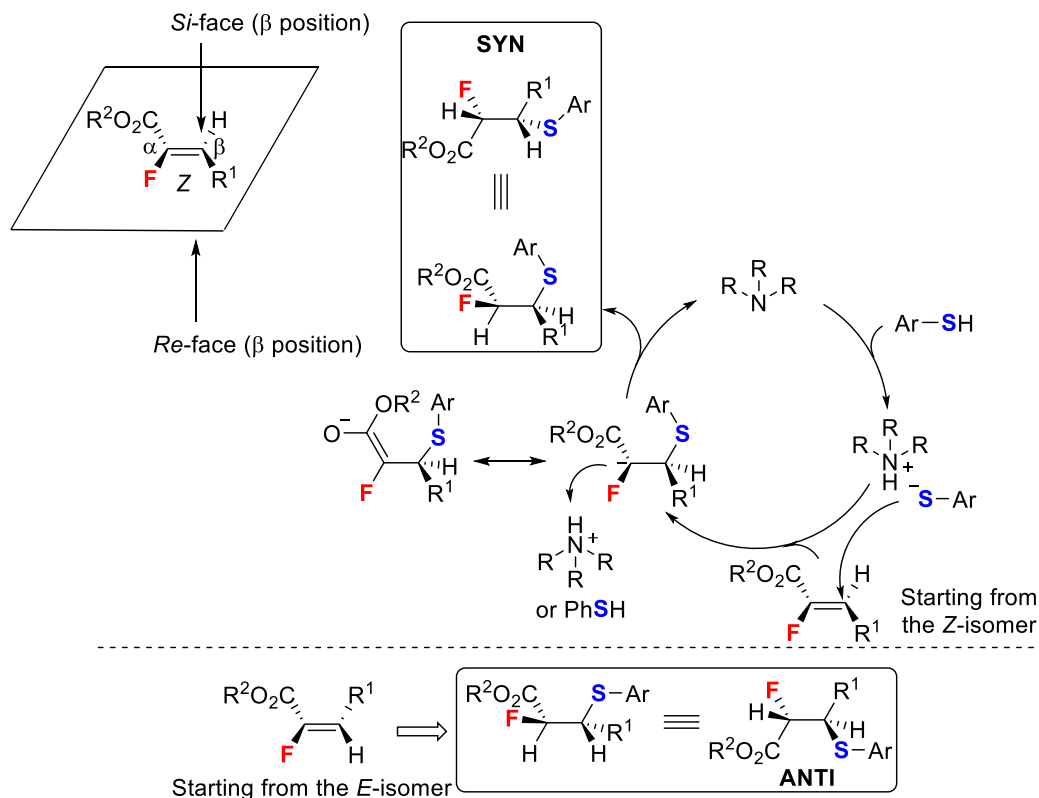
a stepwise mechanism with the thiol addition in favor of the *Si*-face attack of  $\beta$ -position and a concurrent protonation on the *Re*-face of the  $\alpha$ -position (**Scheme 70**).

**Table 10** Influence of the double bond geometry



Entry	Substrates	Conditions	Yield (%) <sup>b</sup>	<i>Dr</i> <sup>c</sup>	<i>Ee</i> (%) <sup>d</sup>
1	( <i>Z</i> )- <b>1a</b>	A	91	76:24	-
2	( <i>E</i> )- <b>1a</b>	A	93	26:74	-
3	( <i>Z</i> )- <b>1a</b>	B	82	84:16	71
4	( <i>E</i> )- <b>1a</b>	B	86	14:86	74
5	( <i>Z</i> )- <b>1d</b>	A	61	87:13	-
6	( <i>E</i> )- <b>1d</b> <sup>e</sup>	A	74	33:67	-
7	( <i>Z</i> )- <b>1d</b>	B	54	88:12	63
8	( <i>E</i> )- <b>1d</b> <sup>e</sup>	B	56	24:76	51

<sup>a</sup>Reaction conditions A : Et<sub>3</sub>N (0.03 mmol, 10 mol%), 80 °C, 16 h, under argon. conditions B : (DHQ)<sub>2</sub>PYR (0.03 mmol, 10 mol%), 0 °C, 5 or 8 days, under argon. <sup>b</sup>Isolated yield of diastereoisomers. <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Determined for the major diastereoisomer by HPLC. <sup>e</sup>Contaminated with 10 % of (*Z*)-**1d**.



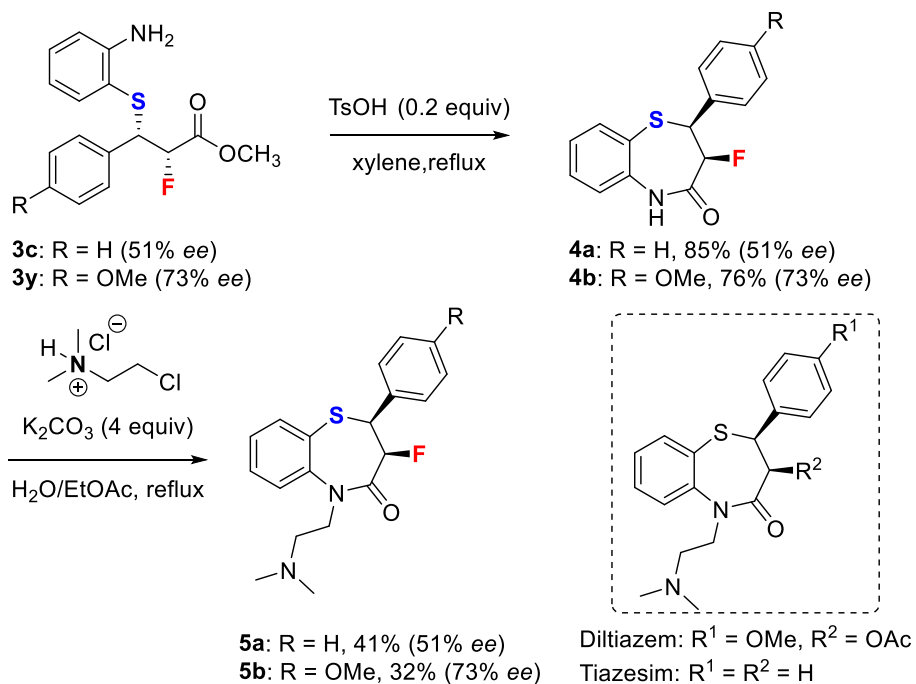
Scheme 70 Proposed mechanism

## 2.6 Synthesis of bioactive molecules

With our methodologies, two fluorinated analogues of bioactive compounds **5a** and **5b** have been synthesized. **5a** is an analogue of the diltiazem, a calcium channel blocker, which has been clinically used since 1974 as an antianginal and antihypertensive agent.<sup>122</sup> **5b** is an analogue of the tiazesim, an antidepressant agent (Scheme 71).<sup>122</sup> Starting from the asymmetric adducts **3s** and **3y** respectively, a two-step synthesis,<sup>123</sup> a cyclization under acid catalysis followed by an alkylation reaction afforded the desired products **5a** and **5b** without any loss in enantiomeric excess.

<sup>122</sup> Bariwal, J. B.; Upadhyay, K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. *Eur. J. Med. Chem.* **2008**, *43*, 2279-2290.

<sup>123</sup> Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851-856.



Scheme 71 Synthesis of biomolecules

## 2.7 Limitations of the reaction

Although we built the organocatalytic routes to access fluorine-containing molecules with  $\alpha$ -fluoroacrylates in both non-enantioselective and enantioselective versions, some limitations cannot be ignored.

Specifically, in the asymmetric process, a long reaction time (5-8 days) was required, some products (**3b**, **3c**, **3n**, **3q**) were obtained with minimal enantioselectivities ( $\leq 38\%$  *ee*) including three no enantioselectivity products (**3j**, **3k**, **3m**) ( $\leq 11\%$  *ee*). The use of other sulfur-nucleophiles such as benzyl mercaptan and thioacetic acid showed very poor <sup>19</sup>F NMR yields (Table 11).

Table 11 The use of other S-nucleophiles

Entry	R-SH	Conversion (%) <sup>b</sup>	<sup>19</sup> F NMR yield (%) <sup>c</sup>	Dr <sup>d</sup>
1	BnSH	57	43	66:34
2	MeC(O)SH	70	8	-

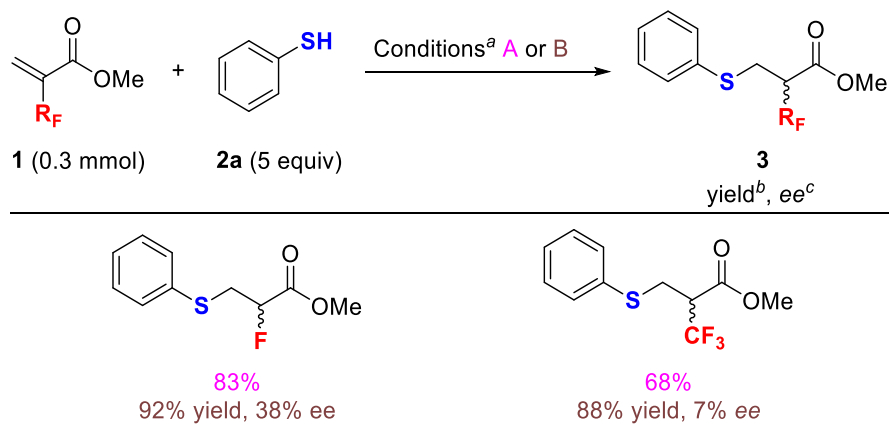
<sup>a</sup>Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2** (1.5 mmol, 5 equiv), Et<sub>3</sub>N (0.03 mmol, 10 mol%), 80 °C, 16 h,

under argon. <sup>b</sup>Determined by <sup>19</sup>F NMR of the reaction mixture. <sup>c</sup>Fluorobenzene as an internal standard.

<sup>d</sup>Determined by <sup>19</sup>F NMR of the reaction crude.

In addition, two commercially available *gem*- $\alpha$ -fluorinated acrylates were employed, which gave unsatisfactory results (**Table 12**).

**Table 12** The use of *gem*- $\alpha$ -fluorinated acrylates

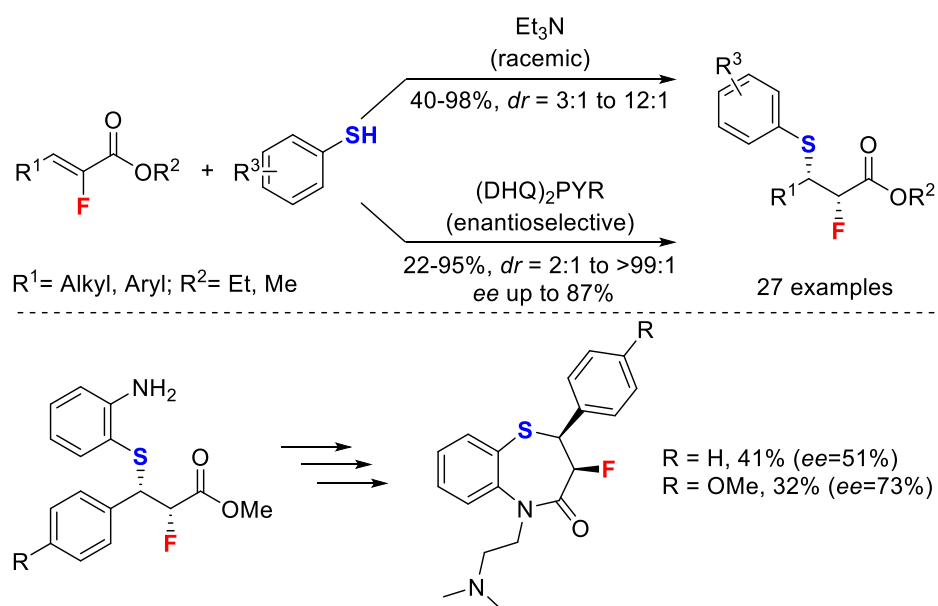


<sup>a</sup>Reaction conditions A: Et<sub>3</sub>N (0.03 mmol, 10 mol%), 80 °C, 16 h, under argon. Conditions B: (DHQ)<sub>2</sub>PYR (0.03 mmol, 10 mol%), 0 °C, 5 days, under argon. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by HPLC.

## 2.8 Conclusion

In summary, we have developed a simple and efficient SMA reaction on  $\beta$ -substituted- $\alpha$ -fluoroacrylates in both non-enantioselective and, for the first time, in the enantioselective versions (**Scheme 72**).<sup>124</sup> This strategy showed great tolerance of various substrates and substituents, providing moderate to excellent yields (40-98%), and moderate to good diastereoselectivities ( $dr = 3/1$  to  $12/1$ ) in a non-enantioselective way. In the enantioselective way we developed, good levels of reactivity, fair to excellent yields and moderate to good enantioselectivities were achieved by using commercially available (DHQ)<sub>2</sub>PYR as a catalyst (22-95% yields,  $dr = 2/1$  to  $>99/1$ ,  $ee$  up to 87%). Two fluorinated analogues of therapeutic agents were successfully synthesized using this SMA strategy.

<sup>124</sup> Huang, X.; David, E.; Jubault, P.; Besset, T.; Couve-Bonnaire, S. *J. Org. Chem.* **2020**, *85*, 14055-14067.



**Scheme 72** SMA of aryl thiols to  $\beta$ -substituted- $\alpha$ -fluoroacrylates

In our quest for the development of new Michael addition with fluorinated acrylates, we will present in the next chapter the phospho-Michael addition with these substrates.

# Chapter 3

## Phospha-Michael Addition on $\alpha$ - Trifluoromethyl- $\alpha,\beta$ -Unsaturated Esters





### 3. Phospha-Michael addition (PMA) on $\alpha$ -trifluoromethyl- $\alpha,\beta$ -unsaturated esters

#### 3.1 Phospha-Michael addition reaction on non-fluorinated $\alpha,\beta$ -unsaturated carbonyl esters

Organophosphorus compounds were found in a wide range of applications in many fields including industrial chemistry and life science.<sup>125</sup> The quest for simple and efficient methods to access these compounds is highly valuable. The conjugate addition of phosphorus nucleophiles to an acceptor-substituted unsaturated bond, which is also known as the phospha-Michael addition (PMA), has been considered as an attractive approach. In many reported PMA reactions,  $\alpha,\beta$ -unsaturated carbonyl compounds (enones, enals and acrylamides), nitroalkenes and olefins bearing sulfones, sulfoxides, phosphonates or phosphane oxides could serve as typical and suitable acceptors for the PMA reactions.<sup>18</sup> Hereafter, we have selected some examples of PMA reactions with acrylates, these reactions are summarized and classified according to the different phosphorus-based nucleophiles.

##### 3.1.1 Trivalent phosphorus-nucleophiles

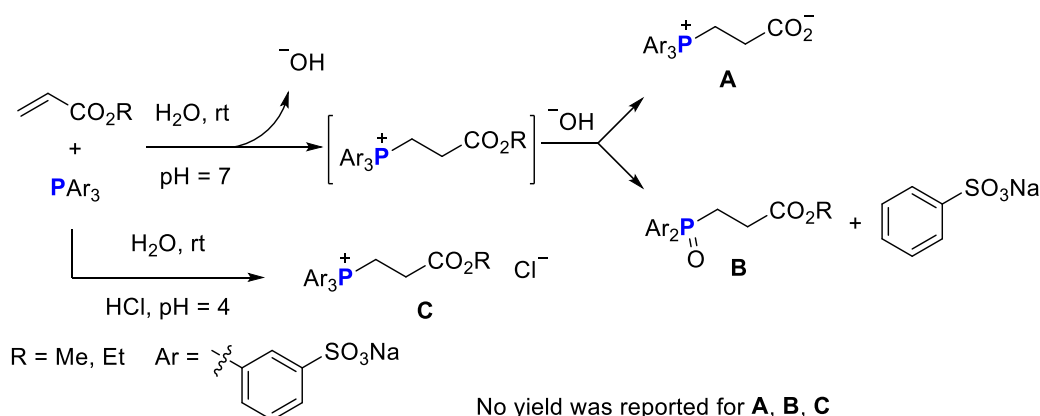
###### 3.1.1.1 Nucleophiles such as $PR_3$ , $P(OR)_3$ and $R^1P(OR^2)_2$

The addition of a trivalent phosphorus nucleophile without P-H bond to  $\alpha,\beta$ -unsaturated carbonyl esters generally generate a phospho-betaine firstly. For example, in 1988, Patin and Larpent reported a nucleophilic addition of water-soluble phosphines on acrylates.<sup>126</sup> In the presence of water, the addition of triphenylphosphine *m*-trisulfonate (TPPTS) to methyl/ethyl acrylate produced a mixture of phosphonium salts (**A**) and phosphine oxides (**B**). The phosphine oxide (**B**)

<sup>125</sup> (a) Toy, A. D. F. W. E. N. *Phosphorus chemistry in everyday living*; American Chemical Society: Washington, D.C., **1987**. (b) Quin, L. D. *A guide to organophosphorus chemistry*; John Wiley & Sons, **2000**. (c) Corbridge, D. E. *Phosphorus: chemistry, biochemistry and technology*; CRC press, **2013**. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3070. (e) Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629-1662. (f) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473.

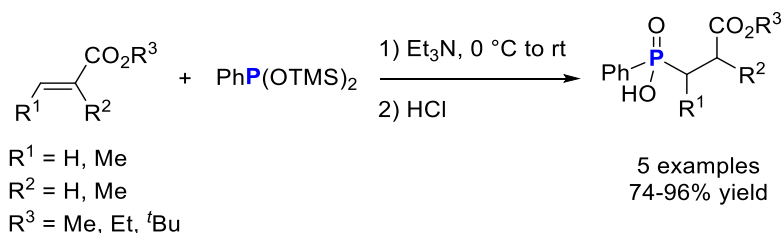
<sup>126</sup> Larpent, C.; Patin, H. *Tetrahedron* **1988**, *44*, 6107-6118.

was resulted from a nucleophilic attack of the  $\text{OH}^-$  (*in situ* generated by the protonation of the carbanion) on the phosphonium with a phenylsulfonate elimination. This  $\text{OH}^-$  can also hydrolyze the ester group to form the phosphonium salts (**A**). When this reaction was performed in an acidic medium, the phosphonium salt (**C**) was afforded as the unique product (**Scheme 73**).



**Scheme 73** Triphenylphosphine *m*-trisulfonate (TPPTS) as the nucleophile

In 1996, Boyd and co-workers described the synthesis of phenylphosphinic acid derivatives by Michael-type addition between bis(trimethylsilyl)phenylphosphonite and several electrophiles.<sup>127</sup> In the case of  $\alpha,\beta$ -unsaturated carbonyl esters, good to excellent yields of the corresponding products were obtained. Substitution of the double bond slightly lowered the yield probably because of the steric and electronic effects (**Scheme 74**).



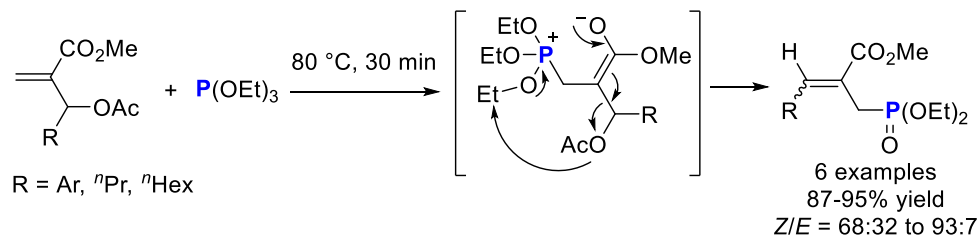
**Scheme 74** Bis(trimethylsilyl)phenylphosphonite as the nucleophile

The same year, Basavaiah and Pandiaraju demonstrated the application of triethyl phosphite as a nucleophile to stereoselectively synthesize allylphosphonates.<sup>128</sup> The reaction started from acetylated Baylis-Hillman adducts, after an intermolecular

<sup>127</sup> Boyd, E. A.; Boyd, M. E. K.; Loh, V. M. *Tetrahedron Lett.* **1996**, *37*, 1651-1654.

<sup>128</sup> Basavaiah, D.; Pandiaraju, S. *Tetrahedron* **1996**, *52*, 2261-2268.

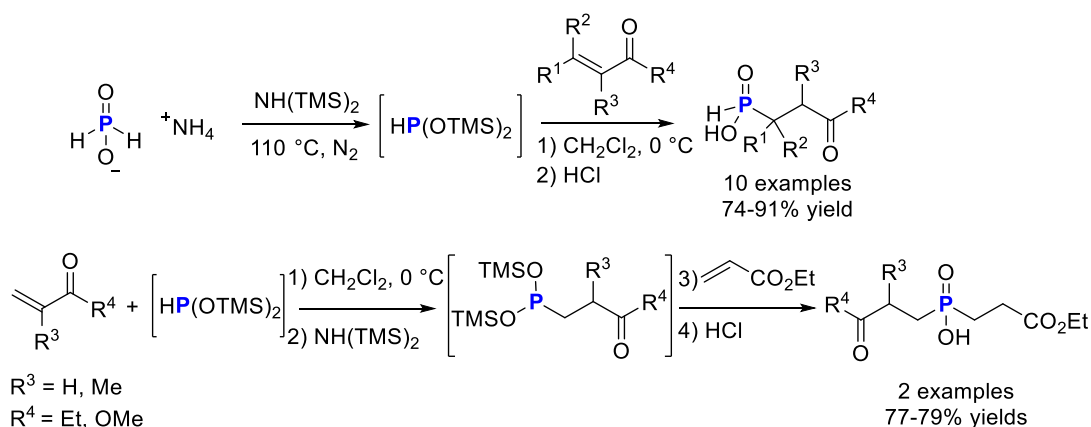
phospha-Michael addition with a subsequent Arbuzov rearrangement, the phosphonates were obtained as a mixture of (*Z*)- and (*E*)-isomers in good to excellent yields (**Scheme 75**).



**Scheme 75** Triethyl phosphite as the nucleophile

### 3.1.1.2 Nucleophiles such as $\text{HPR}_2$ and $\text{HP(OR)}_2$

In contrast to  $\text{PR}_3$  and  $\text{P(OR)}_3$  form nucleophiles, those phosphorus nucleophiles containing a P-H are more common. In 1992, Regan and co-workers reported the syntheses of phosphinic acids by phospha-Michael addition of bis(trimethylsilyl)phosphonite (BTSP) to  $\alpha,\beta$ -unsaturated carbonyl substrates.<sup>129</sup> BTSP was *in situ* generated by heating the ammonium phosphinate with  $\text{NH(TMS)}_2$ . Monosubstituted phosphinic acids could be formed under mild conditions after an acidic work-up. Interestingly, disubstituted phosphinic acids could be also obtained in a one-pot reaction, by adding another equivalent of  $\text{NH(TMS)}_2$  followed by a second Michael acceptor to the reaction mixture (**Scheme 76**).



**Scheme 76** Bis(trimethylsilyl)phosphonite as the nucleophile

In 1995, Minami and co-workers described the synthesis of optically active

<sup>129</sup> Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1992**, *33*, 813-816.

phosphinocarboxylic acids by PMA reaction of  $\text{Ph}_2\text{PH}$  to  $\alpha,\beta$ -unsaturated ester.<sup>130</sup> 1,4-Addition of  $\text{Ph}_2\text{PLi}$  to  $\alpha,\beta$ -unsaturated esters followed by the subsequent treatment with *p*-toluenesulfonic acid (PTSA) led to the racemic phosphinocarboxylic acids in almost quantitative yields. The racemic acids were treated with (+)- or (-)- $\alpha$ -methylbenzylamine (PEA) respectively, giving the optically pure salts after recrystallizations, then the enantiomerically pure acids were obtained by treating the salts with diluted HCl (**Scheme 77**, Eq. a). In the phospha-Michael addition reaction of  $\text{Ph}_2\text{PH}$ , the use of palladium-complex as the catalyst has already been successful with some electron-poor alkenes, such as  $\alpha,\beta$ -unsaturated aldehydes,<sup>131</sup>  $\alpha,\beta$ -unsaturated ketones,<sup>132</sup> and  $\alpha,\beta$ -unsaturated *N*-acylpyrroles.<sup>133</sup> Later, the palladium complex catalyst has also been used with  $\alpha,\beta$ -unsaturated esters. In 2012, Leung and co-workers developed a method for asymmetric PMA of  $\text{Ph}_2\text{PH}$  to methylenemalonate esters under Pd-catalysis.<sup>134</sup> In that case, a palladacycle derived from the corresponding chloro-bridged dimeric palladium compound with silver perchlorate in acetonitrile was the active catalytic species. This protocol gave straightforwardly access to functionalized tertiary phosphines in high conversions and enantioselectivities (**Scheme 77**, Eq. b). In 2013, Duan and co-workers used a chiral palladium complex as the catalyst for the asymmetric PMA reaction of  $\text{Ph}_2\text{PH}$  to  $\alpha,\beta$ -unsaturated carbonyl esters.<sup>76</sup> Under these reaction conditions, various cinnamic acid aryl esters substituted with electron-rich and electron-poor groups were treated with diarylphosphine, providing the oxidative 1,4-adducts in excellent yields and moderate to excellent enantioselectivities (**Scheme 77**, Eq. c).

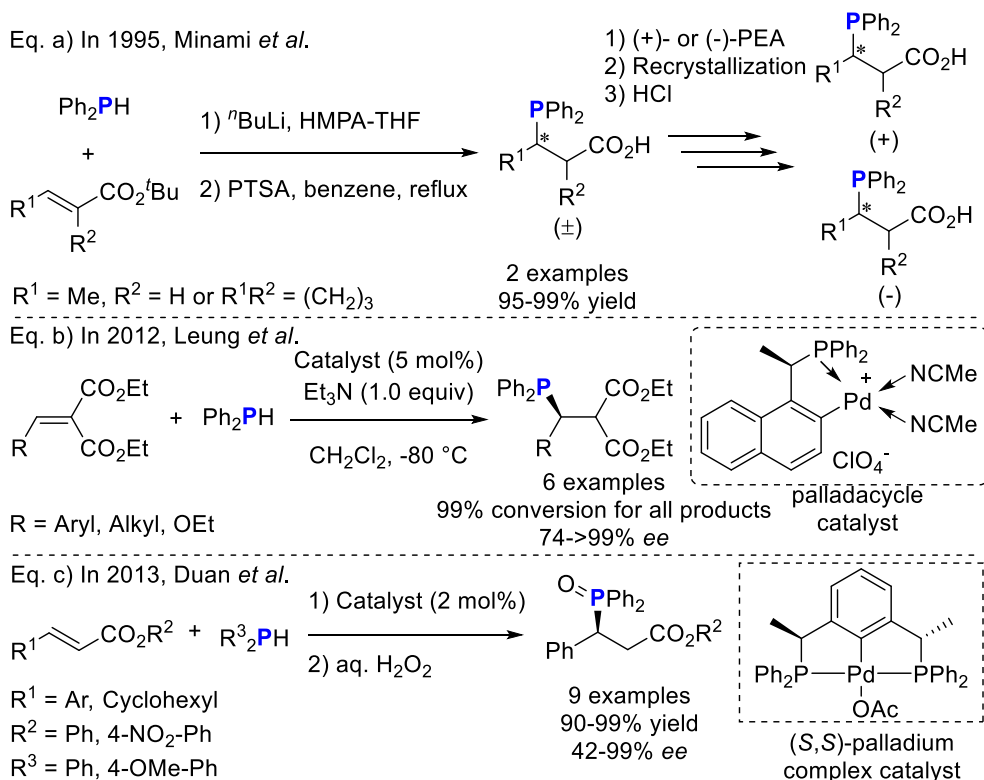
<sup>130</sup> Minami, T.; Okada, Y.; Otaguro, T.; Tawaraya, S.; Furuichi, T.; Okauchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2469-2474.

<sup>131</sup> Chen, Y. R.; Duan, W. L. *Org. Lett.* **2011**, *13*, 5824-5826.

<sup>132</sup> (a) Feng, J. J.; Chen, X. F.; Shi, M.; Duan, W. L. *J. Am. Chem. Soc.* **2010**, *132*, 5562-5563. (b) Huang, Y.; Pullarkat, S. A.; Li, Y.; Leung, P. H. *Chem. Commun.* **2010**, *46*, 6950-6952. (c) Huang, Y.; Chew, R. J.; Li, Y.; Pullarkat, S. A.; Leung, P. H. *Org. Lett.* **2011**, *13*, 5862-5865.

<sup>133</sup> Du, D.; Duan, W. L. *Chem. Commun.* **2011**, *47*, 11101-11103.

<sup>134</sup> Xu, C.; Jun Hao Kennard, G.; Hennesdorf, F.; Li, Y.; Pullarkat, S. A.; Leung, P. H. *Organometallics* **2012**, *31*, 3022-3026.



Scheme 77 Diarylphosphine as the nucleophile

### 3.1.2 Pentavalent phosphorus-nucleophiles

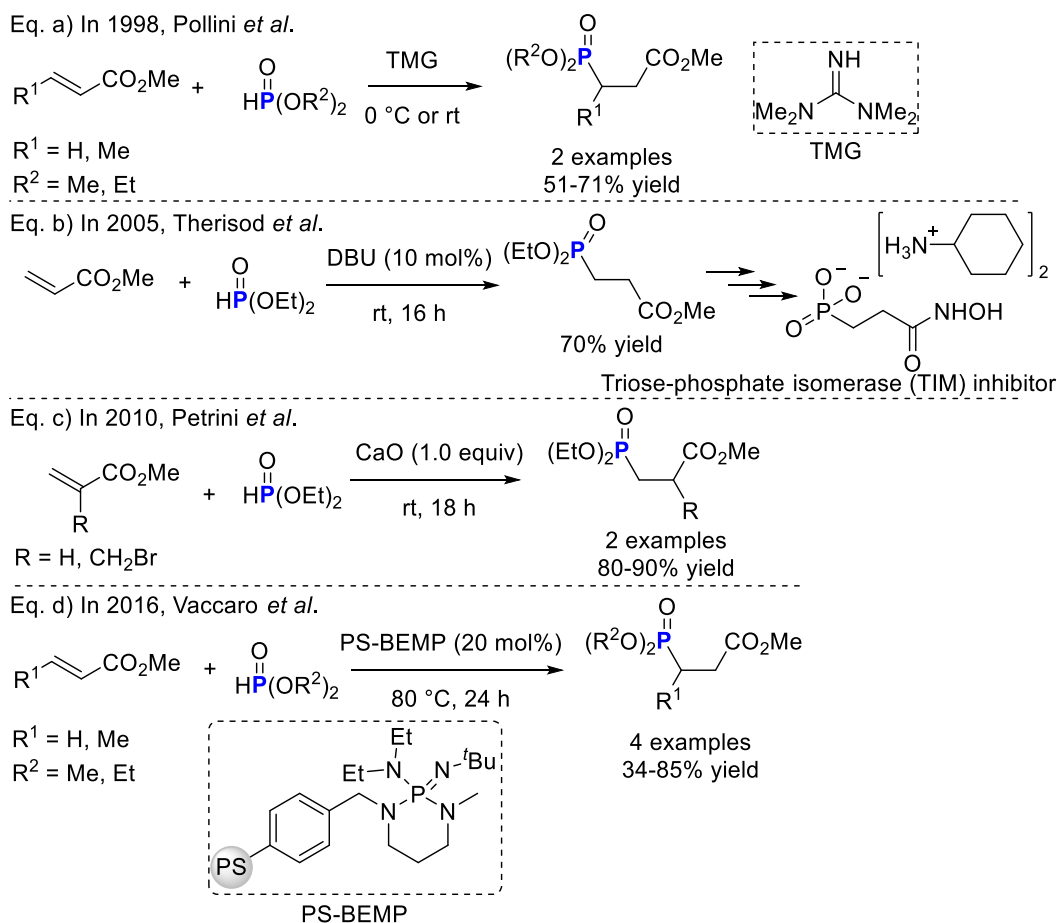
#### 3.1.2.1 Nucleophiles such as $(\text{RO})_2\text{P}(\text{O})\text{H}$ , $(\text{RO})_2\text{P}(\text{S})\text{H}$

$(\text{MeO})_2\text{P}(\text{O})\text{H}$  and  $(\text{EtO})_2\text{P}(\text{O})\text{H}$  represent the two most common nucleophiles with the  $(\text{RO})_2\text{P}(\text{O})\text{H}$  structure in PMA reaction on  $\alpha,\beta$ -unsaturated carbonyl esters, these reactions are usually performed under basic conditions. In 1998, Pollini and co-workers described a tetramethylguanidine (TMG)-catalyzed PMA reaction of dialkyl phosphites to  $\alpha,\beta$ -unsaturated esters.<sup>135</sup> With a catalytic amount of TMG, the reaction furnished the corresponding 1,4-adducts with moderate yields in a short reaction time (**Scheme 78**, Eq. a). In 2005, Therisod and co-workers reported a synthesis of phosphonate inhibitors.<sup>136</sup> A key intermediate of this process was obtained in good yield by a PMA reaction of diethyl phosphite to methyl acrylate under the catalysis of DBU (**Scheme 78**, Eq. b). In 2010, a CaO promoted PMA

<sup>135</sup> Simoni, D.; Invidiata, F. P.; Manfredini, M.; Lampronti, I.; Rondanin, R.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1998**, *39*, 7615-7618.

<sup>136</sup> Fonvielle, M.; Mariano, S.; Therisod, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2906-2909.

reaction of diethyl phosphite to  $\alpha,\beta$ -unsaturated esters was described by Petrini and co-workers.<sup>137</sup> At room temperature, without solvent, the inexpensive CaO showed high efficiency for methyl acrylate and methyl (2-bromomethyl)acrylate (**Scheme 78**, Eq. c). In 2016, Vaccaro and co-workers reported a PMA reaction of dialkyl phosphite to acrylates using a polymer-supported catalyst.<sup>138</sup> The polystyrene supported 2-*tert*-butylimino-2-diethylmanio-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) was used as a basic promoter for this reaction under solvent-free conditions. The substituent on the double bond of Michael acceptor has a significant effect on the 1,4-adduct yield (**Scheme 78**, Eq. d).



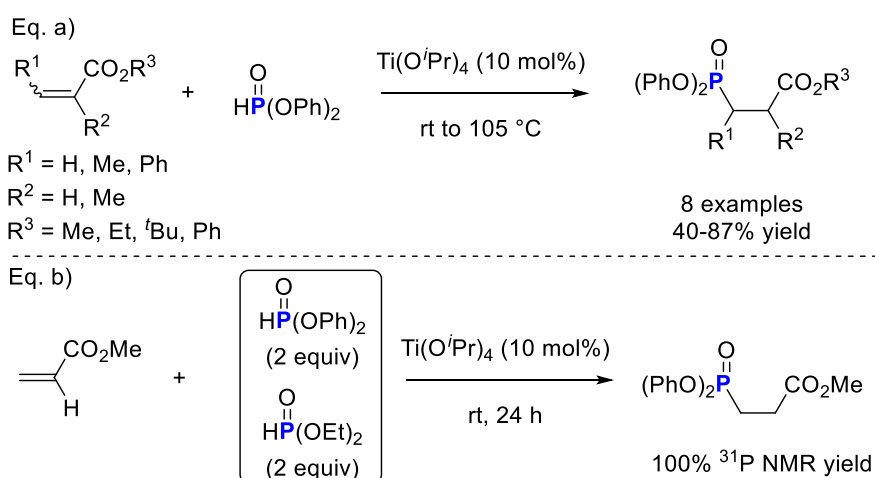
**Scheme 78** Dialkyl phosphite as the nucleophile

In PMA reactions, diaryl phosphites are also used as nucleophiles. In 2007, Yao

<sup>137</sup> Martínez-Castro, E.; López, Ó.; Maya, I.; Fernández-Bolaños, J. G.; Petrini, M. *Green Chem.* **2010**, *12*, 1171-1174.

<sup>138</sup> Strappaveccia, G.; Bianchi, L.; Ziarelli, S.; Santoro, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Org. Biomol. Chem.* **2016**, *14*, 3521-3525.

reported a titanium *iso*-propoxide catalyzed PMA on acrylate-type alkenes.<sup>139</sup> With diphenyl phosphite, the 1,4-adducts were generally obtained in moderate to good yields ((**Scheme 79**, Eq. a). Acrylates with a bulky ester group or with methyl or phenyl substituted-double bond retarded the reaction. Under the catalytic system, when diethyl phosphite was applied as the nucleophile, the corresponding 1,4-adduct was also detected in <sup>31</sup>P NMR. However, when a mixture of diethyl phosphite and diphenyl phosphite was used as nucleophiles, only the product resulting from the reaction with diphenyl phosphite was observed (**Scheme 79**, Eq. b).



**Scheme 79** Diphenyl phosphite as the nucleophile

Cyclic phosphites were also used as nucleophiles in PMA reactions. In 2001, a chiral cyclic phosphite was used in PMA reaction to synthesize  $\beta$ -phosphono malonates.<sup>140</sup> The 1,4-adducts were obtained in moderate to good yields and good diastereoselectivities by using  $\text{Fe}_2\text{O}_3$  supported KOH as a solid base, which led to optically active  $\beta$ -phosphono malonates after easy cleavage of the chiral auxiliary (**Scheme 80**, Eq. a). Ionic liquids are often considered as green chemistry solvents both in laboratory research and industrial practice.<sup>141</sup> In 2009, a PMA reaction of cyclic phosphite to Morita-Baylis-Hillman type substrates was described by Kumara

<sup>139</sup> Yao, Q. *Tetrahedron Lett.* **2007**, *48*, 2749-2753.

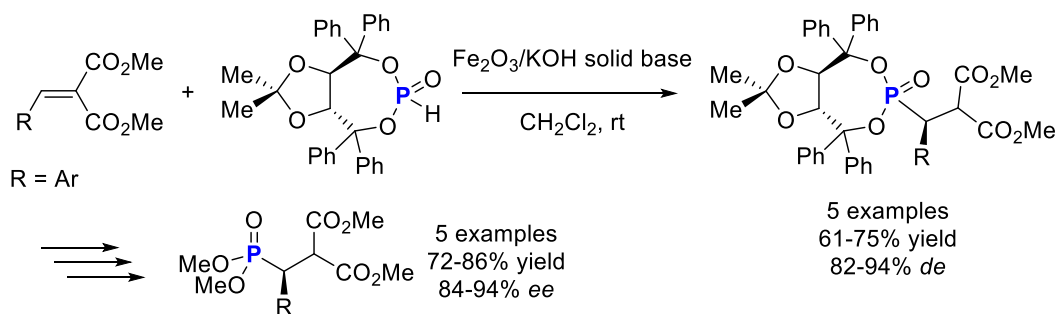
<sup>140</sup> Tedeschi, L.; Enders, D. *Org. Lett.* **2001**, *3*, 3515-3517.

<sup>141</sup> (a) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459-2477. (b) Patel, D. D.; Lee, J. M. *Chem. Rec.* **2012**, *12*, 329-355.

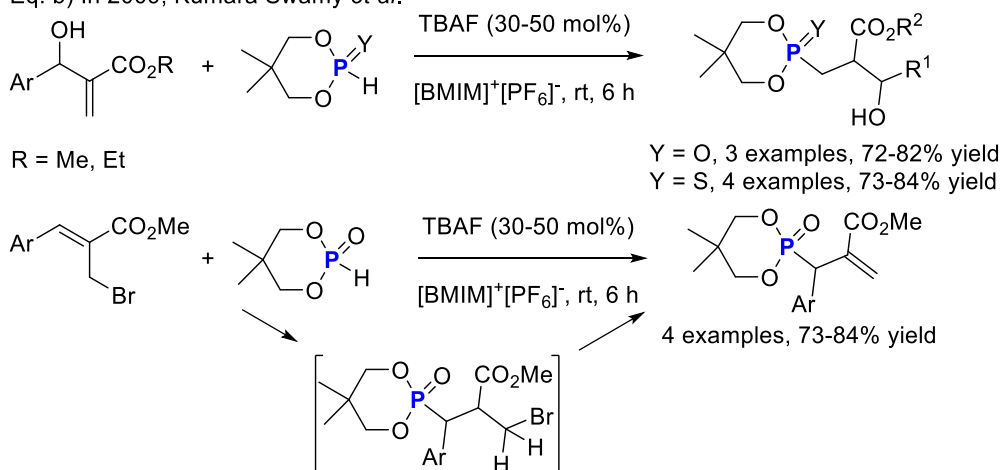


Swamy and co-workers.<sup>142</sup> In the presence of TBAF in  $[\text{BMIM}]^+[\text{PF}_6]^-$ , the Morita-Baylis-Hillman adducts furnished the corresponding  $\gamma$ -hydroxyphosphonates in good yields. With the  $\alpha$ -bromomethyl-cinnamate, the final products formed by the initial 1,4-addition of cyclic phosphites followed by the elimination of HBr were also obtained in good yields (**Scheme 80**, Eq. b).

Eq. a) In 2001, Enders *et al.*



Eq. b) In 2009, Kumara Swamy *et al.*



**Scheme 80** Cyclic phosphite as the nucleophile

### 3.1.2.2 Nucleophiles such as $\text{R}_2\text{P}(\text{O})\text{H}$

Diarylphosphine oxides are typical phosphorus-nucleophiles with the general structure  $\text{R}_2\text{P}(\text{O})\text{H}$ . In 2012, Stockland and co-workers developed a protocol for the PMA reaction on substituted acrylates in a microwave reactor without catalyst.<sup>143</sup> Under a high temperature, by using ditolyphosphine oxide as the nucleophile, this method was successfully applied on various substituted acrylates, giving the

<sup>142</sup> Balaraman, E.; Srinivas, V.; Kumara Swamy, K. C. *Tetrahedron* **2009**, *65*, 7603-7610.

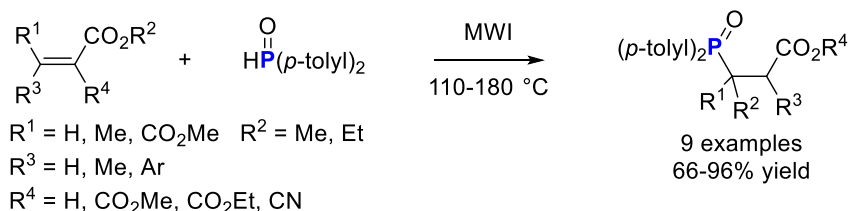
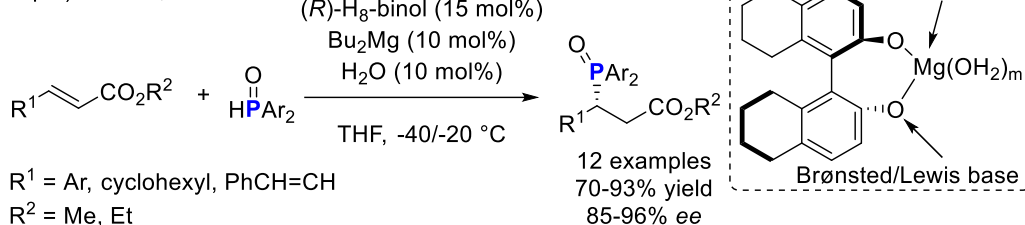
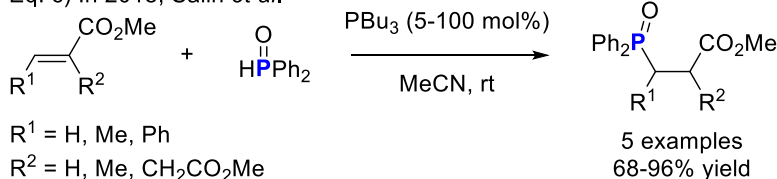
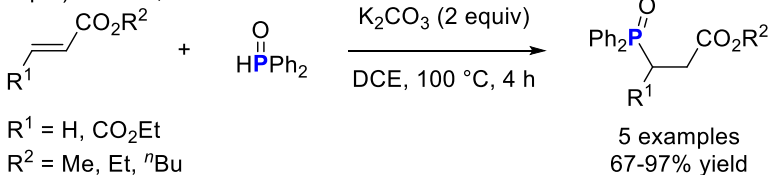
<sup>143</sup> Lenker, H. K.; Richard, M. E.; Reese, K. P.; Carter, A. F.; Zawisky, J. D.; Winter, E. F.; Bergeron, T. W.; Guydon, K. S.; Stockland, R. A., Jr. *J. Org. Chem.* **2012**, *77*, 1378-1385.

phospha-Michael adducts in high yields (**Scheme 81**, Eq. a). Later, Ishihara and co-workers described the enantioselective PMA reaction of diaryl phosphine oxides to  $\alpha,\beta$ -unsaturated carbonyl esters.<sup>144</sup> The chiral magnesium complex catalyst was formed by  $\text{MgBu}_2$  with (*R*)- $\text{H}_8$ -binol and the presence of water, which the magnesium center providing a strong Brønsted/Lewis acidity to activate the Michael acceptor and the oxygen atom of the (*R*)- $\text{H}_8$ -binol moiety providing a strong Brønsted/Lewis basicity to activate  $\text{R}_2\text{P}(\text{O})\text{H}$ . Under the optimized conditions, the 1,4-adducts were obtained in good to excellent yields with a high level of enantioselectivity (**Scheme 81**, Eq. b). In 2018, Salin and co-workers reported a tributylphosphine ( $\text{PBu}_3$ ) catalyzed PMA reaction on  $\alpha,\beta$ -unsaturated carbonyl esters.<sup>145</sup> This methodology afforded a series of tertiary phosphine oxides in good to excellent yields under mild conditions and performed well on a gram-scale (**Scheme 81**, Eq. c). In 2020, Guo and co-workers reported a weak base promoted PMA reaction on several acrylates.<sup>146</sup> With diphenyl phosphine oxide as the nucleophile source,  $\text{K}_2\text{CO}_3$  promoted the reaction furnishing the corresponding phospha-Michael adducts in moderate to excellent yields (**Scheme 81**, Eq. d).

<sup>144</sup> Hatano, M.; Horibe, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4549-4553.

<sup>145</sup> Salin, A. V.; Il'in, A. V.; Faskhutdinov, R. I.; Galkin, V. I.; Islamov, D. R.; Kataeva, O. N. *Tetrahedron Lett.* **2018**, *59*, 1630-1634.

<sup>146</sup> Guo, S.; Huang, Z.; Liu, W.; Li, S.; Yang, Y.; Cai, H. *Synlett* **2020**, *31*, 1295-1297.

Eq. a) In 2012, Stockland *et al.*Eq. b) In 2013, Isihara *et al.*Eq. c) In 2018, Salin *et al.*Eq. d) In 2020, Guo *et al.*

Scheme 81 diaryl phosphine oxides as the nucleophile

### 3.1.2.3 Phosphine-borane nucleophiles

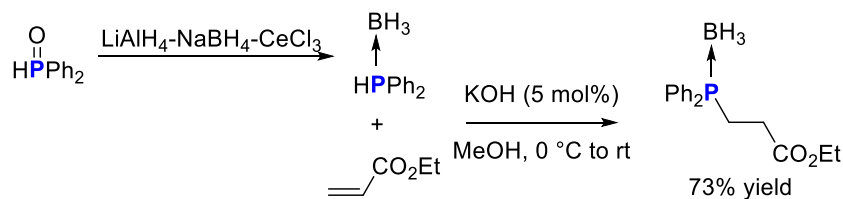
Phosphine-boranes ( $\text{R}_{3-n}\text{H}_n\text{PBH}_3$ ) are Lewis acid-Lewis base adducts derived from phosphines and borane.<sup>147</sup> As they are air-stable, they could be considered as a borane-protected form of the corresponding phosphines ( $\text{R}_{3-n}\text{H}_n\text{P}$ ). Thus, they are used as phosphorus-nucleophiles in some Michael addition reactions. In 1990, Imamoto and co-workers developed a method for the synthesis of phosphine-boranes in a one-pot process.<sup>148</sup> The resulting diphenylphosphine-borane could undergo a 1,4-addition with ethyl acrylate in the presence of KOH, affording the phospho-Michael adduct in 73% yield (Scheme 82, Eq. a). In 1994, Corre and co-workers described a PMA reaction of the same phosphine-borane to a chiral *bis*-

<sup>147</sup> Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023-4078.

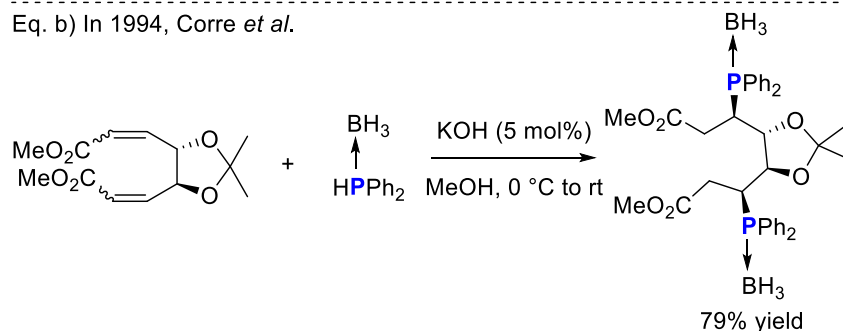
<sup>148</sup> Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244-5252.

acrylate.<sup>149</sup> Interestingly, this reaction gave a single diastereoisomer in 79% yield, even if the *bis*-acrylate was initially obtained as a (*Z*)/(*E*) mixture (**Scheme 82**, Eq. b).

Eq. a) In 1990, Imamoto *et al.*



Eq. b) In 1994, Corre *et al.*



**Scheme 82** phosphine-borane as the nucleophile

### 3.1.3 PMA reaction on fluorinated Michael acceptors: State of the art

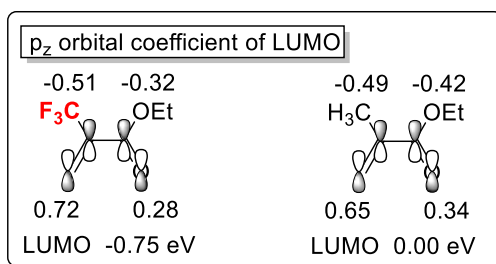
The trifluoromethyl ( $\text{CF}_3$ ) group represents an important fluorine-containing substituent.<sup>150</sup>  $\text{CF}_3$ -containing compounds are very popular due to the effect of  $\text{CF}_3$  group on modulating physical, chemical and biological properties like lipophilicity, acidity, steric hindrance and so on.<sup>4, 6a-e</sup> Moreover, the  $\text{CF}_3$  moiety is a significant electron-withdrawing group owing to the presence of electronegative fluorine atoms.<sup>151</sup> Its strong negative inductive effect on  $sp^2$ -carbon could lower LUMO energy level, for example, the difference of LUMO energy level between ethyl 2-(trifluoromethyl)acrylate and ethyl methacrylate is 0.75 eV (**Figure 18**).<sup>35</sup> These results prompted us to believe that the trifluoromethylated unsaturated compounds can serve as good Michael acceptors, and indeed, some examples have been

<sup>149</sup> Gourdel, Y.; Pellon, P.; Toupet, L.; Le Corre, M. *Tetrahedron Lett.* **1994**, *35*, 1197-1200.

<sup>150</sup> (a) Zanda, M. *New J. Chem.* **2004**, *28*, 1401-1411. (b) Nie, J.; Guo, H. C.; Cahard, D.; Ma, J. A. *Chem. Rev.* **2011**, *111*, 455-529. (c) García-Monforte, M. A.; Martínez-Salvador, S.; Menjón, B. *Eur. J. Inorg. Chem.* **2012**, *2012*, 4945-4966.

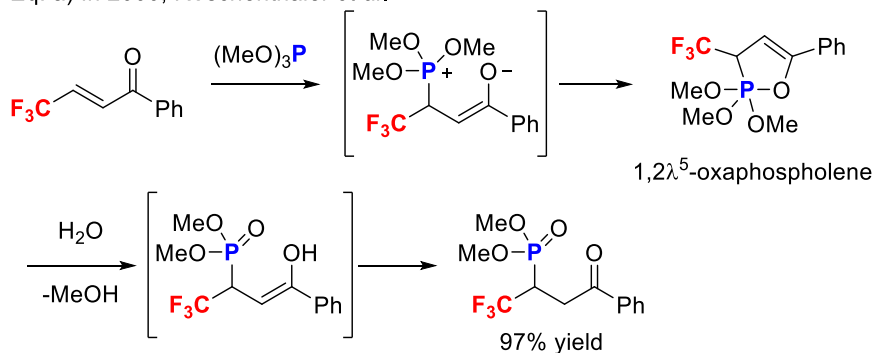
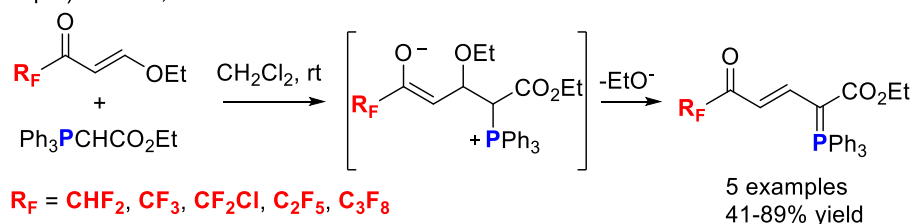
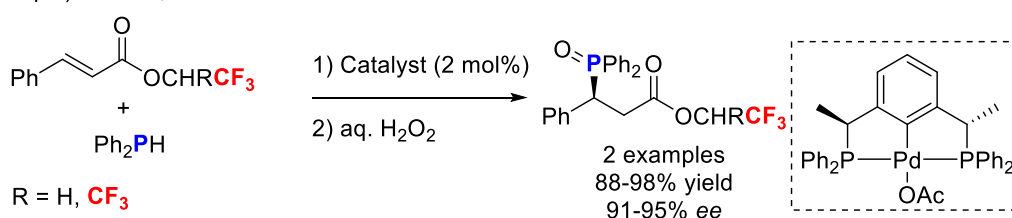
<sup>151</sup> True, J. E.; Thomas, T. D.; Winter, R. W.; Gard, G. L. *Inorg. Chem.* **2003**, *42*, 4437-4441.

reported in the literature (see § 1.4.1.4).



**Figure 18** The  $p_z$  orbital coefficient of LUMO

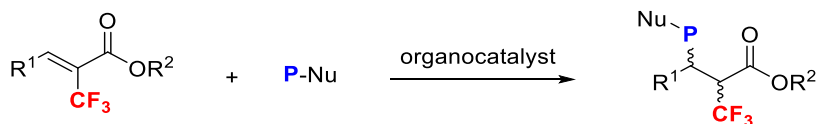
However, in the examples of trifluoromethylated Michael acceptors introduced in chapter 1, we can point out that a very few examples led to the C-P formation even including other fluorinated Michael acceptors. In 2000, Röschenthaler and co-workers described a protocol for the synthesis of  $\gamma$ -ketophosphonate.<sup>48</sup> A [4+1] cycloaddition reaction between (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one and trimethyl phosphite, where the initial attack of phosphorus occurred at the  $\beta$ -position of the enone followed by ring closure, produced 1,2 $\lambda^5$ -oxaphospholene as a sole product which upon hydrolysis furnished  $\gamma$ -ketophosphonate (**Scheme 83**, Eq. a). In 2007, Kondratov and co-workers described the reaction between the  $Ph_3PCHCO_2Et$  ylide and fluorinated  $\beta$ -ketoaldehyde derivatives.<sup>74</sup> The unusual products were formed by the initial ylide attack at the  $\beta$ -position of the enone followed by subsequent  $EtO^-$  elimination (**Scheme 83**, Eq. b). In 2013, Duan and co-workers used a chiral palladium complex as the catalyst for the asymmetric phospha-Michael addition reaction of diphenylphosphine to  $\alpha,\beta$ -unsaturated carboxylic esters.<sup>76</sup> Two fluorinated cinnamate esters, for which the fluorinated substituent was located on the ester group, furnished the corresponding adducts in good yields and excellent enantioselectivities (**Scheme 83**, Eq. c).

Eq. a) In 2000, Röscenthaler *et al.*Eq. b) In 2007, Kondratov *et al.*Eq. c) In 2013, Duan *et al.*

Scheme 83 PMA reactions on fluorinated Michael acceptor

### 3.2 Objectives

Phospha-Michael addition reaction is an attractive strategy for the C-P bond formation. Indeed, various phosphorus-containing compounds could be treated as suitable phosphorus-nucleophiles and the electrophiles are also diverse. However, the  $\alpha,\beta$ -unsaturated ester Michael acceptors are not widely used in the literature and to our knowledge, no  $\alpha$ -fluorinated acrylate has been used in such reactions. Regarding all the described PMA reactions on  $\alpha,\beta$ -unsaturated esters, most of them performed with unsubstituted acrylates or monosubstituted acrylates. Therefore, in this chapter, our goal was to develop the first phospha-Michael addition on  $\beta$ -substituted- $\alpha$ -trifluoromethylacrylates to synthesize original scaffolds bearing both phosphorus and fluorinated moieties (Scheme 84).



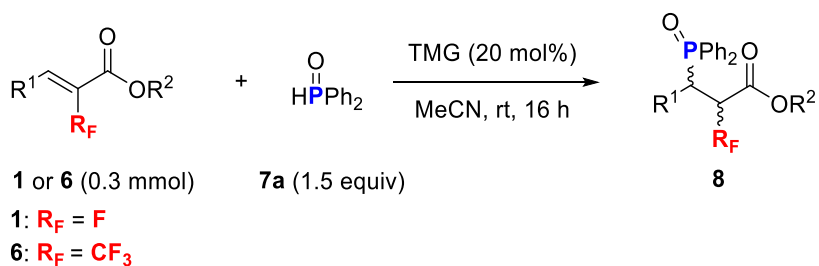
Scheme 84 The first PMA reaction on trifluoromethylated acrylates

### 3.3 Optimization of the reaction conditions

#### 3.3.1 Preliminary results

At the beginning of our investigation, when the  $\alpha$ -fluoroacrylates (**1**) and  $\alpha$ -trifluoromethylacrylates (**6**) reacted with diphenylphosphine oxide (**7a**) in PMA reactions, different behaviors were observed (Table 13). In the presence of TMG,  $\alpha$ -fluoroacrylates (Table 13, entries 1-3), especially those with a  $\beta$ -substituent barely react with **7a** (Table 13, entries 2-3), were less reactive than  $\alpha$ -trifluoromethylacrylates (Table 13, entries 4-5). Both  $\alpha$ -trifluoromethylacrylates gave full conversions and the desired 1,4-adducts were isolated in 68% and 84% (*dr* = 66:34) yields respectively (Table 13, entries 4-5). Considering these results, we decided to continue our investigations with  $\alpha$ -trifluoromethylacrylates as substrates for the PMA reaction.

Table 13 PMA reaction of different fluorinated acrylates



Entry	R <sup>1</sup>	R <sup>2</sup>	R <sub>F</sub>	Conversion% <sup>b</sup>	<sup>19</sup> F NMR yield <sup>b</sup> (isolated yield <sup>c</sup> )%	<i>Dr</i> <sup>d</sup>
1	H	Me	F	83	78 (38)	-
2	Ph(CH <sub>2</sub> ) <sub>2</sub>	Et	F	5	Trace	50:50
3	Ph	Me	F	7	Trace	20:80
4	H	Me	CF <sub>3</sub>	100	89 (68)	-
5	Ph	Me	CF <sub>3</sub>	100	93 (84)	66:34

<sup>a</sup>Reaction conditions: **1** or **6** (0.3 mmol, 1 equiv), **7a** (0.45 mmol, 1.5 equiv), TMG (0.06 mmol, 20 mol%), room temperature, 16 h, in MeCN (0.5 mL). <sup>b</sup>Conversion and <sup>19</sup>F NMR yield were obtained by using PhF or PhCOCF<sub>3</sub> as an internal standard. <sup>c</sup>Isolated yield of (**8**) as a mixture of two diastereoisomers. <sup>d</sup>Determined by the <sup>19</sup>F NMR of

the reaction crude.

### 3.3.2 Screening of the base and the equivalents of $\text{Ph}_2\text{P}(\text{O})\text{H}$

Based on the preliminary results, we decided to choose methyl (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (**6b**) as the Michael acceptor and diphenylphosphine oxide (**7a**) as the phosphorus-nucleophile to optimize this PMA reaction. As the use of TMG led to a full conversion and 84% of isolated yield, but moderate diastereoselectivity (**Table 14**, entry 1), we screened some other bases which all have the potential to promote this reaction. An inorganic base  $\text{K}_2\text{CO}_3$  led to a lower  $^{19}\text{F}$  NMR yield (39%) with a reversed low diastereomeric ratio (**Table 14**, entry 2). The primary amine, isopropylamine (IPA) was inefficient in both yield and diastereoselectivity (**Table 14**, entry 3). Even though IPA and diisopropylamine (DIPA) have very close  $\text{pK}_a$  values, the latter gave a much better result, the 1,4-adduct (**8a**) was obtained in 79%  $^{19}\text{F}$  NMR yield as a mixture of diastereoisomers with a 18:82 *dr* (**Table 14**, entry 4). The use of tertiary amines led to good to high  $^{19}\text{F}$  NMR yields (80-95%) for **8a** except for DBU (47%) (**Table 14**, entries 5-8). Worth mentioning, with triethylamine and DABCO, **8a** was isolated in 94% and 91% respectively, whereas a better but reversed diastereomeric ratio was afforded by DABCO (**Table 14**, entries 5 and 8). The equivalents of **7a** only affect the yield of **8a**, decreasing the equivalent of **7a** led to lower yields (**Table 14**, entries 9-10). The use of 2 equivalents of **7a** did not give a better yield compared to 1.5 equivalents (**Table 14**, entries 8 and 11). Additionally, we tested the reaction at 0 °C and 50 °C (**Table 14**, entries 12-13), the  $^{19}\text{F}$  NMR yields were close to the one obtained when the reaction was carried out at room temperature (**Table 14**, entry 8). The lower temperature did not give a positive effect on diastereoselectivity lowering the *dr* (*dr* = 83:17) whereas the higher temperature furnished the same *dr* compared to the one obtained at room temperature. Finally, we confirmed that the best results were obtained when this reaction was performed with 1.5 equivalents of **7a** under the catalysis of DABCO at room temperature.



**Table 14** Screening of the base and the equivalents of  $\text{Ph}_2\text{P}(\text{O})\text{H}$ 

Entry	Base	x equiv of $\text{Ph}_2\text{P}(\text{O})\text{H}$	$^{19}\text{F}$ NMR yield <sup>b</sup> (isolated yield <sup>c</sup> )%	$Dr^d$
1	TMG	1.5	93 (84)	66:34
2	$\text{K}_2\text{CO}_3$	1.5	39	41:59
3	IPA	1.5	13	32:68
4	DIPA	1.5	79	18:82
5	$\text{Et}_3\text{N}$	1.5	92 (94)	17:83
6	DIPEA	1.5	80	27:73
7	DBU	1.5	47	75:25
8	DABCO	1.5	95 (91)	92:8
9	DABCO	1.0	59	92:8
10	DABCO	1.2	64	92:8
11	DABCO	2.0	94	91:9
12 <sup>e</sup>	DABCO	1.5	94	83:17
13 <sup>f</sup>	DABCO	1.5	96	91:9

<sup>a</sup>Reaction conditions: **6b** (0.3 mmol, 1 equiv), **7a** (x equiv), base (0.06 mmol, 20 mol%), room temperature, 16 h, in MeCN (0.5 mL). <sup>b</sup> $^{19}\text{F}$  NMR yields were obtained by using  $\text{PhCOCF}_3$  as an internal standard. <sup>c</sup>Isolated yield of **8a** as a mixture of two diastereoisomers. <sup>d</sup>Determined by the  $^{19}\text{F}$  NMR of the reaction crude. <sup>e</sup>Reaction carried out at 0 °C. <sup>f</sup>Reaction carried out at 50 °C.

### 3.3.3 Screening of the solvents and the DABCO loading

Herein, the effect of solvent and the loading of DABCO on this PMA reaction were explored. The use of  $\text{CH}_2\text{Cl}_2$  as solvent lowered both  $^{19}\text{F}$  NMR yield and diastereomeric ratio (**Table 15**, entry 1). Compared to MeCN, when THF or  $\text{Et}_2\text{O}$  was used as the solvent, comparable  $^{19}\text{F}$  NMR yields were obtained, with obvious decrease in diastereoselectivities (**Table 15**, entries 2-4). Based on these results, MeCN was chosen as the solvent to study the DABCO loading. A small amount of **8a** with a reversed diastereomeric ratio was observed in the absence of DABCO (**Table 15**, entry 5). Increasing the loading of DABCO improved the  $^{19}\text{F}$  NMR yields as well as

the diastereoselectivities (**Table 15**, entries 4-7). The improvement in  $^{19}\text{F}$  NMR yields was particularly obvious when the loading of DABCO was increased from 5 mol% to 10 mol% (**Table 15**, entries 6-7). In the end, we decided to perform this reaction with 20 mol% of DABCO in MeCN (**Table 15**, entry 4).

**Table 15** Screening of the solvents and the DABCO loading

**6b** (0.3 mmol) + **7a** (1.5 equiv)  $\xrightarrow[\text{solvent, rt, 16 h}]{\text{DABCO (y mol\%)}}$  **8a**

Entry	DABCO (y mol%)	Solvent (0.5 mL)	$^{19}\text{F}$ NMR yield <sup>b</sup>	<i>Dr</i> <sup>c</sup>
1	20	CH <sub>2</sub> Cl <sub>2</sub>	50	56:44
2	20	THF	90	74:26
3	20	Et <sub>2</sub> O	94	77:23
4	20	MeCN	96	92:8
5	0	MeCN	14	23:77
6	5	MeCN	42	82:18
7	10	MeCN	83	89:11

<sup>a</sup>Reaction conditions: **6b** (0.3 mmol, 1.0 equiv), **7a** (0.45 mmol, 1.5 equiv), DABCO (y mol%), room temperature, 16 h, in solvent (0.5 mL). <sup>b</sup> $^{19}\text{F}$  NMR yields were obtained by using PhCOCF<sub>3</sub> as an internal standard. <sup>c</sup>Determined by the  $^{19}\text{F}$  NMR of the reaction crude.

Thus, the optimal experimental conditions were defined as 1.5 equivalent of diphenylphosphine oxide with 20 mol% of DABCO in MeCN at room temperature overnight for 16 h.

### 3.3.4 Enlarge the scope of fluorinated Michael acceptors

As we defined the suitable conditions for the Michael addition of diphenylphosphine oxide (**7a**) to methyl (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (**6b**), we decided not only to use  $\alpha$ -trifluoromethylacrylates as Michael acceptors in this PMA reaction. Hereafter, another fluorinated acrylate was tested, and some further experiments have been done to optimize the reaction (**Table 16**).

The methyl (*Z*)-2-(fluoromethyl)-3-phenylacrylate (**9a**) was employed in PMA reaction, the optimized conditions used with  $\alpha$ -trifluoromethylacrylate were not

suitable for **9a**, because only trace of products were observed in  $^{19}\text{F}$  NMR (**Table 16**, entry 1). Extending the reaction time to 40 h, afforded the corresponding 1,4-adduct in 16%  $^{19}\text{F}$  NMR yield as a mixture of diastereoisomers with a 96:4 *dr* ratio (**Table 16**, entry 2). Carrying out the reaction at 40 °C led to a better NMR yield, with the same *dr* ratio (**Table 16**, entries 1, 3). Increasing the temperature to 80 °C had no positive effect on NMR yield and reduced the diastereoselectivity (**Table 16**, entry 4). So we decided to perform this reaction at 40 °C and to increase the reaction time to enhance the reaction yield (**Table 16**, entries 2, 5-6). Finally, 72 h of reaction time led to a full conversion of **9a**, and **10a** was isolated in 64% yield with a 95:5 *dr* ratio (**Table 16**, entry 6).

**Table 16** Optimization of  $\alpha$ -fluoromethylacrylate

Reaction scheme: **9a** (0.3 mmol) + **7a** (1.5 equiv)  $\xrightarrow[\text{MeCN}]{\text{DABCO (20 mol\%)}}$  **10a**

Entry	T (°C)	Reaction time (h)	$^{19}\text{F}$ NMR yield <sup>b</sup> (isolated yield <sup>c</sup> )%	<i>Dr</i> <sup>d</sup>	Identities of products
1	rt	16	Trace	-	
2	rt	40	16	96:4	<b>Major</b> : -218.6 ppm (td, <i>J</i> = 46.2, 16.9 Hz)
3	40	16	35 (21)	96:4	
4	80	16	38	90:10	<b>Minor</b> : -222.3 ppm (td, <i>J</i> = 46.7, 17.8 Hz)
5	40	40	55	95:5	
6	40	72	79 (64)	95:5	

<sup>a</sup>Reaction conditions: **9a** (0.3 mmol, 1.0 equiv), **7a** (0.45 mmol, 1.5 equiv), DABCO (0.06 mmol, 20 mol%), in MeCN (0.5 mL). <sup>b</sup> $^{19}\text{F}$  NMR yields were obtained by using PhF as an internal standard. <sup>c</sup>Isolated yield of **10a** as a mixture of two diastereoisomers. <sup>d</sup>Determined by the  $^{19}\text{F}$  NMR of the reaction crude.

Worthy to note that we also wanted to use the (*Z*)-2-(difluoromethyl)-3-phenylacrylate as substrates to have a complete picture of the  $\alpha$ -fluorinated methyl acrylate family, but the synthesis of these substrates was rather difficult and, for lack of time, we had to abandon this part.

### 3.5 Substrate scope of the reaction

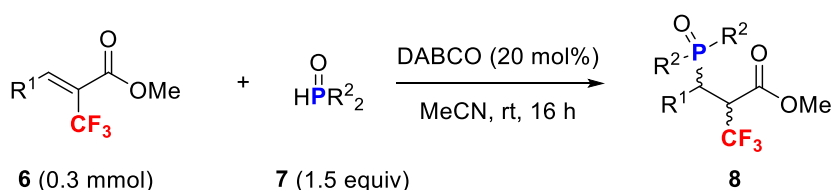
With the optimized conditions in hand, we investigated the scope of DABCO-

promoted phospha-Michael addition reaction of diarylphosphine oxides to  $\alpha$ -trifluoromethylacrylates and  $\alpha$ -fluoromethylacrylates respectively.

### 3.5.1 with $\alpha$ -trifluoromethylacrylates

The investigations showed various  $\alpha$ -trifluoromethylacrylates (**6**) and diarylphosphine oxides (**7**) were tolerated in this PMA reaction. The corresponding phospha-Michael adducts (**8**) were obtained in moderate to excellent yields (55-95%) with moderate to excellent diastereoselectivities (dr = 70:30 to 99:1) (**Table 17**).

**Table 17** Substrate scope on  $\alpha$ -trifluoromethylacrylates



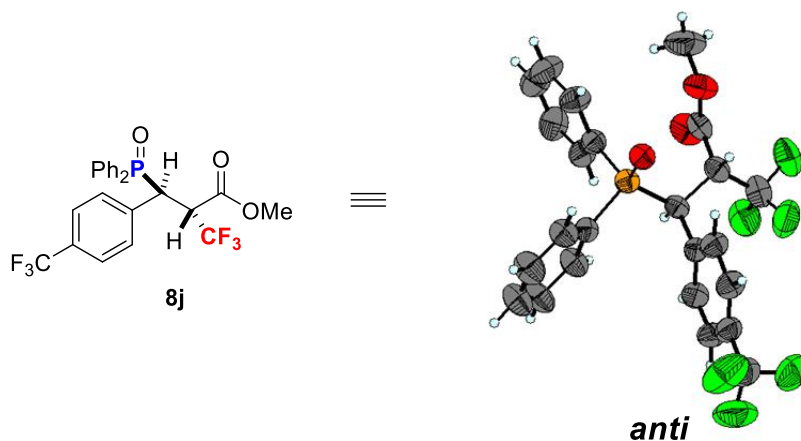
Entry	R <sup>1</sup>	<b>6</b>	R <sup>2</sup>	<b>8</b>	Isolated yield (%) <sup>b</sup>	Dr <sup>c</sup>
1	H	<b>6a</b>	Ph	<b>8a</b>	74	-
2	Ph	<b>6b</b>	Ph	<b>8b</b>	91 (84 <sup>d</sup> )	92:8 (91:9 <sup>d</sup> )
3	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>6c</b>	Ph	<b>8c</b>	84	93:7
4	4-OH-C <sub>6</sub> H <sub>4</sub>	<b>6d</b>	Ph	<b>8d</b>	71	85:15
5	4-NMe <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>6e</b>	Ph	<b>8e</b>	52	93:7
6	4- <sup>t</sup> Bu-C <sub>6</sub> H <sub>4</sub>	<b>6f</b>	Ph	<b>8f</b>	77	81:19
7	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>6g</b>	Ph	<b>8g</b>	91	97:3
8	3-Me-C <sub>6</sub> H <sub>4</sub>	<b>6h</b>	Ph	<b>8h</b>	81	93:7
9	2-Me-C <sub>6</sub> H <sub>4</sub>	<b>6i</b>	Ph	<b>8i</b>	61	70:30
10	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	<b>6j</b>	Ph	<b>8j</b>	88	99:1
11	4-CN-C <sub>6</sub> H <sub>4</sub>	<b>6k</b>	Ph	<b>8k</b>	80	97:3
12	4-F-C <sub>6</sub> H <sub>4</sub>	<b>6l</b>	Ph	<b>8l</b>	95	98:2
13	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>6m</b>	Ph	<b>8m</b>	94	97:3
14	2-Cl-C <sub>6</sub> H <sub>4</sub>	<b>6n</b>	Ph	<b>8n</b>	55	74:26
15	4-Br-C <sub>6</sub> H <sub>4</sub>	<b>6o</b>	Ph	<b>8o</b>	88	99:1
16	3,5-di-OMe-C <sub>6</sub> H <sub>3</sub>	<b>6p</b>	Ph	<b>8p</b>	94	90:10
17	Naphthalen-2-yl	<b>6q</b>	Ph	<b>8q</b>	83	94:6
18	Thiophen-2-yl	<b>6r</b>	Ph	<b>8r</b>	75	96:4
19	( <i>E</i> )-4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>6s</b>	Ph	<b>8m</b>	70	85:15

20	( <i>E</i> )-2,4,6-tri-OMe-C <sub>6</sub> H <sub>2</sub>	<b>6t</b>	Ph	<b>8s</b>	NR <sup>e</sup>	-
21	Ph	<b>6b</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>8t</b>	87	95:5
22	Ph	<b>6b</b>	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>8u</b>	70	91:9
23	Ph	<b>6b</b>	OEt	<b>8v</b>	NR <sup>e</sup>	-

<sup>a</sup>Reaction conditions: **6** (0.3 mmol, 1.0 equiv), **7** (0.45 mmol, 1.5 equiv), DABCO (0.06 mmol, 20 mol%), rt, 16 h, in MeCN (0.5 mL). <sup>b</sup>Isolated yield of **8** as a mixture of two diastereoisomers. <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Reaction was performed on 2.0 mmol scale. <sup>e</sup>NR = No Reaction.

With diphenylphosphine oxide (**7a**) as the nucleophile, the use of commercially available methyl 2-(trifluoromethyl)acrylate smoothly afforded the 1,4-adduct (**8a**) in 74% yield. The use of  $\beta$ -phenyl- $\alpha$ -trifluoromethylacrylate (**6b**) gave the product (**8b**) in 91% yield with a 92:8 *dr* ratio. On a larger scale (2.0 mmol), **6b** also performed well, **8b** was obtained in 84% yield with a 91:9 *dr* ratio. The phenyl moiety at  $\beta$ -position of these  $\alpha$ -trifluoromethylacrylates could bear electron-donating groups, such as methoxy (**6c**, **6p**), hydroxyl (**6d**), dimethylamino (**6e**), *tert*-butyl (**6f**), and methyl (at *para*-, *meta*-, and *ortho*-position) (**6g-i**). It could also bear electron-withdrawing groups, such as trifluoromethyl (**6j**), cyano (**6k**), and halogens (**6l-o,6s**). Those substrates with a *para*-substituted arene usually furnished the products (**8c-g**, **8j-m**, **8o**) in good to high yields with high *dr* ratios (71-95% yield, *dr* = 81:19 to 99:1), except for **8e** (52% yield). The substrates with a *meta*- or *ortho*-substituted arene lowered both the yields and diastereomeric ratios. The use of substrate beared a *meta*-substituted methylphenyl slightly decreased the yield and *dr* ratio (**8h**, 81% yield, 93:7 *dr*), whereas the *ortho*-substituted one led to a significant drop on both yield and *dr* ratio (**8i**, 61% yield, 70:30 *dr*), probably because of the steric hindrance. The same phenomenon was observed for *ortho*-chloro **8n** (55% yield, 74:26 *dr*). When electron-withdrawing groups and halogens were presented at *para*-position of the phenyl moiety, the desired products (**8j-m**, **8o**) were obtained in 80-95% yield with excellent diastereoselectivities (*dr* = 97:3 to 99:1). Additionally, the substrate **6p** containing a disubstituted phenyl (3,5-dimethoxyphenyl) at  $\beta$ -position was also tested and the corresponding product **8p** was obtained in 94% yield with a 90:10 *dr* ratio. The  $\beta$ -substituents of trifluoromethylacrylate could be extended to

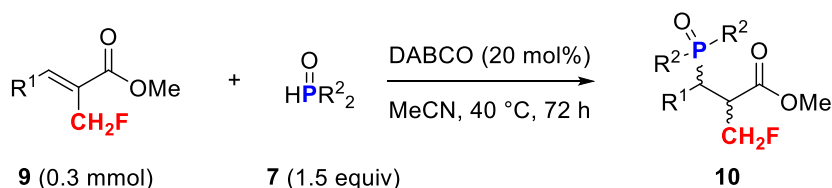
naphthalen-2-yl and thiophen-2-yl, furnishing the products in good yields with excellent *dr* ratios (**8q**, 83% yield, 94:6 *dr*; **8r**, 75% yield, 96:4 *dr*). The product **8m** could be obtained from both (*Z*) and (*E*)-trifluoromethylacrylates, the (*E*)-substrate (**6s**) led to a lower yield and lower *dr* ratio (70% yield, 85:15 *dr*). We were not surprised that the reaction did not occur with **6t** due to its strong steric hindrance (**8s**). In the end, with **6b**, we tested some other phosphorus-nucleophiles. The reactions proceeded smoothly when two other diarylphosphine oxides (**7b-c**) were employed (**8t-u**). However, the use of diethyl phosphite (**7d**) only led to the recovery of the two starting materials. The X-ray analysis of the crystal obtained from **8j** confirmed that the major diastereoisomer was in *anti*-configuration (**Figure 19**).



**Figure 19** X-ray of the major diastereoisomer of **8j**

### 3.5.2 with $\alpha$ -fluoromethylacrylates

In this DABCO-promoted PMA reaction,  $\alpha$ -fluoromethylacrylates (**9**) behaved less reactive compared to  $\alpha$ -trifluoromethylacrylates (**6**). The phospha-Michael adducts (**10**) were obtained in low to moderate yields (29-70%) under long reaction time conditions at 40 °C, fortunately, with excellent diastereoselectivities (*dr*>94:6) (**Table 18**).

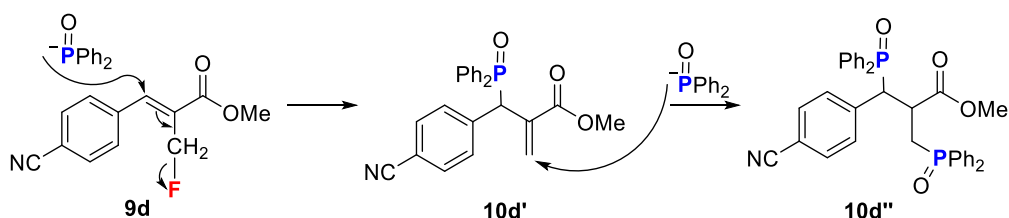
**Table 18** Substrates scope on  $\alpha$ -fluoromethylacrylates

Entry	$R^1$	<b>9</b>	$R^2$	<b>10</b>	Isolated yield (%) <sup>b</sup>	$Dr^c$
1	Ph	<b>9a</b>	Ph	<b>10a</b>	64 (52 <sup>d</sup> )	95:5 (95:5 <sup>d</sup> )
2	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>9b</b>	Ph	<b>10b</b>	51	96 :4
3 <sup>f</sup>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>9c</b>	Ph	<b>10c</b>	44	96 :4
4 <sup>f</sup>	4-CN-C <sub>6</sub> H <sub>4</sub>	<b>9d</b>	Ph	<b>10d</b>	29	97 :3
5 <sup>f</sup>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>9e</b>	Ph	<b>10e</b>	0	-
6	Furan-2-yl	<b>9f</b>	Ph	<b>10f</b>	NR	-
7	<sup>n</sup> Pentyl	<b>9g</b>	Ph	<b>10g</b>	NR	-
8	Ph	<b>9a</b>	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>10h</b>	70	95 :5
9	Ph	<b>9a</b>	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>10i</b>	53	94 :6
10	Ph	<b>9a</b>	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>10j</b>	0	-

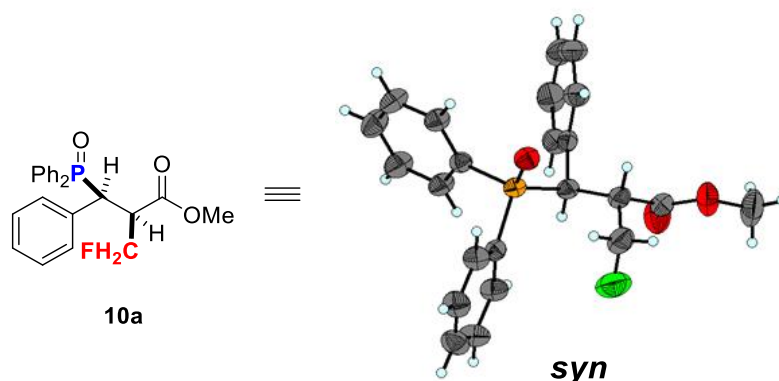
<sup>a</sup>Reaction conditions: **9** (0.3 mmol, 1.0 equiv), **7** (0.45 mmol, 1.5 equiv), DABCO (0.06 mmol, 20 mol%), 40 °C, 72 h, in MeCN (0.5 mL). <sup>b</sup>Isolated yield of **10** as a mixture of two diastereoisomers. <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude. <sup>d</sup>Reaction was performed on 1.0 mmol scale. <sup>e</sup>NR = No Reaction. <sup>f</sup>Reaction was performed under 50 °C for 5 days.

By using methyl (*Z*)-2-(fluoromethyl)-3-phenylacrylate (**9a**), the desired 1,4-adduct was obtained in 64% yield with a 95:5 *dr* ratio (**10a**). The phenyl moiety at  $\beta$ -position could bear methoxy group (**9b**), chlorine (**9c**), and cyano group (**9d**). It did not affect the diastereoselectivities but decreased the yields (**10b-d**, 29-51%, *dr*>96:4). Highlighting that an electron-withdrawing substituent disrupted the reactivity of the substrate, the phenyl moiety bearing a cyano group led to the formation of the desired product in only 29% yield (**10d**) alongside with two major fluorine-free byproducts **10d'** (22%) and **10d''** (16%) (isolated by preparative TLC, structures were identified by NMR and LC-MS). In that case, the presence of electron-withdrawing cyano group seemed to favor the elimination of a fluoride prior to reprotonation leading to compound **10d'**, then a second addition of diphenylphosphine oxide furnished the second byproduct **10d''** (Scheme 85). The use of substrate containing

a *para*-nitrophenyl led to more complex unseparated products without forming desired product (**10e**). We were disappointed to see that furan-2-yl and *n*-pentyl substituted substrates did not work at all in this reaction (**10f-g**). Some other diarylphosphine oxides were employed as the nucleophile, the corresponding 1,4-adducts of bis(4-methoxyphenyl)phosphine oxide and bis(4-methylphenyl)phosphine oxide were obtained in 70% and 53% yield, respectively (**10h-i**). whereas, the use of bis(4-chlorophenyl)phosphine oxide as the nucleophile also led to complex byproducts without forming the desired product **10j**. The major diastereoisomer for this PMA reaction was determined by X-ray analysis of the crystal obtained from **10a** and proved to be in *syn*-configuration (**Figure 20**).



**Scheme 85** The formation of byproducts **10d'** and **10d''**



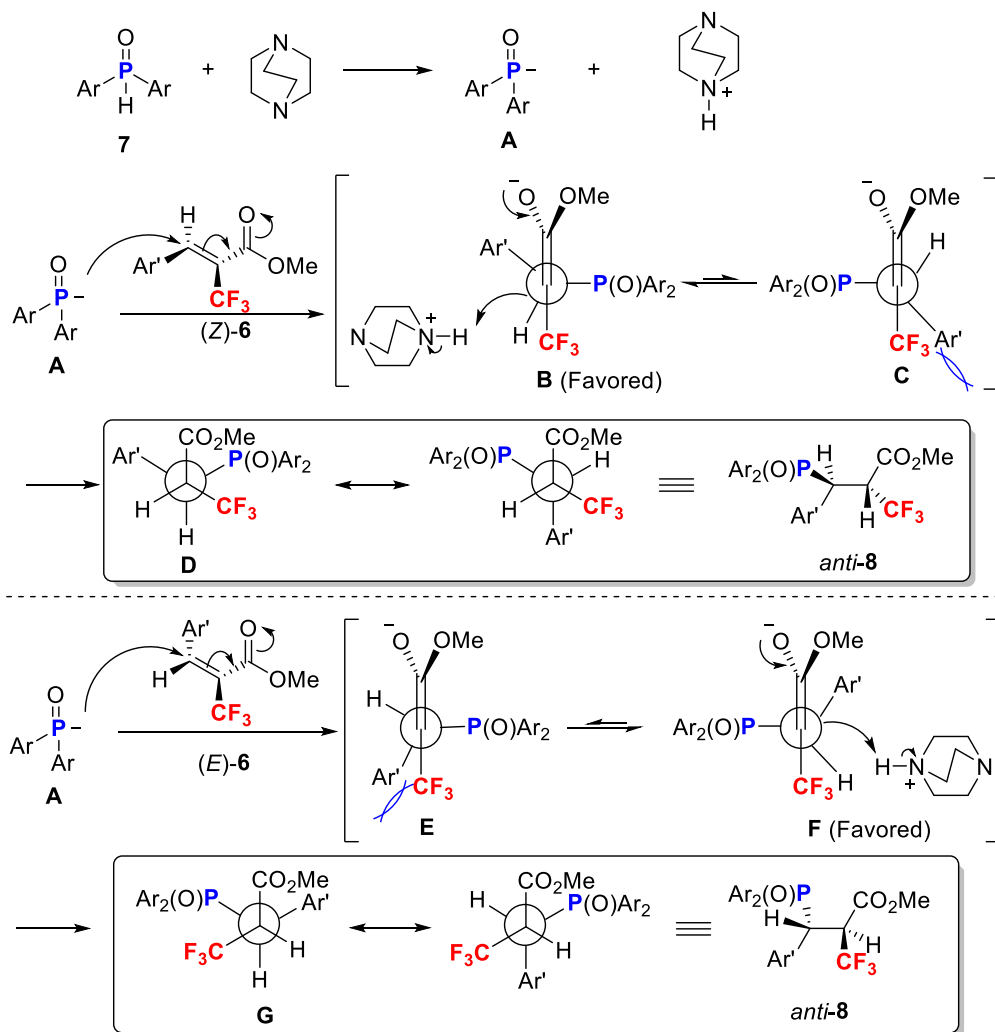
**Figure 20** X-ray of the major diastereoisomer of **10a**

### 3.6 Proposed reaction mechanism

A possible mechanism of DABCO-catalyzed PMA reaction of diarylphosphine oxides to  $\alpha$ -trifluoromethylacrylates **6** was proposed in **Scheme 86**. The phosphorus anion **A** was generated from the deprotonation by DABCO, then attacked the  $\beta$ -position of (*Z*)-**6** to form enolate **B** or **C**, then the proton abstraction from the protonated



DABCO follow the Felkin-Anh rule, occurred at the less hindered side of favored enolate **B**, leading to the formation of **D**, which was the diastereocontrol step to give the thermodynamically favorable *anti*-**8**. When the reaction started with (*E*)-**6**, enolate **F** was the favored one due to the steric interaction of **E** between the aryl and  $\text{CF}_3$  moieties, the proton abstraction also came from the less hindered side leading to the *anti*-**8**.

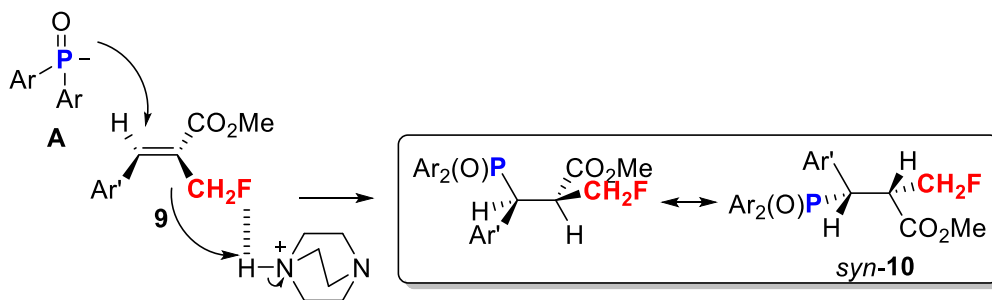


**Scheme 86** Proposed mechanism for the reaction on  $\alpha$ -trifluoromethylacrylates **6**

With  $\alpha$ -fluoromethylacrylates **9** as the Michael acceptors, two important features have to be pointed out: a) the  $\text{CH}_2\text{F}$  moiety is much less hindered than the  $\text{CF}_3$  moiety and b) the fluorine of the  $\text{CH}_2\text{F}$  moiety is known to be a superior hydrogen-bond acceptor compared to the fluorine of  $\text{CF}_3$  moiety,<sup>152</sup> in that context, we

<sup>152</sup> Dalvit, C.; Invernizzi, C.; Vulpetti, A. *Chem. Eur. J.* **2014**, *20*, 11058-11068.

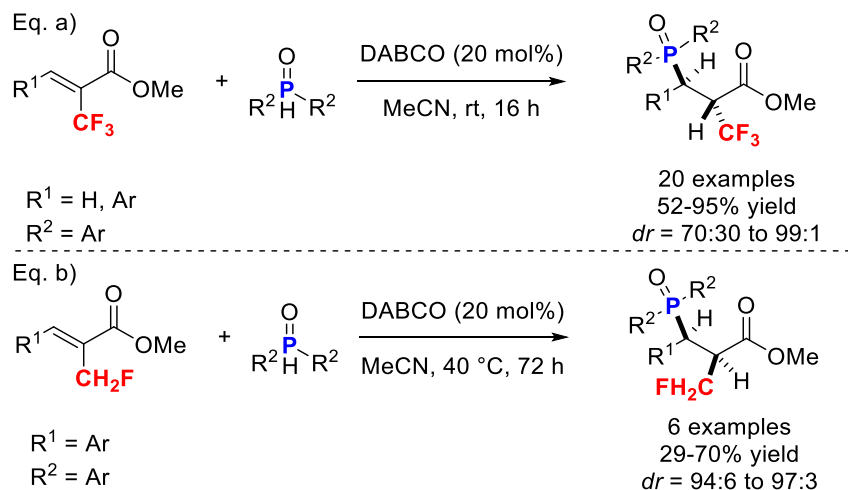
speculated that there was an interaction between the fluorine atom of  $\text{CH}_2\text{F}$  and the protonated DABCO, then the protonation occurred from the *si*-face ( $\alpha$ -position) leading to the corresponding products in *syn*-configuration (**Scheme 87**). It would have been interesting to test the reaction with the alkene in *E*-configuration which should lead to the *anti*-**10** following this concerted mechanism, unfortunately, by lack of time we did not do this experiment.



**Scheme 87** PMA reaction on  $\alpha$ -fluoromethylacrylates **9**

### 3.7 Conclusion

In conclusion, we built the first PMA reaction of diarylphosphine oxides to  $\alpha$ -trifluoromethylacrylates under mild conditions. This reaction provided efficient and highly diastereoselective access to tertiary phosphine oxides among various  $\beta$ -substituted- $\alpha$ -trifluoromethylacrylates. The corresponding products were generally obtained in moderate to excellent yields (52-95%) and good to high diastereoselectivities towards the *anti*-diastereoisomer ( $dr = 70:30$  to  $99:1$ ) (**Scheme 88**, Eq. a). We also demonstrated that this method could also be applicable to  $\beta$ -substituted- $\alpha$ -fluoromethylacrylates, producing the desired products in low to moderate yields (29-70%) but with excellent diastereoselectivities in each case towards the *syn*-diastereoisomer ( $dr >94:6$ ) (**Scheme 88**, Eq. b).



**Scheme 88** PMA reaction of diarylphosphine oxides to  $\beta$ -substituted- $\alpha$ -trifluoromethylacrylates

In this PMA reaction, we made some efforts for the enantioselective formation of C-P bond by using chiral catalysts or introducing chiral moiety to the Michael acceptor. These results including various reactions attempted to enlarge the scope of Michael addition reactions with our  $\alpha$ -fluorinated Michael acceptors will be discussed in the next chapter.

# Chapter 4

## Other Michael Addition Reactions on Fluorinated Substrates



## 4. Other Michael addition reactions on fluorinated substrates

In our previous work, we demonstrated a SMA reaction of arylthiols to  $\alpha$ -fluoroacrylates and a PMA reaction of diarylphosphine oxides to  $\alpha$ -trifluoromethylacrylates and  $\alpha$ -fluoromethylacrylates respectively. These results proved that Michael addition reactions with such substrates were feasible and constituted a nice access to more complex fluorine-containing compounds. Therefore, we used our  $\alpha$ -fluorinated acrylates in hand as well as some newly synthesized  $\alpha$ -fluorinated  $\alpha,\beta$ -unsaturated carbonyl compounds, to explore more possibilities of those substrates as Michael acceptors. Some nucleophiles besides thiols and diarylphosphine oxides, which were commonly used in Michael addition reaction on non-fluorinated analogues, have been tested, including nitromethane,<sup>153</sup> diethyl malonate,<sup>154</sup> lithium dimethylcuprate,<sup>155</sup> and phenylboronic acid.<sup>156</sup>

### 4.1 Michael addition reaction of different nucleophiles to $\alpha$ -fluorinated acrylates.

#### 4.1.1 $\alpha$ -Fluoroacrylates

We first tested the nucleophiles mentioned above with some  $\alpha$ -fluoroacrylates **1** (Table 19). Although we knew that these  $\alpha$ -fluoroacrylates were poorly reactive in Michael addition reactions, we were disappointed to see there was no reaction,

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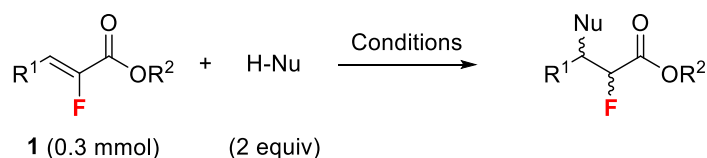
<sup>153</sup> For selected examples, see: (a) Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. *Tetrahedron Lett.* **2004**, *45*, 2649-2651. (b) Richard, M.; Felten, A. S.; Didierjean, C.; Ruiz-Lopez, M.; Chapleur, Y.; Pellegrini-Moise, N. *Eur. J. Org. Chem.* **2014**, *2014*, 7364-7376. (c) Guo, C.; Saifuddin, M.; Saravanan, T.; Sharifi, M.; Poelarends, G. J. *ACS Catal.* **2019**, *9*, 4369-4373.

<sup>154</sup> For selected examples, see: (a) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430-2431. (b) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2011**, *17*, 2266-2271. (c) Hida, T.; Komura, K.; Sugi, Y. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 960-967. (d) Liu, Y.; Wang, X.; Wang, X.; He, W. *Org. Biomol. Chem.* **2014**, *12*, 3163-3166.

<sup>155</sup> For selected examples, see: (a) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437-7444. (b) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900-4910. (c) Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, *5*, 1534-1543.

<sup>156</sup> For selected examples, see: (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047-4056. (b) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951-5955. (c) Chen, W.; Sun, L.; Huang, X.; Wang, J.; Peng, Y.; Song, G. *Adv. Synth. Catal.* **2015**, *357*, 1474-1482. (d) Chen, Q.; Li, L.; Zhou, G.; Ma, X.; Zhang, L.; Guo, F.; Luo, Y.; Xia, W. *Chem. Asian J.* **2016**, *11*, 1518-1522.

when the nitromethane and diethyl malonate were applied as the nucleophiles (**Table 19**, entries 1-2). Two lithium cuprates, namely lithium dimethylcuprate and lithium cyano(methyl)cuprate, which are known as very soft nucleophiles, generally having 1,4- rather than 1,2-regioselectivity,<sup>157</sup> also were used in the Michael addition reaction on  $\alpha$ -fluoroacrylates. However, we only observed the starting material even when we slightly increased the temperature or extended the reaction time (**Table 19**, entries 3-4). In the described Michael addition reactions of phenylboronic acid,  $\beta$ -alkyl-substituted Michael acceptors were generally used.<sup>156a-b</sup> Thus, besides  $\beta$ -phenyl- $\alpha$ -fluoroacrylate, three  $\beta$ -alkyl- $\alpha$ -fluoroacrylates were also tested (**Table 19**, entries 5-8). Only the methyl 2-fluoroacrylate allowed the formation of the suspected product (<sup>19</sup>F NMR: -190.7 ppm, ddd,  $J = 48.8, 28.7, 24.1$  Hz). We failed to confirm the structure of that product due to an unseparated non-fluorine byproduct (**Table 19**, entry 8). As only the unsubstituted  $\alpha$ -fluoroacrylate gave traces of product, we did not search to improve this result. Since we did not get satisfactory results using  $\alpha$ -fluoroacrylates as the Michael acceptors, we turned our attention to more reactive  $\alpha$ -trifluoromethylacrylates.

**Table 19**  $\alpha$ -Fluoroacrylates with different nucleophiles

Entry	R <sup>1</sup>	R <sup>2</sup>	H-Nu	Conditions <sup>a</sup>	Results <sup>b</sup>
1	Ph	Me	MeNO <sub>2</sub>	DIPEA or Et <sub>3</sub> N or DBU (20 mol%) MeCN, reflux, 16 h	NR
2	Ph	Me	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>		NR
3	Ph	Me	CuMe <sub>2</sub> Li	Et <sub>2</sub> O, -78 or -40 °C, 2-6 h	NR
4	Ph	Me	Cu(CN)MeLi	Et <sub>2</sub> O, -78 or -40 °C, 2-6 h	NR
5	Ph	Me			NR
6	Ph(CH <sub>2</sub> ) <sub>2</sub>	Et	PhB(OH) <sub>2</sub>	[Rh(cod)Cl <sub>2</sub> ] (4.5 mol%) (±)-binap (4.5 mol%) dioxane/H <sub>2</sub> O = 3 mL (6/1)	NR
7	Cyclohexyl	Et		100 °C, Ar, 16 h	NR
8	H	Me			-190.7 ppm (ddd, $J = 48.8,$

<sup>157</sup> Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339-2372.

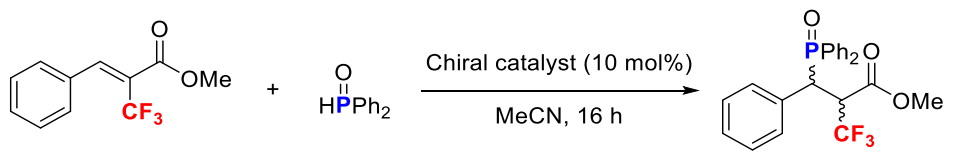
<sup>a</sup>Reaction condition: **1** (0.3 mmol, 1 equiv), nucleophile (0.6 mmol, 2 equiv), specific conditions indicated in the table. <sup>b</sup>NR = No Reaction.

## 4.1.2 $\alpha$ -Trifluoromethylacrylates

### 4.1.2.1 Enantioselective PMA reaction on $\alpha$ -trifluoromethylacrylate **6b**

Even if the  $\alpha$ -position of  $\alpha$ -trifluoromethylacrylate is highly epimerizable, we wanted to test our PMA reaction in an enantioselective way as the experimental conditions used are soft. So, we studied the PMA reaction of diphenylphosphine oxide (**7a**) to methyl (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (**6b**) in an asymmetric process with several organocatalysts (**I-IX**) (for the structures, see **Scheme 69**) (**Table 20**). The use of cinchona alkaloids (**I-III**) did not have diastereocontrol for the formation of **8b** (**Table 20**, entries 1-3). The use of bis-cinchona alkaloids (**IV-VII**) slightly increased the yields and diastereoselectivities (**Table 20**, entries 5-8). Among these bis-cinchona alkaloids catalysts, (DHQ)<sub>2</sub>PYR (**IV**) gave the best *ee* value, albeit still low for the major diastereoisomer (**Table 20**, entry 5). Thiourea-based catalyst (**VIII**) was not efficient for this reaction (**Table 20**, entry 9). Thiourea-based catalyst (**IX**) afforded a reversed *dr* ratio and *ee* value compared to (DHQ)<sub>2</sub>PYR (**IV**) (**Table 20**, entry 10). With (DHQ)<sub>2</sub>PYR (**IV**) as the catalyst, we carried out the reaction at a lower temperature to improve both diastereo- and enantioselectivity (**Table 20**, entries 11-13). In the same reaction time, as the temperature decreased to -20 °C, the yield reduced obviously but a 25:75 *dr* ratio and 39% *ee* value were obtained (**Table 20**, entry 12). So far, the best results to afford **8b** were obtained under -20 °C for 48 h (40% <sup>19</sup>F NMR yield, *dr* = 24:76, 47% *ee*) (**Table 20**, entry 13).

**Table 20** Enantioselective PMA reaction on  $\alpha$ -trifluoromethylacrylates

					
<b>6b</b> (0.3 mmol)	<b>7a</b> (1.5 equiv)	<b>8b</b>			
Entry	Catalyst	T (°C)	<sup>19</sup> F NMR yield (%) <sup>b</sup>	<i>Dr</i> <sup>c</sup>	<i>Ee</i> (%) <sup>d</sup>



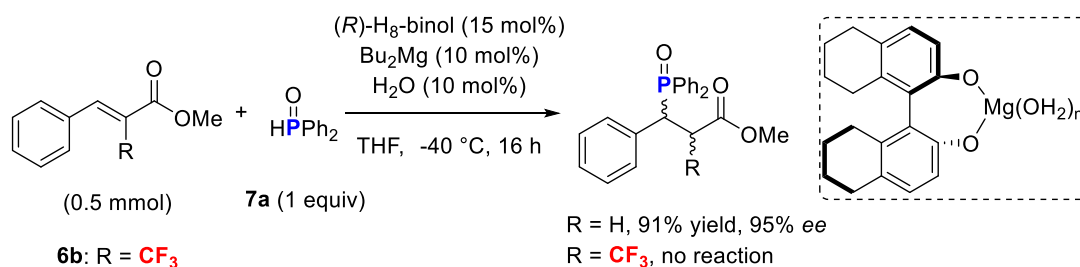
1	Quinine I	rt	79	44:56	-
2	Quinidine II	rt	75	45:55	-
4	Cinchonine III	rt	53	48:52	-
5	(DHQ) <sub>2</sub> PYR IV	rt	74	38:62	33
6	(DHQD) <sub>2</sub> PYR V	rt	94	43:57	22
7	(DHQ) <sub>2</sub> AQN VI	rt	88	37:63	12
8	(DHQD) <sub>2</sub> PHAL VII	rt	88	54:46	-
9	VIII	rt	14	50:50	-
10	IX	rt	63	74:26	-28
11	(DHQ) <sub>2</sub> PYR IV	0	55	34:66	39
12	(DHQ) <sub>2</sub> PYR IV	-20	20	25:75	45
13 <sup>e</sup>	(DHQ) <sub>2</sub> PYR IV	-20	40	24:76	47

<sup>a</sup>Reaction conditions: **6b** (0.3 mmol, 1.0 equiv), **7a** (0.45 mmol, 1.5 equiv), catalyst (0.03 mmol, 10 mol%), rt, 16 h.

<sup>b</sup><sup>19</sup>F NMR yields were obtained by using PhCOCF<sub>3</sub> as an internal standard. <sup>c</sup>Determined by the <sup>19</sup>F NMR of the reaction crude.

<sup>d</sup>Determined for the major diastereoisomers by HPLC. <sup>e</sup>Reaction carried out at -20 °C for 48 h.

In this asymmetric process, we also tried metal/chiral ligand strategy based on the work of Ishihara and co-workers (**Scheme 81**, Eq. b).<sup>144</sup> A chiral magnesium complex catalyst was formed by MgBu<sub>2</sub> with (*R*)-H<sub>8</sub>-binol, exhibiting excellent catalytic efficiency and enantioselectivity for non-fluorinated analogue of (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (**6b**), was not suitable for **6b** (**Scheme 89**).

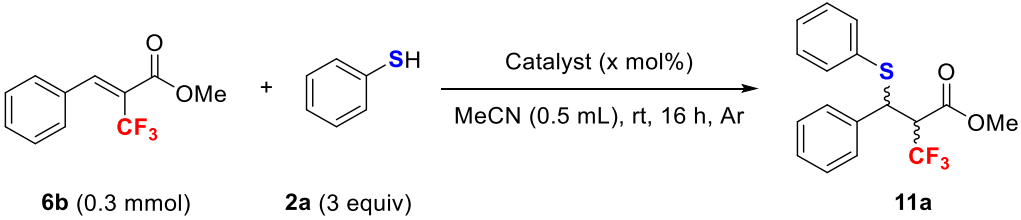


**Scheme 89** PMA reaction under the catalysis of chiral magnesium complex

#### 4.1.2.2 Enantioselective SMA reaction on $\alpha$ -trifluoromethylacrylate **6b**

As we knew that arylthiols are good nucleophiles in Michael addition reaction on  $\alpha$ -fluoroacrylates (see **Chapter 2**), herein, we studied the behavior of (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (**6b**) with thiophenol (**2a**) in Michael addition reaction (**Table 21**). With all the selected catalysts, the corresponding products were

generally obtained in high  $^{19}\text{F}$  NMR yields (83-97%). This reaction occurred even in the absence of catalyst albeit losing diastereocontrol in this case (**Table 21**, entry 6). In general, we found that the use of different catalysts whether it was achiral or chiral, did not affect the diastereoselectivities, except for the thiourea-based catalyst (**IX**). Among all the tested chiral catalysts, the thiourea-based catalyst (**IX**) was the only one afforded enantiomeric excess for the major diastereoisomer (**Table 21**, entry 11). So far, we did not further investigate this reaction.

**Table 21** SMA reaction on  $\alpha$ -trifluoromethylacrylates


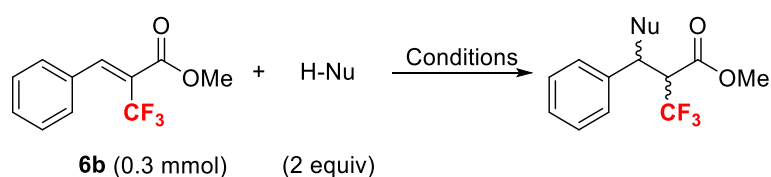
Entry	Catalyst	x (mol%)	$^{19}\text{F}$ NMR yield (%) <sup>b</sup>	<i>Dr</i> <sup>c</sup>	<i>Ee</i> (%) <sup>d</sup>
1	$\text{Et}_3\text{N}$	20	83	28:72	-
2	DIPEA	20	87	28:72	-
3	DABCO	20	85	28:72	-
4	DBU	20	85	29:71	-
5	$\text{K}_2\text{CO}_3$	20	87	28:72	-
6	-	-	27	44:56	-
7	Quinine I	10	93	28:72	0
8	Cinchonine III	10	89	29:71	0
9	(DHQ) <sub>2</sub> PYR IV	10	97	29:71	0
10	(DHQ) <sub>2</sub> AQN VI	10	95	28:72	0
11	<b>IX</b>	10	87	33:67	28

<sup>a</sup>Reaction conditions: **6b** (0.3 mmol, 1.0 equiv), **2a** (0.9 mmol, 3 equiv), catalyst (0.03 or 0.06 mmol, 10 or 20 mol%), MeCN (0.5 mL), rt, 16 h, under argon. <sup>b</sup> $^{19}\text{F}$  NMR yields were obtained by using  $\text{PhCOCF}_3$  as an internal standard. <sup>c</sup>Determined by the  $^{19}\text{F}$  NMR of the reaction crude. <sup>d</sup>Determined for the major diastereoisomers by HPLC.

#### 4.1.2.3 Michael addition of other nucleophiles on $\alpha$ -trifluoromethylacrylates

Owing to the higher reactivity of  $\alpha$ -trifluoromethylacrylates compare to  $\alpha$ -

fluoroacrylates, selected common nucleophiles (see in **Table 19**) were also tested on **6b**, and some preliminary results were obtained (**Table 22**). The use of nitromethane as the nucleophile led to the full recovery of starting material **6b** (**Table 22**, entry 1). We were happy to see that the diethyl malonate, which did not react with  $\alpha$ -fluoroacrylates, furnished the corresponding adducts in 34%  $^{19}\text{F}$  NMR yield with a 22:78 *dr* ratio under the catalysis of DABCO (**Table 22**, entry 2). Moreover, with lithium dimethyl cuprate, we obtained 41%  $^{19}\text{F}$  NMR yield of two peaks of suspected 1,4-adducts ( $^{19}\text{F}$  NMR: -69.1 ppm, s; -73.9 ppm, s) (**Table 22**, entry 3). With phenylboronic acid as the nucleophile, we could form the desired product in 34% isolated yield only when we used the unsubstituted trifluoromethylacrylate (**Table 22**, entry 6), thus we did not study it any further.

**Table 22**  $\alpha$ -Trifluoromethylacrylates with different nucleophiles

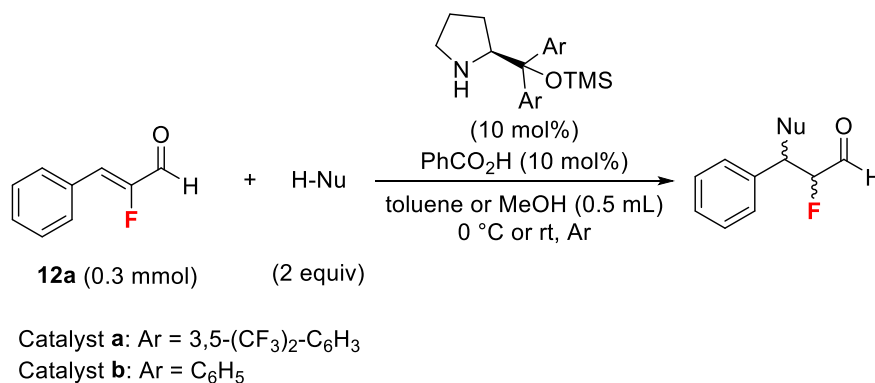
Entry	H-Nu	Conditions <sup>a</sup>	Results
1	MeNO <sub>2</sub>	DIPEA or Et <sub>3</sub> N or DBU (20 mol%) MeCN, rt or reflux, 16 h	NR <sup>b</sup>
2	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	DABCO (20 mol%) MeCN, rt, 16 h	34% $^{19}\text{F}$ NMR yield <sup>c</sup> <i>dr</i> = 22:78 <sup>d</sup>
3	CuMe <sub>2</sub> Li	Et <sub>2</sub> O, -78 to 0 °C, 6 h	41% $^{19}\text{F}$ NMR yield <sup>c</sup> <i>dr</i> = 49:51 <sup>d</sup>
4	Cu(CN)MeLi	Et <sub>2</sub> O, -78 or -40 or -78 to 0 °C, 2-6 h	NR <sup>b</sup>
5	PhB(OH) <sub>2</sub>	[Rh(cod)Cl <sub>2</sub> ] (4.5 mol%) (±)-binap (4.5 mol%) dioxane/H <sub>2</sub> O = 3 mL (6/1) 100 °C, Ar, 16 h	NR <sup>b</sup>
6 <sup>e</sup>			34% isolated yield

<sup>a</sup>Reaction condition: **1** (0.3 mmol, 1 equiv), nucleophile (0.6 mmol, 2 equiv), specific conditions indicated in the table. <sup>b</sup>NR = No Reaction. <sup>c</sup> $^{19}\text{F}$  NMR yields were obtained by using PhCOCF<sub>3</sub> as an internal standard. <sup>d</sup>Determined by the  $^{19}\text{F}$  NMR of the reaction crude. <sup>e</sup>Methyl 2-(trifluoromethyl)acrylate as the Michael acceptor.

## 4.2 Michael addition reaction of different nucleophiles to $\alpha$ -fluorinated enal and enone

In the literature, Michael addition reaction on  $\alpha,\beta$ -unsaturated aldehydes and ketones were also largely described.<sup>15-18</sup> Thus, the  $\alpha$ -fluorinated enal (**12a**) and enone (**13a**) derived from  $\alpha$ -fluoroacrylate (**1d**) were synthesized and used as the Michael acceptors. In the described Michael addition reactions on enals, the iminium ion activation strategy is well-known.<sup>158</sup> This strategy was also used in our investigation on Michael addition reaction of different nucleophiles to **12a** (Table 23). Among all the selected nucleophiles (*S*-, *C*-, *O*-, *N*-, and *P*- nucleophiles), thiophenol was the only one that could give the desired 1,4-adduct but with two other unseparated byproducts (Table 23, entry 1). In all reactions with catalyst **a**, the unknown product **A** was always formed, the same phenomenon was observed with the use of catalyst **b**. We assumed that unknown products **A** and **B** were somehow produced during the activation of **12a** by the two catalysts, which was preliminarily verified in the reactions without nucleophile (Table 23, entries 10-11). When nitromethane was used as the nucleophile, under the catalysis of **b**, the nitro-alkene **C** resulting from the 1,2-addition was formed (Table 23, entry 3). With the aid of NMR, LC-MS and X-ray, the structure of **C** was determined and shown in Figure 21.

Table 23 Michael addition reaction on  $\alpha$ -fluorinated enal

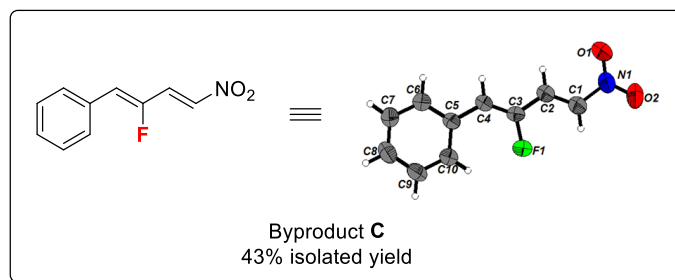


Entry	H-Nu	Catalyst	Conversion (%) <sup>b</sup>	Results
1	PhSH	<b>a</b>	96	-190.1 to -192.9 ppm, 4*ddd

<sup>158</sup> Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470.

2	MeNO <sub>2</sub>	a	21	unknown A
3	MeNO <sub>2</sub>	b	100	byproduct C and unknown B
4	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	a	94	1,2-adduct and unknown A
5	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	b	93	1,2-adduct and unknown B
6	PhOH	a	17	unknown A
7	PhNH <sub>2</sub>	a	13	unknown A
8	HP(O)Ph <sub>2</sub>	a	58	1,2-adduct and unknown A
9	HP(O)Ph <sub>2</sub>	b	44	1,2-adduct and unknown B
10	-	a	13	unknown A
11	-	b	16	unknown B

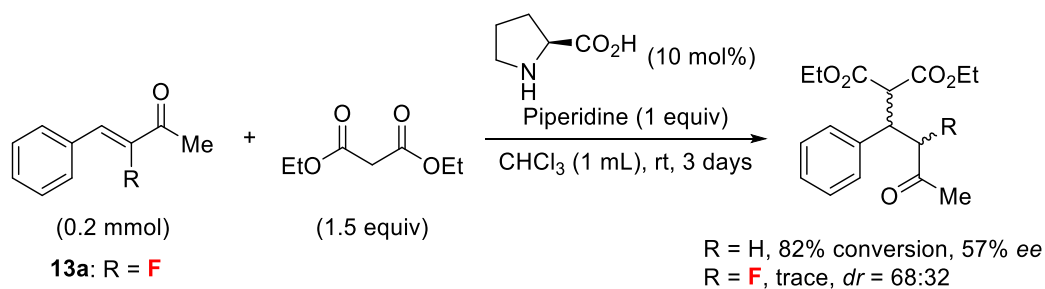
<sup>a</sup>Reaction condition: **12a** (0.3 mmol, 1 equiv), nucleophile (0.6 mmol, 2 equiv), catalyst (0.03 mmol, 10 mol%), PhCO<sub>2</sub>H (0.03 mol, 10 mol%), toluene or MeOH (0.5 mL), 0 °C or rt, under argon. <sup>b</sup>Conversion were obtained by using PhF as an internal standard.



**Figure 21** Structure of byproduct C

With the  $\alpha$ -fluorinated enone (**13a**), we studied the Michael addition of diethyl malonate. The only attempt was under the reported conditions for the non-fluorine analogue of **13a**.<sup>159</sup> Under the catalysis of (*R*)-proline, with 1 equivalent of piperidine as an additive, the addition of diethyl malonate to 4-phenyl-3-buten-2-one furnished 82% conversion and desired 1,4-adduct obtained in 57% *ee* value. However, in our case, we only observed trace of product as a mixture of two diastereoisomers with a 68:32 *dr* ratio (**Scheme 90**).

<sup>159</sup> Knudsen, K. R.; Mitchell, C. E.; Ley, S. V. *Chem. Commun.* **2006**, 66-68.



**Scheme 90** Michael addition of diethyl malonate to  $\alpha$ -fluorinated enone

### 4.3 Conclusions

In summary, we studied the Michael addition reaction of various nucleophiles on different  $\alpha$ -fluorinated Michael acceptors in this chapter. Due to the unique properties of the fluorine atom, the fluorinated substrates showed different reactivities compared to their non-fluorinated analogues. Some undesired products were obtained when the  $\alpha$ -fluorinated enal (**12a**) was used (unknown **A**, unknown **B**, and byproduct **C**). At the same time, in the addition of diethyl malonate and lithium dimethylcuprate to  $\alpha$ -trifluoromethylacrylate (**6b**), some preliminary results were obtained and deserved to be further explored.



# 5 Conclusion and Perspectives



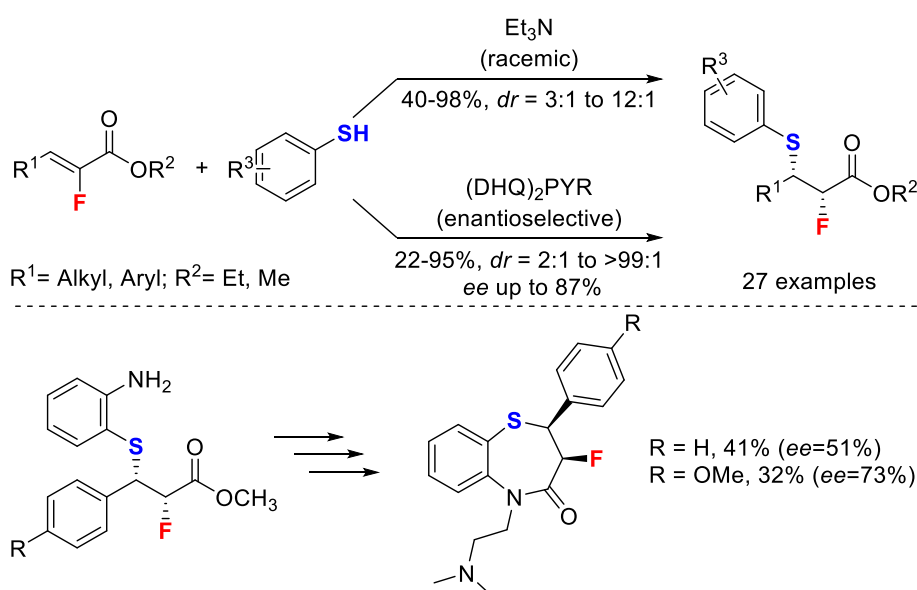


## 5 Conclusion and perspectives

### 5.1 Conclusion

In my Ph.D. thesis, we mainly explored the possibilities of  $\alpha$ -fluorinated substrates used as Michael acceptors.

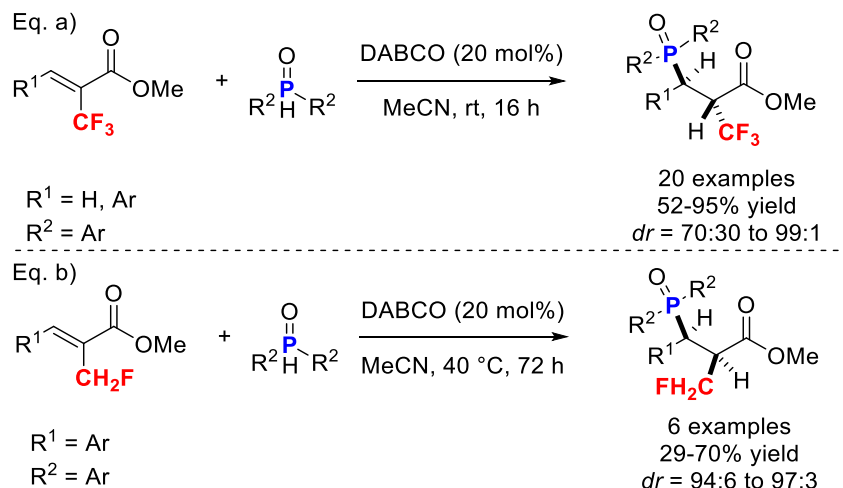
Firstly, we developed a simple and efficient sulfa-Michael addition on  $\beta$ -substituted- $\alpha$ -fluoroacrylates in both non-enantioselective and enantioselective versions. A common  $\text{Et}_3\text{N}$  and a commercially available chiral catalyst  $(\text{DHQ})_2\text{PYR}$  were used. Under the catalysis of  $\text{Et}_3\text{N}$ , a broad range of sulfa-Michael adducts were obtained in moderate to excellent yields with moderate to good diastereoselectivities. Under the catalysis of  $(\text{DHQ})_2\text{PYR}$ , the corresponding products were obtained in low to excellent yields and diastereoselectivities with moderate to good enantioselectivities. Moreover, two fluorinated analogues of therapeutic agents were successfully synthesized using this SMA strategy (**Scheme 91**).<sup>124</sup>



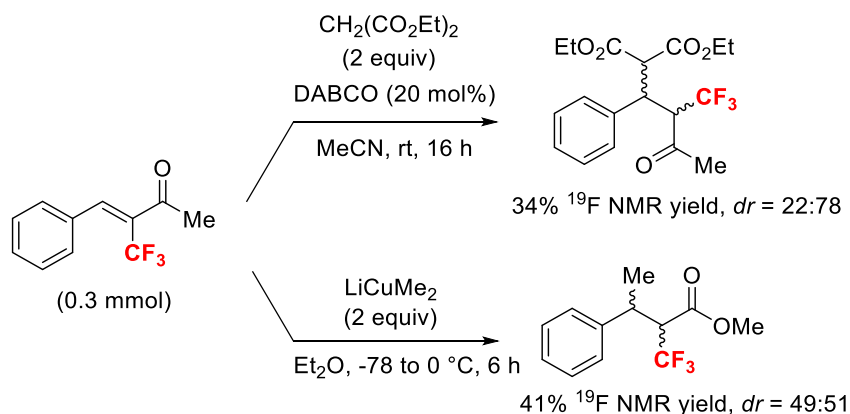
**Scheme 91** SMA of aryl thiols to  $\beta$ -substituted- $\alpha$ -fluoroacrylates

Then, the first PMA reaction on  $\alpha$ -trifluoromethylacrylates under mild conditions has been developed. It provided efficient and highly diastereoselective access to tertiary phosphine oxides among various  $\beta$ -substituted- $\alpha$ -trifluoromethylacrylates. The corresponding products were generally obtained in moderate to excellent yields and

good to high diastereoselectivities. This methodology was applied to  $\beta$ -substituted- $\alpha$ -fluoromethylacrylates, producing the desired products in low to moderate yields but excellent diastereoselectivities in each case (**Scheme 92**).



**Scheme 92** PMA reaction of diarylphosphine oxides to  $\beta$ -substituted- $\alpha$ -trifluoromethylacrylates. In the end, to expand the application of Michael addition reaction on fluorinated substrates, a series of attempts have been made with our fluorinated substrates. The fluorinated Michael acceptors showed different behaviors compared to their non-fluorinated analogues and some preliminary results have been obtained (**Scheme 93**).



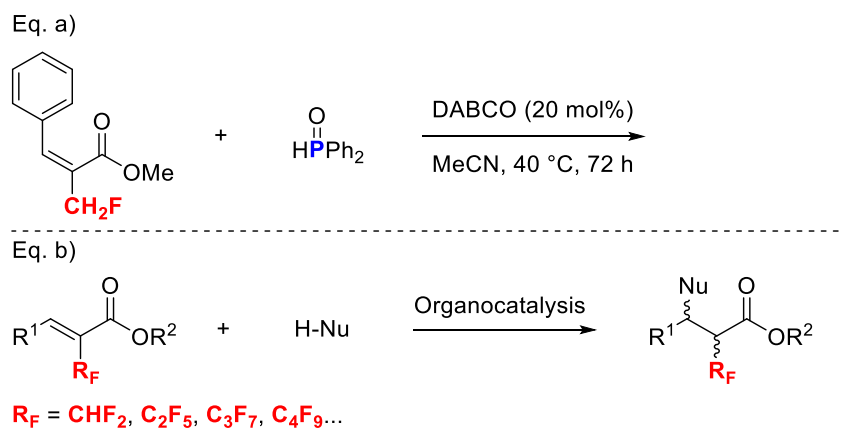
**Scheme 93** Preliminary results

## 5.2 Perspectives

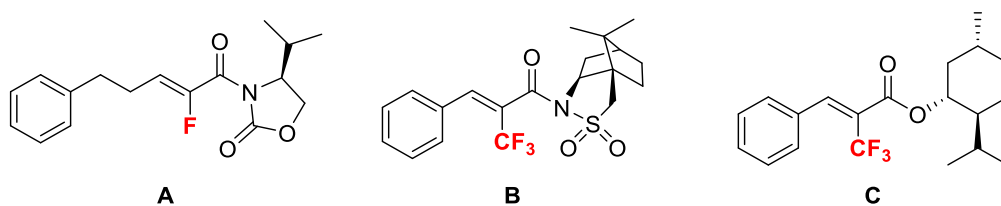
In our developed SMA reaction, the mechanism of the asymmetric process is not clear. Although we proposed a transition state to explain the low enantioselectivities obtained from *para*-substituted thiophenols, more decisive proof was needed (get a

crystal from the complex between the catalyst and thiol, if it is possible). Similarly, more evidence was needed to support the mechanism we proposed in the PMA reaction. For example, in the optimization of PMA reaction, Et<sub>3</sub>N and DABCO are both tertiary amines, but the use of Et<sub>3</sub>N as the base reversed the diastereomeric ratio compared to DABCO. It is worth doing some further studies, such as performing the reaction on (*E*)-trifluoromethylacrylates with Et<sub>3</sub>N, to figure out the role of the base in the diastereocontrol. We should also develop the synthesis of (*E*)- $\alpha$ -fluoromethylacrylate to study, as in the SMA reaction, the influence of configuration of the the double bond, which will be a valuable clue for the mechanism we proposed (**Scheme 94**, Eq. a). It will also be interesting to synthesize the  $\alpha$ -difluoromethylacrylates or  $\alpha$ -perfluorinated acrylates family to have a complete picture of the reactivity of such fluorinated Michael acceptors (**Scheme 94**, Eq. b). Additionally, as we did not obtain good results in enantioselective sulfa- and phospho-Michael addition reactions on  $\alpha$ -trifluoromethylacrylates, we can study the use of chiral auxiliary into our  $\alpha$ -fluorinated substrates to achieve the asymmetric construction of the C-S bond, the C-P bond and some other C-heteroatom bonds (**Figure 22**), or use some metal-catalyzed approach.<sup>160</sup> The study of Michael addition reaction on  $\alpha$ -fluorinated substrates based on the preliminary results obtained in chapter 4 could also be further investigated, especially the addition of cuprate as a chiral ligand could be used in such reaction and induced enantioselectivity. Higher-order cuprates could also be studied for such reactions.

<sup>160</sup> (a) Krause, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 283-285. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *2001*, 0171-0196. (c) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596-2616. (d) Gutnov, A. *Eur. J. Org. Chem.* **2008**, *2008*, 4547-4554. (e) Schmid, T. E.; Drissi-Amraoui, S.; Crevisy, C.; Basle, O.; Mauduit, M. *Beilstein J. Org. Chem.* **2015**, *11*, 2418-2434. (f) Hui, C.; Pu, F.; Xu, J. *Chem. Eur. J.* **2017**, *23*, 4023-4036.



Scheme 94

Figure 22 Chiral  $\alpha$ -fluorinated substrates

# Experimental Section



## Experimental Section

### General Information

All the reactions were performed in oven-dried glassware with a magnetic stirring under the air or argon atmosphere unless otherwise stated. The reaction temperature was reported refers to the temperature of the oil bath around the glassware. Thin-layer chromatography (TLC) analyses were carried out on the silica gel (60 F<sub>254</sub> from Merck) supported on an aluminum sheet. Flash column chromatography was done with Silicaflash P60 silica gel (40-60  $\mu\text{m}$ ). <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F and <sup>31</sup>P NMR spectra were recorded using a Bruker Avance-300 spectrometer operating at 300 MHz (<sup>1</sup>H), 75 MHz (<sup>13</sup>C), 282 MHz (<sup>19</sup>F) and 121 MHz (<sup>31</sup>P). The chemical shifts ( $\delta$ ) of <sup>1</sup>H and <sup>13</sup>C were calibrated on residual proton and carbon resonances of CDCl<sub>3</sub> (<sup>1</sup>H,  $\delta$  = 7.26 ppm and <sup>13</sup>C,  $\delta$  = 77.2 ppm) or CD<sub>3</sub>OD (<sup>1</sup>H,  $\delta$  = 3.31 ppm and <sup>13</sup>C,  $\delta$  = 49.00 ppm) or (CD<sub>3</sub>)<sub>2</sub>SO (<sup>1</sup>H,  $\delta$  = 2.50 ppm and <sup>13</sup>C,  $\delta$  = 39.52 ppm). The <sup>19</sup>F chemical shifts ( $\delta$ ) were determined relative to external CCl<sub>3</sub>F (<sup>19</sup>F,  $\delta$  = 0.0 ppm). The multiplicity signals were indicated with the common abbreviations: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad) and the combinations of them. Melting points (M.P.) were determined on a Fisher Scientific hot stage melting point apparatus and are uncorrected. High Resolution Mass Spectra (HRMS) were recorded on a JEOL AccuTof 4G spectrometer coupled to a GC HP Agilent 7890 in chemical ionization mode (CI). Enantiomeric excesses (ee) were determined by using a SpectraSYSTEM TM HPLC equipped with a P1000XR pump, a UV1000 detector and a Rheodyne injector. See specific conditions detailed for each compound.

### Materials

Unless otherwise specified, all the catalysts and reagents were purchased from commercial sources (Alfa Aesar, Fisher Chemical, Fluorochem, and Acros Organics) and used without further purification. Anhydrous solvents were purchased from

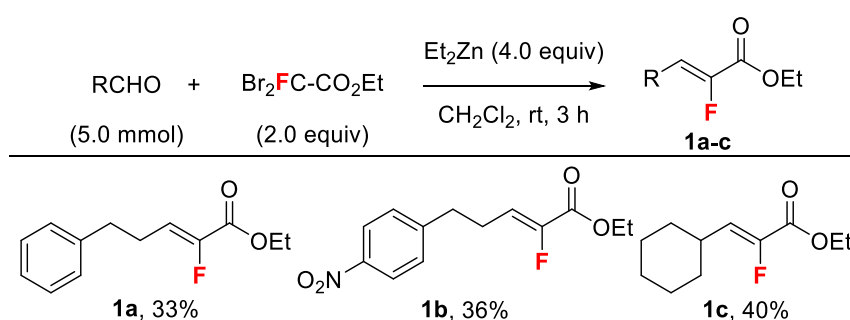


Acros Organics (in a sealed bottle with molecular sieves) except for  $\text{CH}_2\text{Cl}_2$  (distilled from calcium hydride), THF and toluene (distilled from sodium with benzophenone).

## 1 Sulfa-Michael addition (SMA) of thiophenols to $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

### 1.1 Preparation of $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

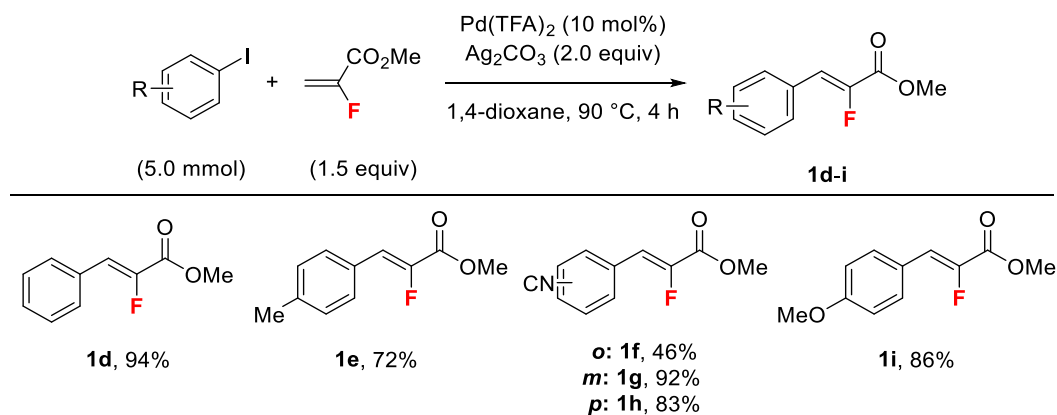
The alkyl  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters (**1a-c**) were synthesized according to the literature in the following procedure (I) (Scheme 96)<sup>21b</sup>: To an anhydrous  $\text{CH}_2\text{Cl}_2$  solution (50 mL) of the appropriate aldehyde (5.0 mmol, 1 equiv) and ethyl dibromofluoroacetate (2 equiv) was added  $\text{Et}_2\text{Zn}$  (1 M in hexane, 4 equiv) dropwise under argon. The reaction mixture was stirred for 3 h at room temperature. The resulting solution was then poured into saturated  $\text{NH}_4\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$  was evaporated under vacuum,  $\text{EtOAc}$  was added, and the mixture was stirred for 15 min. The remaining zinc salts were filtered off through a Büchner funnel. The heterogeneous resulting solution was extracted twice with  $\text{Et}_2\text{O}$  (2×20 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure and then purified by flash silica gel column chromatography (eluent: petroleum ether/ $\text{EtOAc}$ ). The analytic data of **1a-c** were in agreement with those reported in literature.<sup>21a</sup>



**Scheme 95** Synthesis of alkyl  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

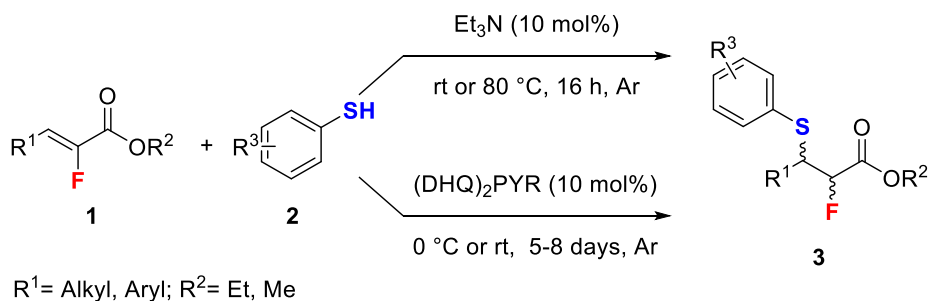
The aryl  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters (**1d-i**) were synthesized according to the literature in the following procedure (II) (Scheme 96)<sup>21a</sup>: In a vial was added iodoarene (5.0 mmol, 1 equiv), methyl 2-fluoroacrylate (1.5 equiv),  $\text{Ag}_2\text{CO}_3$  (2 equiv) and  $\text{Pd}(\text{TFA})_2$  (10 mol %). The vial was then filled with 1,4-dioxane (5 mL), then was

heated to 90 °C for 4 h. The crude was filtrated over celite, washed with EtOAc (3×30 mL), then solvents were evaporated. The crude was then purified by flash silica gel column chromatography (eluent: petroleum ether/EtOAc). The analytic data of **1d-i** were in agreement with those reported in literature.<sup>21a</sup>



**Scheme 96** Synthesis of aryl  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

## 1.2 General procedure for the Sulfa-Michael addition (SMA) of thiophenols to $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters

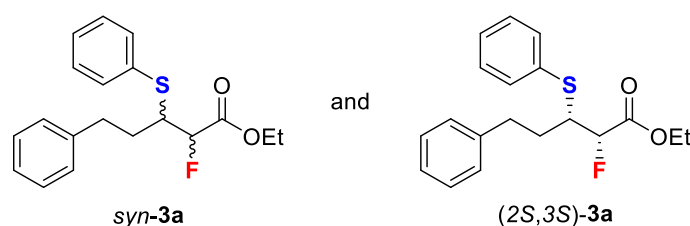


General procedure (III): non-enantioselective pathway

In an oven-dried sealed tube,  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ester **1** (0.3 mmol, 1 equiv), arylthiol **2** (1.5 mmol, 5 equiv) followed by Et<sub>3</sub>N (0.03 mmol 10 mol%) were introduced, the tube was sealed and then frozen by liquid nitrogen, removed the air under high vacuum and introduced argon. The reaction mixture was stirred at 80 °C or room temperature for 16 hours and then was cooled to room temperature. The reaction mixture was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>).

## General procedure (IV): enantioselective pathway

In an oven-dried sealed tube,  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ester **1** (0.3 mmol, 1 equiv), arylthiol **2** (1.5 mmol, 5 equiv) followed by (DHQ)<sub>2</sub>PYR (0.03 mmol 10 mol%) were introduced, the tube was sealed and then freeze-dried by liquid nitrogen, removed the air under high vacuum and introduced argon. The reaction mixture was stirred at 0 °C or room temperature for 5-8 days and then the reaction mixture was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>).

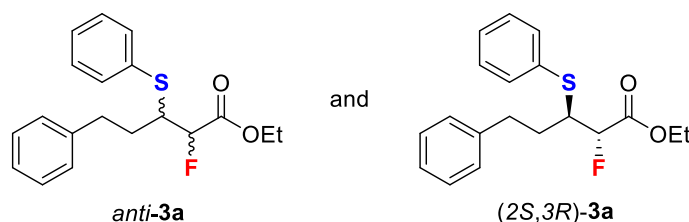
**Ethyl 2-fluoro-5-phenyl-3-(phenylthio)pentanoate (3a):**

The *syn*-**3a** was obtained following the general procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 76:24. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 91% yield (major: 80 mg as a colorless oil; minor: 11 mg as a colorless oil).

The (2*S*,3*S*)-**3a** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 84:16. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 82% yield (major: 67 mg as a colorless oil; minor: 14 mg as a colorless oil). 71% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 6.810 min, *t* (major) = 7.507 min.].

$[\alpha]_D^{20}$  = -18.0 (c 1.23, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.37 – 7.34 (m, 2H), 7.22 – 7.05 (m, 8H), 4.97 (dd,  $J_{H-F}$  = 48.0 Hz,  $J_{H-H}$  = 3.0 Hz, 1H), 4.13 – 3.89 (m, 2H), 3.49 – 3.33 (m, 1H), 2.92 – 2.68 (m, 2H), 2.09 – 1.91 (m, 2H), 1.12 (t,  $J_{H-H}$  = 9.0 Hz, 3H). <sup>19</sup>F

**NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -197.0 (dd,  $J_{F-H} = 48.0$  Hz,  $J_{F-H} = 28.2$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  167.9 (d,  $J_{C-F} = 22.5$  Hz), 140.7, 133.8, 132.9, 129.0, 128.5, 128.5, 127.6, 126.2, 90.5 (d,  $J_{C-F} = 195.0$  Hz), 61.7, 50.5 (d,  $J_{C-F} = 22.5$  Hz), 33.4, 33.2, 14.0. **IR:** 2980, 1761, 1737, 1475, 1266, 1212, 1103, 1024, 745, 692, 557, 491 cm<sup>-1</sup>. **HRMS (API<sup>+</sup>) m/z:** [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>FO<sub>2</sub>S: 333.1325, found: 333.1319.

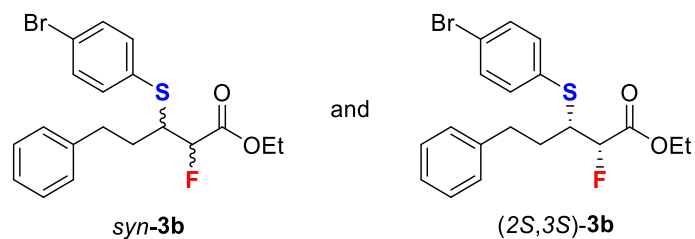


### Ethyl 2-fluoro-5-phenyl-3-(phenylthio)pentanoate (**3a**):

The *anti*-**3a** was obtained following the general procedure (**III**) starting from the (*E*)-**1a**. <sup>19</sup>F NMR of the reaction crude showed *dr* = 26:74. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 93% yield (major: 72 mg as a colorless oil; minor: 21 mg as a colorless oil).

The (*2S,3R*)-**3a** was obtained following the general procedure (**IV**) starting from the (*E*)-**1a**. <sup>19</sup>F NMR of the reaction crude showed *dr* = 14:86. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 86% yield (major: 39 mg as a colorless oil; major and minor mixture: 47 mg). 74% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 5.340 min, *t* (major) = 5.803 min.].

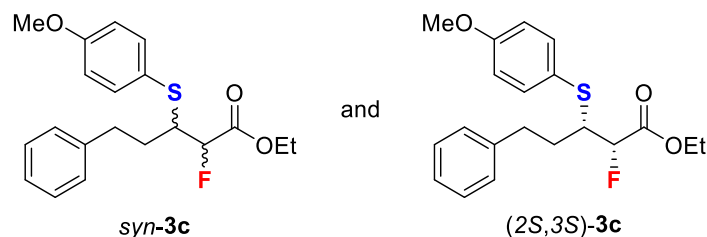
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.40 – 7.37 (m, 2H), 7.25 – 7.09 (m, 8H), 4.80 (dd,  $J_{H-F} = 48.0$  Hz,  $J_{H-H} = 6.0$  Hz, 1H), 4.07 (q,  $J_{H-H} = 6.0$  Hz, 2H), 3.42 – 3.31 (m, 1H), 2.94 – 2.70 (m, 2H), 1.94 – 1.87 (m, 2H), 1.13 (t,  $J_{H-H} = 9.0$  Hz, 3H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -195.7 (dd,  $J_{F-H} = 48.0$  Hz,  $J_{F-H} = 22.6$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  168.1 (d,  $J_{C-F} = 22.5$  Hz), 140.8, 133.2, 132.9, 129.2, 128.5, 127.9, 126.2, 90.3 (d,  $J_{C-F} = 195.0$  Hz), 61.8, 49.5 (d,  $J_{C-F} = 15.0$  Hz), 32.8, 30.6, 14.1.

**Ethyl 3-((4-bromophenyl)thio)-2-fluoro-5-phenylpentanoate (3b):**

The *syn-3b* was obtained following the general procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 73:27. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 98% yield (major: 107 mg as a white solid; minor: 13 mg as a white solid).

The (2*S*,3*S*)-**3b** was obtained according to the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 67:33. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 38% yield (major: 38 mg as a white solid; minor: 9 mg as a white solid). 23% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 98/2, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 9.810 min, *t* (major) = 11.183 min.].

$[\alpha]_{\text{D}}^{20}$  = -6.1 (c 1.09,  $\text{CDCl}_3$ ); **M.P.** 54-56 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34 – 7.31 (m, 2H), 7.22 – 7.06 (m, 7H), 4.97 (dd,  $J_{\text{H-F}}$  = 51.0 Hz,  $J_{\text{H-H}}$  = 3.0 Hz, 1H), 4.13 – 4.02 (m, 2H), 3.41 – 3.29 (m, 1H), 2.85 – 2.73 (m, 2H), 2.07 – 1.93 (m, 2H), 1.17 (t,  $J_{\text{H-H}}$  = 6.0 Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -197.2 (dd,  $J_{\text{F-H}}$  = 51.0 Hz,  $J_{\text{F-H}}$  = 31.0 Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.8 (d,  $J_{\text{C-F}}$  = 22.5 Hz), 140.4, 134.5, 132.8, 132.0, 128.6, 128.5, 126.3, 122.0, 90.6 (d,  $J_{\text{C-F}}$  = 187.5 Hz), 61.8, 50.4 (d,  $J_{\text{C-F}}$  = 15.0 Hz), 33.3, 33.1, 14.1. **IR:** 2920, 1757, 1474, 1209, 1091, 815, 695, 585, 478  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>) *m/z*:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{21}\text{BrFO}_2\text{S}$ : 411.0430, found: 411.0429.

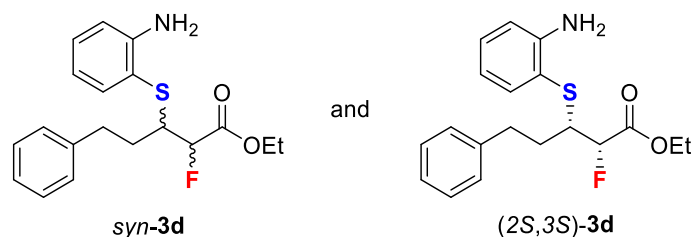


### Ethyl 2-fluoro-3-((4-methoxyphenyl)thio)-5-phenylpentanoate (**3c**):

The *syn-3c* was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 84:16$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 49/1 to 19/1, v/v) affording two diastereoisomers in 87% yield (major: 78 mg as a colorless oil; minor: 19 mg as a colorless oil).

The  $(2S,3S)\text{-3c}$  was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 81:19$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 49/1 to 19/1, v/v) affording two diastereoisomers in 74% yield (major: 71 mg as a colorless oil; minor: 9 mg as a colorless oil; major and minor mixture: 12 mg). 38% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 8.783 min,  $t$  (major) = 9.857 min.].

$[\alpha]_{\text{D}}^{20} = -10.4$  (c 0.57,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36 – 7.33 (m, 2H), 7.19 – 7.06 (m, 5H), 6.75 – 6.73 (m, 2H), 4.92 (d,  $J_{\text{H-F}} = 48.0$  Hz, 1H), 4.16 – 4.01 (m, 2H), 3.71 (s, 3H), 3.27 – 3.17 (m, 1H), 2.89 – 2.70 (m, 2H), 1.99 – 1.88 (m, 2H), 1.17 (t,  $J_{\text{H-H}} = 6.0$  Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -197.1 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.1 (d,  $J_{\text{C-F}} = 30.0$  Hz), 159.9, 140.9, 136.2, 128.6, 128.5, 126.2, 123.4, 114.5, 90.8 (d,  $J_{\text{C-F}} = 187.5$  Hz), 61.7, 55.4, 51.1 (d,  $J_{\text{C-F}} = 22.5$  Hz), 33.2, 33.0, 14.1. IR: 2940, 1760, 1455, 1494, 1245, 1026, 829, 699, 525, 493  $\text{cm}^{-1}$ . HRMS ( $\text{API}^+$ )  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{24}\text{FO}_3\text{S}$ : 363.1430, found: 363.1426.

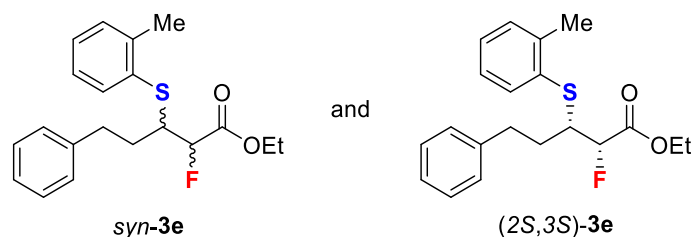


**Ethyl 3-((2-aminophenyl)thio)-2-fluoro-5-phenylpentanoate (3d):**

The *syn*-**3d** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 80:20. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 91% yield (major: 61 mg as a yellow oil; major and minor mixture: 34 mg).

The (2*S*,3*S*)-**3d** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 90:10. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 95% yield (major: 89 mg as a yellow oil; major and minor mixture: 11 mg). 84% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 230 nm, *t* (minor) = 11.380 min, *t* (major) = 15.850 min.].

$[\alpha]_{\text{D}}^{20} = +13.4$  (c 1.08,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.30 – 7.02 (m, 7H), 6.63 – 6.56 (m, 2H), 4.92 (d,  $J_{\text{H-F}} = 48.0$  Hz, 1H), 4.32 (s, 2H), 4.10 – 3.95 (m, 2H), 3.36 (d,  $J = 27$  Hz, 1H), 2.85 – 2.75 (m, 2H), 2.07 – 1.91 (m, 2H), 1.15 (t,  $J_{\text{H-H}} = 6.0$  Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -196.0 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 25.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.1 (d,  $J_{\text{C-F}} = 22.5$  Hz), 149.2, 140.7, 137.3, 130.5, 128.5, 128.4, 126.2, 118.4, 115.1, 114.9, 89.8 (d,  $J_{\text{C-F}} = 187.5$  Hz), 61.8, 49.6 (d,  $J_{\text{C-F}} = 15.0$  Hz), 33.2, 32.9, 14.0. IR: 3468, 3371, 2925, 1754, 1607, 1479, 1216, 1103, 1022, 857, 747, 699, 454  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{23}\text{FNO}_2\text{S}$ : 348.1434, found: 348.1426.

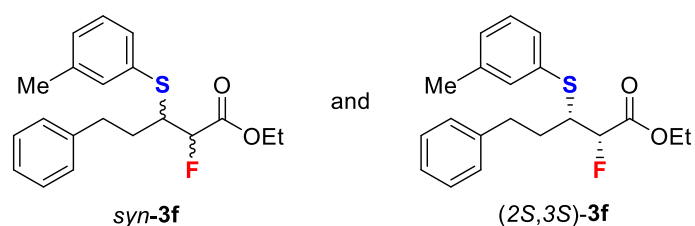


### Ethyl 2-fluoro-5-phenyl-3-(*o*-tolylthio)pentanoate (**3e**):

The *syn*-**3e** was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 73:27. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 91% yield (major: 68 mg as a colorless oil; major and minor mixture: 26 mg).

The (2*S*,3*S*)-**3e** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 95:5. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 91% yield (major: 78 mg as a colorless oil; major and minor mixture: 16 mg). 78% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 5.793 min, *t* (major) = 6.470 min.].

[α]<sub>D</sub><sup>20</sup> = +29.4 (c 0.68, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 – 7.06 (m, 9H), 4.98 (d, *J*<sub>H-F</sub> = 48.0 Hz, 1H), 4.08 – 3.83 (m, 2H), 3.57 – 3.45 (m, 1H), 2.84 – 2.75 (m, 2H), 2.34 (s, 3H), 2.15 – 1.97 (m, 2H), 1.10 (t, *J*<sub>H-H</sub> = 9.0 Hz, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -196.5 (dd, *J*<sub>F-H</sub> = 48.0 Hz, *J*<sub>F-F</sub> = 28.2 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 167.8 (d, *J*<sub>C-F</sub> = 22.5 Hz), 140.6, 140.1, 133.3, 132.3, 130.4, 128.5, 128.5, 127.4, 126.5, 126.2, 90.0 (d, *J*<sub>C-F</sub> = 187.5 Hz), 61.7, 49.7 (d, *J*<sub>C-F</sub> = 22.5 Hz), 33.5, 33.2, 20.9, 13.9. IR: 2935, 1761, 1736, 1454, 1299, 1212, 1025, 747, 699, 558, 438 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>FO<sub>2</sub>S: 347.1481, found: 347.1480.



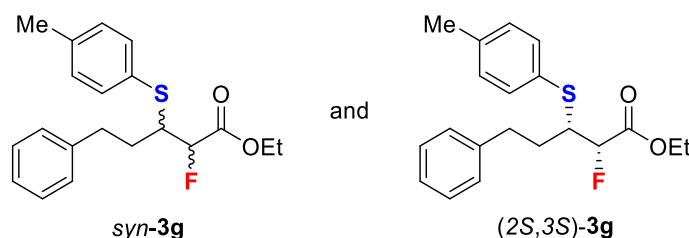


**Ethyl 2-fluoro-5-phenyl-3-(m-tolylthio)pentanoate (3f):**

The *syn*-**3f** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 72:28$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 84% yield (major: 66 mg as a colorless oil; major and minor mixture: 21 mg).

The (2*S*,3*S*)-**3f** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 94:6$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 95% yield (major: 86 mg as a colorless oil; major and minor mixture: 13 mg). 80% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*-PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 6.873 min,  $t$  (major) = 7.530 min.].

$[\alpha]_D^{20} = -18.8$  (c 0.89,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23 – 6.97 (m, 9H), 4.97 (d,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} 3.0$  Hz, 1H), 4.12 – 3.93 (m, 2H), 3.47 – 3.34 (m, 1H), 2.91 – 2.69 (m, 2H), 2.23 (s, 3H), 2.06 – 1.89 (m, 2H), 1.13 (t,  $J_{\text{H-H}} = 9.0$  Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -196.8 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.0 (d,  $J_{\text{C-F}} = 22.5$  Hz), 140.7, 138.7, 133.5, 133.3, 129.7, 128.8, 128.5, 128.4, 126.2, 90.5 (d,  $J_{\text{C-F}} = 187.5$  Hz), 61.7, 50.4 (d,  $J_{\text{C-F}} = 22.5$  Hz), 33.4, 33.1, 21.3, 14.0. IR: 2933, 1762, 1737, 1454, 1299, 1212, 1025, 749, 698, 557, 432  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{24}\text{FO}_2\text{S}$ : 347.1481, found: 347.1479.

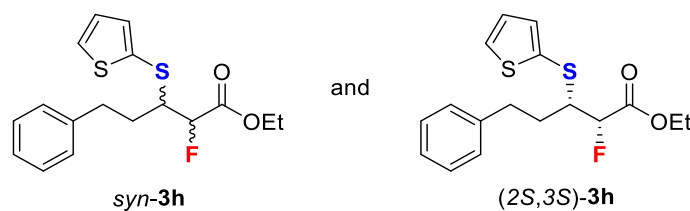
**Ethyl 2-fluoro-5-phenyl-3-(p-tolylthio)pentanoate (3g):**

The *syn*-**3g** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 74:26$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in

67% yield (major: 31 mg as a colorless oil; minor: 9 mg as a colorless oil; major and minor mixture: 30 mg).

The (2*S*,3*S*)-**3g** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 85:15. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 82% yield (major: 77 mg as a colorless oil; minor: 8 mg as a colorless oil). 54% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 7.347 min, *t* (major) = 8.143 min.].

[α]<sub>D</sub><sup>20</sup> = -14.0 (c 0.84, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 – 7.00 (m, 9H), 4.94 (d, *J*<sub>H-F</sub> = 48.0 Hz, 1H), 4.13 – 3.97 (m, 2H), 3.40 – 3.25 (m, 1H), 2.92 – 2.68 (m, 2H), 2.24 (s, 3H), 2.03 – 1.91 (m, 2H), 1.15 (t, *J*<sub>H-H</sub> = 6.0 Hz, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -196.8 (dd, *J*<sub>F-H</sub> = 48.0 Hz, *J*<sub>F-H</sub> = 28.2 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 168.0 (d, *J*<sub>C-F</sub> = 22.5 Hz), 140.8, 137.9, 133.5, 129.7, 129.7, 128.5, 128.5, 126.2, 90.6 (d, *J*<sub>C-F</sub> = 187.5 Hz), 61.7, 50.7 (d, *J*<sub>C-F</sub> = 15.0 Hz), 33.2, 33.2, 21.1, 14.0. IR: 2920, 1762, 1737, 1493, 1300, 1211, 1104, 1020, 811, 749, 699, 556, 496 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>FO<sub>2</sub>S: 347.1481, found: 347.1481.



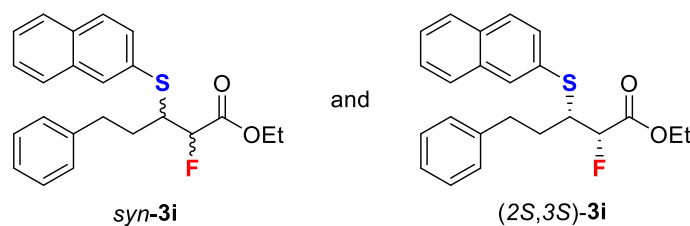
### Ethyl 2-fluoro-5-phenyl-3-(thiophen-2-ylthio)pentanoate (**3h**):

The *syn*-**3h** was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 83:17. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 83% yield (major: 60 mg as a yellow oil; major and minor mixture: 24 mg)

The (2*S*,3*S*)-**3g** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 88:12. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two

diastereoisomers in 73% yield (major: 41 mg as a yellow oil; major and minor mixture: 33 mg ). 67% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 6.183 min, *t* (major) = 7.050 min.].

$[\alpha]_D^{20}$  = -15.7 (c 0.69, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.33 – 7.31 (m, 1H), 7.24 – 7.10 (m, 6H), 6.92 – 6.89 (m, 1H), 4.91 (dd,  $J_{H-F}$  = 48.0 Hz,  $J_{H-H}$  = 6.0 Hz, 1H), 4.20 – 4.08 (m, 2H), 3.21 – 3.14 (m, 1H), 2.95 – 2.73 (m, 2H), 1.99 – 1.91 (m, 2H), 1.21 (t,  $J_{H-H}$  = 6.0 Hz, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$  -196.5 (dd,  $J_{F-H}$  = 48.0 Hz,  $J_{F-H}$  = 25.4 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  167.9 (d,  $J_{C-F}$  = 22.5 Hz), 140.7, 136.5, 130.8, 130.6, 128.6, 128.5, 127.6, 126.2, 90.4 (d,  $J_{C-F}$  = 195.0 Hz), 61.8, 52.4 (d,  $J_{C-F}$  = 15.0 Hz), 33.1, 32.5, 32.4, 14.1. IR: 2940, 1760, 1737, 1216, 1023, 847, 749, 698, 493 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>20</sub>FO<sub>2</sub>S<sub>2</sub>: 339.0889, found: 339.0899.

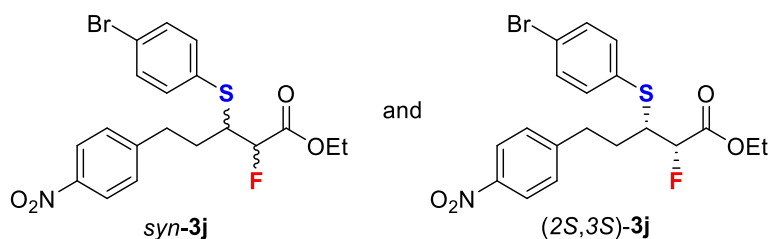


### Ethyl 2-fluoro-3-(naphthalen-2-ylthio)-5-phenylpentanoate (**3i**):

The *syn-3i* was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 80:20. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 84% yield (major: 80 mg as a colorless oil; major and minor mixture: 16 mg).

The (2*S*,3*S*)-**3i** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 73:27. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 31% yield (major: 27 mg as a colorless oil; major and minor mixture: 8 mg ). 29% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 7.777 min, *t* (major) = 8.900 min.].

$[\alpha]_D^{20} = -7.7$  (c 0.57,  $\text{CDCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 – 7.65 (m, 4H), 7.41 – 7.38 (m, 3H), 7.21 – 7.06 (m, 5H), 5.01 (d,  $J_{\text{H-F}} = 48.0$  Hz, 1H), 4.06 – 3.86 (m, 2H), 3.60 – 3.46 (m, 1H), 2.95 – 2.72 (m, 2H), 2.12 – 2.00 (m, 2H), 1.07 (t,  $J_{\text{H-H}} = 6.0$  Hz, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -196.8 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.9 (d,  $J_{\text{C-F}} = 22.5$  Hz), 140.8, 133.5, 132.4, 131.6, 131.1, 129.8, 128.6, 128.5, 127.7, 127.4, 126.6, 126.4, 126.3, 90.5 (d,  $J_{\text{C-F}} = 187.5$  Hz), 61.7, 50.3 (d,  $J_{\text{C-F}} = 22.5$  Hz), 33.4, 33.2, 14.0. IR: 2933, 1760, 1736, 1497, 1454, 1212, 1103, 1023, 858, 814, 744, 699, 475  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>) m/z:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{24}\text{FO}_2\text{S}$ : 383.1481, found: 383.1477.



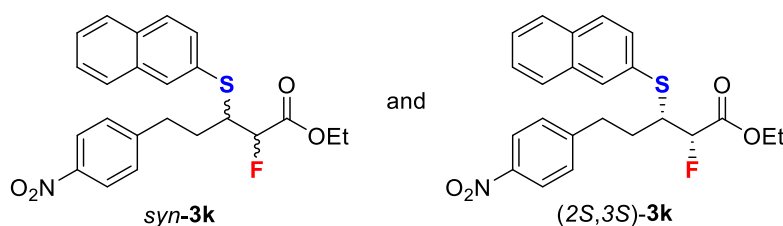
#### Ethyl 3-((4-bromophenyl)thio)-2-fluoro-5-(4-nitrophenyl)pentanoate (**3j**):

The *syn*-**3j** was obtained following the procedure (III).  $^{19}\text{F NMR}$  of the reaction crude showed  $dr = 82:18$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 73% yield (major: 75 mg as a yellow oil; major and minor mixture: 24 mg)

The (2*S*,3*S*)-**3j** was obtained following the general procedure (IV).  $^{19}\text{F NMR}$  of the reaction crude showed  $dr = 80:20$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 77% yield (major: 72 mg as a yellow oil; major and minor mixture: 33 mg). 2% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 99/1, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 125.503 min,  $t$  (major) = 115.393 min.].

$[\alpha]_D^{20} = -0.34$  (c 0.87,  $\text{CDCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.07 (d, 2H,  $J_{\text{H-H}} = 9.0$  Hz), 7.37 – 7.34 (m, 2H), 7.27 – 7.19 (m, 4H), 4.98 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.21 – 4.01 (m, 2H), 3.43 – 3.28 (m, 1H), 3.03 – 2.77 (m, 2H), 2.14 – 1.91 (m, 2H), 1.19

(t,  $J_{\text{H-H}} = 6.0$  Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -196.4 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.6 (d,  $J_{\text{C-F}} = 30.0$  Hz), 148.3, 146.7, 134.7, 132.3, 132.2, 129.2, 123.9, 122.4, 90.5 (d,  $J_{\text{C-F}} = 187.5$  Hz), 62.0, 50.6 (d,  $J_{\text{C-F}} = 22.5$  Hz), 33.0, 32.9, 14.1. IR: 2940, 1759, 1737, 1599, 1516, 1343, 1068, 852, 817, 698, 479  $\text{cm}^{-1}$ . HRMS (API)  $m/z$ :  $[\text{M}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{BrFNO}_4\text{S}$ : 455.0202, found: 455.0193.



### Ethyl 2-fluoro-3-(naphthalen-2-ylthio)-5-(4-nitrophenyl)pentanoate (**3k**):

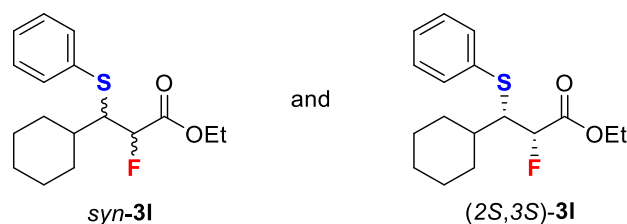
The *syn*-**3k** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 87:13$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 75% yield (major: 71 mg as a yellow oil; major and minor mixture: 25 mg).

The (2*S*,3*S*)-**3k** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 84:16$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 55% yield (major: 47 mg as a yellow solid; major and minor mixture: 23 mg). 8% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 35.240 min,  $t$  (major) = 45.267 min.].

$[\alpha]_{\text{D}}^{20} = -2.2$  (c 0.68,  $\text{CDCl}_3$ ); M.P. 86 – 88 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00 (d,  $J_{\text{H-H}} = 9.0$  Hz, 2H), 7.84 (s, 1H), 7.76 – 7.65 (m, 3H), 7.45 – 7.40 (m, 3H), 7.20 – 7.18 (m, 2H), 5.02 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.16 – 3.93 (m, 2H), 3.59 – 3.44 (m, 1H), 3.07 – 2.82 (m, 2H), 2.19 – 1.97 (m, 2H), 1.13 (t,  $J_{\text{H-H}} = 6.0$  Hz, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -196.0 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.7 (d,  $J_{\text{C-F}} = 30.0$  Hz), 148.5, 146.6, 133.5, 132.6, 131.9, 130.6, 129.8, 129.8, 129.3, 128.8, 127.7, 127.4, 126.9, 126.7, 123.8, 90.5 (d,  $J_{\text{C-F}} = 187.5$  Hz), 61.9, 50.4 (d,  $J_{\text{C-F}} =$

22.5 Hz), 33.1, 33.0, 14.0. IR: 2925, 1764, 1490, 1222, 1109, 1027, 830, 523, 468 $\text{cm}^{-1}$ .

HRMS (API<sup>-</sup>) m/z: [M]<sup>+</sup> calcd for C<sub>23</sub>H<sub>22</sub>FNO<sub>4</sub>S: 427.1254, found: 427.1254.



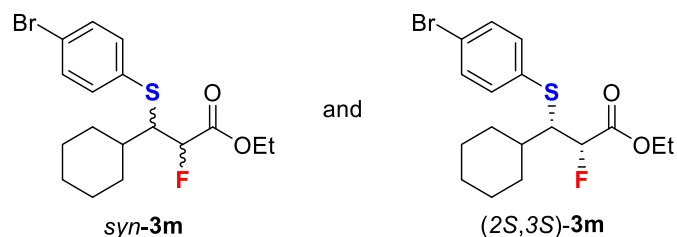
### Ethyl 3-cyclohexyl-2-fluoro-3-(phenylthio)propanoate (3I):

The *syn*-3I was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 82:18. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 86% yield (major: 61 mg as a colorless oil; major and minor mixture: 19 mg).

The (2*S*,3*S*)-3I was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 100:0. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 34% yield (32 mg as a colorless oil). 65% *ee* was obtained for it [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, t (minor) = 6.607 min, t (major) = 7.450 min.].

[α]<sub>D</sub><sup>20</sup> = -5.6 (c 0.32, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.39 – 7.36 (m, 2H), 7.22 – 7.13 (m, 3H), 5.20 (dd, *J*<sub>H-F</sub> = 48.0 Hz, *J*<sub>H-H</sub> = 3.0 Hz, 1H), 4.10 – 3.81 (m, 2H), 3.34 – 3.19 (m, 1H), 2.14 (d, *J*<sub>H-H</sub> = 15.0 Hz, 1H), 1.84 – 1.53 (m, 5H), 1.21 – 1.13 (m, 5H), 1.07 (t, *J*<sub>H-H</sub> = 6.0 Hz, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -197.9 (dd, *J*<sub>F-H</sub> = 48.0 Hz, *J*<sub>F-H</sub> = 36.7 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 168.6 (d, *J*<sub>C-F</sub> = 30.0 Hz), 135.7, 132.0, 128.9, 127.1, 89.3 (d, *J*<sub>C-F</sub> = 187.5 Hz), 61.6, 57.9 (d, *J*<sub>C-F</sub> = 15.0 Hz), 40.7, 31.1, 30.8, 26.2, 26.1, 13.9. IR: 2925, 1763, 1735, 1440, 1214, 1102, 1024, 746, 691, 537, 481  $\text{cm}^{-1}$ .

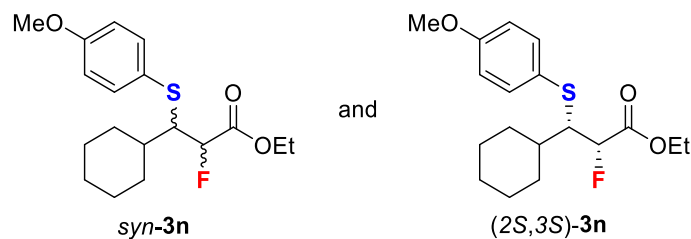
HRMS (API<sup>+</sup>) m/z: [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>24</sub>FO<sub>2</sub>S: 311.1481, found: 311.1491.

**Ethyl 3-((4-bromophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**3m**):**

The *syn*-**3m** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 71:29$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 76% yield (major: 62 mg as a white solid; major and minor mixture: 24 mg).

The (*2S,3S*)-**3m** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 69:31$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 8/1, v/v) affording two diastereoisomers in 38% yield (major: 24 mg as a white solid; major and minor mixture: 20 mg). 11% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 5.987 min,  $t$  (major) = 6.587 min.].

$[\alpha]_{\text{D}}^{20} = +2.5$  (c 1.02,  $\text{CDCl}_3$ ); **M.P.** 31 – 33 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33 – 7.23 (m, 4H), 5.20 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.15 – 3.90 (m, 2H), 3.28 – 3.13 (m, 1H), 2.09 (d,  $J_{\text{H-H}} = 12.0$  Hz, 1H), 1.82 – 1.59 (m, 5H), 1.18 – 0.98 (m, 8H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -197.7 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 33.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.6 (d,  $J_{\text{C-F}} = 30.0$  Hz), 134.7, 133.7, 121.3, 89.3 (d,  $J_{\text{C-F}} = 195.0$  Hz), 61.8, 58.0 (d,  $J_{\text{C-F}} = 22.5$  Hz), 40.5, 31.0, 30.7, 26.1, 26.1, 14.0. **IR:** 2920, 1753, 1472, 1299, 1216, 817, 595, 466, 483  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{23}\text{BrFO}_2\text{S}$ : 389.0586, found: 389.0596.

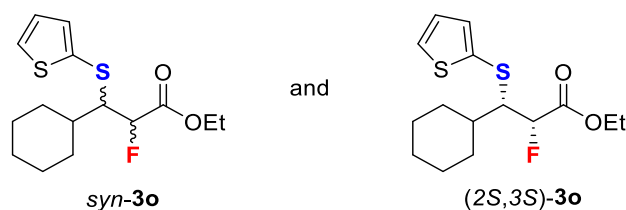


### Ethyl 3-cyclohexyl-2-fluoro-3-((4-methoxyphenyl)thio)propanoate (**3n**):

The *syn*-**3n** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 78:22. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 65% yield (major: 47 mg as a white solid; major and minor mixture: 19 mg).

The (*2S,3S*)-**3n** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 80:20. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v) affording two diastereoisomers in 77% yield (major: 60 mg as a white solid; major and minor mixture: 19 mg). 32% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 8.557 min, *t* (major) = 10.183 min.].

$[\alpha]_{\text{D}}^{20}$  = -5.4 (c 0.61,  $\text{CDCl}_3$ ); **M.P.** 57 – 58 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35 – 7.33 (m, 2H), 6.76 – 6.73 (m, 2H), 5.17 (dd,  $J_{\text{H-F}}$  = 48.0 Hz,  $J_{\text{H-H}}$  = 2.4 Hz, 1H), 4.17 – 3.91 (m, 2H), 3.72 (s, 3H), 3.14 – 3.00 (m, 1H), 2.15 (d,  $J_{\text{H-H}}$  = 6.0 Hz, 1H), 1.81 – 1.58 (m, 5H), 1.18 – 1.01 (m, 8H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -197.9 (dd,  $J_{\text{F-H}}$  = 48.0 Hz,  $J_{\text{F-H}}$  = 36.7 Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.8 (d,  $J_{\text{C-F}}$  = 22.5 Hz), 159.4, 135.2, 125.5, 114.4, 89.4 (d,  $J_{\text{C-F}}$  = 187.5 Hz), 61.6, 58.7 (d,  $J_{\text{C-F}}$  = 15.0 Hz), 55.3, 40.2, 31.1, 30.7, 26.2, 26.2, 14.0. **IR:** 2926, 1763, 1590, 1490, 1222, 1026, 830, 594, 522, 473  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>) m/z:** [M+H]<sup>+</sup> calcd for  $\text{C}_{18}\text{H}_{26}\text{FO}_3\text{S}$ : 341.1587, found: 341.1581.



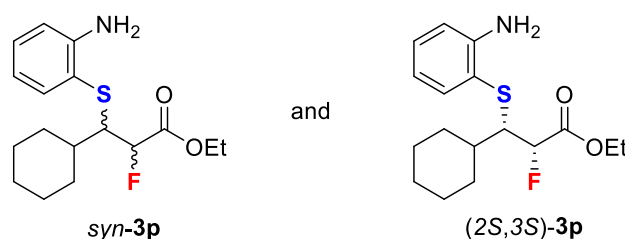
### Ethyl 3-cyclohexyl-2-fluoro-3-(thiophen-2-ylthio)propanoate (**3o**):



The *syn*-**3o** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 82:18$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 43% yield (major: 30 mg as a yellow oil; major and minor mixture: 11 mg).

The (2*S*,3*S*)-**3o** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 100:0$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 32% yield (30 mg as a yellow oil). 59% *ee* was obtained for it [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 6.583 min,  $t$  (major) = 8.433 min.].

$[\alpha]_{\text{D}}^{20} = -8.3$  (c 0.06,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.29 – 7.26 (m, 1H), 7.09 – 7.08 (m, 1H), 6.89 – 6.86 (m, 1H), 5.17 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.26 – 4.02 (m, 2H), 3.11 – 2.96 (m, 1H), 2.19 (d,  $J_{\text{H-H}} = 12.0$  Hz, 1H), 1.83 – 1.63 (m, 5H), 1.22 – 1.05 (m, 8H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -198.3 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 33.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.5 (d,  $J_{\text{C-F}} = 22.5$  Hz), 135.4, 133.2, 130.0, 127.3, 89.1 (d,  $J_{\text{C-F}} = 195.0$  Hz), 61.7, 60.4 (d,  $J_{\text{C-F}} = 15.0$  Hz), 39.8, 31.1, 30.5, 26.2, 26.1, 14.1. IR: 2925, 1762, 1736, 1448, 1216, 1024, 847, 700, 533, 495  $\text{cm}^{-1}$ . HRMS ( $\text{API}^+$ )  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{FO}_2\text{S}_2$ : 317.1045, found: 317.1051.

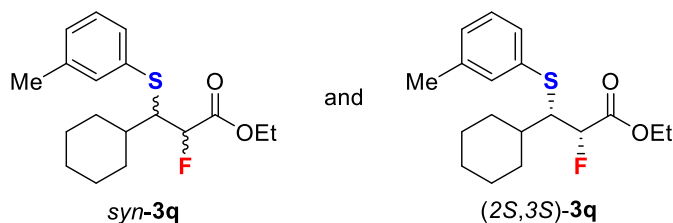


#### Ethyl 3-((2-aminophenyl)thio)-3-cyclohexyl-2-fluoropropanoate (**3p**):

The *syn*-**3p** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 80:20$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 75% yield (major: 38 mg as a yellow solid; minor: 11 mg as a yellow solid; major and minor mixture: 19 mg).

The (2*S*,3*S*)-**3p** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 90:10. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 55% yield (major: 45 mg as a yellow solid, major and minor mixture: 9 mg). 87% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 16.160 min, *t* (major) = 22.437 min.].

[α]<sub>D</sub><sup>20</sup> = +24.1 (c 0.22, CDCl<sub>3</sub>); M.P. 112 – 113 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (d, *J*<sub>H-H</sub> = 6.0 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.61 – 6.56 (m, 2H), 5.09 (dd, *J*<sub>H-F</sub> = 48.0 Hz, *J*<sub>H-H</sub> = 3.0 Hz, 1H), 4.29 (s, 2H), 4.05 – 3.94 (m, 1H), 3.80 – 3.69 (m, 1H), 3.35 – 3.21 (m, 1H), 2.02 – 1.88 (m, 2H), 1.74 – 1.61 (m, 4H), 1.26 – 1.04 (m, 8H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -196.1 (dd, *J*<sub>F-H</sub> = 48.0 Hz, *J*<sub>F-H</sub> = 33.8 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 168.7 (d, *J*<sub>C-F</sub> = 30.0 Hz), 148.7, 136.5, 129.8, 118.4, 116.7, 115.0, 88.7 (d, *J*<sub>C-F</sub> = 187.5 Hz), 61.6, 56.7 (d, *J*<sub>C-F</sub> = 15.0 Hz), 40.9, 31.0, 30.5, 30.5, 26.4, 26.3, 26.2, 13.9. IR: 3445, 3351, 2925, 1748, 1613, 1480, 1233, 737, 602, 454 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>25</sub>FNO<sub>2</sub>S: 326.1590, found: 326.1594.



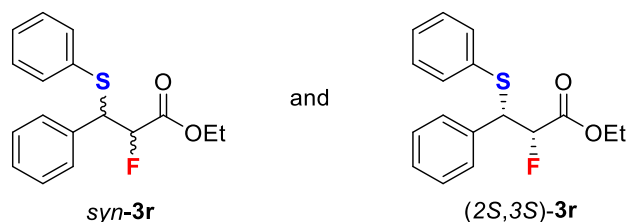
#### Ethyl 3-cyclohexyl-2-fluoro-3-(*m*-tolylthio)propanoate (**3q**):

The *syn*-**3q** was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 80:20. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 67% yield (major: 54 mg as a colorless oil; major and minor mixture: 11 mg).

The (2*S*,3*S*)-**3q** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 81:19. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two

diastereoisomers in 44% yield (major: 35 mg as a colorless oil, major and minor mixture: 8 mg). 26% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow =1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 7.013 min, *t* (major) = 7.820 min.].

$[\alpha]_D^{20}$  = -20.3 (c 0.10, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.19 – 7.15 (m, 2H), 7.11 – 7.05 (m, 1H), 6.96 – 6.93 (m, 1H), 5.19 (dd,  $J_{H-F}$  = 51.0 Hz,  $J_{H-H}$  = 3.0 Hz, 1H), 4.11 – 3.81 (m, 2H), 3.34 – 3.19 (m, 1H), 2.24 (s, 3H), 2.13 (d,  $J_{H-H}$  = 12.0 Hz, 1H), 1.71 – 1.60 (m, 5H), 1.20 – 1.01 (m, 8H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):  $\delta$  -197.7 (dd,  $J_{F-H}$  = 51.0 Hz,  $J_{F-H}$  = 33.8 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  168.6 (d,  $J_{C-F}$  = 22.5 Hz), 138.6, 135.5, 132.4, 128.9, 128.7, 127.9, 89.3 (d,  $J_{C-F}$  = 187.5 Hz), 61.6, 57.8 (d,  $J_{C-F}$  = 22.5 Hz), 40.8, 31.1, 30.8, 26.2, 26.1, 21.3, 13.9. IR: 2925, 1764, 1735, 1600, 1449, 1213, 1102, 1025, 856, 776, 690, 541, 436 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>26</sub>FO<sub>2</sub>S: 325.1638, found: 325.1647.



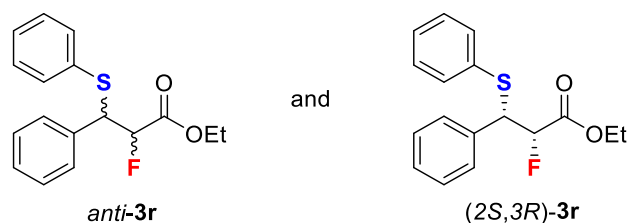
### Methyl 2-fluoro-3-phenyl-3-(phenylthio)propanoate (3r):

The *syn-3r* was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 83:17. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 61% yield (major: 42 mg as a white solid, major and minor mixture: 11 mg).

The (2*S*,3*S*)-**3r** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 88:12. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 54% yield (major: 40 mg as a white solid, major and minor mixture: 7 mg). 63% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/<sup>i</sup>PrOH: 90/10, flow =1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 6.530

min, t (major) = 7.053 min.].

$[\alpha]_D^{20} = +101.4$  (c 0.67,  $\text{CDCl}_3$ ); **M.P.** 52 - 53 °C;  **$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.31 – 7.22 (m, 7H), 7.18 – 7.14 (m, 3H), 5.16 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.60 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 3.61 (s, 3H).  **$^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -194.2 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.0$  Hz).  **$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  167.9 (d,  $J_{\text{C-F}} = 30.0$  Hz), 137.8, 133.6, 132.9, 128.9, 128.7, 128.4, 128.4, 126.2, 127.7, 91.3 (d,  $J_{\text{C-F}} = 187.5$  Hz), 55.8 (d,  $J_{\text{C-F}} = 22.5$  Hz), 52.6. **IR:** 2947, 1755, 1438, 1225, 1087, 1001, 736, 701, 688, 540, 467  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{16}\text{FO}_2\text{S}$ : 291.0855, found: 291.0859.



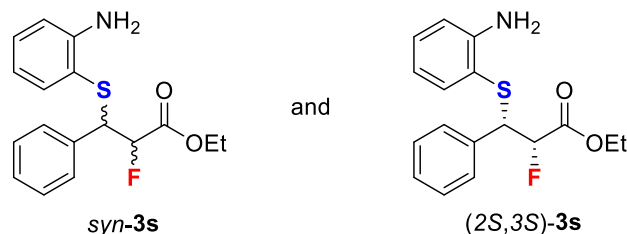
#### Methyl 2-fluoro-3-phenyl-3-(phenylthio)propanoate (**3r**):

The *anti*-**3r** was obtained following the procedure (**III**) starting from the (*E*)-**1d**.  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 33:67. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 74% yield (major: 30 mg as a white solid, major and minor mixture: 34 mg).

The (*2S,3R*)-**3r** was obtained following the general procedure (**IV**) starting from the (*E*)-**1d**.  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 24:76. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 56% yield (major and minor mixture: 49 mg). 51% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, t (minor) = 6.773 min, t (major) = 7.453 min.].

**$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.38 – 7.34 (m, 2H), 7.25 – 7.19 (m, 8H), 5.09 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.56 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 6.0$  Hz, 1H), 3.54 (s, 3H).  **$^{19}\text{F}$**

**NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -195.0 (dd,  $J_{F-H} = 48.0$  Hz,  $J_{F-H} = 26.0$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  168.0 (d,  $J_{C-F} = 22.5$  Hz), 135.5, 133.5, 132.9, 129.2, 128.9, 128.8, 128.6, 128.4, 128.4, 89.2 (d,  $J_{C-F} = 195.0$  Hz), 54.6 (d,  $J_{C-F} = 15.0$  Hz), 52.4.

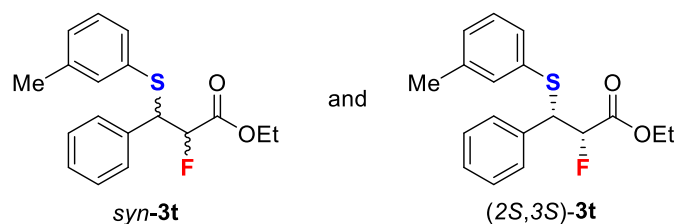


**Methyl 3-((2-aminophenyl)thio)-2-fluoro-3-phenylpropanoate (3s):**

The *syn*-**3s** was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 87:13. The crude was purified by silica gel column chromatography (petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>, from 5/1 to 2/1, v/v) affording two diastereoisomers in 46% yield (major: 34 mg as a yellow solid, major and minor mixture: 8 mg).

The (2*S*,3*S*)-**3s** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 91:9. The crude was purified by silica gel column chromatography (petroleum ether/CH<sub>2</sub>Cl<sub>2</sub>, from 5/1 to 2/1, v/v) affording two diastereoisomers in 22% yield (major: 16 mg as a yellow solid, major and minor mixture: 4 mg). 51% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 11.947 min, *t* (major) = 14.737 min.].

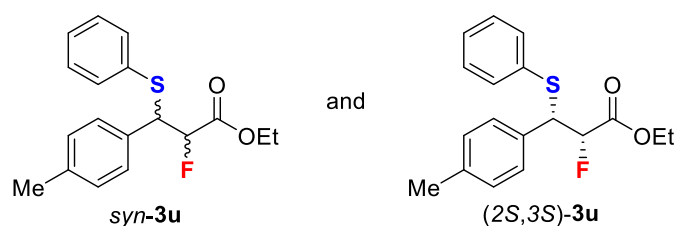
$[\alpha]_D^{20} = +111.2$  (c 1.02, CDCl<sub>3</sub>); **M.P.** 77 – 79 °C; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.24 – 7.21 (m, 5H), 7.10 – 7.00 (m, 2H), 6.62 – 6.47 (m, 2H), 5.13 (dd,  $J_{H-F} = 48.0$ ,  $J_{H-H} = 3.0$  Hz, 1H), 4.48 (dd,  $J_{H-F} = 28.0$  Hz,  $J_{H-H} = 3.0$  Hz, 1H), 4.23 (s, 2H), 3.56 (s, 3H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -194.2 (dd,  $J_{F-H} = 48.0$  Hz,  $J_{F-H} = 28.0$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  168.1 (d,  $J_{C-F} = 30.0$  Hz), 149.2, 138.1, 137.5, 130.8, 128.6, 128.3, 128.3, 128.1, 118.3, 115.0, 89.5 (d,  $J_{C-F} = 195.0$  Hz), 54.0 (d,  $J_{C-F} = 22.5$  Hz), 52.5. **IR:** 3432, 3327, 2951, 1755, 1609, 1217, 1101, 751, 698, 530, 457 cm<sup>-1</sup>. **HRMS (API<sup>+</sup>) *m/z*:** [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>17</sub>FNO<sub>2</sub>S: 306.0964, found: 306.0964.

**Methyl 2-fluoro-3-phenyl-3-(*m*-tolylthio)propanoate (**3t**):**

The *syn*-**3t** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 85:15. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 89% yield (major: 45 mg as a colorless oil, major and minor mixture: 37 mg).

The *(2S,3S)*-**3t** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed *dr* = 87:13. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 72% yield (major: 50 mg as a colorless oil, major and minor mixture: 16 mg). 62% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 6.750 min, *t* (major) = 7.183 min.].

$[\alpha]_{\text{D}}^{20}$  = +113.0 (c 0.70,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.31 – 7.20 (m, 5H), 7.07 – 6.94 (m, 4H), 5.15 (dd,  $J_{\text{H-F}}$  = 48.0 Hz,  $J_{\text{H-H}}$  = 3.0 Hz, 1H), 4.59 (dd,  $J_{\text{H-F}}$  = 28.0 Hz,  $J_{\text{H-H}}$  = 3.0 Hz, 1H), 3.60 (s, 3H), 2.18 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -194.1 (dd,  $J_{\text{F-H}}$  = 48.0 Hz,  $J_{\text{F-H}}$  = 28.0 Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.0 (d,  $J_{\text{C-F}}$  = 22.5 Hz), 138.7, 138.0, 133.5, 133.3, 129.8, 128.8, 128.7, 128.6, 128.4, 128.4, 128.1, 91.3 (d,  $J_{\text{C-F}}$  = 187.5 Hz), 55.7 (d,  $J_{\text{C-F}}$  = 22.5 Hz), 52.5, 21.2. IR: 2960, 1765, 1741, 1437, 1219, 1101, 774, 692, 544, 436  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{18}\text{FO}_2\text{S}$ : 305.1012, found: 305.1024.

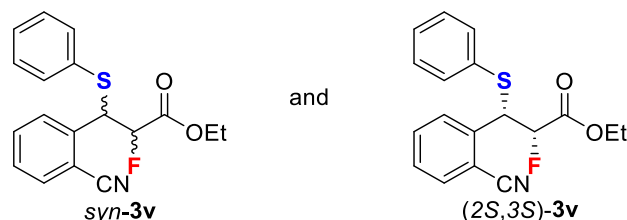


**Methyl 2-fluoro-3-(phenylthio)-3-(p-tolyl)propanoate (3u):**

The *syn*-**3u** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 77:23$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 75% yield (major: 51 mg as a white solid; major and minor mixture: 17 mg).

The (2*S*,3*S*)-**3u** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 88:12$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 36% yield (major: 29 mg as a white solid, major and minor mixture: 4 mg). 69% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 6.490 min,  $t$  (major) = 7.410 min.].

$[\alpha]_{\text{D}}^{20} = +129.6$  (c 0.57,  $\text{CDCl}_3$ ); **M.P.** 82 – 84 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.27 – 7.24 (m, 2H), 7.17 – 7.13 (m, 4H), 7.05 – 7.03 (m, 2H), 5.12 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 6.0$  Hz, 1H), 4.57 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 6.0$  Hz, 1H), 3.60 (s, 3H), 2.24 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -194.0 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.0 (d,  $J_{\text{C-F}} = 22.5$  Hz), 138.0, 134.8, 133.8, 132.8, 129.4, 128.9, 128.3, 128.2, 127.8, 91.5 (d,  $J_{\text{C-F}} = 195.0$  Hz), 55.5 (d,  $J_{\text{C-F}} = 22.5$  Hz), 52.6, 21.2. **IR:** 2927, 1739, 1434, 1269, 1085, 1008, 741, 570, 413  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>)  $m/z$ :**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{18}\text{FO}_2\text{S}$ : 305.1012, found: 305.1009.

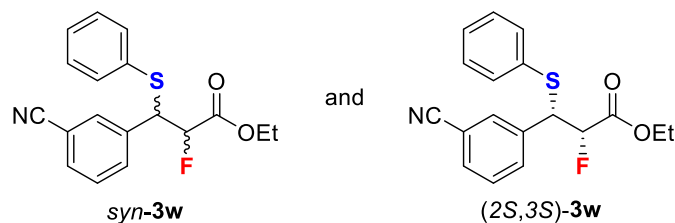
**Methyl 3-(2-cyanophenyl)-2-fluoro-3-(phenylthio)propanoate (3v):**

The *syn*-**3v** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 89:11$ . The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in

62% yield (major: 43 mg as a white solid; major and minor mixture: 16 mg).

The (2*S*,3*S*)-**3v** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 87:13. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 78% yield (major: 56 mg as a white solid, major and minor mixture: 14 mg). 52% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min, λ = 254 nm, *t* (minor) = 12.513 min, *t* (major) = 13.350 min.].

[α]<sub>D</sub><sup>20</sup> = +3.0 (c 1.03, CDCl<sub>3</sub>); M.P. 71 – 72 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.74 – 7.71 (m, 1H), 7.56 – 7.51 (m, 2H), 7.35 – 7.29 (m, 3H), 7.20 – 7.18 (m, 3H), 5.20 (dd, *J*<sub>H-F</sub> = 48.0 Hz, *J*<sub>H-H</sub> = 3.0 Hz, 1H), 5.12 (dd, *J*<sub>H-F</sub> = 28.0 Hz, *J*<sub>H-H</sub> = 3.0 Hz, 1H), 3.64 (s, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -195.8 (dd, *J*<sub>F-H</sub> = 48.0 Hz, *J*<sub>F-H</sub> = 28.0 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 167.0 (d, *J*<sub>C-F</sub> = 22.5 Hz), 141.4, 133.4, 133.2, 132.8, 132.1, 130.0, 129.9, 129.2, 128.6, 128.5, 117.0, 112.1, 89.9 (d, *J*<sub>C-F</sub> = 195.0 Hz), 53.0 (d, *J*<sub>C-F</sub> = 15.0 Hz), 52.8. IR: 2947, 2224, 1732, 1438, 1283, 1106, 1016, 743, 692, 555, 491 cm<sup>-1</sup>. HRMS (API<sup>+</sup>) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>15</sub>FNO<sub>2</sub>S: 316.0808, found: 316.0814.



#### Methyl 3-(3-cyanophenyl)-2-fluoro-3-(phenylthio)propanoate (**3w**):

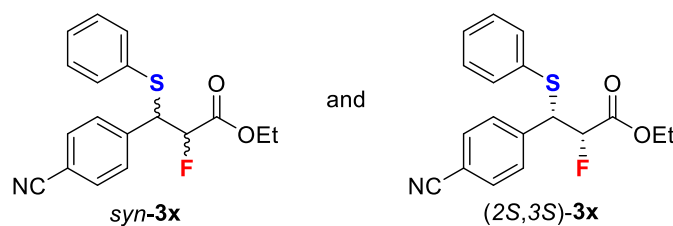
The *syn*-**3w** was obtained following the procedure (III). <sup>19</sup>F NMR of the reaction crude showed *dr* = 92:8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 62% yield (major: 54 mg as a colorless oil; major and minor mixture: 5 mg).

The (2*S*,3*S*)-**3w** was obtained following the general procedure (IV). <sup>19</sup>F NMR of the reaction crude showed *dr* = 92:8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two



diastereoisomers in 76% yield (major: 60 mg as a colorless oil, major and minor mixture: 8 mg). 52% *ee* was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 50.573 min, *t* (major) = 54.183 min.].

$[\alpha]_D^{20} = +85.8$  (c 1.15,  $\text{CDCl}_3$ );  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.56 – 7.48 (m, 3H), 7.37 – 7.32 (m, 1H), 7.23 – 7.16 (m, 5H), 5.16 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.60 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 3.69 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -195.4 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.5 (d,  $J_{\text{C-F}} = 22.5$  Hz), 139.7, 133.4, 133.0, 132.9, 132.4, 132.0, 131.8, 129.5, 129.2, 128.5, 118.4, 112.8, 90.7 (d,  $J_{\text{C-F}} = 195.0$  Hz), 55.2 (d,  $J_{\text{C-F}} = 15.0$  Hz), 52.8. IR: 2953, 2231, 1763, 1438, 1221, 1102, 1008, 801, 739, 690, 528, 479  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{15}\text{FNO}_2\text{S}$ : 316.0808, found: 316.0808.



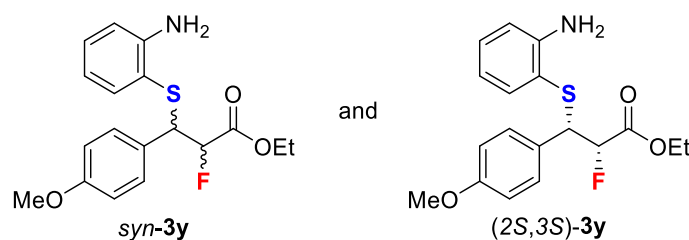
### Methyl 3-(4-cyanophenyl)-2-fluoro-3-(phenylthio)propanoate (**3x**):

The *syn-3x* was obtained following the procedure (III).  $^{19}\text{F NMR}$  of the reaction crude showed *dr* = 81:19. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording two diastereoisomers in 64% yield (major: 51 mg as a white solid; major and minor mixture: 9 mg).

The (2*S*,3*S*)-**3x** was obtained following the general procedure (IV).  $^{19}\text{F NMR}$  of the reaction crude showed *dr* = 100:0. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v) affording an only diastereoisomer in 70% yield (66 mg as a white solid). 68% *ee* was obtained for the it [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 21.380 min, *t* (major) = 23.313 min.].

$[\alpha]_D^{20} = +168.8$  (c 0.32,  $\text{CDCl}_3$ ); M.P. 79 – 80 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.54 –

7.38 (m, 4H), 7.23 – 7.16 (m, 5H), 5.17 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.61 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 3.70 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -195.3 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.5 (d,  $J_{\text{C-F}} = 30.0$  Hz), 143.3, 133.4, 132.4, 132.4, 129.3, 129.3, 129.2, 126.5, 118.4, 112.1, 90.6 (d,  $J_{\text{C-F}} = 195.0$  Hz), 55.6 (d,  $J_{\text{C-F}} = 15.0$  Hz), 52.9. IR: 2967, 2237, 1767, 1441, 1214, 1096, 1003, 836, 745, 570, 437  $\text{cm}^{-1}$ . HRMS (API<sup>+</sup>)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{15}\text{FNO}_2\text{S}$ : 316.0808, found: 316.0790.



**Methyl 3-(2-aminophenylthio)-2-fluoro-3-(4-methoxyphenyl)propanoate (3y):**

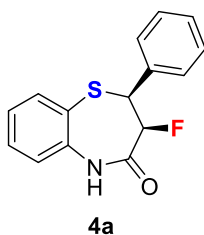
The *syn*-**3x** was obtained following the procedure (III).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 87:13$ . The crude was purified by silica gel column chromatography (petroleum ether/ $\text{CH}_2\text{Cl}_2$ , from 5/1 to 2/1, v/v) affording two diastereoisomers in 40% yield (major: 35 mg as a yellow solid, major and minor mixture: 5 mg).

The (2*S*,3*S*)-**3x** was obtained following the general procedure (IV).  $^{19}\text{F}$  NMR of the reaction crude showed  $dr = 94:6$ . The crude was purified by silica gel column chromatography (petroleum ether/ $\text{CH}_2\text{Cl}_2$ , from 5/1 to 2/1, v/v) affording two diastereoisomers in 37% yield (major: 30 mg as a yellow solid, major and minor mixture: 7 mg). 73% ee was obtained for the major diastereoisomer [determined by HPLC, IC column, Hept/*i*PrOH: 90/10, flow = 1 mL/min,  $\lambda = 254$  nm,  $t$  (minor) = 16.977 min,  $t$  (major) = 23.033 min.].

$[\alpha]_{\text{D}}^{20} = +183.2$  (c 2.20,  $\text{CDCl}_3$ ); M.P. 80 – 82 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 – 6.99 (m, 4H), 6.76 – 6.73 (m, 2H), 6.62 – 6.59 (m, 1H), 6.52 – 6.47 (m, 1H), 5.09 (dd,  $J_{\text{H-F}} = 48.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.44 (dd,  $J_{\text{H-F}} = 28.0$  Hz,  $J_{\text{H-H}} = 3.0$  Hz, 1H), 4.25 (s, 2H), 3.71 (s, 3H), 3.54 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -193.9 (dd,  $J_{\text{F-H}} = 48.0$  Hz,  $J_{\text{F-H}} = 28.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.1 (d,  $J_{\text{C-F}} = 22.5$  Hz), 159.3, 149.2, 137.5,

130.8, 130.1, 129.5, 129.5, 118.3, 115.2, 115.0, 113.9, 91.0 (d,  $J_{C-F} = 195.0$  Hz), 55.3, 53.4 (d,  $J_{C-F} = 22.5$  Hz), 52.5. **IR:** 3354, 2953, 1754, 1605, 1511, 1480, 1243, 1102, 1023, 827, 743, 534, 435  $\text{cm}^{-1}$ . **HRMS (ESI<sup>+</sup>) m/z:**  $[M+H]^+$  calcd for  $\text{C}_{17}\text{H}_{19}\text{FNO}_3\text{S}$ : 336.1070, found: 336.1062.

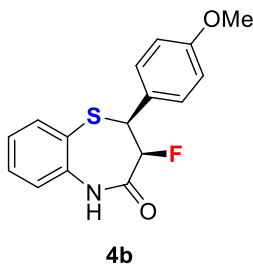
### 1.3 Synthesis of bioactive molecules<sup>123</sup>



#### (2S,3S)-3-fluoro-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5H)-one (4a):

The (2*S*,3*S*)-**3c** (0.35 mmol, 106.8 mg) with *p*-TsOH (0.07 mmol, 6.9 mg) were added into xylene (2 mL) and the resulting mixture was heated to reflux overnight. After completion of the reaction, the solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc, from 5/1 to 4/1, v/v) to give the desired product **4a** in 85% yield (81 mg, white solid) with 51% *ee* [determined by HPLC, AD-H column, Hept/*i*PrOH: 80/20, flow = 1 mL/min,  $\lambda = 254$  nm, *t* (minor) = 10.467 min, *t* (major) = 14.543 min.].

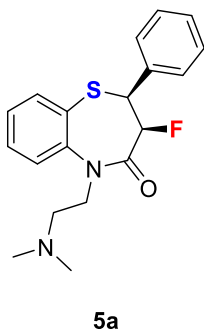
$[\alpha]_D^{23} = +126.1$  (c 0.80,  $\text{CDCl}_3$ ); **M.P.** 161 – 163 °C; **<sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  9.39 (s, 1H), 7.74 (d,  $J_{H-H} = 6.0$  Hz, 1H), 7.59 – 7.58 (m, 2H), 7.45 – 7.35 (m, 4H), 7.27 – 7.21 (m, 2H), 5.36 – 5.18 (m, 2H). **<sup>19</sup>F NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -190.5 (dd,  $J_{F-H} = 47.9$  Hz,  $J_{F-H} = 8.5$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  169.6 (d,  $J_{C-F} = 22.5$  Hz), 140.3, 135.3, 135.3, 134.8, 130.6, 129.3, 128.8, 128.5, 126.7, 126.5, 123.1, 88.8 (d,  $J_{C-F} = 195.0$  Hz), 56.3 (d,  $J_{C-F} = 15.0$  Hz). **IR:** 3188, 3072, 2961, 2903, 1687, 1474, 1306, 1075, 768, 736, 717, 696, 524, 463  $\text{cm}^{-1}$ . **HRMS (API<sup>+</sup>) m/z:**  $[M+H]^+$  calcd for  $\text{C}_{15}\text{H}_{13}\text{FNOS}$ : 274.0702, found: 274.0707.



**(2S,3S)-3-fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5H)-one (4b):**

The (2S,3S)-**3y** (0.2 mmol, 67.0 mg) with *p*-TsOH (0.04 mmol, 3.9 mg) were added into xylene (1.2 mL) and the resulting mixture was heated to reflux overnight. After completion of the reaction, the solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc, from 5/1 to 3/1, v/v) to give the desired product **4b** in 76% yield (46 mg, white solid) with 73% *ee* [determined by HPLC, AD-H column, Hept/*i*PrOH: 80/20, flow = 1 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 13.940 min, *t* (major) = 21.507 min.].

$[\alpha]_D^{23}$  = +122.2 (c 0.54, CDCl<sub>3</sub>); **M.P.** 165 – 166 °C; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  9.00 (s, 1H), 7.63 (d,  $J_{H-H}$  = 9.0 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.18 – 7.11 (m, 2H), 6.81 – 6.75 (m, 2H), 5.22 – 5.04 (m, 2H), 3.71 (s, 3H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -190.4 (ddd,  $J_{F-H}$  = 47.9 Hz,  $J_{F-H}$  = 8.5 Hz,  $J_{F-H}$  = 2.8 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  169.3 (d,  $J_{C-F}$  = 22.5 Hz), 160.0, 140.3, 134.8, 130.5, 130.5, 126.8, 123.1, 113.9, 88.4 (d,  $J_{C-F}$  = 195.0 Hz), 55.6 (d,  $J_{C-F}$  = 22.5 Hz), 55.3. **IR:** 3189, 3076, 2923, 2856, 1684, 1513, 1475, 1306, 1250, 1083, 1027, 785, 764, 652, 490, 410 cm<sup>-1</sup>. **HRMS (API<sup>+</sup>) *m/z*:** [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>FNO<sub>2</sub>S: 304.0808, found: 304.0812.

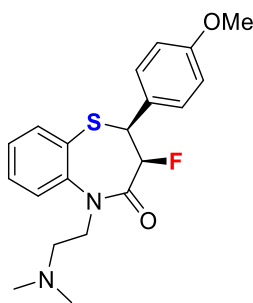


**(2S,3S)-5-(2-(dimethylamino)ethyl)-3-fluoro-2-phenyl-2,3-**

**dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (5a):**

To a solution of **4a** (0.25 mmol, 68.5 mg) in ethyl acetate (1.5 mL) was added 2-dimethylaminoethyl chloride hydrochloride (72.0 mg, 0.50 mmol), followed by potassium carbonate (138.0 mg, 1.0 mmol) and H<sub>2</sub>O (15 μL). After the mixture was stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na<sub>2</sub>SO<sub>4</sub> then the crude mixture was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 10/1 to 8/1, v/v) to give the desired product **5a** in 41% yield (35 mg, white solid) with 51% *ee* [determined by HPLC, luxcell-2 column, Hept/*i*PrOH: 80/20, flow = 1 mL/min, λ = 254 nm, t (minor) = 16.503 min, t (major) = 19.920 min.].

[α]<sub>D</sub><sup>20</sup> = +144.9 (c 0.31, CDCl<sub>3</sub>); **M.P.** 165 – 166 °C; **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.84 – 7.73 (m, 1H), 7.59 – 7.28 (m, 8H), 5.43 – 4.90 (m, 2H), 4.53 – 4.26 (m, 1H), 3.85 – 3.71 (m, 1H), 2.79 – 2.45 (m, 2H), 2.29 (s, 6H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ -189.3 (d, *J*<sub>F-H</sub> = 47.9 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):** δ 166.5 (d, *J*<sub>C-F</sub> = 22.5 Hz), 145.1, 135.5, 131.1, 129.9, 128.9, 128.5, 128.4, 128.2, 128.1, 127.6, 124.7, 86.2 (d, *J*<sub>C-F</sub> = 187.5 Hz), 56.7, 55.0 (d, *J*<sub>C-F</sub> = 22.5 Hz), 47.8, 45.6. **IR:** 3064, 2939, 2765, 1681, 1441, 1179, 1088, 856, 766, 602, 591, 428 cm<sup>-1</sup>. **HRMS (ESI<sup>+</sup>) m/z:** [M+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>FN<sub>2</sub>OS: 345.1437, found: 345.1449.

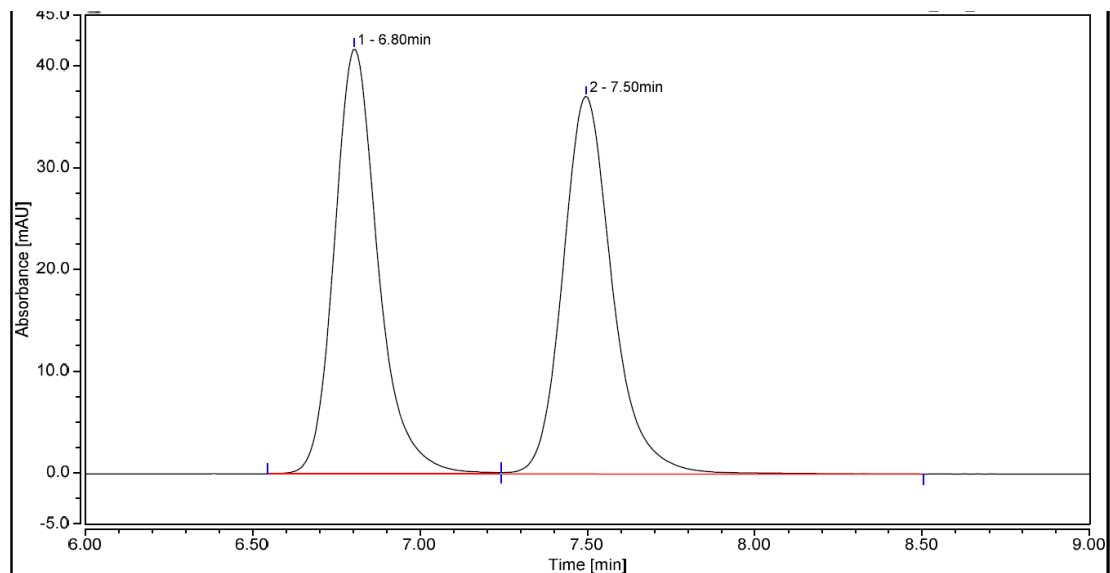
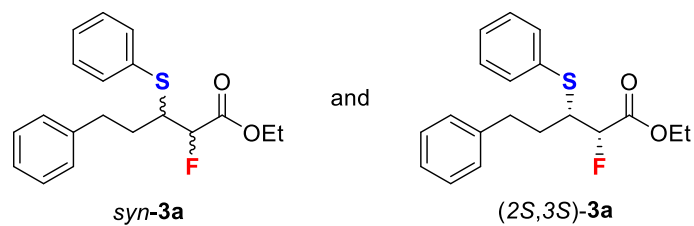
**5b****(2*S*,3*S*)-5-(2-(dimethylamino)ethyl)-3-fluoro-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (31):**

To a solution of **4b** (0.15 mmol, 45.0 mg) in ethyl acetate (1.0 mL) was added 2-dimethylaminoethyl chloride hydrochloride (43.2 mg, 0.30 mmol), followed by potassium carbonate (82.8 mg, 0.6 mmol) and H<sub>2</sub>O (10 μL). After the mixture was

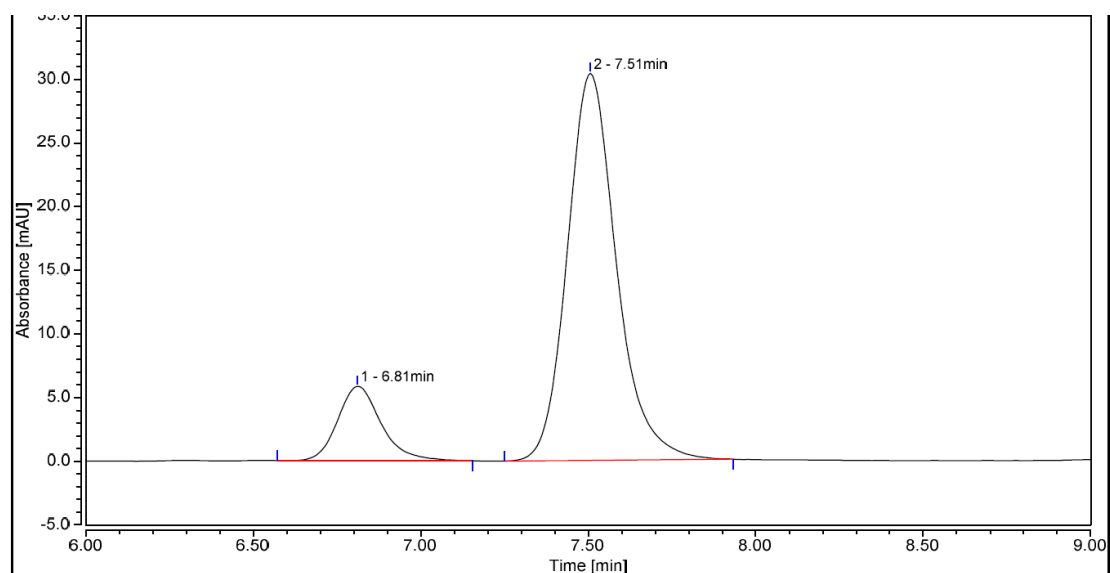
stirred for 24 h under reflux, it was cooled to room temperature. The mixture was dried over Na<sub>2</sub>SO<sub>4</sub> then the crude mixture was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1 to 8/1, v/v) to give the desired product **5b** in 32% yield (18 mg, colorless oil) with 73% *ee* [determined by HPLC, luxcell-2 column, Hept/*i*PrOH: 80/20, flow = 1.2 mL/min,  $\lambda$  = 254 nm, *t* (minor) = 18.370 min, *t* (major) = 23.353 min.].

$[\alpha]_D^{20} = +126.4$  (c 0.47, CDCl<sub>3</sub>); **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.72 – 7.64 (m, 1H), 7.43 – 7.35 (m, 3H), 7.23 – 7.19 (m, 2H), 6.86 – 6.75 (m, 2H), 5.28 – 4.78 (m, 2H), 4.45 – 4.17 (m, 1H), 3.74 (s, 3H), 3.71 – 3.62 (m, 1H), 2.71 – 2.32 (m, 2H), 2.21 (s, 6H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -189.2 (d,  $J_{F-H} = 47.9$  Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  166.6 (d,  $J_{C-F} = 22.5$  Hz), 160.0, 145.0, 135.4, 131.0, 129.4, 128.2, 127.6, 124.6, 113.9, 86.1 (d,  $J_{C-F} = 187.5$  Hz), 56.6, 55.3, 54.5 (d,  $J_{C-F} = 22.5$  Hz), 47.7, 45.5. **IR:** 3058, 2938, 2770, 1676, 1609, 1511, 1251, 1178, 1092, 1029, 732, 602, 407 cm<sup>-1</sup>. **HRMS (ESI<sup>+</sup>) *m/z*:** [M+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>24</sub>FN<sub>2</sub>O<sub>2</sub>S: 375.1543, found: 375.1532.

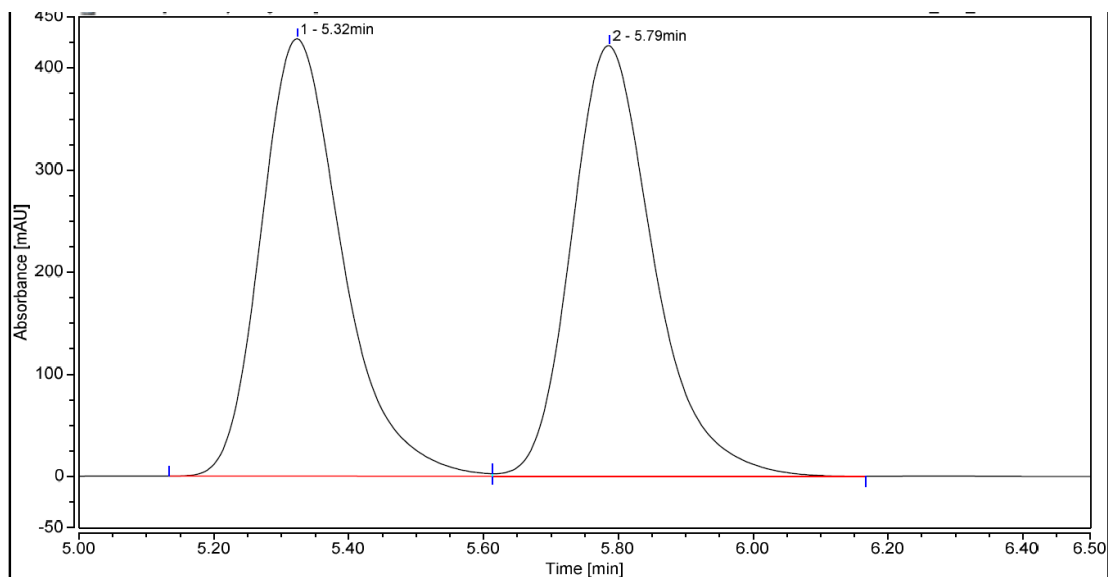
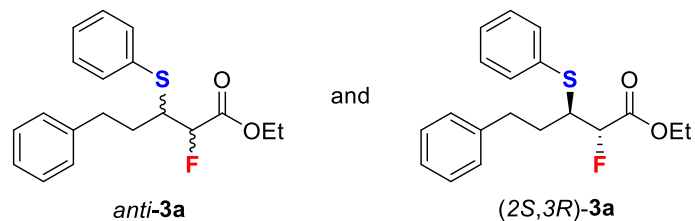
## 1.4 The HPLC chromatograms



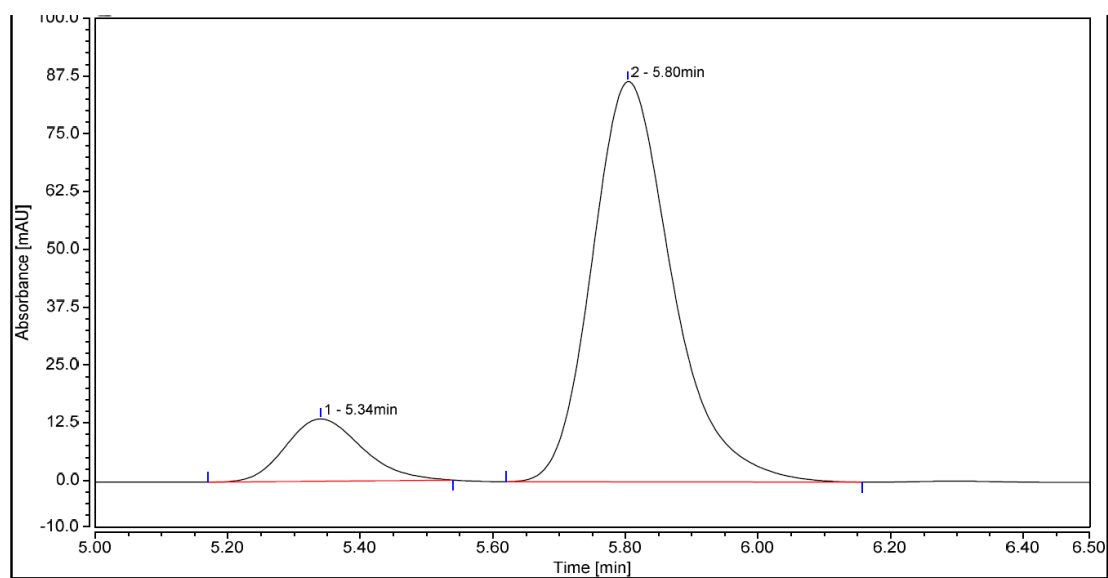
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.803	6.339	41.765	49.82	52.97	n.a.
2		7.497	6.385	37.089	50.18	47.03	n.a.
<b>Total:</b>			<b>12.724</b>	<b>78.854</b>	<b>100.00</b>	<b>100.00</b>	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.810	0.876	5.843	14.51	16.12	n.a.
2		7.507	5.164	30.406	85.49	83.88	n.a.
<b>Total:</b>			<b>6.040</b>	<b>36.249</b>	<b>100.00</b>	<b>100.00</b>	



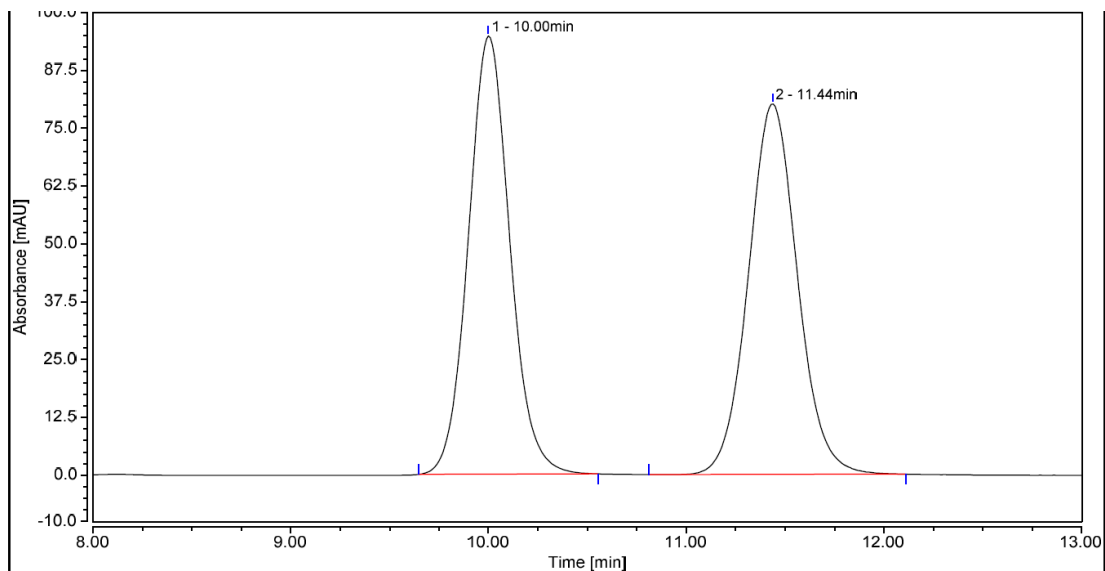
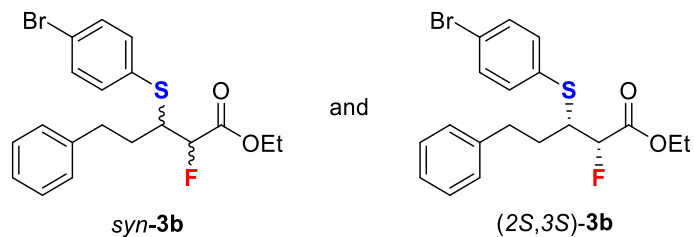
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.323	59.786	427.969	50.05	50.39	n.a.
2		5.787	59.656	421.265	49.95	49.61	n.a.
Total:			119.442	849.233	100.00	100.00	



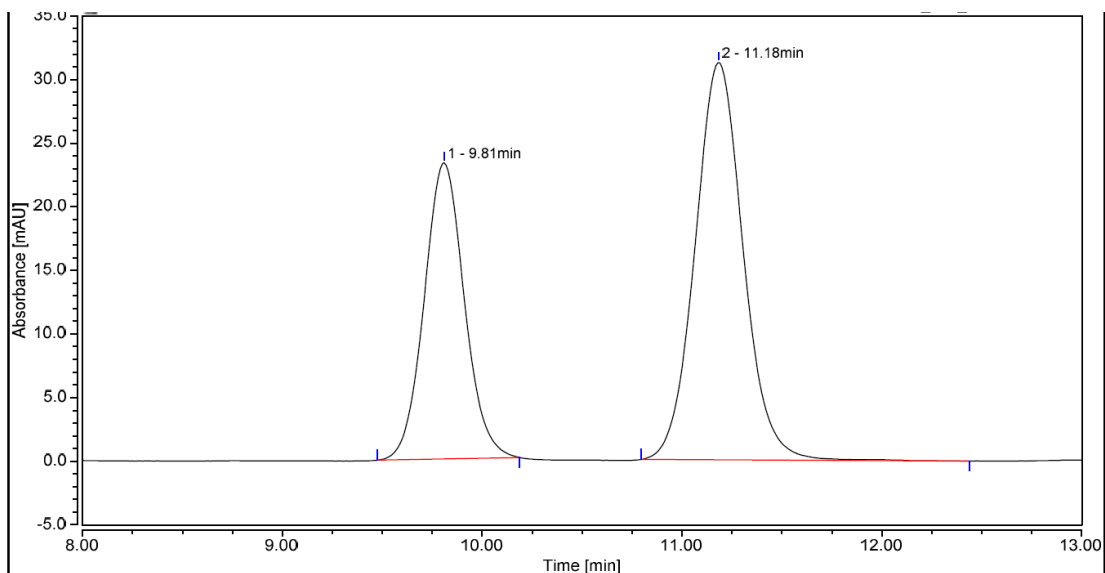
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.340	1.793	13.465	12.87	13.46	n.a.
2		5.803	12.135	86.549	87.13	86.54	n.a.
Total:			13.927	100.014	100.00	100.00	



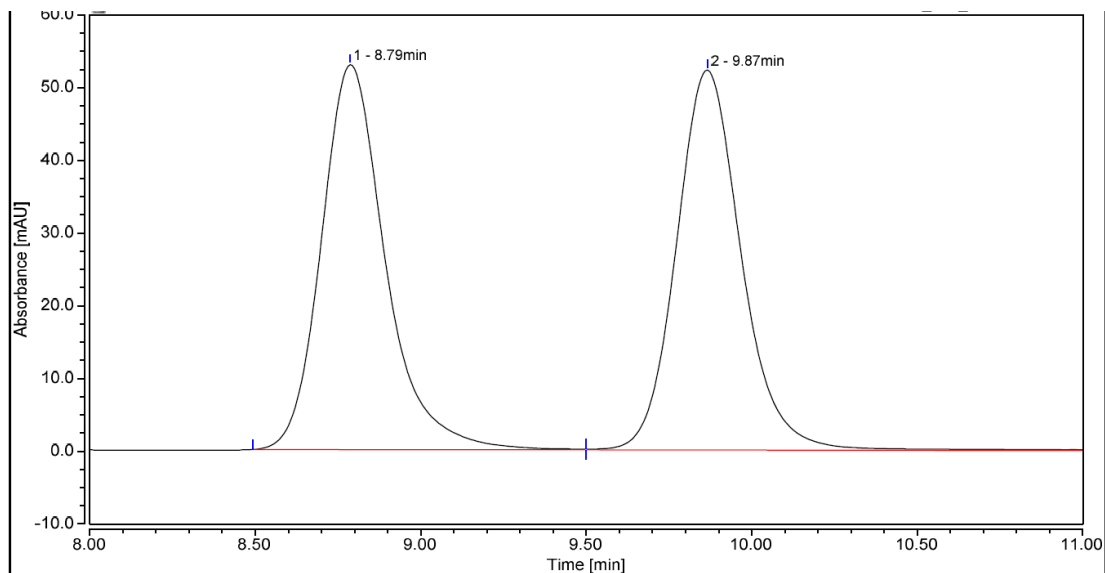
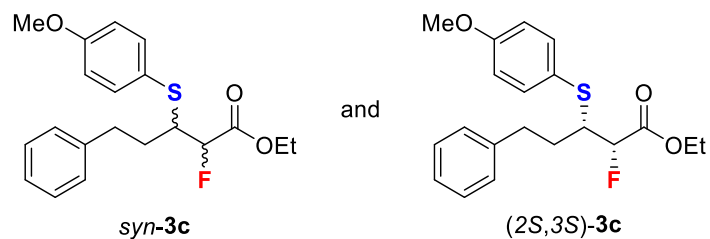
Experimental Section



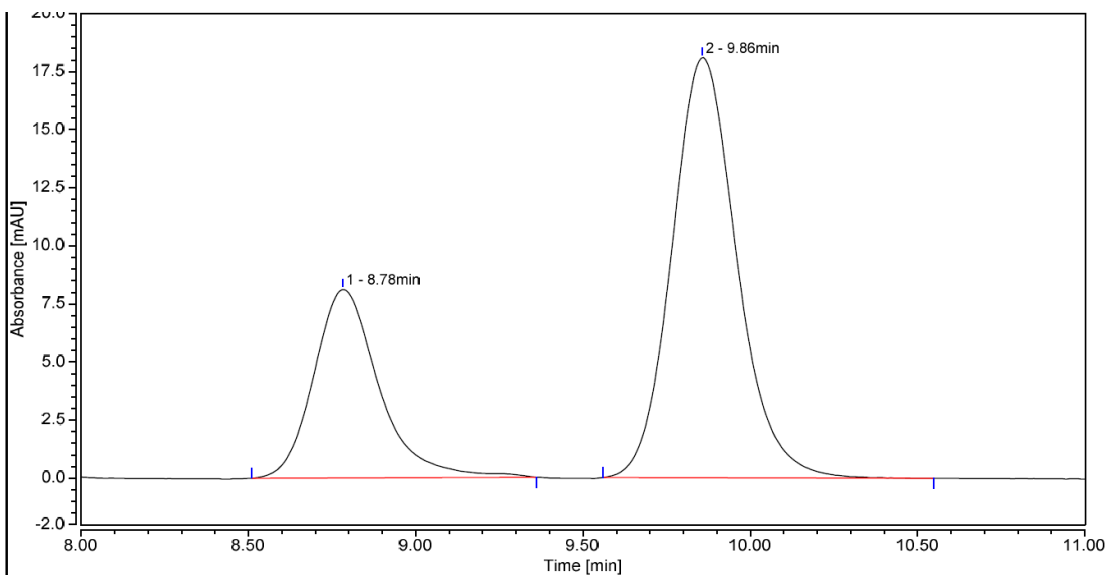
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.000	23.012	94.728	49.99	54.19	n.a.
2		11.437	23.017	80.082	50.01	45.81	n.a.
<b>Total:</b>			<b>46.030</b>	<b>174.811</b>	<b>100.00</b>	<b>100.00</b>	



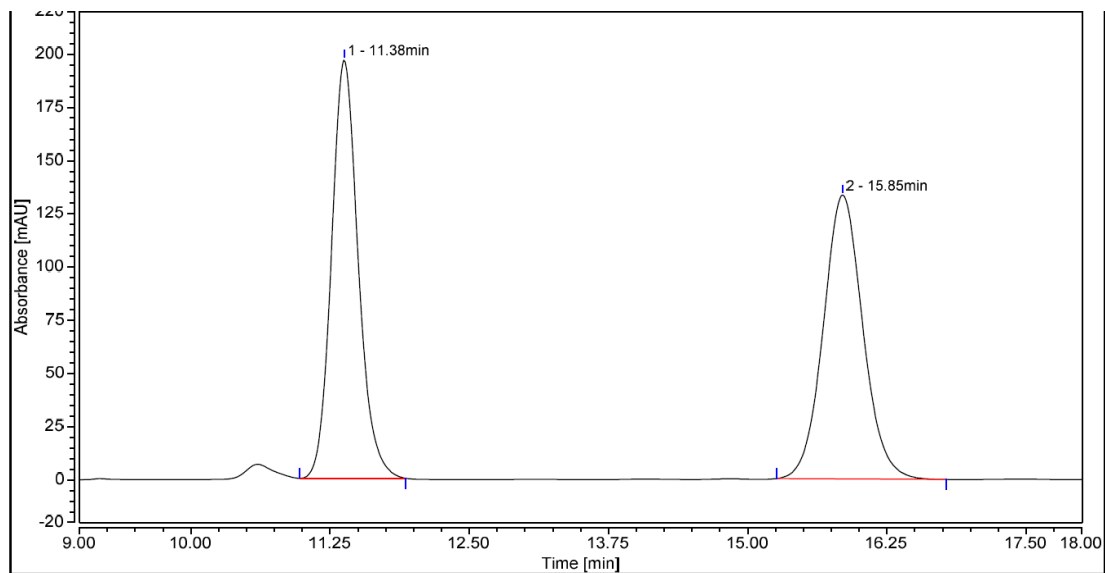
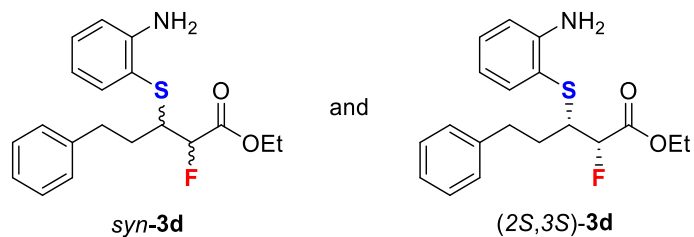
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.810	5.418	23.288	38.33	42.71	n.a.
2		11.183	8.718	31.241	61.67	57.29	n.a.
<b>Total:</b>			<b>14.136</b>	<b>54.529</b>	<b>100.00</b>	<b>100.00</b>	



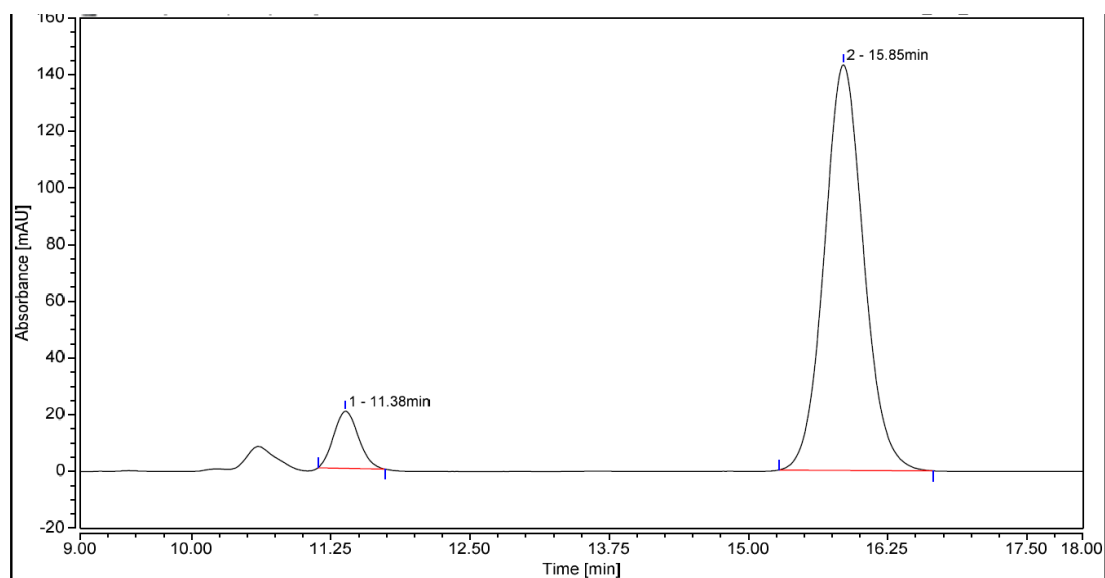
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8.787	11.876	52.936	49.92	50.33	n.a.
2		9.867	11.914	52.251	50.08	49.67	n.a.
<b>Total:</b>			<b>23.791</b>	<b>105.187</b>	<b>100.00</b>	<b>100.00</b>	



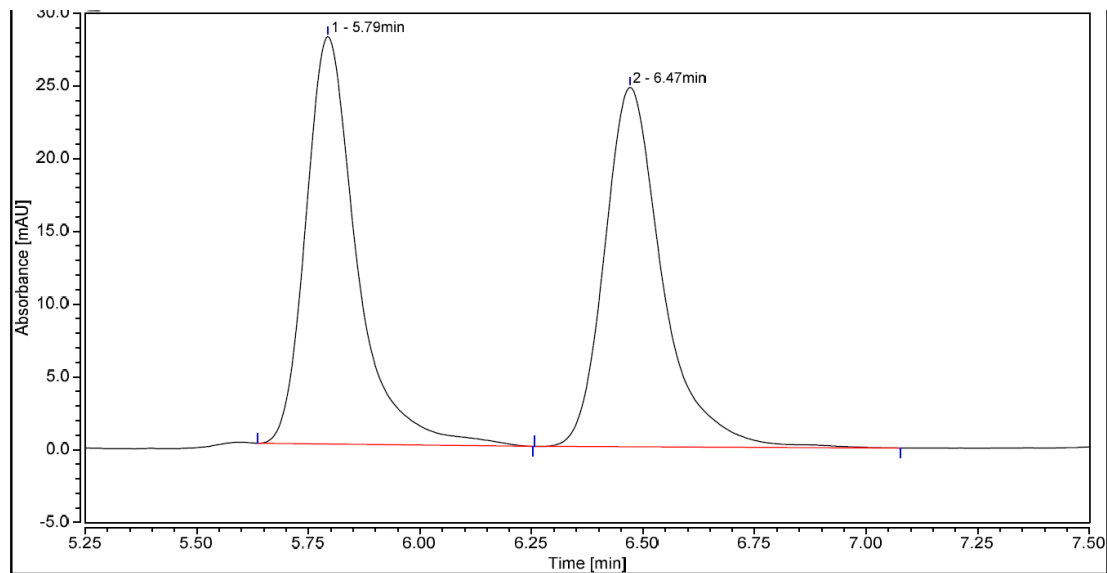
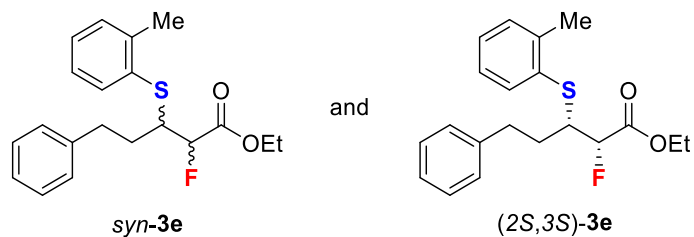
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8.783	1.834	8.109	31.09	30.96	n.a.
2		9.857	4.063	18.087	68.91	69.04	n.a.
<b>Total:</b>			<b>5.897</b>	<b>26.196</b>	<b>100.00</b>	<b>100.00</b>	



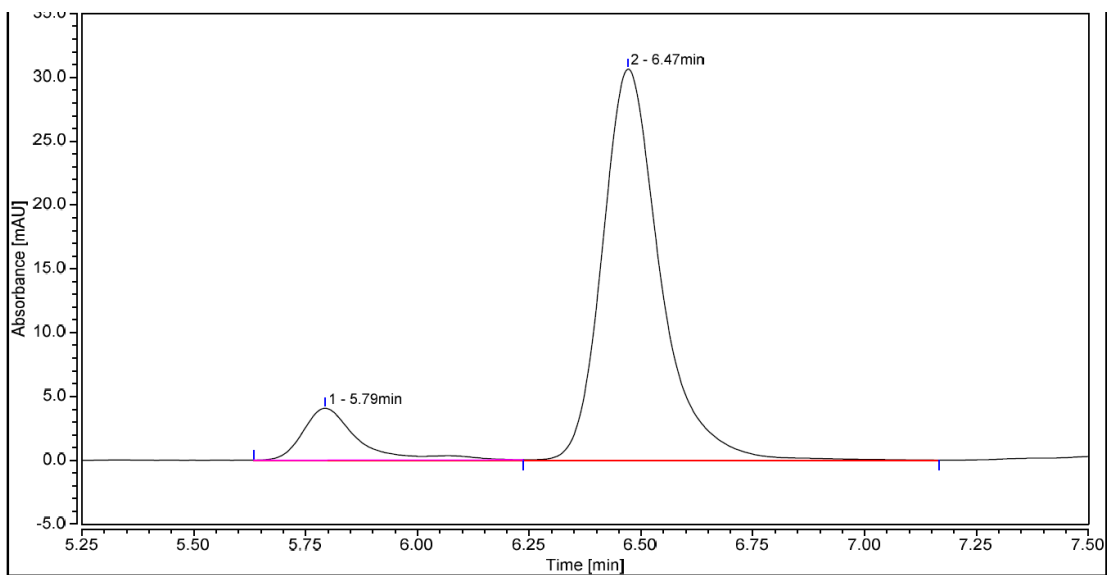
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.377	54.679	196.629	49.85	59.57	n.a.
2		15.850	55.014	133.464	50.15	40.43	n.a.
<b>Total:</b>			<b>109.693</b>	<b>330.094</b>	<b>100.00</b>	<b>100.00</b>	



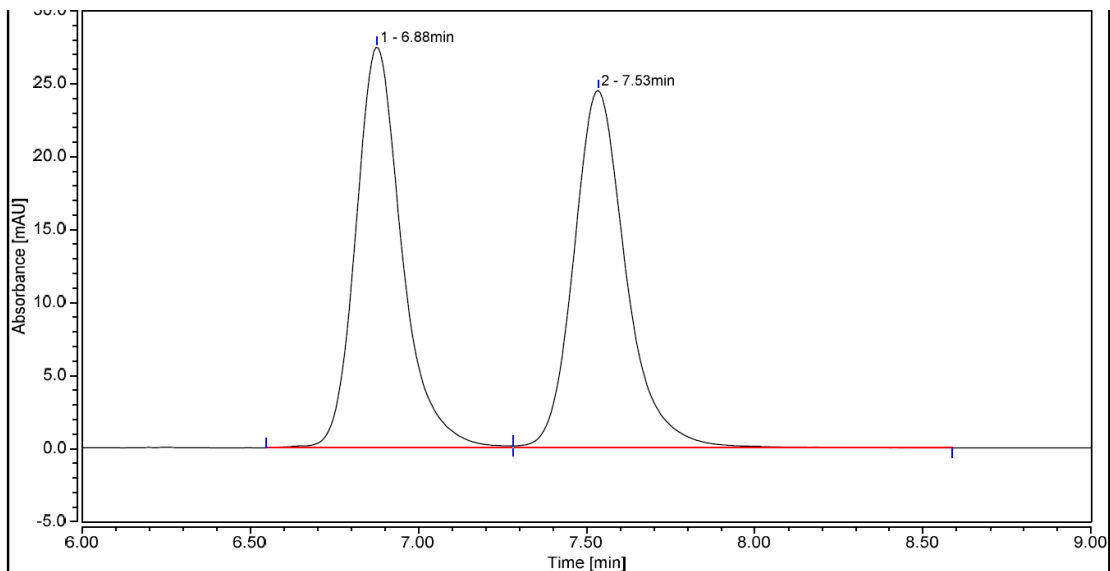
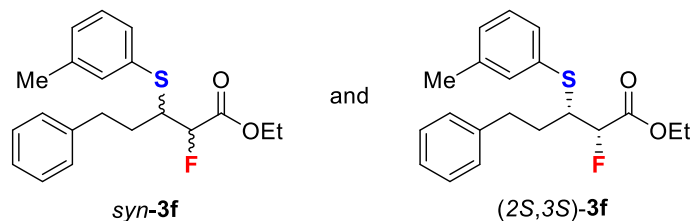
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.380	5.202	20.160	8.13	12.35	n.a.
2		15.850	58.753	143.140	91.87	87.65	n.a.
<b>Total:</b>			<b>63.955</b>	<b>163.300</b>	<b>100.00</b>	<b>100.00</b>	



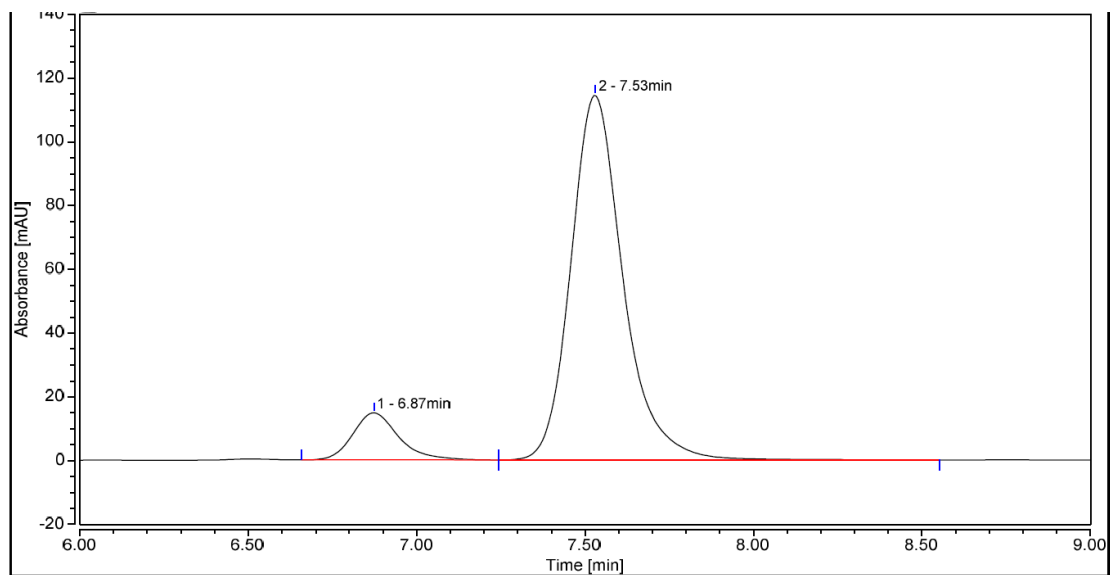
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.793	3.716	28.008	50.02	53.15	n.a.
2		6.470	3.714	24.692	49.98	46.85	n.a.
<b>Total:</b>			<b>7.431</b>	<b>52.700</b>	<b>100.00</b>	<b>100.00</b>	



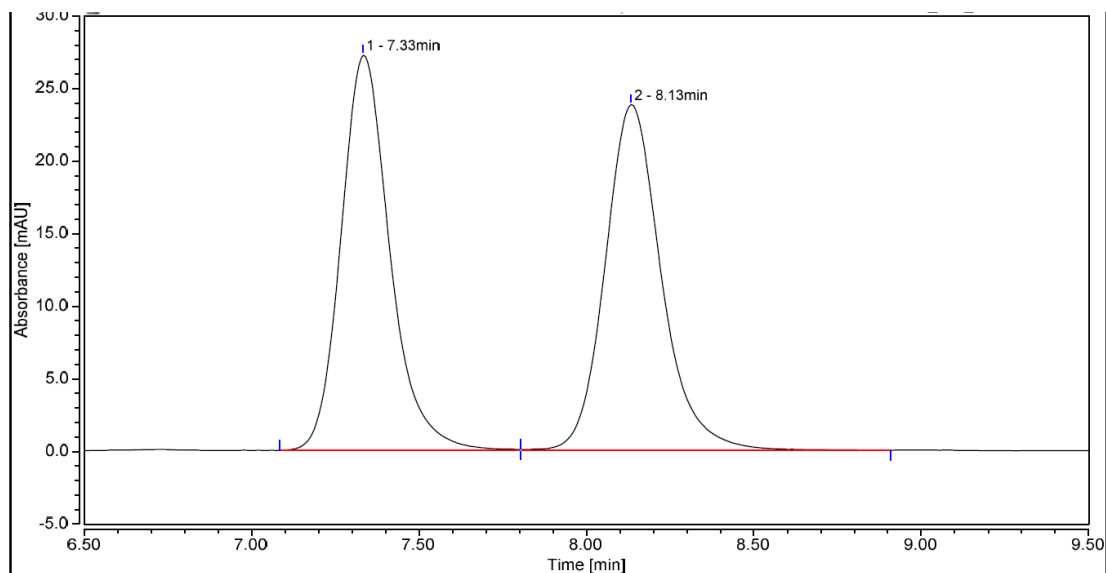
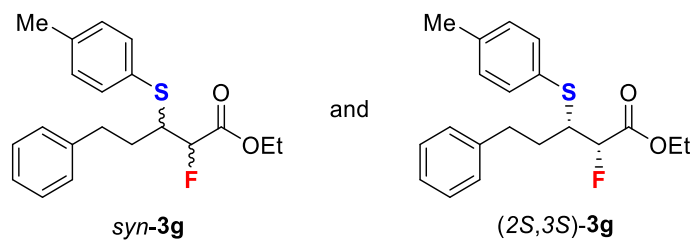
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.793	0.580	4.061	11.21	11.70	n.a.
2		6.470	4.595	30.635	88.79	88.30	n.a.
<b>Total:</b>			<b>5.176</b>	<b>34.695</b>	<b>100.00</b>	<b>100.00</b>	



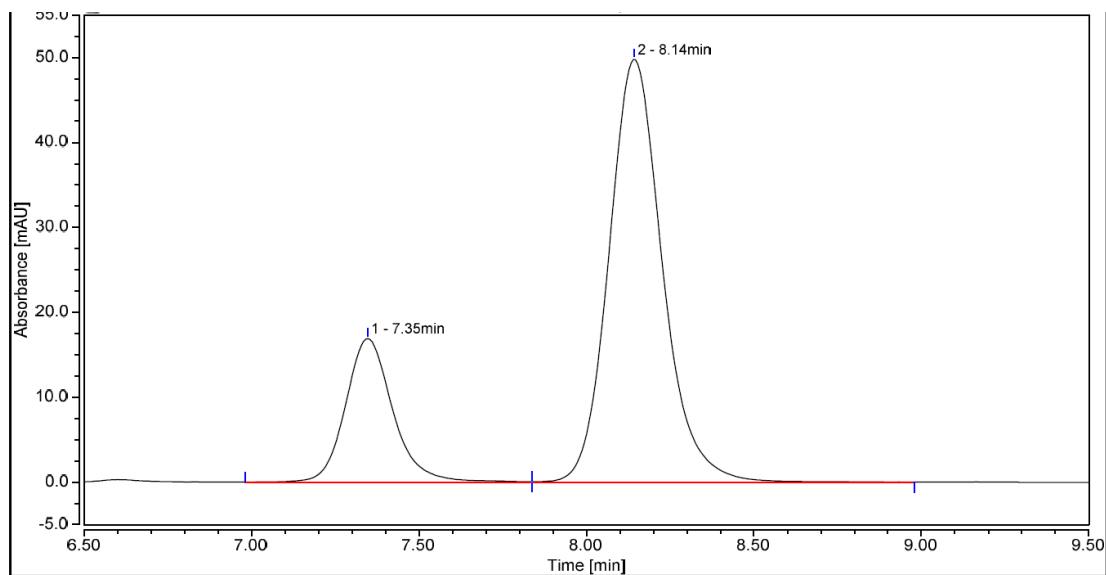
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.877	4.385	27.448	49.81	52.86	n.a.
2		7.533	4.419	24.481	50.19	47.14	n.a.
Total:			8.804	51.930	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.873	2.322	14.743	10.15	11.42	n.a.
2		7.530	20.550	114.399	89.85	88.58	n.a.
Total:			22.872	129.141	100.00	100.00	

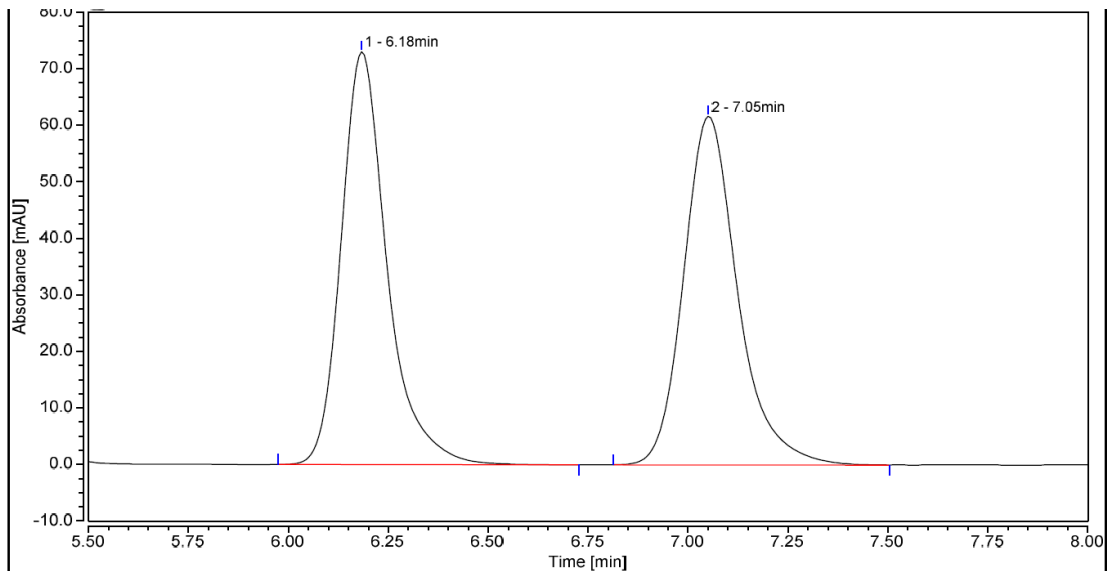
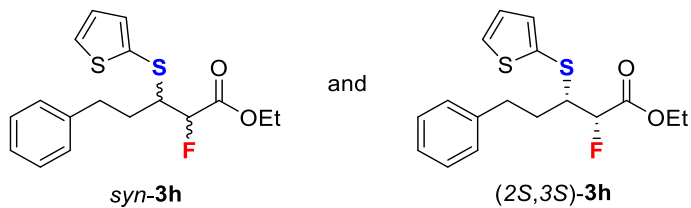


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.333	4.611	27.213	49.85	53.33	n.a.
2		8.133	4.639	23.813	50.15	46.67	n.a.
<b>Total:</b>			<b>9.250</b>	<b>51.026</b>	<b>100.00</b>	<b>100.00</b>	

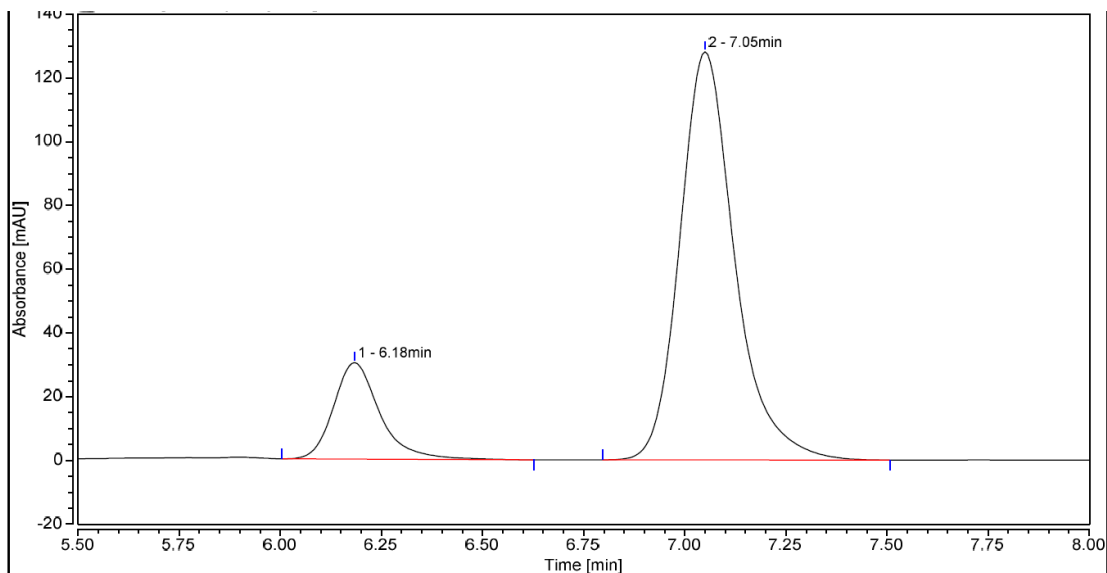


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.347	2.770	16.916	23.13	25.35	n.a.
2		8.143	9.209	49.823	76.87	74.65	n.a.
<b>Total:</b>			<b>11.979</b>	<b>66.739</b>	<b>100.00</b>	<b>100.00</b>	

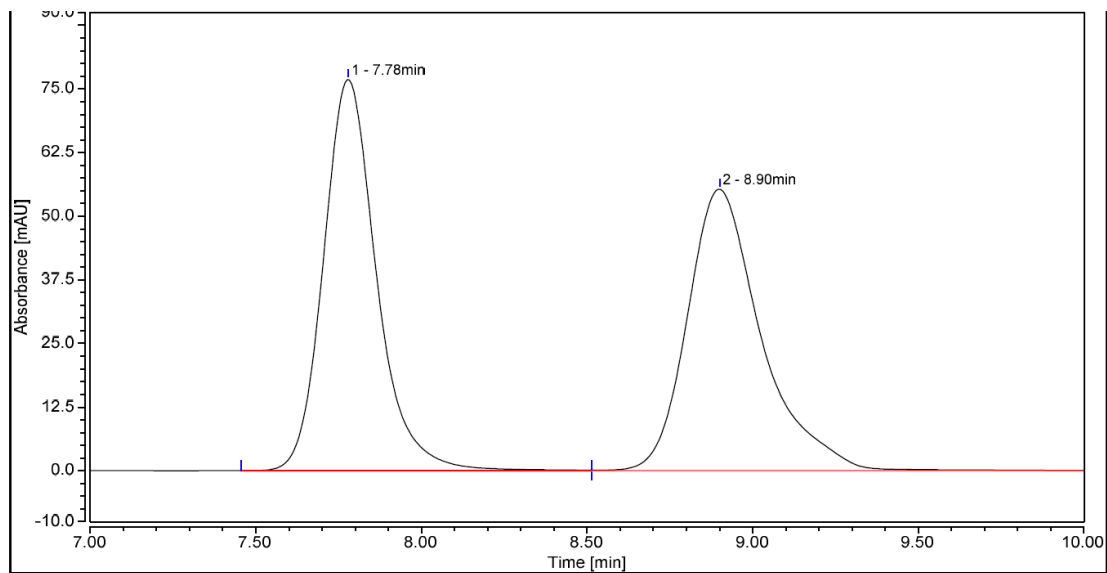
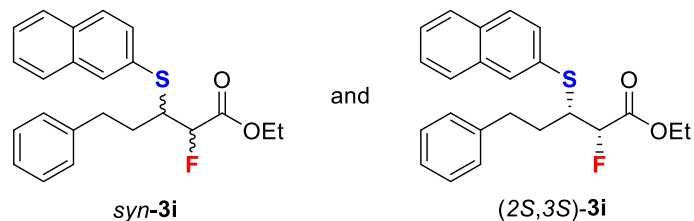
### Experimental Section



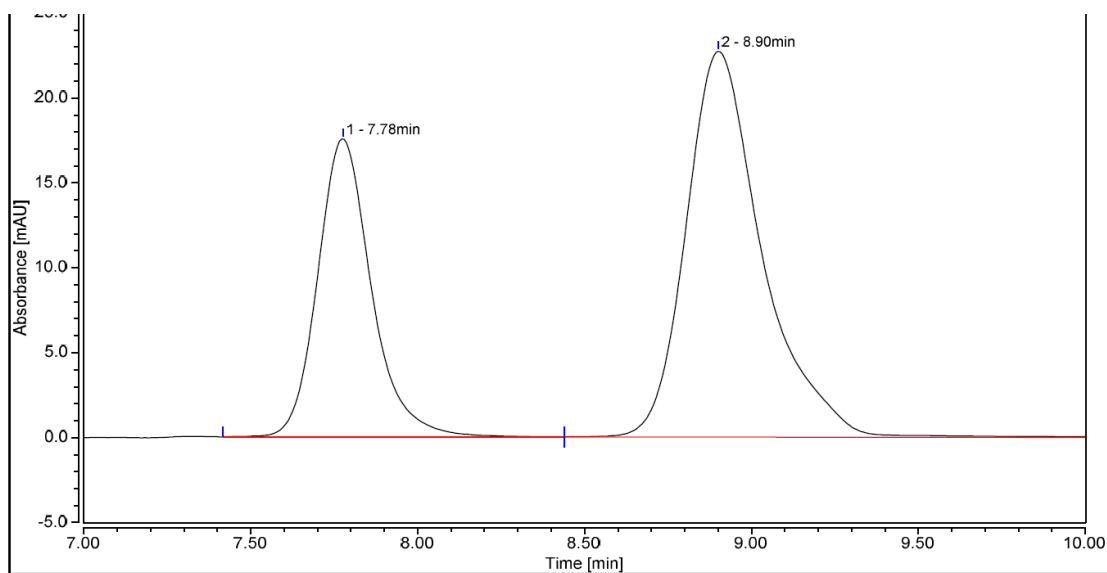
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.183	9.703	73.042	50.10	54.22	n.a.
2		7.050	9.664	61.669	49.90	45.78	n.a.
<b>Total:</b>			<b>19.368</b>	<b>134.711</b>	<b>100.00</b>	<b>100.00</b>	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.183	4.008	30.278	16.61	19.13	n.a.
2		7.050	20.126	127.994	83.39	80.87	n.a.
<b>Total:</b>			<b>24.134</b>	<b>158.272</b>	<b>100.00</b>	<b>100.00</b>	

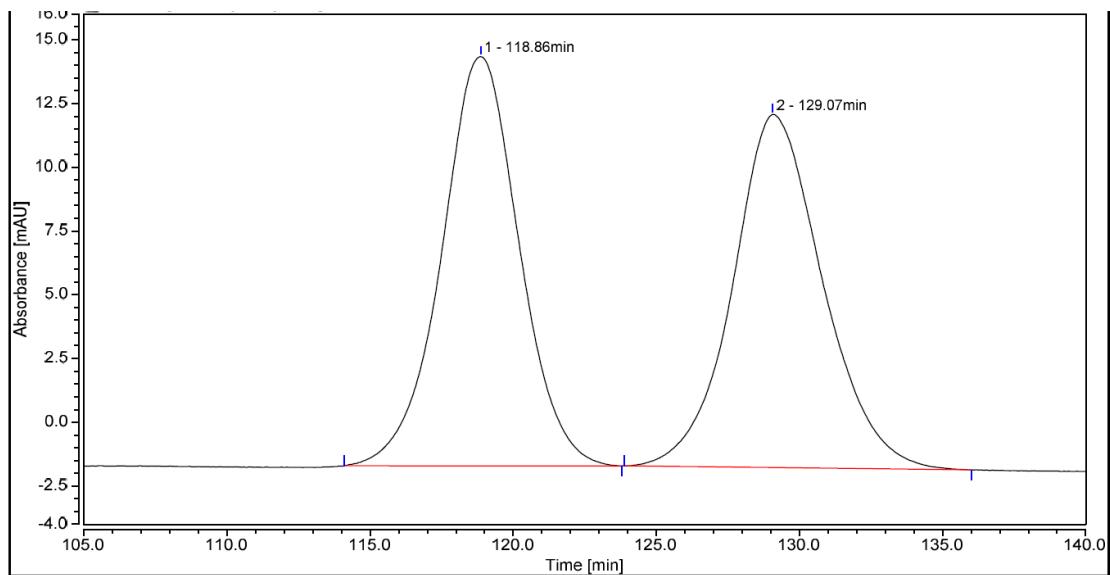
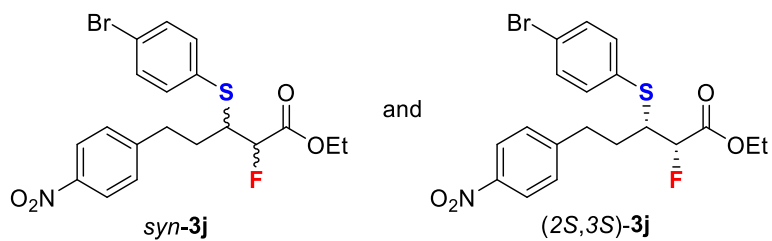


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.780	14.260	76.851	49.99	58.18	n.a.
2		8.900	14.264	55.240	50.01	41.82	n.a.
<b>Total:</b>			<b>28.524</b>	<b>132.091</b>	<b>100.00</b>	<b>100.00</b>	

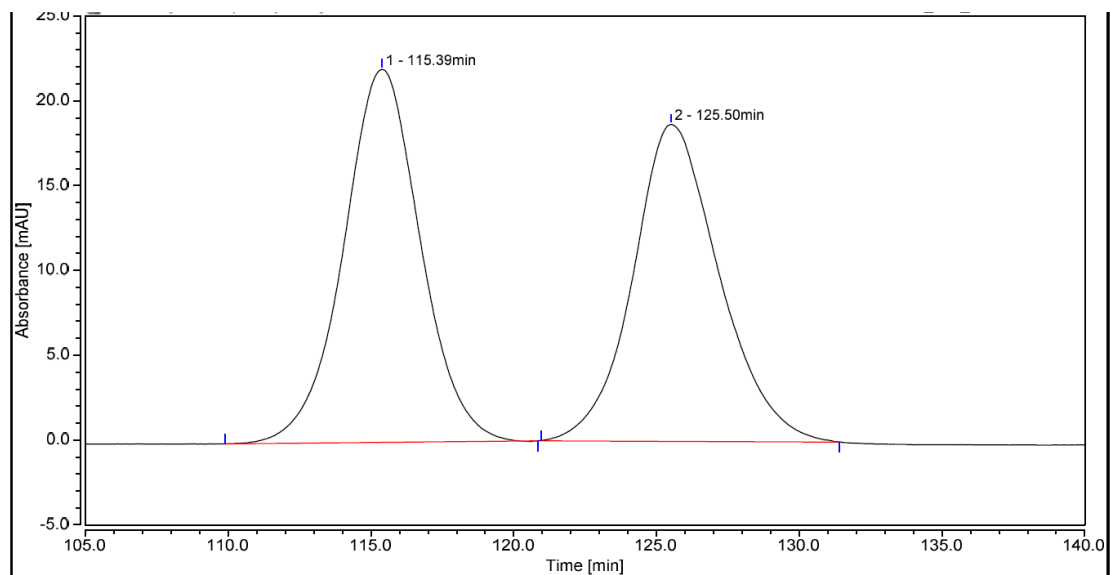


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.777	3.282	17.556	35.34	43.60	n.a.
2		8.900	6.004	22.714	64.66	56.40	n.a.
<b>Total:</b>			<b>9.287</b>	<b>40.270</b>	<b>100.00</b>	<b>100.00</b>	

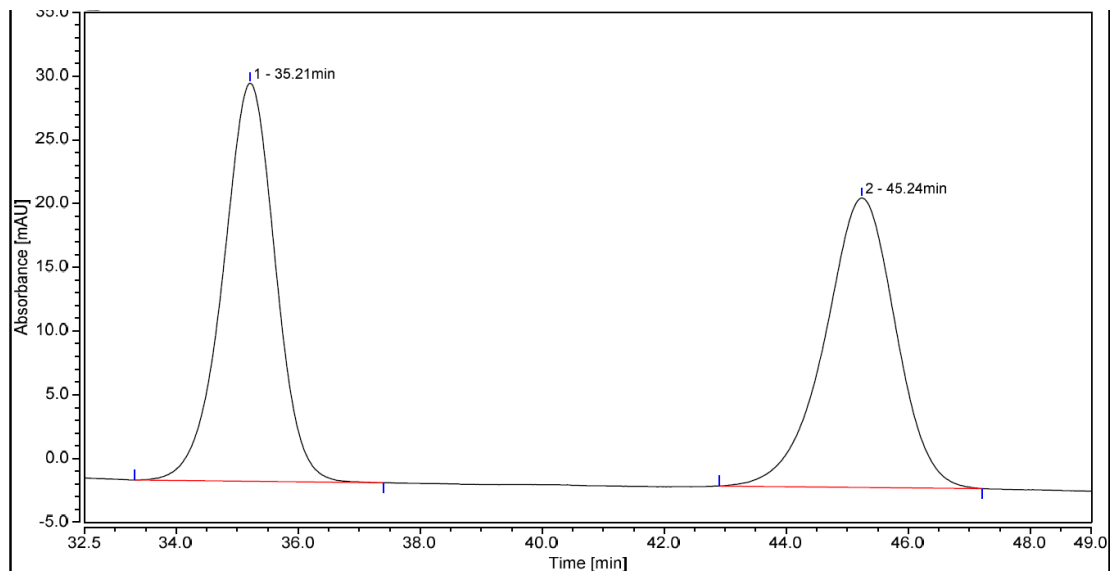
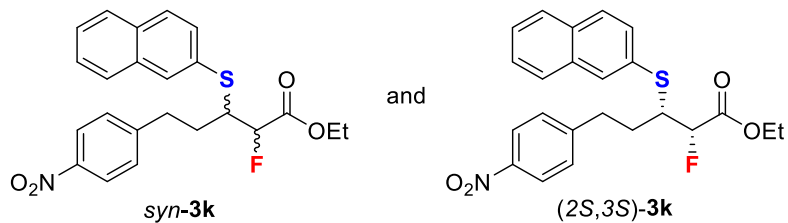




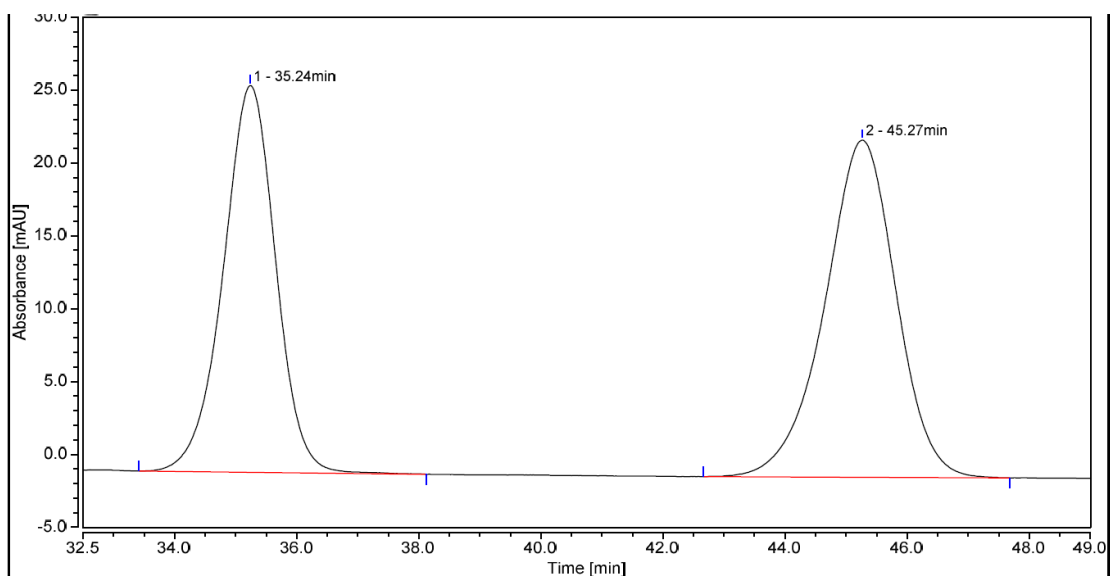
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		118.860	50.303	16.043	49.99	53.68	n.a.
2		129.073	50.333	13.842	50.01	46.32	n.a.
Total:			100.636	29.885	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		115.393	68.615	21.983	51.17	54.06	n.a.
2		125.503	65.472	18.678	48.83	45.94	n.a.
Total:			134.087	40.661	100.00	100.00	

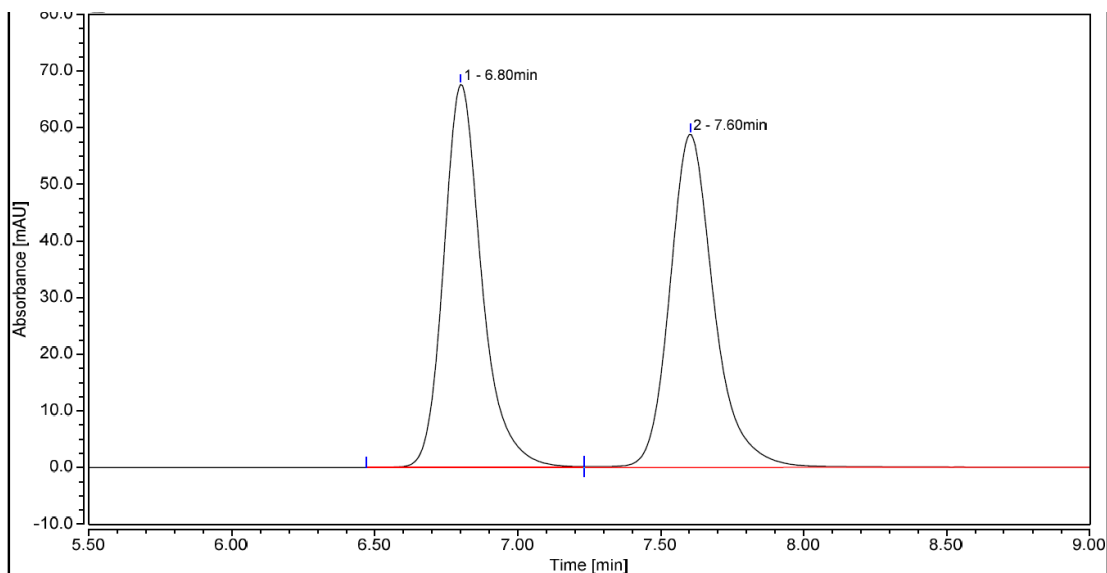
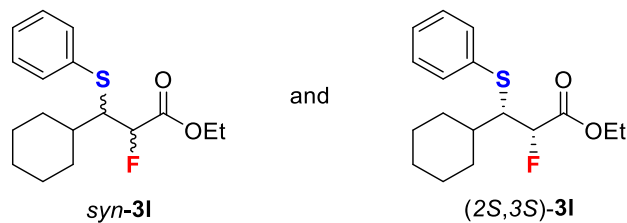


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		35.213	31.197	31.232	50.48	57.90	n.a.
2		45.240	30.607	22.710	49.52	42.10	n.a.
<b>Total:</b>			<b>61.804</b>	<b>53.941</b>	<b>100.00</b>	<b>100.00</b>	

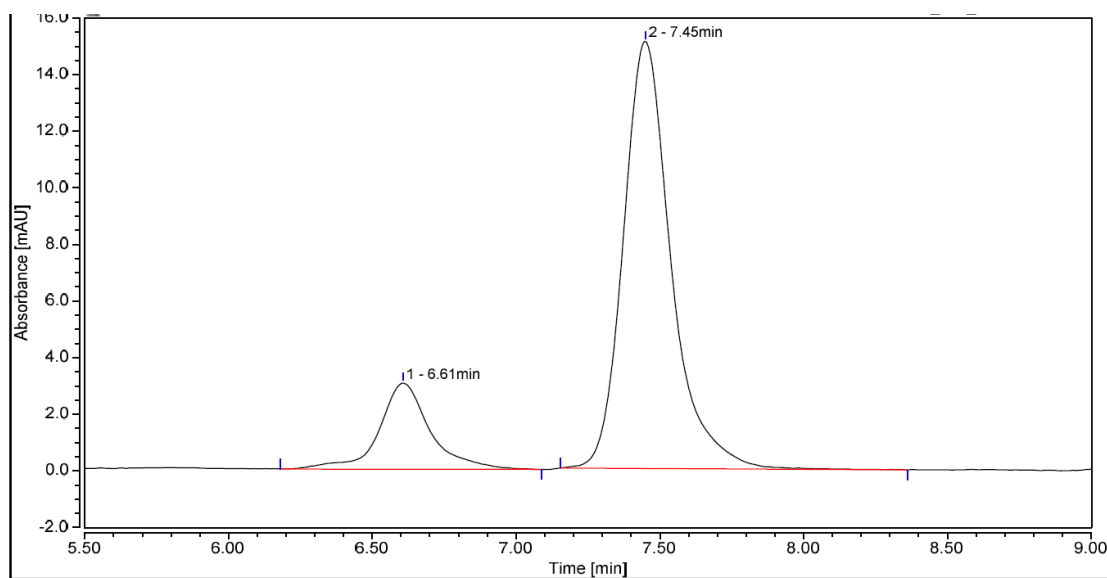


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		35.240	26.477	26.539	45.86	53.43	n.a.
2		45.267	31.257	23.130	54.14	46.57	n.a.
<b>Total:</b>			<b>57.734</b>	<b>49.669</b>	<b>100.00</b>	<b>100.00</b>	

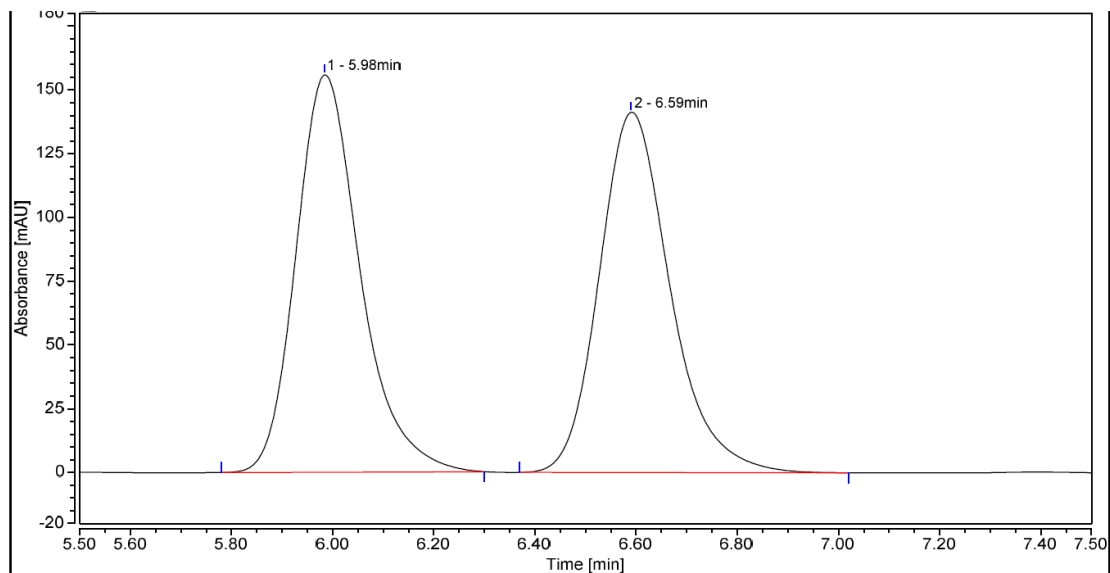
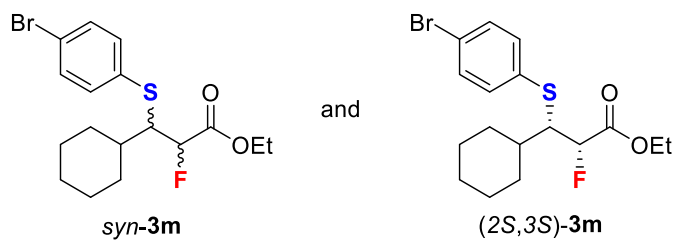
Experimental Section



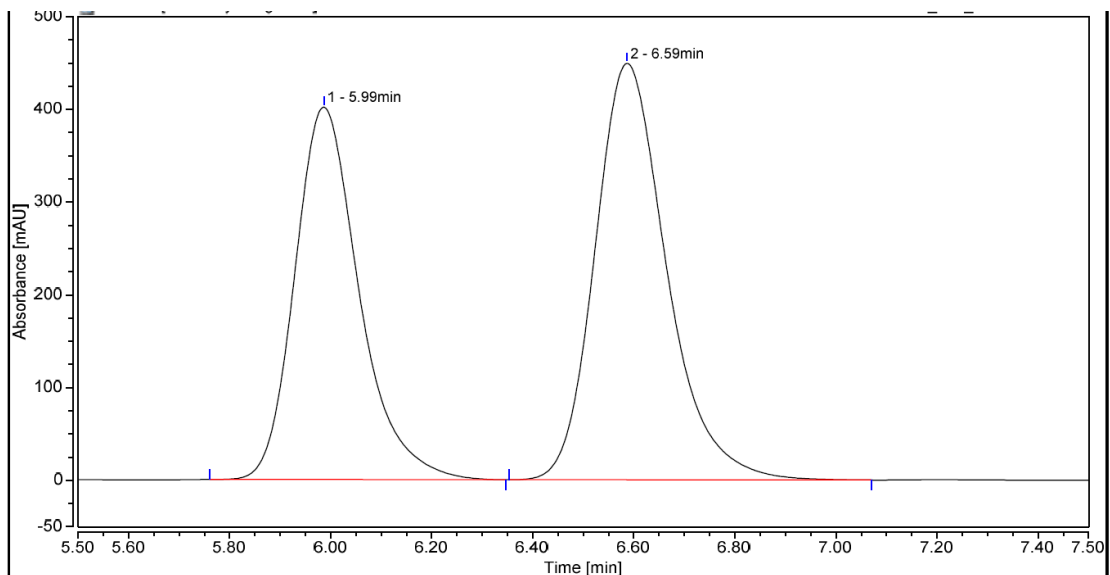
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.800	10.467	67.628	49.68	53.49	n.a.
2		7.603	10.600	58.809	50.32	46.51	n.a.
Total:			21.067	126.437	100.00	100.00	



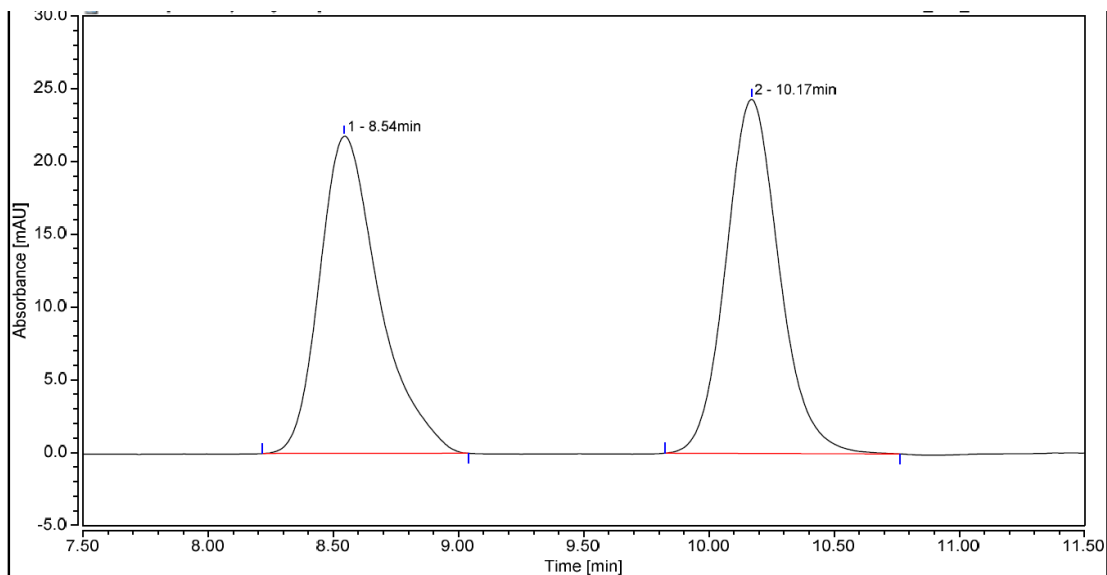
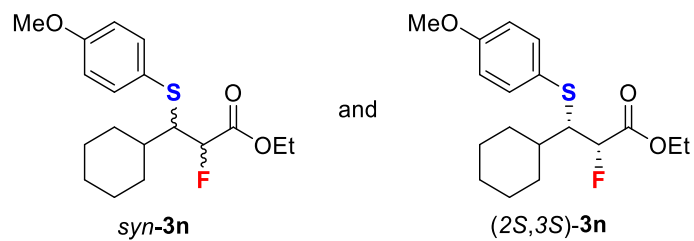
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.607	0.625	3.039	17.71	16.76	n.a.
2		7.450	2.903	15.092	82.29	83.24	n.a.
Total:			3.528	18.132	100.00	100.00	



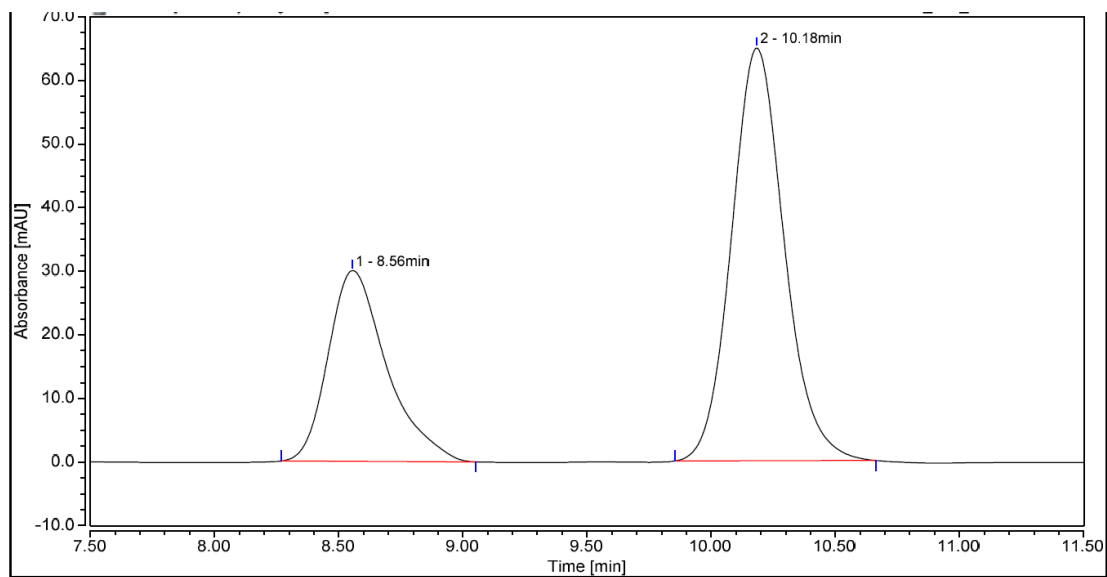
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.983	22.875	155.741	49.91	52.44	n.a.
2		6.590	22.960	141.253	50.09	47.56	n.a.
Total:			45.834	296.994	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		5.987	59.246	401.593	44.57	47.21	n.a.
2		6.587	73.688	449.032	55.43	52.79	n.a.
Total:			132.934	850.625	100.00	100.00	

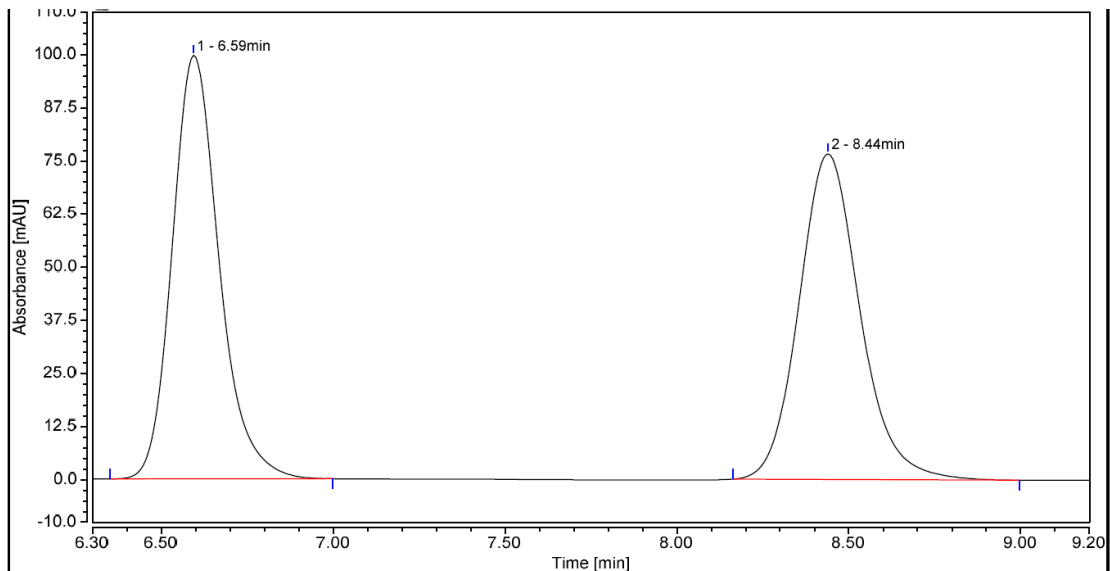
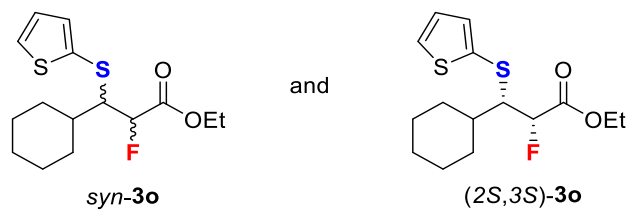


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8.543	5.995	21.796	49.91	47.26	n.a.
2		10.170	6.016	24.325	50.09	52.74	n.a.
Total:			12.012	46.121	100.00	100.00	

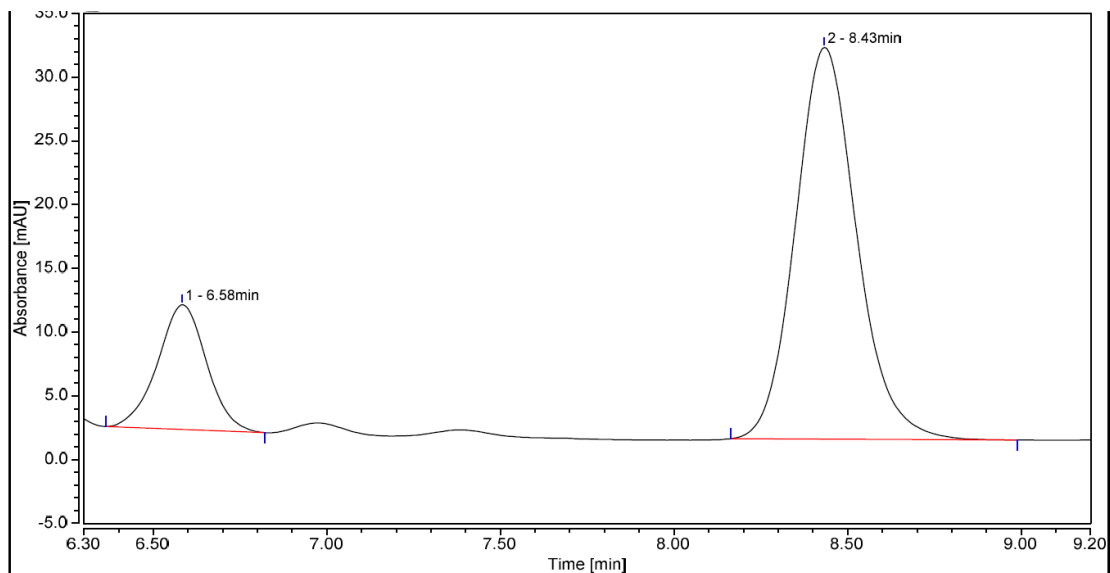


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		8.557	8.201	29.997	33.89	31.61	n.a.
2		10.183	15.998	64.902	66.11	68.39	n.a.
Total:			24.199	94.899	100.00	100.00	

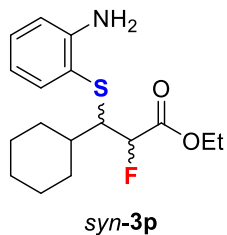
Experimental Section



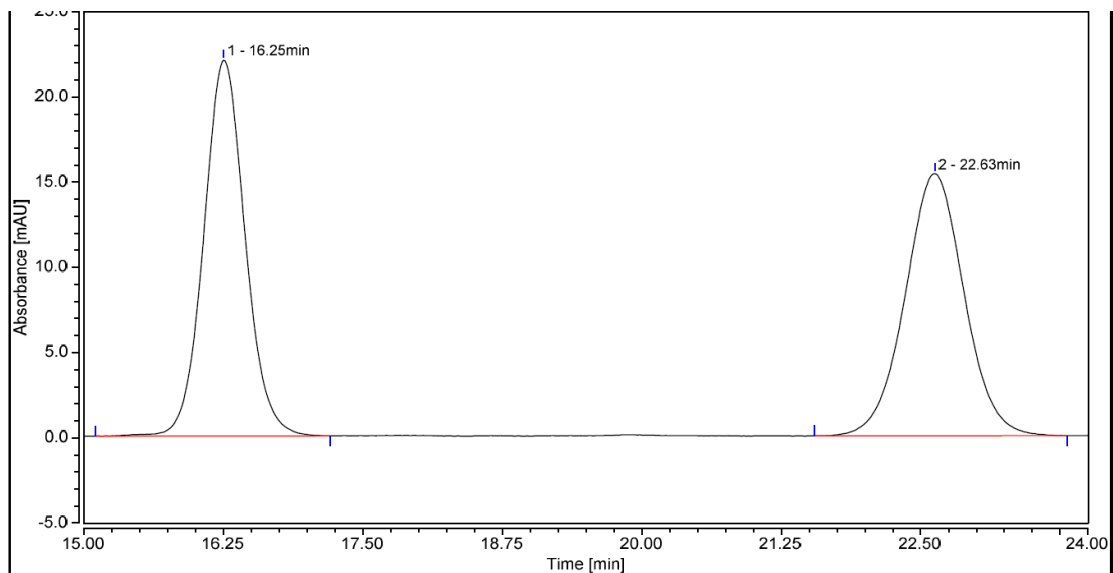
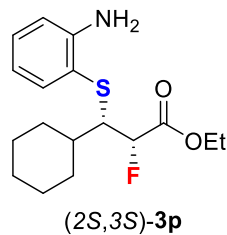
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.593	15.746	99.638	50.00	56.53	n.a.
2		8.440	15.750	76.611	50.00	43.47	n.a.
<b>Total:</b>			<b>31.496</b>	<b>176.249</b>	<b>100.00</b>	<b>100.00</b>	



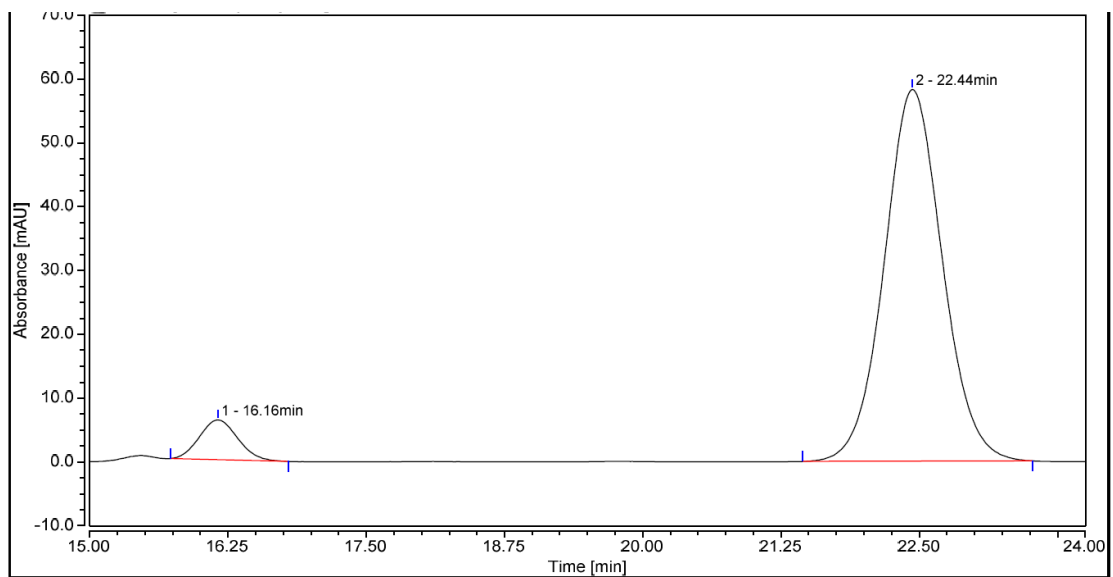
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.583	1.604	9.790	20.30	24.16	n.a.
2		8.433	6.301	30.737	79.70	75.84	n.a.
<b>Total:</b>			<b>7.905</b>	<b>40.527</b>	<b>100.00</b>	<b>100.00</b>	



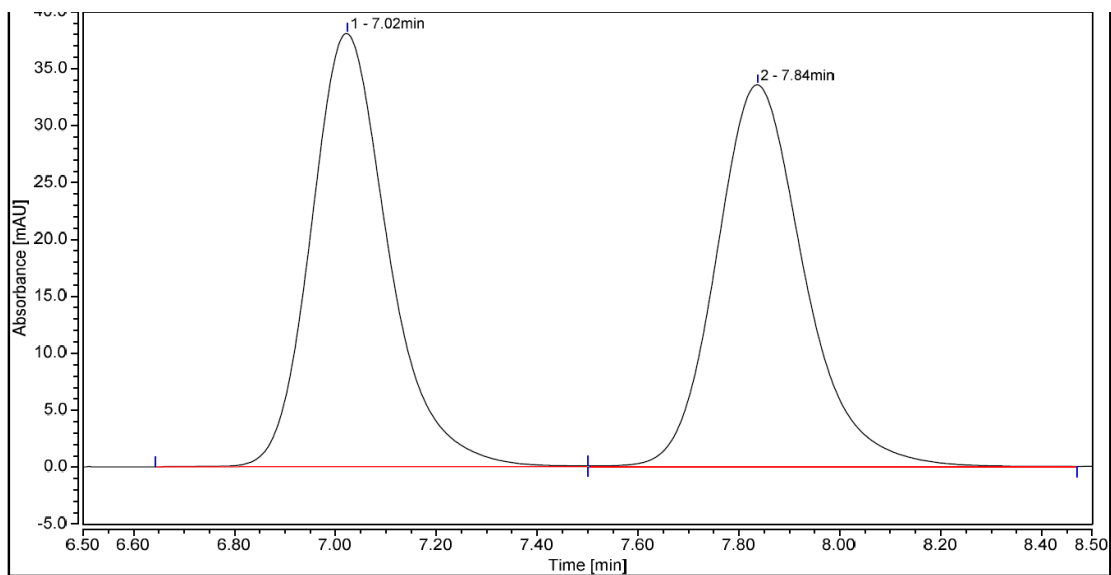
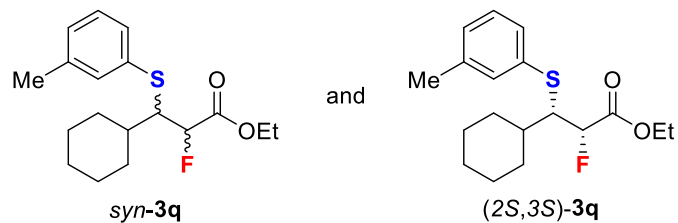
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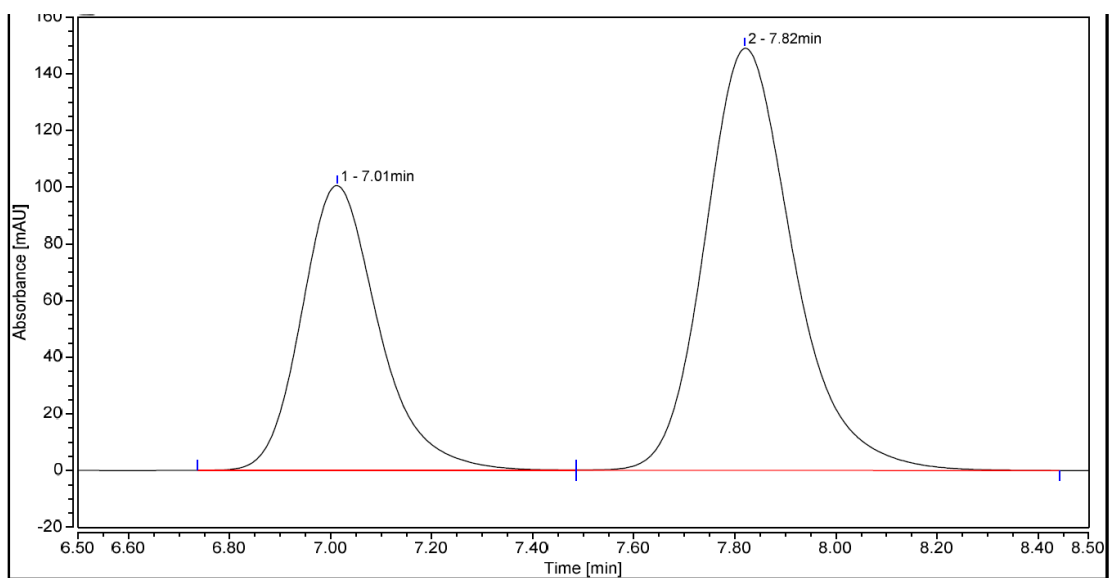
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16.253	9.507	22.055	50.12	58.92	n.a.
2		22.627	9.462	15.379	49.88	41.08	n.a.
<b>Total:</b>			<b>18.970</b>	<b>37.434</b>	<b>100.00</b>	<b>100.00</b>	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16.160	2.498	6.228	6.57	9.66	n.a.
2		22.437	35.511	58.238	93.43	90.34	n.a.
<b>Total:</b>			<b>38.008</b>	<b>64.466</b>	<b>100.00</b>	<b>100.00</b>	

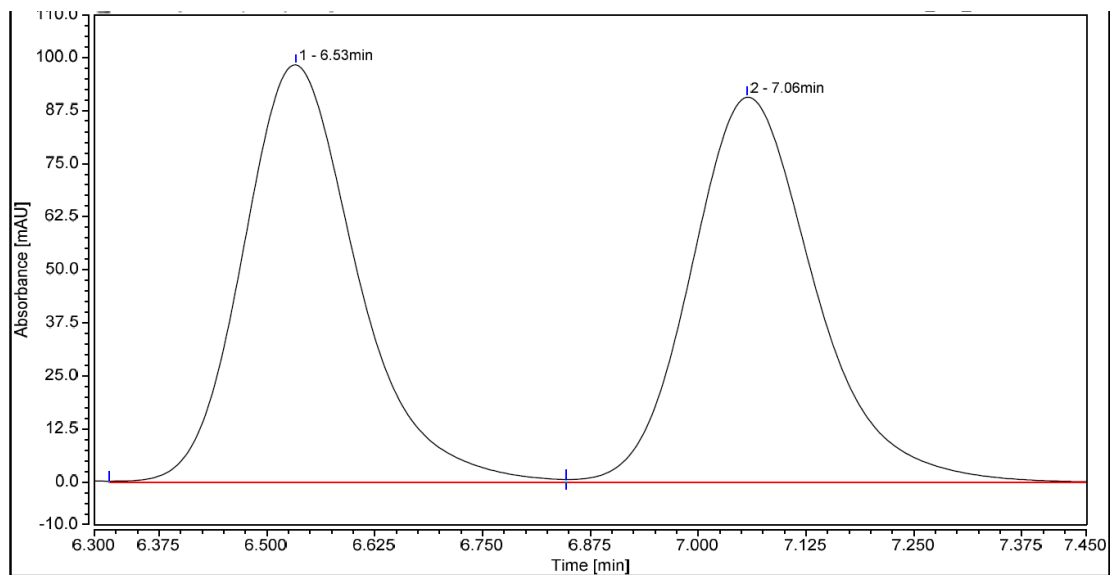
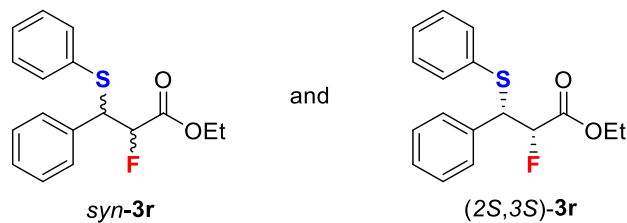


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.023	6.767	38.062	49.91	53.15	n.a.
2		7.837	6.792	33.550	50.09	46.85	n.a.
Total:			13.558	71.612	100.00	100.00	

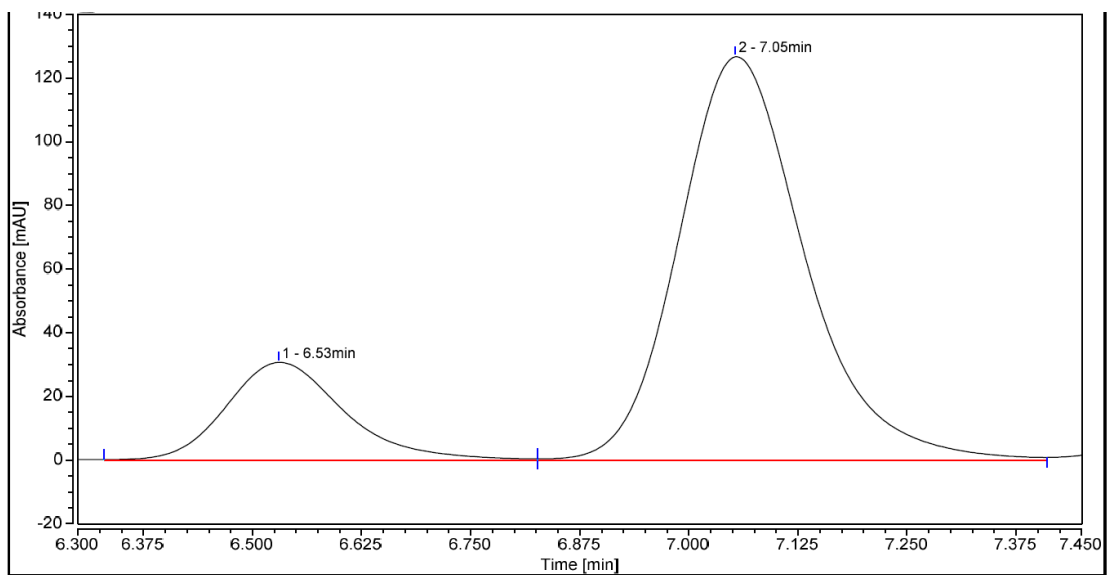


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		7.013	17.820	100.468	37.08	40.28	n.a.
2		7.820	30.237	148.960	62.92	59.72	n.a.
Total:			48.057	249.427	100.00	100.00	



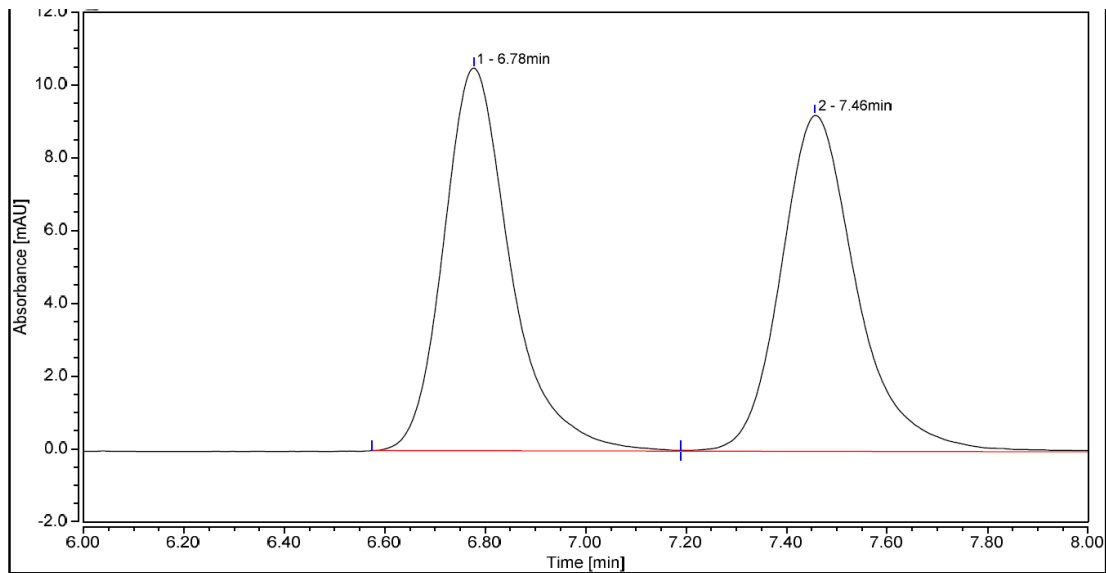
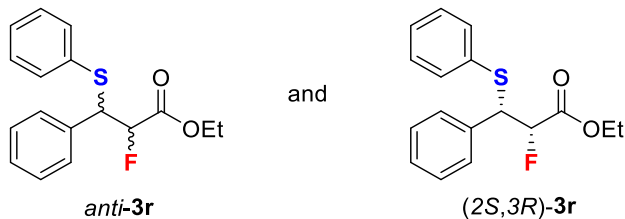


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.533	15.065	98.254	49.98	52.02	n.a.
2		7.057	15.076	90.633	50.02	47.98	n.a.
Total:			30.141	188.887	100.00	100.00	

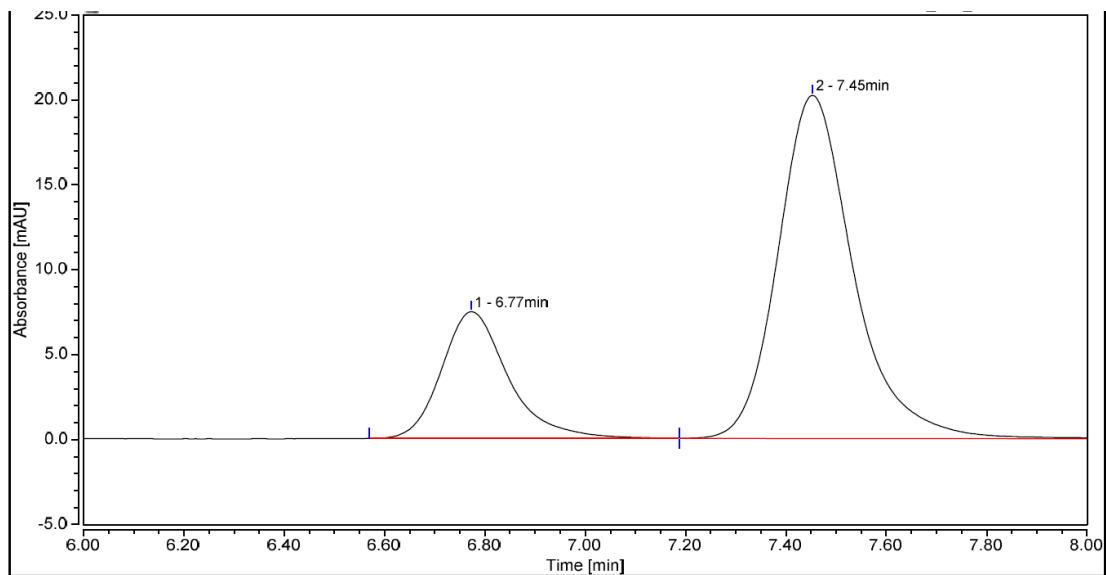


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.530	4.771	30.631	18.40	19.48	n.a.
2		7.053	21.151	126.626	81.60	80.52	n.a.
Total:			25.922	157.257	100.00	100.00	

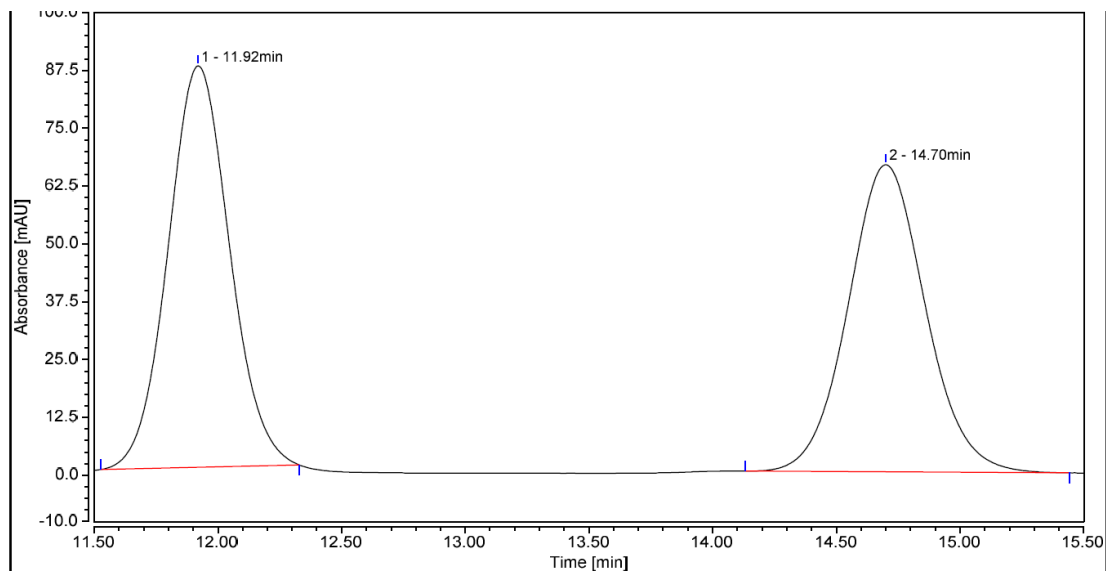
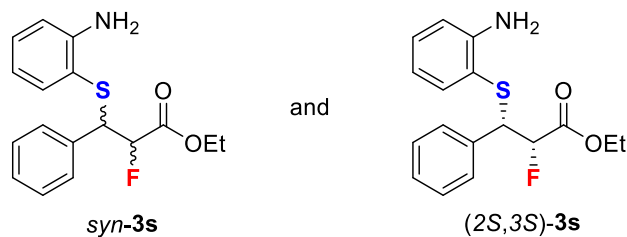
Experimental Section



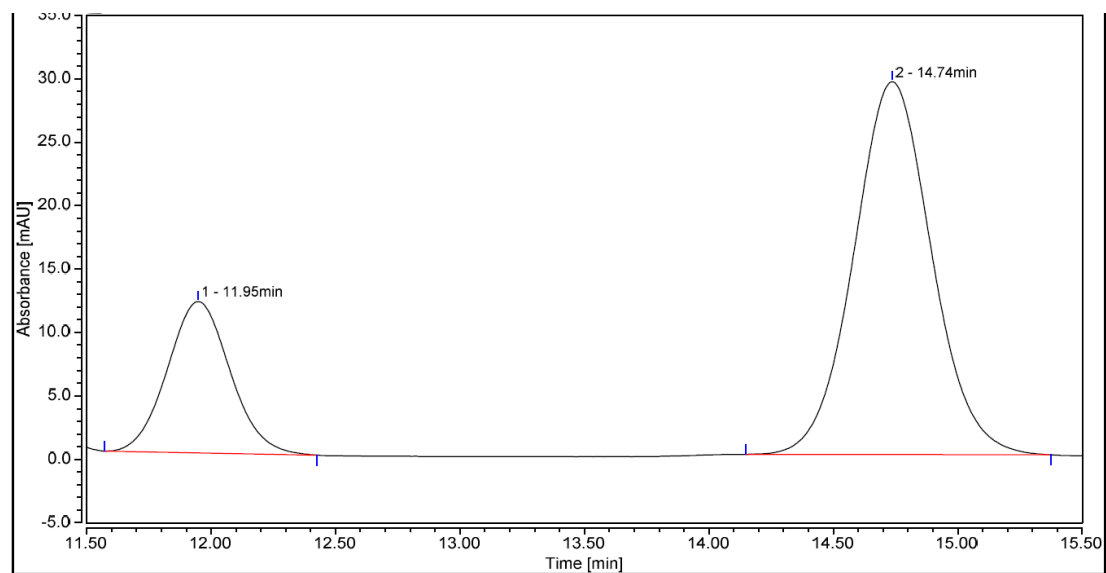
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		6.777	1.627	10.518	50.06	53.26	n.a.
2		7.457	1.623	9.230	49.94	46.74	n.a.
<b>Total:</b>			<b>3.249</b>	<b>19.748</b>	<b>100.00</b>	<b>100.00</b>	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		6.773	1.150	7.461	24.53	26.96	n.a.
2		7.453	3.539	20.210	75.47	73.04	n.a.
<b>Total:</b>			<b>4.689</b>	<b>27.671</b>	<b>100.00</b>	<b>100.00</b>	

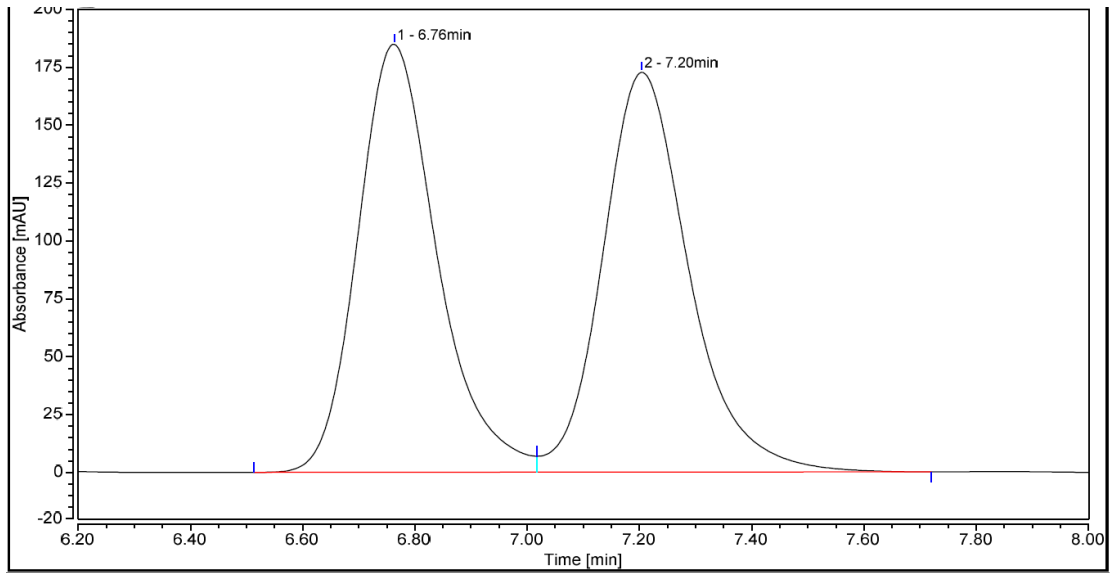
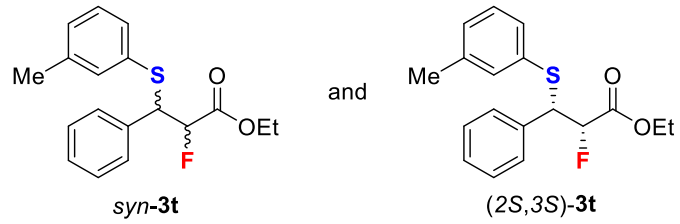


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.920	25.054	86.765	51.00	56.65	n.a.
2		14.700	24.074	66.390	49.00	43.35	n.a.
<b>Total:</b>			<b>49.128</b>	<b>153.155</b>	<b>100.00</b>	<b>100.00</b>	

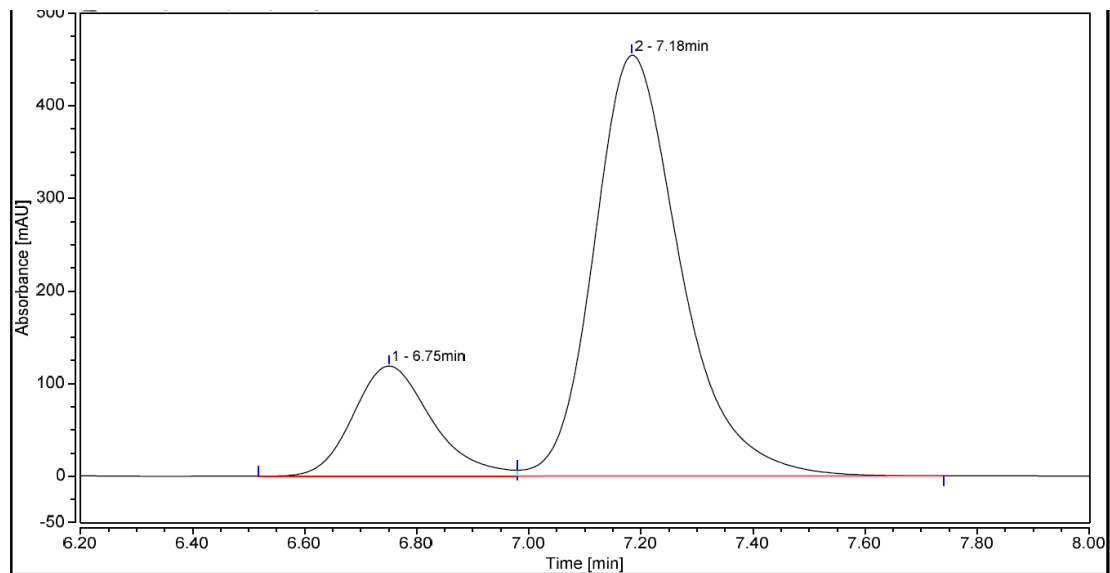


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.947	3.486	11.931	24.64	28.87	n.a.
2		14.737	10.662	29.400	75.36	71.13	n.a.
<b>Total:</b>			<b>14.147</b>	<b>41.332</b>	<b>100.00</b>	<b>100.00</b>	

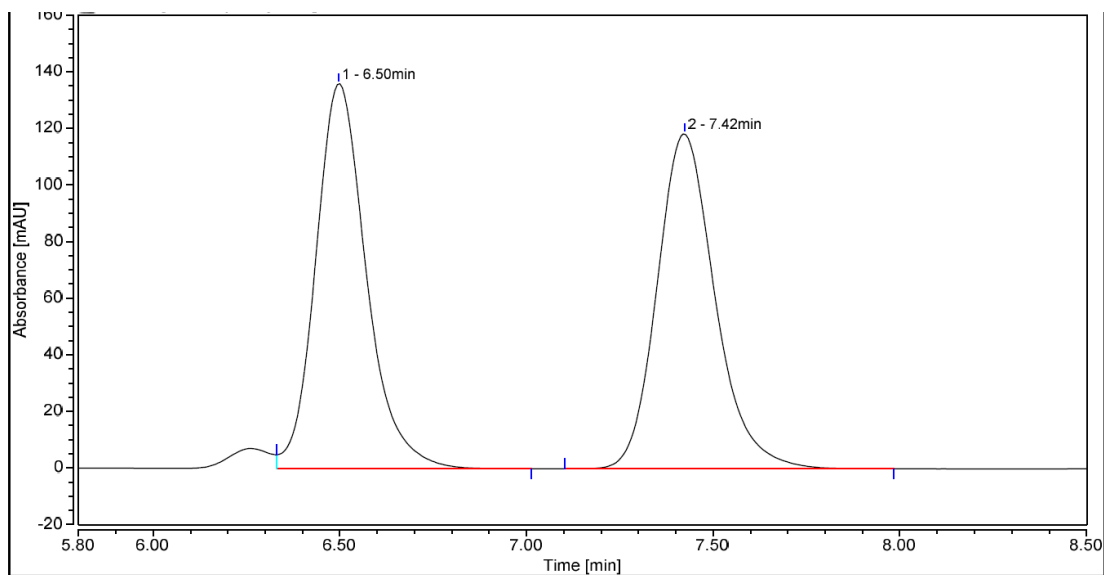
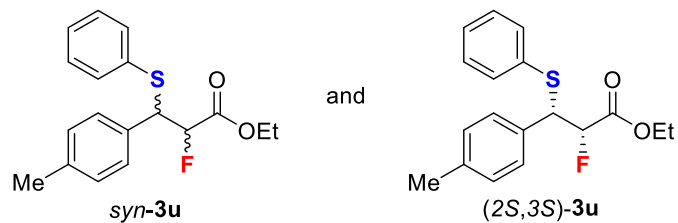
## Experimental Section



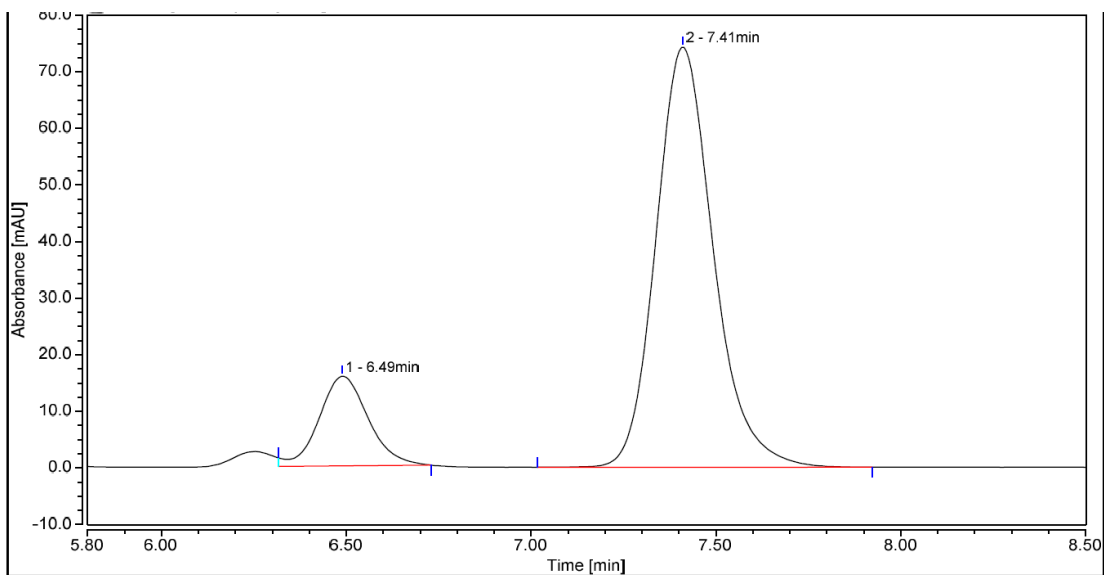
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.763	30.255	184.740	49.56	51.70	n.a.
2		7.203	30.789	172.574	50.44	48.30	n.a.
Total:			61.044	357.314	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.750	19.333	118.900	19.25	20.74	n.a.
2		7.183	81.080	454.259	80.75	79.26	n.a.
Total:			100.413	573.158	100.00	100.00	

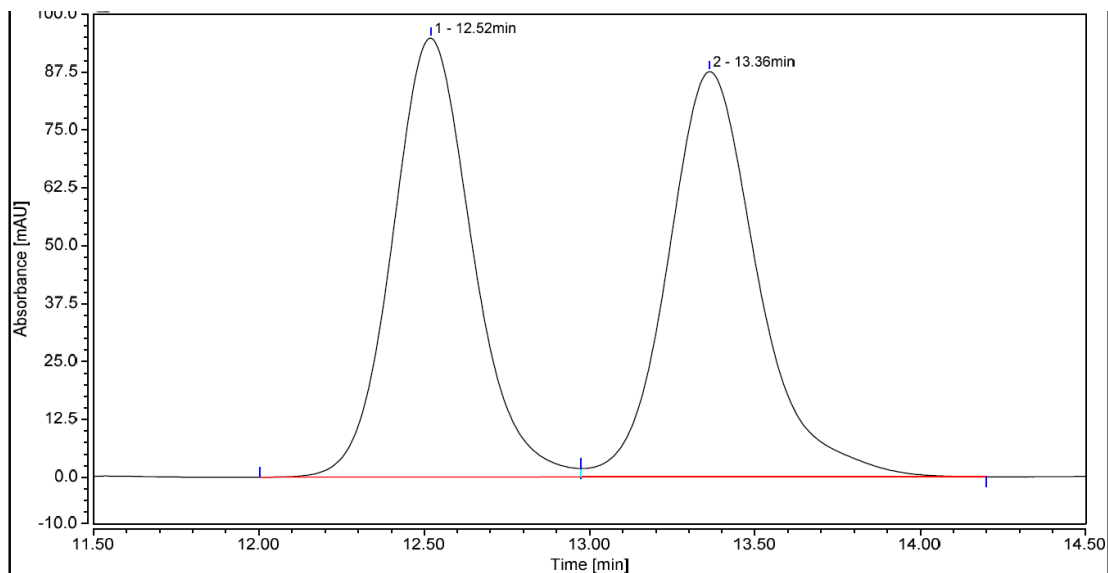
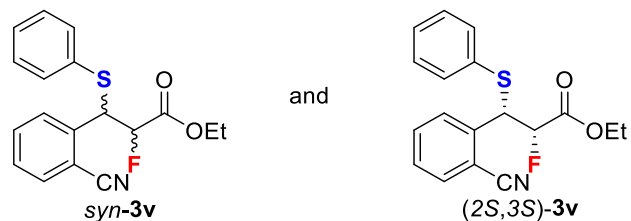


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.497	21.341	136.012	50.12	53.47	n.a.
2		7.423	21.242	118.337	49.88	46.53	n.a.
Total:			42.583	254.349	100.00	100.00	

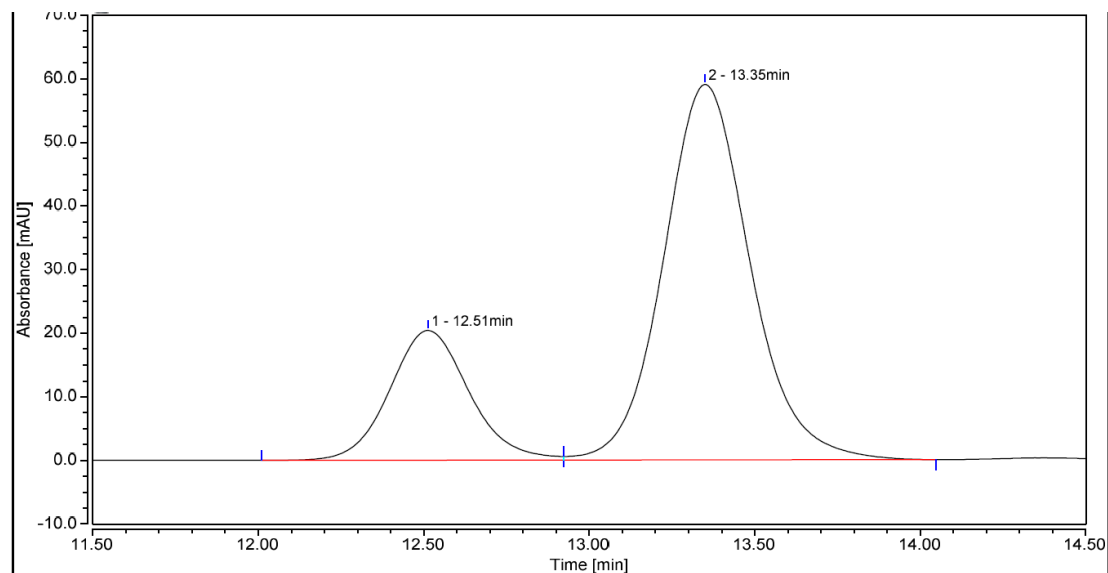


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.490	2.443	15.834	15.46	17.58	n.a.
2		7.410	13.361	74.256	84.54	82.42	n.a.
Total:			15.804	90.090	100.00	100.00	

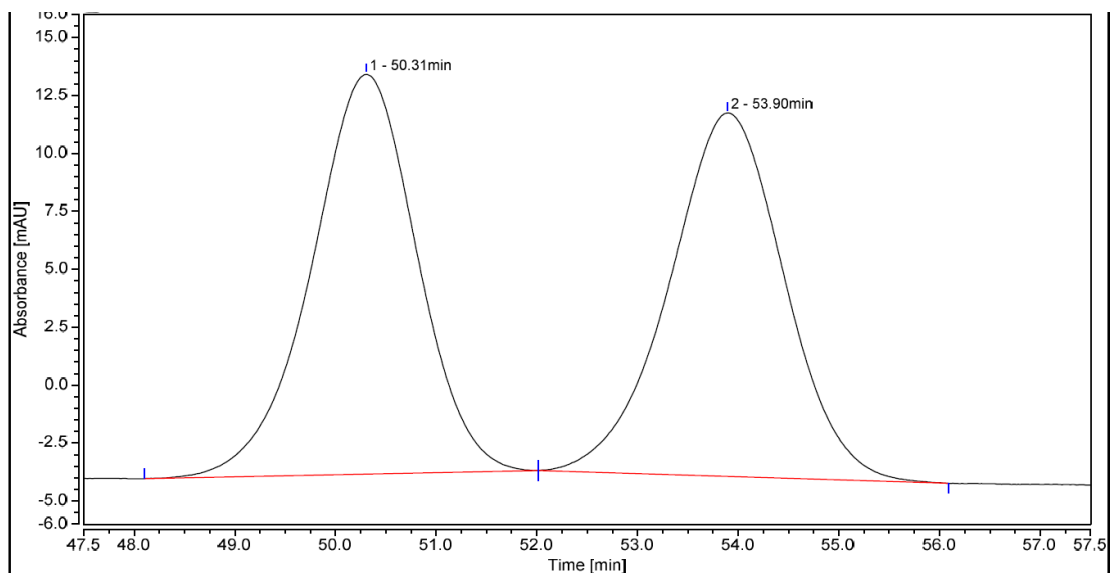
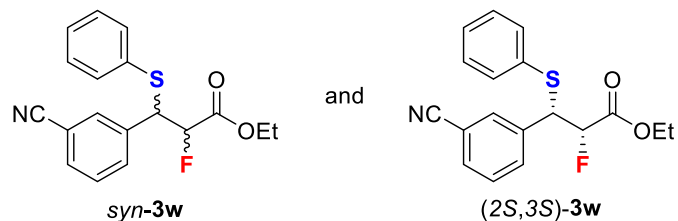
Experimental Section



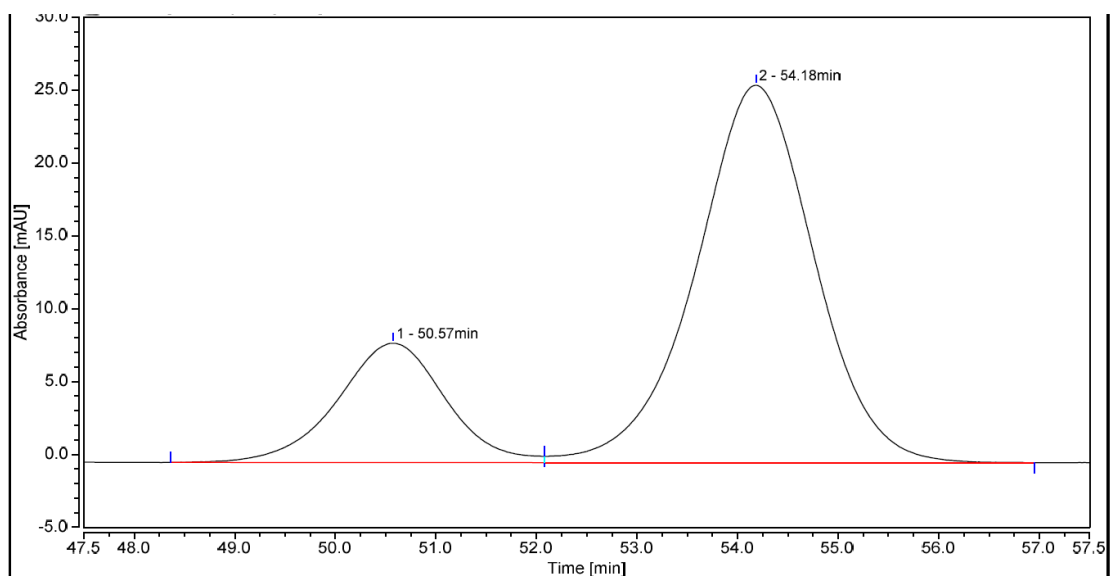
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.520	26.618	94.782	49.13	52.00	n.a.
2		13.363	27.556	87.507	50.87	48.00	n.a.
<b>Total:</b>			<b>54.174</b>	<b>182.289</b>	<b>100.00</b>	<b>100.00</b>	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.513	5.688	20.403	24.10	25.69	n.a.
2		13.350	17.919	59.024	75.90	74.31	n.a.
<b>Total:</b>			<b>23.607</b>	<b>79.428</b>	<b>100.00</b>	<b>100.00</b>	

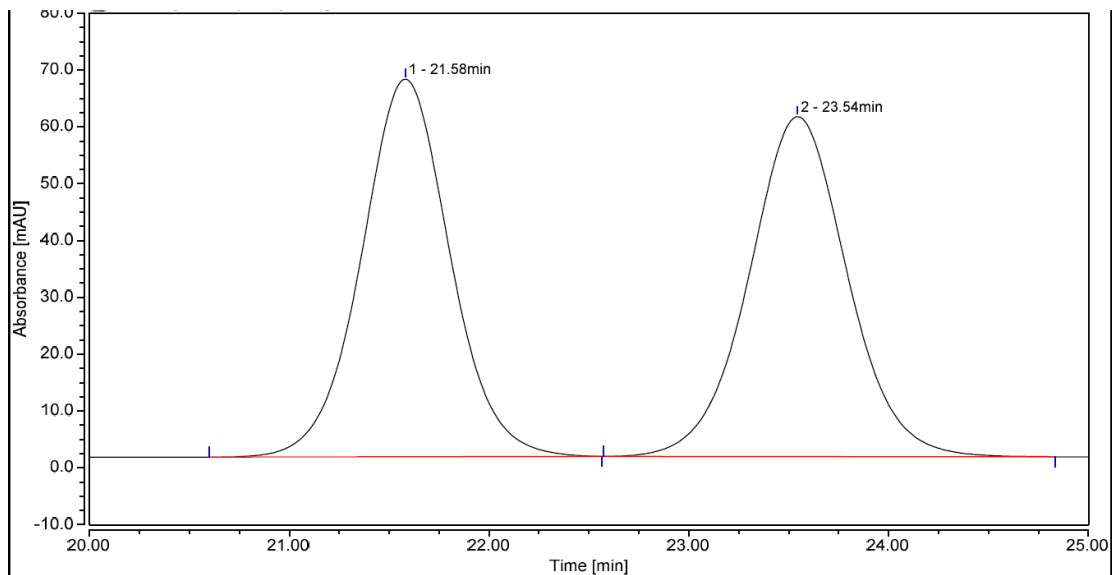
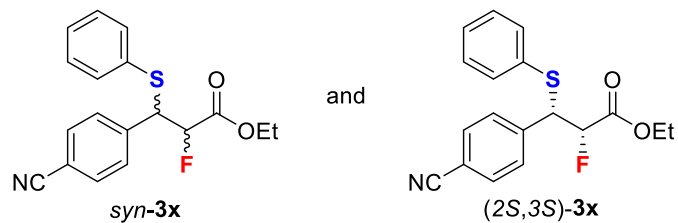


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		50.307	20.853	17.244	50.16	52.37	n.a.
2		53.897	20.721	15.684	49.84	47.63	n.a.
Total:			41.575	32.928	100.00	100.00	

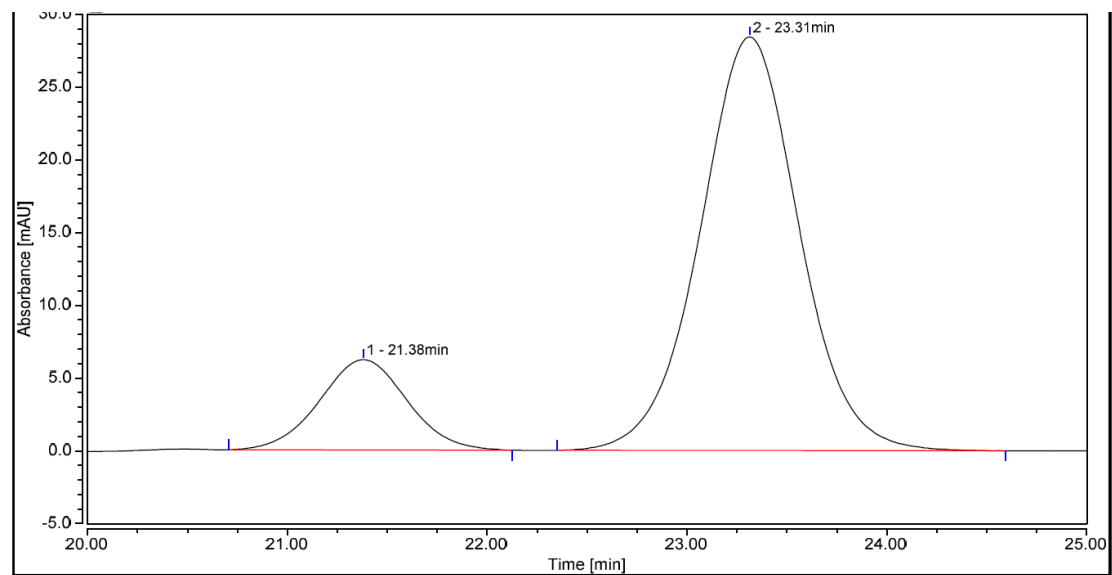


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		50.573	10.241	8.190	22.42	24.03	n.a.
2		54.183	35.445	25.896	77.58	75.97	n.a.
Total:			45.686	34.085	100.00	100.00	

Experimental Section

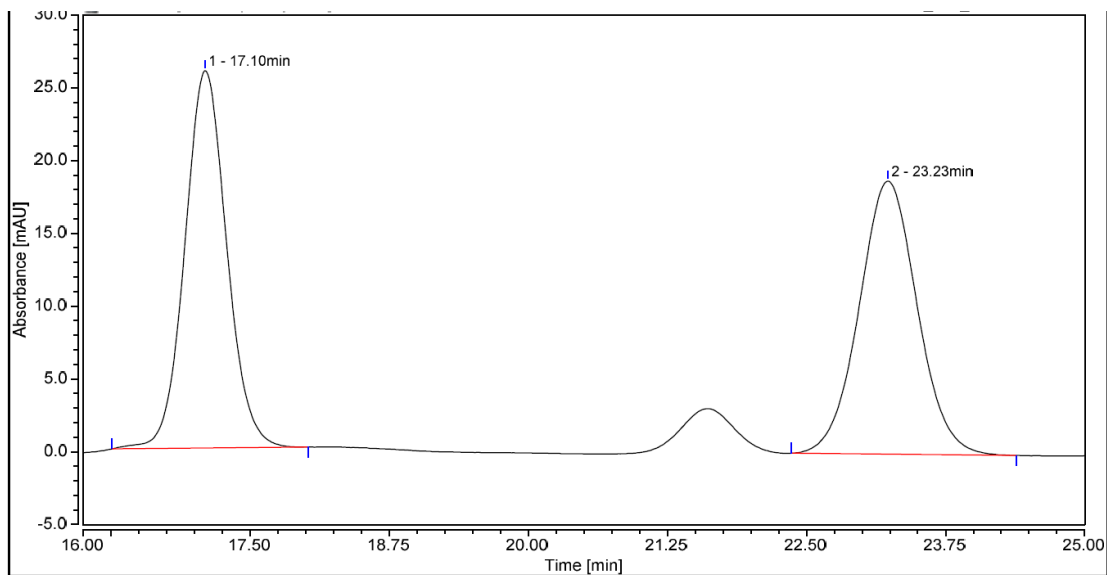
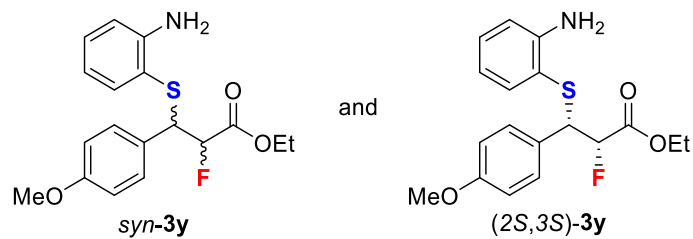


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		21.580	34.194	66.442	49.99	52.63	n.a.
2		23.543	34.204	59.798	50.01	47.37	n.a.
<b>Total:</b>			<b>68.398</b>	<b>126.240</b>	<b>100.00</b>	<b>100.00</b>	

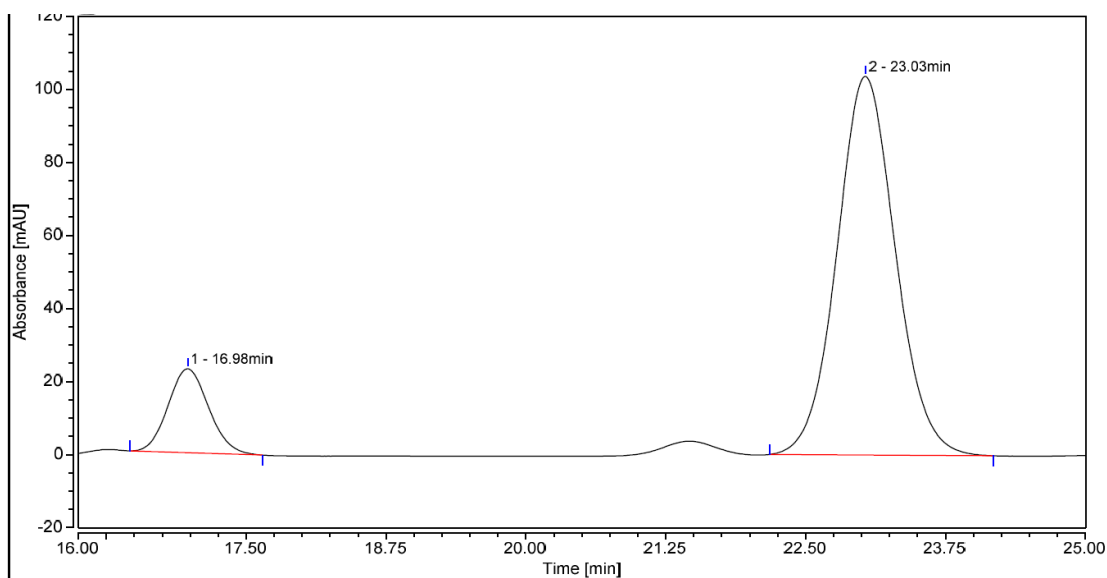


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		21.380	3.155	6.203	16.17	17.92	n.a.
2		23.313	16.363	28.419	83.83	82.08	n.a.
<b>Total:</b>			<b>19.518</b>	<b>34.622</b>	<b>100.00</b>	<b>100.00</b>	

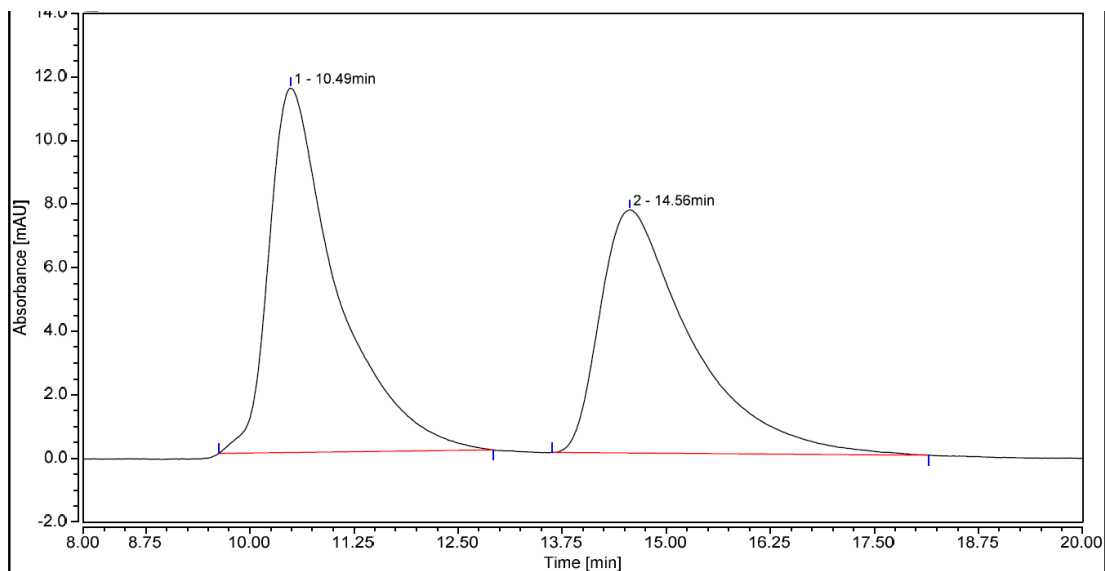
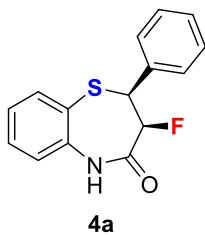




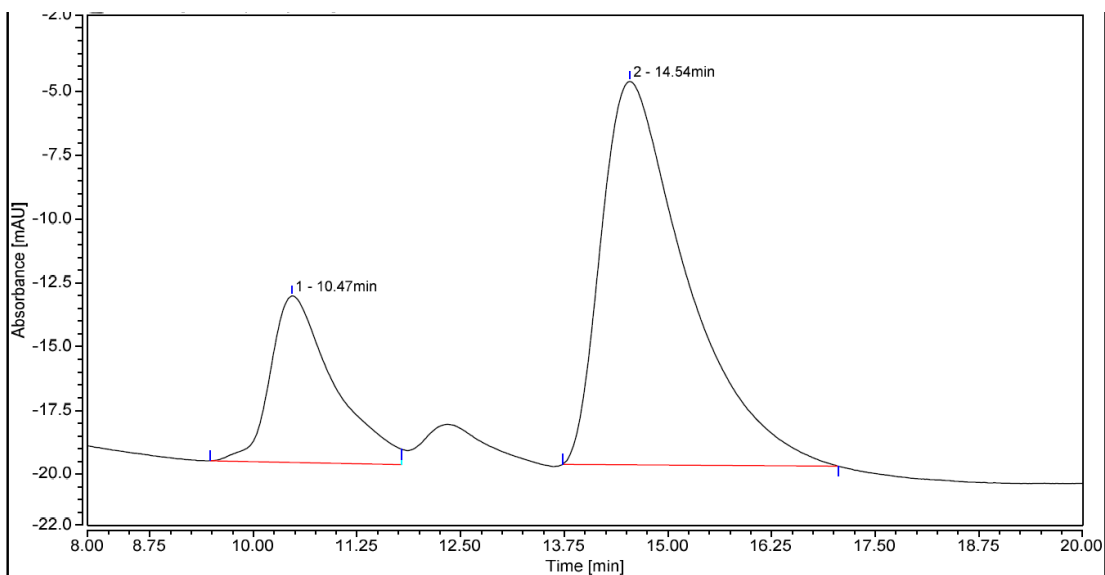
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.097	11.313	25.926	49.94	58.01	n.a.
2		23.233	11.342	18.766	50.06	41.99	n.a.
Total:			22.655	44.693	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16.977	9.645	22.997	13.31	18.15	n.a.
2		23.033	62.844	103.692	86.69	81.85	n.a.
Total:			72.490	126.689	100.00	100.00	

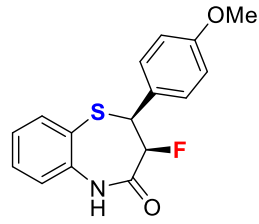


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.490	10.826	11.471	52.72	59.98	n.a.
2		14.563	9.709	7.653	47.28	40.02	n.a.
<b>Total:</b>			<b>20.535</b>	<b>19.124</b>	<b>100.00</b>	<b>100.00</b>	

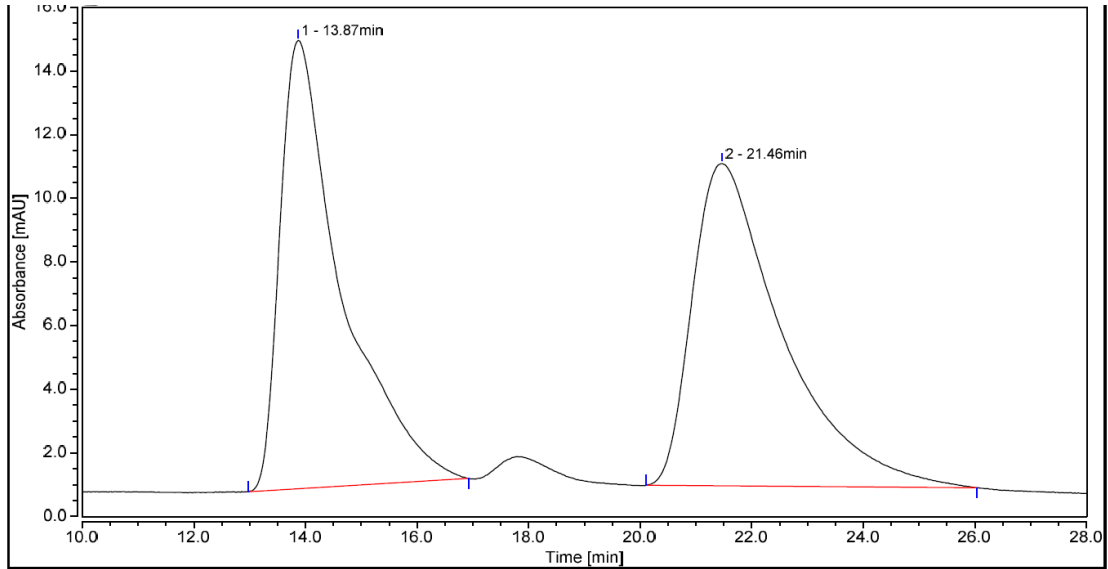


Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.467	5.803	6.533	24.36	30.29	n.a.
2		14.543	18.020	15.033	75.64	69.71	n.a.
<b>Total:</b>			<b>23.822</b>	<b>21.566</b>	<b>100.00</b>	<b>100.00</b>	

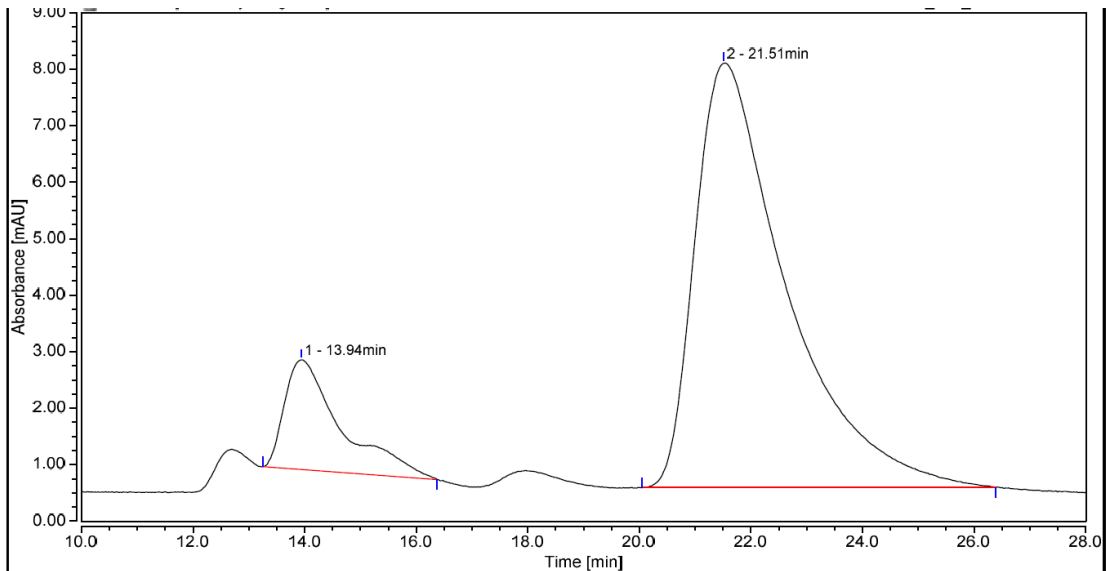
Experimental Section



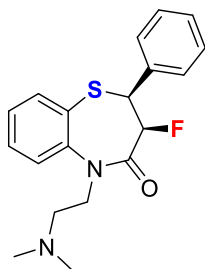
4b



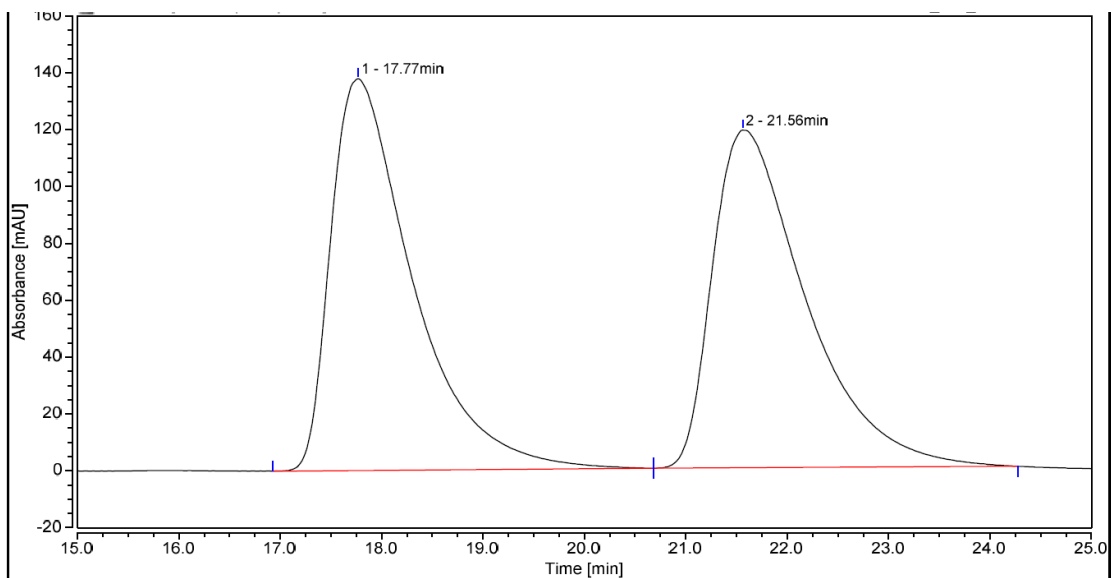
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		13.870	17.929	14.095	48.67	58.17	n.a.
2		21.460	18.910	10.136	51.33	41.83	n.a.
<b>Total:</b>			<b>36.838</b>	<b>24.231</b>	<b>100.00</b>	<b>100.00</b>	



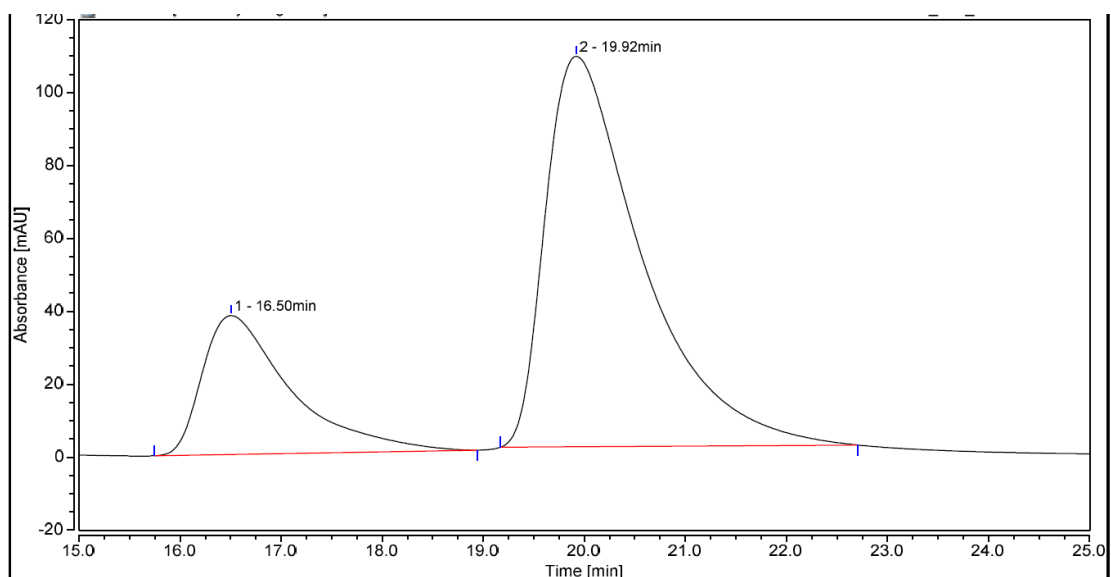
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		13.940	2.266	1.942	13.73	20.52	n.a.
2		21.507	14.234	7.521	86.27	79.48	n.a.
<b>Total:</b>			<b>16.501</b>	<b>9.463</b>	<b>100.00</b>	<b>100.00</b>	



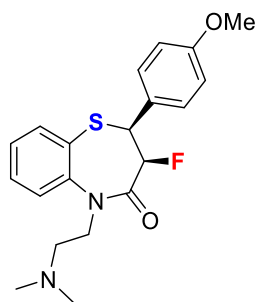
5a



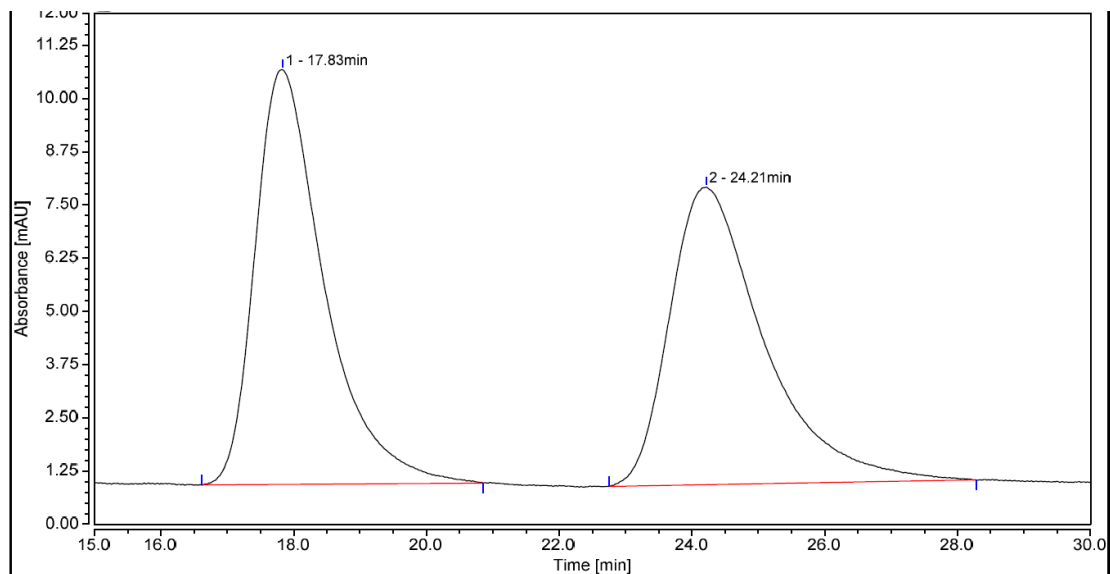
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		17.770	128.905	137.873	50.47	53.72	n.a.
2		21.560	126.511	118.767	49.53	46.28	n.a.
<b>Total:</b>			<b>255.416</b>	<b>256.640</b>	<b>100.00</b>	<b>100.00</b>	



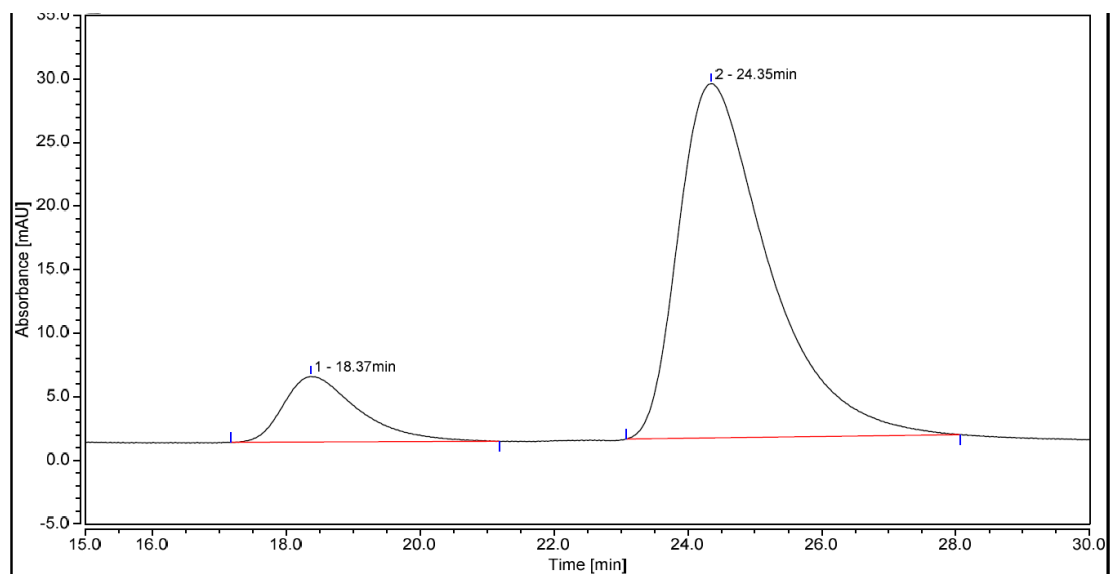
Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount
1		16.503	38.441	38.089	24.44	26.24	n.a.
2		19.920	118.845	107.078	75.56	73.76	n.a.
<b>Total:</b>			<b>157.286</b>	<b>145.167</b>	<b>100.00</b>	<b>100.00</b>	



5b



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.830	11.736	9.748	50.50	58.23	n.a.
2		24.213	11.503	6.992	49.50	41.77	n.a.
Total:			23.239	16.740	100.00	100.00	



Integration Results							
No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		18.370	6.685	5.171	13.32	15.65	n.a.
2		24.353	43.497	27.865	86.68	84.35	n.a.
Total:			50.182	33.035	100.00	100.00	

## 2 Phospha-Michael addition (PMA) on $\alpha$ -trifluoromethyl- $\alpha,\beta$ -unsaturated esters

### 2.1 Preparation of $\alpha$ -trifluoromethyl- $\alpha,\beta$ -unsaturated esters and $\alpha$ -fluoromethyl- $\alpha,\beta$ -unsaturated esters

#### 2.1.1 Preparation of $\alpha$ -trifluoromethylacrylates **6**

We first synthesized the (*Z*)- or (*E*)- $\alpha$ -trifluoromethyl acrylic acids (**6'**-**t**) following Fang's protocol reported in 2011.<sup>161</sup> Then, these pure **6'**-**t**, obtained after further recrystallizations, followed the treatments with thionyl chloride in MeOH affording the corresponding (*Z*)- or (*E*)- $\alpha$ -trifluoromethylacrylates (**6b-t**) (**Scheme 97**).

General procedure (**V**) for the synthesis of  $\alpha$ -trifluoromethyl acrylic acids (**6'**-**t**):

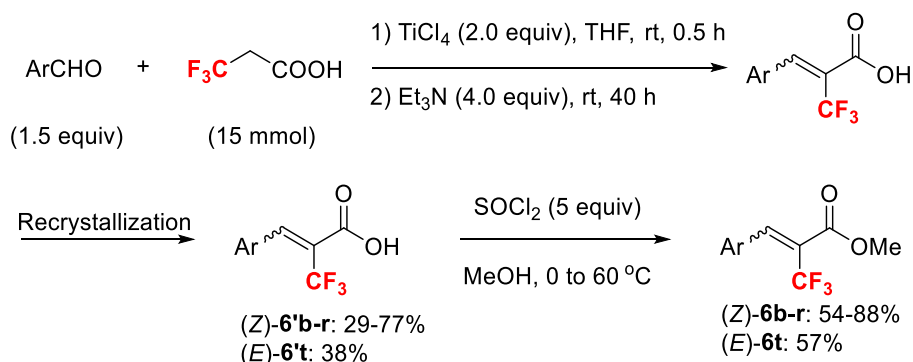
To a stirred solution of aryl aldehyde (22.5 mmol, 1.5 equiv), 3,3,3-trifluoropropionic acid (15 mmol, 1 equiv) in dry THF (40 mL) was added  $\text{TiCl}_4$  (1 M in  $\text{CH}_2\text{Cl}_2$ , 30 mmol, 2 equiv) at room temperature. The mixture was stirred for 0.5 h, followed by adding dropwise  $\text{Et}_3\text{N}$  (60 mmol, 4 equiv). After stirring for an additional 40 h, the reaction was quenched by adding water, then extracted with ethyl acetate (3 $\times$ 50 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  then concentrated under reduced pressure and purified by flash silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ). The pure (*Z*)- or (*E*)  $\alpha$ -trifluoromethyl acrylic acid (**6'**) was obtained by further recrystallization from  $\text{CH}_2\text{Cl}_2$ /pentane mixed solvent.

General procedure (**VI**) for the synthesis of  $\alpha$ -trifluoromethyl acrylates (**6b-t**):

The  $\alpha$ -trifluoromethyl acrylic acid (**6'**) (5 mmol, 1 equiv) was dissolved in anhydrous MeOH (20 mL). The resulting solution was cooled down to 0 °C, then the thionyl chloride (25 mmol, 5equiv) was added dropwise slowly. After the addition, keep the reaction mixture at 0 °C for 0.5 h and then warm to 60 °C for 6 h. The reaction was quenched by adding water and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 20 mL).

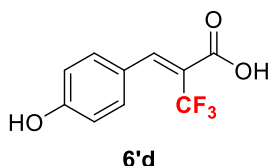
<sup>161</sup> Liu, Y.; Lai, H.; Rong, B.; Zhou, T.; Hong, J.; Yuan, C.; Zhao, S.; Zhao, X.; Jiang, B.; Fang, Q. *Adv. Synth. Catal.* **2011**, *353*, 3161-3165.

The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> followed by concentration under reduced pressure. The obtained residue was purified by flash silica gel column chromatography (eluent: petroleum ether/EtOAc) to give the corresponding  $\alpha$ -trifluoromethyl acrylate (**6**).



**Scheme 97** Synthesis of  $\alpha$ -trifluoromethylacrylates

All the analytic data of  $\alpha$ -trifluoromethyl acrylic acid (**6'b-c**, **6'f**)<sup>161</sup>, **6'e**<sup>162</sup>, (**6'g-i**, **6'l-m**, **6'o**, **6'q-r**)<sup>163</sup>, (**6'k**, **6'n**)<sup>164</sup> and  $\alpha$ -trifluoromethyl acrylate **6b**<sup>165</sup>, (**6c**, **6o**)<sup>166</sup>, (**6d**, **6k**, **6m**)<sup>167</sup> were in agreement with those reported in literature.



**(Z)-3-(4-hydroxyphenyl)-2-(trifluoromethyl)acrylic acid (**6'd**):**

Following the general procedure (**V**): **6'd** was obtained as a pale-yellow solid, 45% yield (1566 mg); **M.P.** 194 – 195 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  8.03 (s, 1H), 7.35 (d,  $J_{\text{H-H}} = 8.4$  Hz, 2H), 6.82 (d,  $J_{\text{H-H}} = 8.7$  Hz, 2H). <sup>19</sup>F NMR (282 MHz, CD<sub>3</sub>OD):  $\delta$  -57.1 (s). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CD<sub>3</sub>OD):  $\delta$  166.7 (d,  $J_{\text{C-F}} = 1.5$  Hz), 161.4, 149.6 (d,  $J_{\text{C-F}} = 2.3$  Hz), 133.7 (q,  $J_{\text{C-F}} = 2.3$  Hz), 125.8, 124.0 (q,  $J_{\text{C-F}} = 271.5$  Hz), 120.0 (q,  $J_{\text{C-F}} = 31.5$  Hz), 116.3. **IR:** 3304, 1686, 1235, 1124, 1106, 1016, 811, 698, 522, 420 cm<sup>-1</sup>. **HRMS (ES-) m/z:**

<sup>162</sup> Basu, D.; Richters, A.; Rauh, D. *Bioorg. Med. Chem.* **2015**, *23*, 2767-2780.

<sup>163</sup> Dong, K.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 14191-14195.

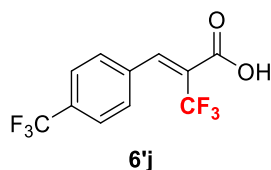
<sup>164</sup> Xiao, P.; Pannecoucke, X.; Bouillon, J. P.; Couve-Bonnaire, S. *Adv. Synth. Catal.* **2020**, *362*, 949-954.

<sup>165</sup> Nowak, I.; Robins, M. J. *J. Org. Chem.* **2007**, *72*, 2678-2681.

<sup>166</sup> Wang, D.; Deng, H.-P.; Wei, Y.; Xu, Q.; Shi, M. *Eur. J. Org. Chem.* **2013**, *2013*, 401-406.

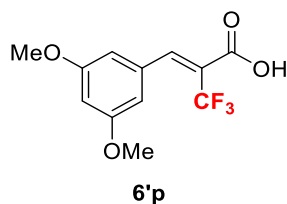
<sup>167</sup> Xiao, P.; Schlinquer, C.; Pannecoucke, X.; Bouillon, J. P.; Couve-Bonnaire, S. *J. Org. Chem.* **2019**, *84*, 2072-2082.

[M-H]<sup>-</sup> calcd for C<sub>10</sub>H<sub>6</sub>F<sub>3</sub>O<sub>3</sub>: 231.0275, found: 231.0264.



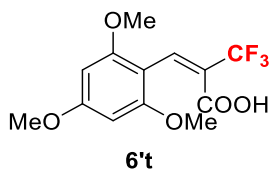
**(Z)-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)acrylic acid (6'j):**

Following the general procedure (V): **6'j** was obtained as a white solid, 44% yield (1874 mg); **M.P.** 110 – 111 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 12.10 (s, 1H), 8.29 (s, 1H), 7.70 (d, *J*<sub>H-H</sub> = 8.4 Hz, 2H), 7.52 (d, *J*<sub>H-H</sub> = 8.1 Hz, 2H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -58.7 (s), -63.5 (s). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 168.3 (q, *J*<sub>C-F</sub> = 1.7 Hz), 149.1 (d, *J*<sub>C-F</sub> = 2.7 Hz), 135.9 (d, *J*<sub>C-F</sub> = 1.2 Hz), 132.3 (q, *J*<sub>C-F</sub> = 32.7 Hz), 129.5 (q, *J*<sub>C-F</sub> = 3.8 Hz), 125.5 (q, *J*<sub>C-F</sub> = 3.8 Hz), 121.4 (q, *J*<sub>C-F</sub> = 273.0 Hz), 123.8 (q, *J*<sub>C-F</sub> = 270.7 Hz), 123.8 (q, *J*<sub>C-F</sub> = 32.3 Hz). **IR:** 2841, 2652, 2543, 1709, 1434, 1319, 1301, 1131, 1113, 841, 622, 447 cm<sup>-1</sup>. **HRMS (EI<sup>+</sup>) m/z:** [M]<sup>+</sup> calcd for C<sub>11</sub>H<sub>6</sub>F<sub>6</sub>O<sub>2</sub>: 284.0267, found: 284.0258.



**(Z)-3-(3,5-dimethoxyphenyl)-2-(trifluoromethyl)acrylic acid (6'p):**

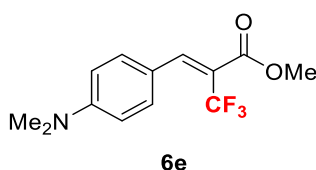
Following the general procedure (V): **6'p** was obtained as a white solid, 46% yield (1904 mg); **M.P.** 137 – 138 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 11.89 (s, 1H), 8.20 (s, 1H), 6.55 – 6.53 (m, 3H), 3.81 (s, 6H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -58.5 (s). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 168.7 (d, *J*<sub>C-F</sub> = 1.8 Hz), 160.7, 150.9 (q, *J*<sub>C-F</sub> = 2.8 Hz), 134.0, 122.0 (q, *J*<sub>C-F</sub> = 32.2 Hz), 121.6 (q, *J*<sub>C-F</sub> = 272.9 Hz), 107.4 (q, *J*<sub>C-F</sub> = 2.4 Hz), 102.9, 55.6. **IR:** 2950, 2847, 2537, 1702, 1593, 1430, 1283, 1164, 1133, 1025, 842, 688, 637, 428 cm<sup>-1</sup>. **HRMS (ES<sup>-</sup>) m/z:** [M-H]<sup>-</sup> calcd for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>O<sub>4</sub>: 275.0537, found: 275.0533.



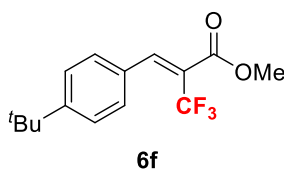


**(E)-2-(trifluoromethyl)-3-(2,4,6-trimethoxyphenyl)acrylic acid (6't):**

Following the general procedure (V): **6't** was obtained as a yellow solid, 38% yield (1744 mg); **M.P.** 196 – 197 °C;  $^1\text{H NMR}$  (300 MHz,  $(\text{CD}_3)_2\text{SO}$ ):  $\delta$  7.27 (d,  $J_{\text{H-F}} = 1.8$  Hz, 1H), 6.26 (s, 1H), 3.82 (s, 3H), 3.76 (s, 6H).  $^{19}\text{F NMR}$  (282 MHz,  $(\text{CD}_3)_2\text{SO}$ ):  $\delta$  -57.3 (d,  $J_{\text{F-H}} = 1.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{SO}$ ):  $\delta$  164.4, 163.2, 159.0, 131.5 (q,  $J_{\text{C-F}} = 6.4$  Hz), 123.3 (q,  $J_{\text{C-F}} = 270.6$  Hz), 121.8 (q,  $J_{\text{C-F}} = 28.5$  Hz), 103.3, 90.8, 55.5, 55.5. **IR:** 3017, 2944, 2847, 1699, 1582, 1432, 1229, 1123, 811, 681, 644, 519, 491  $\text{cm}^{-1}$ . **HRMS (ES-) m/z:**  $[\text{M-H}]^-$  calcd for  $\text{C}_{13}\text{H}_{12}\text{F}_3\text{O}_5$ : 305.0642, found: 305.0640.

**Methyl (Z)-3-(4-(dimethylamino)phenyl)-2-(trifluoromethyl)acrylate (6e):**

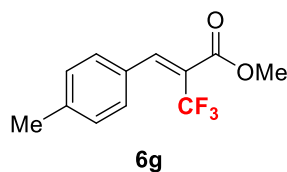
Following the general procedure (VI): **6e** was obtained as a yellow oil, 73% yield (996 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.93 (s, 1H), 7.43 (d,  $J_{\text{H-H}} = 8.8$  Hz, 2H), 6.64 (d,  $J_{\text{H-H}} = 9.0$  Hz, 2H), 3.84 (s, 3H), 3.02 (s, 6H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.3 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.2 (q,  $J_{\text{C-F}} = 2.3$  Hz), 152.2, 149.1 (q,  $J_{\text{C-F}} = 2.7$  Hz), 133.6 (q,  $J_{\text{C-F}} = 3.1$  Hz), 132.5, 123.0 (q,  $J_{\text{C-F}} = 273.2$  Hz), 115.1 (q,  $J_{\text{C-F}} = 32.6$  Hz), 111.2, 52.4, 40.0. **IR:** 2956, 1718, 1586, 1371, 1284, 1110, 945, 815, 756, 521  $\text{cm}^{-1}$ . **HRMS (ES+) m/z:**  $[\text{M+H}]^+$  calcd for  $\text{C}_{13}\text{H}_{15}\text{F}_3\text{NO}_2$ : 274.1049, found: 274.1054.

**Methyl (Z)-3-(4-(tert-butyl)phenyl)-2-(trifluoromethyl)acrylate (6f):**

Following the general procedure (VI): **6f** was obtained as a pale-yellow oil, 73% yield (1044 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.07 (s, 1H), 7.45 – 7.37 (m, 4H), 3.89 (s, 3H), 1.34 (s, 9H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.5 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.1 (d,  $J_{\text{C-F}} = 2.3$  Hz), 154.1, 148.6 (d,  $J_{\text{C-F}} = 3.0$  Hz), 129.9 (q,  $J_{\text{C-F}} = 3.0$  Hz), 129.6, 125.4, 122.1 (q,  $J_{\text{C-F}} = 272.3$  Hz), 121.4 (q,  $J_{\text{C-F}} = 32.3$  Hz), 52.6, 34.9, 31.1. **IR:** 2961,

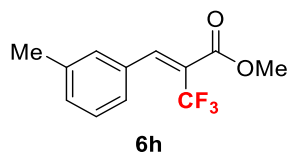
2907, 2865, 1730, 1633, 1438, 1280, 1122, 1108, 1042, 835, 607, 561, 497  $\text{cm}^{-1}$ .

**HRMS (EI+) m/z:**  $[\text{M}]^+$  calcd for  $\text{C}_{15}\text{H}_{17}\text{F}_3\text{O}_2$ : 286.1175, found: 286.1184.



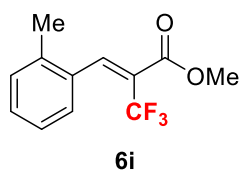
**Methyl (Z)-3-(p-tolyl)-2-(trifluoromethyl)acrylate (6g):**

Following the general procedure (VI): **6g** was obtained as a pale-yellow oil, 88% yield (1073 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.07 (s, 1H), 7.33 (d,  $J_{\text{H-H}} = 7.8$  Hz, 2H), 7.21 (d,  $J_{\text{H-H}} = 8.1$  Hz, 2H), 3.89 (s, 3H), 2.39 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.5 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.8 (d,  $J_{\text{C-F}} = 1.5$  Hz), 148.5 (d,  $J_{\text{C-F}} = 3.0$  Hz), 140.8, 129.7 (q,  $J_{\text{C-F}} = 3.0$  Hz), 129.5, 129.0, 122.1 (q,  $J_{\text{C-F}} = 272.3$  Hz), 121.2 (q,  $J_{\text{C-F}} = 32.3$  Hz), 52.3, 21.1. **IR:** 2956, 1728, 1635, 1438, 1278, 1124, 1041, 818, 607, 507, 407  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[\text{M}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_2$ : 244.0706, found: 244.0711.



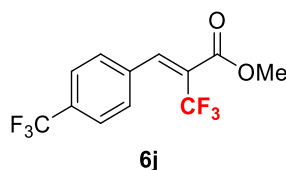
**Methyl (Z)-3-(m-tolyl)-2-(trifluoromethyl)acrylate (6h):**

Following the general procedure (VI): **6h** was obtained as a yellow oil, 84% yield (1025 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.09 (s, 1H), 7.32 – 7.21 (m, 4H), 3.90 (s, 3H), 2.38 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.5 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.7 (d,  $J_{\text{C-F}} = 2.3$  Hz), 148.7 (d,  $J_{\text{C-F}} = 3.0$  Hz), 138.0, 132.5, 130.9, 129.9 (d,  $J_{\text{C-F}} = 2.3$  Hz), 128.2, 126.4 (q,  $J_{\text{C-F}} = 3.0$  Hz), 122.1 (q,  $J_{\text{C-F}} = 31.5$  Hz), 122.0 (q,  $J_{\text{C-F}} = 273.0$  Hz), 52.5, 21.0. **IR:** 2962, 1729, 1636, 1438, 1282, 1224, 1127, 1042, 794, 695, 437  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[\text{M}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_2$ : 244.0706, found: 244.0712.



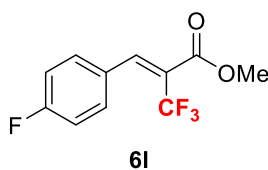
**Methyl (Z)-3-(o-tolyl)-2-(trifluoromethyl)acrylate (6i):**

Following the general procedure (VI): **6i** was obtained as a pale-yellow oil, 69% yield (842 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.23 (s, 1H), 7.32 – 7.19 (m, 4H), 3.91 (s, 3H), 2.31 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.9 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.5 (d,  $J_{\text{C-F}} = 1.5$  Hz), 148.5 (d,  $J_{\text{C-F}} = 3.0$  Hz), 136.0, 132.6, 129.9, 129.7, 128.2 (q,  $J_{\text{C-F}} = 3.0$  Hz), 125.6, 123.5 (q,  $J_{\text{C-F}} = 31.5$  Hz), 122.0 (q,  $J_{\text{C-F}} = 273.0$  Hz), 52.7, 19.9. IR: 2958, 1731, 1642, 1438, 1273, 1129, 1043, 739, 616, 445  $\text{cm}^{-1}$ . HRMS (EI+)  $m/z$ :  $[\text{M}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_2$ : 244.0706, found: 244.0711.



**Methyl (Z)-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)acrylate (6j):**

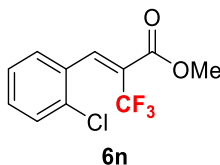
Following the general procedure (VI): **6j** was obtained as a white solid, 44% yield (656 mg); M.P. 37 – 38 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (s, 1H), 7.58 (d,  $J_{\text{H-H}} = 8.4$  Hz, 2H), 7.39 (d,  $J_{\text{H-H}} = 8.1$  Hz, 2H), 3.91 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.5 (s), -63.5 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.3 (d,  $J_{\text{C-F}} = 1.5$  Hz), 146.7 (d,  $J_{\text{C-F}} = 3.0$  Hz), 136.4, 131.8 (q,  $J_{\text{C-F}} = 33.0$  Hz), 129.2 (d,  $J_{\text{C-F}} = 2.3$  Hz), 125.5 (q,  $J_{\text{C-F}} = 3.8$  Hz), 124.7 (q,  $J_{\text{C-F}} = 32.3$  Hz), 123.9 (q,  $J_{\text{C-F}} = 270.8$  Hz), 121.7 (q,  $J_{\text{C-F}} = 272.3$  Hz), 52.9. IR: 2962, 1726, 1638, 1396, 1323, 1272, 1157, 1111, 1049, 1018, 834, 750, 605, 496  $\text{cm}^{-1}$ . HRMS (EI+)  $m/z$ :  $[\text{M}]^+$  calcd for  $\text{C}_{12}\text{H}_8\text{F}_6\text{O}_2$ : 298.0423, found: 298.0427.



**Methyl (Z)-3-(4-fluorophenyl)-2-(trifluoromethyl)acrylate (6l):**

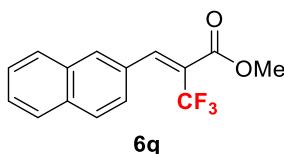
Following the general procedure (VI): **6l** was obtained as a colorless oil, 68% yield (843 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.03 (s, 1H), 7.42 – 7.38 (m, 2H), 7.12 – 7.05 (m, 2H), 3.89 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.5 (s), -109.7 (m).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.8 (d,  $J_{\text{C-F}} = 250.5$  Hz), 163.7, 147.3 (q,  $J_{\text{C-F}} = 3.0$  Hz), 131.8 (dq,  $J_{\text{C-F}} = 3.0$  Hz,  $J_{\text{C-F}} = 8.3$  Hz), 128.6 (d,  $J_{\text{C-F}} = 3.8$  Hz), 122.3 (q,  $J_{\text{C-F}} = 31.5$  Hz), 121.9 (q,  $J_{\text{C-F}}$

= 273.0 Hz), 115.6 (d,  $J_{C-F}$  = 22.5 Hz), 52.7. **IR:** 2962, 1729, 1601, 1509, 1280, 1159, 1127, 1041, 837, 809, 544, 490  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M]^+$  calcd for  $\text{C}_{11}\text{H}_6\text{F}_6\text{O}_2$ : 248.0455, found: 248.0463.



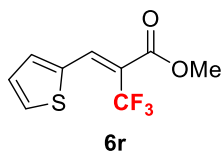
**Methyl (Z)-3-(2-chlorophenyl)-2-(trifluoromethyl)acrylate (6n):**

Following the general procedure (VI): **6n** was obtained as a colorless oil, 77% yield (1016 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.20 (s, 1H), 7.46 – 7.44 (m, 1H), 7.40 – 7.27 (m, 3H), 3.93 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -59.0 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.0 (d,  $J_{C-F}$  = 1.5 Hz), 145.5 (d,  $J_{C-F}$  = 3.0 Hz), 133.2, 131.9, 131.1, 130.1 (q,  $J_{C-F}$  = 3.8 Hz), 129.3, 126.6, 124.3 (q,  $J_{C-F}$  = 31.5 Hz), 121.7 (q,  $J_{C-F}$  = 273.0 Hz), 52.9. **IR:** 2962, 1733, 1647, 1438, 1387, 1289, 1266, 1134, 1043, 747, 453  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M]^+$  calcd for  $\text{C}_{11}\text{H}_8\text{ClF}_3\text{O}_2$ : 264.0159, found: 264.0158.



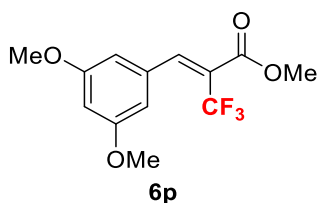
**Methyl (Z)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylate (6q):**

Following the general procedure (VI): **6q** was obtained as a yellow solid, 54% yield (756 mg); **M.P.** 75 – 76  $^{\circ}\text{C}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.27 (s, 1H), 7.91 – 7.84 (m, 4H), 7.59 – 7.48 (m, 3H), 3.93 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.4 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.9 (d,  $J_{C-F}$  = 2.3 Hz), 148.6 (d,  $J_{C-F}$  = 3.0 Hz), 133.8, 132.6, 130.2 (d,  $J_{C-F}$  = 2.3 Hz), 129.9, 128.7, 128.0, 127.7, 127.7, 126.8, 126.0 (q,  $J_{C-F}$  = 2.3 Hz), 122.3 (q,  $J_{C-F}$  = 31.5 Hz), 122.1 (q,  $J_{C-F}$  = 273.0 Hz), 52.7. **IR:** 3047, 2956, 1726, 1626, 1437, 1277, 1259, 1235, 1119, 1039, 823, 748, 665, 480  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M]^+$  calcd for  $\text{C}_{15}\text{H}_{11}\text{F}_3\text{O}_2$ : 280.0706, found: 280.0718.



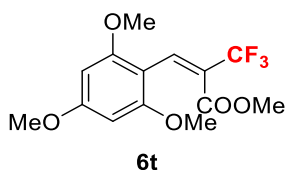
**Methyl (Z)-3-(thiophen-2-yl)-2-(trifluoromethyl)acrylate (6r):**

Following the general procedure (VI): **6r** was obtained as a colorless oil, 66% yield (779 mg);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.10 (s, 1H), 7.68 (d,  $J_{\text{H-H}} = 5.1\text{Hz}$ , 1H), 7.52 (d,  $J_{\text{H-H}} = 3.6\text{Hz}$ , 1H), 7.15 – 7.12 (m, 1H), 3.88 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -59.0 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.3 (d,  $J_{\text{C-F}} = 2.3$  Hz), 139.6 (d,  $J_{\text{C-F}} = 3.0$  Hz), 137.6 (d,  $J_{\text{C-F}} = 2.3$  Hz), 134.4 (d,  $J_{\text{C-F}} = 3.0$  Hz), 134.3 (d,  $J_{\text{C-F}} = 1.5$  Hz), 128.1, 122.3 (q,  $J_{\text{C-F}} = 271.5$  Hz), 116.3 (q,  $J_{\text{C-F}} = 33.0$  Hz), 52.7. IR: 3113, 2956, 1720, 1613, 1422, 1270, 1119, 1039, 862, 714, 651, 614, 475,  $\text{cm}^{-1}$ . HRMS (EI+) m/z:  $[\text{M}]^+$  calcd for  $\text{C}_{11}\text{H}_6\text{F}_6\text{O}_2$ : 236.0113, found: 236.0127.



**Methyl (Z)-3-(3,5-dimethoxyphenyl)-2-(trifluoromethyl)acrylate (6p):**

Following the general procedure (VI): **6p** was obtained as a white solid, 80% yield (1160 mg); M.P. 55 – 56 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (s, 1H), 6.49 – 6.47 (m, 3H), 3.86 (s, 3H), 3.76 (s, 6H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -58.3 (s).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.9 (d,  $J_{\text{C-F}} = 1.9$  Hz), 160.6, 148.5 (q,  $J_{\text{C-F}} = 3.0$  Hz), 134.4, 123.1 (q,  $J_{\text{C-F}} = 32.0$  Hz), 121.8 (q,  $J_{\text{C-F}} = 273.5$  Hz), 107.1 (q,  $J_{\text{C-F}} = 2.5$  Hz), 102.3, 55.5, 52.9. IR: 3004, 2974, 2841, 1720, 1600, 1398, 1282, 1198, 1152, 1117, 1067, 1046, 834, 772, 630, 582  $\text{cm}^{-1}$ . HRMS (ES+) m/z:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{14}\text{F}_3\text{O}_4$ : 291.0839, found: 291.0843.



**Methyl (E)-2-(trifluoromethyl)-3-(2,4,6-trimethoxyphenyl)acrylate (6t):**

Following the general procedure (VI): **6t** was obtained as a white solid, 57% yield (912 mg); **M.P.** 140 – 142 °C;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.45 (q,  $J_{\text{H-F}} = 1.8$  Hz, 1H), 6.09 (s, 2H), 3.84 (s, 3H), 3.79 (s, 6H), 3.69 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.7 (d,  $J_{\text{F-H}} = 2.0$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  164.6, 163.5, 158.5, 133.0 (q,  $J_{\text{C-F}} = 6.2$  Hz), 123.1 (q,  $J_{\text{C-F}} = 270.8$  Hz), 121.9 (q,  $J_{\text{C-F}} = 29.9$  Hz), 104.3, 90.4, 55.7, 55.5, 51.8. **IR**: 3023, 2950, 2853, 2124, 1729, 1649, 1457, 1287, 1217, 1123, 968, 819, 520, 495  $\text{cm}^{-1}$ . **HRMS (ES+) m/z**:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{16}\text{F}_3\text{O}_5$ : 321.0944, found: 321.0951.

### 2.1.2 Preparation of $\alpha$ -fluoromethylacrylates **9**

The  $\alpha$ -fluoromethylacrylates were prepared following the methodology developed by Kim in 2013 (**Scheme 98**).<sup>168</sup>

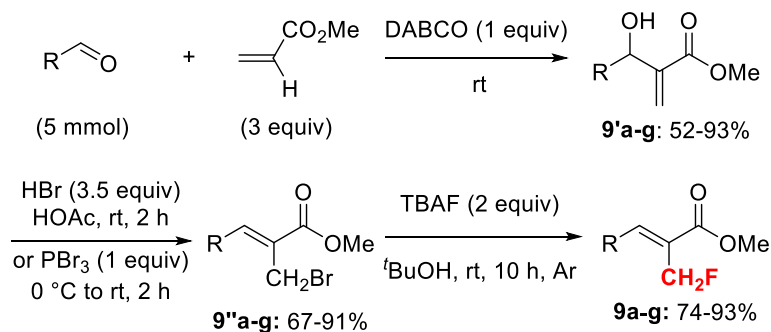
General procedure (VII) for the synthesis of MBH adduct (**9'a-g**): In a round bottom flask charged with a stir bar was added aldehyde (5 mmol), followed by methyl acrylate (15 mmol, 3 equiv) and DABCO (1 equiv). The reaction mixture stirred at room temperature until judged complete by TLC, then water (10 mL) was added into the reaction mixture. The resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 15 mL), the combined organic layer was dried over with  $\text{Na}_2\text{SO}_4$ , then concentrated and purified by flash silica gel column chromatography (petroleum ether/EtOAc) to give **9'**.

General procedure (VIII) for the synthesis of  $\alpha$ -bromomethylacrylates (**9''a-g**): In a round bottom flask charged with a stir bar was added the MBH adduct (3 mmol, 1 equiv), followed by HBr (33 wt% in HOAc, 10.5 mmol, 3.5 equiv) stirred at room temperature for 2 h or followed  $\text{PBr}_3$  (3 mmol, 1 equiv) at 0 °C for 0.5 h then room temperature for 1.5 h. The reaction mixture quenched by adding water (10 mL), then extracted with  $\text{CH}_2\text{Cl}_2$  (3 $\times$ 15 mL). The organic layer was concentrated under reduced pressure and purified by flash silica gel column chromatography (petroleum ether/EtOAc) to give **9''**.

General procedure (IX) for the synthesis of  $\alpha$ -fluoromethylacrylates (**9a-g**): To a stirred solution of  $\alpha$ -bromomethylacrylates **9''** (1 mmol, 1 equiv) in  $t\text{BuOH}$  (2 mL) was

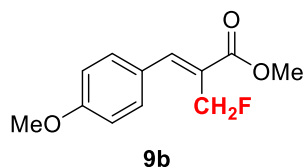
<sup>168</sup> Lim, C. H.; Kim, S. H.; Lee, H. J.; Kim, H. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2013**, *34*, 993-996.

added TBAF (1M in THF, 2 equiv) at room temperature under argon. The reaction mixture was stirred for 10 h then quenched by adding water and extracted with  $\text{CH}_2\text{Cl}_2$  (3×15 mL). The organic layer was concentrated under reduced pressure and purified by flash silica gel column chromatography (petroleum ether/EtOAc) to give **9**.



**Scheme 98** Synthesis of  $\alpha$ -fluoromethylacrylates

All the analytic data of MBH adducts (**9'a-c**,<sup>169</sup> **9'e-f**,<sup>169</sup> **9'd**,<sup>170</sup> **9'g**<sup>171</sup>),  $\alpha$ -bromomethylacrylates (**9''a**,<sup>171</sup> **9''b**,<sup>170</sup> **9''c**,<sup>171</sup> **9''d**,<sup>170</sup> **9''e**,<sup>172</sup> **9''f**,<sup>172</sup> **9''g**<sup>171</sup>) and  $\alpha$ -fluoromethylacrylates (**9a**, **9c**, **9g**)<sup>168</sup> were in agreement with those reported in literature.



### Methyl (Z)-2-(fluoromethyl)-3-(4-methoxyphenyl)acrylate (**9b**):

Following the general procedure (**IX**): **9b** was obtained as a colorless oil, 88% yield (197 mg); <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (d,  $J_{\text{H-F}} = 3.9$  Hz, 1H), 7.46 (d,  $J_{\text{H-H}} = 9.0$  Hz, 2H), 6.92 (d,  $J_{\text{H-H}} = 8.7$  Hz, 2H), 5.22 (d,  $J_{\text{H-F}} = 48.0$  Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H). <sup>19</sup>F NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -204.8 (td,  $J_{\text{F-H}} = 47.9$  Hz,  $J_{\text{F-H}} = 2.8$  Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.5 (d,  $J_{\text{C-F}} = 1.5$  Hz), 161.3 (d,  $J_{\text{C-F}} = 1.5$  Hz), 147.4 (d,  $J_{\text{C-F}} = 6.8$  Hz), 132.0 (d,  $J_{\text{C-F}} = 3.8$  Hz), 126.5 (d,  $J_{\text{C-F}} = 3.8$  Hz), 124.1 (d,  $J_{\text{C-F}} = 14.3$  Hz), 114.3, 77.2 (d,

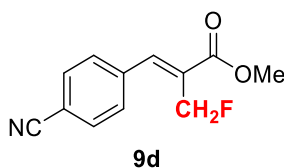
<sup>169</sup> Latorre, A.; Sáez, J. A.; Rodríguez, S.; González, F. V. *Tetrahedron* **2014**, *70*, 97-102.

<sup>170</sup> Ramachandran, P. V.; Nicponski, D. R.; Drolet, M. P.; Schmidt, C. M.; Yip-Schneider, M. T. *Future Med. Chem.* **2013**, *5*, 633-639.

<sup>171</sup> Basavaiah, D.; Reddy, K. R.; Kumaragurubaran, N. *Nat. Protoc.* **2007**, *2*, 2665-2676.

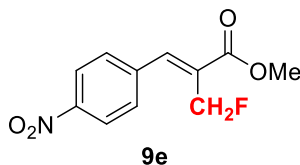
<sup>172</sup> Yu, C. R.; Xu, L. H.; Tu, S.; Li, Z. N.; Li, B. *J. Fluorine Chem.* **2006**, *127*, 1540-1546.

$J_{C-F} = 161.3$  Hz), 55.3, 52.3. **IR:** 2956, 2840, 1706, 1602, 1511, 1234, 1176, 949, 842, 522, 395  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M^+-F]$  calcd for  $\text{C}_{12}\text{H}_{13}\text{O}_3$ : 205.0859, found: 205.0866.



**Methyl (Z)-3-(4-cyanophenyl)-2-(fluoromethyl)acrylate (9d):**

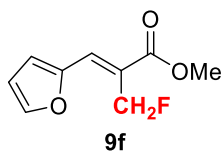
Following the general procedure (IX): **9d** was obtained as a white solid, 79% yield (173 mg); **M.P.** 112 – 113 °C;  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.95 (d,  $J_{H-F} = 4.1$  Hz, 1H), 7.66 (d,  $J_{H-H} = 8.3$  Hz, 2H), 7.51 (d,  $J_{H-H} = 8.5$  Hz, 2H), 5.09 (d,  $J_{H-F} = 47.4$  Hz, 2H), 3.79 (s, 3H).  **$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -205.8 (td,  $J_{F-H} = 47.4$  Hz,  $J_{F-H} = 4.0$  Hz).  **$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  166.1 (d,  $J_{C-F} = 1.5$  Hz), 144.5 (d,  $J_{C-F} = 7.5$  Hz), 138.0 (d,  $J_{C-F} = 3.8$  Hz), 132.2, 130.0 (d,  $J_{C-F} = 4.5$  Hz), 129.0 (d,  $J_{C-F} = 14.3$  Hz), 118.0, 113.0 (d,  $J_{C-F} = 0.75$  Hz), 76.2 (d,  $J_{C-F} = 162.8$  Hz), 52.3. **IR:** 2956, 2229, 1706, 1436, 1230, 972, 845, 549, 392  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M]^+$  calcd for  $\text{C}_{12}\text{H}_{10}\text{FNO}_2$ : 219.0690, found: 219.0687.



**Methyl (Z)-2-(fluoromethyl)-3-(4-nitrophenyl)acrylate (9e):**

Following the general procedure (IX): **9e** was obtained as a pale yellow solid, 74% yield (177 mg); **M.P.** 126 – 127 °C;  **$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.30 – 8.25 (m, 2H), 8.06 (d,  $J_{H-H} = 4.2$  Hz, 1H), 7.64 (d,  $J_{H-H} = 8.7$  Hz, 2H), 5.17 (d,  $J_{H-F} = 47.4$  Hz, 2H), 3.89 (s, 3H).  **$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -206.3 (td,  $J_{F-H} = 47.3$  Hz,  $J_{F-H} = 4.1$  Hz).  **$^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  166.4 (d,  $J_{C-F} = 1.5$  Hz), 148.4, 144.4 (d,  $J_{C-F} = 6.8$  Hz), 140.2 (d,  $J_{C-F} = 3.0$  Hz), 130.6 (d,  $J_{C-F} = 3.8$  Hz), 129.8 (d,  $J_{C-F} = 14.3$  Hz), 124.0, 76.5 (d,  $J_{C-F} = 162.0$  Hz), 52.8. **IR:** 2962, 1703, 1519, 1345, 1240, 980, 863, 715, 474, 384  $\text{cm}^{-1}$ . **HRMS (EI+) m/z:**  $[M]^+$  calcd for  $\text{C}_{11}\text{H}_{10}\text{FNO}_4$ : 239.0588, found: 239.0594.

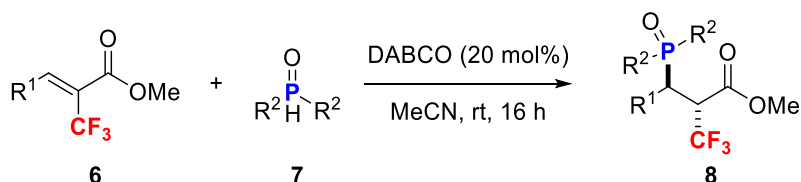




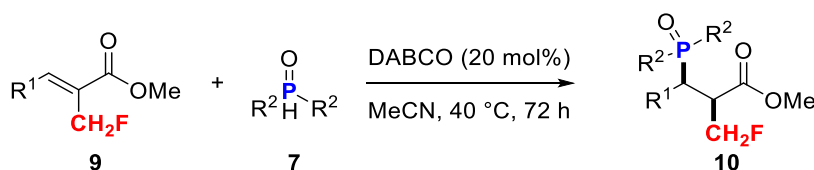
### Methyl (Z)-2-(fluoromethyl)-3-(furan-2-yl)acrylate (**9f**):

Following the general procedure (**IX**): **9f** was obtained as a yellow oil, 79% yield (145 mg); 7.65 (d,  $J_{\text{H-F}} = 3.9$  Hz, 1H), 7.61 (br s, 1H), 6.84 – 6.83 (m, 1H), 6.54 – 6.52 (m, 1H), 5.52 (d,  $J_{\text{H-F}} = 47.4$  Hz, 2H), 3.84 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -211.1 (tdd,  $J_{\text{F-H}} = 48.8$  Hz,  $J_{\text{F-H}} = 3.6$  Hz,  $J_{\text{F-H}} = 1.6$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.4 (d,  $J_{\text{C-F}} = 2.3$  Hz), 150.3 (d,  $J_{\text{C-F}} = 5.3$  Hz), 146.4 (d,  $J_{\text{C-F}} = 2.3$  Hz), 131.7 (d,  $J_{\text{C-F}} = 6.8$  Hz), 122.0 (d,  $J_{\text{C-F}} = 14.3$  Hz), 118.9 (d,  $J_{\text{C-F}} = 4.5$  Hz), 112.7, 77.2 (d,  $J_{\text{C-F}} = 160.5$  Hz), 52.5. IR: 2982, 1708, 1629, 1266, 1210, 714, 651, 614, 475  $\text{cm}^{-1}$ . HRMS (EI+)  $m/z$ :  $[\text{M}]^+$  calcd for  $\text{C}_9\text{H}_9\text{FO}_3$ : 184.0530, found: 184.0527.

## 2.2 General procedure for the Phospha-Michael addition (PMA) on $\alpha$ -trifluoromethyl- $\alpha,\beta$ -unsaturated esters

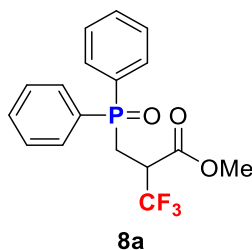


General procedure (**X**): To an oven-dried tube were added  $\alpha$ -trifluoromethylacrylate **6** (0.3 mmol, 1 equiv), diarylphosphine oxide **7** (0.45 mmol, 1.5 equiv), DABCO (0.06 mmol, 20 mol%), and MeCN (0.5 mL). The tube was then sealed. The reaction mixture was stirred at room temperature for 16 h. After removing solvents under reduced pressure, the residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc) to give the desired **8**.



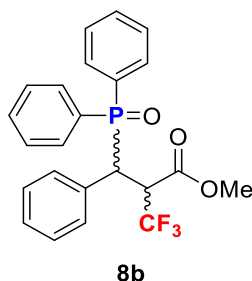
General procedure (**XI**): To an oven-dried tube were added  $\alpha$ -fluoromethylacrylate **9**

(0.3 mmol, 1 equiv), diarylphosphine oxide **7** (0.45 mmol, 1.5 equiv), DABCO (0.06 mmol, 20 mol%), and MeCN (0.5 mL). The tube was then sealed. The reaction mixture was stirred at 40 °C for 72 h and was then cooled down to room temperature. After removing solvents under reduced pressure, the residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc) to give the desired **10**.



**Methyl 2-((diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8a):**

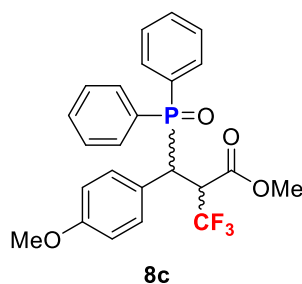
Following the general procedure (X): **8a** was obtained as a white solid, 74% yield (79 mg); **M.P.** 91 – 92 °C.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78 – 7.69 (m, 4H), 7.55 – 7.43 (m, 6H), 3.68 – 3.58 (m, 1H), 3.44 (s, 3H), 3.09 – 2.97 (m, 1H), 2.64 – 2.54 (m, 1H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -69.7 (d,  $J_{\text{F-H}} = 8.5$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7, 132.5 (d,  $J_{\text{C-P}} = 2.3$  Hz), 132.4 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.8 (d,  $J_{\text{C-P}} = 102.8$  Hz), 131.3 (d,  $J_{\text{C-P}} = 101.3$  Hz), 131.1 (d,  $J_{\text{C-P}} = 9.8$  Hz), 130.7 (d,  $J_{\text{C-P}} = 9.0$  Hz), 129.1 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.8 (d,  $J_{\text{C-P}} = 12.0$  Hz), 124.5 (qd,  $J_{\text{C-F}} = 279.0$  Hz,  $J_{\text{C-P}} = 16.5$  Hz), 53.0, 44.2 (q,  $J_{\text{C-F}} = 29.3$  Hz), 26.6 (d,  $J_{\text{C-P}} = 70.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  27.9 (s). **IR:** 3059, 2959, 1750, 1438, 1176, 1116, 820, 759, 695, 530, 510, 420  $\text{cm}^{-1}$ . **HRMS (CI+) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{17}\text{F}_3\text{O}_3\text{P}$ : 357.0862, found: 357.0875.



**Methyl 2-((diphenylphosphoryl)(phenyl)methyl)-3,3,3-trifluoropropanoate (8b):**

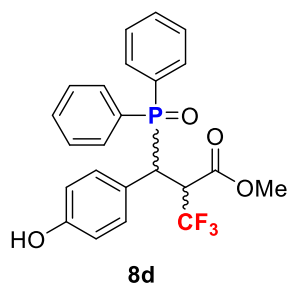
Following the general procedure (X): **8b** was obtained as a mixture of two diastereoisomers, *dr* = 93:7; white solid, 91% yield (118 mg); **M.P.** 246 – 248 °C.

*anti*-**8b**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.97 – 7.91 (m, 2H), 7.53 – 7.42 (m, 5H), 7.28 – 7.10 (m, 8H), 4.32 – 4.20 (m, 2H), 3.15 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 6.8$  Hz,  $J_{\text{F-P}} = 2.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.9 (d,  $J_{\text{C-F}} = 1.5$  Hz), 132.2 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.2, 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.5 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.4 (d,  $J_{\text{C-P}} = 101.3$  Hz), 131.1 (d,  $J_{\text{C-P}} = 92.3$  Hz), 131.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.6 (d,  $J_{\text{C-P}} = 7.5$  Hz), 128.5 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.3 (d,  $J_{\text{C-P}} = 1.5$  Hz), 128.1 (d,  $J_{\text{C-P}} = 12.0$  Hz), 127.9 (d,  $J_{\text{C-P}} = 2.3$  Hz), 124.3 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.6, 50.7 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.9 (d,  $J_{\text{C-P}} = 64.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.3 (d,  $J_{\text{P-F}} = 2.1$  Hz). IR: 3059, 2957, 1752, 1437, 1178, 1143, 832, 722, 698, 542, 507, 433  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{21}\text{F}_3\text{O}_3\text{P}$ : 433.1175, found: 433.1181.



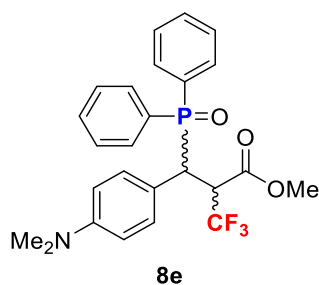
**Methyl 2-((diphenylphosphoryl)(4-methoxyphenyl)methyl)-3,3,3-trifluoropropanoate (8c)**: Following the general procedure (X): **8c** was obtained as a mixture of two diastereoisomers,  $dr = 93:7$ ; white solid, 84% yield (116 mg); **M.P.** 270 – 272  $^{\circ}\text{C}$ .

*anti*-**8c**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 – 7.88 (m, 2H), 7.53 – 7.45 (m, 5H), 7.30 – 7.18 (m, 5H), 6.66 (d,  $J_{\text{H-H}} = 8.8$  Hz, 2H), 4.29 – 4.11 (m, 2H), 3.71 (s, 3H), 3.15 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 6.9$  Hz,  $J_{\text{F-P}} = 2.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ): There was no  $^{13}\text{C}$  NMR data offered because of its bad solubility in most of deuterated solvents (including DMSO- $d_6$ , DMF- $d_7$  and Benzene- $d_6$ ).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.3 (d,  $J_{\text{P-F}} = 2.2$  Hz). IR: 3059, 2960, 1748, 1513, 1254, 1244, 1149, 1113, 845, 761, 720, 567, 521, 498, 456  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{23}\text{F}_3\text{O}_4\text{P}$ : 463.1281, found: 463.1283.



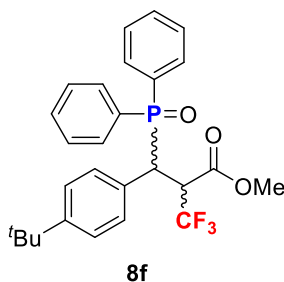
**Methyl 2-((diphenylphosphoryl)(4-hydroxyphenyl)methyl)-3,3,3-trifluoropropanoate (4d):** Following the general procedure (X): **8d** was obtained as a mixture of two diastereoisomers, *dr* = 85:15; white solid, 71% yield (95 mg); **M.P.** 260 – 262 °C.

*anti*-**8d**: **<sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):** δ 9.27 (s, 1H), 8.08 – 8.03 (m, 2H), 7.70 – 7.64 (m, 2H), 7.54 (s, 3H), 7.30 – 7.22 (m, 5H), 6.49 (d, *J*<sub>H-H</sub> = 8.2 Hz, 2H), 4.73 – 4.67 (m, 1H), 4.25 – 4.13 (m, 1H), 2.91 (s, 3H). **<sup>19</sup>F NMR (282 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):** δ -61.6 (dd, *J*<sub>F-H</sub> = 7.6 Hz, *J*<sub>F-P</sub> = 1.7 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):** δ 165.9 (d, *J*<sub>C-F</sub> = 1.9 Hz), 156.5 (d, *J*<sub>C-P</sub> = 2.1 Hz), 132.5 (d, *J*<sub>C-P</sub> = 100.5 Hz), 132.3 (d, *J*<sub>C-P</sub> = 90.0 Hz), 131.8 (d, *J*<sub>C-P</sub> = 2.3 Hz), 131.4 (d, *J*<sub>C-P</sub> = 9.0 Hz), 131.0 (d, *J*<sub>C-P</sub> = 3.0 Hz), 130.5 (d, *J*<sub>C-P</sub> = 9.0 Hz), 128.3 (d, *J*<sub>C-P</sub> = 11.3 Hz), 127.9 (d, *J*<sub>C-P</sub> = 11.3 Hz), 124.6 (qd, *J*<sub>C-F</sub> = 281.3 Hz, *J*<sub>C-P</sub> = 18.8 Hz), 122.6 (d, *J*<sub>C-P</sub> = 6.0 Hz), 114.8, 52.1, 50.4 (q, *J*<sub>C-F</sub> = 25.5 Hz), 41.5 (d, *J*<sub>C-P</sub> = 64.5 Hz). **<sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):** δ 28.9 (d, *J*<sub>P-F</sub> = 1.4 Hz). **IR:** 3164, 2956, 2913, 1738, 1520, 1437, 1269, 1176, 722, 697, 540, 439 cm<sup>-1</sup>. **HRMS (ES+) m/z:** [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>21</sub>F<sub>3</sub>O<sub>4</sub>P: 449.1124, found: 449.1131.



**Methyl 2-((4-(dimethylamino)phenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8e):** Following the general procedure (X): **8e** was obtained as a mixture of two diastereoisomers, *dr* = 93:7; pale yellow solid, 52% yield (74 mg); **M.P.** 258 – 260 °C.

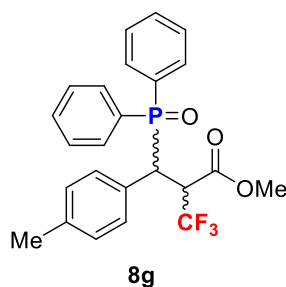
*anti*-**8e**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.92 – 7.85 (m, 2H), 7.53 – 7.45 (m, 5H), 7.32 – 7.18 (m, 3H), 7.06 (d,  $J_{\text{H-H}} = 8.0$  Hz, 2H), 4.25 – 4.10 (m, 2H), 3.20 (s, 3H), 2.85 (s, 6H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 7.0$  Hz,  $J_{\text{F-P}} = 2.7$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.2 (d,  $J_{\text{C-F}} = 2.7$  Hz), 150.1 (d,  $J_{\text{C-P}} = 1.8$  Hz), 132.0 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.6 (d,  $J_{\text{C-P}} = 99.0$  Hz), 131.5 (d,  $J_{\text{C-P}} = 95.3$  Hz), 131.4 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.2 (d,  $J_{\text{C-P}} = 8.3$  Hz), 128.4 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.1 (d,  $J_{\text{C-P}} = 12.0$  Hz), 124.4 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 118.6 (d,  $J_{\text{C-P}} = 5.3$  Hz), 112.1 (d,  $J_{\text{C-P}} = 1.5$  Hz), 52.6, 50.8 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.2 (d,  $J_{\text{C-P}} = 66.0$  Hz), 40.4.  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.6 (d,  $J_{\text{P-F}} = 2.5$  Hz). IR: 3060, 2950, 2810, 1749, 1618, 1522, 1439, 1269, 1177, 1111, 701, 559, 542, 438  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{26}\text{F}_3\text{NO}_3\text{P}$ : 476.1597, found: 476.1611.



**Methyl 2-((4-(tert-butyl)phenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8f)**: Following the general procedure (X): **8f** was obtained as a mixture of two diastereoisomers,  $dr = 81:19$ ; white solid, 77% yield (113 mg); **M.P.** 228 – 229 °C.

*anti*-**8f**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96 – 7.89 (m, 2H), 7.53 – 7.46 (m, 3H), 7.39 – 7.33 (m, 2H), 7.25 – 7.20 (m, 1H), 7.14 – 7.07 (m, 6H), 4.26 – 4.23 (m, 2H), 3.16 (s, 3H), 1.19 (s, 9H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 6.6$  Hz,  $J_{\text{F-P}} = 2.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.0 (d,  $J_{\text{C-F}} = 1.5$  Hz), 151.0 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.2 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.3 (d,  $J_{\text{C-P}} = 103.5$  Hz), 131.2 (d,  $J_{\text{C-P}} = 92.3$  Hz), 131.2 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.1 (d,  $J_{\text{C-P}} = 8.3$  Hz), 130.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 128.8 (d,  $J_{\text{C-P}} = 6.0$  Hz), 128.5 (d,  $J_{\text{C-P}} = 12.0$  Hz), 127.9 (d,  $J_{\text{C-P}} = 12.0$  Hz), 125.1 (d,  $J_{\text{C-P}} = 2.3$  Hz), 124.4 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.8$  Hz), 52.6, 50.6 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.8 (d,  $J_{\text{C-P}} = 64.5$  Hz), 34.5, 31.3.  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.9 (d,  $J_{\text{P-F}} = 2.1$  Hz). IR: 3060,

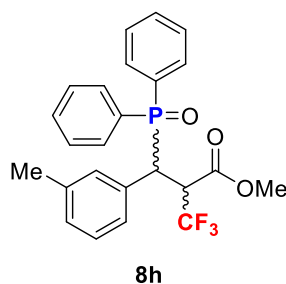
2964, 1748, 1437, 1239, 1179, 1148, 719, 699, 572, 541, 532, 499, 454  $\text{cm}^{-1}$ . **HRMS (ES+) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{27}\text{H}_{29}\text{F}_3\text{O}_3\text{P}$ : 489.1801, found: 489.1815.



**Methyl 2-((diphenylphosphoryl)(p-tolyl)methyl)-3,3,3-trifluoropropanoate (8g):**

Following the general procedure (X): **8g** was obtained as a mixture of two diastereoisomers, *dr* = 97:3; white solid, 91% yield (122 mg); **M.P.** 250 – 251 °C.

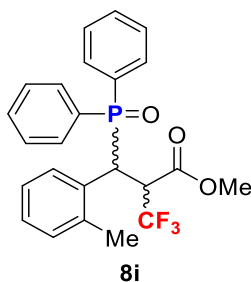
*anti*-**8g**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 – 7.88 (m, 2H), 7.56 – 7.44 (m, 5H), 7.31 – 7.25 (m, 1H), 7.22 – 7.14 (m, 4H), 6.92 (d,  $J_{\text{H-H}} = 8.1$  Hz, 2H), 4.30 – 4.14 (m, 2H), 3.16 (s, 3H), 2.20 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 7.0$  Hz,  $J_{\text{F-P}} = 2.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.0 (d,  $J_{\text{C-F}} = 2.3$  Hz), 137.7 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.1 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.4 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.4 (d,  $J_{\text{C-P}} = 100.5$  Hz), 131.3 (d,  $J_{\text{C-P}} = 96.8$  Hz), 131.1 (d,  $J_{\text{C-P}} = 8.3$  Hz), 130.5 (d,  $J_{\text{C-P}} = 9.0$  Hz), 129.0 (d,  $J_{\text{C-P}} = 2.3$  Hz), 128.8 (d,  $J_{\text{C-P}} = 6.0$  Hz), 128.5 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.1 (d,  $J_{\text{C-P}} = 12.0$  Hz), 124.3 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.6, 50.8 (q,  $J_{\text{C-F}} = 25.5$  Hz), 44.6 (d,  $J_{\text{C-P}} = 65.3$  Hz), 21.2.  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.3 (d,  $J_{\text{P-F}} = 2.4$  Hz). **IR:** 3055, 2924, 1749, 1351, 1181, 1145, 837, 715, 695, 559, 501, 447  $\text{cm}^{-1}$ . **HRMS (ES+) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{23}\text{F}_3\text{O}_3\text{P}$ : 447.1331, found: 447.1332.



**Methyl 2-((diphenylphosphoryl)(m-tolyl)methyl)-3,3,3-trifluoropropanoate (8h):**

Following the general procedure (X): **8h** was obtained as a mixture of two diastereoisomers, *dr* = 93:7; white solid, 81% yield (108 mg); **M.P.** 204 – 205 °C.

*anti*-**8h**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 – 7.88 (m, 2H), 7.53 – 7.41 (m, 5H), 7.27 – 7.12 (m, 3H), 7.05 – 6.87 (m, 4H), 4.29 – 4.17 (m, 2H), 3.17 (s, 3H), 2.14 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 6.8$  Hz,  $J_{\text{F-P}} = 2.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.8 (d,  $J_{\text{C-F}} = 1.5$  Hz), 137.8 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.1 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.8 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.3 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.2 (d,  $J_{\text{C-P}} = 99.0$  Hz), 131.1 (d,  $J_{\text{C-P}} = 102.0$  Hz), 131.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 128.5 (d,  $J_{\text{C-P}} = 2.3$  Hz), 128.4 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.1 (d,  $J_{\text{C-P}} = 2.3$  Hz), 127.9 (d,  $J_{\text{C-P}} = 12.0$  Hz), 127.6 (d,  $J_{\text{C-P}} = 5.3$  Hz), 124.3 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.5, 50.7 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.9 (d,  $J_{\text{C-P}} = 64.5$  Hz), 21.2.  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.4 (d,  $J_{\text{P-F}} = 1.9$  Hz). IR: 3056, 2925, 1748, 1438, 1236, 1182, 1118, 715, 701, 517, 455  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{23}\text{F}_3\text{O}_3\text{P}$ : 447.1331, found: 447.1335.

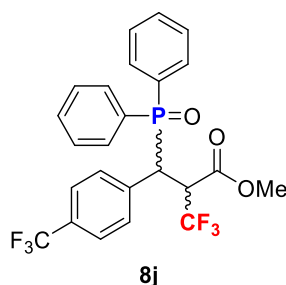


**Methyl 2-((diphenylphosphoryl)(*o*-tolyl)methyl)-3,3,3-trifluoropropanoate (**8i**):**

Following the general procedure (**X**): **8i** was obtained as a mixture of two diastereoisomers,  $dr = 70:30$ ; white solid, 61% yield (82 mg); **M.P.** 150 – 152 °C.

*anti*-**8i**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.94 – 7.87 (m, 2H), 7.59 – 7.49 (m, 4H), 7.38 – 7.31 (m, 2H), 7.28 – 7.22 (m, 1H), 7.15 – 7.00 (m, 4H), 6.87 (d,  $J_{\text{H-H}} = 7.5$  Hz, 1H), 4.54 – 4.47 (m, 1H), 4.34 – 4.19 (m, 1H), 3.16 (s, 3H), 2.09 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.4 (dd,  $J_{\text{F-H}} = 7.5$  Hz,  $J_{\text{F-P}} = 2.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.0 (d,  $J_{\text{C-F}} = 2.3$  Hz), 136.6 (d,  $J_{\text{C-P}} = 6.8$  Hz), 132.3 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.1 (d,  $J_{\text{C-P}} = 8.3$  Hz), 131.6 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.1 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.0 (d,  $J_{\text{C-P}} = 102.8$  Hz), 130.5 (d,  $J_{\text{C-P}} = 1.5$  Hz), 130.4 (d,  $J_{\text{C-P}} = 6.0$  Hz), 130.4 (d,  $J_{\text{C-P}} = 93.8$  Hz), 130.1 (d,  $J_{\text{C-P}} = 3.0$  Hz), 128.5 (d,  $J_{\text{C-P}} = 12.0$  Hz), 127.9 (d,  $J_{\text{C-P}} = 13.0$  Hz), 127.8 (d,  $J_{\text{C-P}} = 12.0$  Hz), 125.9 (d,  $J_{\text{C-P}} = 3.0$  Hz), 124.4 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.5, 50.9 (q,  $J_{\text{C-F}} = 26.3$  Hz), 39.7 (d,  $J_{\text{C-P}} = 64.5$  Hz), 19.7.  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.1 (d,  $J_{\text{P-F}} = 2.2$  Hz). IR: 3059,

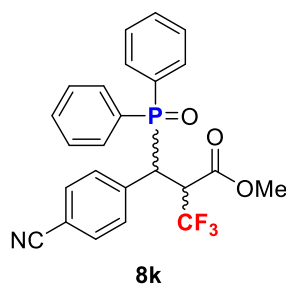
2955, 1751, 1437, 1141, 1112, 881, 719, 699, 550, 536, 461, 423, 394  $\text{cm}^{-1}$ . **HRMS (ES<sup>+</sup>) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{23}\text{F}_3\text{O}_3\text{P}$ : 447.1331, found: 447.1327.



**Methyl 2-((diphenylphosphoryl)(4-(trifluoromethyl)phenyl)methyl)-3,3,3-trifluoropropanoate (8j):**

Following the general procedure (**X**): **8j** was obtained as a mixture of two diastereoisomers, *dr* = 99:1; white solid, 88% yield (132 mg); **M.P.** 252 – 253 °C.

*anti*-**8j**: **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  8.00 – 7.93 (m, 3H), 7.58 – 7.36 (m, 8H), 7.32 – 7.16 (m, 4H), 4.37 – 4.20 (m, 2H), 3.12 (s, 3H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -63.2 (dd,  $J_{\text{F-H}} = 6.7$  Hz,  $J_{\text{F-P}} = 1.8$  Hz); -63.3 (s). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  166.6 (d,  $J_{\text{C-F}} = 1.5$  Hz), 136.6 (d,  $J_{\text{C-P}} = 6.8$  Hz), 132.5 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.9 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.0 (d,  $J_{\text{C-P}} = 5.3$  Hz), 130.8 (d,  $J_{\text{C-P}} = 8.3$  Hz), 130.7 (d,  $J_{\text{C-P}} = 103.5$  Hz), 130.4 (d,  $J_{\text{C-P}} = 94.5$  Hz), 130.4 (d,  $J_{\text{C-F}} = 2.3$  Hz), 129.9 (d,  $J_{\text{C-F}} = 2.3$  Hz), 128.7 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.3 (d,  $J_{\text{C-P}} = 12.0$  Hz), 124.2 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 17.3$  Hz), 124.0 (q,  $J_{\text{C-F}} = 270.8$  Hz), 52.7, 50.5 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.9 (d,  $J_{\text{C-P}} = 63.0$  Hz) **<sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>):** 28.9 (d,  $J_{\text{P-F}} = 1.4$  Hz). **IR:** 3058, 2927, 1749, 1439, 1322, 1182, 1154, 1130, 862, 716, 698, 608, 538, 513, 493  $\text{cm}^{-1}$ . **HRMS (ES<sup>+</sup>) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{20}\text{F}_6\text{O}_3\text{P}$ : 501.1049, found: 501.1048.

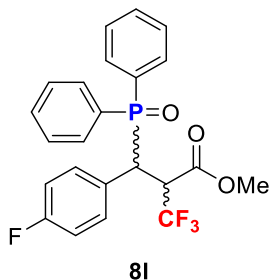


**Methyl 2-((4-cyanophenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8k):**



Following the general procedure (X): **8k** was obtained as a mixture of two diastereoisomers, *dr* = 97:3; white solid, 80% yield (110 mg); **M.P.** 242 – 243 °C.

*anti*-**8k**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00 – 7.93 (m, 2H), 7.59 – 7.39 (m, 9H), 7.32 – 7.27 (m, 1H), 7.23 – 7.17 (m, 2H), 4.38 – 4.19 (m, 2H), 3.08 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.2 (d,  $J_{\text{F-P}} = 1.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.3 (d,  $J_{\text{C-F}} = 1.5$  Hz), 138.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 132.6 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.0 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.9, 131.8 (d,  $J_{\text{C-P}} = 10.5$  Hz), 131.3, 130.6 (d,  $J_{\text{C-P}} = 8.3$  Hz), 130.5 (d,  $J_{\text{C-P}} = 103.5$  Hz), 130.2 (d,  $J_{\text{C-P}} = 94.5$  Hz), 128.7 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.4 (d,  $J_{\text{C-P}} = 12.0$  Hz), 124.1 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 17.3$  Hz), 118.5 (d,  $J_{\text{C-P}} = 1.5$  Hz), 111.8 (d,  $J_{\text{C-P}} = 2.3$  Hz), 52.7, 50.3 (q,  $J_{\text{C-F}} = 26.3$  Hz), 44.9 (d,  $J_{\text{C-P}} = 62.3$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.6 (s). IR: 3058, 2927, 2234, 1747, 1438, 1180, 1158, 1115, 863, 717, 700, 567, 530, 428  $\text{cm}^{-1}$ . HRMS (ES+) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{20}\text{F}_3\text{NO}_3\text{P}$ : 458.1127, found: 458.1122.

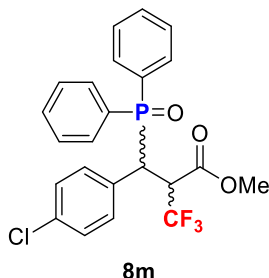


**Methyl 2-((diphenylphosphoryl)(4-fluorophenyl)methyl)-3,3,3-trifluoropropanoate (8l):**

Following the general procedure (X): **8l** was obtained as a mixture of two diastereoisomers, *dr* = 98:2; white solid, 95% yield (128 mg); **M.P.** 230 – 232 °C.

*anti*-**8l**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 – 7.91 (m, 2H), 7.55 – 7.44 (m, 5H), 7.32 – 7.18 (m, 5H), 6.88 – 6.77 (m, 2H), 4.31 – 4.16 (m, 2H), 3.12 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.2 (dd,  $J_{\text{F-H}} = 7.0$  Hz,  $J_{\text{F-P}} = 2.3$  Hz), -114.3 (m).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.8 (d,  $J_{\text{C-F}} = 1.5$  Hz), 162.4 (dd,  $J_{\text{C-F}} = 246.0$  Hz,  $J_{\text{C-P}} = 3.0$  Hz), 132.4 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.2 (d,  $J_{\text{C-F}} = 6.8$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.7 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.2 (d,  $J_{\text{C-P}} = 102.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 93.0$  Hz), 128.6 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.3 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.0 (d,  $J_{\text{C-F}} = 5.3$  Hz), 127.9 (d,  $J_{\text{C-F}} = 6.0$  Hz), 124.2 (qd,  $J_{\text{C-F}} = 282.0$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 115.4 (dd,  $J_{\text{C-F}} = 21.0$  Hz,  $J_{\text{C-P}} = 1.5$  Hz), 52.6, 50.7 (q,  $J_{\text{C-F}} = 26.3$

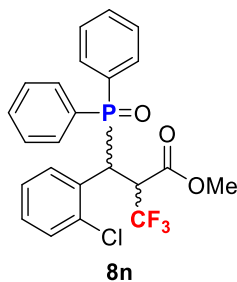
Hz), 44.1 (d,  $J_{C-P} = 64.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.2 (d,  $J_{P-F} = 2.2$  Hz). IR: 3059, 2968, 2926, 1746, 1602, 1507, 1350, 1181, 1147, 1116, 853, 714, 560, 534, 481, 453  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{20}\text{F}_4\text{O}_3\text{P}$ : 451.1081, found: 451.1115.



**Methyl 2-((4-chlorophenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8m):**

Following the general procedure (X): **8m** was obtained as a mixture of two diastereoisomers,  $dr = 97:3$ ; white solid, 94% yield (131 mg); M.P. 249 – 250 °C.

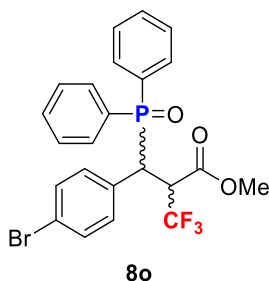
*anti*-**8m**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.97 – 7.90 (m, 2H), 7.55 – 7.44 (m, 5H), 7.34 – 7.19 (m, 5H), 7.10 (d,  $J_{H-H} = 8.7$  Hz, 2H), 4.30 – 4.13 (m, 2H), 3.12 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.2 (d,  $J_{F-H} = 6.8$  Hz,  $J_{F-P} = 2.1$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7 (d,  $J_{C-F} = 1.5$  Hz), 134.1 (d,  $J_{C-P} = 3.0$  Hz), 132.4 (d,  $J_{C-P} = 2.3$  Hz), 131.9 (d,  $J_{C-P} = 9.0$  Hz), 131.8 (d,  $J_{C-P} = 3.0$  Hz), 131.1 (d,  $J_{C-P} = 104.3$  Hz), 130.9 (d,  $J_{C-P} = 9.0$  Hz), 130.8 (d,  $J_{C-P} = 93.0$  Hz), 130.7, 128.7, 128.6 (d,  $J_{C-P} = 13.5$  Hz), 128.3 (d,  $J_{C-P} = 12.0$  Hz), 124.2 (qd,  $J_{C-F} = 282.0$  Hz,  $J_{C-P} = 17.3$  Hz), 52.7, 50.6 (q,  $J_{C-F} = 26.3$  Hz), 44.3 (d,  $J_{C-P} = 63.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.9 (d,  $J_{P-F} = 2.1$  Hz). IR: 3056, 2925, 1747, 1488, 1438, 1152, 1116, 717, 698, 546, 518, 420  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{20}\text{ClF}_3\text{O}_3\text{P}$ : 467.0785, found: 467.0794.



**Methyl 2-((2-chlorophenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8n):**

Following the general procedure (X): **8n** was obtained as a mixture of two diastereoisomers, *dr* = 74:26; white solid, 55% yield (77 mg); **M.P.** 119 – 122 °C.

*anti*-**8n**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 – 8.01 (m, 2H, *syn* + 2H, *anti*), 7.74 – 7.68 (m, 1H, *syn* + 1H, *anti*), 7.51 – 7.39 (m, 5H, *syn* + 5H, *anti*), 5.05 (dd,  $J_{\text{H-H}} = 7.2$  Hz,  $J_{\text{H-P}} = 11.7$  Hz, 1H, *anti*), 4.94 (dd,  $J_{\text{H-H}} = 6.6$  Hz,  $J_{\text{H-P}} = 8.4$  Hz, 1H, *syn*), 4.33 – 4.14 (m, 1H, *syn*+1H, *anti*), 3.41 (s, 3H, *syn*), 3.03 (s, 3H, *anti*).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.4 (dd,  $J_{\text{F-H}} = 7.6$  Hz,  $J_{\text{F-P}} = 2.1$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.0 (d,  $J_{\text{C-F}} = 1.5$  Hz), 134.3 (d,  $J_{\text{C-P}} = 7.5$  Hz), 131.4 (d,  $J_{\text{C-P}} = 7.5$  Hz), 131.4 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.0 (d,  $J_{\text{C-P}} = 3.8$  Hz), 130.8 (d,  $J_{\text{C-P}} = 8.3$  Hz), 130.6 (d,  $J_{\text{C-P}} = 5.3$  Hz), 130.4 (d,  $J_{\text{C-P}} = 9.0$  Hz), 129.4 (d,  $J_{\text{C-P}} = 95.3$  Hz), 129.3 (d,  $J_{\text{C-P}} = 99.0$  Hz), 129.3 (d,  $J_{\text{C-P}} = 1.5$  Hz), 128.9 (d,  $J_{\text{C-P}} = 2.3$  Hz), 128.4 (d,  $J_{\text{C-P}} = 12.0$  Hz), 127.7 (d,  $J_{\text{C-P}} = 12.0$  Hz), 126.6 (d,  $J_{\text{C-P}} = 2.3$  Hz), 124.1 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 17.3$  Hz), 52.3, 50.6 (q,  $J_{\text{C-F}} = 26.3$  Hz), 39.5 (d,  $J_{\text{C-P}} = 63.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.5 (s). IR: 3059, 2956, 1749, 1437, 1365, 1146, 1113, 752, 714, 697, 544, 510, 495, 425  $\text{cm}^{-1}$ . HRMS (ES+) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{20}\text{ClF}_3\text{O}_3\text{P}$ : 467.0785, found: 467.0789.

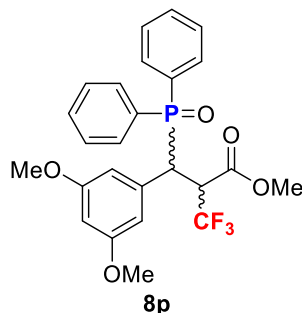


**Methyl 2-((4-bromophenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8o):**

Following the general procedure (X): **8o** was obtained as a mixture of two diastereoisomers, *dr* = 99:1; white solid, 88% yield (135 mg); **M.P.** 242 – 243 °C.

*anti*-**8o**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 – 7.92 (m, 2H), 7.59 – 7.46 (m, 5H), 7.36 – 7.21 (m, 7H), 4.31 – 4.12 (m, 2H), 3.14 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.2 (dd,  $J_{\text{F-H}} = 7.0$  Hz,  $J_{\text{F-P}} = 2.1$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7 (d,  $J_{\text{C-F}} = 2.3$  Hz), 132.4 (d,  $J_{\text{C-P}} = 2.3$  Hz), 132.2 (d,  $J_{\text{C-P}} = 5.3$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.8 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.5 (d,  $J_{\text{C-P}} = 1.5$  Hz), 131.3 (d,  $J_{\text{C-P}} = 5.3$  Hz), 130.9 (d,  $J_{\text{C-P}} = 103.5$  Hz), 130.9

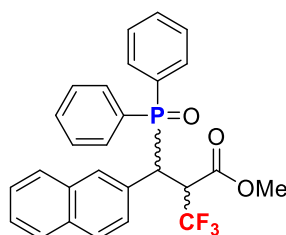
(d,  $J_{C-P} = 9.0$  Hz), 130.7 (d,  $J_{C-P} = 93.8$  Hz), 128.6 (d,  $J_{C-P} = 12.0$  Hz), 128.3 (d,  $J_{C-P} = 12.0$  Hz), 124.2 (qd,  $J_{C-F} = 281.3$  Hz,  $J_{C-P} = 17.3$  Hz), 122.2 (d,  $J_{C-P} = 3.0$  Hz), 52.7, 50.5 (q,  $J_{C-F} = 26.3$  Hz), 44.3 (d,  $J_{C-P} = 63.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.9 (d,  $J_{P-F} = 1.9$  Hz). IR: 3059, 2926, 1748, 1590, 1438, 1238, 1181, 1153, 1116, 716, 697, 542, 513, 446  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{20}\text{BrF}_3\text{O}_3\text{P}$ : 511.0280, found: 511.0302.



**Methyl 2-((3,5-dimethoxyphenyl)(diphenylphosphoryl)methyl)-3,3,3-trifluoropropanoate (8p):**

Following the general procedure (**X**): **8p** was obtained as a mixture of two diastereoisomers,  $dr = 90:10$ ; white solid, 94% yield (139 mg); **M.P.** 181 – 182 °C.

*anti*-**8p**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 – 7.91 (m, 2H), 7.56 – 7.51 (m, 5H), 7.32 – 7.20 (m, 3H), 6.48 (s, 3H), 6.23 – 6.21 (m, 1H), 4.29 – 4.20 (m, 2H), 3.66 (s, 6H), 3.21 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.5 (dd,  $J_{F-H} = 6.6$  Hz,  $J_{F-P} = 2.1$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.6 (d,  $J_{C-F} = 1.5$  Hz), 160.4 (d,  $J_{C-P} = 2.3$  Hz), 134.2 (d,  $J_{C-P} = 5.3$  Hz), 132.1 (d,  $J_{C-P} = 3.0$  Hz), 131.7 (d,  $J_{C-P} = 9.0$  Hz), 131.5 (d,  $J_{C-P} = 3.0$  Hz), 131.2 (d,  $J_{C-P} = 95.3$  Hz), 131.1 (d,  $J_{C-P} = 101.3$  Hz), 131.0 (d,  $J_{C-P} = 9.0$  Hz), 128.5 (d,  $J_{C-P} = 11.3$  Hz), 128.0 (d,  $J_{C-P} = 12.0$  Hz), 124.2 (qd,  $J_{C-F} = 281.3$  Hz,  $J_{C-P} = 18.0$  Hz), 108.6, 100.4 (d,  $J_{C-P} = 2.3$  Hz), 55.3, 52.5, 50.8 (q,  $J_{C-F} = 26.3$  Hz), 45.1 (d,  $J_{C-P} = 63.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.4 (d,  $J_{P-F} = 2.0$  Hz). IR: 3059, 2932, 2841, 1755, 1608, 1591, 1436, 1197, 1143, 1070, 720, 700, 543, 510, 441  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{25}\text{F}_3\text{O}_5\text{P}$ : 493.1386, found: 493.1370.

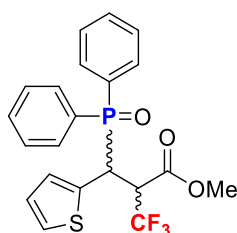


8q

**Methyl 2-((diphenylphosphoryl)(naphthalen-2-yl)methyl)-3,3,3-trifluoropropanoate (8q):**

Following the general procedure (X): **8q** was obtained as a mixture of two diastereoisomers, *dr* = 94:6; white solid, 83% yield (120 mg); **M.P.** 246 – 247 °C.

*anti*-**8q**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.00 – 7.93 (m, 2H), 7.74 – 7.66 (m, 3H), 7.62 – 7.59 (m, 1H), 7.54 – 7.38 (m, 8H), 4.53 – 4.27 (m, 2H), 3.21 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (d,  $J_{\text{F-H}} = 4.9$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.9 (d,  $J_{\text{C-F}} = 1.5$  Hz), 133.0 (d,  $J_{\text{C-P}} = 1.5$  Hz), 132.7 (d,  $J_{\text{C-P}} = 1.5$  Hz), 132.2 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.5 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.3 (d,  $J_{\text{C-P}} = 93.0$  Hz), 131.1 (d,  $J_{\text{C-P}} = 102.8$  Hz), 131.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.5 (d,  $J_{\text{C-P}} = 18.8$  Hz), 130.3 (d,  $J_{\text{C-P}} = 6.8$  Hz), 129.7 (d,  $J_{\text{C-P}} = 6.0$  Hz), 128.6 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.0 (d,  $J_{\text{C-P}} = 13.5$  Hz), 127.9 (d,  $J_{\text{C-P}} = 3.0$  Hz), 127.6 (d,  $J_{\text{C-P}} = 0.8$  Hz), 126.3 (d,  $J_{\text{C-P}} = 8.3$  Hz), 124.3 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.7, 50.9 (q,  $J_{\text{C-F}} = 27.0$  Hz), 45.2 (d,  $J_{\text{C-P}} = 63.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.3 (d,  $J_{\text{P-F}} = 2.0$  Hz). **IR**: 3059, 2956, 1750, 1437, 1272, 1177, 1111, 743, 701, 555, 478, 422  $\text{cm}^{-1}$ . **HRMS (ES+)** *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{27}\text{H}_{23}\text{F}_3\text{O}_3\text{P}$ : 483.1331, found: 483.1343.

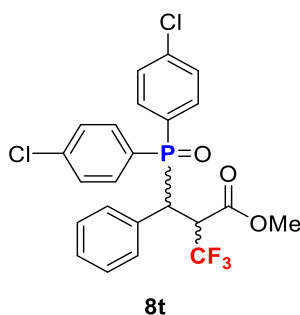


8r

**Methyl 2-((diphenylphosphoryl)(thiophen-2-yl)methyl)-3,3,3-trifluoropropanoate (8r):**

Following the general procedure (X): **8r** was obtained as a mixture of two diastereoisomers, *dr* = 96:4; white solid, 75% yield (99 mg); **M.P.** 244 – 245 °C.

*anti*-**8r**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.97 – 7.88 (m, 2H), 7.64 – 7.46 (m, 5H), 7.38 – 7.23 (m, 3H), 7.08 – 7.06 (m, 2H), 6.81 – 6.78 (m, 1H), 4.69 – 4.62 (m, 1H), 4.23 – 4.09 (m, 1H) 3.17 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.7 (dd,  $J_{\text{F-P}} = 7.4$  Hz,  $J_{\text{F-P}} = 2.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.6 (d,  $J_{\text{C-F}} = 1.5$  Hz), 132.7 (d,  $J_{\text{C-P}} = 6.0$  Hz), 132.4 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 131.7 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.1 (d,  $J_{\text{C-P}} = 8.3$  Hz), 131.0 (d,  $J_{\text{C-P}} = 104.3$  Hz), 130.8 (d,  $J_{\text{C-P}} = 93.0$  Hz), 129.8 (d,  $J_{\text{C-P}} = 6.8$  Hz), 128.6 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.2 (d,  $J_{\text{C-P}} = 12.0$  Hz), 126.9 (d,  $J_{\text{C-P}} = 2.3$  Hz), 126.3 (d,  $J_{\text{C-P}} = 3.0$  Hz), 124.2 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 16.5$  Hz), 52.7, 51.3 (q,  $J_{\text{C-F}} = 26.3$  Hz), 39.9 (d,  $J_{\text{C-P}} = 66.0$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  28.8 (d,  $J_{\text{P-F}} = 2.2$  Hz). IR: 3059, 2960, 2918, 1750, 1437, 1183, 1142, 1114, 723, 696, 535, 505, 434  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{19}\text{F}_3\text{O}_3\text{PS}$ : 439.0739, found: 439.0735.

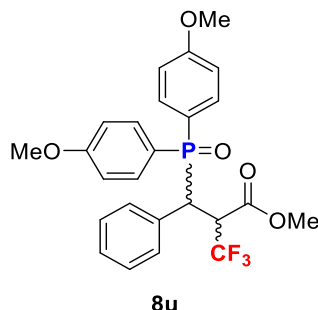


**Methyl 2-((bis(4-chlorophenyl)phosphoryl)(phenyl)methyl)-3,3,3-trifluoropropanoate (8t):**

Following the general procedure (**X**): **8t** was obtained as a mixture of two diastereoisomers,  $dr = 95:5$ ; white solid, 87% yield (131 mg); **M.P.** 209 – 210 °C.

*anti*-**8t**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.87 – 7.80 (m, 2H), 7.50 – 7.46 (m, 2H), 7.39 – 7.26 (m, 4H), 7.17 – 7.12 (m, 5H), 4.30 – 4.14 (m, 2H), 3.23 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.3 (dd,  $J_{\text{F-H}} = 6.7$  Hz,  $J_{\text{F-P}} = 2.2$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.7 (d,  $J_{\text{C-F}} = 0.8$  Hz), 139.2 (d,  $J_{\text{C-P}} = 3.8$  Hz), 138.3 (d,  $J_{\text{C-P}} = 3.0$  Hz), 133.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 132.3 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 114.8$  Hz), 130.8 (d,  $J_{\text{C-P}} = 117.8$  Hz), 130.5 (d,  $J_{\text{C-P}} = 6.0$  Hz), 128.9 (d,  $J_{\text{C-P}} = 12.8$  Hz), 128.7 (d,  $J_{\text{C-P}} = 2.3$  Hz), 128.5 (d,  $J_{\text{C-P}} = 1.5$  Hz), 128.5 (d,  $J_{\text{C-P}} = 12.8$  Hz), 128.3 (d,  $J_{\text{C-P}} = 2.3$  Hz), 124.1 (qd,  $J_{\text{C-F}} = 281.3$  Hz,  $J_{\text{C-P}} = 18.0$  Hz), 52.7, 50.6 (q,  $J_{\text{C-F}} = 27.0$  Hz), 44.9 (d,  $J_{\text{C-P}} = 66.0$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,

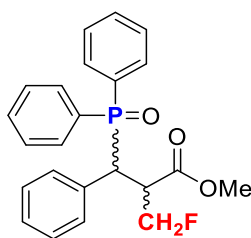
**CDCl<sub>3</sub>**):  $\delta$  28.9 (s). **IR**: 3065, 2968, 2919, 1748, 1585, 1238, 1178, 1146, 1088, 756, 703, 555, 510, 425 cm<sup>-1</sup>. **HRMS (ES<sup>+</sup>) m/z**: [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>F<sub>3</sub>O<sub>3</sub>P: 501.0395, found: 501.0405.



**Methyl 2-((bis(4-methoxyphenyl)phosphoryl)(phenyl)methyl)-3,3,3-trifluoropropanoate (8u):**

Following the general procedure (X): **8u** was obtained as a mixture of two diastereoisomers, *dr* = 91:9; white solid, 70% yield (103 mg); **M.P.** 157 – 158 °C.

*anti*-**8u**: **<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)**:  $\delta$  7.80 – 7.73 (m, 2H), 7.35 – 7.21 (m, 4H), 7.12 – 7.10 (m, 3H), 6.97 (dd,  $J_{H-H}$  = 2.4 Hz,  $J_{H-H}$  = 9.0 Hz, 2H), 6.67 (dd,  $J_{H-H}$  = 2.4 Hz,  $J_{H-H}$  = 8.7 Hz, 2H), 4.20 – 4.18 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.26 (s, 3H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>)**:  $\delta$  -63.2 (dd,  $J_{F-H}$  = 6.7 Hz,  $J_{F-P}$  = 2.1 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)**:  $\delta$  166.9 (d,  $J_{C-F}$  = 1.5 Hz), 162.5 (d,  $J_{C-P}$  = 3.0 Hz), 161.9 (d,  $J_{C-P}$  = 3.0 Hz), 133.7 (d,  $J_{C-P}$  = 10.5 Hz), 132.9 (d,  $J_{C-P}$  = 10.5 Hz), 132.3 (d,  $J_{C-P}$  = 6.0 Hz), 130.5 (d,  $J_{C-P}$  = 5.3 Hz), 128.1 (d,  $J_{C-P}$  = 1.5 Hz), 127.7 (d,  $J_{C-P}$  = 2.3 Hz), 124.3 (qd,  $J_{C-F}$  = 282.0 Hz,  $J_{C-P}$  = 18.0 Hz), 122.4 (d,  $J_{C-P}$  = 110.3 Hz), 122.1 (d,  $J_{C-P}$  = 100.5 Hz), 113.9 (d,  $J_{C-P}$  = 12.0 Hz), 113.5 (d,  $J_{C-P}$  = 12.8 Hz), 55.4, 55.1, 52.6, 50.7 (q,  $J_{C-F}$  = 25.5 Hz), 45.4 (d,  $J_{C-P}$  = 64.5 Hz). **<sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>)**:  $\delta$  29.7 (d,  $J_{P-F}$  = 1.6 Hz). **IR**: 3071, 3035, 2968, 2841, 1749, 1599, 1506, 1258, 1173, 1143, 1113, 804, 704, 545, 526, 449 cm<sup>-1</sup>. **HRMS (ES<sup>+</sup>) m/z**: [M+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>25</sub>F<sub>3</sub>O<sub>5</sub>P: 493.1386, found: 493.1397.

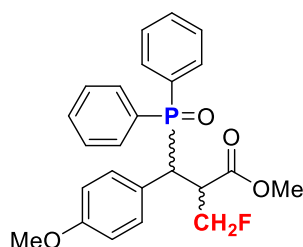


10a

**Methyl 3-(diphenylphosphoryl)-2-(fluoromethyl)-3-phenylpropanoate (10a):**

Following the general procedure (XI): **10a** was obtained as a mixture of two diastereoisomers, *dr* = 95:5; white solid, 64% yield (76 mg); **M.P.** 177 – 178 °C.

*syn*-**10a**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.02 – 7.95 (m, 2H), 7.61 – 7.51 (m, 3H), 7.43 – 7.36 (m, 2H), 7.28 – 7.08 (m, 8H), 4.64 – 4.34 (m, 2H), 4.01 – 3.96 (m, 1H), 3.86 – 3.70 (m, 1H), 3.41 (s, 3H). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ -219.5 (td, *J*<sub>F-H</sub> = 46.4 Hz, *J*<sub>F-H</sub> = 18.3 Hz). <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>): δ 171.6 (dd, *J*<sub>C-P</sub> = 3.8 Hz, *J*<sub>C-F</sub> = 12.8 Hz), 134.4 (d, *J*<sub>C-P</sub> = 5.3 Hz), 132.7 (d, *J*<sub>C-P</sub> = 93.0 Hz), 132.3 (d, *J*<sub>C-P</sub> = 2.3 Hz), 132.0 (d, *J*<sub>C-P</sub> = 102.0 Hz), 131.3 (d, *J*<sub>C-P</sub> = 3.0 Hz), 131.1 (d, *J*<sub>C-P</sub> = 9.0 Hz), 130.9 (d, *J*<sub>C-P</sub> = 8.3 Hz), 130.1 (d, *J*<sub>C-P</sub> = 6.0 Hz), 129.0 (d, *J*<sub>C-P</sub> = 11.3 Hz), 128.4 (d, *J*<sub>C-P</sub> = 1.5 Hz), 128.1 (d, *J*<sub>C-P</sub> = 12.0 Hz), 127.6 (d, *J*<sub>C-P</sub> = 2.3 Hz), 82.2 (dd, *J*<sub>C-P</sub> = 3.0 Hz, *J*<sub>C-F</sub> = 171.8 Hz), 52.1, 48.5 (d, *J*<sub>C-F</sub> = 20.3 Hz), 45.0 (dd, *J*<sub>C-F</sub> = 5.3 Hz, *J*<sub>C-P</sub> = 66.0 Hz). <sup>31</sup>P{<sup>1</sup>H} NMR (121 MHz, CDCl<sub>3</sub>): δ 29.9 (s). IR: 3060, 2944, 1750, 1439, 1174, 721, 700, 545, 525, 480 cm<sup>-1</sup>. HRMS (ES+) *m/z*: [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>23</sub>FO<sub>3</sub>P: 397.1363, found: 397.1359.



10b

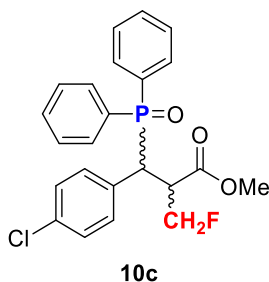
**Methyl 3-(diphenylphosphoryl)-2-(fluoromethyl)-3-(4-methoxyphenyl)propanoate (10b):**

Following the general procedure (XI): **10b** was obtained as a mixture of two diastereoisomers, *dr* = 96:4; white solid, 51% yield (65 mg); **M.P.** 181 – 182 °C.

*syn*-**10b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.99 – 7.92 (m, 2H), 7.57 – 7.50 (m, 3H), 7.45 –



7.39 (m, 2H), 7.27 – 7.13 (m, 5H), 6.65 (d,  $J_{\text{H-H}} = 8.8$  Hz, 2H), 4.61 – 4.31 (m, 2H), 3.96 – 3.90 (m, 1H), 3.81 – 3.61 (m, 1H), 3.69 (s, 3H), 3.44 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -219.4 (td,  $J_{\text{F-H}} = 46.4$  Hz,  $J_{\text{F-H}} = 17.4$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.6 (dd,  $J_{\text{C-P}} = 4.5$  Hz,  $J_{\text{C-F}} = 12.8$  Hz), 158.9 (d,  $J_{\text{C-P}} = 2.3$  Hz), 132.7 (d,  $J_{\text{C-P}} = 92.3$  Hz), 132.2 (d,  $J_{\text{C-P}} = 2.3$  Hz), 132.1 (d,  $J_{\text{C-P}} = 102.0$  Hz), 131.3 (d,  $J_{\text{C-P}} = 1.5$  Hz), 131.3 (d,  $J_{\text{C-P}} = 6.0$  Hz), 131.1 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 129.0 (d,  $J_{\text{C-P}} = 11.3$  Hz), 128.1 (d,  $J_{\text{C-P}} = 11.3$  Hz), 126.0 (d,  $J_{\text{C-P}} = 5.3$  Hz), 113.8 (d,  $J_{\text{C-P}} = 1.5$  Hz), 82.1 (dd,  $J_{\text{C-P}} = 3.0$  Hz,  $J_{\text{C-F}} = 171.0$  Hz), 55.2, 52.1, 48.5 (d,  $J_{\text{C-F}} = 20.3$  Hz), 44.1 (dd,  $J_{\text{C-F}} = 5.3$  Hz,  $J_{\text{C-P}} = 67.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.1 (s). IR: 3054, 2922, 2846, 1741, 1513, 1439, 1252, 1173, 1030, 705, 543, 518, 460  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{FO}_4\text{P}$ : 427.1469, found: 427.1481.

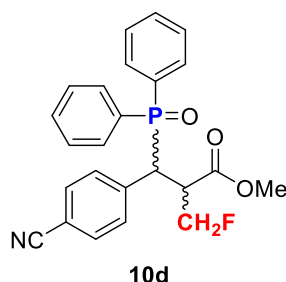


**Methyl 3-(4-chlorophenyl)-3-(diphenylphosphoryl)-2-(fluoromethyl)propanoate (10c):**

Following the general procedure (XI): **10c** was obtained as a mixture of two diastereoisomers,  $dr = 96:4$ ; white solid, 44% yield (57 mg); **M.P.** 184 – 185 °C.

*syn*-**10c**:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 – 7.95 (m, 2H), 7.59 – 7.52 (m, 3H), 7.44 – 7.37 (m, 2H), 7.29 – 7.07 (m, 7H), 4.58 – 4.31 (m, 2H), 4.04 – 3.63 (m, 2H), 3.46 (s, 3H).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -220.2 (td,  $J_{\text{F-H}} = 46.4$  Hz,  $J_{\text{F-H}} = 19.1$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.3 (dd,  $J_{\text{C-P}} = 3.8$  Hz,  $J_{\text{C-F}} = 12.8$  Hz), 133.6 (d,  $J_{\text{C-P}} = 3.0$  Hz), 133.1 (d,  $J_{\text{C-P}} = 4.5$  Hz), 132.5 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.4 (d,  $J_{\text{C-P}} = 93.0$  Hz), 131.8 (d,  $J_{\text{C-P}} = 101.3$  Hz), 131.6 (d,  $J_{\text{C-P}} = 3.0$  Hz), 131.4 (d,  $J_{\text{C-P}} = 6.0$  Hz), 131.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.8 (d,  $J_{\text{C-P}} = 8.3$  Hz), 129.1 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.6 (d,  $J_{\text{C-P}} = 1.5$  Hz), 128.3 (d,  $J_{\text{C-P}} = 11.3$  Hz), 81.9 (dd,  $J_{\text{C-P}} = 3.8$  Hz,  $J_{\text{C-F}} = 172.5$  Hz), 52.2, 48.3 (d,  $J_{\text{C-F}} = 20.3$  Hz), 44.2 (dd,  $J_{\text{C-F}} = 5.3$  Hz,  $J_{\text{C-P}} = 66.0$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.6 (s). IR: 3054, 2956, 1739,

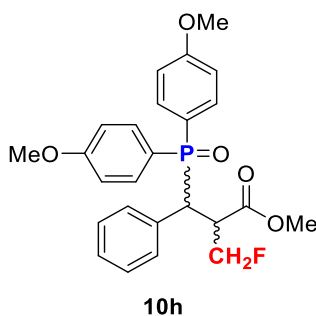
1438, 1221, 837, 722, 698, 545, 518, 413  $\text{cm}^{-1}$ . **HRMS (ES+) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{22}\text{ClFO}_3\text{P}$ : 431.0974, found: 431.0966.



**Methyl 3-(4-cyanophenyl)-3-(diphenylphosphoryl)-2-(fluoromethyl)propanoate (10d):**

Following the general procedure (XI): **10d** was obtained as a mixture of two diastereoisomers, *dr* = 97:3; white solid, 29% yield (37 mg); **M.P.** 169 – 170 °C.

*syn*-**10d**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.05 – 7.98 (m, 2H), 7.63 – 7.55 (m, 3H), 7.42 – 7.27 (m, 7H), 7.22 – 7.16 (m, 2H), 4.58 – 4.32 (m, 2H), 4.13 – 3.68 (m, 2H), 3.47 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -221.1 (td,  $J_{\text{F-H}} = 46.4$  Hz,  $J_{\text{F-H}} = 21.5$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.1 (dd,  $J_{\text{C-P}} = 3.8$  Hz,  $J_{\text{C-F}} = 12.8$  Hz), 140.6 (d,  $J_{\text{C-P}} = 5.3$  Hz), 132.7 (d,  $J_{\text{C-P}} = 3.0$  Hz), 132.0 (d,  $J_{\text{C-P}} = 1.5$  Hz), 131.9 (d,  $J_{\text{C-P}} = 93.8$  Hz), 131.8 (d,  $J_{\text{C-P}} = 2.3$  Hz), 131.5 (d,  $J_{\text{C-P}} = 102.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 15.8$  Hz), 130.8 (d,  $J_{\text{C-P}} = 1.5$  Hz), 130.6 (d,  $J_{\text{C-P}} = 9.0$  Hz), 129.3 (d,  $J_{\text{C-P}} = 12.0$  Hz), 128.4 (d,  $J_{\text{C-P}} = 11.3$  Hz), 118.6 (d,  $J_{\text{C-P}} = 0.75$  Hz), 111.4 (d,  $J_{\text{C-P}} = 2.3$  Hz) 81.7 (dd,  $J_{\text{C-P}} = 3.0$  Hz,  $J_{\text{C-F}} = 172.5$  Hz), 52.4, 48.1 (d,  $J_{\text{C-F}} = 19.5$  Hz), 44.8 (dd,  $J_{\text{C-F}} = 4.5$  Hz,  $J_{\text{C-P}} = 64.5$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  29.2 (s). **IR:** 3055, 2929, 2238, 1747, 1438, 1160, 1138, 1107, 863, 720, 567, 530, 428  $\text{cm}^{-1}$ . **HRMS (ES+) m/z:**  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{22}\text{FNO}_3\text{P}$ : 422.1316, found: 422.1320.

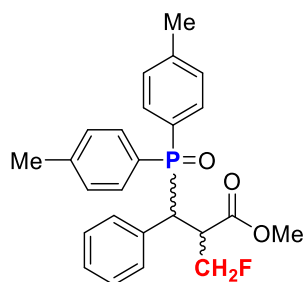


**Methyl 3-(bis(4-methoxyphenyl)phosphoryl)-2-(fluoromethyl)-3-phenylpropanoate**

**(10h):**

Following the general procedure (XI): **10h** was obtained as a mixture of two diastereoisomers, *dr* = 95:5; white solid, 70% yield (96 mg); **M.P.** 154 – 155 °C.

*syn*-**10h**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.86 – 7.80 (m, 2H), 7.29 – 7.10 (m, 7H), 7.05 – 6.99 (m, 2H), 6.69 – 6.64 (m, 2H), 4.68 – 4.34 (m, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 3.39 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -218.9 (td,  $J_{\text{F-H}} = 46.5$  Hz,  $J_{\text{F-H}} = 16.8$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.8 (dd,  $J_{\text{C-P}} = 3.8$  Hz,  $J_{\text{C-F}} = 12.8$  Hz), 162.7 (d,  $J_{\text{C-P}} = 3.0$  Hz), 161.8 (d,  $J_{\text{C-P}} = 3.0$  Hz), 134.7 (d,  $J_{\text{C-P}} = 5.3$  Hz), 132.9 (d,  $J_{\text{C-P}} = 9.8$  Hz), 132.8 (d,  $J_{\text{C-P}} = 10.5$  Hz), 130.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 128.3 (d,  $J_{\text{C-P}} = 1.5$  Hz), 127.5 (d,  $J_{\text{C-P}} = 2.3$  Hz), 123.7 (d,  $J_{\text{C-P}} = 99.8$  Hz), 123.4 (d,  $J_{\text{C-P}} = 108.0$  Hz), 114.5 (d,  $J_{\text{C-P}} = 12.0$  Hz), 113.6 (d,  $J_{\text{C-P}} = 12.8$  Hz), 82.3 (dd,  $J_{\text{C-P}} = 3.0$  Hz,  $J_{\text{C-F}} = 171.0$  Hz), 55.5, 55.3, 52.0, 48.5 (d,  $J_{\text{C-F}} = 20.3$  Hz), 45.6 (dd,  $J_{\text{C-F}} = 5.3$  Hz,  $J_{\text{C-P}} = 66.0$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.2 (s). IR: 3005, 2962, 2846, 1736, 1597, 1501, 1257, 1167, 1120, 827, 801, 704, 548, 450  $\text{cm}^{-1}$ . HRMS (ES+) *m/z*:  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{27}\text{FO}_5\text{P}$ : 457.1575, found: 457.1573.

**10i****Methyl 3-(di-*p*-tolylphosphoryl)-2-(fluoromethyl)-3-phenylpropanoate (10i):**

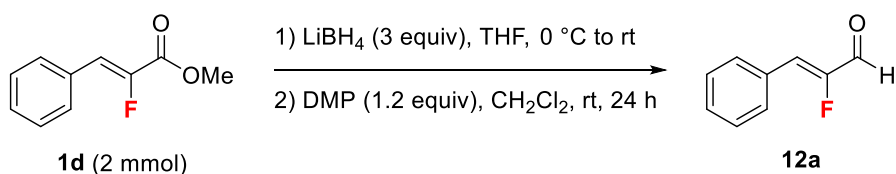
Following the general procedure (XI): **10i** was obtained as a mixture of two diastereoisomers, *dr* = 94:6; white solid, 53% yield (67 mg); **M.P.** 172 – 173 °C.

*syn*-**10i**:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88 – 7.82 (m, 2H), 7.38 – 7.32 (m, 3H), 7.30 – 7.24 (m, 3H), 7.16 – 7.12 (m, 3H), 7.01 – 6.97 (m, 2H), 4.67 – 4.36 (m, 2H), 3.97 – 3.72 (m, 2H), 3.42 (s, 3H), 2.44 (s, 3H), 2.23 (s, 3H).  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -219.0 (td,  $J_{\text{F-H}} = 46.4$  Hz,  $J_{\text{F-H}} = 16.9$  Hz).  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7 (dd,  $J_{\text{C-P}} = 3.8$  Hz,  $J_{\text{C-F}} = 13.5$  Hz), 142.7 (d,  $J_{\text{C-P}} = 3.0$  Hz), 141.6 (d,  $J_{\text{C-P}} = 3.0$  Hz), 135.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 131.0 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.9 (d,  $J_{\text{C-P}} = 9.0$  Hz), 130.1 (d,  $J_{\text{C-P}} = 5.3$  Hz), 129.7 (d,  $J_{\text{C-P}} =$

11.3 Hz), 129.5 (d,  $J_{C-P} = 96.8$  Hz), 128.8 (d,  $J_{C-P} = 104.3$  Hz), 128.8 (d,  $J_{C-P} = 12.8$  Hz), 128.3 (d,  $J_{C-P} = 2.3$  Hz), 127.5 (d,  $J_{C-P} = 2.3$  Hz), 82.3 (dd,  $J_{C-P} = 3.0$  Hz,  $J_{C-F} = 171.0$  Hz), 52.0, 48.5 (d,  $J_{C-F} = 20.3$  Hz), 45.2 (dd,  $J_{C-F} = 5.3$  Hz,  $J_{C-P} = 66.0$  Hz), 21.7 (d,  $J_{C-P} = 0.8$  Hz), 21.5 (d,  $J_{C-P} = 0.8$  Hz).  $^{31}\text{P}\{^1\text{H}\}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  30.3 (s). IR: 3036, 2950, 2920, 1741, 1602, 1456, 1170, 846, 807, 659, 537, 499, 474  $\text{cm}^{-1}$ . HRMS (ES+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{27}\text{FO}_3\text{P}$ : 425.1676, found: 425.1687.

### 3. Other Michael addition reactions on fluorinated substrates

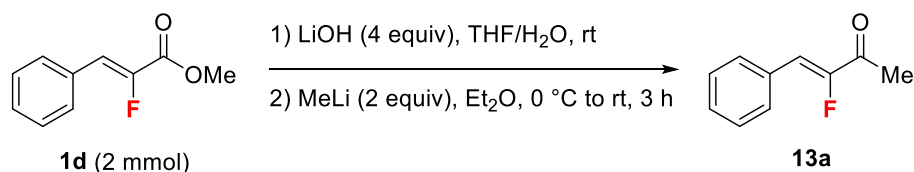
#### 3.1 Preparation of $\alpha$ -fluorinated enal **12a**



To an oven-dried flask equipped with a stir bar and flushed with argon, the dry THF (5 mL) solution of  $\alpha$ -fluoroacrylate **1d** (2 mmol) was added and cooled down to 0 °C. The lithium borohydride (6 mmol, 3 equiv) was added into the solution slowly, then the mixture was allowed to warm to room temperature and stir until no detection of **1d** by TLC. The resulting mixture was quenched by  $\text{NH}_4\text{Cl}_{(\text{aq})}$  and extracted with EtOAc (3×15 mL). The organic layers were combined, washed with brine, and dried over  $\text{Na}_2\text{SO}_4$ . Then, removed the solvents under the reduced pressure affording a white solid. The resulting solid without further purification was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) followed by adding the DMP (2372.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 24 h then quenched by adding  $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq})}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3×15 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  then concentrated under reduced pressure and purified by flash silica gel column chromatography (eluent: petroleum ether/EtOAc). **12a** was isolated as a white solid in 83% yield (249 mg) and its analytic data were in agreement with those reported in the literature.<sup>173</sup>

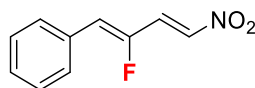
<sup>173</sup> Zemmouri, R.; Kajjout, M.; Castanet, Y.; Eddarir, S.; Rolando, C. *J. Org. Chem.* **2011**, *76*, 7691-7698.

### 3.2 Preparation of $\alpha$ -fluorinated enone **13a**



To an oven-dried flask were added  $\alpha$ -fluoroacrylate **1d** (2 mmol), LiOH (8 mmol, 4 equiv), THF/H<sub>2</sub>O (6 mL, v/v = 1/1). The reaction mixture was stirred at room temperature until no detection of **1d** by TLC, then adjusting the pH of the reaction mixture to  $\leq 7$  by adding 1 M HCl<sub>(aq)</sub>. The mixture was extracted EtOAc (3 $\times$ 15 mL), the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under the reduced pressure affording a white solid. This white solid without further purification was dissolved in dry Et<sub>2</sub>O (5 mL). Then, the MeLi (1.6 M in Et<sub>2</sub>O, 2 equiv) was added dropwise to the reaction mixture over 30 min at 0 °C. The reaction mixture was stirred at room temperature for an additional 2.5 h then quenched by adding 0.1 M HCl<sub>(aq)</sub> and the resulting mixture was extracted with Et<sub>2</sub>O (3 $\times$ 15 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> then concentrated under reduced pressure and purified by flash silica gel column chromatography (eluent: petroleum ether/EtOAc). **13a** was isolated as a yellow solid in 39% yield (128 mg) and its analytic data were in agreement with those reported in the literature.<sup>174</sup>

### 3.3 Byproduct C



Byproduct C

#### **((1Z,3E)-2-fluoro-4-nitrobuta-1,3-dien-1-yl)benzene (byproduct C):**

To an oven-dried tube were added (*Z*)-2-fluoro-3-phenylacrylaldehyde **12a** (0.3 mmol, 1 equiv), nitromethane (0.9 mmol, 3 equiv), benzoic acid (0.03 mmol, 10 mol%), (*S*)-2-(Diphenyl-trimethylsilyloxy-methyl)-pyrrolidine (Catalyst **b**) (0.03

<sup>174</sup> Patrick, T. B.; Agboka, T. Y.; Gorrell, K. J. *Fluorine Chem.* **2008**, *129*, 983-985.

mmol, 10 mol%) and methanol (0.5 mL). The tube was sealed and stirred at room temperature for 24 h. After removing solvents under reduced pressure, the residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc) to give the byproduct **C** as a yellow solid in 43% (25 mg). **M.P.** 139 – 140 °C.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.86 – 7.84 (m, 2H), 7.77 – 7.53 (m, 5H), 6.45 (d,  $J_{\text{H-F}}$  = 36.3 Hz, 1H). **<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  -117.2 (ddd,  $J_{\text{F-H}}$  = 36.3, 26.4, 1.5 Hz). **<sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  151.6 (d,  $J_{\text{C-F}}$  = 259.3 Hz), 137.0 (d,  $J_{\text{C-F}}$  = 2.3 Hz), 131.9 (d,  $J_{\text{C-F}}$  = 3.9 Hz), 131.3 (d,  $J_{\text{C-F}}$  = 21.3 Hz), 130.3 (d,  $J_{\text{C-F}}$  = 8.0 Hz), 130.1 (d,  $J_{\text{C-F}}$  = 2.6 Hz), 129.0, 122.2 (d,  $J_{\text{C-F}}$  = 7.7 Hz).

## 4. X-ray analysis

### 4.1 X-ray analysis of *syn-3k*

Crystal preparation: The *syn-3k* (15 mg) was added into a 2 mL glass vial and dissolved in CHCl<sub>3</sub> (0.3 mL), then *n*-hexane (1 mL) was added slowly into the vial to form two phases. The solvents were evaporated slowly at 3-5 °C and the crystal was then formed.

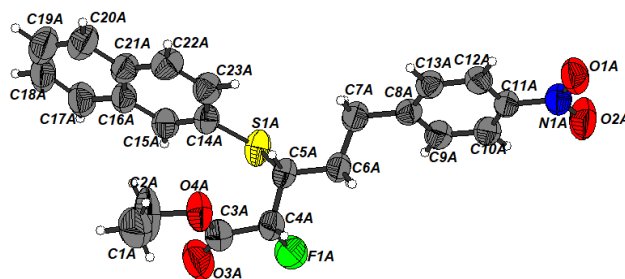
Crystallographic data: The crystal data of *syn-3k* are collected in **Table 24**.

**Table 24** Crystal data of *syn-3k*

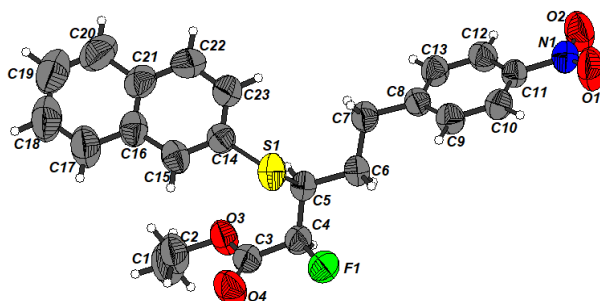
Chemical Formula	C <sub>23</sub> H <sub>22</sub> FNO <sub>4</sub> S
Molecular Weight / <i>g.mol</i> <sup>-1</sup>	427.5
Crystal System	Triclinic
Space Group	<i>P</i> -1
Z, Z' (asymmetric units per unit cell)	4, 2
<i>a</i> / Å	10.866(1)
<i>b</i> / Å	13.597(1)
<i>c</i> / Å	16.769(1)
$\alpha$ / °	103.930(2)
$\beta$ / °	103.924(2)
$\gamma$ / °	109.759(2)
<i>V</i> / Å <sup>3</sup>	2117.8(3)
<i>d</i> <sub>calc</sub> / <i>g.cm</i> <sup>-3</sup>	1.341

F(000) / $e^-$	896
Absorption coefficient $\mu$ (MoK $\alpha_1$ ) / $mm^{-1}$	0.191

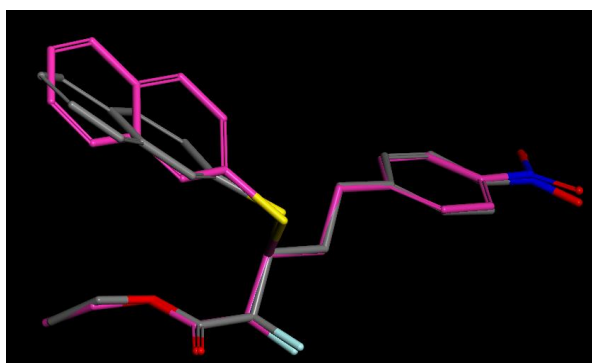
Structural description: The asymmetric unit is composed of two molecules of  $C_{23}H_{22}FNO_4S$  (**Figure 25**), labelled Mol A (**Figure 23**) and Mol O (**Figure 24**). These two molecules are the same diastereoisomer. They differ by the relative orientation of the naphthyl moiety. In the packing, two identical molecules (Mol A /Mol A or Mol O/Mol O) establish some  $\pi$ - $\pi$  interactions that leads to dimers (**Figure 26**). The cohesion between the dimers is ensured by vdW interactions and some long-range  $\pi$  interactions (**Figure 27**, **Figure 28**, and **Figure 29**).



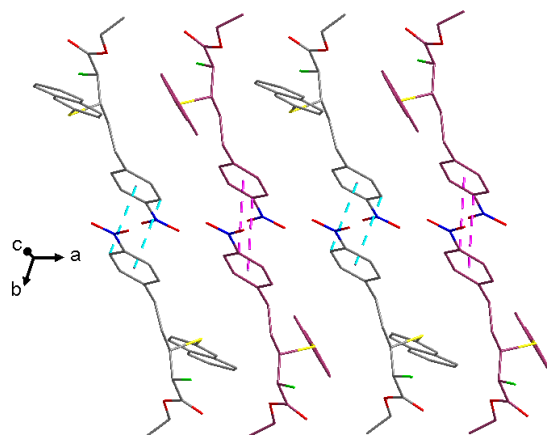
**Figure 23** Mol A from the asymmetric unit in thermal ellipsoidal representation



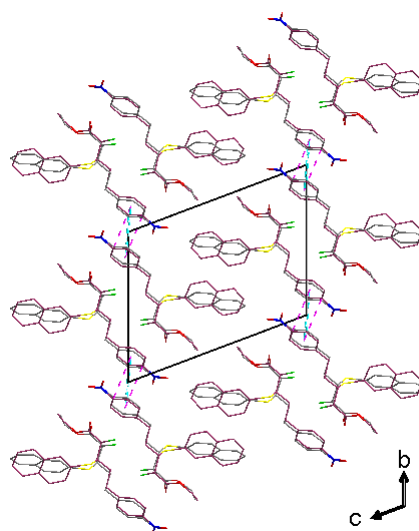
**Figure 24** Mol O from the asymmetric unit in thermal ellipsoidal representation



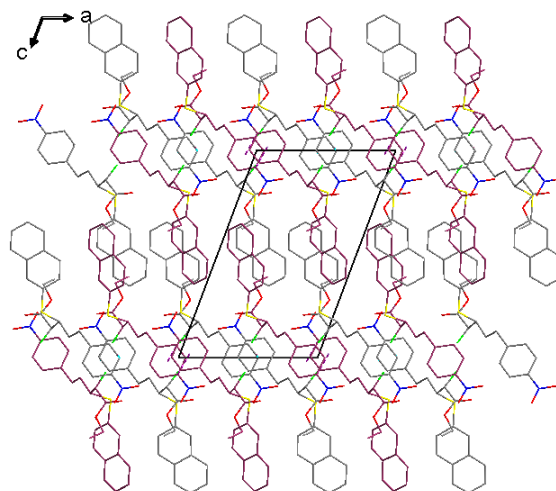
**Figure 25** Superimposition of Mol A (grey) and Mol O (purple)



**Figure 26** Dimers built from identical molecules (Mol A in grey, Mol O in purple), the  $\pi$ - $\pi$  interactions are presented in dashed lines.



**Figure 27** Projection along a



**Figure 28** Projection along b



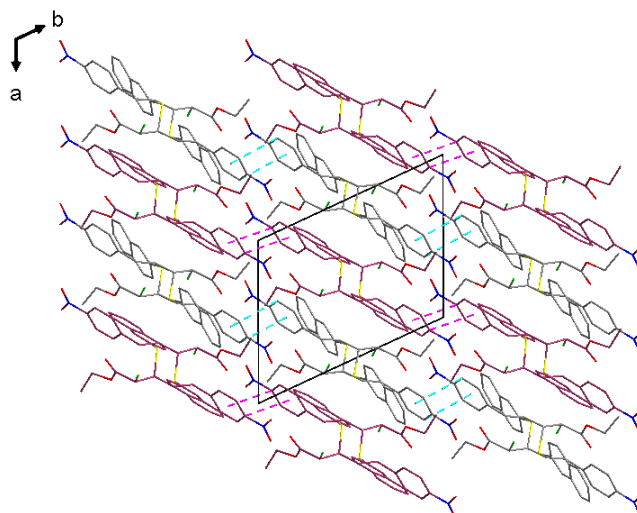


Figure 29 Projection along c

## 4.2 X-ray analysis of (2*S*, 3*S*)-3p

Crystal preparation: The (2*S*, 3*S*)-3p (22 mg) was added into a 2 mL glass vial and dissolved in CHCl<sub>3</sub> (0.5 mL), then *n*-hexane (1.2 mL) was added slowly into the vial to form two phases. The solvents were evaporated slowly at 3-5 °C and the crystal was then formed.

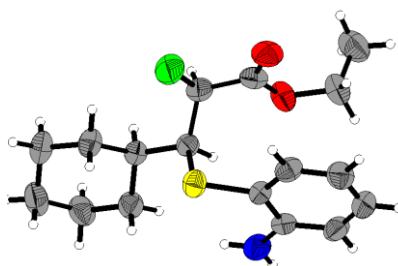
Crystallographic data: The crystal data of (2*S*, 3*S*)-3p are collected in Table 25.

Table 25 Crystal data of (2*S*, 3*S*)-3p

Chemical Formula	C <sub>17</sub> H <sub>24</sub> FNO <sub>2</sub> S
Molecular Weight / <i>g.mol</i> <sup>-1</sup>	325.43
Crystal System	orthorhombic
Space Group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Z, Z' (asymmetric units per unit cell)	4, 1
<i>a</i> / Å	8.1448(2)
<i>b</i> / Å	9.6689(2)
<i>c</i> / Å	21.6673(1)
α / °	65.785(2)
β / °	90
γ / °	90
<i>V</i> / Å <sup>3</sup>	90
<i>d</i> <sub>calc</sub> / <i>g.cm</i> <sup>-3</sup>	1.267

F(000) / $e^-$	696
Absorption coefficient $\mu$ (MoK $\alpha_1$ ) / $mm^{-1}$	0.206
Absolute structure parameter	0.05(9)

Structural description: The asymmetric unit is composed of one molecule of [C<sub>17</sub>H<sub>24</sub>FNO<sub>2</sub>S] (**Figure 30**). The stereogenic centers C7 and C14 are both in *S* absolute configuration. Molecules establish hydrogen bonds (**Table 26**, **Figure 31**) that generate molecular chains spreading along a axis. The cohesion between these molecular chains is ensured by vdW interactions. (**Figure 32**, **Figure 33**).

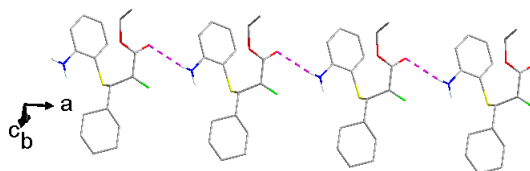


**Figure 30** Asymmetric unit in thermal ellipsoidal representation.

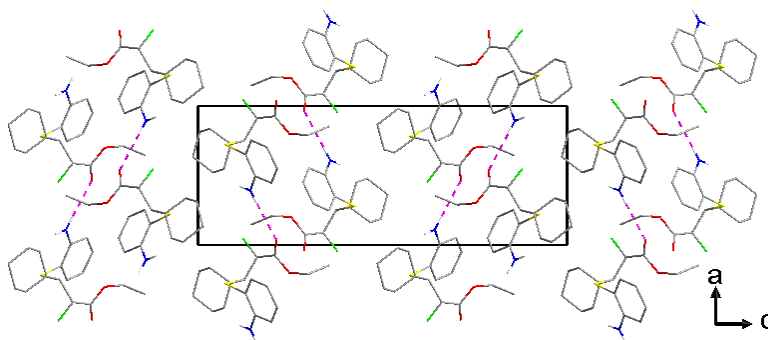
**Table 26** Hydrogen bond table

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...O(1)#1	0.86	2.45	3.284(3)	164.6

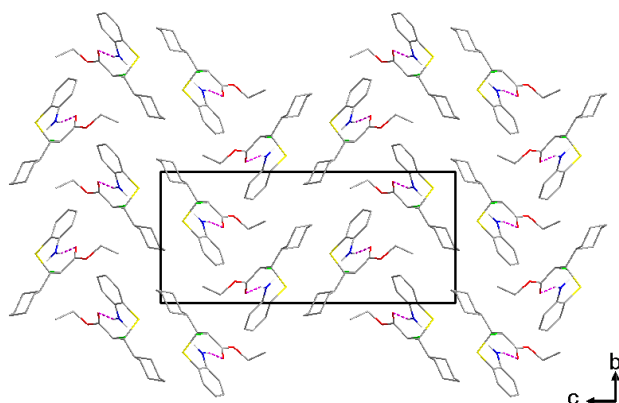
Symmetry transformation used to generate equivalent atoms: #1  $x-1, y, z$



**Figure 31** Molecular bond chain, the hydrogen bonds are displayed in dashed pink lines



**Figure 32** Projection along b axis



**Figure 33** Projection along a axis

### 4.3 X-ray analysis of *anti-8j*

Crystal preparation: The *anti-8j* (14 mg) was added into a 2 mL glass vial and dissolved in  $\text{CH}_2\text{Cl}_2$  (0.5 mL). The solvent was evaporated slowly at 3-5 °C and the crystal was then formed.

Crystallographic data: The crystal data of *anti-8j* are collected in **Table 27**.

**Table 27** Crystal data of *anti-8j*

Chemical Formula	$\text{C}_{24}\text{H}_{19}\text{F}_6\text{O}_3\text{P}$
Molecular Weight / $\text{g.mol}^{-1}$	500.36
Crystal System	Monoclinic
Space Group	$P2_1/a$
Z, Z' (asymmetric units per unit cell)	4,2
a / Å	11.374(3)
b / Å	13.663(3)
c / Å	14.832(4)
$\alpha / ^\circ$	90
$\beta / ^\circ$	99.268(5)
$\gamma / ^\circ$	90
V / Å <sup>3</sup>	2274.9(1)
$d_{\text{calc}} / \text{g.cm}^{-3}$	1.461
F(000) / e <sup>-</sup>	1024
Absorption coefficient $\mu (\text{MoK}\alpha_1) / \text{mm}^{-1}$	0.194

Structural description: The asymmetric unit is composed of one molecule of

$C_{24}H_{19}F_6O_3P$  (Figure 34, Figure 35).

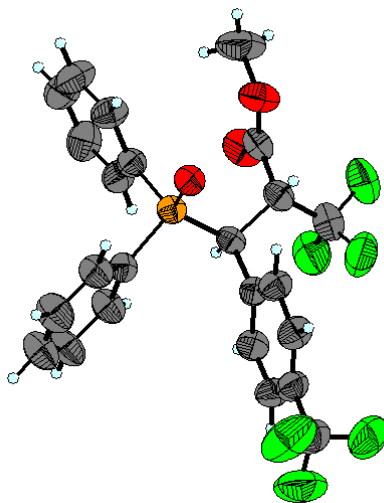


Figure 34 Asymmetric unit in thermal ellipsoidal representation

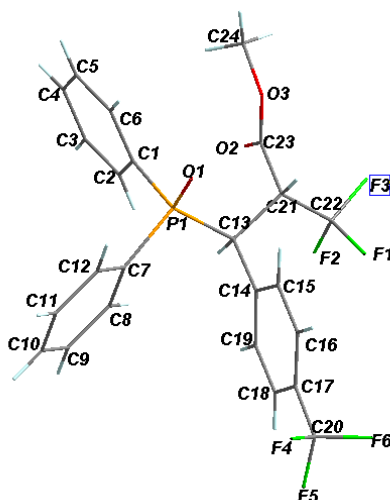


Figure 35 Asymmetric unit with atoms labels

#### 4.4 X-ray analysis of *syn-10a*

Crystal preparation: The *syn-10a* (17 mg) was added into a 2 mL glass vial and dissolved in  $CH_2Cl_2$  (0.5 mL). The solvent was allowed to evaporate at room temperature and the crystal was then formed.

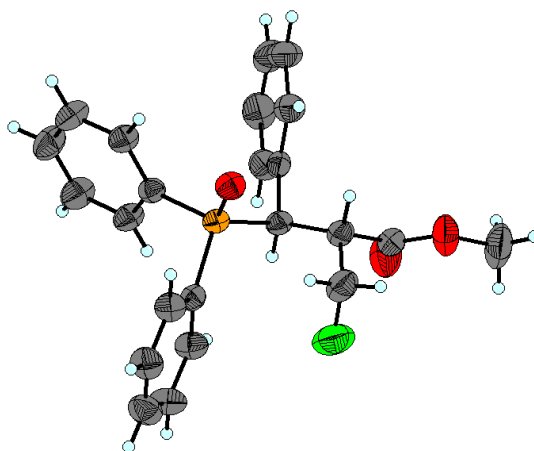
Crystallographic data: The crystal data of *syn-10a* are collected in **Table 28**.

Table 28 Crystal data of *syn-10a*

Chemical Formula	$C_{23}H_{21}FO_3P$
Molecular Weight / $g.mol^{-1}$	395.37

Crystal System	Orthorhombic
Space Group	<i>Pbca</i>
Z, Z' (asymmetric units per unit cell)	8,1
a / Å	11.6118(2)
b / Å	17.990(3)
c / Å	19.585(3)
$\alpha$ / °	90
$\beta$ / °	90
$\gamma$ / °	90
V / Å <sup>3</sup>	4091.3(1)
d <sub>calc</sub> / g.cm <sup>-3</sup>	1.287
F(000) / e <sup>-</sup>	1664
Absorption coefficient $\mu$ (MoK $\alpha_1$ ) / mm <sup>-1</sup>	0.164

Structural description: The asymmetric unit is composed of one molecule of C<sub>23</sub>H<sub>21</sub>FO<sub>3</sub>P (**Figure 36**, **Figure 37**). The compound crystallized in a centrosymmetric space group so that both enantiomers are present.



**Figure 36** Asymmetric unit in thermal ellipsoidal representation

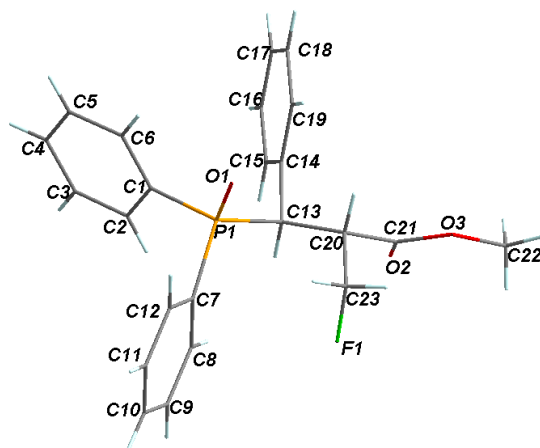


Figure 37 Asymmetric unit with labels

#### 4.5 X-ray analysis of (1Z, 3E)-byproduct C

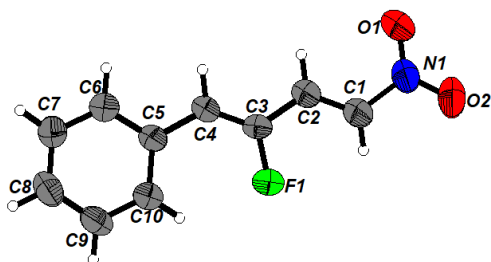
Crystal preparation: The (1Z, 3E)-byproduct **C** (15 mg) was added into a standard NMR tube and dissolved in  $\text{CDCl}_3$  (0.5 mL). The solvent was allowed to evaporate at room temperature and the crystal was then formed.

Crystallographic data: The crystal data of (1Z, 3E)-byproduct **C** are collected in **Table 29**.

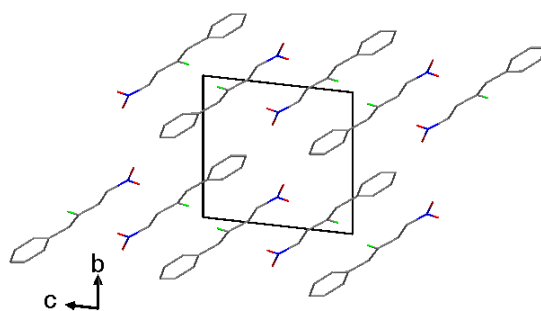
Table 29 Crystal data of (1Z, 3E)-byproduct C

Chemical Formula	$\text{C}_{10}\text{H}_8\text{FNO}_2$
Molecular Weight / $\text{g.mol}^{-1}$	193.17
Crystal System	Triclinic
Space Group	P-1 ( $n^{\circ}2$ )
Z, Z' (asymmetric units per unit cell)	2, 1
a / Å	5.845(4)
b / Å	8.682(5)
c / Å	9.308(6)
$\alpha$ / °	83.449(1)
$\beta$ / °	83.321(1)
$\gamma$ / °	88.294(1)
V / Å <sup>3</sup>	466.0(5)
$d_{\text{calc}}$ / $\text{g.cm}^{-3}$	1.377
F(000) / e <sup>-</sup>	200
Absorption coefficient $\mu$ (MoK $\alpha_1$ ) / $\text{mm}^{-1}$	0.110

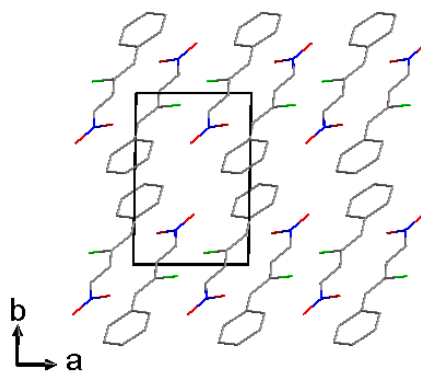
Structural description: The asymmetric unit is composed of one molecule of  $C_{10}H_8FNO_2$  (**Figure 38**).



**Figure 38** Asymmetric unit in thermal ellipsoidal representation



**Figure 39** Projection along a



**Figure 40** Projection along c

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