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Xiaoyang Dai

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THESE

Présentée à :

L'Institut National des Sciences Appliquées de Rouen

En vue de l'obtention du grade de :

Docteur en « Chimie Organique »

Par

Xiaoyang DAI

Hydride Transfer Reactions of Trifluoromethylated Allylic Alcohols and Ketimines

&

Nucleophilic Trifluoromethylthiolation of Morita-Baylis-Hillman Carbonates

Date de soutenance

12 Décembre 2014

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Acknowledgements

First and foremost, I would like to express my sincere appreciation to the juries of my PhD defense: Dr. Thierry Billard, Director of research CNRS in University of Lyon 1; Dr. Barbara Mohar, Director of research in the National Institute of Chemistry, Ljubljana, and Dr. Christine Baudequin, lecturer in University of Rouen.

I would like to give my deep gratitude to my supervisor Dr. Dominique Cahard, research director in CNRS, who always has plenty of sparkling ideas in chemistry. He provided me many useful suggestions and encouraged me to think around and go ahead when there were difficulties in my Ph.D. subject. Without his incredible patience and enthusiasm, I would have given up the pursuit of my thesis work.

I would like to thank the Chinese Scholarship Council who gave me a financial support for my whole Ph.D period.

I am also grateful to my colleagues and all the members of the fluorine group in IRCOF who helped me a lot with the chemical experiments. Besides, my dear friend Dr. Sophie Letort always came to help me in volunteer to adapt to the life in France and bring laughter; my big brother Dr. Vincent Bizet gave me lots of advices in the hydride transfer part of work; Dr. Natalie Fresneau, who worked with me around two years in the lab, taught me french frequently. With her company, I had a happy time in the first two years of my Ph.D.

My deep gratitude extends to my family, especially my husband Haibin Zhu who was always ready to give me a warm hug and told me that I was not alone. Thanks to their unconditional supports, I had the motivation to finish my Ph.D work without any delay.

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Abbreviations and acronyms

Ac	Acetyl
aq.	Aqueous
bda	<i>trans</i> -Benzylideneacetone
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyle
Boc	<i>tert</i> -Butyloxycarbonyl
CFC	Chlorofluorocarbon
cod	Cycloocta-1,5-diene
cot	Cyclooctatetraene
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
(DHQD) ₂ PHAL	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dmpy	4, 4'-Dimethoxybipyridine
DPEN	1,2-Diphenyl-1,2-ethylenediamine
EA	Ethyl acetate
<i>ee</i>	Enantiomeric excess
hr	Hour
HMRS	High resolution mass spectrometry
Min	Minute
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
PMP	<i>para</i> -Methoxyphenyl

PTFE	Polytetrafluoroethylene
<i>p</i> -TSA	<i>para</i> -Toluenesulfonyl acid
r.t.	Room temperature
Selectfluor™	1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane ditetrafluoroborate
T	Temperature
t	Time
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TLC	Thin-layer chromatography

1. General introduction

Fluorine, the so-called “savage beast among the elements” in the Nobel Prize award ceremony speech in 1906 by Pr. P. Klason,¹ is derived from the Latin word “fluo” meaning “flow” and is linked with the major mineral source of fluorine, fluorite (also called fluorspar), because fluorite, first described by Georgius Agricola in 1529, was used to lower the melting points of metal ores during smelting.

1.1 Brief history of fluorine

The discovery of fluorine is one of the most significant issues in the field of chemistry in the 19th century. In 1764, A. S. Marggraf first prepared hydrofluoric acid from fluorspar with sulfuric acid;² however, due to the toxic and corrosive character of hydrofluoric acid and particularly the high redox potential of fluorine itself, the real development of organofluorine chemistry was after 100 years when Henri Moissan first synthesized elemental fluorine in 1886. This access to fluorine from electrolysis of a solution of KHF_2 in liquid HF using platinum/iridium electrodes at low temperature won him a Nobel Prize in 1906.³

From late 1920s, fluorine compounds chlorofluorocarbon (CFC) refrigerants also called “Freon” were greatly used in industry. In 1930, General Motors (GM) and Dupont companies won great commercial success of Freon-12 (CCl_2F_2) contributing to the market of refrigerators.⁴

Polytetrafluoroethylene (PTFE: $(\text{C}_2\text{F}_4)_n$) which is known to be resistant to corrosion and stable at high temperature is widely used as coating for non-stick cookwares, containers and pipeworks and also as lubricant for machinery. The story goes that this synthetic fluoropolymer was accidentally discovered by R. J. Plunkett in 1938. Later, Dupont company registered the well-known trademark of PTFE, TeflonTM.

¹ *Nobel Lectures, Chemistry 1901-1921*, Elsevier Publishing Company, Amsterdam, **1966**.

² P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

³ a) H. Moissan, *C. R. Acad. Sci.* **1886**, *102*, 1543-1544; b) H. Moissan, *C. R. Acad. Sci.* **1886**, *103*, 202-205; c) H. Moissan, *C. R. Acad. Sci.* **1886**, *103*, 256-258.

⁴ A. J. Elliott, *Organofluorine Chemistry: Principles and Commercial Applications*, R. E. Banks, B. E. Smart, J. C. Tatlow, eds., Plenum Press, New York, **1994**, 145-157.

In 1941, the Manhattan Project accelerated the large scale production of fluorine compounds particularly the corrosive fluoroinorganic gas UF_6 , which was found to be efficient for the separation of the isotope ^{235}U from the heavier ^{238}U .⁵ This also stimulated the development of highly resistant fluoroorganic materials for handling the corrosive fluoroinorganic compounds. After the World War II, in the need for the defense program of the Cold War, organofluorine chemistry in military and special materials was still soaringly developed. From 1950s, organofluorinated pharmaceuticals and agrochemicals began to walk into people's daily life.⁴

However, with the prediction of the ozone-depleting effect of CFC in 1974⁶ and the appearance of ozone hole over the Antarctic in 1980, the prohibition of these refrigerants was proposed in the Montreal protocol in 1987. Thus, new fluorine-containing chemical compounds i.e. hydrofluorocarbons (HFC) and fluorinated ethers were taken into account.

Moreover, the application of fluorinated chemistry in the electronic industry has also emerged from 1990s; for example, the fluorinated liquid crystals for active matrix liquid crystal displays (AM-LCD) and the fluorinated photoresists for the manufacture of integrated electronic circuits.

Since the discovery of fluorine, this mysterious chemistry has gradually shown the great power and irresistible charm to people. Organofluorine chemistry has permeated tremendously into pharmaceuticals, agrochemicals, materials, aerospace, electronics, nuclear industry and our daily lives in recent years.

1.2 Fluorine on earth

Although fluorine is the 24th most abundant element in universe and the 13th most common element in the earth's crust (0.027% by weight), it is almost absent from the natural products and the fluoroorganic metabolites are rare to be identified in the biosphere. The most obvious reason is that the three richest natural sources of fluorine, the minerals fluorospar (CaF_2), fluorapatite ($\text{Ca}_5(\text{PO}_4)_3\text{F}$) and cryolite (Na_3AlF_6) are not soluble under aqueous biological conditions. In biochemistry, the high oxidation potential of fluorine (-3.06 V, much

⁵ R. Rhodes, *Dark Sun: The Making of the Hydrogen Bomb*, Simon and Schuster, New York, 1995.

⁶ M. J. Molina, F. S. Rowland, *Nature* **1974**, 249, 810-812.

higher than the other halogens) hinders the formation of intermediate hypohalous species and thus blocked enzymatic halogenation. Besides, the high hydration energy of fluorine (117 kcal/mol) makes it a poor nucleophile in aqueous biological system where halide anion is required in enzymatic incorporation of halogens through a nucleophilic opening of epoxide intermediates. Thus, organofluorine chemistry has attracted many chemists who have focussed on the synthesis and application of organofluorinated compounds.⁷

1.3 The properties of fluorine and fluorine effects

Despite the almost absence of fluorinated molecules in nature, fluorine has become a key element in drug design process. The fast-growing number of fluorine-containing compounds is attributed to the unique properties of fluorine atom and fluorine effects, which offer interesting behaviour to fluorinated organic compounds.

Steric effect: Fluorine, the 9th element in periodic table, has the smallest van der Waals radius after that of hydrogen and similar to that of oxygen ($r_{\text{H}} = 1.20 \text{ \AA}$, $r_{\text{O}} = 1.52 \text{ \AA}$, $r_{\text{F}} = 1.47 \text{ \AA}$). Therefore, it could be incorporated into organic compounds as a substitution for hydrogen atoms or hydroxyl groups. Fluoroalkanes including the difluoromethylene group and fluoroalkenes are regarded as isosteric or isoelectronic of several groups (**Figure 1-1**).⁸ This so-called “mimic effect” makes it possible to change the electronic environment with minimal steric alteration in physiologically active compounds.

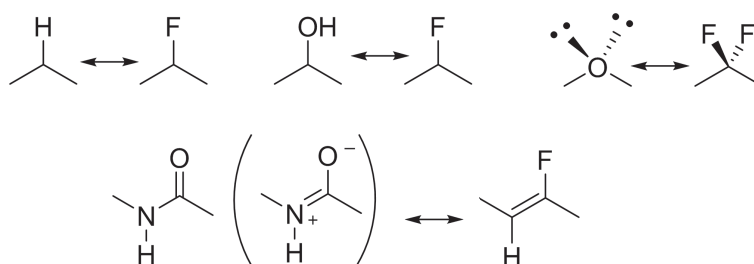


Figure 1-1

Electronic effect: Fluorine has the highest electronegativity among all the elements in a value of 4.0 on the Pauling scale and has a strong tendency to draw its three lone pairs

⁷ J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506.

⁸ K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.* **2004**, *104*, 1-16.

towards the nucleus.⁹ Thus, C-F bond is very short, strong, highly polarized and fluorine atom bears a partial negative charge. Besides, due to the unreactive electron pairs of fluorine, it becomes a very weak hydrogen bond acceptor.¹⁰ The introduction of fluorine atom(s) into organic molecules could greatly modify the whole electron cloud distribution; make a great influence on dipole moment, pKa, and conformation of molecules. The modification of pKa could have a strong effect on binding affinity and pharmacokinetic properties in pharmaceuticals.¹¹ The absorption could be changed after the perturbation of pKa and consequently affect the bioavailability.

Bond energy: The carbon-fluorine bond energy (105 kcal/mol) is much greater than carbon-hydrogen one (98 kcal/mol), which provides a strong resistance to metabolism.

Electrostatic interaction: The short, strong and highly polarized C-F bond could impact on the conformation of molecules through electrostatic (dipole-dipole and charge-dipole) interactions, which contribute to the increased binding affinity of fluorinated compounds. For example, 4-fluorophenyl substitution of thrombin inhibitors gives an outstanding activity in a series of thrombin inhibitors because the C-F bond has a strong interaction with H-C unit of Asn₉₈ and C=O moiety in D-pocket. These two dipolar interactions contribute to the increase in potency among all the fluorinated and chlorinated inhibitors (**Figure 1-2**).¹¹

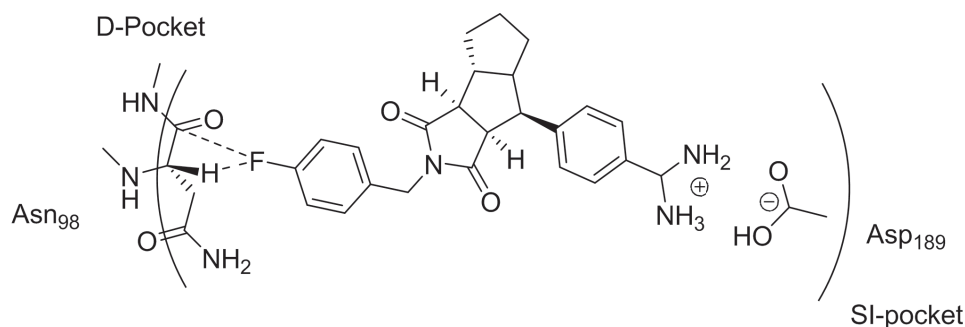


Figure 1-2

Stereoelectronic effect: Another significant effect originated from the C-F bond is the hyperconjugation effect. The well-studied example is 1,2-difluoroethane. Between two possible *gauche* and *anti* conformers, the preferential *gauche* conformation of 1,2-difluoroethane is due to the vacant low-energy $\sigma^*_{\text{C-F}}$ antibonding orbital associated with

⁹ L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, No. 38.

¹⁰ D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308-319.

¹¹ S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330.

C-F bond that is aligned with adjacent $\sigma_{\text{C-H}}$ orbital which feeds electron density into the σ^* orbital (**Figure 1-3**).⁹

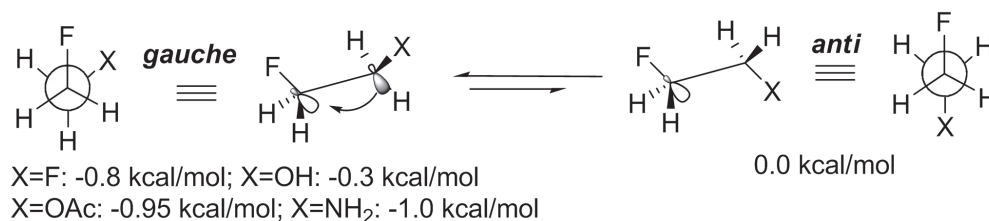


Figure 1-3

When this stabilizing hyperconjugation ($\sigma \rightarrow \sigma^*$) occurs, the energy of the *gauche* conformer becomes lower, and thus the *gauche* conformer is preferred despite dipole or steric repulsion of fluorine atoms. When a fluorine atom is replaced by another electronegative substituent, the *gauche* effect is also observed. These conformational effects help optimize the properties of functional fluorinated compounds through selective fluorination.¹²

Lipophilic effect: Lipophilicity (π) is a key factor in drug design. It is expressed by $\log P$ (a partition coefficient between octanol and water) and $\log D$ (a distribution coefficient between octanol and water at a given pH, typically 7.4).

$$\pi = \log P - \log D$$

The increase of lipophilicity could improve fat solubility. Thus, it aids the partition of molecules into membranes and enhances bioavailability. On the other side, excess lipophilicity ($\log P > 5$) will cause poor solubility and result in incomplete absorption.

Moreover, monofluorination or trifluoromethylation of saturated alkyl substituents usually decreases lipophilicity due to the strong electronegativity of fluorine atom. On the contrary, aromatic fluorination and fluorination adjacent to atoms with π bonds give increased lipophilicity because of the overlap between 2s or 2p orbitals of fluorine with the corresponding orbitals of carbon rendering the C-F bond quite non-polarizable.¹¹ Therefore, it is a big challenge for chemists to find the right balance between a suitable lipophilicity and a certain polarity of molecules.

Despite the fluorine effects listed above, it is still rather subtle and difficult to predict the influence of fluorine on biological activity in pharmaceuticals. The modulation of pKa, conformation, lipophilicity, and metabolic stability after selective fluorination should be

¹² D. Cahard, V. Bizet, *Chem. Soc. Rev.* **2014**, *43*, 135-147.

comprehensively considered during the optimization of pharmaceutical and agrochemical products. Hence, there are great needs of efficient new molecules which requires the stimulatingly development in fluorination methodology.

1.4 Fluorinated pharmaceuticals

Before 1954, the application of fluorine was limited to military and special materials until the discovery of the first fluorinated pharmaceutical product fludrocortisone possessing a remarkable glucocorticoid activity.¹³ Later, in 1957, another fluorinated drug, 5-fluorouracil (5-FU), was found to serve as an antimetabolite and a potent inhibitor of thymidylate synthase.¹⁴ These two great breakthroughs made fluorine walk into medicinal chemistry and biological research. Besides, they provided an orientation of the drug design, which led to the rapid development of fluorinated drugs in the coming several decades (Figure 1-4).¹⁵

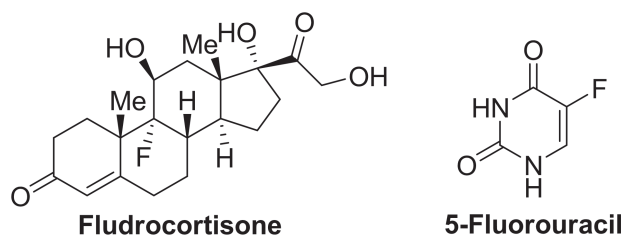


Figure 1-4

It is universally acknowledged that the introduction of fluorine atom(s) into organic molecules could cause profound effects in their physicochemical and biological properties. Thus, it is not surprising that in 1970, only about 2% of the drugs contained fluorine while nowadays the number has grown to 25% and around one-third of the top-performing drugs contain at least one fluorine atom in their molecular structures. Fluorine has been regarded as the second best heteroatom after nitrogen. The main recent progress concerns fluorinated nucleosides, alkaloids, macrolides, steroids, amino acids, and prostaglandins.^{15a}

Lots of fluorinated drugs have emerged in the market in current years, including 1)

¹³ a) J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1953**, 75, 2273-2273; b) J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, 76, 1455-1456.

¹⁴ C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Plevin, J. Scheiner, *Nature* **1957**, 179, 663-666.

¹⁵ a) J. P. Bégué, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, 127, 992-1012; b) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, 127, 303-319; c) K. L. Kirk, *J. Fluorine Chem.* **2006**, 127, 1013-1029.

anticancer drugs such as fulvestrant (faslodex), sorafenib (nexavar); 2) drugs acting on the central nervous system such as aprepitant (emend); 3) drugs affecting the cardiovascular system such as ezetimibe (zetia); 4) drugs for infectious diseases such as voriconazole (vfenid) (**Figure 1-5**).

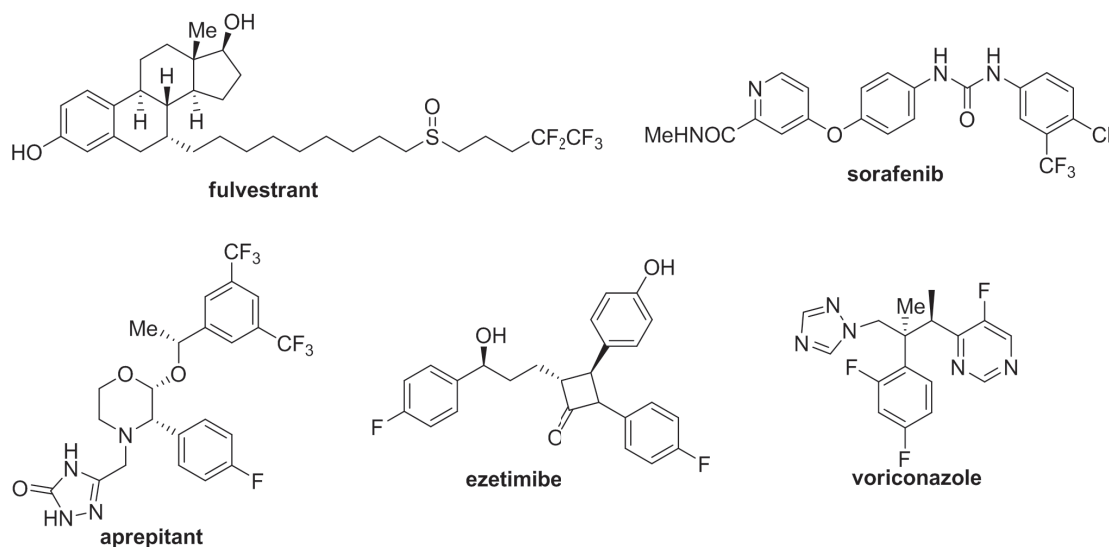


Figure 1-5

Fluorinated molecules with ^{18}F are widely used as radiotracers for positron emission tomography (PET) in cancer diagnosis by mapping functional processes *in vivo*.¹⁶ Since the radionuclide ^{18}F tracer bears a 110 minutes' half-life, much longer than that of other radionuclides, PET imaging with ^{18}F -containing radiotracers rapidly develops in medical chemistry. PET scans could show biological process and offer metabolic information. The most frequently used radiopharmaceutical for PET is [^{18}F]FDG (2-deoxy-2- [^{18}F]fluoro-D-glucose) in oncology, neurology and cardiology by reflecting glucose metabolism *in vivo* (**Figure 1-6**). Due to the absence of a hydroxy group at C2 position, it could not undergo glycolysis before ^{18}F decays and keeps trapped in the tissues.¹¹

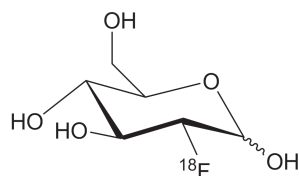


Figure 1-6

¹⁶ a) M. E. Phelps, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9226-9233; b) R. Bolton, *J. Labelled Compd. Radiopharm.* **2002**, *45*, 485-528; c) S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501- 1516; d) B. Halford, *Chemical & Engineering News*, **2014**, *92*, 33-35.

In recent years, many new methods have emerged for the incorporation of ^{18}F .^{16d,17} For nucleophilic fluorination, the nucleophilic [^{18}F] fluoride sources (K^{18}F , [^{18}F] TBAF) are used as the most practical sources of ^{18}F for the reactions of alkyl or aryl electrophiles bearing appropriate leaving groups (OTf, OCOOR, Me_3N^+). In electrophilic radiofluorination, several ^{18}F -labeled fluorinating reagents have been synthesized from [^{18}F] fluorine gas including [^{18}F] acetyl hypofluorite,¹⁸ [^{18}F] xenon difluoride,¹⁹ [^{18}F] *N*-fluoropyridinium salts,²⁰ and [^{18}F] Selectfluor salts²¹. Besides, radical fluorometalation has been developed for selective fluorination.²²

1.5 Synthesis of fluorinated compounds

Although there have been continuous advances over the last decade, the demand of new synthetic methodologies for fluorinated compounds is still high, particularly for the chemo-, regio- and stereoselective introduction of fluorine into organic compounds.

1.5.1 Direct fluorination

Direct fluorination is a very efficient way to synthesize fluorinated compounds, but it remains quite challenging particularly in the formation of C-F bond due to the highly electronegative nature of fluorine and great hydration energy of fluoride. Since fluorine gas and hydrogen fluoride are very toxic, corrosive and rather indiscriminate, many alternate fluorinating agents have been considered as fluorine sources to involve in carbon-fluorine bond forming reactions.

The fluorinating agents could be classified into nucleophilic and electrophilic species for the construction of fluorinated aromatic carbon centers and sp^3 carbon centers.

There are many well-known nucleophilic fluorinating reagents such as $(\text{HF})_n$ -Pyridine

¹⁷ T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264.

¹⁸ a) R. Chirakal, G. Firnau, J. Couse, E. S. Garnett, *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 651-653; b) M. Namavari, A. Bishop, N. Satyamurthy, G. Bida, J. R. Barrio, *Appl. Radiat. Isot.* **1992**, *43*, 989-996.

¹⁹ N. Vasdev, B. E. Pointner, R. Chirakal, G. J. Schrobilgen, *J. Am. Chem. Soc.* **2002**, *124*, 12863-12868.

²⁰ F. Oberdorfer, E. Hofmann, W. Maier-Borst, *J. Labelled Compd. Radiopharm.* **1988**, *25*, 999-1006.

²¹ H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem.* **2010**, *122*, 6973-6976; *Angew. Chem. Int. Ed.* **2010**, *49*, 6821-6824.

²² a) P. Di Raddo, M. Diksic, D. Jolly, *J. Chem. Soc. Chem. Commun.* **1984**, 159-160; b) M. Speranza, C. Y. Shiue, A. P. Wolf, D. S. Wilbur, G. Angelini, *J. Fluorine Chem.* **1985**, *30*, 97-107; c) N. Satyamurthy, G. T. Bida, M. E. Phelps, J. R. Barrio, *Appl. Radiat. Isot.* **1990**, *41*, 733-738.

(Olah's reagent), DAST, DEOXOFLUOR, XtalFluorsTM, FluoleadTM, MF (M = Cs, Rb, K, Na, Li), TBAT, TBAF, and TMAF (**Figure 1-7**).

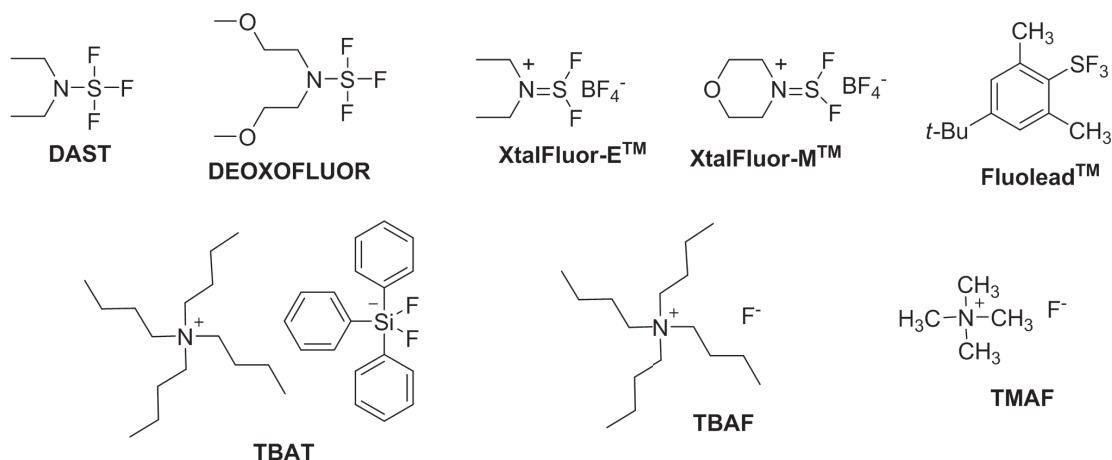


Figure 1-7

The relatively low-cost alkali-metal fluoride salts are quite desirable nucleophilic fluorinated reagents but they are poorly soluble in organic solvents. It is worth mentioning that TBAT and TMAF are commonly used soluble fluoride sources.

Most electrophilic fluorinating reagents are derived from fluorine gas such as XeF₂, and most commonly used electrophilic N-F reagents like F-TEDA-BF₄ (SelectfluorTM), NFSI and NFOBS (**Figure 1-8**).

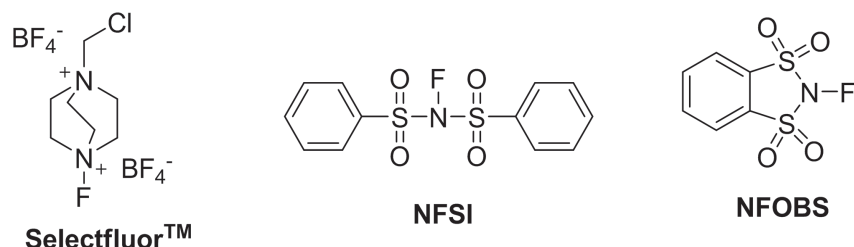


Figure 1-8

These reagents are effective in the fluorination of aromatics, alkenes, carbanions, and ketone enolates. The reactivity is enhanced by decreasing the reaction density on nitrogen by the fluorosulfonyl groups in NFSI and NFOBS. Selectfluor has similar reactivity but poor to moderate solubility in organic solvents.

1.5.2 Direct trifluoromethylation

The trifluoromethyl (CF₃) group is an electron-withdrawing substituent which helps to increase the lipophilicity of aromatic molecules. It is very interesting to develop methods for

the controlled introduction of CF₃ group into small molecules to broaden the substrate scope.¹⁷

Similar to direct fluorination, trifluoromethylation could also be divided into nucleophilic and electrophilic, including radical trifluoromethylation.

Nucleophilic trifluoromethylation with trifluoromethyl anion (CF₃⁻) is challenging due to the fluoride elimination. Thus, it is of great importance for the selection of a pronucleophile. Trimethylsilyltrifluoromethane (TMSCF₃), also called Ruppert-Prakash reagent, is a commonly employed pronucleophile of the trifluoromethyl anion despite its moisture sensitivity.²³ This kind of trifluoromethylorganosilane could be desilylated with fluoride to afford the active species trifluoromethyl anion.

The most widely used electrophilic trifluoromethylating reagents are the crystalline reagents such as *S*-(trifluoromethyl)dibenzothiophenium salts developed by Umemoto,²⁴ *S*-(trifluoromethyl)diarylsulfonium salts prepared by Yagupolskii,²⁵ Shreeve and Magnier,²⁶ hypervalent iodine reagents also called Togni reagents²⁷ and fluorinated Johnson's type reagent reported by Shibata (Figure 1-9).²⁸

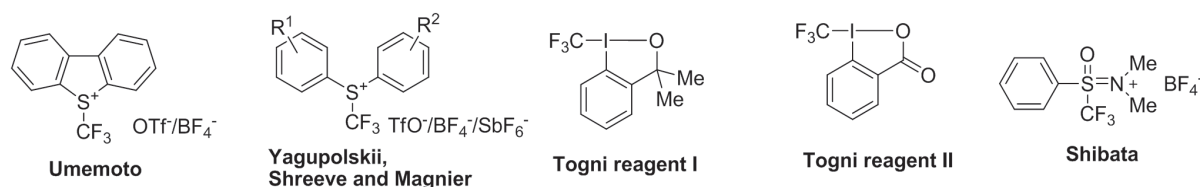


Figure 1-9

An alternative way for electrophilic trifluoromethylation is to use nucleophilic trifluoromethylating reagents in conjunction with oxidants (oxygen,²⁹ AgOTf,³⁰ Cu(I)X,³¹)

²³ a) I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.* **1984**, 25, 2195-2198; b) H. Urata, T. Fuchikami, *Tetrahedron Lett.* **1991**, 32, 91-94; c) G. G. Dubinina, H. Furutachi, D. A. Vivic, *J. Am. Chem. Soc.* **2008**, 130, 8600-8601; d) G. G. Dubinina, J. Ogikubo, D. A. Vivic, *Organometallics* **2008**, 27, 6233-6235; e) H. Kawai, K. Tachi, E. Tokunaga, M. Shiro, N. Shibata, *Org. Lett.* **2010**, 12, 5104-5107; f) G. K. S. Prakash, R. Mogi, G. A. Olah, *Org. Lett.* **2006**, 8, 3589-3592; g) S. Mizuta, N. Shibata, M. Hibino, S. Nagano, S. Nakamura, T. Toru, *Tetrahedron* **2007**, 63, 8521-8528; h) H. Kawai, A. Kusuda, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem.* **2009**, 121, 6442-6445; *Angew. Chem. Int. Ed.* **2009**, 48, 6324-6327.

²⁴ a) T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, 31, 3579-3582; b) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, 115, 2156-2164; c) T. Umemoto, *Chem. Rev.* **1996**, 96, 1757-1778.

²⁵ L. M. Yagupolskii, N. V. Kondratenko, G. N. Timofeeva, *J. Org. Chem. USSR* **1984**, 20, 103-106.

²⁶ a) J.-J. Yang, R. I. Kirchmeier, J. M. Shreeve, *J. Org. Chem.* **1998**, 63, 2656-2660; b) E. Magnier, J.-C. Blazejewski, M. Tordeux, C. Wakselman, *Angew. Chem. Int. Ed.* **2006**, 45, 1279-1282; c) Y. Macé, B. Raymondeau, C. Pradet, J.-C. Blazejewski, E. Magnier, *Eur. J. Org. Chem.* **2009**, 1390-1397.

²⁷ a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, 12, 2579-2586; b) I. Kieltch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, 46, 754-757.

²⁸ a) S. Noritake, N. Shibata, S. Nakamura, T. Toru, *Eur. J. Org. Chem.* **2008**, 3465-3468; b) N. Shibata, A. Matsnev, D. Cahard, *Beilstein J. Org. Chem.* **2010**, 6, 1159-1166.

²⁹ P. Novák, A. Lishchynskiy, V. V. Grushin, *Angew. Chem.* **2012**, 124, 7887-7890; *Angew. Chem. Int. Ed.* **2012**, 51,

through an oxidative trifluoromethylation.

1.5.3 The association of CF₃ group with a heteroatom (XCF₃)

The association of the trifluoromethyl group with a heteroatom, such as O, S, N is another branch of fluorinated compounds. Significantly, the trifluoromethoxylated (OCF₃) and trifluoromethylthiolated (SCF₃) compounds have been used as agrochemicals, pharmaceuticals, and electrooptical materials. The increase of lipophilicity after the incorporation of these two groups makes the products promising drug candidates in medicinal chemistry. This kind of molecules could readily pass through cell membranes and approach active sites effectively; drug potency is increased and side effects are limited.

The nucleophilicity of the heteroatom is the main factor that affects the trifluoromethylation of the heteroatom; trifluoromethylation at N and O atoms are more difficult than S.

The synthesis of aryl and alkyl trifluoromethyl ethers have been realized by nucleophilic fluorination and *O*-trifluoromethylation, but direct addition of trifluoromethoxide anion to form the C-OCF₃ has not yet been widely explored.^{17,32}

On the contrary, the direct trifluoromethylthiolation to construct C-SCF₃ has dramatically developed by a series of nucleophilic and electrophilic trifluoromethylthiolating reagents. The “renaissance” of SCF₃ chemistry has occurred during the past 3 years.³³

As to trifluoromethyl amines, the primary and secondary alkyl trifluoromethyl amines are difficult to synthesize due to the facile decomposition by elimination of fluoride; whereas tertiary alkyl trifluoromethyl amines have been prepared by fluorodesulfurization and *N*-trifluoromethylation.¹⁷

7767-7770.

³⁰ a) Y. Ye, S. H. Lee, M. S. Sanford, *Org. Lett.* **2011**, *13*, 5464-5467; b) K. Zhang, X.-L. Qiu, Y. Huang, F.-L. Qing, *Eur. J. Org. Chem.* **2012**, 58-61.

³¹ a) L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060-5063; b) X. Jiang, L. Chu, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 1251-1257; c) B. A. Khan, A. E. Buba, L. J. Gooßen, *Chem. Eur. J.* **2012**, *18*, 1577-1581.

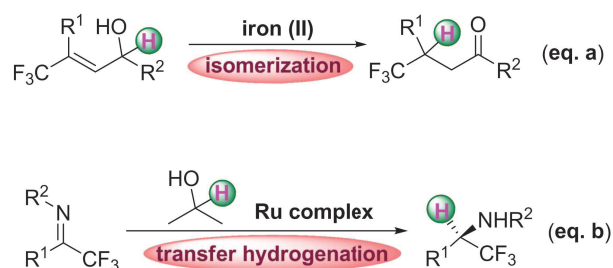
³² a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827-856; b) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann, A. Togni, *Angew. Chem. Int. Ed.* **2009**, *48*, 4332-4336; c) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B. R. Langlois, *Adv. Synth. Catal.* **2010**, *352*, 2831-2837.

³³ F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415-2428.

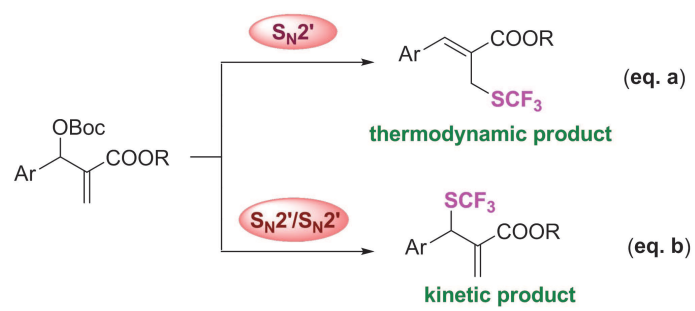
2. Objectives of the PhD work

Since trifluoromethylated and trifluoromethylthiolated compounds increasingly exist in pharmaceuticals and agrochemicals, it is very useful to develop new methods for the construction of molecules containing $C_{sp^3}\text{-CF}_3$ and $C_{sp^3}\text{-SCF}_3$ moieties. Of special interest are the asymmetric versions for which we will focus our attention.

For the construction of molecules bearing trifluoromethylated sp^3 carbon center, we focused on the atom-economic transition-metal catalyzed hydride transfer reactions of trifluoromethylated compounds. In this part, two reactions have been studied: 1) the isomerization of trifluoromethylated allylic alcohols by iron (II) complexes for the synthesis of trifluoromethylated dihydrochalcones (**Scheme 2-1, eq. a**); 2) the enantioselective transfer hydrogenation of trifluoromethylated ketimines by a chiral complex of ruthenium and isopropanol as hydride source for the preparation of optically pure trifluoromethylated amines (**Scheme 2-1, eq. b**).



For the construction of molecules bearing trifluoromethylthiolated sp^3 carbon center, we investigated the nucleophilic allylic trifluoromethylthiolation of Morita-Baylis-Hillman derivatives. We anticipated two possible trifluoromethylthiolated products from the direct trifluoromethylthiolation. One is the primary allylic SCF_3 product bearing the double bond conjugated with the aromatic ring (**Scheme 2-2, eq. a**). The other is the secondary allylic SCF_3 product with a terminal alkene motif (**Scheme 2-2, eq. b**).



Scheme 2-2

3. Transition-metal catalyzed hydride transfer reactions of CF₃ compounds

The trifluoromethyl group has been greatly employed in the organic synthesis of pharmaceutical and agrochemical compounds during the past decades. In contrast to the small van der Waals radius of fluorine, trifluoromethyl group has a much larger size which is between *i*-Pr and *t*-Bu groups (van der Waals radius: H = 1.2 Å, CF₃ = 2.7 Å) (Taft's Es values: H = 0, *i*-Pr = -1.71, CF₃ = -2.40, *t*-Bu = -2.78).^{34,8} The CF₃ group appears in many biologically active compounds and provides enhanced lipophilicity and metabolic stability compared to the non-fluorinated analogues.

In order to meet the growing demand for chiral novel and structurally diverse trifluoromethyl compounds, it is desirable to develop efficient methods for the construction of stereogenic centers featuring a CF₃ motif.³⁵ Hydride transfer reaction by organometallic catalysis provides an efficient way to generate enantiopure molecules in an atom-economical process. Herein, we have investigated two reactions:

3. 1 - the isomerization of trifluoromethylated allylic alcohols
3. 2 - the transfer hydrogenation of trifluoromethylated ketimines

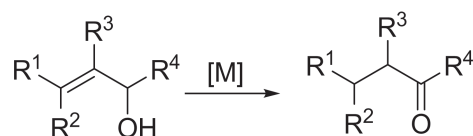
³⁴ D. Seebach, *Angew. Chem., Int. Ed. Eng.* **1990**, *29*, 1320-1367.

³⁵ a) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119-6146; b) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455-529.

3.1 Isomerization of CF₃ allylic alcohols catalyzed by iron (II) complexes

3.1.1 Literature data and objective

Isomerization of allylic alcohols is an efficient synthetic process to convert allylic alcohols to saturated carbonyl compounds. It is an atom-economical and a one-pot transformation mediated by various transition metals such as Ru, Rh, Ir, Ni, Co, Pt, Pd, Os, Mo, and Fe (**Scheme 3-1**). The most employed metals are Ru, Rh, and Ir.³⁶



Scheme 3-1

Among all these transition metal catalysts, iron derivatives are usually less expensive because of the natural abundancy of this metal, less toxic, and accordingly environmentally friendly.³⁷ However, isomerization by iron catalyst is still underdeveloped. Up to now, only some toxic iron(0) carbonyl complexes have been used in this reaction either at high temperature or by irradiation to generate the real catalytic species that was assigned as [Fe(CO)₃],³⁸ including homoleptic [Fe(CO)₅],³⁹ [Fe₂(CO)₉],⁴⁰ [Fe₃(CO)₁₂]⁴¹ as well as heteroleptic [(bda)Fe(CO)₃] (bda = *trans*-benzylideneacetone),⁴² [Fe(cot) (CO)₃] (cot = cyclooctatetraene)⁴² and [Fe(cod) (CO)₃] (cod = cycloocta-1,5-diene).⁴³

³⁶ a) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27-51; b) L. Mantilli, C. Mazet, *Chem. Lett.*, **2011**, *40*, 341-344; c) N. Ahlsten, A. Bartoszewicz, B. Martin-Matute, *Dalton Trans.*, **2012**, *41*, 1660-1670.

³⁷ a) S. Gaillard, J.-L. Renaud, *ChemSusChem*. **2008**, *1*, 505-508; b) K. Junge, K. Schröder, M. Beller, *Chem. Commun.* **2011**, *47*, 4849-4859; c) C. Bolm, J. Legros, J.L. Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217-6254; d) W. M. Czaplik, M. Mayer, J. Cvengroš, A. J. Von Wangelin, *ChemSusChem*. **2009**, *2*, 396-417; e) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500-1511.

³⁸ a) V. Branchadell, C. Crévisy, R. Grée, *Chem. Eur. J.* **2003**, *9*, 2062-2067; b) V. Branchadell, C. Crévisy, R. Grée, *Chem. Eur. J.* **2004**, *10*, 5795-5803.

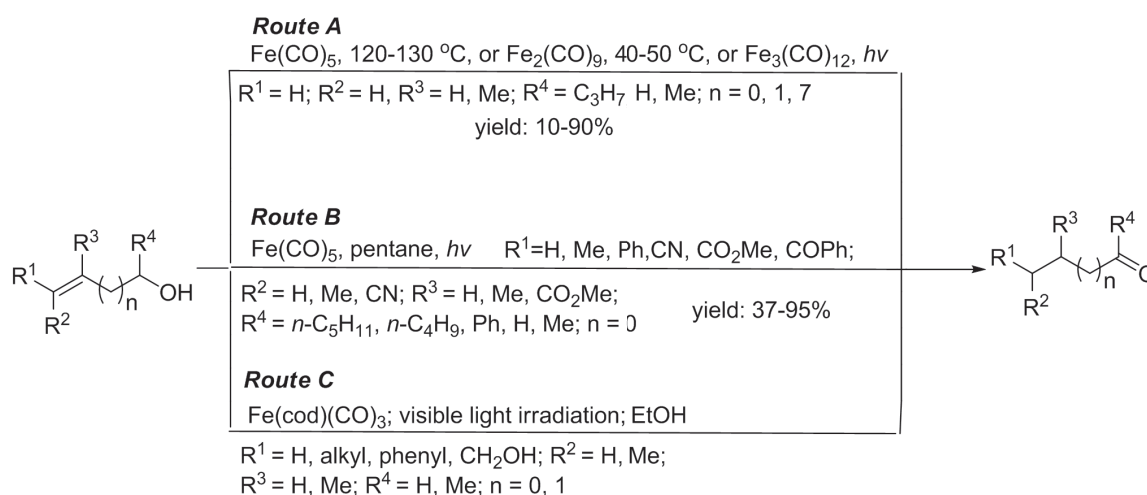
³⁹ a) T. A. J. Manuel, *J. Org. Chem.* **1962**, *27*, 3941-3945; b) H. Cherkaoui, M. Soufiaoui, R. Grée, *Tetrahedron* **2001**, *57*, 2379-2383; c) C. Crévisy, M. Wietrich, V.L. Boulaire, R. Uma, R. Grée, *Tetrahedron Lett.* **2001**, *42*, 395-398; d) J. Petriguet, I. Prathap, S. Chandrasekhar, J. S. Yadav, R. Grée, *Angew. Chem. Int. Ed.* **2007**, *46*, 6297-6300; e) D. Cuperly, C. Crévisy, R. Grée, *J. Org. Chem.* **2003**, *68*, 6392-6399; f) H. T. Cao, T. Roisnel, R. Grée, *Eur. J. Org. Chem.* **2011**, 6405-6408.

⁴⁰ N. Iranpoor, H. Imanieh, E.J. Forbes, *Synth. Commun.* **1989**, *19*, 2955-2961.

⁴¹ N. Iranpoor, E. Mottaghinejad, *J. Organomet. Chem.* **1992**, *423*, 399-404.

⁴² R. Uma, N. Gouault, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2003**, *44*, 6187-6190.

⁴³ H. Li, M. Achard, C. Bruneau, J.-B. Sortais, C. Darcel, *RSC Advances* **2014**, *4*, 25892-25897.



Scheme 3-2

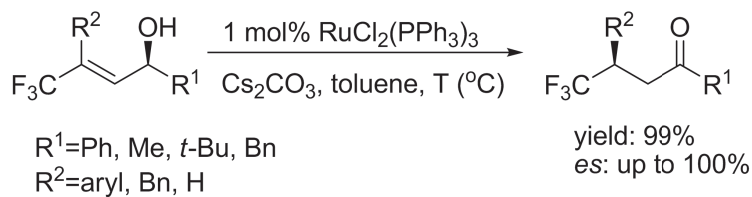
Iranpoor group used nonacarbonyl diiron catalyst ($[\text{Fe}_2(\text{CO})_9]$, 20 mol%) for the isomerization of unsaturated alcohols in benzene at 40-50 °C to obtain the saturated ketones in higher yields and faster reaction rates than that catalyzed by pentacarbonyl iron catalyst ($[\text{Fe}(\text{CO})_5]$, 10 or 20 mol%) at 120-130 °C (**Scheme 3-2, Route A**).

Under irradiation, Grée group developed a very efficient isomerization of sterically hindered trisubstituted allylic alcohols bearing either alkyl or aryl groups on carbinol center (R^4). This reaction is compatible with alkyl, aryl as well as electron-withdrawing groups on the double bond (R^1 or R^3) (**Scheme 3-2, Route B**).

In 2014, Darcel group reported a iron(0)-catalyzed cascade synthesis of *N*-alkylated anilines by using $\text{Fe}(\text{cod})(\text{CO})_3$ complex as precatalyst under visible light irradiation in ethanol to generate in situ saturated ketone intermediates by isomerization, which could further undergo condensation with anilines in good yields (**Scheme 3-2, Route C**).

Recently, our lab has achieved good results in isomerization of allylic alcohols containing a CF₃-olefin moiety by means of ruthenium catalysts⁴⁴ (**Scheme 3-3**). The CF₃ group is beneficial to accelerate the hydride insertion step to accomplish the isomerization of allylic alcohols bearing trisubstituted double bonds. This allowed the development of an enantiospecific isomerization to get enantiopure $\beta\text{-CF}_3$ ketones.

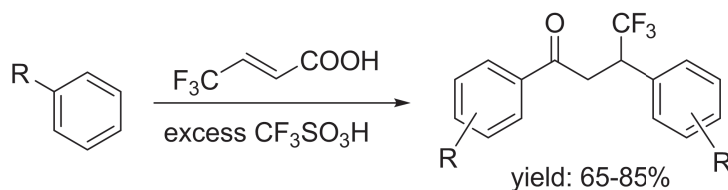
⁴⁴ V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6467-6470.



Scheme 3-3

3.1.2 Synthesis of CF₃ dihydrochalcones by isomerization of CF₃ allylic alcohols

Dihydrochalcones could be considered as key intermediates for the synthesis of potential biologically active compounds which possess a wide range of properties acting as anticancer, antiviral, antibacterial and antioxidant.⁴⁵ Therefore, it is quite desirable to search for novel substitution patterns for dihydrochalcones containing fluorinated motifs which could contribute to a great impact on biological activity. In 2012, Prakash reported the synthesis of trifluoromethylated dihydrochalcones in good yields through superacid catalyzed Friedel-Crafts acylation and alkylation of 4,4,4-trifluorocrotonic acid with arenes (Scheme 3-4). However, under these conditions, only CF₃-dihydrochalcones with identical aromatic substituents on C1 and C3 positions could be successfully synthesized. Moreover, other regioisomers than p,p'-dihydrochalcones are formed in up to 27% yield.⁴⁶



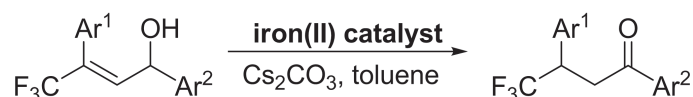
Scheme 3-4

In order to find an alternative way for the synthesis of various aromatic substituted CF₃-dihydrochalcones, we decided to synthesize this kind of ketones featuring two different Ar¹ and Ar² substituents through isomerization of allylic alcohols by employing several iron(II) complexes as catalysts instead of the previously used toxic iron(0) complexes

⁴⁵ a) A. Amin, M. Buratovich, *Frontiers in Anti-Cancer Drug Discovery*, **2010**, *1*, 552-587; b) A.D. Agrawal, *Int. J. Pharm. Sci. Nanotechnol.*, **2011**, *4*, 1394-1398; c) P. Russo, A. Del Bufalo, A. Cesario, *Curr. Med. Chem.*, **2012**, *19*, 5287-5293; d) M. Saxena, J. Saxena, A. Pradhan, *Int. J. Pharm. Sci. Rev. Res.*, **2012**, *16*, 130-134; e) J.-H. Yang, L.-C. Meng, *Ningxia Gongcheng Jishu*, **2007**, *6*, 43-46.

⁴⁶ G. K. S Prakash, F. Paknia, A. Narayanan, G. Rasul, T. Mathew, G. A. Olah, *J. Fluorine Chem.* **2012**, *143*, 292-302.

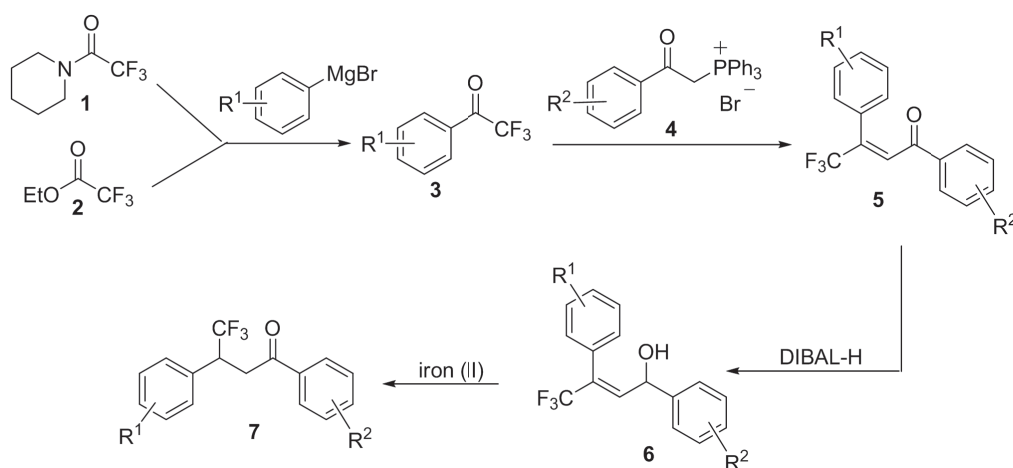
(Scheme 3-5).



Scheme 3-5

3.1.2.1 Preparation of CF₃ allylic alcohols

Key intermediates towards the synthesis of CF₃-dihydrochalcones are trifluoromethylated allylic alcohols **6**. For the construction of the carbon skeleton, our lab has previously developed two synthetic routes for the preparation of β -trifluoromethylated ketones **5** starting from 2,2,2-trifluoro-1-piperidin-1-yl-ethanone **1** or from trifluoroethyl acetate **2** by reaction with aryl magnesium bromide to get the trifluoromethylated ketones **3** which could go through Wittig reaction with phosphonium salts **4** to afford the corresponding trifluoromethylated enones **5**.⁴⁴ Then, the trifluoromethylated allylic alcohols **6** which are key substrates for the isomerization are prepared after selective reduction by means of diisobutylaluminum hydride (DIBAL-H) (Scheme 3-6).

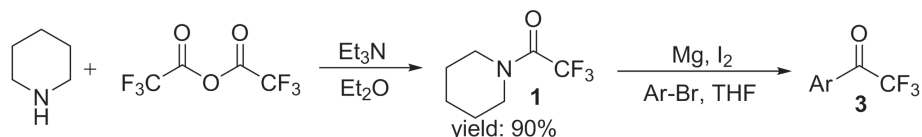


Scheme 3-6

According to the literature,⁴⁷ we prepared the 2,2,2-trifluoro-1-piperidin-1-yl-ethanone **1** in up to 90% yield from piperidine and trifluoroacetic anhydride in the presence of triethylamine in diethyl ether at 0 °C. The CF₃ aromatic ketones **3** were synthesized in moderate to good yields by the reaction of the CF₃ piperidinyl ethanone **1** and fresh Grignard

⁴⁷ H. A. Schenck, P. W. Lenkowski, I. Choudhury-Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979-993.

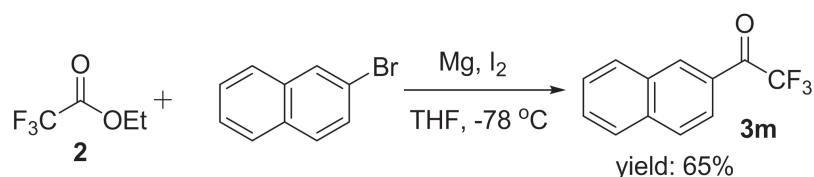
reagents formed from aromatic bromides and magnesium turnings except **3a** (Ar = C₆H₅), **3c** (Ar = 4-BrC₆H₄), **3f** (Ar = 4-CF₃C₆H₄) and **3j** (Ar = 4-*t*-BuC₆H₄) that are commercially available (**Table 3-1**).



entry	Ar	ketone 3	yield (%)
1	4-MeOC ₆ H ₄	3b	58
2	4-MeC ₆ H ₄	3d	80
3	3, 4-Me ₂ C ₆ H ₃	3e	65
4	4-ClC ₆ H ₄	3g	60
5	3-ClC ₆ H ₄	3h	67
6	3, 4-Cl ₂ C ₆ H ₃	3i	42
7	3- <i>i</i> -PrC ₆ H ₄	3k	72
8	2-MeOC ₆ H ₄	3l	49

Table 3-1

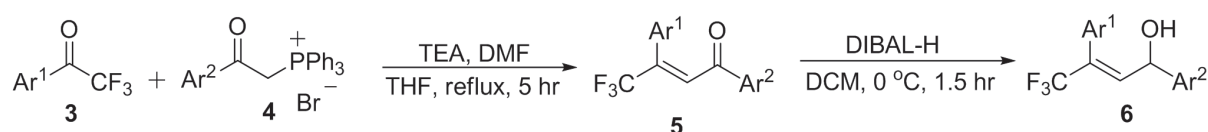
For the synthesis of CF₃ 2-naphthalenyl ethanone, the reaction did not work when the CF₃ amide **1** was used as trifluoromethyl source. Fortunately, when we changed CF₃ amide **1** for trifluoroethyl acetate **2** at -78 °C for 1 hour, the desired CF₃ ketone **3m** was obtained. However, the reaction time should be precisely controlled. If the time lengthened, the ketone product further reacted to get byproducts (**Scheme 3-7**).



Scheme 3-7

Next, the α , β -unsaturated trifluoromethylated enones **5** were successfully synthesized through Wittig reactions by using trifluoromethylated ketone **3** and (2-oxo-2-arylethyl)triphenylphosphonium bromide **4**, which could be easily prepared from 2-bromo-1-arylethanone and triphenylphosphine. The major products observed were the *E*

isomers.⁴⁸ The two isomers were isolated after carefully-performed column chromatography to afford the CF₃ *E* isomers in good to excellent yields. The trifluoromethylated allylic alcohols **6** could be subsequently obtained after the reduction of pure *E* isomers of trifluoromethylated enones **5** with DIBAL-H in DCM (**Table 3-2**). The non-mentioned enones **5a** (Ar¹ = C₆H₅, Ar² = C₆H₅), **5b** (Ar¹ = 4-OMeC₆H₄, Ar² = C₆H₅), **5c** (Ar¹ = 4-BrC₆H₄, Ar² = C₆H₅), **5f** (Ar¹ = 4-CF₃C₆H₄, Ar² = C₆H₅) and the corresponding allylic alcohols **6a**, **6b**, **6c**, **6f** were previously prepared by Dr. Vincent Bizet in our lab.



entry	Ar ¹	Ar ²	yield of enone 5 (%)	yield of allylic alcohol 6 (%)
1	4-MeC ₆ H ₄	C ₆ H ₅	82 (5d)	69 (6d)
2	3, 4-Me ₂ C ₆ H ₃	C ₆ H ₅	41 (5e)	87 (6e)
3	4-ClC ₆ H ₄	C ₆ H ₅	88 (5g)	84 (6g)
4	C ₆ H ₅	4-BrC ₆ H ₄	82 (5h)	94 (6h)
5	C ₆ H ₅	4-ClC ₆ H ₄	90 (5i)	80 (6i)
6	C ₆ H ₅	3-OMeC ₆ H ₄	95 (5j)	96 (6j)
7	C ₆ H ₅	2-OMeC ₆ H ₄	89 (5k)	99 (6k)
8	C ₆ H ₅	4-NO ₂ C ₆ H ₄	91 (5l)	59 (6l)
9	4-ClC ₆ H ₄	4-OMeC ₆ H ₄	86 (5m)	95 (6m)

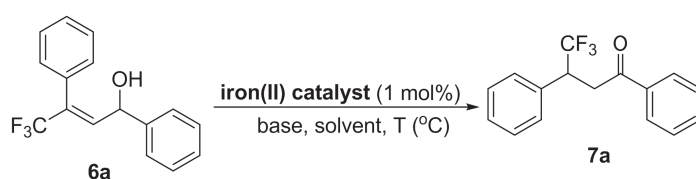
Table 3-2

3.1.2.2 Optimization of reaction conditions for isomerization of CF₃ allylic alcohols

We used the CF₃ allylic alcohol **6a** in the presence of 1 equivalent of cesium carbonate (Cs₂CO₃) in 0.5 M toluene at 25-50 °C with 1 mol% iron catalyst for the test of isomerization. We first selected the iron (II) complexes containing tetradentate P₂N₂-ligands bearing bridging diamines **C1-C3** which were developed by Morris for the transfer hydrogenation of

⁴⁸ T. Konno, T. Takehana, M. Mishima, T. Ishihara, *J. Org. Chem.* **2006**, *71*, 3545-3550.

acetophenone and ketimines in basic isopropanol (**Table 3-3**, entries 1-3).⁴⁹ However, this kind of iron (II) complexes could not fully isomerize allylic alcohol **6a** even at 50 °C. Indeed, **6a** was not fully converted and aldolisation byproducts were observed (**Table 3-3**, entries 1-3). With the non-classical tetrakisphosphorus iron complex **C4**,⁵⁰ the reaction did not work at all (**Table 3-3**, entry 4). The tetra-isonitrile iron catalysts **C5** and **C6** were reported by Reiser in 2010 for the asymmetric transfer hydrogenation of aromatic and heteroaromatic ketones.⁵¹ For example, the tetra-isonitrile catalyst **C5** was easily synthesized by treatment of 2,2,4,4-tetramethylbutyl isonitrile with FeCl₂·4H₂O in methanol.⁵¹ When catalysts **C5** and **C6** were employed in the isomerization, full conversions were obtained at 25 °C (**Table 3-3**, entries 5-7). In reaction run at 25 °C, the yield was up to 72% by using the iron catalyst **C5**, which was much higher than the yield obtained at 50 °C because of the generation of more aldolisation byproducts at higher temperature (**Table 3-3**, entries 5, 6). The iron complexes containing tridentate nitrogen ligands **C7** and **C8** were reported by Chirik for the aldehyde and ketone reductions with hydrosilanes.⁵² We decided to employ for the first time these two catalysts in isomerization, although there were less byproducts observed by ¹⁹F NMR, the reactions were not complete even after 24 hour at 50 °C (**Table 3-3**, entries 8-9). From the screening of catalysts, we demonstrated that the tetra-isonitrile iron catalysts were the most efficient catalysts for our isomerization of CF₃-allylic alcohol **6a** (**Table 3-3**). We selected **C5** catalyst for further optimization.

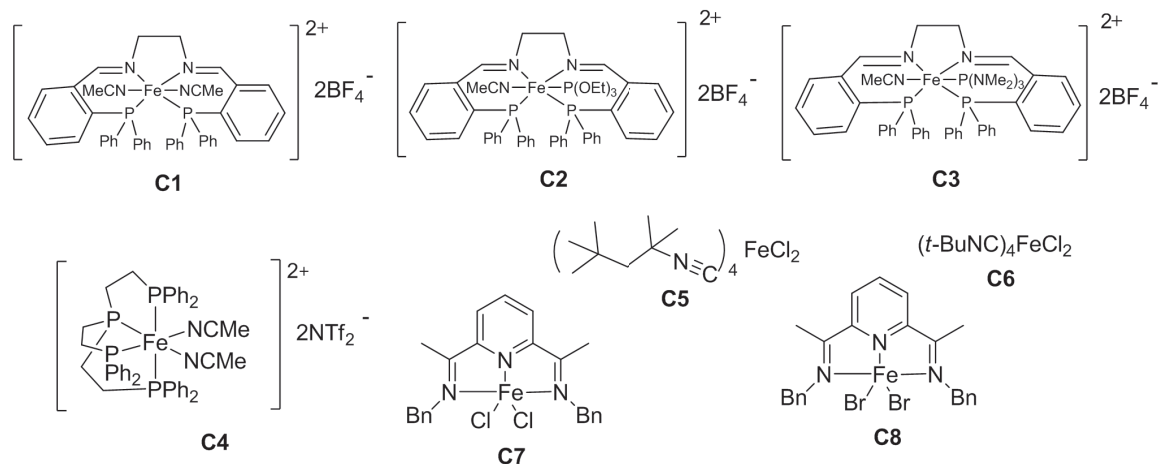


⁴⁹ a) C. Sui-Seng, F. Nipa Haque, A. Hadzovic, A.-M. Putz, V. Reuss, N. Meyer, A. J. Lough, M. Z.-D. Iulius, R. H. Morris, *Inorg. Chem.* **2009**, *48*, 735-743; b) A. A. Mikhailine, R. H. Morris, *Inorg. Chem.* **2010**, *49*, 11039-11044; c) P. E. Sues, A. J. Lough, R. H. Morris, *Organometallics* **2011**, *30*, 4418-4431; d) J. F. Sonnenberg, N. Coombs, P. A. Dube, R. H. Morris, *J. Am. Chem. Soc.* **2012**, *134*, 5893-5899.

⁵⁰ a) C. Bianchini, A. Meli, M. Peruzzini, F. Vizza, F. Zanobini, P. Frediani, *Organometallics* **1989**, *8*, 2080-2082; b) C. Bianchini, A. Meli, M. Peruzzini, P. Frediani, C. Bohanna, M. A. Esteruelas, L. A. Oro, *Organometallics* **1992**, *11*, 138-145; c) C. Bianchini, E. Farnetti, M. Graziani, M. Peruzzini, A. Polo, *Organometallics*, **1993**, *12*, 3753-3761.

⁵¹ A. Naik, T. Maji, O. Reiser, *Chem. Commun.* **2010**, *46*, 4475-4477.

⁵² A. M. Tondreau, J. M. Darmon, B. M. Wile, S. K. Floyd, E. Lobkovsky, P. J. Chirik, *Organometallics* **2009**, *28*, 3928-3940.



entry	solvent	cat.	base	T (°C)	time (h)	conv. (%) ^a	yield (%) ^b
1	toluene	C1	Cs ₂ CO ₃	50	18	93	70
2	toluene	C2	Cs ₂ CO ₃	50	22	67	24
3	toluene	C3	Cs ₂ CO ₃	50	22	88	40
4	toluene	C4	Cs ₂ CO ₃	25	27	-	-
5	toluene	C5	Cs ₂ CO ₃	50	6.5	full conv.	35
6	toluene	C5	Cs ₂ CO ₃	25	22	full conv.	72
7	toluene	C6	Cs ₂ CO ₃	25	20.5	full conv.	69
8	toluene	C7	Cs ₂ CO ₃	50	24	54	47
9	toluene	C8	Cs ₂ CO ₃	50	24	33	31
10	toluene	C5	-	25	24	-	-
11	toluene	C5	K ₂ CO ₃	25	22	16	16
12	toluene	C5	<i>t</i> -BuOK	25	22	full conv.	58
13	DCM	C5	Cs ₂ CO ₃	25	47	full conv.	60
14	CHCl ₃	C5	Cs ₂ CO ₃	25	28	-	-
15	THF	C5	Cs ₂ CO ₃	25	51.5	full conv.	42
16	MeOH	C5	Cs ₂ CO ₃	25	25.5	-	-
17	MeCN	C5	Cs ₂ CO ₃	25	25	full conv.	59

^a Conversions were determined by ¹⁹F NMR using trifluorotoluene as internal standard. ^b Yields of isolated products by column chromatography.

Table 3-3

Then, we evaluated the base. The isomerization of CF₃-allylic alcohol **6a** did not go ahead without base (Table 3-3, entry 10). This observation implied that the reaction

proceeded through an iron alkoxide intermediate by displacement of a chloride of the catalyst as shown in the literature.⁵¹ With the inorganic base K₂CO₃ and the strong base *t*-BuOK, we obtained poor to moderate yields (**Table 3-3**, entries 11-12). Hence, Cs₂CO₃ was selected as base.

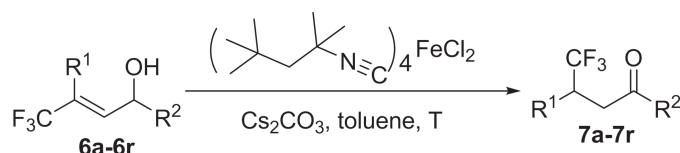
For the study of solvent effects, we noticed that acidic solvents such as CHCl₃, MeOH failed to realize the isomerization (**Table 3-3**, entries 14, 16). With DCM, THF, MeCN, and toluene, full conversions were observed (**Table 3-3**, entries 6, 13, 15 and 17). Among them, longer reaction times were needed for DCM and THF (**Table 3-3**, entries 13, 15). Toluene gave the best result (**Table 3-3**, entry 6). Besides the 1 mol% loading of catalyst, we also performed the reaction with 0.1 mol% and 10 mol% amount of iron catalyst for examination of the efficiency of the catalyst. Full conversions were provided under all conditions, but the isolated yield was the highest by using 1 mol% iron catalyst. These results showed that neither less nor more amount of catalyst were not appropriate for the isomerization of CF₃-allylic alcohol **6a**.

3.1.2.3 Substrate scope for isomerization of CF₃ allylic alcohols

Under the optimized conditions, a range of trifluoromethylated dihydrochalcones were prepared in good yields (**Table 3-4**). Both the electron-rich and electron-deficient aromatics, no matter they are identical or not at R¹ and R² positions, resulted in good yields (**Table 3-4**, entries 1-10). Substrate **6f** bearing the strong electron-withdrawing CF₃ on aromatic R¹ group gave a slightly lower yield (65%) (**Table 3-4**, entry 6). Compound **6k** featuring an *ortho*-methoxy aryl substituent gave only 28% yield of the dihydrochalcone after more than 5 days at high temperature due to the steric hindrance (**Table 3-4**, entry 11). With a strong electron-withdrawing *para*-nitro aryl R² substituent, substrate **6l** gave no desired carbonyl compound (**Table 3-4**, entry 12). In this case, the more acidic hydrogen atom at C1, in other words its lower hydride character, could be responsible for the poor reactivity of substrate **6l**. We also tested two different electron-withdrawing and electron-donating substituents on aryls at R¹ and R² positions in **6m** and got moderate yield (**Table 3-4**, entry 13). Allylic alcohols with aliphatic R¹ group **6n** and **6o** were also subjected to the isomerization in good yields

(Table 3-4, entries 14 and 15).

However, allylic alcohols with aliphatic R² groups **6p** and **6q** failed to provide the desired dihydrochalcones (Table 3-4, entries 16 and 17). The absence of conjugation between the enone intermediate and the aromatic R² group is perhaps responsible for the lack of reactivity. Besides, our methodology was not efficient for the isomerization of the primary allylic alcohol **6r** (Table 3-4, entry 18).

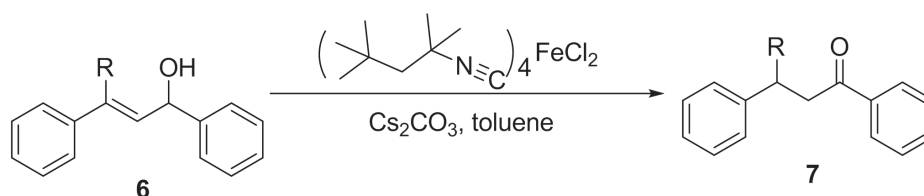


entry	R ¹	R ²	T (°C)	time (h)	conv. (%)	yield (%)
1	Ph	Ph	25	22	full conv.	72 (7a)
2	4-OMeC ₆ H ₄	Ph	40	22	full conv.	76 (7b)
3	4-BrC ₆ H ₄	Ph	40	21	full conv.	72 (7c)
4	4-MeC ₆ H ₄	Ph	40	22	full conv.	75 (7d)
5	3,4-MeC ₆ H ₃	Ph	40	23	full conv.	69 (7e)
6	4-CF ₃ C ₆ H ₄	Ph	40	13	full conv.	65 (7f)
7	4-ClC ₆ H ₄	Ph	40	23	full conv.	74 (7g)
8	Ph	4-BrC ₆ H ₄	40	23	full conv.	85 (7h)
9	Ph	4-ClC ₆ H ₄	40	22	full conv.	69 (7i)
10	Ph	3-OMeC ₆ H ₄	40	22	full conv.	70 (7j)
11	Ph	2-OMeC ₆ H ₄	100	5 days	50	28 (7k)
12	Ph	4-NO ₂ C ₆ H ₄	40-80	48	-	- (7l)
13	4-ClC ₆ H ₄	4-OMeC ₆ H ₄	40	42	87	49 (7m)
14	Me	Ph	55	22	full conv.	75 (7n)
15	Bn	Ph	40	21	full conv.	69 (7o)
16	H	Bn	40	28	-	- (7p)
17	Ph	Me	70	62	-	- (7q)
18	Ph	H	40-80	42	-	- (7r)

Table 3-4

3.1.2.4 Comparison CF₃ versus CH₃ allylic alcohols

When the trifluoromethyl group of the substrate **6a** was replaced by a methyl **6a'**, we could not observe the desired dihydrochalcone by ¹H NMR even after a long reaction time at 60 °C. Moreover, there is still the starting material CH₃-allylic alcohol according to TLC monitoring whereas the CF₃-allylic alcohol was fully converted to furnish the desired dihydrochalcone after 22 hours at 25 °C (**Table 3-5**). The comparison between trifluoromethylated and non-fluorinated substrates in isomerization showed that the electron-withdrawing CF₃ group plays a significant role in accelerating the reaction and illustrates once more the so-called “fluorine effect”.¹²

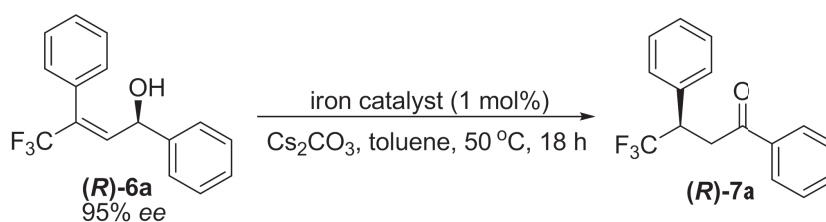


entry	R	T (°C)	time (h)	yield (%)
1	CF ₃ (6a)	25	22	72 (7a)
2	CH ₃ (6a')	25-60	22	- (7a')

Table 3-5

3.1.2.5 Asymmetric version: stereospecificity versus stereoselectivity

The stereocontrol of Csp₃-CF₃ stereogenic centres at the β-position of the carbonyl function in the dihydrochalcone motif would be of great added value to the method. Towards this goal, we performed the enantiospecific 1,3-hydride transfer reaction with optically enriched allylic alcohol (*R*)-**6a**. Morris complex **C1** gave β-CF₃ dihydrochalcone (*R*)-**7a** in 84% *ee* and 89% *es*; whereas the tetra-isonitrile catalyst **C6** afforded the isomerized product in only 34% *ee* with 36% enantiospecificity. These results indicated that the iron(II) catalyzed isomerization could enantiospecifically undergo *syn*-specific 1,3-hydride shift.

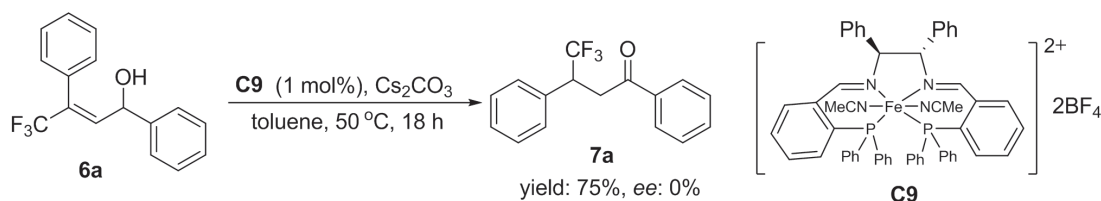


entry	iron catalyst	yield (%)	ee (%) ^a	es (%) ^b
1	C1	86	84	89
2	C6	75	34	36

^a Enantiomeric excess measured by HPLC using OD-H column. ^b Enantiospecificity: $es = 100 \times (ee \text{ product}) / (ee \text{ reactant})$.

Table 3-6

In addition, we attempted the enantioselective version by the chiral Morris-type iron (II) complex bearing enantiopure diamine (*R, R*)-diphenylethylenediamine group **C9**.⁵³ However, under the optimized reaction conditions, this kind of iron (II) catalyst was not suitable for the synthesis of optically enriched trifluoromethyl dihydrochalcones. The reaction proceeded but we only got the racemic ketone (**Scheme 3-8**).



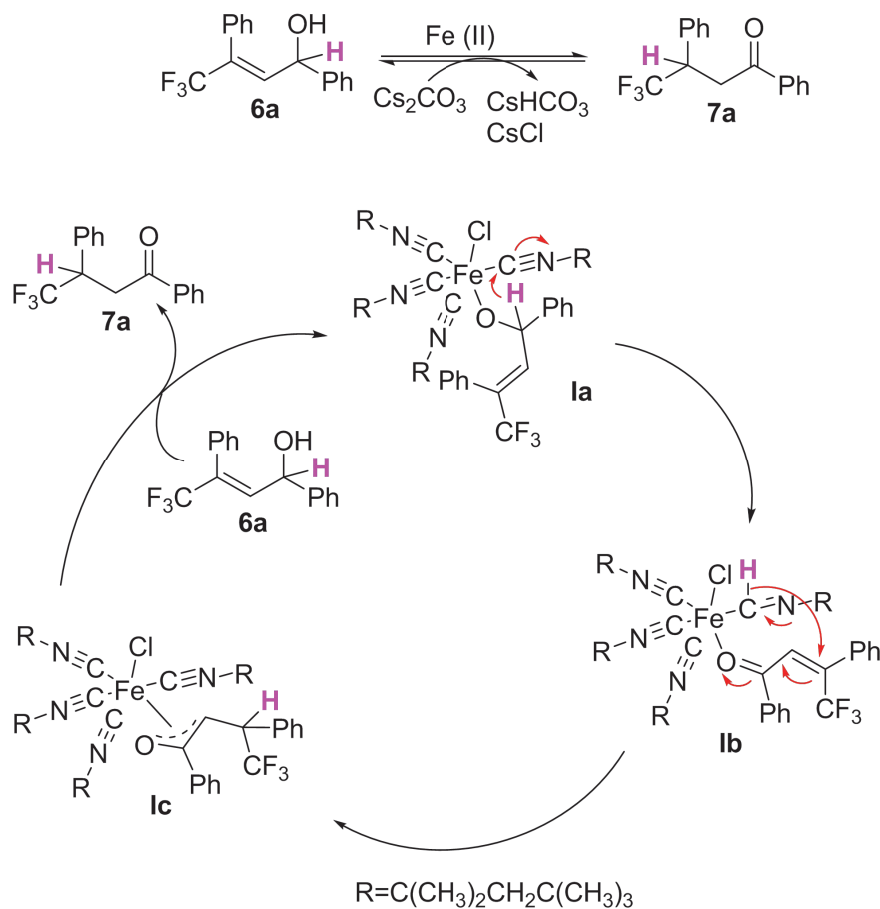
Scheme 3-8

3.1.2.6 Mechanism investigation

Reiser group has already investigated the mechanism of iron(II)-tetra-isonitrile complex catalyzed asymmetric transfer hydrogenations of aromatic ketones through IR experiments, which showed the reduction of isonitrile to the corresponding imine instead of the formation of an iron hydride (Fe-H bond).⁵¹ According to this report, we proposed the following mechanism for the isomerization. The allylic alcohol **6a** was combined with iron catalyst in the presence of cesium carbonate to generate the intermediate **Ia**. Then, the hydride from CF₃ allylic alcohol **6a** was transferred to the isonitrile of iron complex to generate imine **Ib**. This imine intermediate reacted as a hydrogen donor to proceed 1,4-hydride addition (**Ib** to **Ic**).

⁵³ A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394-1395.

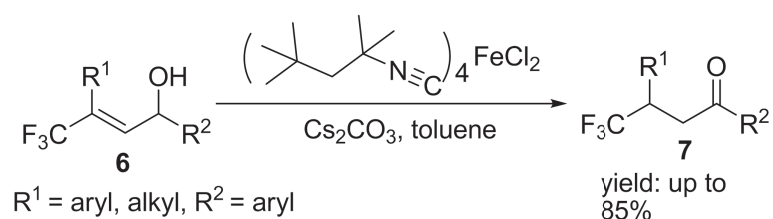
The resulting enolate **1c** was protonated by an incoming allylic alcohol and tautomerized into the final saturated ketone with the release of the catalyst (**Scheme 3-9**).



Scheme 3-9

3.1.3 Conclusion and perspectives

In this first example of hydride transfer reaction, we have developed the isomerization of CF₃-allylic alcohols catalyzed by tetra-isonitrile iron (II) complex for the synthesis of a series of aromatic substituted CF₃-dihydrochalcones in up to 85% yield under mild reaction conditions (**Scheme 3-10**).



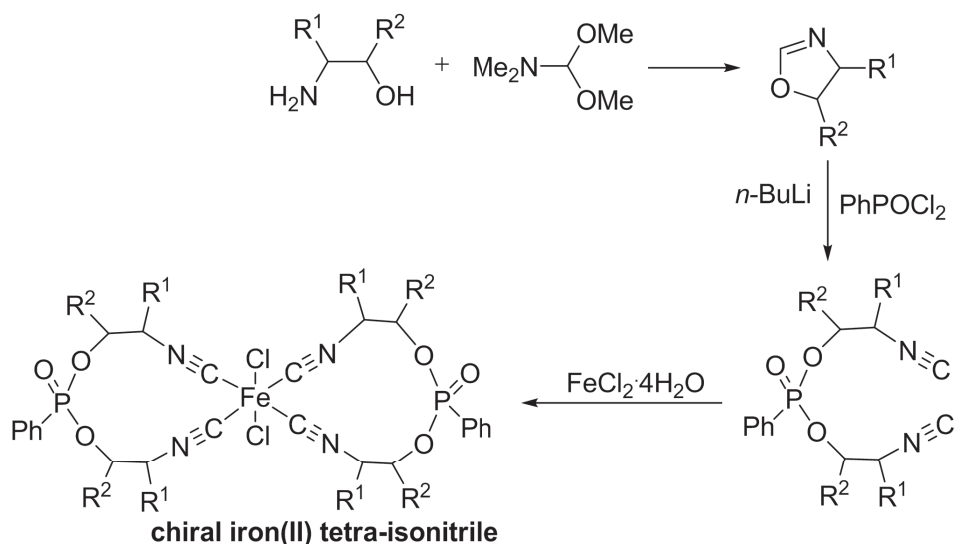
Scheme 3-10

Moreover, the comparison with the isomerization of CH₃-allylic alcohols provides the

persuasive illustration that the strongly electronegative fluorine atom is the key point for this accomplishment.

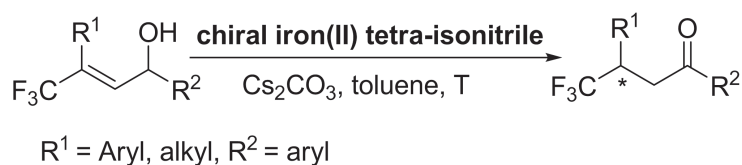
We have also demonstrated a high enantiospecific process from enantioenriched allylic alcohol leading to optically enriched β -CF₃ dihydrochalcone in up to 84% ee with 1 mol% Morris type iron(II) catalyst.

However, the asymmetric isomerization of CF₃-allylic alcohols with a chiral iron (II) complex is still undeveloped. Because the Morris type chiral iron (II) complexes with PNNP ligands are not appropriate for the asymmetric version and tetra-isonitrile ligand provided good results in racemic version, we will try to synthesize chiral tetra-isonitrile catalysts from the bidentate bis-isonitrile which could be prepared from simple amino alcohols (**Scheme 3-11**).



Scheme 3-11

This chiral iron(II) tetra-isonitrile catalyst could be employed in the asymmetric isomerization of CF₃-allylic alcohols to furnish the enantio-enriched CF₃-dihydrochalcones (**Scheme 3-12**).



Scheme 3-12

3.2 Asymmetric transfer hydrogenation of CF₃ ketimines catalyzed by Ru (II) complexes

3.2.1 Literature data and objective

Chiral amines are very common subunits not only in natural products, pharmaceutical drugs and biologically active compounds but also in asymmetric synthesis as chiral auxiliaries, organocatalysts and chiral bases.⁵⁴ Among chiral amines, α -trifluoromethyl amino molecules are quite promising in the improvement of biological activity of compounds containing a CF₃ group versus non-fluorinated ones. The strongly electronegative trifluoromethyl group could lower the basicity of an adjacent nitrogen atom in some extent while retaining the N-H function as an H-bond donor. Besides, α -trifluoromethyl amino motif also has been used as a mimic of the classical amide in pseudopeptides.⁵⁵

There are three main ways to construct the chiral trifluoromethyl amine motif [R¹CH(NHR²)(CF₃)] from imines including direct trifluoromethylation, C-C bond formation and reduction of imines (**Figure 3-1**).

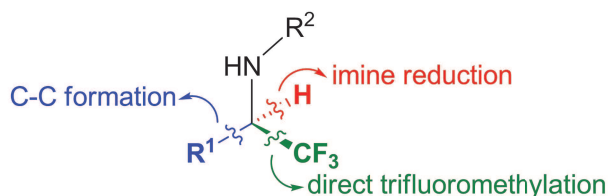


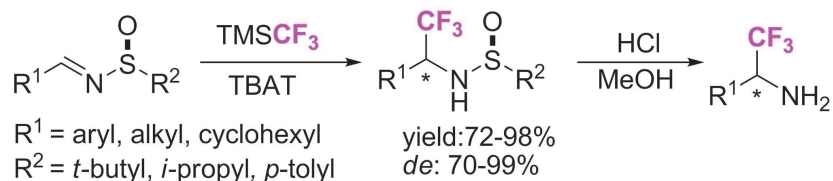
Figure 3-1

Direct trifluoromethylation was realized by using *N*-sulfinylimine as activated imine and Ruppert-Prakash's reagent as the trifluoromethylating reagent (**Scheme 3-13**).⁵⁶ Chiral sulfinyl group in *N*-sulfinylimine acts as a chiral controller as well as a protecting group to efficiently construct chiral trifluoromethylated amines.

⁵⁴ T. C. Nugent, (Ed.), *Chiral Amine Synthesis: Methods, Developments and Applications*, Wiley-VCH, Weinheim, **2010**.

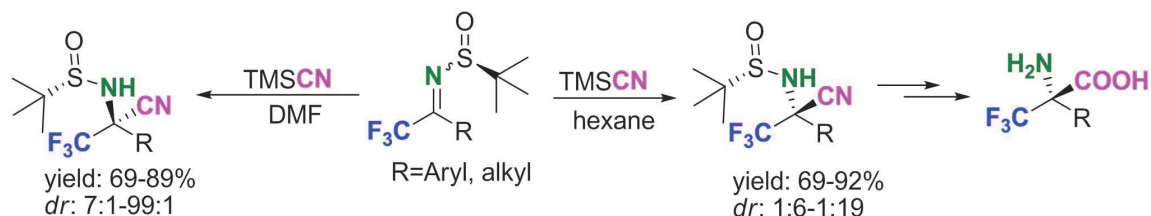
⁵⁵ a) A. Volonterio, P. Bravo, M. Zanda, *Org. Lett.* **2000**, *2*, 1827-1830; b) A. Volonterio, P. Bravo, M. Zanda, *Tetrahedron Lett.* **2001**, *42*, 3141-3144.

⁵⁶ a) G. K. S. Prakash, M. Mandal, G. A. Olah, *Angew. Chem. Int. Ed.* **2001**, *40*, 589-590; b) I. Fernandez, V. Valdivia, A. Alcudia, A. Chelouan, N. Khiar, *Eur. J. Org. Chem.* **2010**, 1502-1509; c) Y. Kawano, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 894-895.



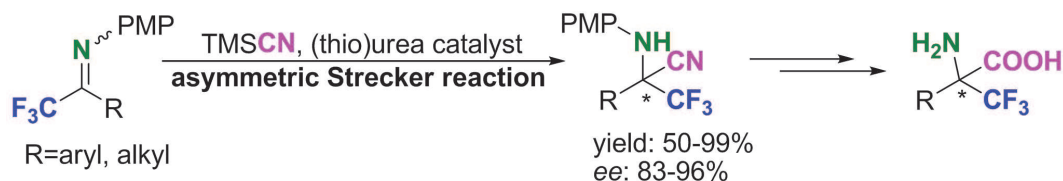
Scheme 3-13

C-C Bond formation is illustrated in the Strecker synthesis of α -trifluoromethylated amino acids bearing a stereogenic quaternary center by using trimethylsilyl cyanide (TMSCN).^{57,58} Excellent diastereoselectivities (up to 99:1 *dr*) have been achieved under solvent-controlled asymmetric Strecker reaction by Lu group. The predominant (*S*, *Rs*)-product was obtained in hexane; whereas in DMF, the reverse (*R*, *Ss*)-isomer was the major product (Scheme 3-14).⁵⁷



Scheme 3-14

Enders and Zhou groups have reported the enantioselective Strecker synthesis of α -CF₃ amino nitriles with trimethylsilyl cyanide and trifluoromethyl ketimines by (thio)urea catalyst in good to excellent yields (up to 99%) and enantioselectivities (up to 96% *ee*) (Scheme 3-15). After deprotection and hydrolysis, the α -CF₃ amino acids were obtained.⁵⁸



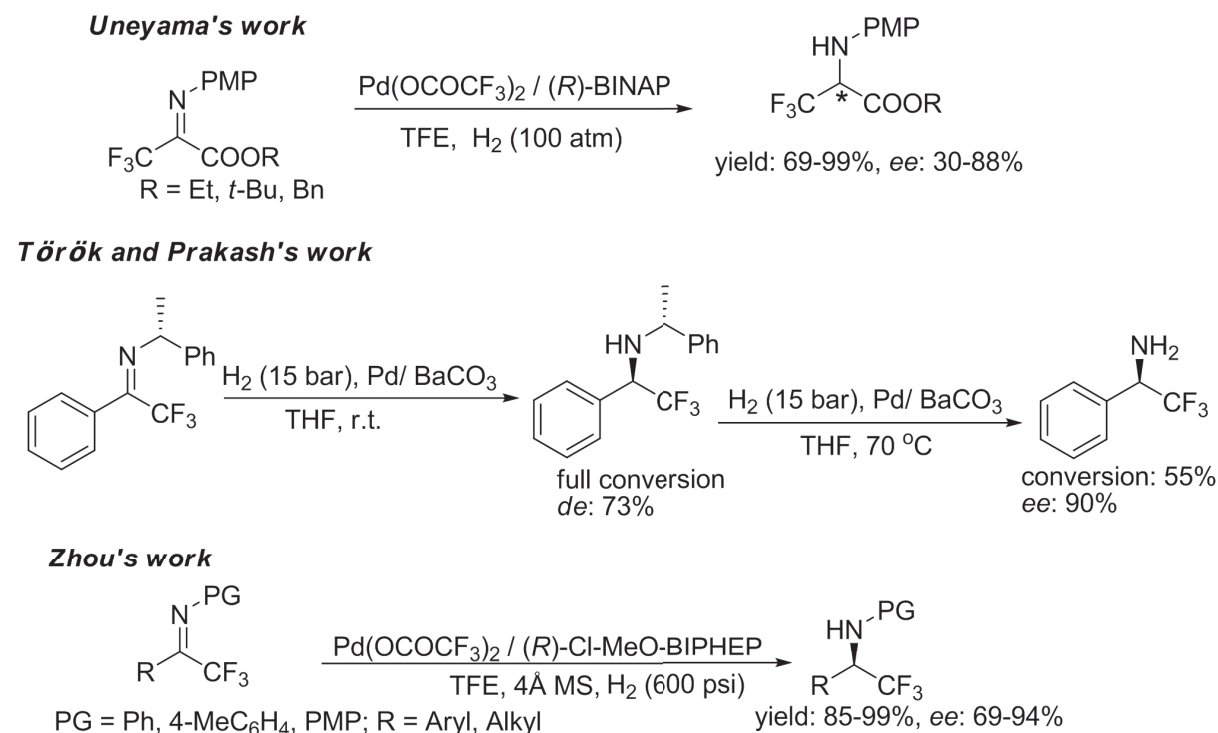
Scheme 3-15

Catalytic asymmetric reduction, particularly the asymmetric hydrogenation of trifluoromethylated imines as RC(CF₃)=NX precursors has become another powerful method to access enantioenriched α -trifluoromethylated amines. Asymmetric hydrogenation has been

⁵⁷ H. Wang, X. Zhao, Y. Li, L. Lu, *Org. Lett.* **2006**, *8*, 1379-1381.

⁵⁸ a) D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147-3152; b) Y.-L.Liu, T.-D. Shi, F. Zhou, X.-L. Zhao, X. Wang, J. Zhou, *Org. Lett.* **2011**, *13*, 3826-3829; c) Y.-L.Liu, X.-P. Zeng, J. Zhou, *Chem. Asian. J.* **2012**, *7*, 1759-1763.

widely studied in academy and applied in industry.⁵⁹ The two prominent chemists Knowles and Noyori were awarded Nobel Prize in Chemistry in 2001 for their great effort in this field.⁶⁰ Uneyama group,⁶¹ Török, Prakash⁶² and later Zhou group⁶³ reported on palladium-catalyzed hydrogenation of activated α -fluorinated iminoesters and ketimines under high pressure of hydrogen gas (**Scheme 3-16**).



Scheme 3-16

In traditional asymmetric hydrogenation process, hydrogen gas is utilized as reducing agent under transition metal catalysis, while in asymmetric transfer hydrogenation, isopropanol and azeotropic mixture (NEt₃/HCOOH) are frequently employed as hydride sources. The asymmetric transfer hydrogenation is a simple operation and it facilitates the isolation of the reduction products due to the volatile reaction byproducts and it avoids the handling of hydrogen gas.⁶⁴ Thus, in the last decade, it has attracted considerable attention

⁵⁹ For selected reviews on asymmetric reduction of imines see: J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713-1760; D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557-2590. For selected articles on asymmetric reduction of imines see: C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450-14451; N. Mrcic, A. J. Minnaard, B. L. Feringa, J. G. Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358-8359; G. Hou, F. Gosselin, W. Li, J. C. McWilliams, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882-9883; S. Zhou, S. Fleischer, K. Junge, S. Das, D. Addis, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 8121-8125.

⁶⁰ a) W. S. Knowles, *Angew. Chem., Int. Ed.* **2002**, *41*, 1998-2007; b) R. Noyori, *Angew. Chem., Int. Ed.* **2002**, *41*, 2008-2022.

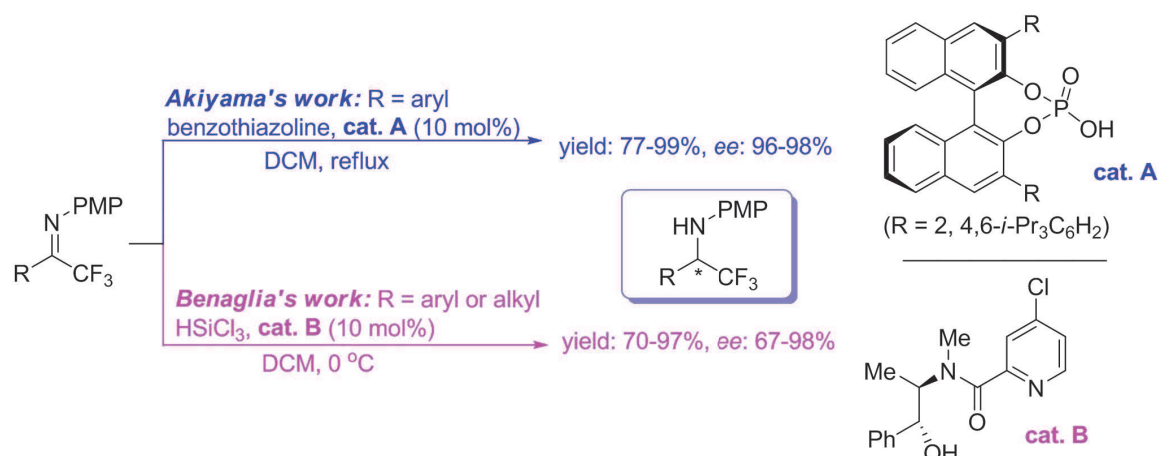
⁶¹ H. Abe, H. Amii, K. Uneyama, *Org. Lett.* **2001**, *3*, 313-315.

⁶² B. Török, G. K. S. Prakash, *Adv. Synth. Catal.* **2003**, *345*, 165-168.

⁶³ M.-W. Chen, Y. Duan, C.-B. Yu, Y.-G. Zhou, *Org. Lett.* **2010**, *12*, 5075-5077.

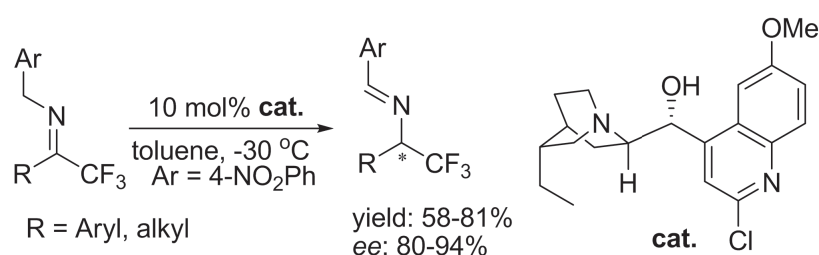
⁶⁴ D. Guijarro, G. Ujaque, M. Yus, *Chem. Eur. J.* **2012**, *18*, 1969-1983.

among the approaches for reduction of imines.⁶⁵ In 2011, Akiyama group first introduced chiral phosphoric acid organocatalysts in the transfer hydrogenation of aromatic and heteroaromatic trifluoromethylated imines with benzothiazoline as source of hydride providing excellent results (77-99% yield; up to 98% *ee*) (**Scheme 3-17**).⁶⁶ In 2013, Benaglia group reported an organocatalyzed hydrosilylation of trifluoromethylated ketimines by means of a chiral Lewis base and trichlorosilane was used as hydride source leading to chiral amines in good yields (up to 97%) and high enantioselectivities (up to 98% *ee*) (**Scheme 3-17**).⁶⁷



Scheme 3-17

In addition to these methods for the construction of the chiral trifluoromethyl amine motif, asymmetric 1,3-proton shift of *N*-benzyl trifluoromethylated imines by chiral cinchona alkaloid catalysts allowed to access optically active trifluoromethylated amines;⁶⁸ see for example the work by Wu and Deng (**Scheme 3-18**).^{68a}



Scheme 3-18

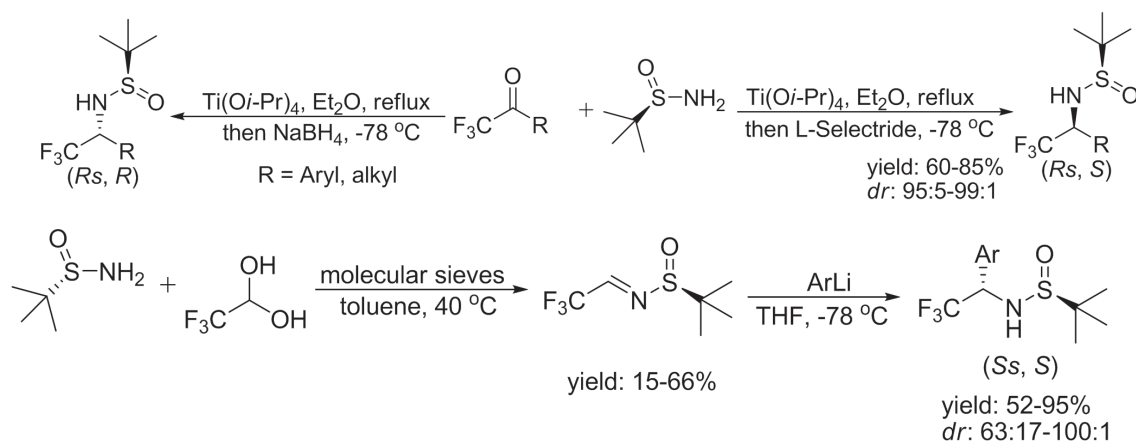
⁶⁵ a) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498-2518; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226-236; c) S. Hoffmann, A. Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427; d) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781-3783; e) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830-5831.

⁶⁶ A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

⁶⁷ A. Genoni, M. Benaglia, E. Massolo, S. Rossi, *Chem. Comm.* **2013**, *49*, 8365-8367.

⁶⁸ a) Y. Wu, L. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 14334-14337; b) V. A. Soloshonok, H. Ohkura, M. Yasumoto, *J. Fluorine Chem.* **2006**, *127*, 930-935; c) V. A. Soloshonok, M. Yasumoto, *J. Fluorine Chem.* **2007**, *128*, 170-173; d) V. A. Soloshonok, A. G. Kirilenko, S. V. Galushko, V. P. Kukhar, *Tetrahedron Lett.* **1993**, *34*, 3621-3624; e) V. A. Soloshonok, T. Ono, *J. Org. Chem.* **1997**, *62*, 3030-3031; f) V. Michaut, F. Metz, J.-M. Paris, J.-C. Plaquevent, *J. Fluorine Chem.* **2007**, *128*, 500-506.

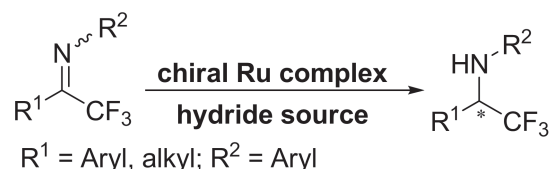
The atom-economic diastereoselective reductive aminations of 2,2,2-trifluoroarylethanone and trifluoroacetaldehyde hydrate with *N*-*tert*-butane-sulfinamide were also reported for the obtention of chiral trifluoromethylated amine derivatives (**Scheme 3-19**).⁶⁹



Scheme 3-19

However, to the best of our knowledge, the enantioselective transfer hydrogenation by means of an organometallic catalyst has never been applied to the reduction of trifluoromethylated imines. Our aim is to develop a reaction that employs a simple source of chirality and a cheap source of hydrogen for enantioselective transfer hydrogenation.

As a new example of hydride transfer applied to fluorinated compounds, in this chapter, we disclose the first enantioselective ruthenium-catalyzed transfer hydrogenation of trifluoromethylated ketimines by using two different types of hydride sources that are azeotropic mixture (NEt₃/HCOOH) and isopropanol with various amino alcohol ligands as chiral inducers (**Scheme 3-20**).

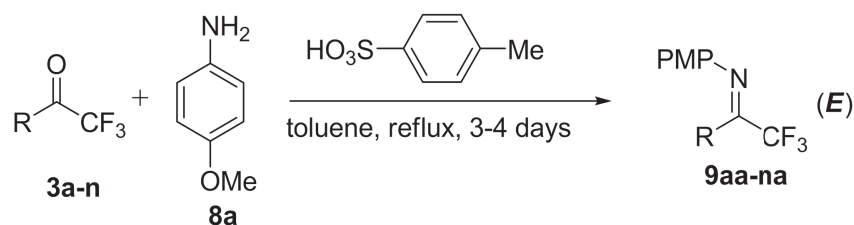


Scheme 3-20

⁶⁹ a) V. L. Truong, M. S. Ménard, I. Dion, *Org. Lett.* **2007**, *9*, 683-685; b) J. Xu, Z.-J. Liu, X.-J. Yang, L.-M. Wang, G.-L. Chen, J.-T. Liu, *Tetrahedron* **2010**, *66*, 8933-8937; c) G. Hughes, P. N. Devine, J. R. Naber, P. D. O Shea, B. S. Foster, D. J. McKay, R. P. Volante, *Angew. Chem.* **2007**, *119*, 1871-1874; *Angew. Chem. Int. Ed.* **2007**, *46*, 1839-1842.

3.2.2 Synthesis of trifluoromethylated ketimines

We first synthesized a series of trifluoromethylated ketimines as substrates for the transfer hydrogenation by using trifluoromethylated ketones **3a-m** and *p*-methoxyaniline **8a**.



entry	R	CF ₃ ketimine 9	yield (%)
1	Ph	9aa	85
2	4-MeOC ₆ H ₄	9ba	79
3	4-BrC ₆ H ₄	9ca	91
4	4-MeC ₆ H ₄	9da	98
5	3,4-Me ₂ C ₆ H ₃	9ea	89
6	4-CF ₃ C ₆ H ₄	9fa	99
7	4-ClC ₆ H ₄	9ga	81
8	3-ClC ₆ H ₄	9ha	65
9	3,4-Cl ₂ C ₆ H ₃	9ia	99
10	4- <i>t</i> -BuC ₆ H ₄	9ja	99
11	3- <i>i</i> -PrC ₆ H ₄	9ka	99
12	2-MeOC ₆ H ₄	9la	81
13	2-naphthyl	9ma	68
14	Bn	9na	86 ^a
15	COOMe	9oa	92

^a mixture of two tautomers in ratio of 22:78.

Table 3-7

The reactions were conducted in toluene at reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA). After heated for 3 to 4 days, we got the corresponding trifluoromethylated ketimines **3a-m** as single *E* isomer in good to high yields (Table 3-7, entries 1-13).⁶⁶ Notably, the *N*-benzyl substituted imine **9na**, gave 22:78 ratio of two

tautomers that could not be separated by column chromatography (Table 3-7, entry 14). The α -CF₃-iminoester **9oa** was also prepared under these conditions in high yield (Table 3-7, entry 15).

Several groups prepared trifluoromethylated ketimines,^{58,63,66,67} but the configuration of the CF₃ imines was not exactly identified. Moreover, transition-state models are often proposed in which the imine has the wrong configuration. Since the configuration of the CF₃ imines plays a crucial role in enantiofacial discrimination, we conducted a comprehensive study to ascertain the geometry of aryl trifluoromethylated ketimines.

Although most of CF₃ imines we synthesized were oil and not suitable to get crystal, fortunately 2-naphthyl substituted CF₃ imine **9ma** was a solid prone to crystalize easily. So, we successfully got the crystal and studied its structure by X-ray diffraction which showed a *E* configuration (Figure 3-2). Next, the ¹⁹F, ¹H HOESY NMR of phenyl substituted imine **9aa** was performed and an interaction between fluorine and aromatic C-H in the phenyl group was observed but not with the aromatic C-H of PMP group which further indicated the *E* configuration (Figure 3-3). In addition, DFT calculations were realized. The geometries of the *E* and *Z* isomers of **9aa** were first optimized at the B3LYP/6-311++G (d, p) level of theory. As stacking interactions could stabilize the *E* isomer, we also performed calculations at the ω B97X-D/6-311++G (d, p) level of theory. The use of the latter functional indicated that the *E* isomer of **9aa** was 4.5 kcal/mol more stable than the *Z* isomer whereas the difference was only 2 kcal/mol with the widespread B3LYP functional.⁷⁰

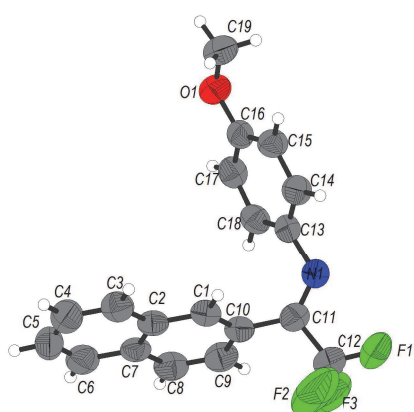


Figure 3-2 X-Ray of CF₃ imine **9ma**

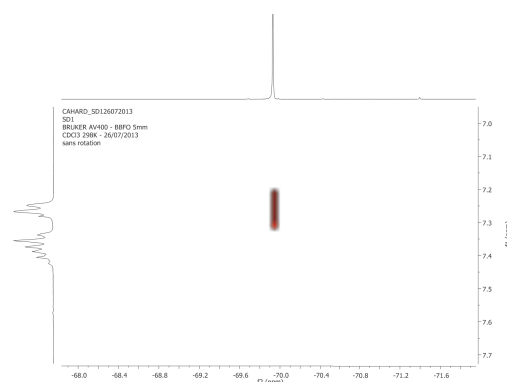
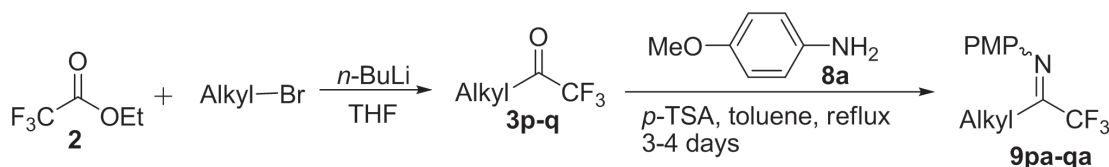


Figure 3-3 HOESY of CF₃ imine **9aa**

⁷⁰ We thank Pr. Georges Dupas for DFT calculations.

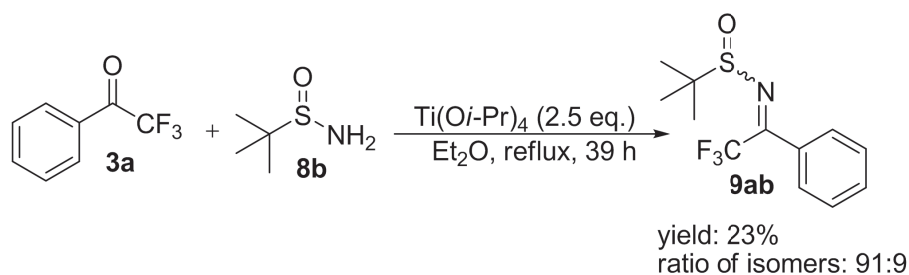
In addition to arylimines, we also synthesized the alkyl substituted CF₃ imines featuring *n*-hexyl chain **9pa** and a cyclohexyl **9qa** which were directly synthesized from the crude ketones without further purification. However, mixtures of *E/Z* isomers were obtained after the imination with *para*-methoxyaniline **8a** (Table 3-8).



entry	alkyl	CF ₃ ketimine 9	yield (%)	<i>E/Z</i> ratio
1	hexyl	9pa	34	20:80
2	cyclohexyl	9qa	41	11:89

Table 3-8

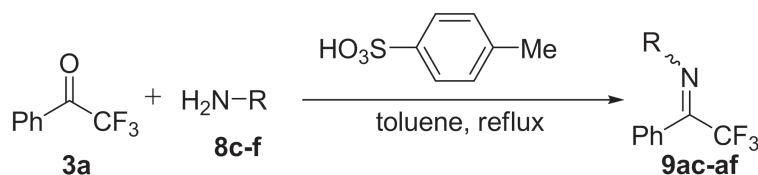
Then, we changed the protecting group from PMP to *tert*-butylsulfinyl group.⁷¹ *Tert*-butylsulfinyl trifluoromethylated imine **9ab** was synthesized from 2,2,2-trifluoro-1-phenylethanone **3a** and *tert*-butanesulfinamide **8b** in the presence of titanium isopropoxide in diethyl ether. As the literature reported, the *tert*-butylsulfinyl CF₃-ketimine was not stable on silica gel and we got only 23% yield of imine product (Scheme 3-21).



Scheme 3-21

The CF₃-imine **9ac** with alkyl group on nitrogen atom was also synthesized in 76% yield (Table 3-9, entry 1). Moreover, the more bulky 1-naphthyl, 2-naphthyl and 2,4-dimethoxyphenyl substituted imines were successfully obtained (Table 3-9, entries 2-4).

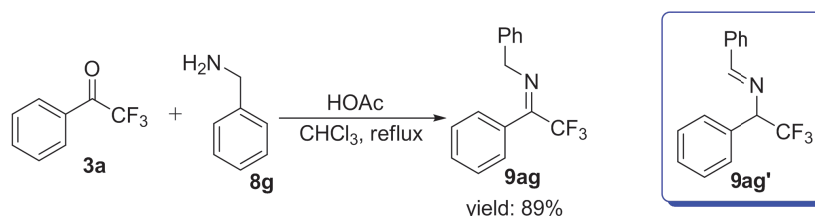
⁷¹ a) H. Wang, X. Zhao, Y. Li, L. Lu, *Org. Lett.* **2006**, *8*, 1379-1381; b) J. Xu, Z.-J. Liu, X.-j. Yang, L.-M. Wang, G.-L. Chen, J.-T. Liu, *Tetrahedron* **2010**, *66*, 8933-8937.



entry	R	CF ₃ ketimine 9	yield (%)
1	<i>n</i> -butyl	9ac	76
2	1-naphthyl	9ad	45
3	2-naphthyl	9ae	61
4	2,4-(MeO) ₂ C ₆ H ₃	9af	82

Table 3-9

The benzyl ketimine was synthesized according to the literature in “low-basicity” reaction conditions using benzylamine and acetic acid, instead of benzylamine and a catalytic amount of *p*-TSA. The traditional method for the imination with *p*-TSA in toluene resulted in the tautomeric Schiff base **9ag'**, which was difficult to separate from **9ag**.⁷² Hence, we conducted the reaction of CF₃-ketone **3a** with 1.1 equivalent of acetic acid to form the salt of benzylamine in CHCl₃ and obtained 89% yield of isolated pure ketimine **9ag** (Scheme 3-22).

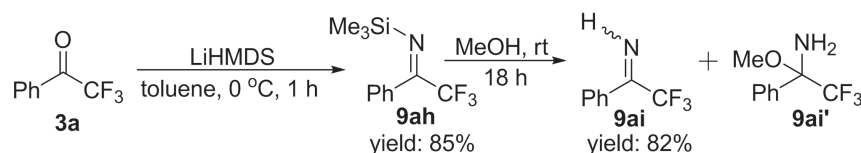


Scheme 3-22

A step-economic synthetic plan would be to utilize N-H imines to avoid a deprotection step after asymmetric transfer hydrogenation.⁷³ In order to synthesize the CF₃-imine without any protecting group, *N*-trimethylsilyl CF₃-imine **9ah** was first prepared from the CF₃-phenylacetone **3a** with lithium bis(trimethylsilyl)amide (LiHMDS) at 0 °C for 1 hour. The crude product after treatment with water was used directly for the desilylation without further purification. The unprotected CF₃-imine **9ai** was obtained as a 32:68 mixture of *E/Z* isomers in 82% yield, along with the methanol adduct **9ai'** (Scheme 3-23).^{73a}

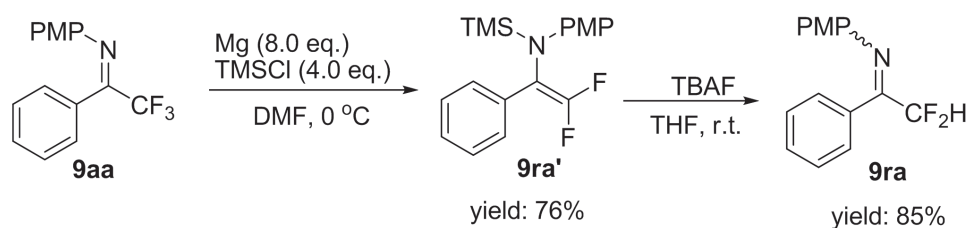
⁷² a) D. O. Berbasov, I. D. Ojemaye, V. A. Soloshonok, *J. Fluorine Chem.* **2004**, *125*, 603-607; b) T. Ono, V. P. Kukhar, V. A. Soloshonok, *J. Org. Chem.* **1996**, *61*, 6563-6569.

⁷³ a) F. Gosselin, P. D. O'Shea, S. Roy, R. A. Reamer, C. Chen, R. P. Volante, *Org. Lett.* **2005**, *7*, 355-358; b) Q. Zhao, J. Wen, R. Tan, K. Huang, P. Metola, R. Wang, E. V. Anslyn, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 8467-8470.



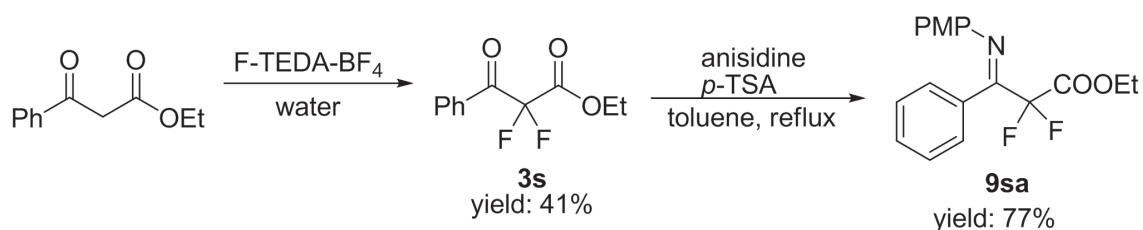
Scheme 3-23

Compared with CF₃ group, CF₂H group is much less investigated. Thus, it is interesting to synthesis CF₂H-ketimines for study in the transfer hydrogenation. The intermediate β,β -difluoroenamine **9ra'** whose amino group was trimethylsilylated was prepared from CF₃-PMP ketimine **9aa** in the presence of Me₃SiCl by Mg(0)-promoted reductive defluorination.⁷⁴ The desilylative imine formation occurred smoothly with TBAF in THF to give difluoroimine **9ra** as a 36:64 mixture of *E/Z* isomers in 85% yield (Scheme 3-24).



Scheme 3-24

It is reported that F-TEDA-BF₄, one of the most commonly used electrophilic fluorinating reagents, could be used for direct fluorination of 1,3-dicarbonyl compounds in aqueous medium.⁷⁵ After the difluorination of the ethyl 3-oxo-3-phenylpropanoate, we continued by synthesizing the corresponding *N*-PMP ketimine **9sa** from the difluorinated β -keto ester **3s** under the same imination conditions as the other ketimines in 77% yield. This difluorinated ketimine has a much bulkier ester group but less electronegative nature compared with *N*-PMP CF₃ ketimine **9aa** (Scheme 3-25).



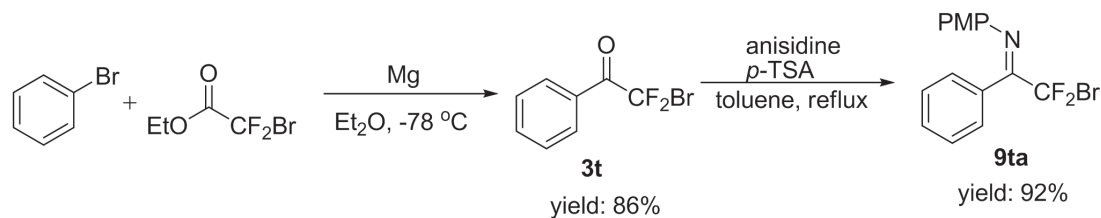
Scheme 3-25

Another difluorinated ketimine is *N*-PMP CF₂Br-ketimine **9ta** which could be

⁷⁴ a) K. Uneyama, T. Kato, *Tetrahedron Lett.* **1998**, 39, 587-590; b) M. Mae, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2000**, 41, 7893-7896

⁷⁵ G. Stavber, S. Stavber, *Adv. Synth. Catal.* **2010**, 352, 2838-2846.

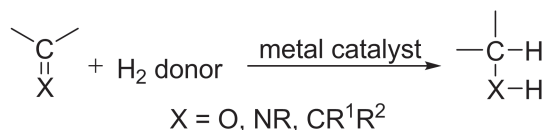
synthesized as a single *E* isomer from ethyl bromodifluoroacetate by a Grignard condensation, followed by the imination with anisidine through the same route as the synthesis of *N*-PMP CF₃ ketimine **9aa** (Scheme 3-26).



Scheme 3-26

3.2.3 Asymmetric transfer hydrogenation: optimization of the reaction conditions

Hydride transfer reaction is another way to realize the reduction of prochiral compounds besides hydrogenation by means of hydrogen gas. The hydride could be transferred from the hydride donor to the substrate such as imine, ketone, and olefin (Scheme 3-27).⁷⁶



Scheme 3-27

Although enzymes are highly enantioselective in asymmetric transfer hydrogenation by using NADH or NADPH as a hydrogen donor, several decades were spent by chemists to develop alternative chemical catalysts.⁷⁷ In 1950, the first asymmetric transfer hydrogenation was reported by using an achiral catalyst aluminum butoxide and a chiral hydride source, (+)-2-butanol or (+)-3-methyl-2-butanol, through Meerwein-Ponndorf-Verley reduction.⁷⁸ Later in the 1970s, the transition-metal catalyst [RuCl₂(PPh₃)₃] and [RuH₂(PPh₃)₄] were reported by using glucides as hydride sources.⁷⁹ Since then, many chiral catalysts have been developed particularly by Pfaltz (Ir),⁸⁰ Genet (Ru),⁸¹ Lemaire (Rh)⁸² and Evans (Sm)⁸³. The

⁷⁶ R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97-102.

⁷⁷ C. Wang, X. Wu, J. Xiao, *Chem. Asian. J.* **2008**, *3*, 1750-1770.

⁷⁸ W. V. E. Doering, R. W. Young, *J. Am. Chem. Soc.* **1950**, *72*, 631-631.

⁷⁹ a) G. Descotes, D. Sinou, *Tetrahedron Lett.* **1976**, *17*, 4083-4086; b) K. Ohkubo, K. Hirata, K. Yoshinaga, M. Okada, *Chem. Lett.* **1976**, 183-184.

⁸⁰ D. Muller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta.* **1991**, *74*, 232-240.

breakthrough of transition-metal catalysts for ATH was Noyori's work with Ru (II) catalytic systems featuring a monotosylated 1,2-diamine or an amino alcohol with isopropanol or formic acid/triethylamine azeotrope for the reduction of ketones and imines. Besides, inspired by nature, artificial metalloenzymes and organocatalysis with NADH analogues such as Hantzsch ester as hydride source have been developed to mimic the function of enzymes.⁷⁷

The azeotropic mixture (NEt₃/HCOOH) and isopropanol are by far the most used hydride donors in transfer hydrogenation.⁸⁴ Enantioselective reductions using these hydride sources could be accomplished with some transition metals such as ruthenium (Ru), rhodium (Rh), and iridium (Ir).⁷⁷ So, we tested these two types of hydride sources for the asymmetric transfer hydrogenation of CF₃-ketimines by using chiral ruthenium catalysts.

3.2.3.1 Screening of the hydrogen source and ligand's type

We have evaluated the azeotrope of formic acid/NEt₃ and isopropanol as sources of hydrogen in the catalytic system of half-sandwich ruthenium complexes ([RuCl₂(η⁶-arene)]₂) with 1,2-amino alcohols or monotosylated diamine ligands. Historically, half-sandwich π-complexes of Ru (II) catalysts are the most efficient metal source for the association with 1,2-amino alcohols or monotosylated diamine ligands.^{84,85} These kinds of [RuCl₂(η⁶-arene)]₂ complexes combined with protic ligands could go through a "metal-ligand bifunctional catalysis" after being activated by a base such as sodium or potassium carbonates, hydroxides, and alkoxides.

The azeotrope formic acid/triethylamine is an inexpensive hydride source. Previously, our lab has already achieved the synthesis of optically enriched CF₃-allylic alcohols from the corresponding enones by Noyori's ruthenium (II) catalyzed transfer hydrogenation using [RuCl(*p*-cymene){(*R,R*)-Tsdpen}] (Tsdpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene-diamine)⁸⁶ and the 2:5 HCOOH/NEt₃ azeotropic mixture. The enantioselectivities of the

⁸¹ J. P. Genet, V. Ratovelomanana Vidal, C. Pinel, *Synlett* **1993**, 478-480.

⁸² P. Gamez, F. Fache, M. Lemaire, *Tetrahedron: Asymmetry* **1995**, 6, 705-718.

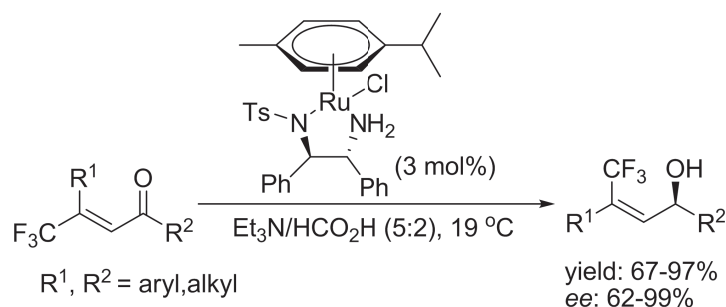
⁸³ D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J. Am. Chem. Soc.* **1993**, 115, 9800-9801.

⁸⁴ S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, 35, 226-236.

⁸⁵ C. Ganter, *Chem. Soc. Rev.* **2003**, 32, 130-138.

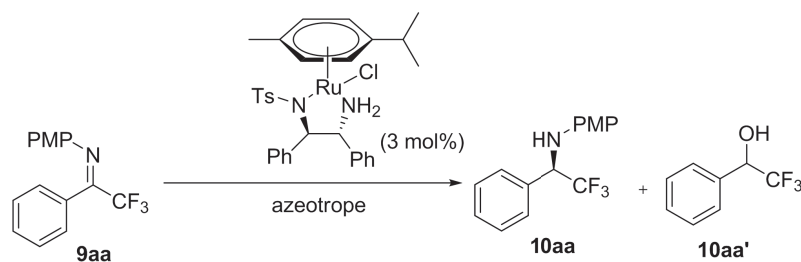
⁸⁶ a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 2521-2522; b) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 4916-4917.

transfer hydrogenation were high with enones having an aryl ketone moiety (**Scheme 3-28**).⁴⁴



Scheme 3-28

Hereby, we employed the 2:5 HCOOH/NEt₃ azeotropic mixture as reducing reagent with ketimine **9aa** under the well-known conditions of asymmetric transfer hydrogenation discovered by Noyori with the chiral diamine Ru catalyst depicted in **Scheme 3-28**. After 72 hours, only 45% conversion was obtained with mainly the 2,2,2-trifluoro-1-phenylethanol **10aa'** byproduct (**Table 3-10**, entry 1). When the reaction was performed with the opposite ratio of HCO₂H/NEt₃, the reaction did not work (**Table 3-10**, entry 2). A higher concentration gave a similar moderate conversion (**Table 3-10**, entry 3). In order to improve the reactivity of this transfer hydrogenation, we increased the temperature from 25 °C to 40 °C, the conversion increased to 73%. The isolated yield of desired CF₃-amine was 58% and the enantioselectivity was 81% (**Table 3-10**, entry 4). With this promising result, we then changed the concentration of the CF₃-ketimine at 40 °C; however, only moderate conversions were observed (**Table 3-10**, entries 5-6). Besides, the higher temperature 60 °C was not suitable for the conversion (**Table 3-10**, entry 7). When the reaction was conducted in toluene as a second solvent at high temperature, the conversion diminished to 20% (**Table 3-10**, entry 8). DMF has been employed as an effective solvent for the dynamic kinetic asymmetric transfer hydrogenation of β-aryl α-keto esters with Noyori's catalyst at high temperature.⁸⁷ But again, with DMF we only got a moderate conversion (**Table 3-10**, entries 9-10).



⁸⁷ K. M. Steward, E. C. Gentry, J. S. Johnson, *J. Am. Chem. Soc.* **2012**, *134*, 7329-7332.

entry	azeotrope	T (°C)	time (h)	Conv. (%) ^a
1	Et ₃ N/HCO ₂ H (5/2) (1 M)	25	72	45 (mainly byproduct 10aa')
2	Et ₃ N/HCO ₂ H (2/5) (1 M)	25	24	-
3	Et ₃ N/HCO ₂ H (5/2) (4 M)	25	72	41 (mainly byproduct 10aa')
4	Et ₃ N/HCO ₂ H (5/2) (1 M)	40	72	73(58), <i>ee</i> = 81%
5	Et ₃ N/HCO ₂ H (5/2) (0.5 M)	40	72	65
6	Et ₃ N/HCO ₂ H (5/2) (2 M)	40	72	49 (42)
7	Et ₃ N/HCO ₂ H (5/2) (2 M)	60	17	33 (30)
8	Et ₃ N/HCO ₂ H (5/2) in toluene	60	17	20
9	Et ₃ N/HCO ₂ H (5/2) (add in by portion of 0.1mL) in DMF with MgSO ₄	70	>72	53 (39)
10	Et ₃ N/HCO ₂ H (2/5) (add in by portion of 0.1 mL) in DMF with MgSO ₄	70	>72	65 (56)

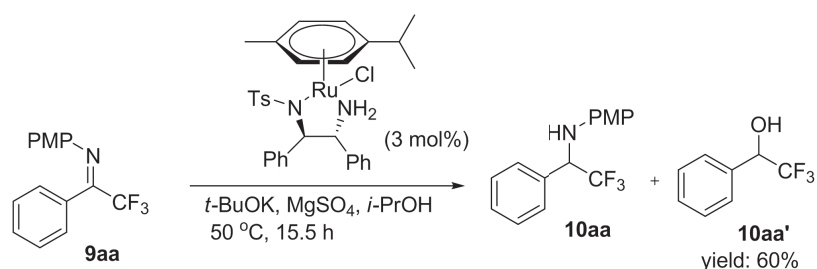
^a yield of isolated pure product is given in parentheses.

Table 3-10

From these results, we could conclude that Noyori's conditions for transfer hydrogenation by using azeotropic mixture of HCO₂H/NEt₃ and Ru (II) catalyst combined with a diamine ligand are not very efficient for the asymmetric reduction of CF₃-ketimines. Alcohol **10aa'** was often observed as undesired product. The best result we obtained was 58% yield and 81% *ee* in 1M 2:5 azeotropic mixture of HCOOH/NEt₃ (Table 3-10, entry 4).

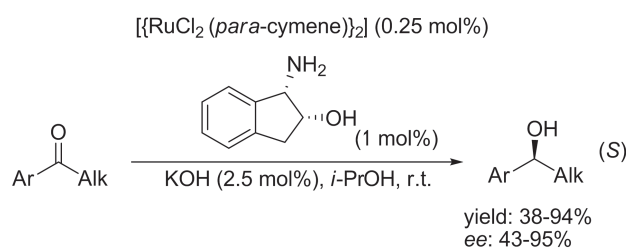
Apart from HCO₂H/NEt₃ azeotropic mixture, isopropanol is another most used conventional hydride source due to its non toxic, environmentally friendly properties. It is an inexpensive solvent which renders the life time of many metal catalysts reasonably long. The corresponding byproduct acetone is readily removable.

Although *N*-tosylated ethylenediamine was reported as an excellent ligand with the half-sandwich ruthenium complexes in catalyzed transfer hydrogenation with isopropanol,⁷⁶ we found that it was not appropriate for our transfer hydrogenation. We got 64% conversion after 15.5 hours, but the CF₃-ketimine was mainly converted into the 2,2,2-trifluoro-1-phenylethanol **10aa'** byproduct in 60% yield (Scheme 3-29).



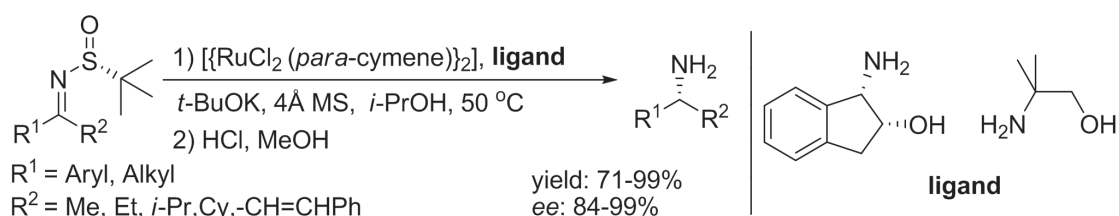
Scheme 3-29

In the literature, high enantioselectivity has been obtained by the combination of an appropriate Ru arene and chiral amino alcohol auxiliary for the asymmetric transfer hydrogenation of ketones. Wills group first employed the commercially available chiral (1*S*, 2*R*)-1-amino-2-indanol as amino alcohol ligand to combine with [RuCl₂(*para*-cymene)]₂ by using KOH as base and isopropanol as solvent as well as hydride source for the asymmetric transfer hydrogenation of aromatic/alkyl ketones in good results (Scheme 3-30).⁸⁸



Scheme 3-30

In addition to the enantioselective version, Yus group has reported the diastereoselective transfer hydrogenation of chiral *N*-(*tert*-butylsulfinyl)imines with a chiral Ru complex featuring the (1*S*, 2*R*)-1-amino-2-indanol ligand to obtain high diastereoselectivities with match effect.⁸⁹ Later, achiral ligand, 2-amino-2-methylpropan-1-ol, was introduced into the ATH and also led to good results (Scheme 3-31).⁶⁴



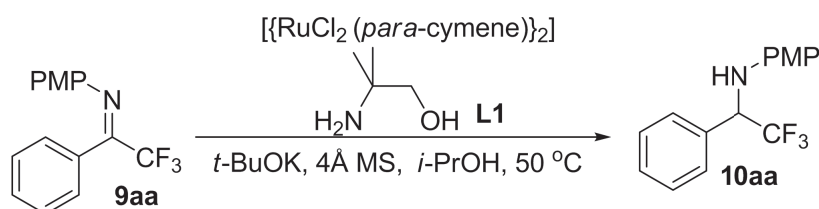
Scheme 3-31

Inspired by Yus' work, we envisaged the development of an enantioselective approach

⁸⁸ a) M. Palmer, T. Walsgrove, M. Wills, *J. Org. Chem.* **1997**, *62*, 5226-5228; b) M. Wills, M. Palmer, A. Smith, J. Kenny, T. Walsgrove, *Molecules* **2000**, *5*, 4-18.

⁸⁹ a) D. Guijarro, Ó. Pablo, M. Yus, *Tetrahedron Lett.* **2009**, *50*, 5386-5388; b) D. Guijarro, Ó. Pablo, M. Yus, *J. Org. Chem.* **2010**, *75*, 5265-5270.

for the asymmetric transfer hydrogenation of prochiral trifluoromethylated ketimines and a chiral aminol alcohol as ligand. Compared with the *N*-(*tert*-butylsulfonyl)imines, which were used by Yus, our substrate **9aa** has a *p*-methoxyphenyl (PMP) protected nitrogen atom to undergo an enantioselective transfer hydrogenation reaction rather than a diastereoselective version. So we first selected the same achiral ligand as Yus, 2-amino-2-methylpropan-1-ol **L1** to test the reactivity of the transfer hydrogenation using potassium *tert*-butoxide as base to activate the ruthenium complex precursor and isopropanol as hydride source. Delightfully, we obtained 88% conversion after 12 hours and all converted into the desired CF₃-amine **10aa** without any alcohol byproduct **10aa'** (Scheme 3-32).



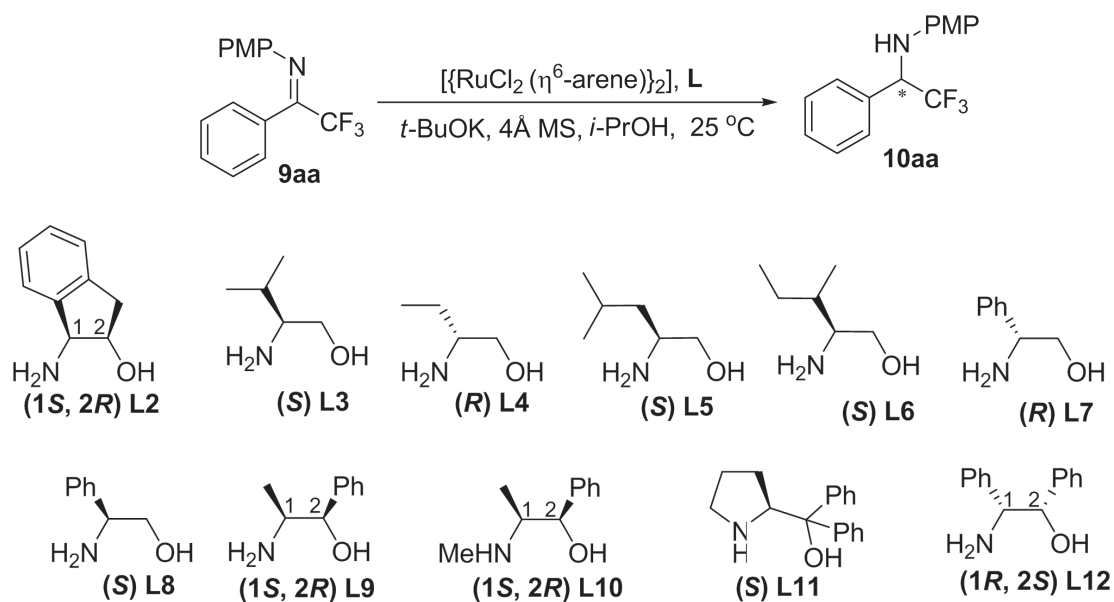
Scheme 3-32

Isopropanol is a convenient solvent as well as an excellent hydride source in transfer hydrogenation. It has been successfully used in industrial processes. When we replaced the isopropanol with ethanol, we did not obtain the amine product but only got the 2,2,2-trifluoro-1-phenylethanol **10aa'**.

3.2.3.2 Screening of chiral ligand and ruthenium arene

Since the use of an amino alcohol ligand and isopropanol could completely avoid the hydrolysis of CF₃-ketimine, we then evaluated several simple commercially available enantiomerically pure *N,O*-type ligands to generate the chiral ruthenium catalysts for the synthesis of optically enriched CF₃-amine products (Table 3-11). The amino alcohols having two stereogenic centers at C1 and C2 (**L2**, **L9**, **L10**, **L12**) appeared much more efficient than the other ligands (Table 3-11, entries 1, 8, 9 and 11). Substrate **9aa** was fully converted with **L2**, **L9** and **L12** (Table 3-11, entries 1, 8 and 11). Besides, the enantioselectivities were high by using **L2** and **L12**, affording 93% and 90% *ee* respectively. In order to increase the enantioselectivity, the bulkier secondary amino alcohols **L10** and **L11** were introduced to this

reaction. With *N*-methyl derivative **L10** a lower reactivity and a slightly increased enantioselectivity was observed while the (*S*)-diphenylprolinol **L11** was not successful for this transfer hydrogenation (**Table 3-11**, entries 9-10).



entry	$\{[\text{RuCl}_2(\eta^6\text{-arene})\}_2\}$ arene	ligand	yield (%) ^a	ee (%)
1	<i>p</i> -cymene	L2	>98	93 (<i>R</i>) ^b
2	<i>p</i> -cymene	L3	53	42 (<i>S</i>)
3	<i>p</i> -cymene	L4	79	0
4	<i>p</i> -cymene	L5	92	26 (<i>S</i>)
5	<i>p</i> -cymene	L6	96	48 (<i>S</i>)
6	<i>p</i> -cymene	L7	69	20 (<i>S</i>)
7	<i>p</i> -cymene	L8	85	23 (<i>R</i>)
8	<i>p</i> -cymene	L9	>98	67 (<i>R</i>)
9	<i>p</i> -cymene	L10	72	69 (<i>R</i>)
10	<i>p</i> -cymene	L11	0	-
11	<i>p</i> -cymene	L12	>98	90 (<i>S</i>)
12 ^c	<i>p</i> -cymene	L2	>98	94 (<i>R</i>)
13	benzene	L2	>98	87 (<i>R</i>)

^a Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard. ^b The absolute configuration was determined by comparison with literature data.^{66,90} ^c Reaction was performed with a catalytic amount of additive (CF₃COOAg).

Table 3-11

⁹⁰ I. Fernández, V. Valdivia, A. Alcudia, A. Chelouan, N. Khair, *Eur. J. Org. Chem.* **2010**, 1502-1509.

Compared with asymmetric transfer hydrogenation of imines, the asymmetric reduction of ketone is much more investigated. According to the literature,⁹¹ in asymmetric transfer hydrogenation of ketones, the outcome of asymmetric induction with chiral *N,O*-type ligands bearing one or two stereogenic centers predominantly depends on the configuration of the hydroxyl substituted carbon. In contrast, the amine substituted carbon has a much less influence on the enantioselectivity. Our results are in accord with the previous observations. The amino alcohol ligands bearing a stereogenic center at C2 such as **L2**, **L9**, **L10** and **L12** all lead to the CF₃-amine in the configuration of the main enantiomer identical with that of the C2 (**Table 3-11**, entries 1, 8, 9 and 11).

However, we are puzzled to find the inversion of the configuration of the main enantiomer when more attention was focused on the ligands bearing only one stereogenic center at amine substituted carbons **L3-L8**. Because this type of ligands did not have a stereogenic center at hydroxyl substituted carbon, the rule we concluded above was not suitable to predict the configuration. While with **L8**, (*S*)-2-amino-2-phenylethanol, the (*R*) enantiomer of the CF₃-amine was observed which was the same as that of **L2**, **L9** and **L12**, the change of phenyl group to an alkyl group on that (*S*)-carbon **L3**, **L5** and **L6** gave the main enantiomer of CF₃-amine with the opposite (*S*) configuration. Although these ligands did not offer excellent enantioselectivities, it is such a unique observation that we could not find a precedent in the literature. Otherwise, the two enantiomers **L7** and **L8** provided opposite configurations of the amine product as expected.

The additive silver trifluoroacetate CF₃COOAg which was reported to be a crucial factor for reactivity and enantioselectivity in rhodium system⁹² turned out to be not necessary for the ruthenium-catalyzed transfer hydrogenation of CF₃-ketimine, although the *ee* slightly increased in the presence of this additive (**Table 3-11**, entry 12).

When the arene of the ruthenium catalyst was changed from *para*-cymene to less bulky arene benzene, the *ee* was reduced to 87% (**Table 3-11**, entry 13). Moreover, the arene Ru complex replaced by [RuCp*(ACN)₃]⁺PF₆⁻ (Cp* = η⁵-pentamethylcyclopentadienyl, ACN =

⁹¹ a) J. Takehara, S. Hashiguchi, A. Fujii, S.-I. Inoue, T. Ikariya, R. Noyori, *Chem. Commun.* **1996**, 233-234; b) M. Hennig, K. Puntener, M. Scalone, *Tetrahedron: Asymmetry* **2000**, *11*, 1849-1858; c) D. G. I. Petra, J. N. H. Reek, J.-W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2000**, *6*, 2818-2829; d) K. Everaere, A. Mortreux, J.-F. Carpentier, *Adv. Synth. Catal.* **2003**, *345*, 67-77.

⁹² K. Ren, L. Zhang, B. Hu, M. Zhao, Y. Tu, X. Xie, T. Zhang, Z. Zhang, *ChemCatChem.* **2013**, *5*, 1317-1320.

CH₃CN) gave the 2,2,2-trifluoro-1-phenylethanol as the sole product **10aa'**. In addition to amino alcohol ligands **L1-L12**, we also evaluated (*R*)-1,1'-binaphthyl-2,2'-diamine **L13**, the amino acid valine **L14** and the diphosphine ligand (*S*)-BINAP **L15**, but the reaction did not work at all.

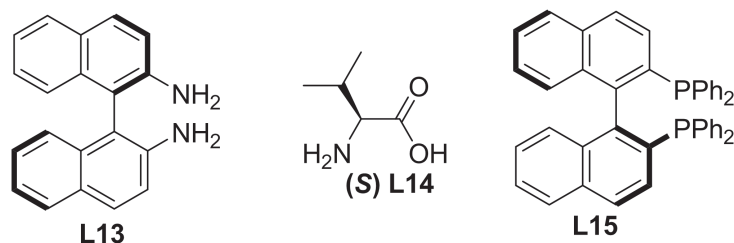


Figure 3-4

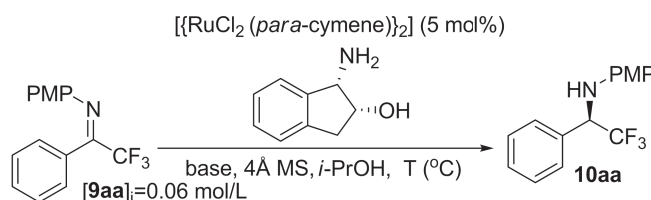
So we chose *para*-cymene as the arene and amino indanol **L2** as the ligand to continue the optimization of the reaction conditions.

3.2.3.3 Screening of base, temperature, concentration, and ratio of reaction partners

The transfer hydrogenation performed well with strong bases such as KOH, *t*-BuOK and *i*-PrONa, but with weaker bases Cs₂CO₃ and K₂CO₃, the transfer hydrogenation did not work at all (**Table 3-12**, entries 1-5). The temperature was also studied on the course of the reaction with *t*-BuOK and we found that conversions and enantioselectivities almost did not vary at higher temperature while the reaction time was significantly shortened (**Table 3-12**, entries 2, 7 and 8); however, transfer hydrogenation at lower temperature (0 °C) led to a low conversion even after a longer reaction time (**Table 3-12**, entry 6). Anyway, the difference of enantioselectivity was very slight in the range of temperature from 0 °C to 60 °C. So, we decided to perform further transfer hydrogenations at 25 °C.

Furthermore, the concentration and the ratio Ru dimer/ligand/base were investigated. We tested the transfer hydrogenation of trifluoromethyl imine **9aa** at 0.06 mol/L, 0.04 mol/L and 0.1 mol/L concentration and the results were the same. So, we chose 0.1 mol/L concentration for further optimization. At the beginning, we used 5 mol% Ru dimer and the ratio of Ru dimer/ligand/base was 1:2:5 (**Table 3-12**, entry 2). Then, we reduced the Ru dimer to 3 mol% and kept unchanged the ratio Ru dimer/ligand/base, but the conversion was only 79 % (**Table**

3-12, entry 9). In order to improve the conversion with a lower amount of the Ru catalyst, we increased the temperature to 40 °C; to our delight, full conversion was observed after the same reaction time and *ee* was 91% (**Table 3-12**, entry 10). The doubling of ligand amount did not give a higher enantioselectivity; moreover, it slowed down the reduction (**Table 3-12**, entry 11). The yield and *ee* neither increased nor reduced when more amount of base was used (**Table 3-12**, entry 12). Besides, the presence of molecular sieves could efficiently avoid the hydrolysis of CF₃-ketimine **9aa**, because without molecular sieves the yield of amine product **10aa** decreased to 88%, along with a small part of byproduct **10aa'**. It is important to note that all these changes only have a tiny impact on the enantioselectivities (**Table 3-12**, entries 9-13).



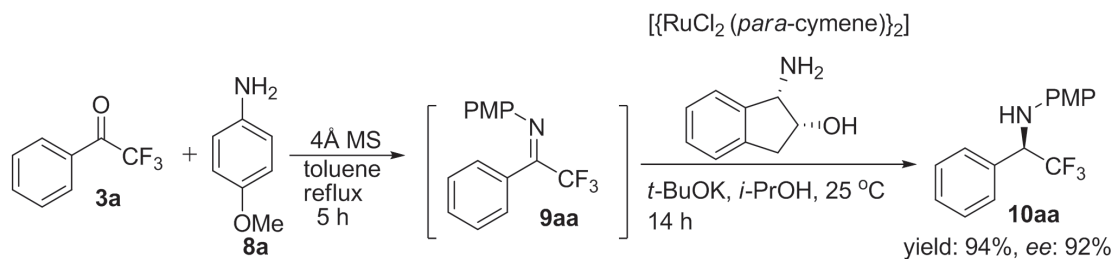
entry	T (°C)	base	Ratio Ru dimer/L ^a /base	T (h)	yield ^b (%)	<i>ee</i> (%)
1	25	KOH	1:2:5	14	>98	92
2	25	<i>t</i> -BuOK	1:2:5	14	>98	93
3	25	<i>i</i> -PrONa	1:2:5	14	>98	93
4	25	CS ₂ CO ₃	1:2:5	14	0	-
5	25	K ₂ CO ₃	1:2:5	14	0	-
6	0	<i>t</i> -BuOK	1:2:5	21	59	94
7	40	<i>t</i> -BuOK	1:2:5	5	>98	93
8	80	<i>t</i> -BuOK	1:2:5	5	>98	92
9	25	<i>t</i> -BuOK	1:2:5 ^c	14	79	93
10	40	<i>t</i> -BuOK	1:2:5 ^c	14	>98	91
11	25	<i>t</i> -BuOK	1:4:5	22	87	93
12	25	<i>t</i> -BuOK	1:2:10	14	>98	93
13	25	<i>t</i> -BuOK	1:2:5 ^d	14	88	92

^a L: ligand. ^b Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard. ^c 3 mol% of ruthenium dimer was used. ^d The reaction was performed without molecular sieves.

Table 3-12

After this screening of reaction conditions, we decided to choose the conditions of entry 2 as the optimum ones. The reaction could be conducted with the aid of the ruthenium catalyst precursor generated by 5 mol% [$\{\text{RuCl}_2(\textit{para}\text{-cymene})\}_2$], 10 mol% (1*S*, 2*R*)-1-amino-2-indanol and 4Å molecular sieves in isopropanol. After 20 minutes refluxing, this catalyst solution was cooled to room temperature. The solution of CF₃-ketimine and *t*-BuOK was subsequently added into the catalyst system to perform the asymmetric transfer hydrogenation.

Next, a more convenient one-pot consecutive imination-reduction was examined. The intermediate CF₃-ketimine **9aa** was generated from 2,2,2-trifluoro-1-phenylethanone **3a** and 4-methoxyaniline **8a** in the presence of 4Å molecular sieves in refluxing toluene, followed by the asymmetric transfer hydrogenation. To our delight, this one-pot process resulted in the formation of CF₃-amine **10aa** in high yield (94%) and slightly reduced enantioselectivity (92% ee) (**Scheme 3-33**). The overall reaction must be achieved stepwise in one-pot otherwise mixing all reactants and reagents together resulted in the 2,2,2-trifluoro-1-phenylethanol **10aa'** byproduct.



Scheme 3-33

We also investigated the relationship between reaction time, conversion and enantioselectivity. From the diagram (**Figure 3-5**), we could easily see that the conversion increased dramatically in the first 2 hours and then, it smoothly reached full conversion. However, the enantioselectivity decreased slightly from 96% to 92%. This result showed that the longer time it reacted, the less stereoselective is the hydride transfer to the substrate.

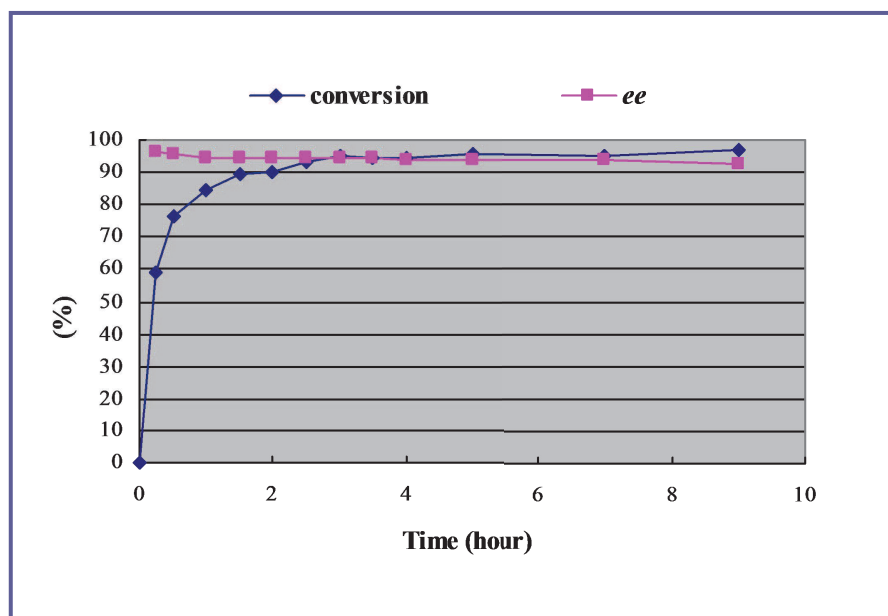
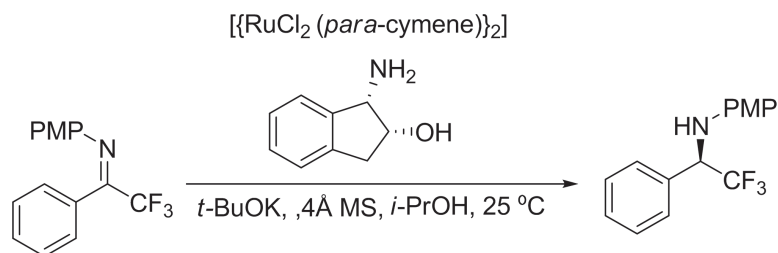
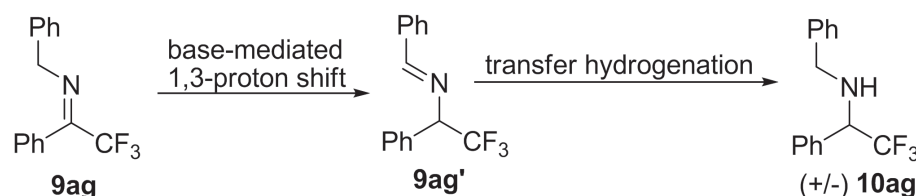


Figure 3-5

3.2.3.4 Screening of the nitrogen substituent

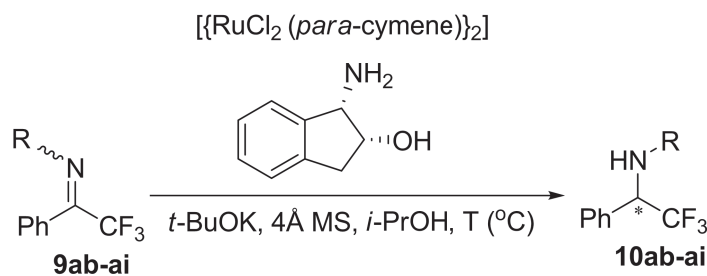
Considering that *p*-methoxyphenyl (PMP) could be easily removed, we first chose PMP as nitrogen substituent for the imines. Apart from the PMP group, some other substituents were also taken into account (Table 3-13, entries 1-8). The ketimine with *N*-(*t*-butylsulfinyl) protecting and activating group at nitrogen atom **9ab** was much more electrophilic than *N*-PMP ketimine. Due to the greater instability and tendency to hydrolysis, it was fully converted into 2,2,2-trifluoro-1-phenylethanol **10aa'** (Table 3-13, entry 2). This outcome also indicated that the conditions reported by Yus⁸⁹ could not be transposed to our case of trifluoromethyl aryl ketimines.¹² The CF₃-ketimine with *n*-butyl substituent on nitrogen atom did not provide any good result (Table 3-13, entry 3). Some bulky *N*-aryl substituted imines **9ad**, **9ae** and **9af** were also employed in this reaction; we got the corresponding amines in good yields but lower *ee*'s were observed compared with PMP (Table 3-13, entries 4-6).

Benzyl protected imine **9ag** gave the desired amine product in the form of a racemic compound (**Table 3-13**, entry 7) because of base-mediated 1,3-hydrogen shift involving an azaallylic anion intermediate that led to the regioisomeric imine not producing a stereogenic center by transfer hydrogenation⁷² (**Scheme 3-34**).



Scheme 3-34

Since the trimethylsilyl group could be removed easily,^{73a} we then examined the *N*-SiMe₃ ketimine for the ATH. The ketimine **9ah** was fully converted and we obtained 77% free CF₃-amine **10ah** as we have expected, but the *ee* was low, only 32% (**Table 3-13**, entry 8).



entry	R	temperature (°C)	time (h)	yield (%) ^a	<i>ee</i> (%)
1	PMP	25	14	98 (10aa)	93 (<i>R</i>)
2	<i>t</i> -busulfinyl	40	14	0 ^b (10ab)	-
3	<i>n</i> -butyl	40	13	0 (10ac)	-
4	1-naphthyl	25	14	99 (10ad)	72 (+)
5	2-naphthyl	25	15	99 (10ae)	84 (-)
6	2,4-(MeO) ₂ C ₆ H ₃	25	22	80 ^c (10af)	90 (-)
7	Bn	40-80	5 days	86 (10ag)	0
8	Me ₃ Si	25	13.5	77 ^c (10ai)	32 (nd)
9	H	25	14	99 ^c (10ai)	32 (nd)

^a Yields of isolated pure products. ^b Only 2,2,2-trifluoro-1-phenylethanol was obtained. ^c Conversion was determined by ¹⁹F NMR spectroscopy. nd: not determined.

Table 3-13

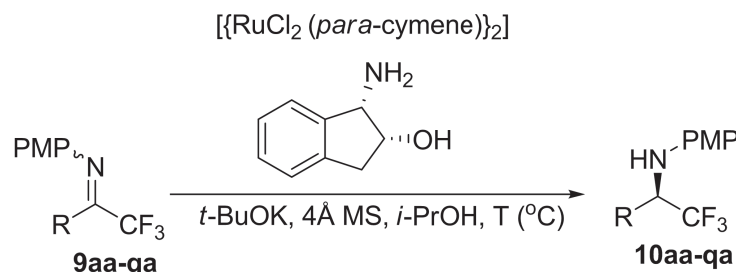
Besides, the imine without substituent group **9ai** was also evaluated in the asymmetric reduction of ketimine and it gave a full conversion but with 32% *ee*, the same as that of trimethylsilyl ketimine **9ah** (Table 3-13, entry 9). Thus, we could envisage that the trimethylsilyl group was removed before the asymmetric transfer hydrogenation occurred. These results clearly indicated that a sterically hindered R group on the nitrogen is crucial for high enantiofacial discrimination of the imine.

3.2.4 Substrate scope

With optimized conditions in hand, we evaluated other trifluoromethyl ketimines with PMP as nitrogen substituent in ATH reaction (Table 3-14). Different substituted aromatic groups at R position were used and led to a series of chiral CF₃-amines with high enantioselectivities and high yields (Table 3-14, entries 1-11), although the two electron-rich ketimines **9ba** and **9ja** were somehow less reactive and required heating at 40 °C in order to reach a full conversion within the same reaction time (Table 3-14, entries 2 and 10). The use of substrates bearing an electron-withdrawing aryl substituent gave slightly decreased enantioselectivities (Table 3-14, entries 3, 6, 7, 8). A methoxy substituent in the *ortho* position of phenyl group in **9la** caused steric hindrance that disfavored the reaction even at higher temperature (Table 3-14, entry 12). With the 2-naphthyl substituent, we obtained the corresponding CF₃-amine **10ma** also in high yield and *ee*. The (*R*) absolute configuration of CF₃-amine **10aa** was determined by polarimetry and comparison with literature data.^{66,90} The absolute configurations of other aryl CF₃-amines **10ba-ma** were assigned by analogy.

In order to broaden the substrate scope, we introduced other substituents than aryl ones for R group. Ketimine **9na** bearing a benzyl group existing as a mixture of imine/enamine tautomers did not work at all. We did not observe the new doublet signal in ¹⁹F NMR even at high temperature (Table 3-14, entry 14). Fluorinated amino acids are important organic compounds with biological applications; up to now only asymmetric hydrogenation of α -imino ester by palladium was reported by Uneyama group.⁶¹ Thus, we tested the reactivity of the CF₃- α -imino ester **9oa** in the asymmetric transfer hydrogenation. Unfortunately, it did not provide any result (Table 3-14, entry 15). From the aliphatic hexylimine **9pa**, we

observed a moderate yield and 22% *ee* (Table 3-14, entry 16). In this case, we could not separate the *E* and *Z* isomers of the starting imine **9pa** which may explain the low *ee* value. However, the reaction of cyclohexyl ketimine **9qa** did not give any positive result (Table 3-14, entry 17).



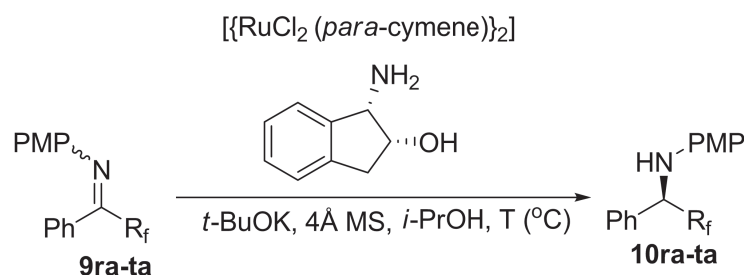
entry	R	temperature (°C)	time (h)	yield (%) ^a	<i>ee</i> (%)
1	C ₆ H ₅	25	14	98 (10aa)	93 (<i>R</i>)
2	4-OMeC ₆ H ₄	40	13.5	99 (10ba)	91 (<i>R</i>)
3	4-BrC ₆ H ₄	25	14	94 (10ca)	90 (<i>R</i>)
4	4-MeC ₆ H ₄	25	14	99 (10da)	92 (<i>R</i>)
5	3,4-Me ₂ C ₆ H ₃	25	14	94 (10ea)	90 (<i>R</i>)
6	4-CF ₃ C ₆ H ₄	25	14	99 (10fa)	89 (<i>R</i>)
7	4-ClC ₆ H ₄	25	14	98 (10ga)	90 (<i>R</i>)
8	3-ClC ₆ H ₄	25	13	99 (10ha)	89 (<i>R</i>)
9	3,4-Cl ₂ C ₆ H ₃	25	13.5	81 (10ia)	84 (<i>R</i>)
10	4- <i>t</i> -BuC ₆ H ₄	40	14	99 (10ja)	92 (<i>R</i>)
11	3- <i>i</i> -PrC ₆ H ₄	25	14	98 (10ka)	91 (<i>R</i>)
12	2-MeOC ₆ H ₄	90	16	0 (10la)	-
13	2-naphthyl	25	14	99 (10ma)	91 (<i>R</i>)
14	Bn	80	14	0 (10na)	-
15	COOMe	80	14	0 (10oa)	-
16	hexyl	40-80	5 days	52 ^b (10pa)	22 ^c (nd)
17	cyclohexyl	25	14.5	0 (10qa)	-

^a Yields of isolated pure products. ^b Conversion was determined by ¹⁹F NMR spectroscopy using trifluorotoluene as internal standard. ^c Mixture of imine-enamine tautomers (1:1). nd: not determined.

Table 3-14

The difluoromethyl group has attracted less attention than trifluoromethyl group because

of synthetic difficulties.⁴ Nevertheless, difluoromethylated amines possessing potential biological activities are worthwhile to explore. Thus we synthesized three different fluorinated ketimines **9ra-ta** for the test of asymmetric transfer hydrogenation. Difluoromethylated ketimine **9ra** was prepared as a 36:64 mixture of *E/Z* isomers whereas CF₃ ketimine **9aa** was obtained as a single *E* isomer. This mixture was subjected to our ATH conditions to furnish difluoromethyl amine **10ra** in good yield and moderate *ee* value that we reasonably ascribed to the initial mixture of stereoisomers (Table 3-15, entry 2). In order to get a single isomer of difluorinated ketimine, we tried to separate the isomers by silica gel chromatography but without success. We then synthesized the more sterically demanding and less electronegative difluoroester ketimine **9sa** and bromodifluoromethyl ketimine **9ta** as single isomer. However, none of them gave positive result (Table 3-15, entries 3-4).

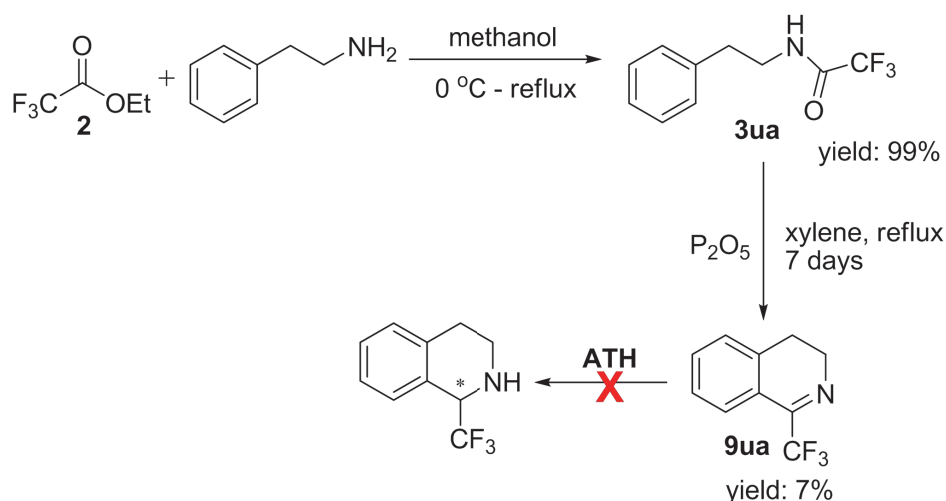


entry	R _f	temperature (°C)	time (h)	yield (%)	ee (%)
1	CF ₃	25	14	98 (10aa)	93 (<i>R</i>)
2	CF ₂ H	25	14	82 (10ra)	57 (<i>R</i>)
3	CF ₂ COOEt	90	21	0 (10sa)	-
4	CF ₂ Br	80	21	0 (10ta)	-

Table 3-15

In order to test the asymmetric transfer hydrogenation method on cyclic CF₃-ketimine, we prepared the 1-(trifluoromethyl)-3,4-dihydroisoquinoline **9ua** in a low yield by cyclization of 2,2,2-trifluoro-*N*-phenethylacetamide **3ua** which could be quantitatively obtained by amination of ethyl 2,2,2-trifluoroacetate **2** with 2-phenylethanamine (Scheme 3-35).⁹³ However, the structurally rigid cyclic ketimine **9ua** could not provide any corresponding amine product under our transfer hydrogenation condition.

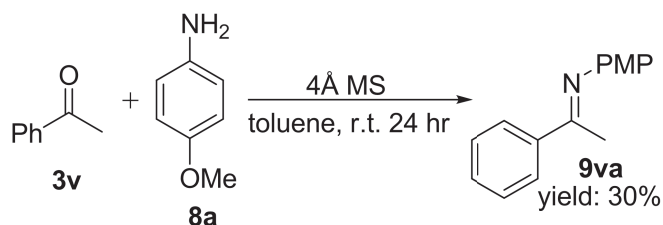
⁹³ R. Pastor, A. Cambon, *J. Fluorine Chem.* **1979**, *13*, 279-296.



Scheme 3-35

3.2.5 Comparison with non-fluorinated imine

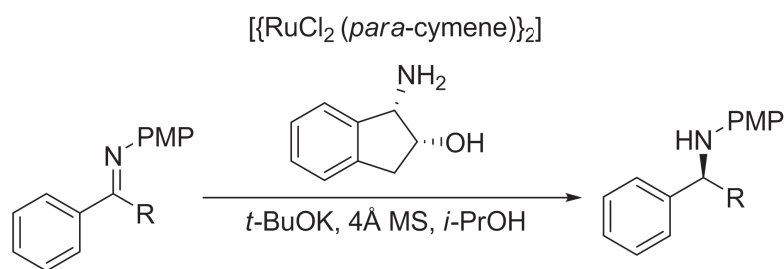
In order to provide a comparison of the behaviour of fluorinated *versus* non-fluorinated ketimines, we synthesized the CH₃-ketimine **9va** as the *E*-isomer from acetophenone **3v** and *para*-methoxyaniline **8a** with 4Å molecular sieves in toluene at room temperature for 24 hours (Scheme 3-36).⁹⁴



Scheme 3-36

When the nonfluorinated methyl ketimine **9va** was employed in the ATH reaction, we only observed 8% of amine product even at high temperature (Table 3-16, entries 2 and 3), which clearly indicates that the presence of the electron-withdrawing CF₃ group in **9aa** significantly enhanced the electrophilic character of the iminic carbon and thus increased the ketimine reactivity. This result confirms, one more time, that the chemistry developed for non-fluorinated substrates can not be simply translated to fluorinated molecules and *vice versa*.¹²

⁹⁴ P. Schnider, G. Koch, R. Pretot, G. Z. Wang, F. M. Bohnen, C. Kruger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887-892.



entry	R	temperature (°C)	time (h)	yield (%)	ee (%)
1	CF ₃	25	14	98 (10aa)	93 (<i>R</i>)
2	CH ₃	25	14	0 (10ua)	-
3	CH ₃	80	14	8 (10ua)	-

Table 3-16

3.2.6 Mechanism investigation

For the asymmetric hydride transfer reaction of polar C=X (X = N, O) bonds with ruthenium complexes, there are two main mechanisms: a metal hydride inner-sphere mechanism and a metal-templated bifunctionally catalyzed outer-sphere mechanism.^{64,84}

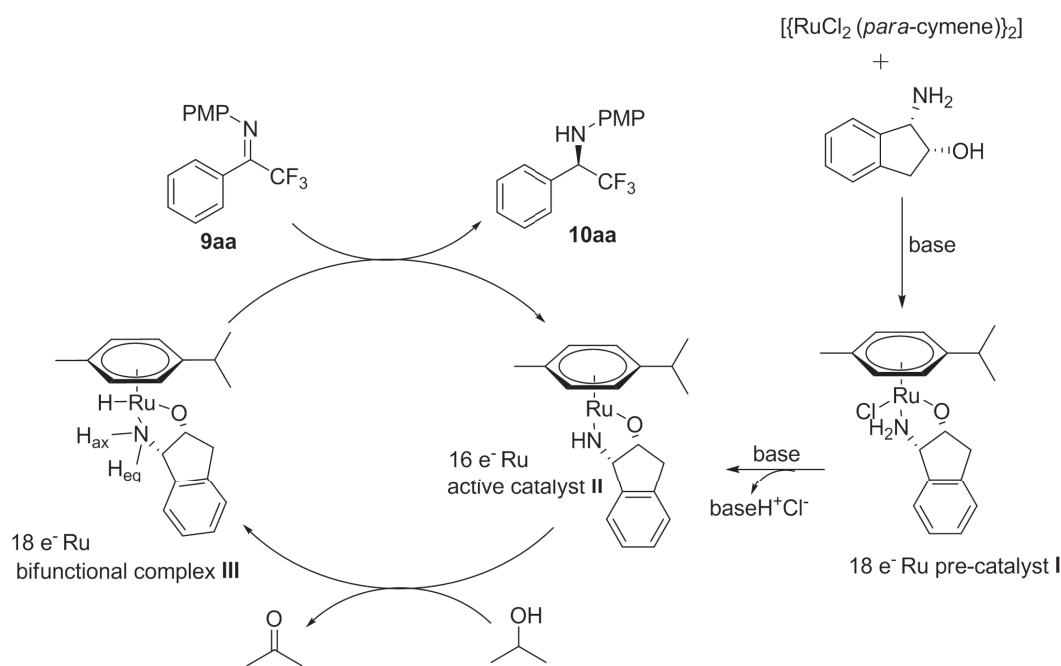
The inner-sphere mechanism is mainly proposed in the hydrogenation of ketones with [RuCl₂(PPh₃)₃]-type catalyst where both the hydride donor and acceptor interact with the metal. The outer-sphere mechanism involves the formation of a metal hydride by the interaction of the catalyst and hydride donor where the heteroatom (N or O) in neither hydride donor nor hydride acceptor interacts with the metal directly.

In the outer-sphere mechanism, the activated 18-electron Ru catalysts contain two hydrogens: one bearing hydridic property and the other one having protic character. Once the active catalyst species generated, these two hydrogen atoms transfer simultaneously to the C=X bond of substrate to achieve the transfer hydrogenation. This kind of mechanism conquering a relatively low energy barrier has been confirmed by theoretical calculation of the energies by Noyori, Andersson and Handgraaf groups.^{95,91c} The most efficient Ru catalysts [Ru(NHCH₂CH₂Y)(η⁶-arene)] (Y = O, NTs) in terms of reactivity and enantioselectivity for the outer-sphere mechanism are formed by the ruthenium dimer with bidentate protic

⁹⁵ a) M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466-1478; b) D. A. Alonso, P. Brandt, S. J. M. Nordin, P. G. Andersson, *J. Am. Chem. Soc.* **1999**, *121*, 9580-9588.

monotosylated diamines or amino alcohol ligands.

We conducted our asymmetric transfer hydrogenation with chiral amino alcohol ligands as well as a monotosylated diamine ligand. The satisfactory results were obtained under Ru catalyst with amino alcohol ligands, especially with (1*S*, 2*R*)-1-amino-2-indanol. Hereby, according to literature precedence,^{91c,95,96} the mechanism of asymmetric transfer reaction of CF₃-ketimine is proposed in **Scheme 3-36**: the 18-electron Ru chloride precatalyst **I** was generated from ruthenium dimer and amino alcohol ligand in the presence of a base followed by elimination of HCl to afford the active Ru species **II** bearing an electronically deficient 16 electrons metal center which was able to dehydrogenate isopropanol into acetone and to form the 18 electrons Ru-hydride complex **III**. In this case, the H_{ax} in an axial position of the pyramidal shape on nitrogen atom was apt to transfer to the substrate **9aa** together with the hydride of Ru-H to obtain the amine product **10aa**.



The η^6 -arene such as [$\{\text{RuCl}_2(\text{benzene})\}_2$] contributes to the performance of Ru catalysts through a Csp₂-H/ π interaction to stabilize the transition state (**Figure 3-6**). Moreover, more sterically demanding polyalkylated arenes provide higher ee values mainly due to the increased π -donation of the arene and Csp₃-H/ π interaction as observed with [$\{\text{RuCl}_2(\textit{para-cymene})\}_2$], which helps to stabilize the transition state (**Figure 3-7**).

⁹⁶ R.-V. Wisman, J.-G. Vries, B.-J. Deelman, H. J. Heeres, *Org. Process Res. Dev.* **2006**, *10*, 423-429.

Consequently, we obtained higher enantioselectivity by using [$\{\text{RuCl}_2(\textit{para}\text{-cymene})\}_2$] as Ru dimer. In detail, the (*E*)-CF₃-ketimine underwent a six-membered ring to transfer the hydride from the ruthenium atom to the iminic carbon through the *Si*-face of the ketimine, followed by a proton transfer to the iminic nitrogen to produce the major *R* enantiomer of the CF₃-amine.

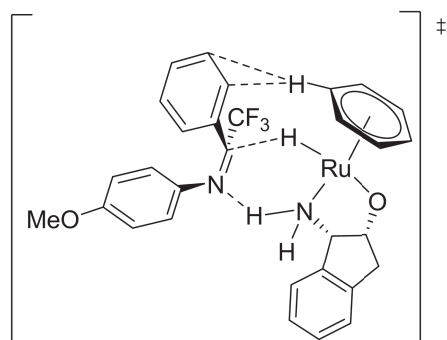


Figure 3-6

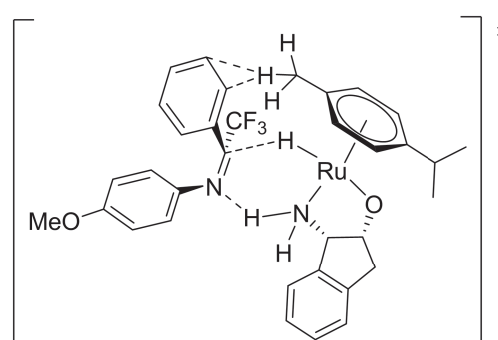
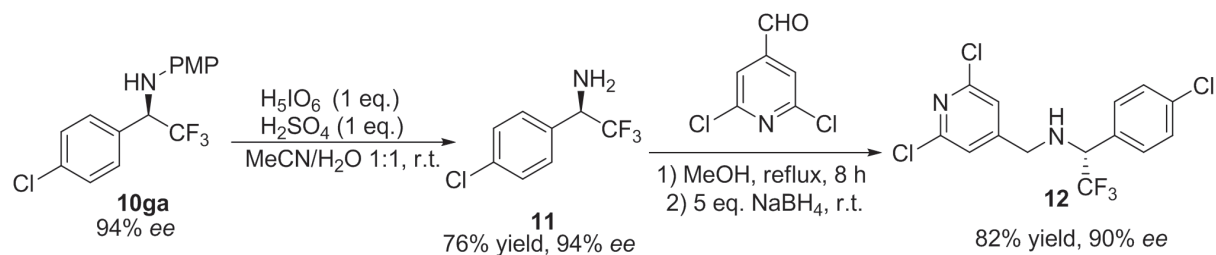


Figure 3-7

3.2.7 Application of ATH

As an application of these chiral trifluoromethyl amines, we successfully synthesized the 2,6-dichloro-4-pyridylmethylamine derivative **12**, which is a CF₃ analogue of a known molecule used as agricultural and horticultural disease control agent.⁹⁷ From the key step asymmetric transfer hydrogenation, we obtained the *N*-PMP CF₃-amine **10ga** in 90% *ee* (Table 3-14, entry 7). After crystallisation, the enantioselectivity increased to 94% *ee*. Then, the crystallized *N*-PMP CF₃-amine **10ga** was converted into free amine **11** with orthoperiodic acid in good yield and without any loss of enantioselectivity. The commonly used deprotective reagent Ce(NH₄)₂(NO₃)₆ (CAN) was not efficient for our deprotection step. After the reductive amination of 2,6-dichloroisonicotinaldehyde with amine **11**, the final product **12** was obtained in 82% yield and 90% *ee* (Scheme 3-37).⁶⁶ Erosion of enantioselectivity was noticed in the process but will hopefully be avoided by testing other conditions in the reductive amination step.

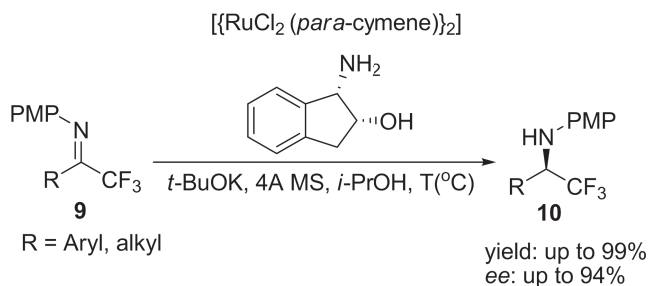
⁹⁷ K. Nobuyuki, K. Yuichi, N. Yoshitaka, WO 2006/004062, PCT/JP2005/012247.



Scheme 3-37

3.2.8 Conclusion

In this chapter regarding a second type of hydride transfer reaction, we developed a convenient method for enantioselective transfer hydrogenation of trifluoromethylated imines by means of a chiral ruthenium catalyst. The commercially available (1*S*, 2*R*)-1-amino-2-indanol was selected as ligand and chirality source, while isopropanol was employed as solvent and hydride source. We obtained optically active trifluoromethylated amines in high yields and high enantioselectivities (**Scheme 3-38**).



Scheme 3-38

4. Nucleophilic trifluoromethylthiolation of Morita-Baylis-Hillman carbonates

4.1 Literature data and objective

4.1.1 Brief introduction of trifluoromethylthiolated compounds

As we have mentioned before, lipophilicity is an important parameter in drug design and life science. In recent years, the association of a trifluoromethylated group with a heteroatom has attracted considerable attention due to the strong electronegativities (σ) and high lipophilicities (π) of these functional groups such as trifluoromethoxy (OCF₃), trifluoromethylthiol (SCF₃) and trifluoromethanesulfonyl (SO₂CF₃) (**Table 4-1**).⁹⁸

	F	CF ₃	CH ₃	OCF ₃	OCH ₃	SCF ₃	SCH ₃	SO ₂ CF ₃	SO ₂ CH ₃
π	0.14	0.88	0.56	1.04	-0.02	1.44	0.61	0.55	1.23
σ_m	0.34	0.43	-0.07	0.38	0.12	0.40	0.15	0.83	0.60
σ_p	0.06	0.54	-0.17	0.35	-0.27	0.50	0.00	0.96	0.72

Table 4-1

Among them, trifluoromethylthiol (SCF₃) bearing the highest lipophilicity has become a hotspot in fluorine chemistry in the past 3 years. Many new methods for the construction of the SCF₃ motif and new trifluoromethylthiolating reagents for direct nucleophilic, electrophilic and radical trifluoromethylthiolation have emerged (**Figure 4-1**).³³

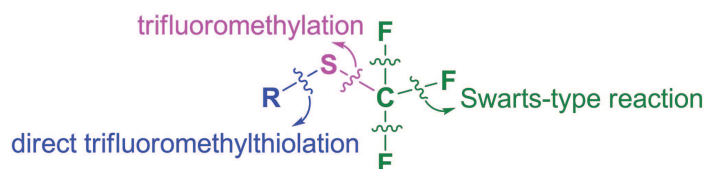


Figure 4-1

Until recently, most of the trifluoromethylthiolated compounds were synthesized by

⁹⁸ a) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165-195; b) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Xikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207-1216.

indirect methods. The traditional way to prepare trifluoromethylthiolated compounds was the Swarts-type fluorination of the trichloromethyl sulfides, which were obtained by photochemical chlorination of the methyl group.⁹⁹ Besides, the trifluoromethylation of thiols, thiolates, and disulfides was also a major way to get the trifluoromethylthiolated compounds by using electrophilic or nucleophilic trifluoromethylating reagents.¹⁰⁰

In order to avoid the harsh conditions of this halogen-fluorine exchange and the inconvenient way to get the sulfur-containing precursors, direct trifluoromethylthiolations were realized by using trifluoromethanesulfonyl chloride (CF₃SOCl) with various alkenes, aromatics, and heteroaromatics through a radical or electrophilic way. For nucleophilic trifluoromethylthiolation, (trifluoromethylthio)copper was mostly utilized through S_NAr mechanism to get aryl trifluoromethyl sulfides.^{33,101}

More recently, the traditional highly toxic gas CF₃SOCl has been gradually replaced by some new electrophilic SCF₃ reagents such as trifluoromethanesulfenamide reported by Billard's group obtained from DAST, CF₃SiMe₃ and primary amines (**S1** and **S2**),¹⁰² trifluoromethyl-substituted thioperoxide reported by Shen's group,¹⁰³ whose structure was recently corrected by Buchwald (**S3**),¹⁰⁴ *N*-(trifluoromethylthio)phthalimide also called Munavalli's reagent (**S4**),¹⁰⁵ *N*-trifluoromethylthiosuccinimide synthesized by Haas's group (**S5**),¹⁰⁶ the *N*-trifluoromethylthiosaccharin also developed by Shen's group (**S6**),¹⁰⁷ and the trifluoromethanesulfonyl hypervalent iodonium ylide prepared by Shibata's group (**S7**)¹⁰⁸

⁹⁹ a) J. Swarts, *Bull. Acad. R. Med. Belg.* **1892**, *24*, 309; b) O. Scherer, *Angew. Chem.* **1939**, *52*, 457-459.

¹⁰⁰ a) B. Quiclet-Sire, R. N. Saicic, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 9057-9058; b) C. Pooput, W. R. Dolbier, Jr., M. Médebielle, *J. Org. Chem.* **2006**, *71*, 3564-3568; c) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848-8856; d) G. Blond, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473-2475; e) T. Billard, S. Large, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65-68; f) T. Billard, B. R. Langlois, *Tetrahedron Lett.* **1996**, *37*, 6865-6868. g) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156-2164; h) T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, *31*, 3579-3582; i) I. Kietlsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754-757; *Angew. Chem.* **2007**, *119*, 768-771.

¹⁰¹ X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2014**, DOI: 10.1021/cr500193b.

¹⁰² a) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *J. Org. Chem.* **2008**, *73*, 9362-9365; b) S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589-8593; c) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem.* **2009**, *121*, 8703-8707; *Angew. Chem. Int. Ed.* **2009**, *48*, 8551-8555; d) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528-10531; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382-10385; e) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160-163; f) S. Alazet, K. Ollivier, T. Billard, *Beilstein J. Org. Chem.* **2013**, *9*, 2354-2357; g) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem.* **2013**, *125*, 11014-11017; *Angew. Chem. Int. Ed.* **2013**, *52*, 10814-10817.

¹⁰³ X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457-3460; *Angew. Chem.* **2013**, *125*, 3541-3544.

¹⁰⁴ E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125-3128.

¹⁰⁵ a) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Comm.* **2000**, *30*, 2847-2854; b) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856-12859; *Angew. Chem.* **2013**, *125*, 13093-13097.

¹⁰⁶ a) A. Haas, G. Möller, *Chem. Ber.* **1996**, *129*, 1383-1388; b) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046-2049.

¹⁰⁷ C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316-9320.

¹⁰⁸ Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782- 8785.

(Figure 4-2).

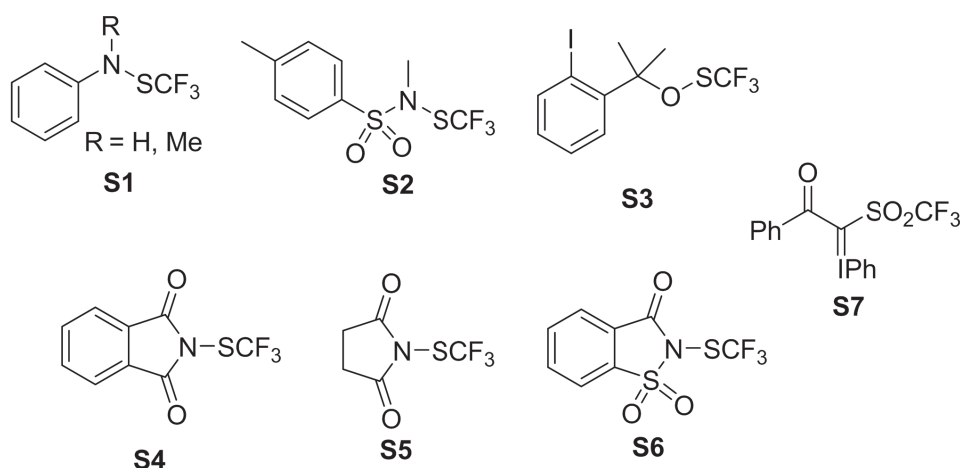
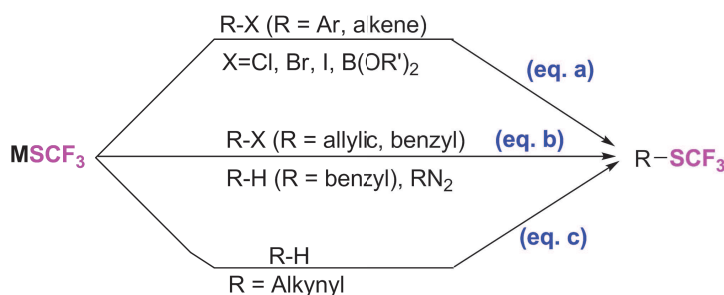


Figure 4-2

In nucleophilic trifluoromethylthiolation, the nucleophilic trifluoromethylthiolating reagents, particularly the salts $\text{Me}_4\text{N}^+\text{SCF}_3^-$ and M^+SCF_3^- ($\text{M} = \text{Hg}, \text{K}, \text{Cs}, \text{Ag}, \text{Cu}$), are efficiently applied in the formation of C-SCF₃ bond from aryl,¹⁰⁹ benzyl,¹¹⁰ allylic halides,¹¹¹ aryl boronic acids,¹¹² diazo compounds¹¹³ and terminal alkynes¹¹⁴ (Scheme 4-1). Among these reactions, the majority are aromatic trifluoromethylthiolation by Csp²-SCF₃ coupling (eq. a). On the contrary, there are only a few examples of formation of Csp³-SCF₃ by using benzyl, allylic halides or diazo compounds (eq. b) and Csp-SCF₃ by using terminal alkynes (eq. c).



Scheme 4-1

¹⁰⁹ a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450-7452; b) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183-185; c) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548-1552.

¹¹⁰ a) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan, Z. Weng, *Tetrahedron*, **2013**, *69*, 6046-6050; b) C. Chen, X.-H. Xu, B. Yang, F.-L. Qing, *Org. Lett.* **2014**, *16*, 3372-3375.

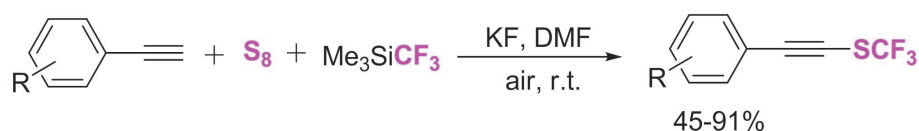
¹¹¹ J. Tan, G. Zhang, Y. Ou, Y. Yuan, Z. Weng, *Chin. J. Chem.* **2013**, *31*, 921-926.

¹¹² C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542-1545.

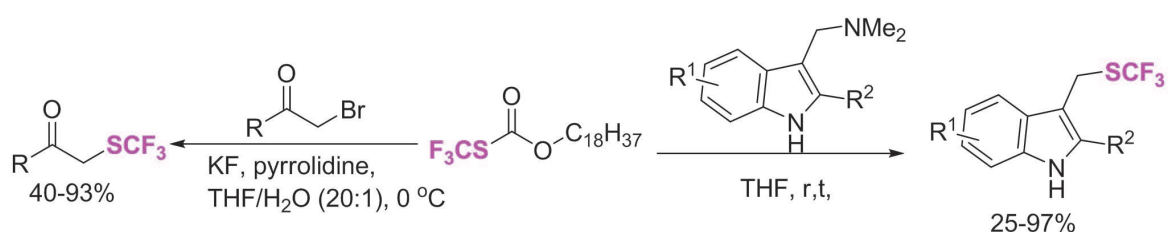
¹¹³ a) M. Hu, J. Rong, W. Miao, C. Ni, Y. Han, J. Hu, *Org. Lett.* **2014**, *16*, 2030-2033; b) X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, 3093-3096; c) Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.* **2014**, 6617-6619.

¹¹⁴ a) Q. Xiao, J. Sheng, Q. Ding, J. Wu, *Eur. J. Org. Chem.* **2014**, 217-221; b) S. Q. Zhu, X.-H. Xu, F.-L. Qing, *Eur. J. Org. Chem.* **2014**, 4453-4456.

Besides the above-mentioned trifluoromethylthiolates, the SCF_3 anion could also be generated by combination of $\text{S}_8/\text{CF}_3\text{SiMe}_3/\text{KF}/\text{DMF}$ (**Scheme 4-2**)¹¹⁵ or by the reaction of nucleophilic tertiary amine and long chain *O*-octadecyl *S*-trifluoromethyl carbonothioate (**Scheme 4-3**)¹¹⁶ to avoid the use of metal and achieve the nucleophilic trifluoromethylation under gentle conditions.



Scheme 4-2



Scheme 4-3

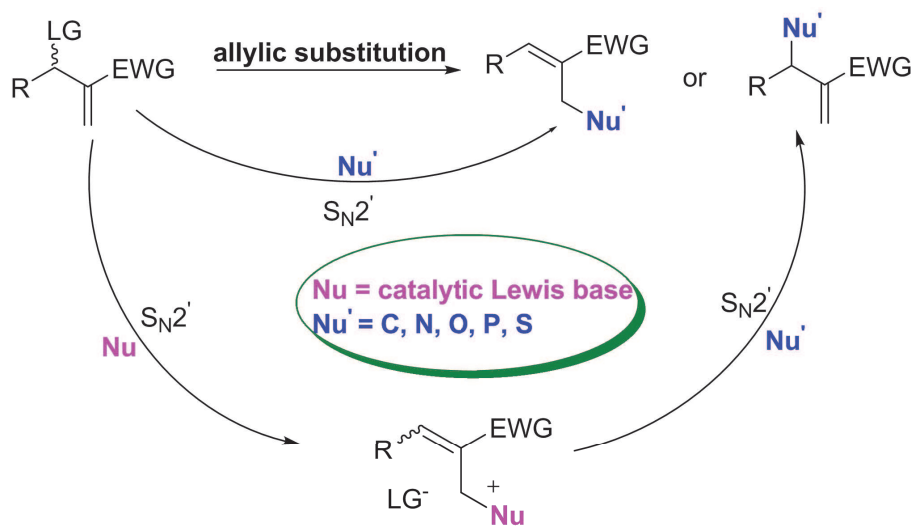
4.1.2 Allylic substitution of Morita-Baylis-Hillman carbonates

The properly modified Morita-Baylis-Hillman (MBH) derivatives, particularly the carbonates could act as very useful synthetic intermediates. As a Michael acceptor, MBH adduct derivative, bear a leaving group (LG) acetoxy or a *tert*-butoxycarbonyloxy group and a vinylic moiety conjugated to an electron-withdrawing group. Thus, there is an electrophilic site at the terminal alkene that allows nucleophilic attacks with removal of the leaving group. It undergoes allylic substitution with a wide range of nucleophiles such as C-, N-, O-, P- and S-nucleophiles in the presence of a Lewis base such as a tertiary amine or phosphine via a $\text{S}_{\text{N}}2'$ or a successive $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2'$ mechanism to form C-C or C-heteroatom bonds (**Scheme 4-4**).¹¹⁷

¹¹⁵ C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454-12457.

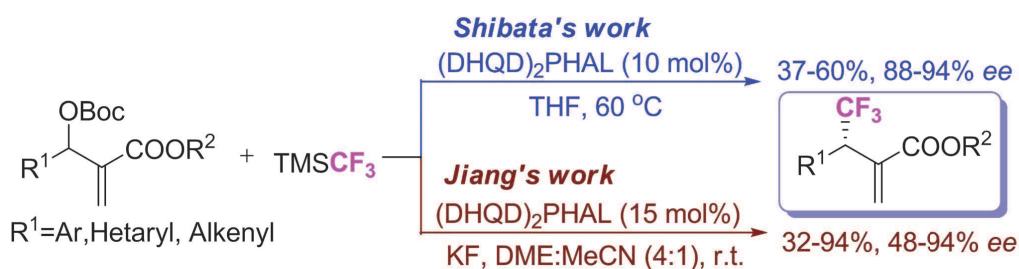
¹¹⁶ S.-G. Li, S. Z. Zard, *Org. Lett.* **2013**, *15*, 5898-5901.

¹¹⁷ a) T.-Y. Liu, X. Min, Y.-C. Chen, *Chem. Soc. Rev.* **2012**, *41*, 4101-4112; b) R. Rios, *Catal. Sci. Technol.* **2012**, *2*, 267-278.



Scheme 4-4

Among all the reports on allylic substitution of MBH derivatives, only a few of them concern the introduction of fluorinated motifs. There are two publications in 2011 by Shibata and Jiang groups on the allylic trifluoromethylation by using Ruppert-Prakash reagent as CF_3 source. They reported the asymmetric allylic trifluoromethylation of MBH carbonates with Ruppert-Prakash reagent by means of a chiral bis-cinchona alkaloid $(\text{DHQD})_2\text{PHAL}$ to get the corresponding trifluoromethylated acrylates in good yields and moderate to high *ee*'s (Scheme 4-5).¹¹⁸

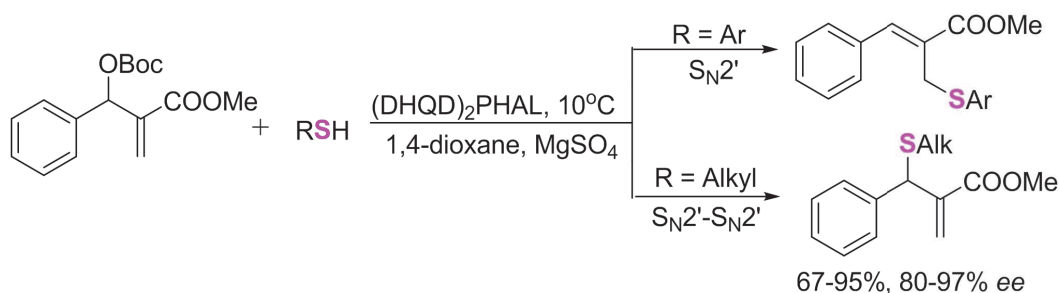


Scheme 4-5

Regarding the use of sulfur nucleophiles, thiols have been reported for the allylic substitution of MBH carbonates in the presence of the same chiral Lewis base $(\text{DHQD})_2\text{PHAL}$ and MgSO_4 . In this case, aromatic thiols led to $\text{S}_{\text{N}}2'$ product, while alkyl thiols provided the $\text{S}_{\text{N}}2^2/\text{S}_{\text{N}}2'$ products in good yields and high *ee*'s (Scheme 4-6).¹¹⁹

¹¹⁸ a) T. Furukawa, T. Nishimine, E. Tokunaga, K. Hasegawa, M. Shiro, N. Shibata, *Org. Lett.*, **2011**, *13*, 3972- 3975; b) Y. Li, F. Liang, Q. Li, Y.-C. Xu, Q.-R. Wang, I. Jiang, *Org. Lett.*, **2011**, *13*, 6082-6085.

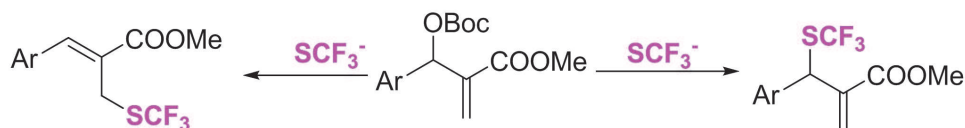
¹¹⁹ a) A. Lin, H. Mao, X. Zhu, H. Ge, R. Tan, C. Zhu, Y. Cheng, *Adv. Synth. Catal.* **2011**, *353*, 3301-3306.



Scheme 4-6

4.1.3 Objective

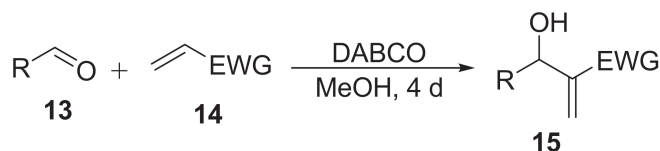
To the best of our knowledge, the trifluoromethylthiolation of MBH derivatives has not been reported yet. Because there are not many methods for the formation of Csp³-SCF₃ bond, it is quite desirable to develop a new method of allylic trifluoromethylthiolation in order to enlarge the library of trifluoromethylthiolated compounds. We anticipated the two possible SCF₃ products depicted in **Scheme 4-7**. The primary allylic SCF₃ product (left) having the alkene conjugated with the aromatic ring and the secondary allylic SCF₃ product (right) that retains the terminal alkene motif.



Scheme 4-7

4.2 Synthesis of Morita-Baylis-Hillman derivatives

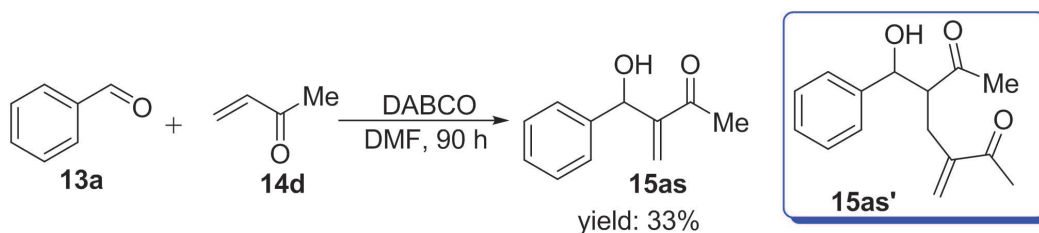
The Morita-Baylis-Hillman adducts **15** were prepared by reaction of 1 eq. aldehydes **13** with 3 eq. acrylates or acrylonitrile **14** in the presence of 10 mol% DABCO in methanol for 4 days (**Table 4-2**).



entry	R	EWG	yield (%)
1	Ph	COOMe	36 (15aa)
2	PhCH ₂ CH ₂	COOMe	55 (15ap)
3	Ph	COOEt	29 (15aq)
4	Ph	COO <i>t</i> -Bu	50 (15ar)
5	Ph	CN	86 (15at)

Table 4-2

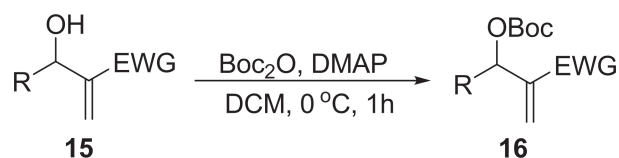
However, the obtention of MBH adduct **15as** from methylvinyl ketone (MVK) could not be realized under these reaction conditions. The MBH adduct was totally converted into the bis-adduct **15as'** (Scheme 4-8). Thus, we reduced the amount of MVK from 3 eq. to 1 eq., and changed the solvent from methanol to DMF to avoid the generation of bis-adduct **15as'**.¹²⁰ After purification and column chromatography, we got the desired MBH adduct **15as** (Scheme 4-8).



Scheme 4-8

With the MBH adducts in hand, we synthesized the corresponding MBH carbonates with di-*tert*-butyl dicarbonate in the presence of 4-dimethylaminopyridine (DMAP) at 0 °C for 1 hour. After column chromatography, the corresponding MBH carbonates were obtained in moderate yields (Table 4-3). Other MBH carbonates with methyl group in ester part **16aa** (R = Ph), **16ab** (R = 2-ClC₆H₄), **16ac** (R = 3-ClC₆H₄), **16ad** (R = 4-ClC₆H₄), **16ae** (R = 2,4-Cl₂C₆H₃), **16af** (R = 2-BrC₆H₄), **16ag** (R = 3-BrC₆H₄), **16ah** (R = 4-BrC₆H₄), **16ai** (R = 4-FC₆H₄), **16aj** (R = 2-OMeC₆H₄), **16ak** (R = 4-OMeC₆H₄), **16al** (R = 4-MeC₆H₄), **16am** (R = 1-naphthyl), **16an** (R = 2-naphthyl), **16ao** (R = 2-thienyl) were synthesized by Chuan-Le Zhu in our laboratory.

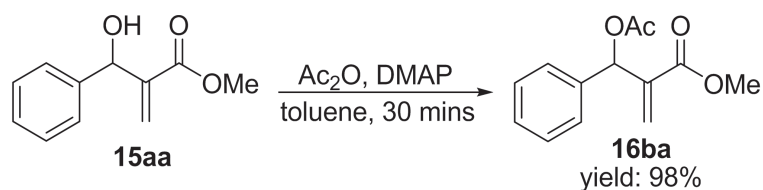
¹²⁰ M. Shi, C.-Q. Li, J.-K. Jiang, *Tetrahedron* **2003**, *59*, 1181-1189.



entry	R	EWG	yield (%)
1	PhCH ₂ CH ₂	CO ₂ Me	42 (16ap)
2	Ph	CO ₂ Et	29 (16aq)
3	Ph	CO ₂ <i>t</i> -Bu	61 (16ar)
4	Ph	COMe	58 (16as)
5	Ph	CN	56 (16at)

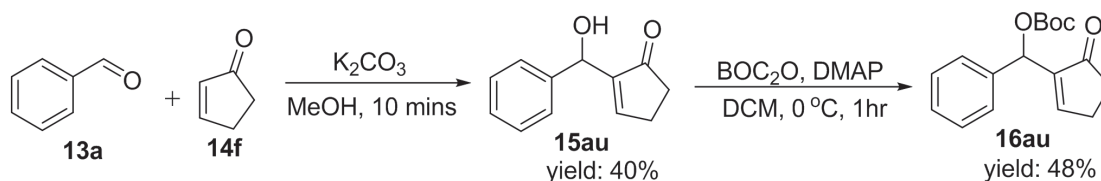
Table 4-3

Besides, the MBH acetate **16ab** was prepared by using acetic anhydride in toluene. After the evaporation of solvent, the pure MBH acetate **16ab** was afforded in 98% yield (Scheme 4-9).



Scheme 4-9

The cyclic enone **16au** was also synthesized as a substrate for the nucleophilic trifluoromethylthiolation from the alcohol **15au**, which could be easily obtained by the reaction of benzaldehyde **13a** and cyclopent-2-enone **14f** in the presence of potassium carbonate in methanol for 10 minutes.¹²¹ After reacted with Boc₂O, we got the MBH carbonate **16au** in 48% yield (Scheme 4-10).

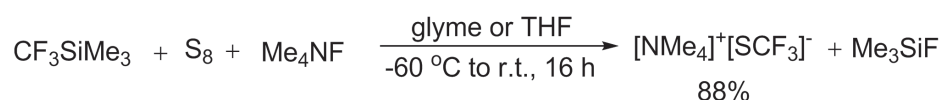


Scheme 4-10

¹²¹ S. Luo, X. Mi, H. Xu, P. G. Wang, J.-P. Cheng, *J. Org. Chem* **2004**, *69*, 8413-8422.

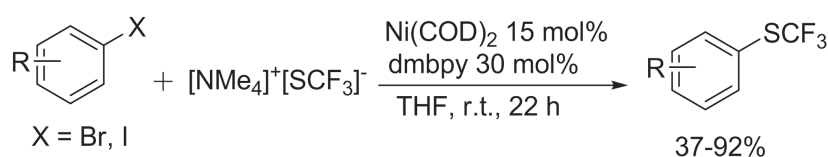
4.3 Attempts using $\text{Me}_4\text{N}^+\text{SCF}_3^-$ and M^+SCF_3^- ($\text{M} = \text{Ag}, \text{Cu}$) as nucleophilic SCF_3 transfer reagents

Tetramethylammonium trifluoromethylthiolate ($[\text{NMe}_4]^+[\text{SCF}_3]^-$) was prepared by Y. L. Yagupolskii in 2003 from Ruppert-Prakash reagent (Me_3SiCF_3), elemental sulfur (S_8) and tetramethylammonium fluoride (Me_4NF) in glyme or THF (**Scheme 4-11**).¹²² Despite the facile method for its preparation, this white solid was very moisture sensitive.



Scheme 4-11

In 2011, Zhang and Vivic used the tetramethylammonium trifluoromethylthiolate for trifluoromethylthiolation of aryl iodides and aryl bromides at room temperature with nickel-bipyridine complexes to get the aryl trifluoromethyl sulfides in 37 to 92 % yield (**Scheme 4-12**).¹²³



Scheme 4-12

Since $[\text{NMe}_4]^+[\text{SCF}_3]^-$ has achieved good results in transition-metal catalyzed cross-coupling for aryl- SCF_3 synthesis, we tried to extend the use of this convenient nucleophilic SCF_3 reagent to the construction of $\text{Csp}_3\text{-SCF}_3$ bond with MBH derivatives through allylic trifluoromethylthiolation. The target product is the secondary allylic SCF_3 ester depicted in **Figure 4-3**.

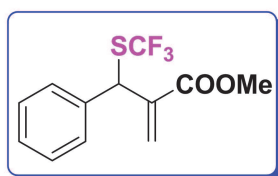


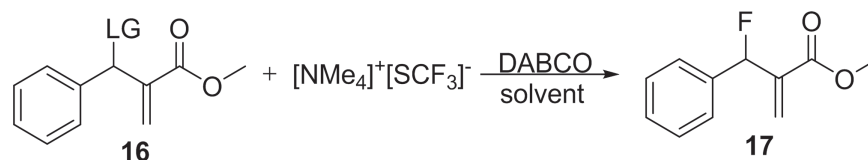
Figure 4-3

$[\text{NMe}_4]^+[\text{SCF}_3]^-$ salt is not soluble in THF, so we used a mixture of MeCN and THF as

¹²² W. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluorine Chem.* **2003**, *119*, 101-107.

¹²³ C.-P. Zhang, D. A. Vivic, *J. Am. Chem. Soc.* **2012**, *134*, 183-185.

solvent to dissolve the SCF_3 salt. We first generated the ammonium intermediate from MBH carbonate **16aa** and DABCO in THF, followed by addition of $[\text{NMe}_4]^+[\text{SCF}_3]^-$ in MeCN. After 2 days, we observed a new spot by TLC and by ^{19}F NMR, a new multiple signal around -171 ppm and a weak signal at -42.3 ppm were observed. After purification and identification by ^1H NMR and ^{19}F NMR, we assured that monofluorine product **17** was obtained under these conditions (**Table 4-4**, entry 1).



entry	LG	solvent	additive	yield (%)
1	OBoc (16aa)	THF/MeCN (2:5)	-	around 50% ^a
2	OAc (16ba)	MeCN	-	trace
3	OAc (16ba)	MeCN	CuI	trace
4	OAc (16ba)	MeCN	KF	trace
5	OAc (16ba)	DMF	-	trace

^a Due to volatility, the yield of **17** was under estimated.

Table 4-4

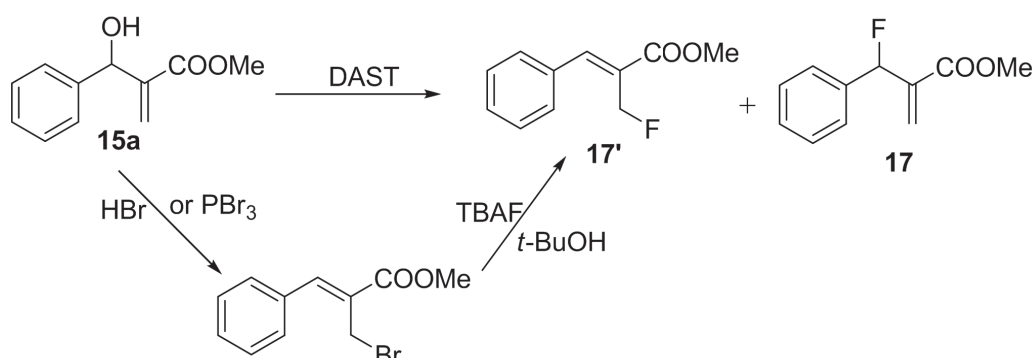
In order to find appropriate conditions to get the expected SCF_3 product, which has been observed as a weak signal at -42.3 ppm in ^{19}F NMR, we changed the MBH carbonate **16aa** to MBH acetate **16ba** to avoid the generation of the strong *tert*-butoxide base, which might cause the decomposition of $[\text{NMe}_4]^+[\text{SCF}_3]^-$ salt. However, only a slight signal for **17** was found by ^{19}F NMR without any trace of the product at -42.3 ppm (**Table 4-4**, entry 2). Then, we added CuI or KF as additive; similarly, only a tiny signal of monofluorinated product was observed (**Table 4-4**, entries 3-4). Even though we changed the solvent to more polar DMF to better dissolve the SCF_3 salt, the result was still negative (**Table 4-4**, entry 5). The decomposition of $[\text{NMe}_4]^+[\text{SCF}_3]^-$ to fluoride and thiocarbonyl difluoride (F_2CS) was a major obstacle under these conditions (**Scheme 4-13**).¹²⁴



Scheme 4-13

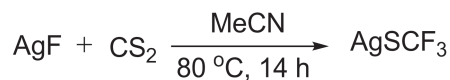
¹²⁴ S. J. Tavener, D. J. Adams, J. H. Clark, *J. Fluorine Chem.* **1999**, *95*, 171-176.

Although the secondary allylic fluoride product **17** was not our target molecule, it is of interest because it is otherwise difficult to prepare. All the literature methods for the synthesis of monofluorinated product having the fluorine atom at the congested, stereogenic allylic site involve the use of DAST as fluorinating agent to react with allylic alcohols affording mixtures of primary **17'** and secondary **17** allylic fluorides.¹²⁵ Besides, the fluoride ion originated from MF (M = Cs, K) or TBAF only gave the primary allylic fluoride **17'** by nucleophilic substitution of the corresponding bromide precursor (**Scheme 4-14**).¹²⁶



Scheme 4-14

In order to solve this problem, we changed [NMe₄]⁺[SCF₃]⁻ to the more covalent silver trifluoromethylthiolate (AgSCF₃), which has been broadly used in the metal mediated trifluoromethylthiolation of terminal alkynes,¹¹⁴ aromatic halides^{109a} and diazo compounds¹¹³ for the formation of Csp-SCF₃, Csp₂-SCF₃, Csp₃-SCF₃ bonds, respectively. The relatively easy preparation of AgSCF₃ from silver fluoride (AgF) and carbon disulfide (CS₂) in MeCN is also an advantage for its broad usage (**Scheme 4-15**).¹²⁷



Scheme 4-15

However, in our case, the reaction of MBH derivatives with AgSCF₃ did not work at all. We did not observe the signal at -171 ppm nor the one at -42.3 ppm by ¹⁹F NMR. Since the employment of copper salt could generate (trifluoromethylthio)copper (I) (CuSCF₃), we also added copper iodide (CuI) as an additive, but the reaction did not work either.

¹²⁵ a) M. Baumann, I. R. Baxendale, S. V. Ley, *Synlett* **2008**, 2011-2014; b) E. Farrington, M. C. Franchini, J. M. Brown, *Chem. Commun.* **1998**, 277-278; c) L. Bernardi, B. F. Bonini, M. Comes-Franchini, M. Fochi, M. Folegatti, S. Grilli, A. Mazzanti, A. Ricci, *Tetrahedron: Asymmetry* **2004**, *15*, 245-250; d) M. Baumann, I. R. Baxendale, L. J. Martin, S. V. Ley, *Tetrahedron* **2009**, *65*, 6611-6625.

¹²⁶ C. H. Lim, S. H. Kim, H. J. Lee, H. J. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2013**, *34*, 993-996.

¹²⁷ X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457-3460.

None of the two SCF_3 nucleophilic reagents was efficient to get the trifluoromethylthiolated compound with MBH substrates.

4.4 Metal-free nucleophilic trifluoromethylthiolation of Morita-Baylis-Hillman carbonates

4.4.1 Combination of $\text{S}_8/\text{CF}_3\text{SiMe}_3/\text{KF}$ as nucleophilic SCF_3 transfer reagent

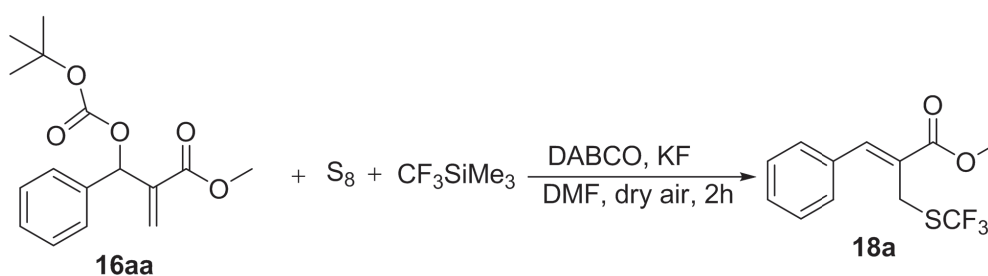
4.4.1.1 Introduction

It is an efficient way to generate SCF_3 anion by combination of $\text{S}_8/\text{CF}_3\text{SiMe}_3/\text{MF}$. As we have mentioned before, it has already been reported in 2003 for the synthesis of $[\text{NMe}_4]^+[\text{SCF}_3]^-$ by using Me_4NF as fluoride source (**Scheme 4-11**).¹²² Later, in 2012, Qing group employed this one-pot generation of SCF_3 anion for a metal-free oxidative trifluoromethylthiolation of terminal alkynes and obtained alkynyl trifluoromethyl sulfides in moderate to good yields (**Scheme 4-2**).¹¹⁵ Inspired by this convenient protocol, we carried out our reaction in a one-pot procedure with DMF as solvent for the synthesis of two possible SCF_3 products depicted in **Scheme 4-7**.

4.4.1.2 Optimization of reaction conditions

The procedure consisted in preparing a solution of sulfur and KF in DMF, followed by the addition of MBH carbonate **16aa**, CF_3SiMe_3 (Ruppert-Prakash's reagent), and DABCO. In this order, after 2 hours, 45% yield of the product at -42.3 ppm, which was identified as the primary allylic SCF_3 product **18a**, was observed by ^{19}F NMR; but there was no MBH carbonate **16aa** left according to the TLC (**Table 4-5**, entry 1). Of the byproducts isolated, we identified the MBH alcohol and some byproducts from the decomposition of MBH carbonate. To gain a further understanding of the reaction, we changed the addition order of reagents by adding Ruppert-Prakash's reagent before MBH carbonate, and 58% yield of **18a** was obtained

(Table 4-5, entry 2). This higher yield indicated that CF_3SiMe_3 helped generation of SCF_3 anion rapidly and efficiently as soon as it was added into the solution of S_8/KF in DMF. However, when the MBH carbonate and DABCO were added into the system in a 1 mL solution of DMF, the reaction became much slower, and only 28% yield of thermodynamic SCF_3 product **18a** was observed (Table 4-5, entry 3). This clearly showed that the direct addition of MBH carbonate followed by DABCO instead of the solution of both was preferred in the reaction.

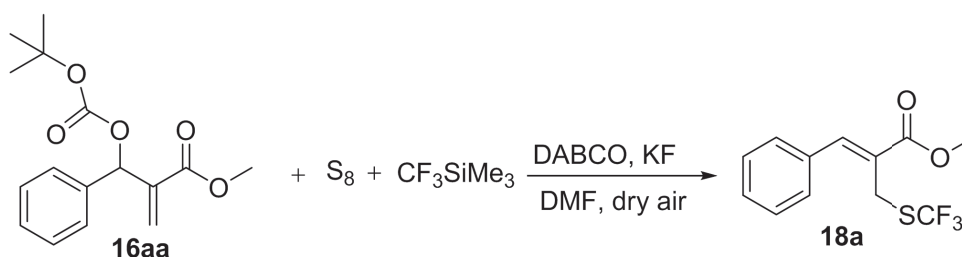


entry	order of addition of reagent	yield (%) ^a
1	MBH + CF_3SiMe_3 + DABCO	45
2	CF_3SiMe_3 + MBH + DABCO	58
3	CF_3SiMe_3 + MBH + DABCO (in 1 mL DMF solution)	28

^a yields were determined by ^{19}F NMR using trifluorotoluene as internal standard.

Table 4-5

So we continued to investigate this reaction by addition of the reagents and substrate in the order of $\text{S}_8/\text{KF}/\text{DMF}/\text{CF}_3\text{SiMe}_3/\text{MBH}/\text{DABCO}$. Since KF plays an important role in the stability of SCF_3 anion, we increased the amount of KF from 2 eq. to 10 eq.. Delightfully, the yield of SCF_3 product **18a** rised up to 88% (Table 4-6, entry 2). The temperature also had a great effect in this reaction. When the reaction temperature was at 0 °C, we did not observe any SCF_3 product with 2 eq. of KF (Table 4-6, entry 3).

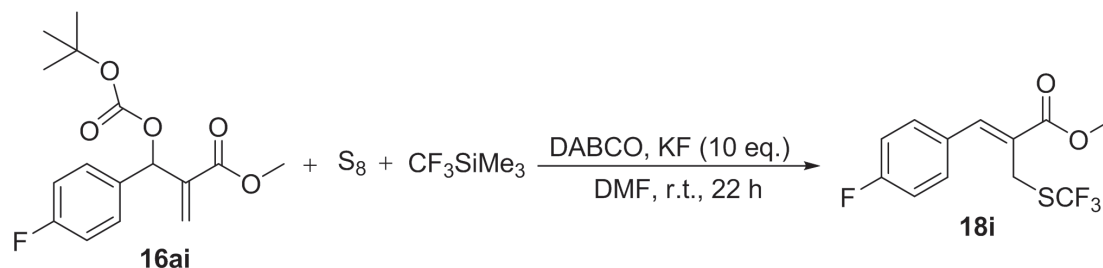


entry	amount of KF	temperature (°C)	time (h)	yield of 18a (%)
1	2 eq.	r.t.	3.5	58
2	10 eq.	r.t.	3	88 (71) ^a
3	2 eq.	0	3	-

^a In parentheses, yield of isolated pure product.

Table 4-6

For the next experiments, we chose substrate **16ai** featuring a 4-fluoroaromatic ring for easy monitoring by ¹⁹F NMR of the starting material, intermediate(s), and products. Under different atmospheres, we observed considerable differences. Under dry air (the air was passed through a tube filled with CaCl₂), we got up to 84% isolated yield of **18ai**, which was much higher than that under normal air (plenty of water in air in Normandy and hygrometry can differ very significantly from one day to another) (**Table 4-7**, entries 1-2). To our surprise, under argon the yield was similar to air (not dry), much less efficient than that in dry air (**Table 4-7**, entry 3).



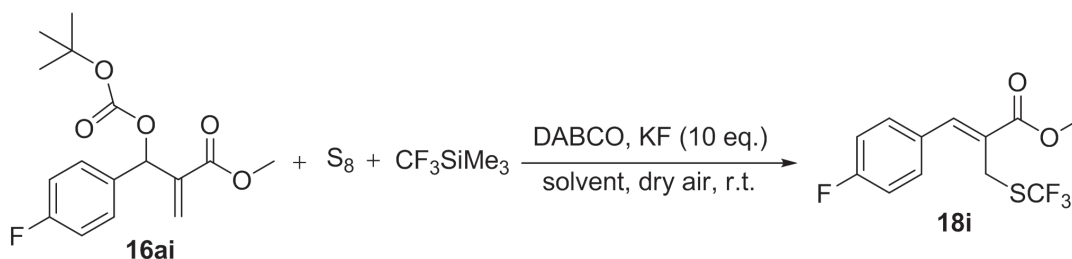
entry	atmosphere	yield (%)
1	air	54
2	dry air	84
3	argon	53
4	MgSO ₄ + dry air	7
5	4Å MS + dry air	-

Table 4-7

However, when the reaction was performed under much drier condition with MgSO₄ or 4Å molecular sieves powder, the reaction almost did not work (**Table 4-7**, entries 4-5). We only observed the signals of S(CF₃)₂ (-38.0 ppm), CF₃H (-78.6 ppm), MBH carbonate **16ai** (-113.9 ppm), and Me₃SiF (-157.8 ppm) in ¹⁹F NMR. The generation of SCF₃ anion was

totally impeded under strict dry conditions implying that a little amount of water was necessary for the reaction. The water may help to dissolve KF and allow the reaction to take place. An excess of water may solvate the fluoride ions and slow down the reaction.

During the test of various solvents, we found that DMF was the only solvent that gave the thermodynamic SCF_3 product in good yield; whereas other solvents such as DCM, toluene, THF and MeCN were not efficient for the reaction. We still observed the signal of Me_3SiCF_3 (-67.2 ppm) after 22h in ^{19}F NMR in DCM and toluene (Table 4-8, entries 2-3). In THF, there was not the signal of neither Me_3SiCF_3 nor thermodynamic SCF_3 product. But we found the signals of SCF_3 anion (-7.7 ppm) and $\text{S}(\text{CF}_3)_2$ (38 ppm) (Table 4-8, entry 4). In MeCN, only the signal of CF_3H was found (Table 4-8, entry 5). These observations indicated that DMF also acted as a reagent in the generation of SCF_3 anion and permitted the allylic trifluoromethylation with MBH carbonates.

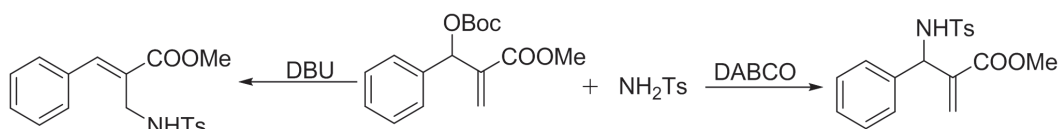


entry	solvent	time (h)	yield (%)
1	DMF	22	84
2	DCM	22	trace
3	toluene	22	-
4	THF	22	trace
5	MeCN	16	-

Table 4-8

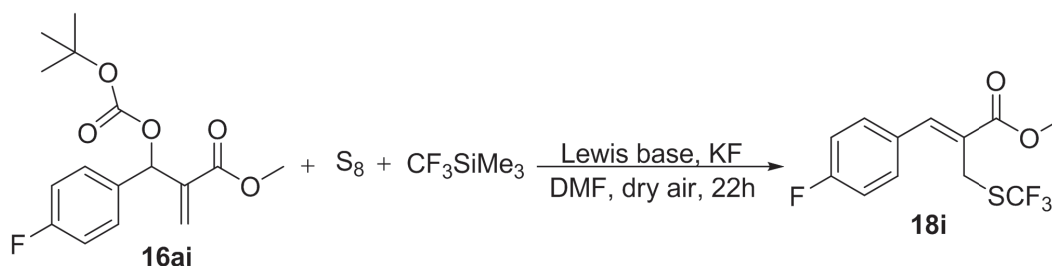
Among the reports on allylic substitution of MBH derivatives, different Lewis bases led to either $\text{S}_{\text{N}}2'$ or $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2'$ substitution products (Scheme 4-16).¹²⁸ The more basic and less nucleophilic DBU provides $\text{S}_{\text{N}}2'$ product whereas the less basic and more nucleophilic DABCO provides the $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2'$ product.

¹²⁸ M. Ciclosi, C. Fava, R. Galeazzi, M. Orena, J. Sepulveda-Arques, *Tetrahedron Lett.* **2002**, 43, 2199-2202.



Scheme 4-16

So we selected several Lewis bases to test the reaction. In our case, DABCO provided 84% yield of thermodynamic SCF₃ product **18i**, while DBU only gave 46% yield **18i** (Table 4-9, entries 1-2). The tertiary phosphine base cyclohexyl phosphine also function well in our reaction to give **18i** in 75% yield (Table 4-9, entry 3). But DMAP, a not frequently used Lewis base in such reaction, was not efficient (Table 4-9, entry 4). Moreover, without Lewis base, we also obtained 69% yield of thermodynamic SCF₃ product (Table 4-9, entry 5). Hence, the active SCF₃ anion could directly acts as a nucleophile to go through a S_N2' mechanism to get the thermodynamic SCF₃ product.

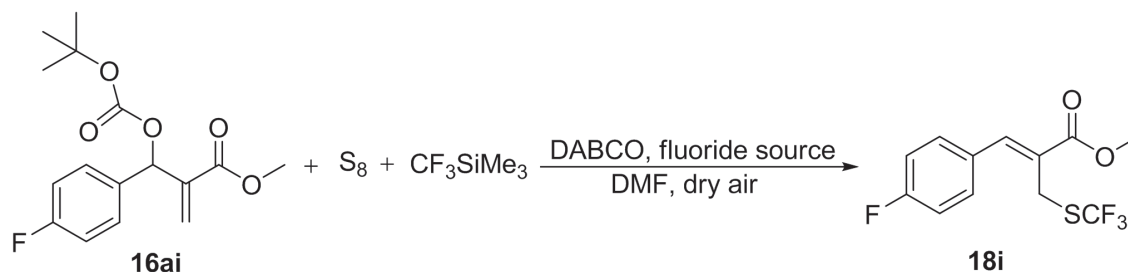


entry	Lewis base	yield (%)
1	DABCO	84
2	DBU	46
3	PCy ₃	75
4	DMAP	36
5	-	69

Table 4-9

Since we have tested the reaction with phenyl substituent **16aa** at 0 °C with 2 eq. KF, we then performed an extended control of the reaction at higher temperature. So we checked the reaction at 50 °C with MBH carbonate **16ai** and obtained lower yield than that at room temperature probably due to the fact that active SCF₃ anion could not exist long time at higher temperature and decomposed into fluoride anion and SCF₂. Besides, several species such as of S(CF₃)₂, S₂(CF₃)₂, CF₃H and Me₃SiF evaporated from liquid phase were detected

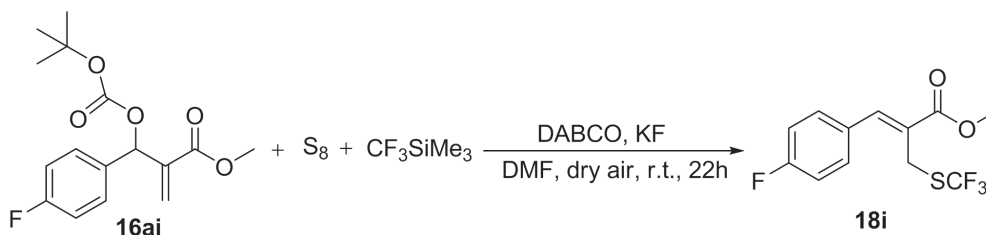
in gas phase at 50 °C by GC-MS (**Table 4-10**, entry 1). Moreover, we changed the fluoride source from KF to Me₄NF, which has a better solubility in DMF but it was not efficient in this reaction (**Table 4-10**, entry 3).



entry	temperature (°C)	fluoride source	time (h)	yield (%)
1	50	KF	22	75
2	r.t.	KF	22	84
3	r.t.	Me ₄ NF	22	-

Table 4-10

In addition, it is essential to optimize the amount and the ratio of S₈/CF₃SiMe₃/KF/DMF. We set the original 6 eq. of S₈, 5 eq. of CF₃SiMe₃, 10 eq. of KF and 4 mL DMF on 0.1 mmol scale of MBH adduct (**Table 4-11**, entry 1). When the amount of KF was reduced from 10 eq. to 5 eq., the yield was much lower (**Table 4-11**, entry 2). Under a more concentrated condition, the demi volume 2 mL DMF gave up to 94% yield of primary allylic SCF₃ product (**Table 4-11**, entry 3). The decrease of Ruppert-Prakash's reagent resulted in only 50% yield (**Table 4-11**, entry 4). When we kept the ratio of S₈/CF₃SiMe₃/KF but halved their amount, only 31% yield of product was obtained (**Table 4-11**, entry 5). So, we imagine that an increase of the concentration may achieve a better yield. Therefore, we also decreased DMF to 2 mL, the yield improved to 53% (**Table 4-11**, entry 6), but still much lower than that under the double amount of reagents ((**Table 4-11**, entries 1-2). Hence, we decided to perform further reactions for the study of the substrate scope on 0.1 mmol scale with 6 eq. of S₈, 5 eq. of CF₃SiMe₃, 10 eq. of KF and 2 mL DMF (**Table 4-11**, entry 3). Regarding the geometry of the new C=C bond formed, we always obtained a single stereoisomer of Z configuration as ascertained by 2D-NOESY experiment conducted with 4-fluorophenyl substituted SCF₃ product **18i**.



entry	amounts of reagent				yield (%)
	S_8 (eq.)	CF_3SiMe_3 (eq.)	KF (eq.)	DMF (mL)	
1	6	5	10	4	84
2	6	5	5	4	71
3	6	5	10	2	94
4	6	2.5	10	4	50
5	3	2.5	5	4	31
6	3	2.5	5	2	53

Table 4-11

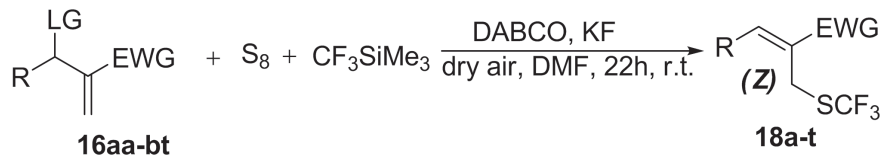
4.4.1.3 Substrate scope

Under the optimum reaction conditions, we examined the substrate scope for the regioselective and stereoselective allylic trifluoromethylthiolation (Table 4-12).

Either electron-withdrawing (chloro, bromo, fluoro) or electron-donating (methyl, methoxy) substituents on aromatic groups provided good to excellent yields after 22 hours (Table 4-12, entries 1, 3-13). Multiple substituted 2,4-dichlorophenyl group **16ae** was subjected to nucleophilic trifluoromethylthiolation and SCF_3 product **18e** was obtained in up to 93% yield (Table 4-12, entry 6). The reaction of sterically demanding naphthyl groups **16am-an** and heteroaromatic 2-thienyl substituent **16ao** proceeded well in 88-95% yields (Table 4-12, entries 14-16). The bulky 2-methoxy phenyl group **16aj** gave a relatively lower 64% yield (Table 4-12, entry 11). Besides, the alkyl phenylethyl substituted MBH carbonate **16ap** was also examined in this regioselective trifluoromethylthiolation, but the yield of SCF_3 product **18p** dropped dramatically to 20%, mainly because of the loose of conjugation system (Table 4-12, entry 17).

Apart from the MBH carbonates, MBH acetate **16ba** was also tested in the

stereoselective allylic trifluoromethylthiolation. However, after 22 hours, only 34% isolated yield was obtained (Table 4-12, entry 2). This poor result revealed the difficulty of removal of the acetoxy group.



entry	MBH adduct	R	EWG	LG	SCF ₃ product	yield (%) ^a
1	16aa	Phenyl	CO ₂ Me	OBoc	18a	93
2	16ba	Phenyl	CO ₂ Me	OAc	18a	34
3	16ab	2-ClC ₆ H ₄	CO ₂ Me	OBoc	18b	79
4	16ac	3-ClC ₆ H ₄	CO ₂ Me	OBoc	18c	80
5	16ad	4-ClC ₆ H ₄	CO ₂ Me	OBoc	18d	86
6	16ae	2,4-Cl ₂ C ₆ H ₃	CO ₂ Me	OBoc	18e	93
7	16af	2-BrC ₆ H ₄	CO ₂ Me	OBoc	18f	86
8	16ag	3-BrC ₆ H ₄	CO ₂ Me	OBoc	18g	69
9	16ah	4-BrC ₆ H ₄	CO ₂ Me	OBoc	18h	99
10	16ai	4-FC ₆ H ₄	CO ₂ Me	OBoc	18i	94
11	16aj	2-OMeC ₆ H ₄	CO ₂ Me	OBoc	18j	64
12	16ak	4-OMeC ₆ H ₄	CO ₂ Me	OBoc	18k	88
13	16al	4-MeC ₆ H ₄	CO ₂ Me	OBoc	18l	93
14	16am	1-naphthyl	CO ₂ Me	OBoc	18m	95
15	16an	2-naphthyl	CO ₂ Me	OBoc	18n	94
16	16ao	2-thienyl	CO ₂ Me	OBoc	18o	88
17	16ap	PhCH ₂ CH ₂	CO ₂ Me	OBoc	18p	20
18	16aq	Phenyl	CO ₂ Et	OBoc	18q	84
19 ^b	16ar	Phenyl	CO ₂ <i>t</i> -Bu	OBoc	18r	28
20	16as	Phenyl	COMe	OBoc	18s	65
21 ^c	16at	Phenyl	CN	OBoc	18t	79

^a yields of isolated products. ^b reaction was run at 80 °C. ^c the ratio *E*:*Z* was 82:18.

Table 4-12

The replacement of methyl group in ester part with ethyl **16aq** resulted in good yield (Table 4-12, entry 18); whereas the much sterically demanding *tert*-butyl ester **16ar** was much less efficient for this allylic trifluoromethylthiolation. We got a mixture of the conjugated SCF₃ product and MBH carbonate starting material after 22 hours at room temperature. In order to have a better conversion, we increased the temperature to 80 °C; nevertheless, only 28% yield of pure conjugated SCF₃ product **18r** was isolated (Table 4-12, entry 19). A major part of the MBH carbonate decomposed at high temperature.

We then evaluated the reactivity of MBH carbonates with ketone and nitrile groups. With methyl ketone **16as**, we got the SCF₃-containing product **18s** in 65% yield as a single *Z* isomer (Table 4-12, entry 20). In the case of nitrile **16at**, 79% isolated yield of the corresponding SCF₃ product **18t** was obtained as a 82:18 mixture of *E/Z* isomers (Table 4-12, entry 21).

For the esters and ketone, this regioselective allylic trifluoromethylthiolation provided all the conjugated SCF₃ products in exclusive *Z* isomers. The stereochemistry can be explained by considering the transition state models **A** and **B**. Transition state **A** is less favored than **B** because of steric congestion between the ester (ketone) and the phenyl group (Figure 4-4, eq.a). The major *E* configuration for **18t** could be rationalized by a greater thermodynamic stability, because the *Z* isomer suffers from strong 1, 3-allylic interactions between Ph and CH₂ group; the linear nitrile group is far less sterically hindered than the ester or ketone functions. Hence, transition state **C** is more favored than transition state **D** (Figure 4-4, eq.b).¹²⁹

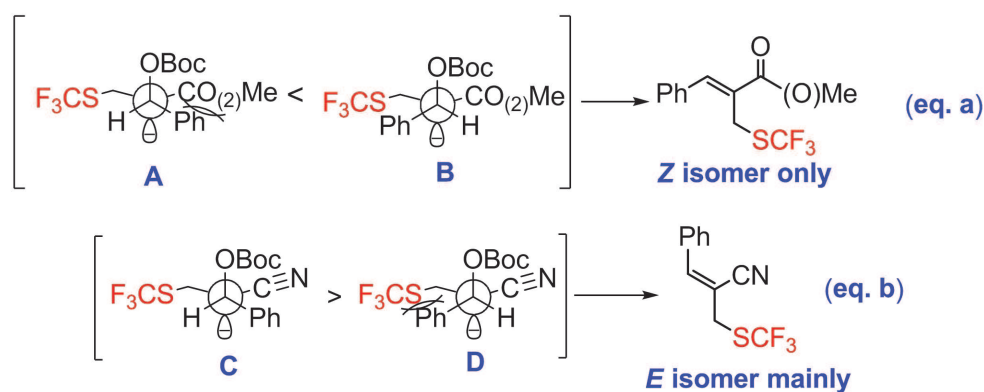


Figure 4-4

¹²⁹ A. A. Zemtsov, V. V. Levin, A. D. Dilman, M. I. Struchkova, P. A. Belyakov, V. A. Tartakovskiy, J. Hu, *Eur. J. Org. Chem.* **2010**, 6779-6785.

So far, the reactions were performed with MBH substrates featuring a terminal C=C bond. We wondered if trisubstituted C=C bond in a MBH substrate would also be suitable (Figure 4-5).

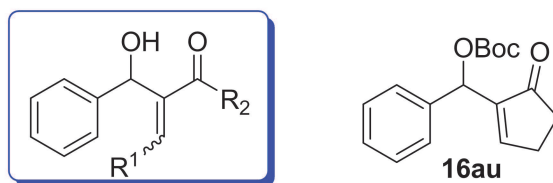


Figure 4-5

Thus, the cyclic ketone **16au** was synthesized for the allylic substitution. However, the SCF_3^- anion could not attack at the double bond of the five-membered ring, even at 80 °C. The reaction with such a trisubstituted alkene is prohibited and we couldn't find any example in the literature in allylic substitution.

4.4.1.4 Mechanism investigation by ^{19}F NMR and GC-MS

When we conducted the reaction of $\text{S}_8/\text{KF}/\text{CF}_3\text{SiMe}_3$ without the substrate and DABCO and followed by ^{19}F NMR after 15 minutes, we only observed the signals of $\text{S}(\text{CF}_3)_2$, $\text{S}_2(\text{CF}_3)_2$, CF_3H , Me_3SiF . But the signal of SCF_3^- was not found (Figure 4-6).

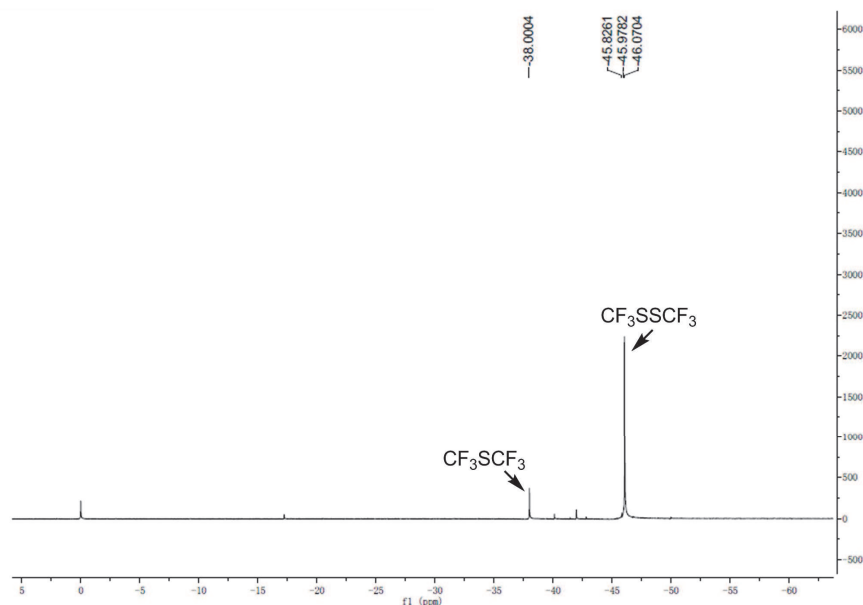


Figure 4-6

After the addition of MBH substrate **16ai** and DABCO, the signal of SCF_3^- anion was clearly observed in ^{19}F NMR, together with the signal of primary allylic SCF_3 product

(Figure 4-7).

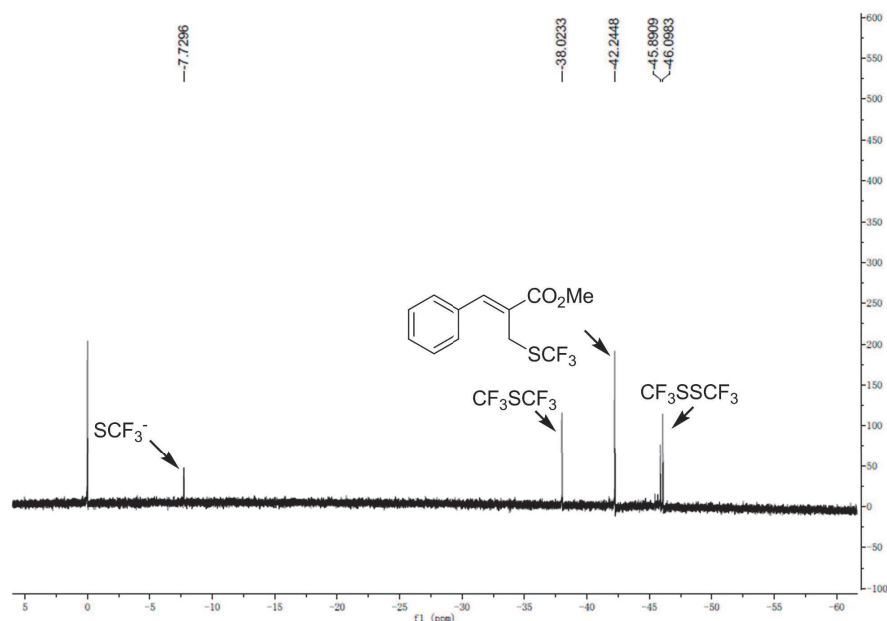


Figure 4-7

To have a further investigation of the one-pot generation of SCF_3^- anion, we carried out the control experiment without MBH carbonate and DABCO by GC-MS (Figure 4-8). As we expected, we observed Me_3SiF , $\text{Me}_3\text{SiOSiMe}_3$, CF_3H which were obtained from Me_3SiCF_3 . The COS and CS_2 which were formed by the reaction of S_8 and CO_2 were also separated and identified in GC-MS. $(\text{CH}_3)_2\text{NC}=\text{S}$ was obtained from DMF by oxidation with S_8 . Moreover, the reaction of S_8 with the trifluoromethyl anion resulted in the $\text{S}_n(\text{CF}_3)_2$ ($n = 1, 2, 3, 4$) which were observed in much more quantity than that reported in the literature by Qing's group.¹¹⁵

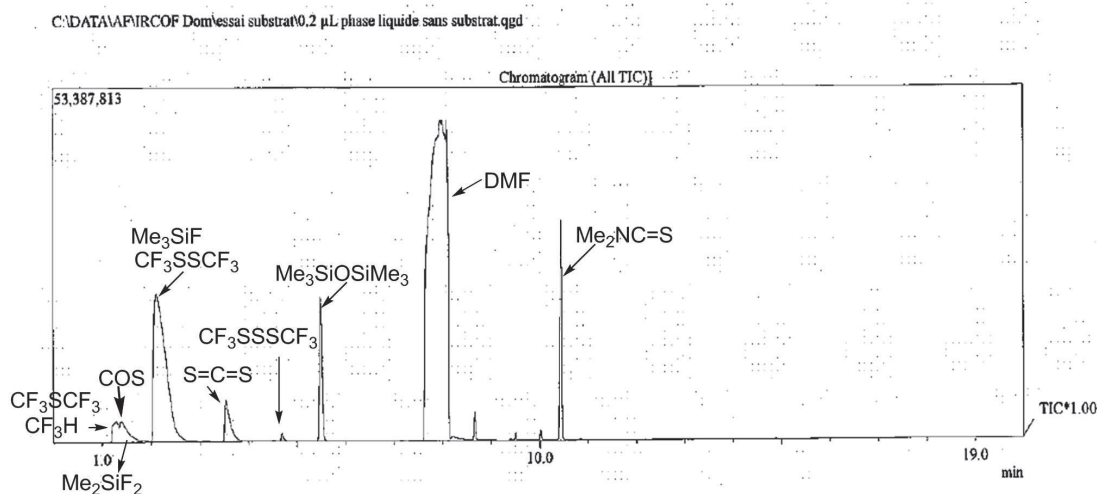
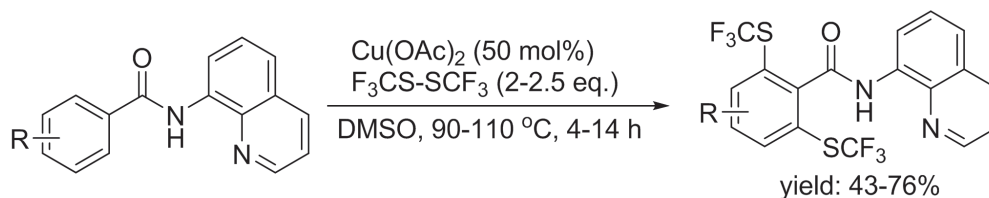


Figure 4-8

It has been determined that $S(\text{CF}_3)_2$ was not an active species to generate SCF_3 anion.¹¹⁵ We wondered if higher analogues with two and more sulfur atoms could be possible SCF_3 precursor. Recently, Daugulis and co-workers reported an amide-directed C-H functionalization of arenes with trifluoromethyl disulfide through copper catalysis, which illustrated that $S_2(\text{CF}_3)_2$ could act as SCF_3 precursor (**Scheme 4-17**).¹³⁰



Scheme 4-17

Thus, we designed a reaction by adding CF_3SSCF_3 into the solution of MBH carbonate **16ai** and DABCO in DMF.¹³¹ The corresponding thermodynamic SCF_3 product was obtained in only 4% yield by ^{19}F NMR. Although the yield was low, the right product was obtained and somehow provided evidence of the reaction mechanism. Because tri- and tetra sulfur bistrifluoromethyl compounds were detected by GC-MS, these reagents might be more reactive in the trifluoromethylthiolation reaction. Unfortunately, we do not have these reagents to test their reactivity.

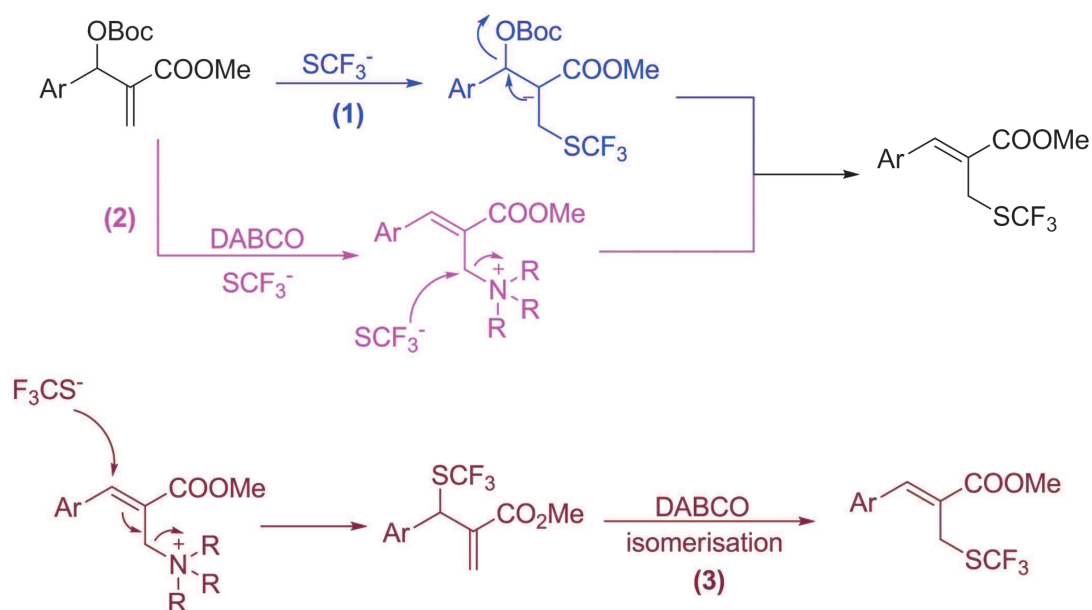
According to the literature and our observations by GC-MS and ^{19}F -NMR, we thereby envisaged that the active SCF_3 anion was generated from $S_n(\text{CF}_3)_2$ ($n \geq 2$), with the aid of strong base *tert*-butoxide formed from MBH carbonate and this hypothesis is in line with the poor result of MBH acetate. A thiophilic attack of *t*-BuO⁻ at a sulfur atom in $S_n(\text{CF}_3)_2$ could generate the SCF_3 anion.

We proposed three pathways for the regio- and stereoselective allylic trifluoromethylthiolation. **(1) Direct addition-elimination mechanism, apparent S_N2' mechanism:** in the absence of DABCO, the SCF_3 anion attacks directly onto the terminal double bond of MBH carbonate followed by removal of the OBoc leaving group to afford the conjugated SCF_3 product (**Scheme 4-18, route 1**). **(2) Lewis base catalyzed S_N2'/S_N2 mechanism:** in the presence of DABCO, MBH carbonate reacts with DABCO to form the ammonium salt intermediate. Then, SCF_3 anion substitutes the tertiary amine DABCO to get

¹³⁰ L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237-18240.

¹³¹ We thank Dr. Vitaliy Petrik for the gift of the $S_2(\text{CF}_3)_2$ reagent.

the same SCF_3 product (**Scheme 4-18, route 2**). **(3) $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2'$ mechanism followed by isomerisation of the secondary allylic SCF_3 product to primary allylic SCF_3 product:** After the formation of the ammonium salt intermediate in the route 2, the SCF_3 anion went through a $\text{S}_{\text{N}}2'$ mode to get the secondary allylic SCF_3 product first. With the released DABCO, this SCF_3 product isomerized to the more stable conjugated primary allylic SCF_3 product (**Scheme 4-18, route 3**).



Scheme 4-18

4.4.2 Use of Zard's reagent as nucleophilic SCF_3 transfer reagent

4.4.2.1 Introduction

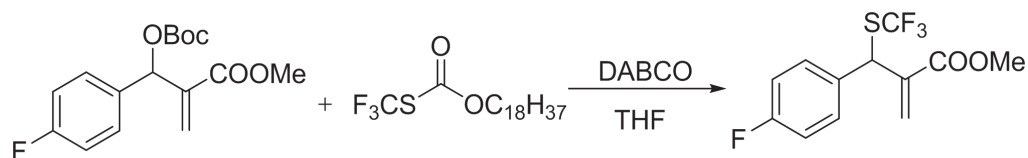
Although we have found good conditions to prepare the primary allylic SCF_3 products through regioselective and stereoselective allylic trifluoromethylthiolation, the obtention of the kinetic SCF_3 product was so far impossible. Compared with the fully conjugated thermodynamic SCF_3 product, it is more appealing to find an efficient way for the synthesis of kinetic SCF_3 product that contains a stereogenic center and a terminal vinyl functional group ready for further transformation (**Figure 4-3**).

Since in our one-pot $\text{S}_8/\text{CF}_3\text{SiMe}_3/\text{KF}/\text{DMF}$ system, there are many signals of byproducts around -40 ppm in ^{19}F NMR, it is not easy to discern the signal of a possible

kinetic SCF_3 product, even though a slight amount of this kinetic product might be generated in the early stage of the reaction. Therefore, the change of the nucleophilic SCF_3 reagent was taken into account.

In literature data part, we have briefly mentioned Zard's reagent. This long chain ester *O*-octadecyl *S*-trifluoromethyl carbonothioate ultimately originated from trifluoroacetic anhydride worked well as an efficient nucleophilic trifluoromethylating reagent. The active SCF_3 anion was generated in the presence of an amine to give the corresponding trifluoromethyl sulfides in generally high yields (**Scheme 4-3**).¹¹⁶

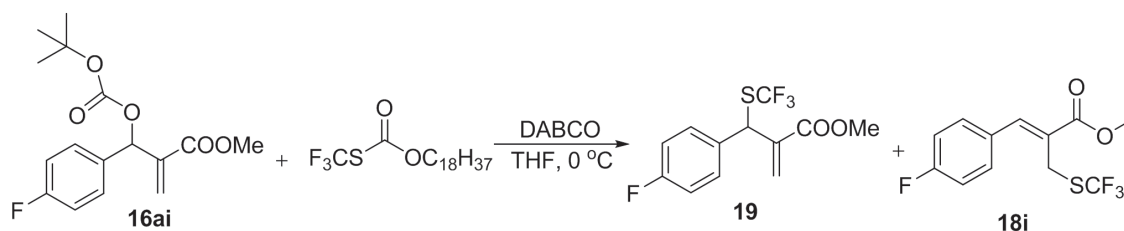
Thus, we decided to use this long chain SCF_3 carbonate as nucleophilic reagent for the allylic trifluoromethylthiolation. Fortunately, we were able to catch the fleeting secondary allylic product during its brief existence under our new reaction conditions (**Scheme 4-19**).



Scheme 4-19

4.4.2.2 Optimization of reaction conditions

We examined the reaction by adding Zard's reagent¹³² into the solution of MBH carbonate **16ai** and 10 mol% DABCO in THF at 0 °C. After 5 minutes, the SCF_3 reagent was fully converted (**Table 4-13**, entry 1). The ratio of product **19** (^{19}F NMR $\delta = -41.8$ ppm) and product **18i** (^{19}F NMR $\delta = -42.3$ ppm) was 61:39. However, after 30 minutes, the ratio **19/18i** was reversed to give almost exclusively compound **18i**. This result clearly indicated that **19** is the kinetic product, which quickly isomerizes into thermodynamic product **18i** (**Table 4-13**, entry 2).

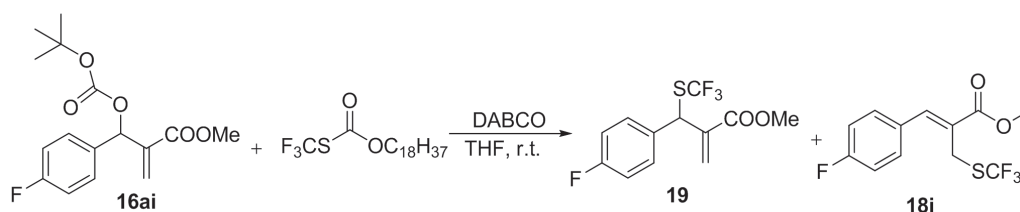


¹³² We thank Dr. S. Zard for providing us with a sample of his reagent.

entry	time (min)	conversion of SCF ₃ reagent (%)	19/18i
1	5	100	61:39
2	30	100	8:92

Table 4-13

When the reaction was performed at room temperature, from 5 minutes to 30 minutes, the ratio of the two SCF₃ products reversed from 78:11 to 4:89 (**Table 4-14**).



entry	time (min)	conversion of SCF ₃ reagent (%)	yield (%) ^a	
			kinetic SCF ₃ product 19	thermodynamic SCF ₃ product 18i
1	5	100	78	11
2	10	100	29	68
3	30	100	4	89

^a Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

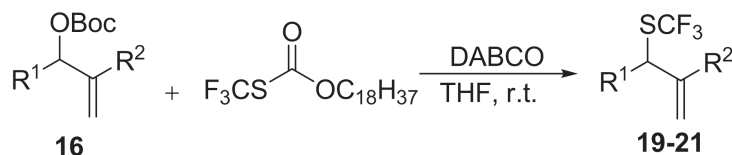
Table 4-14

After quenching the reaction and purification of the kinetic product **19**, we could not isolate pure **19** from the long chain octadecan-1-ol by either column chromatography or preparative TLC.

So far, the best conditions for the synthesis of kinetic SCF₃ product **19** was the use of 1 eq. MBH carbonate **16ai** and 10 mol% DABCO in 0.5 mL THF followed by loading 0.9 eq. Zard's reagent at room temperature, which afforded 78% yield of **19** within 5 minutes (**Table 4-14**, entry 1).

Under these conditions, we expanded the reaction scope with much bulkier *tert*-butyl MBH ester **16ap** and the phenylethyl substituted methyl MBH ester **16ar**, which have a poor reactivity in the preparation of thermodynamic SCF₃ products using the condition S₈/CF₃SiMe₃/KF/DMF. With *tert*-butyl MBH ester **16ap**, Zard's reagent was fully converted

after 20 minutes giving 52% yield of kinetic SCF₃ product **20** and only 6% yield of thermodynamic SCF₃ product **18p** (Table 4-15, entry 2). Unfortunately, after purification, we got a mixture of the kinetic product **20**, along with the long chain alcohol and also a little amount of thermodynamic product. In the case of alkyl MBH carbonate **16ar**, we could not get the kinetic product due to the messy reaction system (Table 4-15, entry 2).



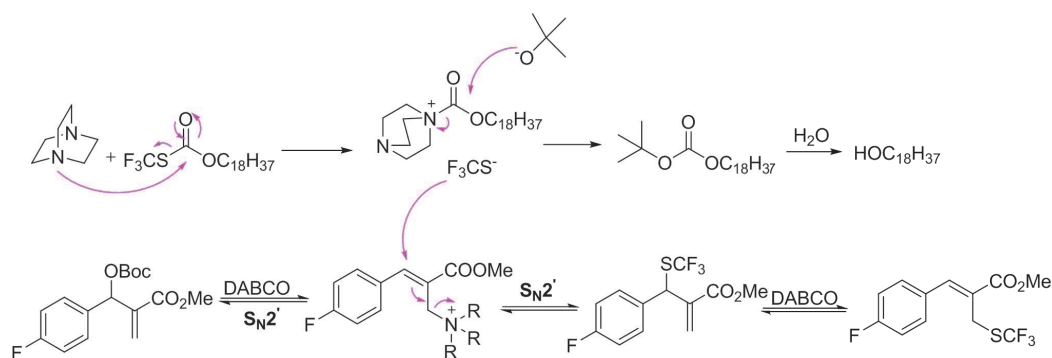
entry	MBH carbonate	R ¹	R ²	time (min)	SCF ₃ product	yield (%) ^a
1	16ai	4-FC ₆ H ₄	CO ₂ Me	5	19	78
2	16ap	Phenyl	CO ₂ <i>t</i> -Bu	20	20	52
3	16ar	PhCH ₂ CH ₂	CO ₂ Me	30	21	-

^a Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

Table 4-15

4.4.2.3 Mechanism investigation

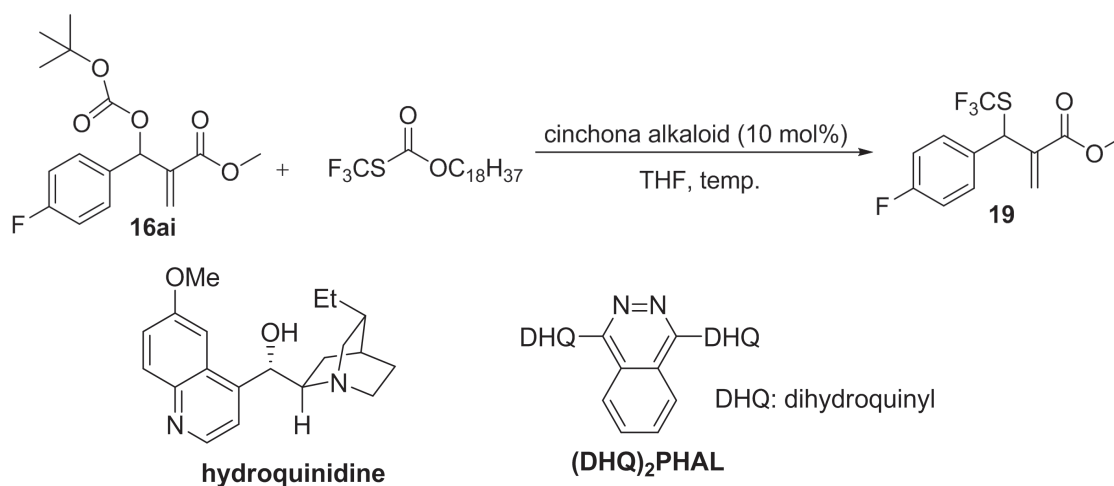
According to the results we have accumulated, we demonstrate that DABCO is essential for the reaction and plays a dual role in activating both Zard's reagent and MBH substrate. We propose that the active species SCF₃ anion is liberated by the combination of Zard's reagent and DABCO. Then, the SCF₃ anion attacks the ammonium intermediate which is formed by MBH carbonate and DABCO through a second S_N2' mechanism. The addition-elimination of SCF₃ anion is a reversible process and thus the thermodynamic product is obtained when reaction time progresses. (Scheme 4-20).



Scheme 4-20

4.4.2.4 Asymmetric version

In order to develop an asymmetric version of this reaction, we also tested chiral cinchona alkaloids, which are traditionally used in MBH S_N2'/S_N2' allylic substitution.¹¹⁸ To our surprise, the bulky (DHQ)₂PHAL was not efficient for this trifluoromethylthiolation even at higher temperature (**Table 4-16**, entry 1). It was the same result for the less sterically demanding hydroquinidine catalyst. We only observed Zard's reagent by ¹⁹F NMR (**Table 4-16**, entry 2). These observations demonstrated that only the DABCO motif without bulky substituent could react with Zard's reagent to generate the active SCF₃ anion. Thus, besides 10 mol% chiral catalyst (DHQ)₂PHAL, we added 5 mol% DABCO into the reaction system after the loading of Zard's reagent. Rapidly, after 3 minutes, it furnished the kinetic product **19** in 58% yield (**Table 4-16**, entry 3). But the product always mixed with a part of the long chain alcohol and, moreover, we could not separate the two enantiomers by HPLC with a chiral column.



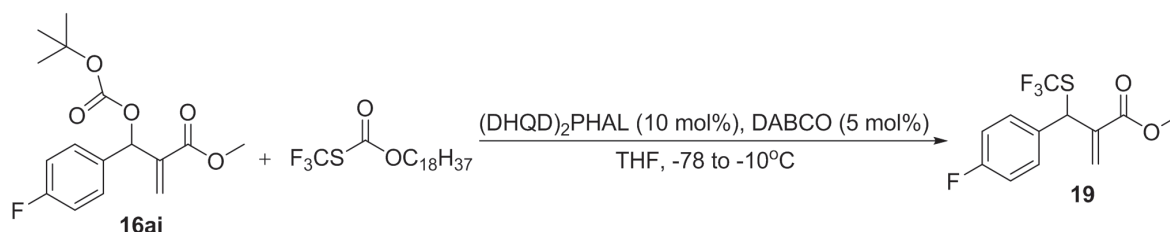
entry	Cinchona alkaloid	time (h)	temperature (°C)	yield of 19 (%) ^a
1	(DHQ) ₂ PHAL (10 mol%)	5	20-50	-
2	Hydroquinidine (10 mol%)	4	20-50	-
3	(DHQ) ₂ PHAL (10 mol%) and DABCO (5 mol%)	3 mins	20	58

^a Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

Table 4-16

In order to stabilize the kinetic SCF₃ product for a longer time, we carried out the

reaction at -78 °C but the reaction did not go ahead until rising the temperature to -10 °C (Table 4-17, entries 1-4). We got 61% conversion and 26% kinetic product **19** at -10 °C (Table 4-17, entry 4). After we continued the reaction for another 2 hours; although the conversion of SCF₃ reagent was up to 92% and the yield of thermodynamic SCF₃ product remained to be around 6%, the yield of kinetic SCF₃ product stayed in the range 26-31% (Table 4-17, entries 5-6).



entry	temperature (°C)	time (h)	conversion of SCF ₃ ester (%)	yield (%) ^a	
				19	18i
1	-78	0.5	0	0	0
2	-40	1	0	0	0
3	-30	1.5	0	0	0
4	-10	2	61	26	6
5	-10	2.5	80	31	5
6	-10	3.5	92	26	6

^a Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

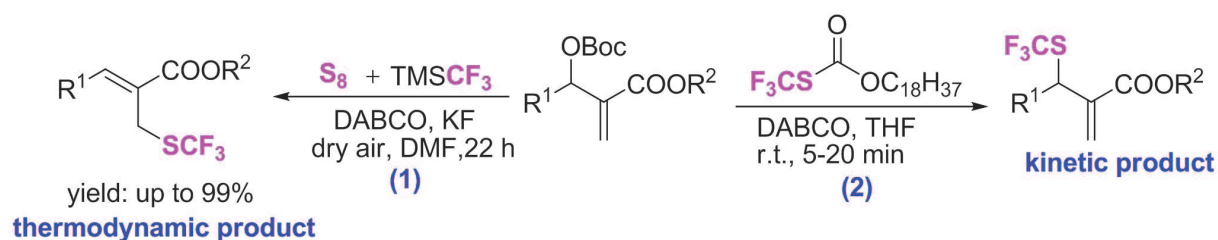
Table 4-17

4.5 Conclusion and perspectives

For the construction of Csp³-SCF₃ motif, which is less reported compared with the Csp²-SCF₃ and Csp-SCF₃ formation, we have achieved the preparation of thermodynamic trifluoromethylthiolated products through regioselective and stereoselective allylic substitution with MBH carbonates in moderate to excellent yields (up to 99%) and investigated the reaction mechanism by GC-MS and ¹⁹F NMR to have a better understanding of the generation of active trifluoromethylthiolated anion (Scheme 4-21, route 1).

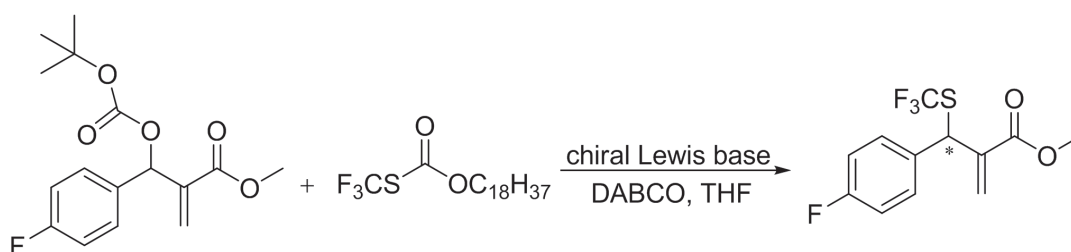
Besides, we preliminarily studied the synthesis of the kinetic trifluoromethylthiolated products by using Zard's reagent and obtained the "elusive" kinetic trifluoromethylthiolated

products in up to 78% yield of ^{19}F -NMR (**Scheme 4-21, route 2**).



Scheme 4-21

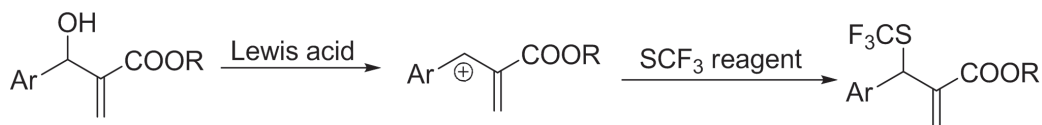
In order to develop the methodology for the allylic trifluoromethylthiolation and in particular the asymmetric version, it is crucial to find a solution to isolate or remove the long chain octadecan-1-ol byproduct to get the pure kinetic SCF_3 product. Furthermore, we will have a further exploration for separation of the two enantiomers by HPLC (**Scheme 4-22**).



Scheme 4-22

In order to optimize the reaction conditions for asymmetric allylic trifluoromethylthiolation by means of a chiral Lewis base, we will consider other amines that could selectively activate Zard's reagent and not the MBH carbonate. A series of cinchona alkaloid derivatives will be evaluated in the reaction as the source of chirality.

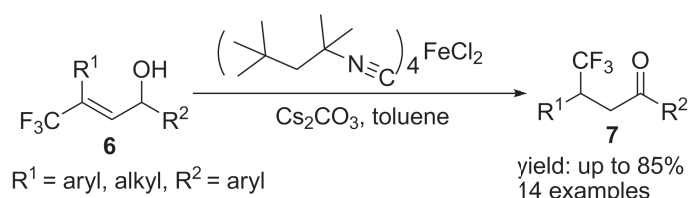
Since up to now, the thermodynamic SCF_3 product is the major one through Lewis base catalyzed nucleophilic trifluoromethylthiolation, we envisage that the generation of the more stable allylic carbocation by means of a Lewis acid such as LiPF_6 or FeCl_3 would be an alternative way to get the kinetic SCF_3 product through $\text{S}_{\text{N}}1$ mode (**Scheme 4-23**).



Scheme 4-23

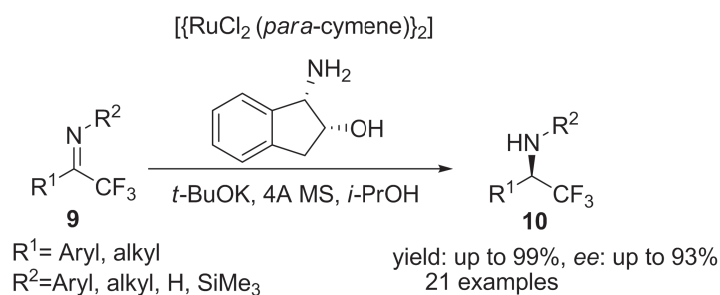
5. General conclusion

We have developed new methodologies for the construction of molecules featuring Csp³-CF₃ and Csp³-SCF₃ motifs. We have realized two hydride transfer reactions of trifluoromethylated compounds catalyzed by transition metal complexes. One part is the isomerization of trifluoromethylated allylic alcohols catalyzed by iron (II) complexes to synthesize various CF₃ dihydrochalcones (14 examples, up to 85% yield) (**Scheme 5-1**). This is the first time that iron(II) catalysts are efficiently applied in the isomerization of allylic alcohols.



Scheme 5-1

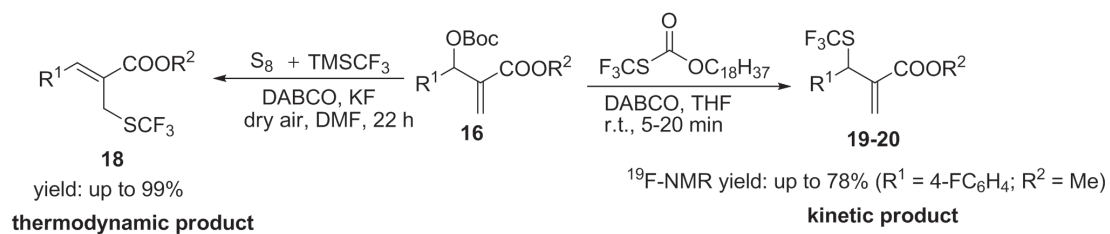
The second part is the ruthenium-catalyzed enantioselective transfer hydrogenation of trifluoromethylated imines by using isopropanol as hydride source and a chiral amino alcohol ligand to obtain optically active trifluoromethylated amines in high yields (up to 99%) and high enantioselectivities (up to 93%) (**Scheme 5-2**).



Scheme 5-2

Apart from the construction of Csp³-CF₃ stereogenic center, the construction of Csp³-SCF₃ motif by nucleophilic allylic trifluoromethylthiolation of Morita-Baylis-Hillman carbonates is another section of the PhD work. The regio- and stereoselective access to thermodynamic and kinetic trifluoromethylthiolated products has been achieved under different reaction conditions. The combination of S_8 , KF , Me_3SiCF_3 in DMF was employed

for the one-pot generation of trifluoromethylthiol anion to get the thermodynamic trifluoromethylthiolated products in moderate to excellent yields (up to 99%); whereas Zard's trifluoromethylthiolating reagent has been applied for the synthesis of the kinetically controlled trifluoromethylated products in up to 78% yield by ^{19}F NMR with $\text{R}^1 = 4\text{-FC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$ (Scheme 5-3).



Scheme 5-3

6. Experimental section

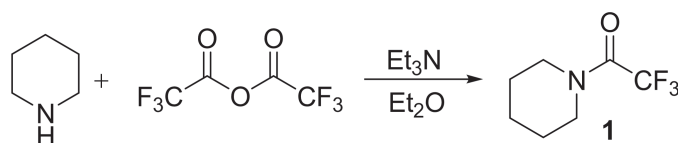
6.1 General information

^1H (300 MHz), ^{13}C (75.5 MHz), and ^{19}F (282 MHz) NMR spectra were recorded on a Bruker AVANCE 300. Chemical shifts in NMR spectra were reported in parts per million with reference to solvent residues in CDCl_3 (7.26 for proton and 77.16 for carbon, internal standard) or CFCl_3 (external standard for fluorine). IR spectra were recorded on a Perkin-Elmer IRFT 1650 spectrometer. The enantiomeric excesses (ee's) were determined by HPLC analysis. HPLC analysis were performed on Agilent HPLC 1100 Series system, column DAICEL CHIRALCEL OD-H, OJ-H or AD-H, mobile phase, *n*-heptane/2-propanol, UV detector at 254 or 210 nm. High-resolution mass spectrometry was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. All reactions were monitored by TLC or ^{19}F NMR. THF and toluene were distilled from sodium and benzophenone under a positive pressure of nitrogen and toluene was bubbled with argon before used. Dichloromethane was distilled over calcium hydride. In transfer hydrogenation reactions of trifluoromethylated ketimines, isopropanol was dried over molecular sieves under argon atmosphere. In nucleophilic trifluoromethylthiolation of Morita-Baylis-Hillman carbonates, DMF was dried over molecular sieves. Xyd numbers in parentheses referred to my labbook experiment numbers.

6.2 Isomerization of CF_3 allylic alcohols catalyzed by iron (II) complexes

6.2.1 Synthesis of CF_3 ketones

Synthesis of 2,2,2-trifluoro-1-piperidin-1-yl-ethanone (1)



Trifluoroacetic anhydride (7.4 mL, 52.5 mmol) was added via a dropping funnel over 3 h to NEt_3 (7.3 mL, 52.5 mmol), piperidine (6.2 mL, 63 mmol) and diethyl ether (5 mL) at 0 °C and stirred for 30 minutes. The mixture was warmed to room temperature and allowed to stir vigorously for 1 h. The mixture was washed with 1M HCl (10 mL) and extracted with diethyl ether. The combined organic layers were dried over MgSO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 40/1) to give 2,2,2-trifluoro-1-piperidin-1-yl-ethanone **1** (8.6 g, 90%) as colorless liquid.

H. A. Schenck *et al.* *Bioorg. Med. Chem.* **2004**, *12*, 979-993.

2,2,2-Trifluoro-1-piperidin-1-yl-ethanone (1) (xyd 298)

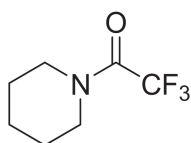
CAS number : [340-07-8]

Formula : $\text{C}_7\text{H}_{10}\text{F}_3\text{NO}$

M.W. : 181.2 g/mol

Yield : 90%

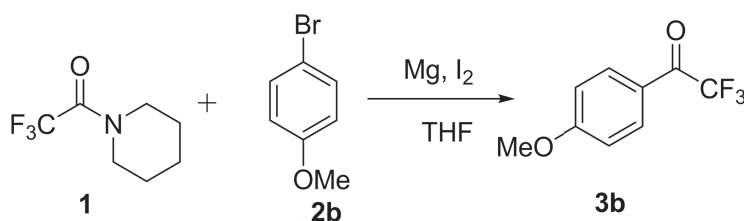
Aspect : Colorless liquid



$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 3.52-3.63 (m, 4H), 1.62-1.68 (m, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 155.5 (q, $^2J_{\text{CF}} = 30.8$ Hz), 116.8 (q, $^1J_{\text{CF}} = 286.5$ Hz), 47.0 (q, $^4J_{\text{CF}} = 3.8$ Hz), 44.7, 26.5, 25.5, 24.3; $^{19}\text{F NMR}$ (CDCl_3 , 282 MHz): -69.4.

For a complete characterization see H. A. Schenck *et al.* *Bioorg. Med. Chem.* **2004**, *12*, 979-993.

Typical procedure for the synthesis of CF_3 ketones (3)

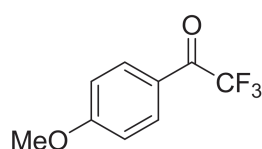


In a two-neck 50 mL flask equipped with condenser and dropping funnel was placed magnesium turnings (240 mg, 10 mmol), one piece of iodine and a little part of 4-bromoanisole in THF (10 mL). The mixture was heated until reflux. Then, the solution of 4-bromoanisole (1.25 mL, 10 mmol) in THF (15 mL) was added dropwise. Reflux was kept

for 2 hr and then the mixture was allowed to cool to room temperature. The mixture was cooled in an ice bath. 2,2,2-Trifluoroacetyl piperidine (1.45 mL, 10 mmol) in THF (20 mL) was slowly added into Grignard reagent over a period of 0.5 hr at 0 °C. The reaction mixture was stirred for 2 hr at ambient temperature. After 2 hr, the reaction was quenched with NH₄Cl aq. and extracted with EA. The combined organic layers were dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 30/1) to give 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone **3b** (1.2 g, 58%) as colorless liquid.

H. A. Schenck *et al. Bioorg. Med. Chem.* **2004**, *12*, 979-993.

2,2,2-Trifluoro-1-(4-methoxy-phenyl)-ethanone (**3b**) (xyd 164)



CAS number : [711-38-6]

Formula : C₉H₇F₃O₂

M.W. : 204.2 g/mol

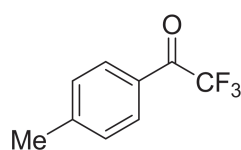
Yield : 58%

Aspect : Colorless liquid

¹H NMR (CDCl₃, 300 MHz): δ 8.05-8.07 (m, 2H), 6.99-7.02 (m, 2H), 3.92 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 178.9 (q, ²J_{CF} = 34.5 Hz), 165.4, 132.8 (q, ³J_{CF} = 2.2 Hz), 123.0, 117.1 (q, ¹J_{CF} = 289.5 Hz), 114.6, 55.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.5.

For a complete characterization see H. A. Schenck *et al. Bioorg. Med. Chem.* **2004**, *12*, 979-993.

2,2,2-Trifluoro-1-*p*-tolylethanone (**3d**) (xyd 180)



CAS number : [394-59-2]

Formula : C₉H₇F₃O

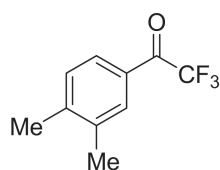
M.W. : 188.2 g/mol

Yield : 80%

Aspect : colorless liquid

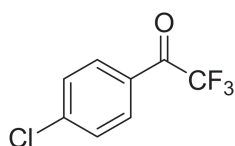
¹H NMR (CDCl₃, 300 MHz): δ 7.96-7.99 (m, 2H), 7.33-7.36 (m, 2H), 2.46 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 180.2 (q, ²J_{CF} = 34.5 Hz), 147.2, 130.4 (q, ³J_{CF} = 2.2 Hz), 130.0, 127.6, 116.9 (q, ¹J_{CF} = 290.2 Hz), 22.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.8.

For a complete characterization see H. A. Schenck *et al. Bioorg. Med. Chem.* **2004**, *12*, 979-993.

1-(3,4-Dimethylphenyl)-2,2,2-trifluoroethanone (3e) (xyd 275)**CAS number** : [75833-26-0]**Formula** : C₁₀H₉F₃O**M.W.** : 202.2 g/mol**Yield** : 65%**Aspect** : white solid

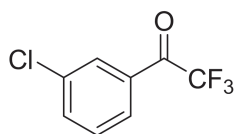
¹H NMR (CDCl₃, 300 MHz): δ 7.80-7.84 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 180.4 (q, ²*J*_{CF} = 27.8 Hz), 146.0, 137.9, 131.2 (q, ³*J*_{CF} = 1.5 Hz), 130.4, 128.0 (q, ³*J*_{CF} = 2.2 Hz), 127.9, 117.0 (q, ¹*J*_{CF} = 290.0 Hz), 20.5, 19.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.6.

For a complete characterization see K. C. Teo *et al.* *Can. J. Chem.* **1980**, *58*, 2491-2496.

1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (3g) (xyd 176)**CAS number** : [321-37-9]**Formula** : C₈H₄ClF₃O**M.W.** : 208.6 g/mol**Yield** : 60%**Aspect** : pale yellow liquid

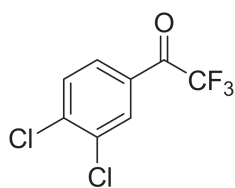
¹H NMR (CDCl₃, 300 MHz): δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 179.6 (q, ²*J*_{CF} = 35.3 Hz), 142.6, 131.6 (q, ³*J*_{CF} = 2.1 Hz), 129.8, 128.4, 116.7 (q, ¹*J*_{CF} = 289.3 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -72.0.

For a complete characterization see Y. L. Yagupolskii *et al.* *J. Fluorine. Chem.* **2007**, *128*, 1385-1389.

1-(3-Chlorophenyl)-2,2,2-trifluoroethanone (3h) (xyd 184)**CAS number** : [321-31-3]**Formula** : C₈H₄ClF₃O**M.W.** : 208.6 g/mol**Yield** : 67%**Aspect** : colorless liquid

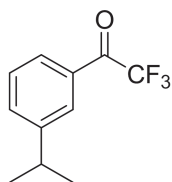
¹H NMR (CDCl₃, 300 MHz): δ 8.04 (s, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 179.6 (q, ²*J*_{CF} = 36 Hz), 135.7, 135.6, 131.5, 130.6, 130.1 (q, ³*J*_{CF} = 2.2 Hz), 128.3 (q, ³*J*_{CF} = 2.2 Hz), 116.5 (q, ¹*J*_{CF} = 289.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -71.6.

For a complete characterization see H. A. Schenck *et al.* *Bioorg. Med. Chem.* **2004**, *12*, 979-993.

1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethanone (3i) (xyd 279)**CAS number** : [125733-43-9]**Formula** : C₈H₃Cl₂F₃O**M.W.** : 243.0 g/mol**Yield** : 42%**Aspect** : white solid

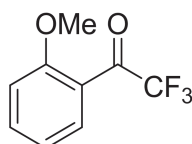
¹H NMR (CDCl₃, 300 MHz): δ 8.15 (s, 1H), 7.88-7.92 (m, 1H), 2.36 (d, *J* = 8.5 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 178.8 (q, ²*J*_{CF} = 36 Hz), 140.1, 134.3, 132.0 (q, ³*J*_{CF} = 2.2 Hz), 131.5, 129.5, 129.0 (q, ³*J*_{CF} = 2.2 Hz), 116.4 (q, ¹*J*_{CF} = 288.8 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -72.1.

For a complete characterization see H. A. Schenck *et al. Bioorg. Med. Chem.* **2004**, *12*, 979-993.

2,2,2-Trifluoro-1-(3-isopropylphenyl)ethanone (3k) (xyd 299)**CAS number** : [155628-02-7]**Formula** : C₁₁H₁₁F₃O**M.W.** : 216.2 g/mol**Yield** : 72%**Aspect** : colorless liquid

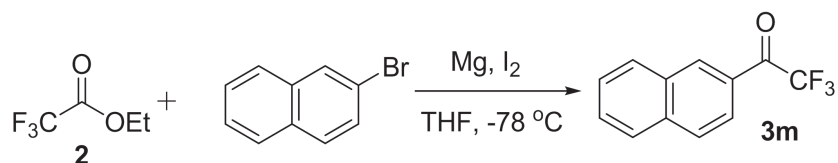
¹H NMR (CDCl₃, 300 MHz): δ 7.94 (s, 1H), 7.88-7.90 (m, 1H), 7.58-7.60 (m, 1H), 7.44-7.50 (m, 1H), 2.96-3.05 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 180.8 (q, ²*J*_{CF} = 34.5 Hz), 150.2, 134.1, 130.1, 129.2, 128.2 (q, ⁴*J*_{CF} = 1.5 Hz), 127.9 (q, ³*J*_{CF} = 2.2 Hz), 116.3 (q, ¹*J*_{CF} = 198.8 Hz), 34.2, 23.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.7.

For a complete characterization see D. M. Quinn *et al. Bioorg. Med. Chem. Lett.* **1993**, *3*, 2619-2622.

2,2,2-Trifluoro-1-(2-methoxy-phenyl)-ethanone (3l) (xyd 168)**CAS number** : [26944-43-4]**Formula** : C₉H₇F₃O₂**M.W.** : 204.2 g/mol**Yield** : 49%**Aspect** : Colorless liquid

¹H NMR (CDCl₃, 300 MHz): δ 7.57-7.69 (m, 2H), 7.01-7.08 (m, 2H), 3.92 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 182.9 (q, ²*J*_{CF} = 36 Hz), 159.9, 135.9, 131.4 (q, ³*J*_{CF} = 2.2 Hz), 121.6, 120.7, 116.2 (q, ¹*J*_{CF} = 288.8 Hz), 112.1, 55.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.6.

For a complete characterization see H. A. Schenck *et al. Bioorg. Med. Chem.* **2004**, *12*, 979-993.

Synthesis of 2,2,2-trifluoro-1-(naphthalen-2-yl)ethanone (3m)

In a two-neck 25 mL flask equipped with condenser and dropping funnel were placed magnesium turnings (240 mg, 10 mmol), one piece of iodine and a little part 2-bromonaphthalene in THF (10 mL). The mixture was heated until reflux. Then, the solution 2-bromonaphthalene (2.07 g, 10 mmol) in THF (15 mL) was added dropwise. Reflux was kept for 2hr and the Grignard reagent was cooled to room temperature and added dropwise into the ethyl trifluoroacetate (1.19 mL, 10 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred for 1 hr at -78 °C. Then, the reaction was quenched with NH₄Cl aq. and extracted with ethyl acetate. The combined organic layer was dried over MgSO₄ and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 30/1) to give 2,2,2-trifluoro-1-(naphthalen-2-yl)ethanone **3m** (1.45 g, 65%) as white solid.

T. Konno *et al. J. Org. Chem.* **2006**, *71*, 3545-3550.

2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanone (3m) (xyd 393)

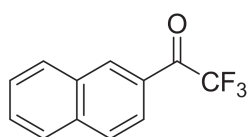
CAS number : [1800-42-6]

Formula : C₁₂H₁₇F₃O

M.W. : 224.2 g/mol

Yield : 65%

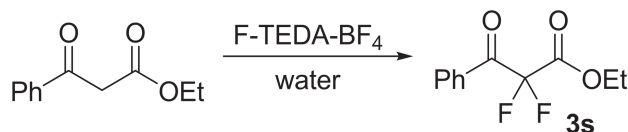
Aspect : white solid



¹H NMR (CDCl₃, 300 MHz): δ 8.62 (s, 1H), 7.89-8.09 (m, 4H), 7.59-7.71 (m, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 180.6 (q, ²J_{CF} = 34.6 Hz), 136.6, 133.4 (q, ³J_{CF} = 2.7 Hz), 132.4, 130.4, 130.2, 129.3, 128.1, 127.6, 127.4, 124.4 (q, ⁴J_{CF} = 1.4 Hz), 117.0 (q, ¹J_{CF} = 289.6 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -71.2.

For a complete characterization see T. Konno *et al. J. Org. Chem.* **2006**, *71*, 3545-3550.

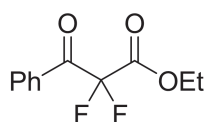
Synthesis of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3s)



Ethyl 3-oxo-3-phenylpropanoate (961 mg, 5 mmol) was placed in a glass flask equipped with a magnetic stirrer, 5 mL of deionized water was then added and the reaction system was intensively stirred at 60-80 °C to obtain a well dispersed aqueous system. F-TEDA-BF₄ (3.9 g, 11 mmol) was added in two portions to the aqueous dispersion and stirred at 60-80 °C until full consumption of the fluorinating reagent as monitored by ¹⁹F NMR. The reaction mixture was cooled to room temperature. The reaction system was diluted with water (10 mL) and extracted with *tert*-butyl methyl ether. The combined ether phase was dried over MgSO₄ and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 20/1) to give ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate **3s** (465.6 mg, 41%) as colorless liquid.

S. Stavber *et al.* *Adv. Synth. Catal.* **2010**, 352, 2838-2846.

Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3s) (xyd 302)



CAS number : [114701-62-1]

Formula : C₁₁H₁₀F₂O₃

M.W. : 228.2 g/mol

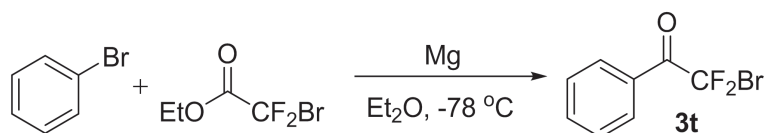
Yield : 41%

Aspect : colorless liquid

¹H NMR (CDCl₃, 300 MHz): δ 8.08 (d, *J* = 7.6 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 185.6 (t, ²*J*_{CF} = 27.8 Hz), 162.0 (t, ²*J*_{CF} = 30 Hz), 135.3, 130.1 (t, ³*J*_{CF} = 3 Hz), 129.1, 111.3 (t, ¹*J*_{CF} = 252 Hz), 109.9 (t, ¹*J*_{CF} = 262.5 Hz), 63.9, 13.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -108.1.

For a complete characterization see S. Stavber *et al.* *Adv. Synth. Catal.* **2010**, 352, 2838-2846.

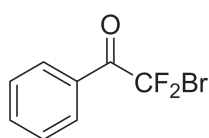
Synthesis of 2-bromo-2,2-difluoro-1-phenylethanone (3t)



In a two-necked 25 mL flask equipped with condenser and dropping funnel were placed magnesium turnings (264 mg, 11 mmol), one piece of iodine in diethyl ether (5 mL) and a little part of bromobenzene in diethyl ether. The mixture was heated until reflux. Then, the solution of bromobenzene (1.73 g, 11 mmol) in diethyl ether (5 mL) was added dropwise. Reflux was kept for 2hr and then the mixture was allowed to cool to room temperature. To a solution of ethyl bromodifluoroacetate (2 g, 10 mmol) in diethyl ether (10 mL) was added the solution of phenylmagnesium bromide in diethyl ether at $-78\text{ }^\circ\text{C}$ under argon atmosphere. After the solution was stirred at that temperature for 3 hr, the mixture was quenched with 2M HCl and then extracted with diethyl ether. The extract was dried over anhydrous MgSO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 40/1) to give 2-bromo-2,2-difluoro-1-phenylethanone **3t** (2 g, 86%) as colorless liquid.

T. Kitazume *et al.* *J. Org. Chem.* **2005**, *70*, 5912-5915.

2-Bromo-2,2-difluoro-1-phenylethanone (**3t**) (xyd 379)



CAS number : [1610-04-4]

Formula : $\text{C}_8\text{H}_5\text{BrF}_2\text{O}$

M.W. : 235.0 g/mol

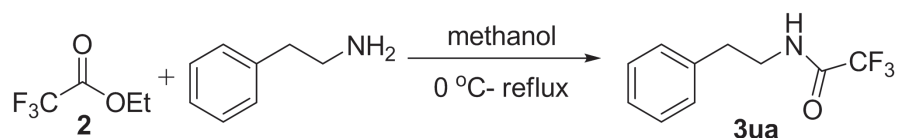
Yield : 86%

Aspect : colorless liquid

^1H NMR (CDCl_3 , 300 MHz): δ 8.16 (d, $J = 7.8$ Hz, 2H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 2H); **^{13}C NMR** (CDCl_3 , 75 MHz): δ 181.5 (t, $^2J_{\text{CF}} = 25.7$ Hz), 135.3, 130.8 (t, $^3J_{\text{CF}} = 2.6$ Hz), 129.2, 129.0, 113.7 (t, $^1J_{\text{CF}} = 316.6$ Hz); **^{19}F NMR** (CDCl_3 , 282 MHz): -58.3.

For a complete characterization see G. A. Olah *et al.* *J. Fluorine Chem.* **2003**, *121*, 239-243.

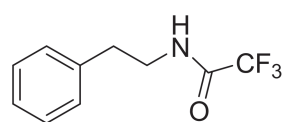
Synthesis of 2,2,2-trifluoro-*N*-phenethylacetamide (**3ua**)



In a 25 mL round bottom flask fitted with a reflux condenser were added ethyl trifluoroacetate (1.42 g, 10 mmol) and dry methanol (15 mL). Then, 2-phenylethanamine (1.48 g, 12 mmol) was added dropwise at 0 °C. The temperature of the mixture was gradually increased and to reflux for 12 hours. After cooling down, the solvent and excess amine were evaporated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 20/1) to give 2,2,2-trifluoro-*N*-phenethylacetamide **3ua** (2.4 g, 99%) as colorless liquid.

A. Cambon *et al.* *J. Fluorine Chem.*, **1979**, *13*, 279-296.

2,2,2-Trifluoro-*N*-phenethylacetamide (**3ua**) (xyd 383)



CAS number : [458-85-5]

Formula : C₁₀H₁₀NF₃O

M.W. : 217.2 g/mol

Yield : 99%

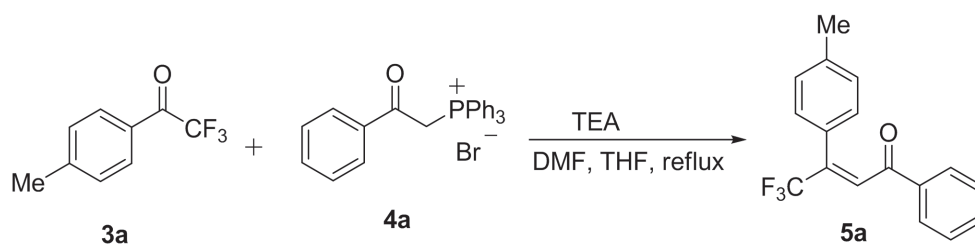
Aspect : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.29-7.39 (m, 3H), 7.20-7.23 (m, 2H), 6.57 (s, 1H), 3.63 (q, *J* = 6.6 Hz, 2H), 2.91 (t, *J* = 7.1 Hz, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.3 (q, ²*J*_{CF} = 36.5 Hz), 137.7, 129.1, 128.8, 127.2, 115.9 (q, ¹*J*_{CF} = 286.2 Hz), 41.2, 35.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -76.5.

For a complete characterization see A. Cambon *et al.* *J. Fluorine Chem.*, **1979**, *13*, 279-296.

6.2.2 Synthesis of β-CF₃ enones

Typical procedure for the synthesis of β-CF₃ enones (**5**)

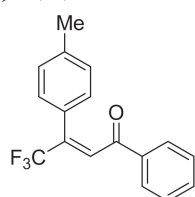


To a THF (5 ml) solution of (2-oxo-2-phenylethyl)triphenylphosphonium bromide (1.38 g, 3 mmol) and triethylamine (0.4 mL, 3 mmol) was added a solution of

2,2,2-trifluoro-1-*p*-tolylethanone (376 mg, 2 mmol) in DMF (0.5 mL) at 0 °C. The mixture was stirred for 15 min. Then, the reaction mixture was heated at 80 °C for 3 h. The mixture was quenched with NH₄Cl aqueous solution, extracted with EA. The combined organic layers were dried over MgSO₄ and concentrated in *vacuo*. The residue containing *E/Z* isomers in a ratio 94/6 was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 50/1) to give pure (*E*)-4,4,4-trifluoro-1-phenyl-3-*p*-tolylbut-2-en-1-one **5d** (475 mg, 82%) as yellow liquid.

N. Shibata *et al.* *Angew. Chem. Int. Ed.*, **2010**, *49*, 5762-5766

(*E*)-4,4,4-Trifluoro-1-phenyl-3-*p*-tolylbut-2-en-1-one (5d) (xyd 323)



CAS number : [1245905-77-4]

Formula : C₁₇H₁₃F₃O

M.W. : 290.3 g/mol

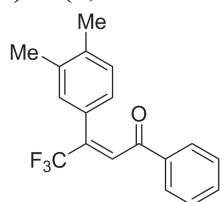
Yield : 82%

Aspect : yellow liquid

¹H NMR (CDCl₃, 300 MHz): δ 7.82-7.85 (m, 2H), 7.52 (t, *J* = 6.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.24-7.25 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 2.28 (s, 3H) ; **¹³C NMR** (CDCl₃, 75 MHz): δ 192.4, 139.6, 139.2 (q, ²*J*_{CF} = 30.4 Hz), 136.2, 134.0, 130.5 (q, ³*J*_{CF} = 5.1 Hz), 129.3, 129.1, 129.0, 128.8, 128.0, 123.0 (q, ¹*J*_{CF} = 273 Hz), 21.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -66.8.

For a complete characterization see N. Shibata *et al.* *Angew. Chem. Int. Ed.*, **2010**, *49*, 5762-5766.

(*E*)-3-(3,4-Dimethylphenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (5e) (xyd 327)



CAS number : unknown

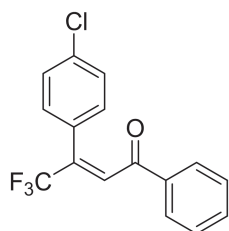
Formula : C₁₈H₁₅F₃O

M.W. : 304.3 g/mol

Yield : 41%

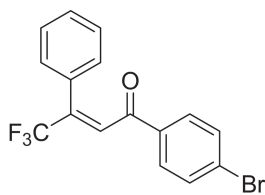
Aspect : yellow liquid

¹H NMR (CDCl₃, 300 MHz): δ 7.82-7.85 (m, 2H), 7.51-7.56 (m, 1H), 7.38-7.43 (m, 2H), 7.23-7.24 (m, 1H), 7.01-7.04 (m, 3H), 2.18 (s, 3H), 2.16 (s, 3H) ; **¹³C NMR** (CDCl₃, 75 MHz): δ 192.4, 139.3 (q, ²*J*_{CF} = 30.3 Hz), 138.3, 136.8, 136.3, 133.9, 130.2 (q, ³*J*_{CF} = 5.1 Hz), 130.1, 129.8, 129.0, 128.8, 128.4, 126.6, 123.1 (q, ¹*J*_{CF} = 273 Hz), 19.8, 19.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -66.7; **IR** (neat) ν 3072, 1672, 1598, 1449, 1314, 1272, 1171, 1121, 1020, 975, 877, 822, 765, 729, 706 cm⁻¹; **HRMS** Calcd for C₁₈H₁₆F₃O ([M+H]⁺): 305.1153, Found: 305.1144.

(E)-3-(4-Chlorophenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (5g) (352)**CAS number** : [1245905-79-6]**Formula** : C₁₆H₁₀ClF₃O**M.W.** : 310.7 g/mol**Yield** : 88%**Aspect** : yellow liquid

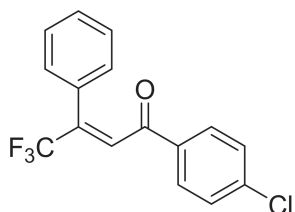
¹H NMR (CDCl₃, 300 MHz): δ 7.82-7.84 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.33 (m, 1H), 7.23-7.28 (m, 4H); **¹³C NMR** (CDCl₃, 75 MHz): δ 191.7, 138.1 (q, ²*J*_{CF} = 30.8 Hz), 136.1, 135.8, 134.3, 131.4 (q, ³*J*_{CF} = 5.2 Hz), 130.6, 129.3, 129.0, 129.0, 128.9, 122.8 (q, ¹*J*_{CF} = 273 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -66.9.

For a complete characterization see N. Shibata *et al. Angew. Chem. Int. Ed.*, **2010**, *49*, 5762-5766.

(E)-1-(4-Bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-one (5h) (xyd 335)**CAS number** : [1245905-88-7]**Formula** : C₁₆H₁₀BrF₃O**M.W.** : 355.2 g/mol**Yield** : 82%**Aspect** : yellow liquid

¹H NMR (CDCl₃, 300 MHz): δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.21-7.31 (m, 6H); **¹³C NMR** (CDCl₃, 75 MHz): δ 191.3, 139.4 (q, ²*J*_{CF} = 30.8 Hz), 134.9, 132.2, 130.8, 130.5, 130.3 (q, ³*J*_{CF} = 4.5 Hz), 129.8, 129.4, 129.1, 128.6, 122.9 (q, ¹*J*_{CF} = 273 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -66.8.

For a complete characterization see N. Shibata *et al. Angew. Chem. Int. Ed.*, **2010**, *49*, 5762-5766.

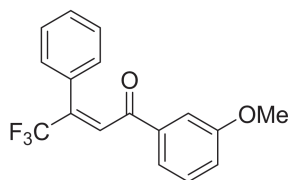
(E)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-one (5i) (xyd 360-1)**CAS number** : [1245905-87-6]**Formula** : C₁₆H₁₀ClF₃O**M.W.** : 310.7 g/mol**Yield** : 90%**Aspect** : yellow liquid

¹H NMR (CDCl₃, 300 MHz): δ 7.73-7.76 (m, 2H), 7.34-7.37 (m, 2H), 7.24-7.29 (m, 5H), 7.21 (m, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 191.1, 140.6, 139.4 (q, ²*J*_{CF} = 30.8 Hz), 134.5, 130.8, 130.4 (q, ³*J*_{CF} = 5.2 Hz), 130.4, 129.8, 129.2, 129.1, 128.6, 122.9 (q, ¹*J*_{CF} = 273 Hz);

^{19}F NMR (CDCl_3 , 282 MHz): -66.8.

For a complete characterization see N. Shibata *et al. Angew. Chem. Int. Ed.*, **2010**, *49*, 5762-5766.

(E)-4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-one (5j) (xyd 371)



CAS number : [1466438-82-3]

Formula : $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_2$

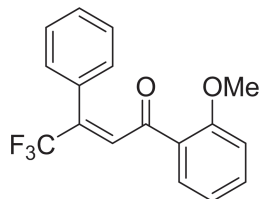
M.W. : 306.3 g/mol

Yield : 95%

Aspect : yellow liquid

^1H NMR (CDCl_3 , 300 MHz): δ 7.39-7.42 (m, 1H), 7.25-7.31 (m, 8H), 7.04-7.08 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 191.7, 159.8, 139.0 (q, $^2J_{\text{CF}} = 30.8$ Hz), 137.4, 130.8, 130.8 (q, $^3J_{\text{CF}} = 5.2$ Hz), 129.7, 129.4, 129.0, 128.4, 122.8 (q, $^1J_{\text{CF}} = 273$ Hz), 122.0, 120.8, 112.4, 55.4; ^{19}F NMR (CDCl_3 , 282 MHz): -66.8; **IR** (neat) ν 2935, 1674, 1597, 1486, 1168, 1122, 1030, 871, 778, 697, 627 cm^{-1} ; **HRMS** Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 307.0946, Found: 307.0949.

(E)-4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-one (5k) (xyd 360-2)



CAS number : [1513855-46-3]

Formula : $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_2$

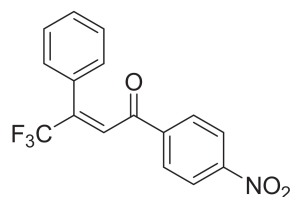
M.W. : 306.3 g/mol

Yield : 89%

Aspect : yellow liquid

^1H NMR (CDCl_3 , 300 MHz): δ 7.54 (dd, $J = 7.6$ Hz, $J = 1.7$ Hz, 1H), 7.39-7.45 (m, 1H), 7.21-7.27 (m, 6H), 6.87-6.93 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 192.0, 159.2, 135.6 (q, $^2J_{\text{CF}} = 30.8$ Hz), 134.5, 134.8 (q, $^3J_{\text{CF}} = 6$ Hz), 131.4, 130.8, 129.3, 129.1, 128.3, 127.2, 123.4 (q, $^1J_{\text{CF}} = 272.2$ Hz), 120.9, 111.7, 55.7; ^{19}F NMR (CDCl_3 , 282 MHz): -67.0; **IR** (neat) ν 2944, 1662, 1597, 1484, 1292, 1162, 1115, 1016, 968, 879, 754, 697, 625 cm^{-1} ; **HRMS** Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 307.0946, Found: 307.0949.

(E)-4,4,4-Trifluoro-1-(4-nitrophenyl)-3-phenylbut-2-en-1-one (5l) (xyd 367-1)



CAS number : [1380297-42-6]

Formula : C₁₆H₁₀F₃NO₃

M.W. : 321.2 g/mol

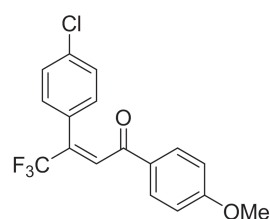
Yield : 91%

Aspect : yellow solid

mp : 106 °C

¹H NMR (CDCl₃, 300 MHz): δ 8.17-8.20 (m, 2H), 7.89-7.92 (m, 2H), 7.21-7.30 (m, 5H); **¹³C NMR** (CDCl₃, 75 MHz): δ 191.1, 150.6, 140.8 (q, ²J_{CF} = 30.8 Hz), 140.5, 130.5, 130.1, 130.0, 129.7 (q, ³J_{CF} = 5.2 Hz), 129.2, 128.8, 123.9, 122.7 (q, ¹J_{CF} = 273 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -66.8; **IR** (neat) ν 2919, 1679, 1526, 1349, 1272, 1224, 1158, 1124, 867, 802, 777, 699, 656 cm⁻¹; **HRMS** Calcd for C₁₆H₁₀F₃NO₃ ([M]⁻): 321.0613, Found: 321.0620.

(E)-3-(4-Chlorophenyl)-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-one (5m) (xyd 367-2)



CAS number : unknown

Formula : C₁₇H₁₂ClF₃O₂

M.W. : 340.7 g/mol

Yield : 86%

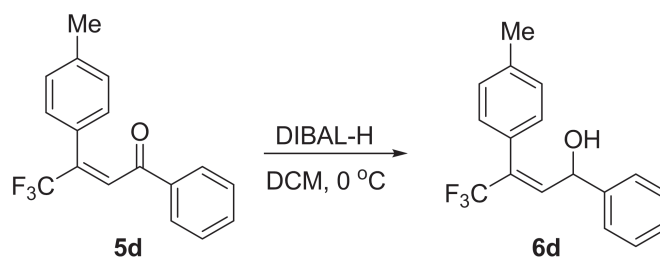
Aspect : yellow solid

mp : 86 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.81 (d, *J* = 8.9 Hz, 2H), 7.28-7.29 (m, 1H), 7.20-7.26 (m, 4H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 190.2, 164.5, 137.1 (q, ²J_{CF} = 30.8 Hz), 135.7, 131.8 (q, ³J_{CF} = 5.2 Hz), 131.5, 130.5, 129.5, 129.1, 128.8, 122.8 (q, ¹J_{CF} = 273 Hz), 114.2, 55.7; **¹⁹F NMR** (CDCl₃, 282 MHz): -66.8; **IR** (neat) ν 2927, 1659, 1588, 1510, 1263, 1245, 1160, 1107, 1025, 964, 843, 692 cm⁻¹; **HRMS** Calcd for C₁₇H₁₃F₃O₂Cl ([M+H]⁺): 341.0556, Found: 341.0548.

6.2.3 Synthesis of CF₃ allylic alcohols

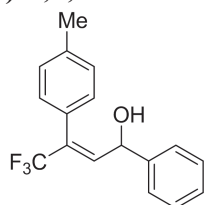
Typical procedure for the synthesis of CF₃ allylic alcohols (6)



To a 5 mL DCM solution of (*E*)-4,4,4-trifluoro-1-phenyl-3-*p*-tolylbut-2-en-1-on (460 mg, 1.58 mmol) was added diisobutylaluminum hydride (1.9 mL, 1.9 mmol) in 1.0 M DCM solution at 0 °C, and the reaction mixture was stirred for 1.5 h at that temperature. The reaction was quenched with NH₄Cl aqueous solution carefully until a white solid appeared. Then, 2 M HCl was added and the whole mixture was extracted with DCM. The combined organic phase was dried over MgSO₄ and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 20/1) to give (*E*)-4,4,4-trifluoro-1-phenyl-3-*p*-tolylbut-2-en-1-ol **6d** (318.8 mg, 69%) as colorless oil.

V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 6467-6470.

(*E*)-4,4,4-Trifluoro-1-phenyl-3-*p*-tolylbut-2-en-1-ol (6d) (xyd 326)



CAS number : [1458062-78-6]

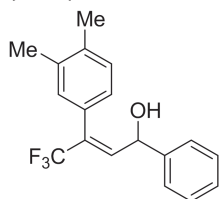
Formula : C₁₇H₁₅F₃O

M.W. : 292.3 g/mol

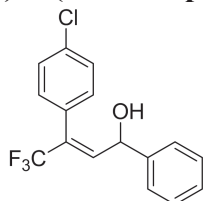
Yield : 69%

Aspect : colorless oil

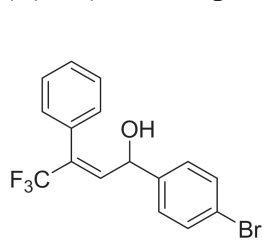
¹H NMR (CDCl₃, 300 MHz): δ 7.31-7.39 (m, 3H), 7.28-7.29 (m, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.56-6.59 (m, 1H), 5.14 (d, *J* = 9.3 Hz, 1H), 2.40 (s, 3H), 2.00 (d, *J* = 2.9 Hz, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ 141.7, 139.1, 136.4 (q, ³*J*_{CF} = 5.2 Hz), 132.2 (q, ²*J*_{CF} = 30 Hz), 129.6, 129.4, 129.0, 128.5, 128.4, 126.3, 123.3 (q, ¹*J*_{CF} = 271.5 Hz), 70.5, 21.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -67.1; **IR** (neat) ∪ 3326, 2926, 1516, 1456, 1307, 1241, 1168, 1113, 1013, 929, 906, 820, 730 cm⁻¹; **HRMS** Calcd for C₁₇H₁₄F₃O ([M-H]): 291.0997, Found: 291.1001.

(E)-3-(3,4-Dimethylphenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-ol (6e) (xyd 330)**CAS number** : [1458062-79-7]**Formula** : C₁₈H₁₇F₃O**M.W.** : 306.3 g/mol**Yield** : 87%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.26-7.40 (m, 5H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.00-7.04 (m, 2H), 6.55-6.59 (m, 1H), 5.16 (dd, *J* = 9.2 Hz, *J* = 3.1 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.95 (d, *J* = 3.6 Hz, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ 141.8, 137.8, 137.0, 136.2 (q, ³*J*_{CF} = 5.2 Hz), 132.3 (q, ²*J*_{CF} = 30 Hz), 130.8, 129.9, 129.0, 128.8, 128.4, 127.2, 126.4, 123.3 (q, ¹*J*_{CF} = 272.2 Hz), 70.6, 19.9, 19.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -67.0; **IR** (neat) ν 3330, 2923, 1494, 1452, 1309, 1232, 1170, 1118, 1021, 959, 907, 819, 728 cm⁻¹; **HRMS** Calcd for C₁₈H₁₆F₃O ([M-H]⁻): 305.1153, Found: 305.1157.

(E)-3-(4-Chlorophenyl)-4,4,4-trifluoro-1-phenylbut-2-en-1-ol (6g) (355)**CAS number** : [1458062-80-0]**Formula** : C₁₆H₁₂ClF₃O**M.W.** : 312.7 g/mol**Yield** : 84%**Aspect** : colorless oil

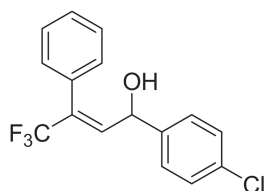
¹H NMR (CDCl₃, 300 MHz): δ 7.33-7.43 (m, 5H), 7.20-7.27 (m, 4H), 6.62-6.66 (m, 1H), 5.10 (dd, *J* = 9.2 Hz, *J* = 2.5 Hz, 1H), 2.00 (d, *J* = 3.5 Hz, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ 141.5, 137.2 (q, ³*J*_{CF} = 5.2 Hz), 135.5, 131.2, 131.1 (q, ²*J*_{CF} = 30.8 Hz), 129.8, 129.2, 129.1, 128.7, 126.3, 123.0 (q, ¹*J*_{CF} = 272.2 Hz), 70.6; **¹⁹F NMR** (CDCl₃, 282 MHz): -67.0; **IR** (neat) ν 3312, 1493, 1311, 1170, 1120, 1092, 1015, 907, 831, 731, 697, 609 cm⁻¹; **HRMS** Calcd for C₁₆H₁₁F₃OCl ([M-H]⁻): 311.0451, Found: 311.0453.

(E)-1-(4-Bromophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (6h) (xyd 338)**CAS number** : [1458062-81-1]**Formula** : C₁₆H₁₂BrF₃O**M.W.** : 357.2 g/mol**Yield** : 94%**Aspect** : white solid**mp** : 68 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.43-7.50 (m, 5H), 7.24-7.27 (m, 2H), 7.11-7.14 (m, 2H), 6.52-6.56 (m, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 1.95 (bs, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ

140.6, 136.2 (q, $^3J_{CF} = 5.2$ Hz), 132.7 (q, $^2J_{CF} = 30$ Hz), 132.1, 131.3, 129.7, 129.3, 128.8, 128.0, 123.1 (q, $^1J_{CF} = 272.2$ Hz), 122.4, 70.0; ^{19}F NMR (CDCl_3 , 282 MHz): -67.2; IR (neat) ν 3337, 1490, 1312, 1271, 1246, 1168, 1118, 1011, 908, 823, 753, 706 cm^{-1} ; HRMS Calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{OBr}$ ($[\text{M}-\text{H}]^-$): 354.9945, Found: 354.9962.

(E)-1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenylbut-2-en-1-ol (6i) (xyd 361)



CAS number : [1458062-82-2]

Formula : $\text{C}_{16}\text{H}_{12}\text{ClF}_3\text{O}$

M.W. : 312.7 g/mol

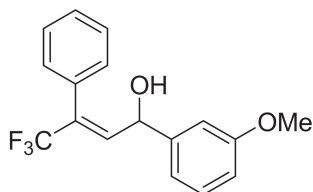
Yield : 80%

Aspect : colorless oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.34-7.37 (m, 3H), 7.24-7.27 (m, 2H), 7.17-7.20 (m, 2H), 7.10-7.12 (m, 2H), 6.48 (dd, $J = 9.2$ Hz, $J = 1.4$ Hz, 1H), 5.03-5.06 (m, 1H), 1.90 (d, $J = 3.4$ Hz, OH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 140.1, 136.2 (q, $^3J_{CF} = 5.2$ Hz), 134.3, 132.6 (q, $^2J_{CF} = 30.8$ Hz), 131.2, 129.7, 129.3, 129.2, 128.8, 127.7, 123.1 (q, $^1J_{CF} = 271.5$ Hz), 69.9; ^{19}F NMR (CDCl_3 , 282 MHz): -67.2.

For a complete characterization see T. Konno, S. Yamada, A. Tani, M. Nishida, T. Miyabe, T. Ishihara, *J. Fluorine Chem.* **2009**, *130*, 913-921.

(E)-4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbut-2-en-1-ol (6j) (xyd 373)



CAS number : [1458062-84-4]

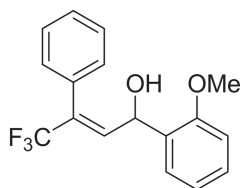
Formula : $\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_2$

M.W. : 308.1 g/mol

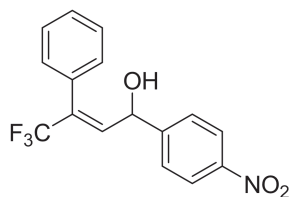
Yield : 96%

Aspect : colorless oil

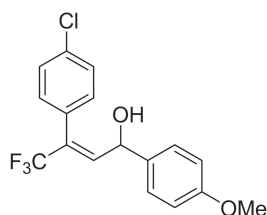
^1H NMR (CDCl_3 , 300 MHz): δ 7.44-7.46 (m, 3H), 7.26-7.32 (m, 3H), 6.83-6.88 (m, 3H), 6.60 (dd, $J = 9.2$ Hz, $J = 1.4$ Hz, 1H), 5.11 (d, $J = 7.9$ Hz, OH), 3.81 (s, 3H), 2.30 (d, $J = 3.2$ Hz, OH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 160.0, 143.2, 136.5 (q, $^3J_{CF} = 5.2$ Hz), 132.2 (q, $^2J_{CF} = 30$ Hz), 131.4, 130.0, 129.8, 129.2, 128.7, 123.2 (q, $^1J_{CF} = 271.5$ Hz), 118.5, 113.8, 111.8, 70.4, 55.3; ^{19}F NMR (CDCl_3 , 282 MHz): -67.0; IR (neat) ν 3387, 2959, 1601, 1488, 1258, 1170, 1117, 1035, 906, 734, 699, 677 cm^{-1} ; HRMS Calcd for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_2\text{Cl}$ ($[\text{M}+\text{Cl}]^+$): 343.0713, Found: 343.0714.

(E)-4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-phenylbut-2-en-1-ol (6k) (xyd 363)**CAS number** : [1458062-83-3]**Formula** : C₁₇H₁₅F₃O**M.W.** : 308.3 g/mol**Yield** : 99%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.40-7.42 (m, 3H), 7.26-7.29 (m, 3H), 7.02-7.05 (m, 1H), 6.89-6.95 (m, 2H), 6.76-6.80 (m, 1H), 5.17 (t, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.11-3.14 (m, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ 156.9, 136.2 (q, ³*J*_{CF} = 5.2 Hz), 131.9 (q, ²*J*_{CF} = 30 Hz), 131.6, 129.9, 129.6, 129.3, 129.0, 128.5, 128.1, 123.4 (q, ¹*J*_{CF} = 271.5 Hz), 121.2, 111.0, 69.1, 55.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -66.8; **IR** (neat) ν 3378, 2952, 1492, 1308, 1242, 1167, 1112, 1026, 939, 751, 701, 609 cm⁻¹; **HRMS** Calcd for C₁₇H₁₄F₃O₂ ([M-H]⁻): 307.0946, Found: 307.0945.

(E)-4,4,4-Trifluoro-1-(4-nitrophenyl)-3-phenylbut-2-en-1-ol (6l) (xyd 370)**CAS number** : [1458062-85-5]**Formula** : C₁₆H₁₂NF₃O₃**M.W.** : 323.1 g/mol**Yield** : 59%**Aspect** : brown solid**mp** : 77 °C

¹H NMR (CDCl₃, 300 MHz): δ 8.20-8.23 (m, 2H), 7.44-7.48 (m, 5H), 7.27-7.30 (m, 2H), 6.52 (dd, *J* = 9.2 Hz, *J* = 1.4 Hz, 1H), 5.26 (dd, *J* = 9 Hz, *J* = 3.2 Hz, 1H), 2.10 (d, *J* = 3.6 Hz, OH); **¹³C NMR** (CDCl₃, 75 MHz): δ 148.4, 147.8, 135.4 (q, ³*J*_{CF} = 5.2 Hz), 133.8 (q, ²*J*_{CF} = 30 Hz), 131.0, 129.6, 129.6, 129.0, 127.1, 124.2, 122.9 (q, ¹*J*_{CF} = 272.2 Hz), 69.6; **¹⁹F NMR** (CDCl₃, 282 MHz): -67.3; **IR** (neat) ν 3492, 1608, 1516, 1346, 1170, 1110, 940, 855, 709, 652 cm⁻¹; **HRMS** Calcd for C₁₆H₁₁F₃ N O₃ ([M-H]⁻): 322.0691, Found: 322.0696.

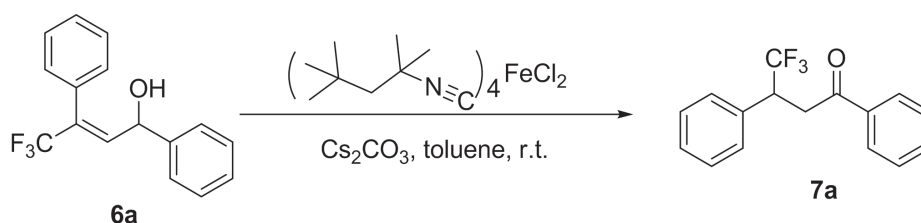
(E)-3-(4-Chlorophenyl)-4,4,4-trifluoro-1-(4-methoxyphenyl)but-2-en-1-ol (6m) (xyd 369)**CAS number** : [1458062-86-6]**Formula** : C₁₇H₁₄ClF₃O**M.W.** : 342.7 g/mol**Yield** : 95%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.38-7.41 (m, 2H), 7.16-7.20 (m, 4H), 6.88-6.90 (m, 2H),

6.63-6.66 (m, 1H), 5.04 (d, $J = 7.1$ Hz, 1H), 3.81 (s, 3H), 1.88 (d, $J = 3.4$ Hz, OH); ^{13}C NMR (CDCl₃, 75 MHz): δ 156.9, 137.5 (q, $^3J_{\text{CF}} = 5.2$ Hz), 135.4, 133.7, 131.2, 130.6 (q, $^2J_{\text{CF}} = 30.7$ Hz), 129.9, 129.0, 127.7, 123.0 (q, $^1J_{\text{CF}} = 271.5$ Hz), 114.5, 70.2, 55.5; ^{19}F NMR (CDCl₃, 282 MHz): -67.0; IR (neat) ν 3386, 2927, 1512, 1494, 1249, 1169, 1120, 1016, 929, 831, 730, 655 cm⁻¹; HRMS Calcd for C₁₇H₁₃F₃O₂Cl ([M-H]⁻): 341.0556, Found: 341.0558; HRMS Calcd for C₁₇H₁₄F₃O₂Cl₂ ([M+Cl]⁻): 377.0323, Found: 377.0323.

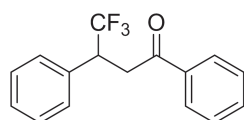
6.2.4 Synthesis of β -CF₃ dihydrochalcones

Typical procedure for the synthesis of β -CF₃ dihydrochalcones (7)



In a Schlenk tube under argon, were added the (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol (0.2 mmol), cesium carbonate (65.2 mg, 0.2 mmol), degassed toluene (0.4 mL) and iron catalyst (1.4 mg, 1 mol%). The reaction mixture was heated and monitored by ^{19}F NMR until there was no signal of starting allylic alcohol left. Then, the mixture was filtered through a celite plug, concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ dichloromethane: 20:1 to 2:1) to give 4,4,4-trifluoro-1,3-diphenylbutan-1-one **7a** (40.1 mg, 72%) as a white solid.

4,4,4-Trifluoro-1,3-diphenylbutan-1-one (7a) (xyd 55-1)



CAS number : [158723-31-0]

Formula : C₁₆H₁₃F₃O

M.W. : 278.3 g/mol

Yield : 72%

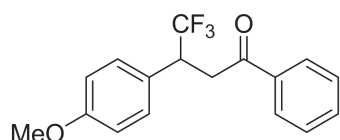
Aspect : white solid

^1H NMR (CDCl₃, 300 MHz): δ 7.83-7.86 (m, 2H), 7.46-7.51 (m, 1H), 7.17-7.40 (m, 7H), 4.10-4.34 (m, 1H), 3.64 (dd, $J = 17.7$ Hz, $J = 9$ Hz, 1H), 3.52 (dd, $J = 17.7$ Hz, $J = 4.2$ Hz, 1H); ^{19}F NMR (CDCl₃, 282 MHz): -70.1 (d, $J = 9.7$ Hz).

For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int.*

Ed., 2012, 51, 6467-6470.

4,4,4-Trifluoro-3-(4-methoxyphenyl)-1-phenylbutan-1-one (7b) (xyd 88)



CAS number : [921932-51-6]

Formula : C₁₇H₁₅F₃O₂

M.W. : 308.3 g/mol

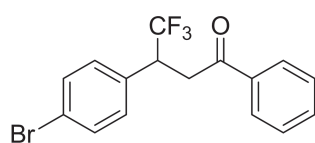
Yield : 76%

Aspect : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.04-4.18 (m, 1H), 3.68 (s, 3H), 3.61 (dd, *J* = 17.7 Hz, *J* = 9.2 Hz, 1H), 3.48 (dd, *J* = 17.7 Hz, *J* = 4.2 Hz, 1H); **¹⁹F NMR** (CDCl₃, 282 MHz): -70.5 (d, *J* = 9.7 Hz).

For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.*, 2012, 51, 6467-6470.

3-(4-Bromophenyl)-4,4,4-trifluoro-1-phenylbutan-1-one (7c) (xyd 102)



CAS number : [921932-54-9]

Formula : C₁₆H₁₂BrF₃O

M.W. : 357.2 g/mol

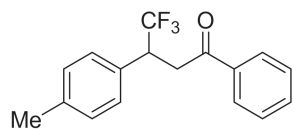
Yield : 72%

Aspect : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.84 (d, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.36-7.38 (m, 4H), 7.20 (d, *J* = 8.8 Hz, 2H), 4.06-4.20 (m, 1H), 3.61 (dd, *J* = 17.8 Hz, *J* = 9 Hz, 1H), 3.51 (dd, *J* = 17.9 Hz, *J* = 4.4 Hz, 1H); **¹⁹F NMR** (CDCl₃, 282 MHz): -69.7 (d, *J* = 9.6 Hz).

For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.*, 2012, 51, 6467-6470.

4,4,4-Trifluoro-1-phenyl-3-*p*-tolylbutan-1-one (7d) (xyd 328)



CAS number : [921932-49-2]

Formula : C₁₇H₁₅F₃O

M.W. : 292.3 g/mol

Yield : 75%

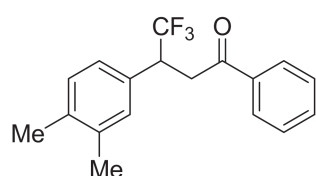
Aspect : white solid

mp : 98 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 2H), 4.19-4.25 (m, 1H), 3.73 (dd, *J* = 17.8 Hz, *J* = 9.2 Hz, 1H), 3.59 (dd, *J* = 17.7 Hz, *J* = 3.9 Hz, 1H), 2.32 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 195.5, 138.2, 136.4, 133.7, 131.6 (q, ³*J*_{CF} = 2.2 Hz), 129.5, 129.0, 128.8,

128.2, 127.1 (q, $^1J_{CF} = 277.5$ Hz), 44.6 (q, $^2J_{CF} = 27$ Hz), 38.3 (q, $^3J_{CF} = 1.5$ Hz), 21.2; ^{19}F NMR (CDCl_3 , 282 MHz): -70.3 (d, $J = 9.7$ Hz); IR (neat) ν 2924, 1682, 1595, 1450, 1300, 1252, 1148, 1096, 1001, 808, 764, 742, 718 cm^{-1} ; HRMS Calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 293.1153, Found: 293.1166.

3-(3,4-Dimethylphenyl)-4,4,4-trifluoro-1-phenylbutan-1-one (7e) (xyd 332)



CAS number : [1458062-73-1]

Formula : $\text{C}_{18}\text{H}_{17}\text{F}_3\text{O}$

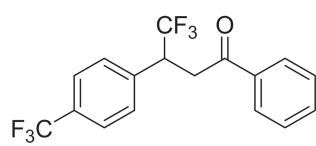
M.W. : 306.3 g/mol

Yield : 69%

Aspect : colorless oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.95 (d, $J = 7.4$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.26 (s, 1H), 7.12 (d, $J = 4.5$ Hz, 2H), 4.13-4.28 (m, 1H), 3.69 (dd, $J = 17.8$ Hz, $J = 8.8$ Hz, 1H), 3.60 (dd, $J = 17.8$ Hz, $J = 4.2$ Hz, 1H), 2.26 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 195.6, 137.0, 136.9, 136.5, 133.6, 132.0 (q, $^3J_{CF} = 1.5$ Hz), 130.4, 130.0, 128.8, 128.2, 127.2 (q, $^1J_{CF} = 277.5$ Hz), 126.3, 44.4 (q, $^2J_{CF} = 27$ Hz), 38.4 (q, $^3J_{CF} = 1.5$ Hz), 20.0, 19.6; ^{19}F NMR (CDCl_3 , 282 MHz): -70.2 (d, $J = 9.8$ Hz); IR (neat) ν 2928, 1689, 1597, 1449, 1299, 1256, 1150, 1102, 1002, 908, 817, 733 cm^{-1} ; HRMS Calcd for $\text{C}_{18}\text{H}_{18}\text{F}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 307.1310, Found: 307.1314.

4,4,4-Trifluoro-1-phenyl-3-(4-(trifluoromethyl)phenyl)butan-1-one (7f) (xyd 119)



CAS number : [1392505-53-1]

Formula : $\text{C}_{17}\text{H}_{12}\text{F}_6\text{O}$

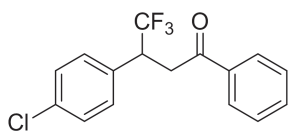
M.W. : 346.3 g/mol

Yield : 69%

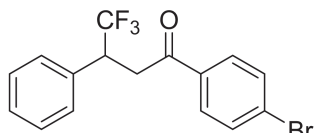
Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 7.93 (d, $J = 7.3$ Hz, 2H), 7.44-7.62 (m, 7H), 4.25-4.39 (m, 1H), 3.75 (dd, $J = 18$ Hz, $J = 9.2$ Hz, 1H), 3.65 (dd, $J = 18.0$ Hz, $J = 4.2$ Hz, 1H); ^{19}F NMR (CDCl_3 , 282 MHz): -63.3 (s), -69.9 (d, $J = 9.5$ Hz).

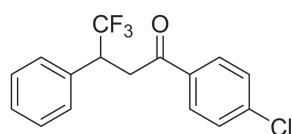
For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.*, **2012**, *51*, 6467-6470.

3-(4-Chlorophenyl)-4,4,4-trifluoro-1-phenylbutan-1-one (7g) (xyd 356)**CAS number** : [921932-53-8]**Formula** : C₁₆H₁₂ClF₃O**M.W.** : 312.7 g/mol**Yield** : 74%**Aspect** : white solid**mp** : 118 °C

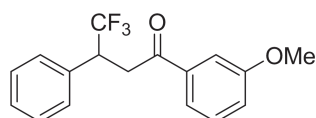
¹H NMR (CDCl₃, 300 MHz): δ 7.92 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.30-7.36 (m, 4H), 4.16-4.30 (m, 1H), 3.68 (dd, *J* = 17.8 Hz, *J* = 9.1 Hz, 1H), 3.60 (dd, *J* = 17.9 Hz, *J* = 4.3 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 195.1, 136.2, 134.4, 133.8, 133.2 (q, ³*J*_{CF} = 1.5 Hz), 130.5, 129.1, 128.9, 128.2, 126.8 (q, ¹*J*_{CF} = 277.5 Hz), 44.4 (q, ²*J*_{CF} = 27 Hz), 38.3 (q, ³*J*_{CF} = 1.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -70.2 (d, *J* = 9.6 Hz); **IR** (neat) ν 2923, 1684, 1452, 1308, 1248, 1153, 1091, 1016, 823, 754, 684 cm⁻¹; **HRMS** Calcd for C₁₆H₁₂F₃OCl₂ ([M+Cl]⁺): 347.0217, Found: 347.0228; **HRMS** Calcd for C₁₆H₁₁F₃OCl ([M-H]⁻): 311.0451, Found: 311.0459.

1-(4-Bromophenyl)-4,4,4-trifluoro-3-phenylbutan-1-one (7h) (xyd 345)**CAS number** : [1458062-74-2]**Formula** : C₁₆H₁₂BrF₃O**M.W.** : 357.2 g/mol**Yield** : 85%**Aspect** : white solid**mp** : 95 °C

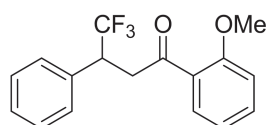
¹H NMR (CDCl₃, 300 MHz): δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.30-7.40 (m, 5H), 4.16-4.30 (m, 1H), 3.66 (dd, *J* = 17.7 Hz, *J* = 8.8 Hz, 1H), 3.57 (dd, *J* = 17.7 Hz, *J* = 4.4 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 194.5, 135.1, 134.5 (q, ³*J*_{CF} = 1.5 Hz), 132.2, 129.7, 129.1, 129.0, 128.9, 128.5, 127.0 (q, ¹*J*_{CF} = 277.5 Hz), 44.9 (q, ²*J*_{CF} = 27 Hz), 38.4 (q, ³*J*_{CF} = 1.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -70.2 (d, *J* = 9.6 Hz); **IR** (neat) ν 2923, 1686, 1586, 1302, 1244, 1162, 1102, 987, 830, 704, 661 cm⁻¹; **HRMS** Calcd for C₁₆H₁₁F₃OBr ([M-H]⁻): 354.9945, Found: 354.9933.

1-(4-Chlorophenyl)-4,4,4-trifluoro-3-phenylbutan-1-one (7i) (xyd 365)**CAS number** : [1226965-57-6]**Formula** : C₁₆H₁₂ClF₃O**M.W.** : 312.7 g/mol**Yield** : 69%**Aspect** : white solid**mp** : 84 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.28-7.40 (m, 7H), 4.12-4.26 (m, 1H), 3.64 (dd, *J* = 17.8 Hz, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 17.8 Hz, *J* = 4.4 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 194.2, 140.2, 134.7, 134.5 (q, ³*J*_{CF} = 1.5 Hz), 129.6, 129.2, 129.1, 128.9, 128.5, 127.0 (q, ¹*J*_{CF} = 277.5 Hz), 44.9 (q, ²*J*_{CF} = 27 Hz), 38.4 (q, ³*J*_{CF} = 1.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -70.2 (d, *J* = 9.6 Hz) ; **IR** (neat) ν 2944, 1686, 1587, 1302, 1244, 1162, 1103, 831, 754, 699, 665 cm⁻¹; **HRMS** Calcd for C₁₆H₁₁F₃OCl ([M-H]⁻): 311.0451, Found: 311.0441.

4,4,4-Trifluoro-1-(3-methoxyphenyl)-3-phenylbutan-1-one (7j) (xyd 375)**CAS number** : [1458062-76-4]**Formula** : C₁₇H₁₅F₃O₂**M.W.** : 308.3 g/mol**Yield** : 70%**Aspect** : colorless oil

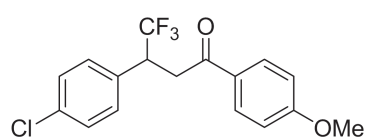
¹H NMR (CDCl₃, 300 MHz): δ 7.39 (d, *J* = 7.6 Hz, 1H), 7.17-7.30 (m, 7H), 6.96-7.00 (m, 1H), 4.05-4.19 (m, 1H), 3.69 (s, 3H), 3.60 (dd, *J* = 17.8 Hz, *J* = 9 Hz, 1H), 3.46 (dd, *J* = 17.8 Hz, *J* = 4.2 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 195.2, 160.0, 137.7, 134.7 (q, ³*J*_{CF} = 2.2 Hz), 129.8, 129.1, 128.8, 128.4, 127.1 (q, ¹*J*_{CF} = 278.2 Hz), 120.7, 120.2, 112.4, 55.5, 45.0 (q, ²*J*_{CF} = 27 Hz), 38.5 (q, ³*J*_{CF} = 2.2 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -70.1 (d, *J* = 9.7 Hz); **IR** (neat) ν 2935, 1688, 1597, 1430, 1292, 1253, 1152, 1102, 1044, 875, 783, 733, 699, 683 cm⁻¹; **HRMS** Calcd for C₁₇H₁₆F₃O₂ ([M+H]⁺): 309.1102, Found: 309.1106.

4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-phenylbutan-1-one (7k) (xyd 368)**CAS number** : [1458062-75-3]**Formula** : C₁₇H₁₅F₃O₂**M.W.** : 308.3 g/mol**Yield** : 28%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.46-7.50 (m, 1H), 7.35-7.41 (m, 1H), 7.18-7.26 (m, 5H),

6.84-6.90 (m, 2H), 4.04-4.18 (m, 1H), 3.85 (s, 3H), 3.64 (dd, $J = 17.9$ Hz, $J = 3.2$ Hz, 1H), 3.53 (dd, $J = 13.2$ Hz, $J = 1.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 197.5, 158.6, 134.9 (q, $^3J_{\text{CF}} = 1.5$ Hz), 134.0, 130.6, 129.1, 128.5, 128.1, 127.3, 127.0 (q, $^1J_{\text{CF}} = 278.2$ Hz), 120.8, 111.5, 55.5, 45.0 (q, $^2J_{\text{CF}} = 27$ Hz), 43.4 (q, $^3J_{\text{CF}} = 1.5$ Hz); ^{19}F NMR (CDCl_3 , 282 MHz): -70.2 (d, $J = 9.7$ Hz); IR (neat) ν 2944, 1667, 1596, 1484, 1299, 1244, 1153, 1096, 1015, 755, 700, 608 cm^{-1} ; HRMS Calcd for $\text{C}_{17}\text{H}_{16}\text{F}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 309.1102, Found: 309.1111.

3-(4-Chlorophenyl)-4,4,4-trifluoro-1-(4-methoxyphenyl)butan-1-one (7m) (xyd 372)



CAS number : [1458062-77-5]

Formula : $\text{C}_{17}\text{H}_{14}\text{ClF}_3\text{O}_2$

M.W. : 342.7 g/mol

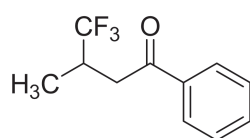
Yield : 49%

Aspect : white solid

mp : 89 °C

^1H NMR (CDCl_3 , 300 MHz): δ 7.84 (d, $J = 8.9$ Hz, 2H), 7.21-7.30 (m, 4H), 6.88 (d, $J = 8.9$ Hz, 2H), 4.09-4.24 (m, 1H), 3.81 (s, 3H), 3.68 (dd, $J = 17.6$ Hz, $J = 9.3$ Hz, 1H), 3.60 (dd, $J = 17.6$ Hz, $J = 4.1$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 193.6, 164.1, 134.4, 133.3 (q, $^3J_{\text{CF}} = 1.5$ Hz), 130.5, 129.3, 128.8, 128.2, 114.0, 126.9 (q, $^1J_{\text{CF}} = 277.5$ Hz), 55.6, 44.5 (q, $^2J_{\text{CF}} = 27.8$ Hz), 37.8 (q, $^3J_{\text{CF}} = 1.5$ Hz); ^{19}F NMR (CDCl_3 , 282 MHz): -70.2 (d, $J = 9.6$ Hz); IR (neat) ν 2976, 1670, 1602, 1310, 1253, 1162, 1101, 1030, 962, 847, 819, 727, 667 cm^{-1} ; HRMS Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{O}_2\text{Cl}_2$ ($[\text{M}+\text{Cl}]^+$): 377.0323, Found: 377.0329.

4,4,4-Trifluoro-3-methyl-1-phenylbutan-1-one (7n) (xyd 81-1)



CAS number : [106352-39-0]

Formula : $\text{C}_{11}\text{H}_{11}\text{F}_3\text{O}$

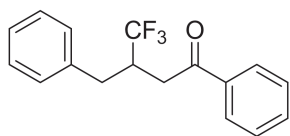
M.W. : 216.2 g/mol

Yield : 75%

Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 7.97 (d, $J = 7.6$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 2H), 3.28-3.33 (m, 1H), 3.00-3.05 (m, 2H), 1.19 (d, $J = 5.9$ Hz, 3H); ^{19}F NMR (CDCl_3 , 282 MHz): -73.9 (d, $J = 9.0$ Hz).

For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.*, **2012**, *51*, 6467-6470.

3-Benzyl-4,4,4-trifluoro-1-phenylbutan-1-one (7o) (xyd 83)**CAS number** : [1392505-54-2]**Formula** : C₁₇H₁₅F₃O**M.W.** : 292.3 g/mol**Yield** : 69%**Aspect** : white solid

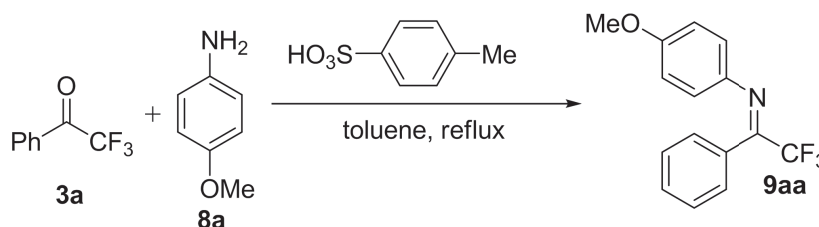
¹H NMR (CDCl₃, 300 MHz): δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.30-7.20 (m, 5H), 3.40-3.52 (m, 1H), 3.27 (dd, *J* = 17.7 Hz, *J* = 5.4 Hz, 1H), 3.11 (dd, *J* = 11.1 Hz, *J* = 7.2 Hz, 1H), 3.02 (dd, *J* = 17.7 Hz, *J* = 6.3 Hz, 1H), 2.76 (dd, *J* = 14.1 Hz, *J* = 8.3 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz): -71.2 (d, *J* = 8.9 Hz).

For a complete characterization see V. Bizet, X. Pannecoucke, J.-C. Renaud, D. Cahard, *Angew. Chem. Int. Ed.*, **2012**, *51*, 6467-6470.

6.3 Asymmetric transfer hydrogenation of CF₃ ketimines catalyzed by Ru (II) complexes

6.3.1 Synthesis of CF₃ ketimines

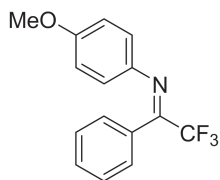
Typical procedure for the synthesis of CF₃ ketimines (9)



In a 50 mL round bottom flask equipped with a Dean-Stark water trap and reflux condenser were added 2,2,2-trifluoroacetophenone (1.4 mL, 10 mmol) and *p*-anisidine (1.48 g, 12 mmol), along with dry toluene (25 mL) and *p*-toluene-sulfonic acid (57 mg, 0.3 mmol). The mixture was refluxed until the theoretical amount of water had been collected in the trap. After the reaction was completed (also monitored by ¹⁹F NMR analysis), it was quenched with NaHCO₃ aq. and extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ dichloromethane: 30:1) to give (*E*)-4-methoxy-*N*-(2,2,2-trifluoro-1-phenylethylidene)aniline **9aa** (2.37 g, 85%) as yellow oil.

A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(E)-4-Methoxy-N-(2,2,2-trifluoro-1-phenylethylidene)aniline (9aa) (xyd 112)



CAS number : [869652-95-9]

Formula : C₁₅H₁₂F₃NO

M.W. : 279.3 g/mol

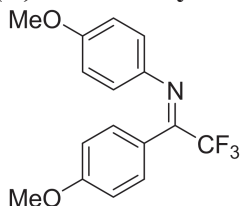
Yield : 85%

Aspect : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.22-7.30 (m, 3H), 7.14-7.17 (m, 2H), 6.61-6.68 (m, 4H), 3.65 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.9, 155.6 (q, ²J_{CF} = 33.4 Hz), 139.8, 130.8, 130.2, 128.9, 128.7, 123.5, 120.2 (q, ¹J_{CF} = 277.0 Hz), 114.1, 55.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.4.

For a complete characterization see 1) S. R. Stauffer, J. Sun, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *Bioorg. Med. Chem.* **2000**, *8*, 1293-1316; 2) M. Abid, M. Savolainen, S. Landge, J. Hu, G. K. Prakash, G. A. Olah, B. Torok, *J. Fluorine Chem.* **2007**, *128*, 587-594.

(E)-4-Methoxy-N-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethylidene)aniline (9ba) (xyd 166)



CAS number : [179763-53-2] (without *E* or *Z* detail)

Formula : C₁₆H₁₄F₃NO₂

M.W. : 309.3 g/mol

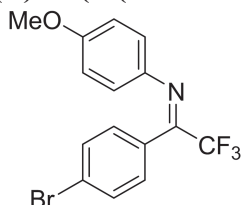
Yield : 79%

Aspect : yellow solid

¹H NMR (CDCl₃, 300 MHz): δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.72-6.78 (m, 4H), 3.74 (s, 3H), 3.78 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 160.8, 157.5, 155.0 (q, ²J_{CF} = 33 Hz), 140.1, 130.4, , 123.0, 122.4, 120.2 (q, ¹J_{CF} = 276.8 Hz), 114.1, 114.1, 55.3, 55.2; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.0.

For a complete characterization see 1) H. Abe, H. Amii, K. Uneyama, *Org. Lett.* **2001**, *3*, 313-315; 2) D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147-3152.

(E)-N-(1-(4-Bromophenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ca) (xyd 161)



CAS number : [1210049-13-0] (without *E* or *Z* detail)

Formula : C₁₅H₁₁BrF₃NO

M.W. : 358.2 g/mol

Yield : 91%

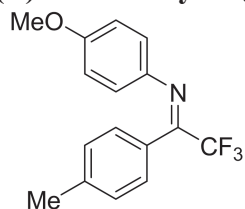
Aspect : yellow solid

¹H NMR (CDCl₃, 300 MHz): δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.62-6.68 (m, 4H), 3.66 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.6, 154.7 (q, ²J_{CF} = 33.8 Hz), 140.0,

132.7, 130.8, 130.0, 125.4, 123.8, 120.4 (q, $^1J_{CF} = 277.5$ Hz), 114.7, 55.9; ^{19}F NMR (CDCl_3 , 282 MHz): -70.3.

For a complete characterization see 1) D. Enders, A. Henseler, S. Lowins, *Synthesis* **2009**, 4125-4128; 2) D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, 352, 3147–3152.

(E)-4-Methoxy-N-(2,2,2-trifluoro-1-p-tolylythyldene)aniline (9da) (xyd 185)



CAS number : [313353-90-1] (without *E* or *Z* detail)

Formula : $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}$

M.W. : 293.3 g/mol

Yield : 98%

Aspect : yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.13 (m, 4H), 6.70-6.77 (m, 4H), 3.74 (s, 3H), 2.34 (s, 3H);

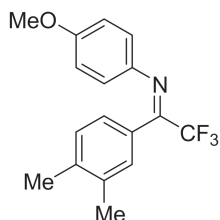
^{13}C NMR (CDCl_3 , 75 MHz): δ 157.8, 155.7 (q, $^2J_{CF} = 33.8$ Hz), 140.6, 140.1, 129.5, 128.7,

127.7, 123.3, 120.2 (q, $^1J_{CF} = 276.8$ Hz), 114.1, 55.4, 21.6; ^{19}F NMR (CDCl_3 , 282 MHz):

-69.8.

For a complete characterization see D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, 352, 3147–3152.

(E)-N-(1-(3,4-Dimethylphenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ea) (xyd 276)



CAS number : unknown

Formula : $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NO}$

M.W. : 307.3 g/mol

Yield : 89%

Aspect : yellow oil

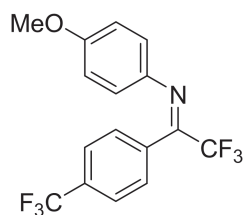
^1H NMR (CDCl_3 , 300 MHz): δ 7.03-7.08 (m, 2H), 6.93 (d, $J = 7.8$ Hz, 1H), 6.71-6.78 (m, 4H), 3.75 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 157.7, 155.8 (q,

$^2J_{CF} = 33.8$ Hz), 140.1, 139.2, 137.3, 130.0, 129.5, 128.1, 126.3, 123.4, 120.3 (q, $^1J_{CF} = 276.8$

Hz), 114.1, 55.4, 19.9; ^{19}F NMR (CDCl_3 , 282 MHz): -70.3; IR (neat) ν 2954, 1651, 1602,

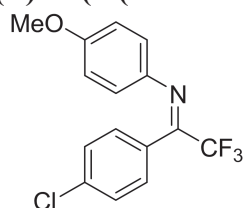
1503, 1442, 1328, 1239, 1203, 1153, 1123, 1032, 980, 871, 766, 733 cm^{-1} ; HRMS Calcd for

$\text{C}_{17}\text{H}_{17}\text{NF}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 308.1262, Found: 308.1264.

(E)-4-Methoxy-N-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethylidene)aniline (9fa) (xyd 201)**CAS number** : [1263498-93-6] (without *E* or *Z* detail)**Formula** : C₁₆H₁₁F₆NO**M.W.** : 347.3 g/mol**Yield** : 99%**Aspect** : yellow oil

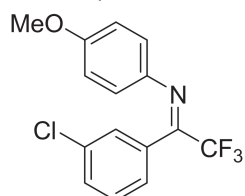
¹H NMR (CDCl₃, 300 MHz): δ 7.62 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 6.70-6.76 (m, 4H), 3.75 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.3, 153.8 (q, ²*J*_{CF} = 34.5 Hz), 139.1, 134.4, 132.2 (q, ¹*J*_{CF} = 33 Hz), 129.3, 125.9 (q, ²*J*_{CF} = 3.8 Hz), 123.5, 119.9 (q, ¹*J*_{CF} = 281.2 Hz), 114.3, 55.5; **¹⁹F NMR** (CDCl₃, 282 MHz): -63.6, -70.4.

For a complete characterization see D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147–3152.

(E)-N-(1-(4-Chlorophenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ga) (xyd 183)**CAS number** : [202869-52-1] (without *E* or *Z* detail)**Formula** : C₁₅H₁₁ClF₃NO**M.W.** : 313.7 g/mol**Yield** : 81%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.32 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.70-6.77 (m, 4H), 3.75 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.1, 154.2 (q, ²*J*_{CF} = 33.8 Hz), 139.5, 136.6, 130.2, 129.3, 129.1, 123.4, 120.0 (q, ¹*J*_{CF} = 277.5 Hz), 114.3, 55.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -69.8.

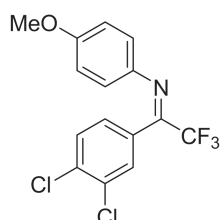
For a complete characterization see D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147–3152.

(E)-N-(1-(3-Chlorophenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ha) (xyd 188/218)**CAS number** : unknown**Formula** : C₁₅H₁₁ClF₃NO**M.W.** : 313.7 g/mol**Yield** : 65%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.28-7.29 (m, 1H), 7.17-7.20 (m, 2H), 7.28-7.29 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.67 (m, 4H), 3.68 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.2, 153.6 (q, ²*J*_{CF} = 33.8 Hz), 139.2, 135.0, 132.5, 130.5, 130.3, 128.6, 127.0, 123.6, 120.0 (q, ¹*J*_{CF} =

277 Hz), 114.3, 55.5; ^{19}F NMR (CDCl_3 , 282 MHz): -70.4; IR (neat) ν 2958, 1602, 1503, 1293, 1231, 1193, 1125, 982, 835, 759 cm^{-1} ; HRMS Calcd for $\text{C}_{15}\text{H}_{12}\text{NF}_3\text{O}^{35}\text{Cl}$ ($[\text{M}+\text{H}]^+$): 314.0560, Found: 314.0552.

(E)-N-(1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ia) (xyd 280)



CAS number : unknown

Formula : $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{F}_3\text{NO}$

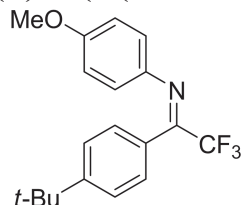
M.W. : 348.2 g/mol

Yield : 99%

Aspect : yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.39-7.42 (m, 2H), 7.01-7.04 (m, 1H), 6.72-6.79 (m, 4H), 3.76 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 158.4, 152.5 (q, $^2J_{\text{CF}} = 34.5$ Hz), 139.0, 135.0, 133.6, 131.1, 130.6, 130.5, 128.2, 123.5, 119.8 (q, $^1J_{\text{CF}} = 276.8$ Hz), 114.4, 55.5; ^{19}F NMR (CDCl_3 , 282 MHz): -70.3; IR (neat) ν 2967, 1601, 1503, 1470, 1326, 1247, 1195, 1126, 1033, 984, 839, 763, 732 cm^{-1} ; HRMS Calcd for $\text{C}_{15}\text{H}_{11}\text{NF}_3\text{Cl}_2\text{O}$ ($[\text{M}-\text{H}]^-$): 348.0170, Found: 348.0176.

(E)-N-(1-(4-tert-Butylphenyl)-2,2,2-trifluoroethylidene)-4-methoxyaniline (9ja) (xyd 191)



CAS number : unknown

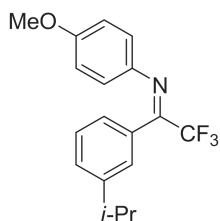
Formula : $\text{C}_{19}\text{H}_{20}\text{F}_3\text{NO}$

M.W. : 335.4 g/mol

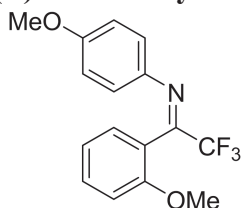
Yield : 99%

Aspect : yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.31-7.34 (m, 2H), 7.15-7.18 (m, 2H), 6.70-6.78 (m, 4H), 3.76 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 157.7, 155.6 (q, $^2J_{\text{CF}} = 33$ Hz), 153.6, 140.1, 128.6, 127.5, 125.8, 123.4, 120.3 (q, $^1J_{\text{CF}} = 277.5$ Hz), 114.1, 55.5, 35.0, 31.2; ^{19}F NMR (CDCl_3 , 282 MHz): -70.2; IR (neat) ν 2965, 1602, 1503, 1463, 1329, 1233, 1189, 1124, 1033, 971, 830 cm^{-1} ; HRMS Calcd for $\text{C}_{19}\text{H}_{21}\text{NF}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 336.1575, Found: 336.1569.

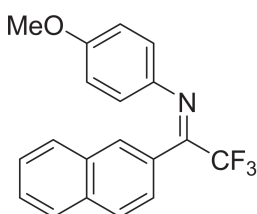
(E)-4-Methoxy-N-(2,2,2-trifluoro-1-(3-isopropylphenyl)ethylidene)aniline (9ka) (xyd 301)**CAS number** : unknown**Formula** : C₁₈H₁₈F₃NO**M.W.** : 321.3 g/mol**Yield** : 99%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.28-7.31 (m, 2H), 7.15 (d, *J* = 7.0 Hz, 1H), 7.07 (s, 1H), 6.74-6.80 (m, 4H), 3.78 (s, 3H), 2.85 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.8, 156.0 (q, ²*J*_{CF} = 33 Hz), 149.4, 140.1, 130.5, 128.8, 128.5, 127.1, 126.0, 123.3, 120.2 (q, ¹*J*_{CF} = 277.5 Hz), 114.1, 55.5, 34.0, 23.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.2; **IR** (neat) ν 2963, 1602, 1503, 1465, 1325, 1237, 1186, 1125, 1118, 1033, 988, 835, 763, 700 cm⁻¹; **HRMS** Calcd for C₁₈H₁₉NF₃O ([M+H]⁺): 322.1419, Found: 322.1413.

(E)-4-Methoxy-N-(2,2,2-trifluoro-1-(2-methoxyphenyl)ethylidene)aniline (9la) (xyd 172)**CAS number** : [1263498-90-3]**Formula** : C₁₆H₁₄F₃NO₂**M.W.** : 309.3 g/mol**Yield** : 81%**Aspect** : yellow solid

¹H NMR (CDCl₃, 300 MHz): δ 7.32-7.38 (m, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.90-6.95 (m, 1H), 6.77-6.85 (m, 3H), 6.68-6.71 (m, 2H), 3.71 (s, 3H), 3.64 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.7, 156.8, 154.5 (q, ²*J*_{CF} = 34.4 Hz), 140.5, 131.6, 129.3, 122.5, 120.7, 120.4, 119.9 (q, ¹*J*_{CF} = 277.0 Hz), 113.6, 111.1, 55.4, 55.2; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.3.

For a complete characterization see D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, 352, 3147–3152.

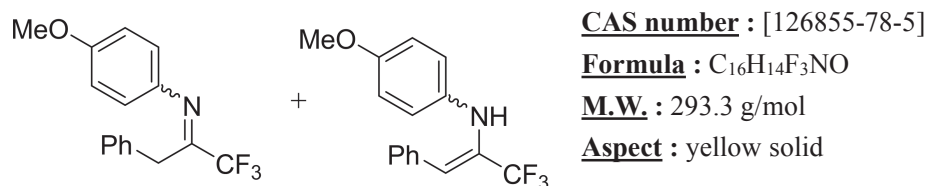
(E)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethylidene)aniline (9ma) (xyd 394)**CAS number** : [1334287-92-1] (without *E* or *Z* detail)**Formula** : C₁₉H₁₄F₃NO**M.W.** : 329.3 g/mol**Yield** : 68%**Aspect** : yellow solid

¹H NMR (CDCl₃, 300 MHz): δ 7.88 (s, 1H), 7.81-7.83 (m, 2H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.50-7.58 (m, 2H), 7.17-7.20 (m, 1H), 6.77-6.82 (m, 2H), 6.66-6.71 (m, 2H), 3.71 (s, 3H); **¹³C**

NMR (CDCl₃, 75 MHz): δ 158.0, 155.2 (q, $^2J_{CF} = 33.4$ Hz), 139.8, 133.7, 132.9, 129.0, 128.8, 128.6, 128.2, 127.9, 127.8, 127.0, 125.3, 123.7, 120.3 (q, $^1J_{CF} = 277.1$ Hz), 114.2, 55.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.0.

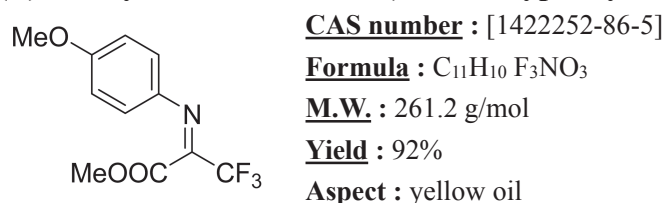
For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

4-Methoxy-*N*-(1,1,1-trifluoro-3-phenylpropan-2-ylidene)aniline 9na (xyd 210) (2 tautomers mixtures)



¹⁹F NMR (CDCl₃, 282 MHz): -68.7, -70.5, -70.9 (ratio = 9:13:78).

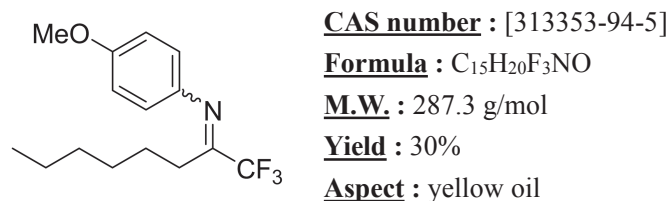
(*E*)-Methyl 3,3,3-trifluoro-2-(4-methoxyphenylimino)propanoate (9oa) (xyd 189)



¹H NMR (CDCl₃, 300 MHz): δ 7.00-7.03 (m, 2H), 6.88-6.91 (m, 2H), 3.83 (s, 3H), 3.78 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 160.9, 159.5, 138.9, 122.4, 118.4 (q, $^1J_{CF} = 276.8$ Hz), 114.4, 55.5, 53.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -69.5.

For a complete characterization see H. Amii, Y. Kishikawa, K. Kageyama, K. Uneyama, *J. Org. Chem.* **2000**, *65*, 3404-3408.

4-Methoxy-*N*-(1,1,1-trifluorooctan-2-ylidene)aniline (9pa) (xyd 287)

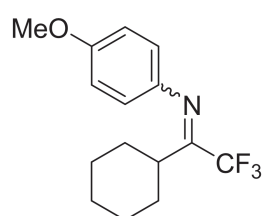


¹H NMR (CDCl₃, 300 MHz): δ 6.82-6.85 (m, 2H), 6.58-6.68 (m, 2H), 3.74 (s, 3H), 2.34 (t, $J = 8.2$ Hz, 2H), 1.33-1.48 (m, 3H), 1.10-1.21 (m, 4H), 0.78-0.83 (m, 1H), 0.74 (t, $J = 1.8$ Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.0, 155.2 (q, $^2J_{CF} = 33.4$ Hz), 139.8, 133.7, 132.9, 129.0, 128.8, 128.6, 128.2, 127.9, 127.8, 127.0, 125.3, 123.7, 120.3 (q, $^1J_{CF} = 277.1$ Hz), 114.2, 55.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.0 (minor isomer), -72.2 (major isomer) (ratio

= 20:80).

For a complete characterization see 1) M. Mae, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2000**, *41*, 7893-7896; 2) Y.-L. Liu, X.-P. Zeng, J. Zhou, *Chem. Asian J.* **2012**, *7*, 1759-1763.

***N*-(1-Cyclohexyl-2,2,2-trifluoroethylidene)-4-methoxyaniline (9qa) (xyd 226)**



CAS number : [1263498-99-2]

Formula : C₁₅H₁₈F₃NO

M.W. : 285.3 g/mol

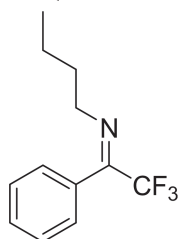
Yield : 54%

Aspect : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 6.71-6.77 (m, 2H), 6.88-6.94 (m, 2H), 3.82 (s, 3H), 2.41 (t, *J* = 7.9 Hz, 2H), 1.45-1.53 (m, 2H), 1.17-1.27 (m, 3H), 0.81 (t, *J* = 7.3 Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 161.4 (q, ²*J*_{CF} = 32.2 Hz), 157.2, 140.8, 120.2, 116.5 (q, ¹*J*_{CF} = 264.8 Hz), 114.4, 55.6, 28.7, 28.4, 22.8, 13.6; **¹⁹F NMR** (CDCl₃, 282 MHz): -69.3 (minor isomer), -72.2 (major isomer) (ratio = 11:89).

For a complete characterization see D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147-3152.

***(E)*-N-(2,2,2-Trifluoro-1-phenylethylidene)butan-1-amine (9ac) (xyd 395)**



CAS number : [1391155-90-0]

Formula : C₁₂H₁₄F₃N

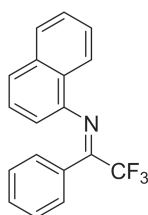
M.W. : 229.2 g/mol

Yield : 76%

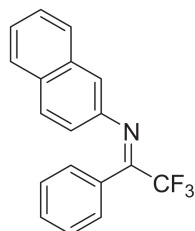
Aspect : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.46-7.48 (m, 3H), 7.21-7.24 (m, 2H), 3.38 (t, *J* = 8.5 Hz, 2H), 1.59-1.68 (m, 2H), 1.23-1.36 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.2 (q, ²*J*_{CF} = 33.3 Hz), 130.7, 130.1, 128.9, 127.8, 119.8 (q, ¹*J*_{CF} = 276.8 Hz), 53.2, 32.4, 20.5, 13.9; **¹⁹F NMR** (CDCl₃, 282 MHz): -71.6.

For a complete characterization see P. Cherkupally, P. Beier, *J. Fluorine Chem.* **2012**, *141*, 76-82.

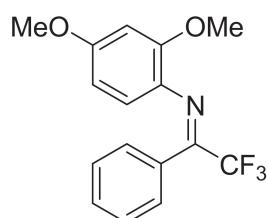
(E)-N-(2,2,2-Trifluoro-1-phenylethylidene)naphthalen-1-amine (9ad) (xyd 324)**CAS number** : [1481615-46-6]**Formula** : C₁₈H₁₂F₃N**M.W.** : 299.3 g/mol**Yield** : 45%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 8.01-8.04 (m, 1H), 7.81-7.84 (m, 1H), 7.52-7.58 (m, 3H), 7.28-7.32 (m, 1H), 7.15-7.24 (m, 5H), 6.46 (d, *J* = 7.3 Hz, 1H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.9 (q, ²*J*_{CF} = 34.5 Hz), 143.9, 133.9, 130.5, 130.1, 128.6, 128.3, 128.2, 127.0, 126.7, 126.4, 123.3, 120.0 (q, ¹*J*_{CF} = 277.5 Hz), 114.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.0; **IR** (neat) ν 3065, 1661, 1392, 1328, 1190, 1127, 968, 780, 772, 696 cm⁻¹; **HRMS** Calcd for C₁₈H₁₃NF₃O([M+H]⁺): 300.1000, Found: 300.0988.

(E)-N-(2,2,2-Trifluoro-1-phenylethylidene)naphthalen-2-amine (9ae) (xyd 325)**CAS number** : [1012308-71-2]**Formula** : C₁₈H₁₂F₃N**M.W.** : 299.3 g/mol**Yield** : 61%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.63-7.74 (m, 6H), 7.38-7.45 (m, 4H), 6.87 (dd, *J* = 8.7 Hz, *J* = 2.0 Hz, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 157.3 (q, ²*J*_{CF} = 33.8 Hz), 144.7, 133.7, 131.4, 130.5, 130.1, 128.8, 128.8, 128.0, 127.8, 126.6, 125.7, 120.5, 118.4, 120.1 (q, ¹*J*_{CF} = 277.5 Hz), 114.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -70.3.

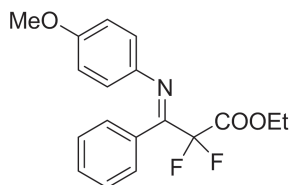
For a complete characterization see M. Abid, M. Savolainen, S. Landge, J. Hu, G. K. Prakash, G. A. Olah, B. Torok, *J. Fluorine Chem.* **2007**, *128*, 587-594.

(E)-2,4-Dimethoxy-N-(2,2,2-trifluoro-1-phenylethylidene)aniline (9af) (xyd 331)**CAS number** : unknown**Formula** : C₁₆H₁₄F₃NO₂**M.W.** : 309.3 g/mol**Yield** : 80%**Aspect** : yellow solid**mp** : 87 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.22-7.37 (m, 5H), 6.55-6.58 (m, 1H), 6.34-6.36 (m, 1H), 6.27-6.31 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 158.8, 157.3,

150.7, 131.4, 130.1, 128.4, 128.1, 122.0, 120.1 (q, $^1J_{CF} = 276.8$ Hz), 104.2, 99.4, 55.5; ^{19}F NMR (CDCl_3 , 282 MHz): -69.9; IR (neat) ν 2966, 1601, 1438, 1333, 1311, 1211, 1129, 1030, 971, 856 cm^{-1} ; HRMS Calcd for $\text{C}_{16}\text{H}_{15}\text{NF}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 310.1055, Found: 310.1057.

(E)-Ethyl 2,2-difluoro-3-(4-methoxyphenylimino)-3-phenylpropanoate (9sa) (xyd 305)



CAS number : unknown

Formula : $\text{C}_{18}\text{H}_{17}\text{F}_2\text{NO}_3$

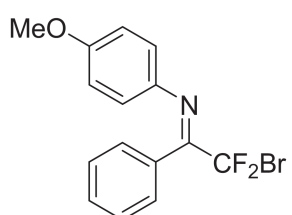
M.W. : 333.3 g/mol

Yield : 77%

Aspect : yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 6.69-7.38 (m, 5H), 6.69 (m, 4H), 4.44 (q, $J = 7.1$ Hz 2H), 3.73 (s, 3H), 1.40 (t, $J = 1.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 163.4 (t, $^2J_{CF} = 30.8$ Hz), 159.7 (t, $^2J_{CF} = 30$ Hz), 157.8, 139.9, 130.9, 130.1, 128.9, 128.7, 123.7, 114.8 (t, $^1J_{CF} = 252.8$ Hz), 63.1, 55.4, 14.2; ^{19}F NMR (CDCl_3 , 282 MHz): -105.1; HRMS Calcd for $\text{C}_{18}\text{H}_{18}\text{NF}_2\text{O}_3$ ($[\text{M}+\text{H}]^+$): 334.1255, Found: 334.1250.

(E)-N-(2-Bromo-2,2-difluoro-1-phenylethylidene)-4-methoxyaniline (9ta) (xyd 380)



CAS number : [871503-69-4]

Formula : $\text{C}_{15}\text{H}_{12}\text{BrF}_2\text{NO}$

M.W. : 340.2 g/mol

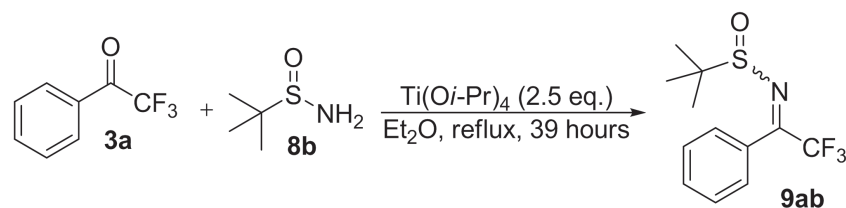
Yield : 92%

Aspect : yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.26-7.28 (m, 2H), 7.34-7.39 (m, 3H), 6.68-6.75 (m, 4H), 3.73 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 159.7 (t, $^2J_{CF} = 24.0$ Hz), 157.9, 139.6, 131.0, 130.7, 129.4, 128.8, 123.8, 117.4 (t, $^1J_{CF} = 307.0$ Hz), 114.0, 55.4; ^{19}F NMR (CDCl_3 , 282 MHz): -53.3.

For a complete characterization see Y.-M. Wu, Y. Li, J. Deng, *J. Fluorine Chem.* **2005**, *126*, 791-795.

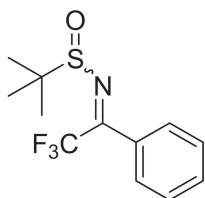
Synthesis of 2-methyl-N-(2,2,2-trifluoro-1-phenylethylidene) propane-2-sulfonamide (9ab)



2,2,2-trifluoro-1-phenylethanone **3a** (0.42 mL, 3 mmol) was added to a solution of *tert*-butanesulfonamide **8b** (454.5 mg, 3.75 mmol) and titanium isopropoxide (2.24 mL, 7.5 mmol) in diethyl ether (20 mL) at room temperature. The reaction mixture was stirred at reflux and the reaction was monitored by ^{19}F NMR. After 39 hours, the reaction was quenched with brine and extracted with diethyl ether. The combined organic layer was dried over MgSO_4 , filter through silica and concentrated in *vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate: 30/1) to give 2-methyl-*N*-(2,2,2-trifluoro-1-phenylethylidene)propane-2-sulfonamide **9ab** (194.8 mg, 23%) as a white solid.

1) H. Wang, X. Zhao, Y. Li, L. Lu, *Org. Lett.* **2006**, *8*, 1379-1381; 2) J. Xu, Z.-J. Liu, X.-j. Yang, L.-M. Wang, G.-L. Chen, J.-T. Liu, *Tetrahedron* **2010**, *66*, 8933-8937.

2-Methyl-*N*-(2,2,2-trifluoro-1-phenylethylidene)propane-2-sulfonamide (**9ab**) (xyd 244)



CAS number : [884595-96-4]

Formula : $\text{C}_{12}\text{H}_{14}\text{SF}_3\text{NO}$

M.W. : 277.3 g/mol

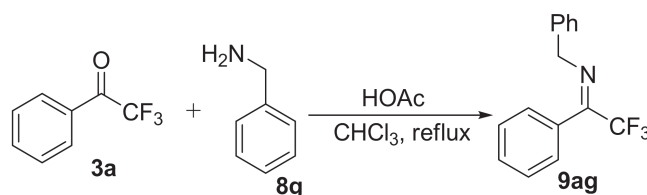
Yield : 23%

Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 7.69-7.72 (m, 2H), 7.39-7.43 (m, 3H), 1.26 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 133.8, 129.8, 128.8, 128.1, 123.3 (q, $^1J_{\text{CF}} = 285.8$ Hz), 86.7 (q, $^2J_{\text{CF}} = 30.8$ Hz), 57.2, 22.6; ^{19}F NMR (CDCl_3 , 282 MHz): -83.0.

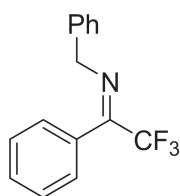
For a complete characterization see 1) H. Wang, X. Zhao, Y. Li, L. Lu, *Org. Lett.* **2006**, *8*, 1379-1381; 2) J. Xu, Z.-J. Liu, X.-j. Yang, L.-M. Wang, G.-L. Chen, J.-T. Liu, *Tetrahedron* **2010**, *66*, 8933-8937.

Synthesis of 2-methyl-*N*-(2,2,2-trifluoro-1-phenylethylidene)propane-2-sulfonamide (**9ag**)



To a mixture of benzylamine (0.6 mL, 5.5 mmol) and acetic acid (0.32 mL, 5.5 mmol) in 5 ml chloroform was added the solution of trifluoromethyl ketone **3a** (0.7 mL, 5 mmol) in chloroform. The resulting mixture was refluxed until all the ketone was consumed. After cooling down to room temperature, DCM was added and the mixture was washed with NaHCO₃. The aqueous layer was extracted with DCM for 3 times. The combined organic layers were dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate: 30/1) to give 2-methyl-*N*-(2,2,2-trifluoro-1-phenylethylidene) propane-2-sulfonamide **9ag** (549 mg, 89%) as colorless oil.

(*E*)-1-Phenyl-*N*-(2,2,2-trifluoro-1-phenylethylidene)methanamine (9ag) (xyd 284)



CAS number : [849774-19-2]

Formula : C₁₅H₁₂F₃N

M.W. : 263.3 g/mol

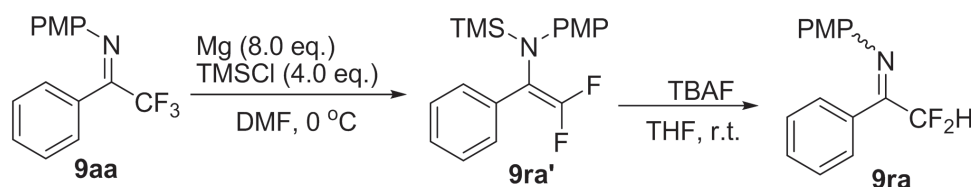
Yield : 89%

Aspect : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.39-7.45 (m, 3H), 7.16-7.28 (m, 7H), 4.53 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.1 (q, ²J_{CF} = 33 Hz), 138.1, 130.4, 130.4, 129.0, 128.7, 127.8, 127.7, 127.4, 119.8 (q, ¹J_{CF} = 276.8 Hz), 57.0; ¹⁹F NMR (CDCl₃, 282 MHz): -71.4.

For a complete characterization see 1) T. Ono, V.A. Soloshonok, Kukhar, *J. Org. Chem.* **1996**, *61*, 6563-6569; 2) D. O. Berbasov, I. D. Ojemaye, V. A. Soloshonok, *J. Fluorine Chem.* **2004**, *125*, 603-607.

Synthesis of *N*-(2,2-difluoro-1-phenylethylidene)-4-methoxyaniline (9ra)

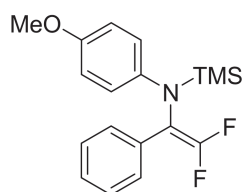


Me₃SiCl (TMSCl) (0.5 mL, 4mmol) and a solution of (*E*)-4-methoxy-*N*-(2,2,2-trifluoro-1-phenylethylidene)aniline **9aa** (279 mg, 1 mmol) in dried DMF (1 ml) was added to a suspension of Mg (192 mg, 8 mmol) in DMF (3 ml) at 0 °C under argon atmosphere. After stirring for 30 min at that temperature, TMSCl was removed under reduced pressure and a solution of TEA/cyclohexane (1/9, 5 ml) was added in and then washed with

water (8-10 ml) and extracted with cyclohexane and ethyl acetate. The yellow organic layer was dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate: 30/1) to give *N*-(2,2-difluoro-1-phenylvinyl)-*N*-(4-methoxyphenyl)-1,1,1-trimethylsilanamine **9ra'** (254 mg, 76%) as yellow oil.

1) K. Uneyama, T. Kato, *Tetrahedron Lett.* **1998**, *39*, 587-590; 2) M. Mae, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2000**, *41*, 7893-7896.

***N*-(2,2-Difluoro-1-phenylvinyl)-*N*-(4-methoxyphenyl)-1,1,1-trimethylsilanamine **9ra'** (xyd 261)**



CAS number : [202869-58-7]

Formula : C₁₈H₂₁F₂NOSi

M.W. : 333.4 g/mol

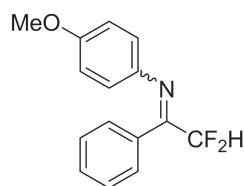
Yield : 76%

Aspect : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.46-7.48 (m, 2H), 7.22-7.35 (m, 3H), 6.86-6.90 (m, 2H), 6.72-6.77 (m, 2H), 3.73 (s, 3H), 0.29 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 153.6, 141.2, 134.0 (d, ²J_{CF} = 7.5 Hz), 128.6, 127.6, 126.9 (q, ¹J_{CF} = 7.5 Hz), 119.6, 114.5, 55.6, 0.7; ¹⁹F NMR (CDCl₃, 282 MHz): -88.5 (d, *J* = 9 Hz), -94.3 (d, *J* = 9 Hz).

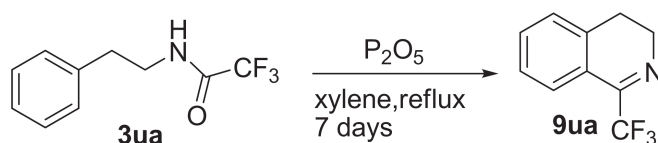
For a complete characterization see 1) K. Uneyama, T. Kato, *Tetrahedron Lett.* **1998**, *39*, 587-590; 2) M. Mae, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2000**, *41*, 7893-7896.

A 25 ml round-bottomed flask equipped with a magnetic stirring bar under argon was charged with *N*-(2,2-difluoro-1-phenylvinyl)-*N*-(4-methoxyphenyl)-1,1,1-trimethylsilanamine **9ra'** (254 mg, 0.76 mmol) and THF (5 mL). The mixture was stirred and a 1 M solution of TBAF in THF (0.76 mL) was added. After the solution was stirred for 10 min at room temperature, a saturated solution of sodium carbonate (6 ml) was added and extracted with DCM (3x5 ml). The combined organic layers were dried over MgSO₄ and evaporated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/ethyl acetate: 30/1) to give *N*-(2,2-difluoro-1-phenylethylidene)-4-methoxyaniline **9ra** (131.5 mg, 85%) as yellow oil.

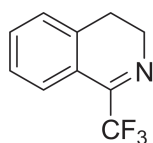
***N*-(2,2-Difluoro-1-phenylethylidene)-4-methoxyaniline 9ra (xyd 263) (mixture of two isomers in ratio 64/36)****CAS number** : [445468-02-0]**Formula** : C₁₅H₁₃F₂NO**M.W.** : 261.3 g/mol**Yield** : 85%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.23-7.50 (m, 7H), 6.86-6.94 (m, 2H), 6.43 (t, *J* = 53.0 Hz, CF₂H, minor), 6.33 (t, *J* = 55.4 Hz, CF₂H, major), 3.81 (s, OCH₃, minor), 3.72 (s, OCH₃, major); **¹⁹F NMR** (CDCl₃, 282 MHz): -115.7 (d, *J* = 53.6 Hz, CF₂H, minor); -117.3 (d, *J* = 56.4 Hz, CF₂H, major).

For a complete characterization see 1) M. Aae, M. Matsuura, H. Amii, K. Uneyama, *Tetrahedron Lett.* **2002**, *43*, 2069-2072; 2) N. V. Kirij, L. A. Babadzhanova, V. N. Movchun, Y. L. Yagupolskii, W. Tyrra, D. Naumann, H. T. M. Fischer, H. Scherer, *J. Fluorine Chem.* **2008**, *129*, 14-21.

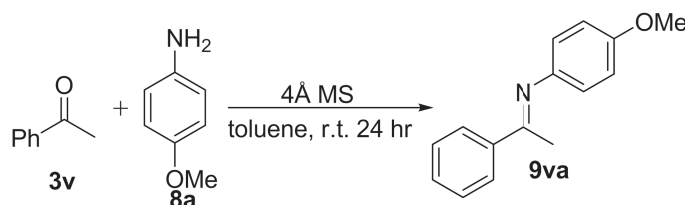
Synthesis of 1-(trifluoromethyl)-3,4-dihydroisoquinoline (9ua)

To a 250 mL round bottom flask equipped with a reflux condenser and a dropping funnel were added 100 ml xylene and 16 g diphosphorus pentoxide. The dropping funnel was filled with the solution of 2,2,2-trifluoro-*N*-phenethylacetamide **3ua** (434.4 mg, 2 mmol) along with dry xylene (50 mL) and the solution was added into the flask dropwise. Then, the mixture was heated to reflux at 140 °C for 24 hours. Another 16 g diphosphorus pentoxide was added into the mixture without stop refluxing (in 3 portions). After the last 24 hours, the mixture was cooled down and 250 ml water was added in for the quench. The solution became milky. The pH was adjusted to 10 by adding 40% soude. The aqueous phase was washed several times with diethyl ether. The collected organic phase was dried over MgSO₄ and concentrated in vivo. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate: 20/1) to give 1-(trifluoromethyl)-3,4-dihydroisoquinoline **9ua** (29.7 mg, 7%) as colorless oil.

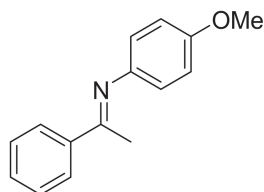
1-(Trifluoromethyl)-3,4-dihydroisoquinoline (9ua) (xyd 384)**CAS number** : [70414-06-1]**Formula** : C₁₀H₈F₃N**M.W.** : 199.2 g/mol**Yield** : 7%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.59-7.62 (m, 1H), 7.42-7.47 (m, 1H), 7.31-7.37 (m, 1H), 7.24-7.26 (m, 1H), 3.88-3.94 (m, 1H), 2.79 (t, *J* = 7.9 Hz, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 155.8 (q, ²*J*_{CF} = 32.7 Hz), 137.9, 132.2, 128.0, 127.4, 125.6 (q, ³*J*_{CF} = 2.9 Hz), 123.7, 120.3 (q, ¹*J*_{CF} = 276.5 Hz), 47.2, 25.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -68.5.

For a complete characterization see R. Pastor, A. Cambon, *J. Fluorine Chem.* **1979**, *13*, 279-296.

Synthesis of (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (9va)

In a toluene (15 mL) solution of acetophenone (1.43 mL, 15 mmol) was added *p*-anisidine (2.22 g, 18 mmol) along with 4Å molecular sieves (6 g). The mixture was stirred for 24 hours at room temperature. Then, the suspension was filtered and washed with ethyl acetate. After the collected solution was concentrated in *vacuo*, a part of the residue was recrystallized and another part of the residue was purified by column chromatography (petroleum ether/ethyl acetate: 5/1) to give (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline **9va** (1.01 g, 30%) as pale yellow solid.

(*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline (9va) (xyd 252)**CAS number** : [125231-22-3]**Formula** : C₁₅H₁₅NO**M.W.** : 225.3 g/mol**Yield** : 30%**Aspect** : pale yellow solid

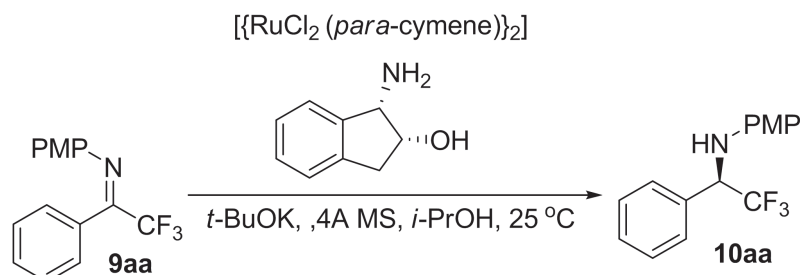
¹H NMR (CDCl₃, 300 MHz): δ 7.94-7.98 (m, 2H), 7.44-7.46 (m, 3H), 6.89-6.93 (m, 2H), 6.75-6.78 (m, 2H), 3.82 (s, 3H), 2.26 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 165.9, 156.0, 144.9, 139.9, 130.5, 128.5, 127.2, 120.9, 114.4, 55.9, 17.5.

For a complete characterization see P. Schnider, G. Koch, R. Pretot, G. Z. Wang, F. M. Bohnen, C. Kruger,

A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887-892.

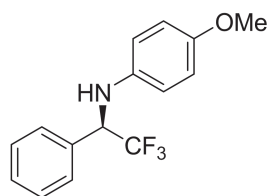
6.3.2 Asymmetric transfer hydrogenation of CF₃ ketimines

Typical procedure for the ATH of CF₃ ketimines (10)



In an oven-dried tube, a mixture of [$\{\text{RuCl}_2(\textit{p}\text{-cymene})\}_2$] (6.1 mg, 0.01 mmol), (1*S*, 2*R*)-1-amino-2-indanol ligand (3 mg, 0.02 mmol), 4Å molecular sieves (100 mg) and anhydrous isopropanol (0.5 mL) was heated at 90 °C for 20 minutes under argon. During this heating period, the initially orange reaction mixture turned dark red in colour. The reaction was then cooled to room temperature and a solution of (*E*)-4-methoxy-*N*-(2,2,2-trifluoro-1-phenylethylidene)aniline (55.8 mg, 0.2 mmol) in isopropanol (2 mL) and *t*-BuOK (5.5 mg, 0.05 mmol) in 0.5 mL isopropanol were successively added. After 14 hours, the reaction went to completion (monitoring by ¹⁹F NMR analysis). The reaction mixture was filtered through a small amount of silica gel and washed with ethyl acetate. The combined organic phase was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 30:1) to give the corresponding (*R*)-4-methoxy-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline **10aa** (55.7 mg, 99%) as colorless oil.

(*R*)-4-Methoxy-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline (10aa) (xyd 168)



CAS number : [1253518-84-1]

Formula : C₁₅H₁₄F₃NO

M.W. : 281.3 g/mol

Yield : 99%

ee : 93%; [α]_D²⁰ -64.5 (*c* 1.40, CHCl₃)

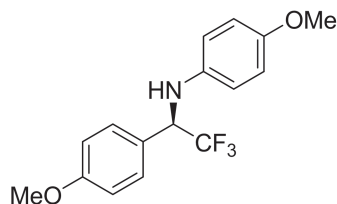
Aspect : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.37-7.46 (m, 5H), 6.71-6.77 (m, 2H), 6.58-6.63 (m, 2H), 4.78-4.83 (m, 1H), 4.08 (d, *J* = 7.1 Hz, NH), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.9, 140.1, 134.9, 129.6, 129.5, 128.5, 125.7 (q, ¹*J*_{CF} = 280.5 Hz), 116.3, 115.4, 62.3 (q,

$^2J_{CF} = 29.2$ Hz), 56.2; ^{19}F NMR (CDCl_3 , 282 MHz): -74.6 (d, $J = 7.3$ Hz); HPLC (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, $\lambda = 254$ nm): $\tau_R = 16.0$ min (minor enantiomer), $\tau_R = 16.8$ min (major enantiomer).

For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(R)-4-Methoxy-N-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)aniline (10ba) (xyd 171)



CAS number : [1253519-18-4]

Formula : $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_2$

M.W. : 311.3 g/mol

Yield : 99%

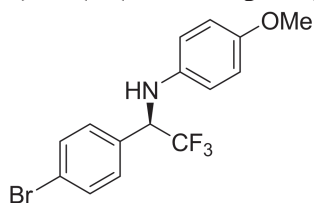
ee : 91%

Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 7.38 (d, $J = 8.6$ Hz, 2H), 6.91-6.94 (m, 2H), 6.74-6.79 (m, 2H), 6.59-6.65 (m, 2H), 4.76-4.81 (m, 1H), 4.08 (d, $J = 6.5$ Hz, NH), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 160.0, 153.2, 139.6, 129.1, 126.2, 125.2 (q, $^1J_{CF} = 279.8$ Hz), 115.7, 114.8, 114.3, 61.0 (q, $^2J_{CF} = 29.2$ Hz), 55.6, 55.2; ^{19}F NMR (CDCl_3 , 282 MHz): -74.8 (d, $J = 7.4$ Hz); HPLC (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, $\lambda = 254$ nm): $\tau_R = 27.8$ min (major enantiomer), $\tau_R = 30.4$ min (minor enantiomer).

For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(R)-N-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ca) (xyd 165)



CAS number : unknown

Formula : $\text{C}_{15}\text{H}_{13}\text{BrF}_3\text{NO}$

M.W. : 360.2 g/mol

Yield : 94%

ee : 90%

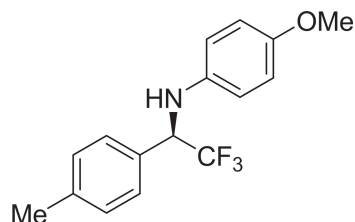
Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 7.50-7.54 (m, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 6.72-6.77 (m, 2H), 6.54-6.59 (m, 2H), 4.73-4.83 (m, 1H), 4.06 (d, $J = 7.0$ Hz, NH), 3.72 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 153.6, 139.1, 133.4, 132.2, 129.8, 124.9 (q, $^1J_{CF} = 280.0$ Hz), 123.4, 115.9, 115.0, 61.4 (q, $^2J_{CF} = 29.5$ Hz), 55.8; ^{19}F NMR (CDCl_3 , 282 MHz): -74.7 (d, $J = 7.2$ Hz); HPLC (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, $\lambda = 254$ nm): $\tau_R = 25.2$ min (minor enantiomer), $\tau_R = 29.2$ min (major

enantiomer).

For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(R)-4-Methoxy-N-(2,2,2-trifluoro-1-*p*-tolylethyl)aniline (10da) (xyd 190/199)



CAS number : [1253519-12-8]

Formula : C₁₆H₁₆F₃NO

M.W. : 295.3 g/mol

Yield : 99%

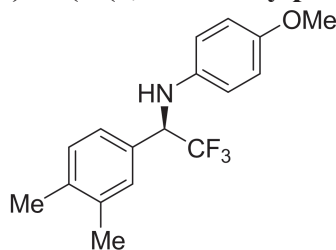
ee : 92%

Aspect : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.73-6.78 (m, 2H), 6.60-6.65 (m, 2H), 4.75-4.84 (m, 1H), 4.08 (d, *J* = 7.3 Hz, NH), 3.73 (s, 3H), 2.36 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.3, 139.7, 139.1, 131.4, 129.7, 127.9, 125.3 (q, ¹*J*_{CF} = 279.8 Hz), 115.8, 114.9, 61.6 (q, ²*J*_{CF} = 29.2 Hz), 55.7, 21.3; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.6 (d, *J* = 7.4 Hz); **HPLC** (Daicel CHIRALCEL OJ-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 52.5 min (minor enantiomer), τ_R = 58.7 min (major enantiomer).

For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(R)-N-(1-(3,4-Dimethylphenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ea) (xyd 277-1)



CAS number : unknown

Formula : C₁₇H₁₈F₃NO

M.W. : 309.3 g/mol

Yield : 94%

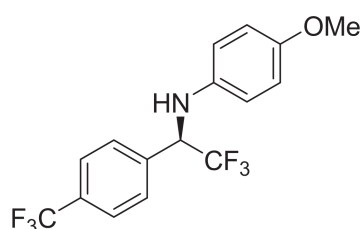
ee : 90%; [α]_D²⁰ -85.8 (*c* 1.50, CHCl₃)

Aspect : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.14-7.20 (m, 3H), 6.73-6.79 (m, 2H), 6.60-6.66 (m, 2H), 4.70-4.80 (m, 1H), 4.07 (d, *J* = 6.5 Hz, NH), 3.73 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.3, 139.8, 137.8, 137.3, 131.8, 130.2, 129.2, 125.4, 125.4 (q, ¹*J*_{CF} = 280.5 Hz), 115.7, 114.9, 61.6 (q, ²*J*_{CF} = 29.2 Hz), 55.8, 20.0, 19.6; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.6 (d, *J* = 7.4 Hz); **IR** (neat) ν 3372, 2923, 1511, 1455, 1348, 1233, 1179, 1158, 1115, 1035, 816, 757, 689 cm⁻¹; **HRMS** Calcd for C₁₇H₁₉NF₃O ([M+H]⁺): 310.1419, Found: 310.1411; **HPLC** (Daicel CHIRALCEL OJ-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 36.8 min (minor enantiomer), τ_R = 49.1 min (major

enantiomer).

(R)-4-Methoxy-N-(2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)aniline (10fa) (xyd 204/216)



CAS number : [1253519-20-8]

Formula : C₁₆H₁₃F₆NO

M.W. : 349.3 g/mol

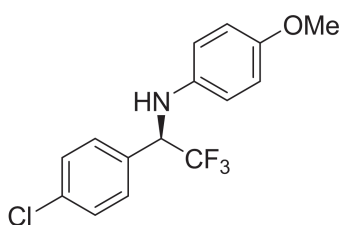
Yield : 99%

ee : 89%

Aspect : pale yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 6.73-6.78 (m, 2H), 6.55-6.60 (m, 2H), 4.85-4.95 (m, 1H), 4.14 (d, *J* = 7.0 Hz, NH), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.7, 139.0, 138.4, 131.5 (q, ²*J*_{CF} = 32.2 Hz), 128.6, 126.0 (q, ³*J*_{CF} = 3.8 Hz), 124.9 (q, ¹*J*_{CF} = 280.5 Hz), 124.0 (q, ¹*J*_{CF} = 270.8 Hz), 115.9, 115.0, 61.6 (q, ²*J*_{CF} = 29.2 Hz), 55.7; **¹⁹F NMR** (CDCl₃, 282 MHz): 163.3, -74.4 (d, *J* = 7.2 Hz); **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 21.6 min (minor enantiomer), τ_R = 28.0 min (major enantiomer).

(R)-N-(1-(4-Chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ga) (xyd 186)



CAS number : [1453102-14-1]

Formula : C₁₅H₁₃F₃ClNO

M.W. : 315.7 g/mol

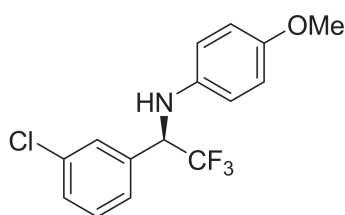
Yield : 98%

ee : 90%

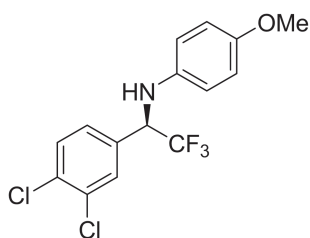
Aspect : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.35-7.42 (m, 4H), 6.73-6.77 (m, 2H), 6.55-6.61 (m, 2H), 4.76-4.86 (m, 1H), 4.09 (d, *J* = 7.0 Hz, NH), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.5, 139.2, 135.2, 132.8, 129.4, 129.2, 125.0 (q, ¹*J*_{CF} = 279.8 Hz), 115.9, 115.0, 61.0 (q, ²*J*_{CF} = 29.2 Hz), 55.6, 55.2; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.1 (d, *J* = 7.2 Hz); **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 23.6 min (minor enantiomer), τ_R = 27.5 min (major enantiomer).

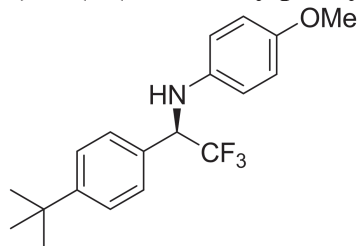
For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(R)-N-(1-(3-Chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ha) (xyd 192/221)**CAS number** : unknown**Formula** : C₁₅H₁₃F₃ClNO**M.W.** : 315.7 g/mol**Yield** : 99%**ee** : 89%; [α]_D²⁰ -41.2 (*c* 1.04, CHCl₃)**Aspect** : pale yellow oil

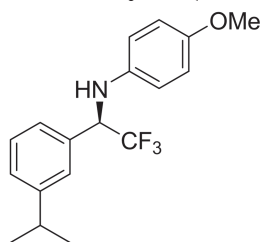
¹H NMR (CDCl₃, 300 MHz): δ 7.47 (s, 1H), 7.32-7.38 (m, 3H), 6.73-6.78 (m, 2H), 6.56-6.61 (m, 2H), 4.75-4.85 (m, 1H), 4.10 (d, *J* = 7.1 Hz, NH), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.5, 139.1, 136.4, 135.0, 130.3, 129.5, 128.3, 126.3, 124.9 (q, ¹*J*_{CF} = 280.5 Hz), 115.8, 115.8, 61.4 (q, ²*J*_{CF} = 30 Hz), 55.7; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.5 (d, *J* = 7.2 Hz); **IR** (neat) ν 3372, 2936, 1575, 1512, 1233, 1172, 1119, 1033, 818, 785, 697 cm⁻¹; **HRMS** Calcd for C₁₅H₁₃NF₃O ([M⁺]): 315.0638, Found: 315.0635; **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 26.0 min (minor enantiomer), τ_R = 29.5 min (major enantiomer).

(R)-N-(1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ia) (xyd 281)**CAS number** : unknown**Formula** : C₁₅H₁₂F₃Cl₂NO**M.W.** : 350.2 g/mol**Yield** : 81%**ee** : 84%; [α]_D²⁰ -42.4 (*c* 1.12, CHCl₃)**Aspect** : yellow oil

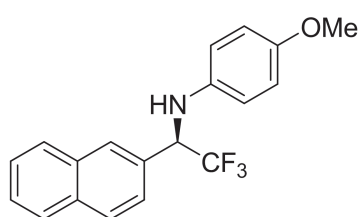
¹H NMR (CDCl₃, 300 MHz): δ 7.57-7.58 (m, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.30-7.33 (m, 1H), 6.73-6.79 (m, 2H), 6.54-6.59 (m, 2H), 4.74-4.83 (m, 1H), 4.09 (d, *J* = 6.5 Hz, NH), 3.73 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.7, 138.8, 134.6, 133.6, 133.3, 131.0, 130.1, 127.4, 124.7 (q, ¹*J*_{CF} = 280.5 Hz), 115.9, 115.0, 60.9 (q, ²*J*_{CF} = 30 Hz), 55.7; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.6 (d, *J* = 7.1 Hz); **IR** (neat) ν 3378, 2941, 1512, 1470, 1401, 1347, 1234, 1175, 1122, 1032, 917, 816, 769, 711 cm⁻¹; **HRMS** Calcd for C₁₅H₁₃NF₃Cl₂O ([M+H]⁺): 350.0326, Found: 350.0322; **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 27.8 min (minor enantiomer), τ_R = 34.1 min (major enantiomer).

(R)-N-(1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline (10ja) (xyd 206)**CAS number** : unknown**Formula** : C₁₉H₂₂F₃NO**M.W.** : 337.4 g/mol**Yield** : 99%**ee** : 92%; [α]_D²⁰ -85.6 (*c* 1.22, CHCl₃)**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.37-7.44 (m, 4H), 6.75-6.79 (m, 2H), 6.63-6.67 (m, 2H), 4.77-4.86 (m, 1H), 4.08 (d, *J* = 7.5 Hz, NH), 3.74 (s, 3H), 1.34 (s, 9H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.3, 152.2, 139.8, 131.4, 127.6, 125.4 (q, ¹*J*_{CF} = 280.5 Hz), 126.0, 115.7, 114.9, 61.4 (q, ²*J*_{CF} = 29.2 Hz), 55.7, 34.7, 31.4; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.5 (d, *J* = 7.4 Hz); **IR** (neat) ν 3394, 2968, 1513, 1233, 1182, 1177, 1118, 1028, 825, 684 cm⁻¹; **HRMS** Calcd for C₁₉H₂₂NF₃O ([M⁺]): 337.1653, Found: 337.1653; **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 13.4 min (minor enantiomer), τ_R = 15.2 min (major enantiomer).

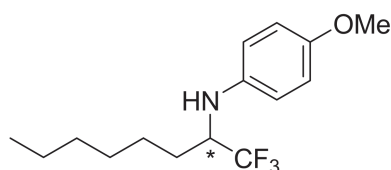
(R)-4-Methoxy-N-(2,2,2-trifluoro-1-(3-isopropylphenyl)ethyl)aniline (10ka) (xyd 303)**CAS number** : unknown**Formula** : C₁₈H₂₀F₃NO**M.W.** : 323.4 g/mol**Yield** : 98%**ee** : 91%; [α]_D²⁰ -55.7 (*c* 1.08, CHCl₃)**Aspect** : pale yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.21-7.32 (m, 4H), 6.72-6.76 (m, 2H), 6.60-6.63 (m, 2H), 4.73-4.83 (m, 1H), 4.05 (d, *J* = 7.3 Hz, NH), 3.70 (s, 3H), 2.83-2.97 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.3, 149.7, 139.8, 134.4, 129.0, 127.2, 126.4, 125.3, 125.4 (q, ¹*J*_{CF} = 280.5 Hz), 115.8, 114.9, 61.9 (q, ²*J*_{CF} = 29.2 Hz), 55.7, 34.2, 24.0; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.4 (d, *J* = 7.3 Hz); **IR** (neat) ν 3379, 2961, 1608, 1512, 1443, 1347, 1234, 1164, 1118, 1118, 1035, 818, 708 cm⁻¹; **HRMS** Calcd for C₁₈H₂₁NF₃O ([M+H]⁺): 324.1575, Found: 324.1568; **HPLC** (Daicel CHIRALCEL OJ-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 20.2 min (minor enantiomer), τ_R = 24.5 min (major enantiomer).

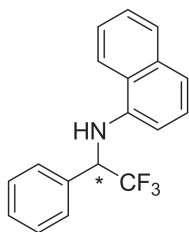
(R)-4-Methoxy-N-(2,2,2-trifluoro-1-(naphthalen-2-yl)ethyl)aniline (10ma) (xyd 396)**CAS number** : unknown**Formula** : C₁₉H₁₆F₃NO**M.W.** : 331.3 g/mol**Yield** : 99%**ee** : 91%**Aspect** : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.70-7.81 (m, 4H), 7.35-7.44 (m, 3H), 6.60-6.63 (m, 2H), 6.51-6.54 (m, 2H), 4.82-4.92 (m, 1H), 4.09 (d, *J* = 6.4 Hz, NH), 3.57 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.5, 139.6, 133.6, 133.3, 131.8, 129.0, 128.2, 127.8, 126.8, 126.7, 125.4 (q, ¹*J*_{CF} = 280.3 Hz), 115.9, 115.0, 62.0 (q, ²*J*_{CF} = 29.4 Hz), 55.7; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.2 (d, *J* = 7.3 Hz); **HPLC** (Daicel CHIRALCEL AD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 26.4 min (major enantiomer), τ_R = 30.3 min (minor enantiomer).

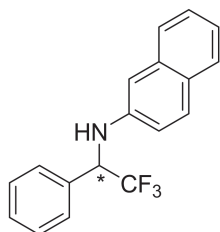
For a complete characterization see A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

N-(1,1,1-Trifluorooctan-2-yl)-4-methoxyaniline (10pa) (xyd 310)**CAS number** : unknown**Formula** : C₁₅H₂₂F₃NO**M.W.** : 289.3 g/mol**Yield** : 52%**ee** : 22%**Aspect** : yellow oil

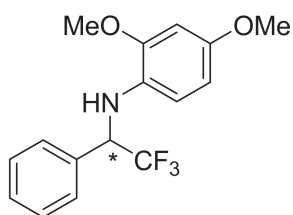
¹H NMR (CDCl₃, 300 MHz): δ 6.76-6.81 (m, 2H), 6.60-6.65 (m, 2H), 3.75 (s, 3H), 3.65-3.72 (m, 1H), 3.26 (d, *J* = 9.0 Hz, NH), 1.81-1.92 (m, 1H), 1.11-1.59 (m, 8H), 0.87-0.92 (m, 4H); **¹³C NMR** (CDCl₃, 75 MHz): δ 151.7, 139.9, 125.4 (q, ¹*J*_{CF} = 282 Hz), 113.8, 113.7, 55.8 (q, ²*J*_{CF} = 28.5 Hz), 54.6, 50.9, 30.7, 28.3, 26.6, 21.3, 12.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -76.6 (d, *J* = 6.9 Hz); **IR** (neat) ν 3003, 2955, 1619, 1512, 1234, 1165, 1130, 1033, 817, 691 cm⁻¹; **HRMS** Calcd for C₁₅H₂₃NF₃O ([M+H]⁺): 290.1732, Found: 290.1724; **HPLC** (Daicel CHIRALCEL OJ-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 15.3 min (minor enantiomer), τ_R = 16.7 min (major enantiomer).

(+)-*N*-(2,2,2-Trifluoro-1-phenylethyl)naphthalen-1-amine (10ad) (xyd 337)**CAS number** : unknown**Formula** : C₁₈H₁₄F₃N**M.W.** : 301.3 g/mol**Yield** : 99%**ee** : 72%; [α]_D²⁰ 171.7 (*c* 0.82, CHCl₃)**Aspect** : pale yellow oil

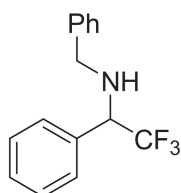
¹H NMR (CDCl₃, 300 MHz): δ 7.90-7.93 (m, 1H), 7.75-7.78 (m, 1H), 7.42-7.50 (m, 4H), 7.31-7.38 (m, 3H), 7.26-7.29 (m, 1H), 7.15-7.20 (m, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 5.03-5.13 (m, 1H), 4.98 (d, *J* = 6.6 Hz, NH); **¹³C NMR** (CDCl₃, 75 MHz): δ 140.6, 134.4, 133.9, 129.3, 129.1, 129.0, 128.0, 126.2, 125.6, 124.2, 125.3 (q, ¹*J*_{CF} = 280.5 Hz), 119.9, 119.7, 107.3, 60.8 (q, ²*J*_{CF} = 29.2 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -74.4 (d, *J* = 7.0 Hz); **IR** (neat) ν 3425, 3064, 1583, 1527, 1407, 1245, 1168, 1119, 888, 766 cm⁻¹; **HRMS** Calcd for C₁₈H₁₅NF₃O([M+H]⁺): 302.1157, Found: 302.1159; **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 15.3 min (major enantiomer), τ_R = 19.3 min (minor enantiomer).

(-)-*N*-(2,2,2-Trifluoro-1-phenylethyl)naphthalen-2-amine (10ae) (xyd 333)**CAS number** : [1259501-01-3]**Formula** : C₁₈H₁₄F₃N**M.W.** : 301.3 g/mol**Yield** : 99%**ee** : 84%; [α]_D²⁰ -14.8 (*c* 1.14, CHCl₃)**Aspect** : white solid; mp: 83 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.53-7.58 (m, 2H), 7.38-7.46 (m, 3H), 7.22-7.32 (m, 4H), 7.10-7.15 (m, 1H), 6.83 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.70-6.71 (m, 1H), 4.91-5.00 (m, 1H), 4.39 (d, *J* = 7.4 Hz, NH); **¹³C NMR** (CDCl₃, 75 MHz): δ 143.2, 134.8, 134.0, 129.4, 129.3, 129.1, 128.3, 128.0, 127.7, 126.7, 126.4, 125.2 (q, ¹*J*_{CF} = 280.5 Hz), 123.1, 118.0, 106.9, 60.6 (q, ²*J*_{CF} = 29.2 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -74.3 (d, *J* = 7.2 Hz); **IR** (neat) ν 3397, 2923, 1722, 1632, 1497, 1248, 1169, 1121, 844, 800, 747 cm⁻¹; **HPLC** (Daicel CHIRALCEL AD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 18.0 min (minor enantiomer), τ_R = 28.9 min (major enantiomer).

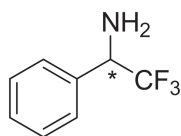
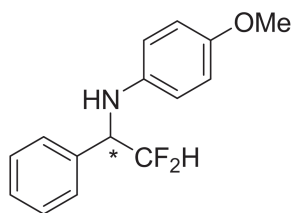
(-)-2,4-Dimethoxy-N-(2,2,2-trifluoro-1-phenylethyl)aniline (10af) (xyd 336/342)**CAS number** : unknown**Formula** : C₁₆H₁₆F₃NO₂**M.W.** : 311.3 g/mol**Yield** : 80%**ee** : 90%; [α]_D²⁰ -31.4 (c 0.55, CHCl₃)**Aspect** : white solid; mp: 86 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.37-7.48 (m, 5H), 6.43-6.47 (m, 2H), 6.30-6.32 (m, 1H), 4.80-4.89 (m, 1H), 4.73 (d, J = 6.2 Hz, NH), 3.86 (s, 3H), 3.72 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.2, 148.5, 134.6, 129.7, 129.1, 128.9, 128.1, 125.4 (q, $^1J_{CF}$ = 279.8 Hz), 112.1, 103.8, 99.4, 61.4 (q, $^2J_{CF}$ = 29.2 Hz), 55.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.6 (d, J = 7.2 Hz); IR (neat) ν 3408, 2957, 1598, 1512, 1457, 1268, 1206, 1119, 1025, 840, 762 cm⁻¹; **HRMS** Calcd for C₁₆H₁₇NF₃O₂ ([M+H]⁺): 312.1211, Found: 312.1217; **HPLC** (Daicel CHIRALCEL AD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 12.0 min (minor enantiomer), τ_R = 15.2 min (major enantiomer).

N-Benzyl-2,2,2-trifluoro-1-phenylethanamine (10ag) (xyd 297)**CAS number** : [1035954-38-1]**Formula** : C₁₅H₁₄F₃N**M.W.** : 265.3 g/mol**Yield** : 86%**ee** : 0%**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.40-7.45 (m, 5H), 7.29-7.35 (m, 5H), 4.11-4.19 (m, 1H), 3.85 (d, J = 13.4 Hz, 1H), 3.68 (d, J = 13.4 Hz, 1H), 2.06 (br s, NH); **¹³C NMR** (CDCl₃, 75 MHz): δ 139.1, 134.3, 129.2, 128.9, 128.8, 128.7, 128.3, 127.5, 125.6 (q, $^1J_{CF}$ = 284.2 Hz), 63.5 (q, $^2J_{CF}$ = 28.5 Hz), 51.1; **¹⁹F NMR** (CDCl₃, 282 MHz): -74.4 (d, J = 7.4 Hz); **HPLC** (Daicel CHIRALCEL OJ-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 254 nm): τ_R = 17.3 min, τ_R = 23.5 min.

For a complete characterization see V. Levin, A. Dilman, P. Belyakov, M. Struchkova, V. Tartakovsky, *Eur. J. Org.Chem.* **2008**, 5226-5230.

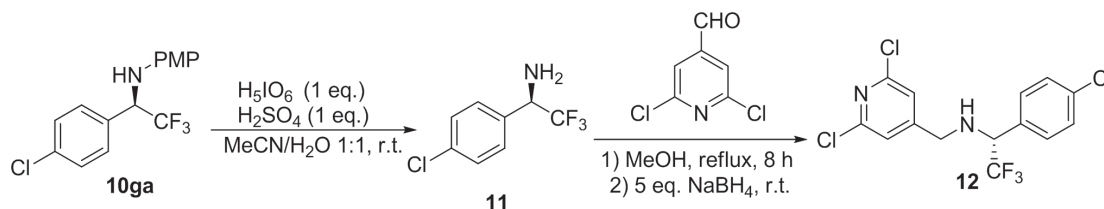
2,2,2-Trifluoro-1-phenylethanamine (10ai) (xyd 274)**CAS number** : [51586-24-4]**Formula** : C₈H₈F₃N**M.W.** : 175.2 g/mol**Yield** : 99%**ee** : 32%**Aspect** : yellow oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.38-7.44 (m, 5H), 4.36-4.43 (m, 1H), 1.78 (br s, 2H, NH₂);**¹³C NMR** (CDCl₃, 75 MHz): δ 135.6, 131.4, 129.1, 128.8, 125.8 (q, ¹J_{CF} = 279.8 Hz), 58.1 (q,²J_{CF} = 30 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -77.2 (q, 2F); **HPLC** (Daicel CHIRALCELOD-H column, Heptane : Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 210 nm): τ_R = 22.4min (minor enantiomer), τ_R = 26.7 min (major enantiomer).For a complete characterization see I. Fernandez, V. Valdivia, A. Alcludia, A. Chelouan, N. Khlar, *Eur. J. Org.Chem.* **2010**, 1502-1509.**(R)-N-(2,2-Difluoro-1-phenylethyl)-4-methoxyaniline (10ra) (xyd 265)****CAS number** : [908603-29-2]**Formula** : C₁₅H₁₅F₂NO**M.W.** : 263.3 g/mol**Yield** : 82%**ee** : 57%**Aspect** : pale yellow oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.34-7.44 (m, 5H), 6.70-6.76 (m, 2H), 6.55-6.60 (m, 2H),5.99 (td, *J* = 55.9 Hz, 3.2 Hz, 1H), 4.63 (td, *J* = 13.2 Hz, 2.9 Hz, 1H), 4.16 (br s, NH), 3.71 (s,3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 153.0, 140.1, 135.7, 129.0, 128.7, 127.9, 116.0 (t, ¹J_{CF} =245.2 Hz), 115.6, 114.9, 61.3 (t, ²J_{CF} = 21 Hz), 55.8; **¹⁹F NMR** (CDCl₃, 282 MHz): -126.4 (d,*J* = 7.5 Hz); **HPLC** (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 95:5, flowrate = 0.5 mL/min, λ = 254 nm): τ_R = 26.6 min (minor enantiomer), τ_R = 31.2 min (major

enantiomer).

For a complete characterization see M.-W. Chen, Y. Duan, C-B. Yu, Y.-G. Zhou, *Org. Lett.* **2010**, 12, 5075-5077.

6.3.3 Application of asymmetric transfer hydrogenation

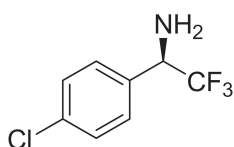
Synthesis of (*R*)-1-(4-chlorophenyl)-*N*-((2,6-dichloropyridin-4-yl)methyl)-2,2,2-trifluoroethanamine (**12**)



(*R*)-*N*-(1-(4-chlorophenyl)-2,2,2-trifluoroethyl)-4-methoxyaniline **10ga** (52.6 mg, 0.17 mmol, 1 eq.) was dissolved in 4 ml of MeCN/H₂O (1:1). Periodic acid (0.17 mmol, 38 mg, 1 eq.) and concentrated H₂SO₄ (0.17 mmol, 16.7 mg, 1 eq.) were subsequently added into the solution. After 24 hours, the reaction went to completion (monitoring by ¹⁹F NMR analysis). The aqueous solution was made alkaline by adding 10% NaOH to pH=8 and then extracted with ethyl acetate. The combined organic solution was washed with brine and dried over MgSO₄. The solvent was removed under vacuum and purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 5:1) to afford (*R*)-1-(4-chlorophenyl)-2,2,2-trifluoroethanamine **11** (27.1 mg, 76%) as pale yellow oil.

A. Henseler, M. Kato, K. Mori, T. Akiyama, *Angew. Chem. Int. Ed.* **2011**, *50*, 8180-8183.

(*R*)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanamine (**11**) (xyd 354)



CAS number : [1187931-01-6]

Formula : C₈H₇ClF₃N

M.W. : 209.6 g/mol

Yield : 76%

ee : 94%

Aspect : pale yellow oil

¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.40 (m, 4H), 4.37-4.40 (m, 1H), 1.76 (br s, 2H, NH₂);

¹³C NMR (CDCl₃, 75 MHz): δ 135.1, 134.0, 129.3, 129.0, 125.5 (q, ¹J_{CF} = 279.8 Hz), 57.5 (q,

²J_{CF} = 29.1 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -77.3 (d, *J* = 7.3 Hz); **IR** (neat) ν 3402, 1598,

1494, 1257, 1116, 1091, 1015, 889, 830 cm⁻¹; **HRMS** Calcd for C₈H₈NF₃Cl ([M+H]⁺):

210.0297, Found: 210.0294; **HPLC** (Daicel CHIRALCEL OD-H column, Heptane :

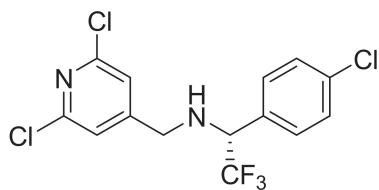
Isopropanol = 95:5, flow rate = 0.5 mL/min, λ = 210 nm): τ_R = 22.5 min (minor enantiomer),

τ_R = 24.2 min (major enantiomer).

(*R*)-1-(4-chlorophenyl)-2,2,2-trifluoroethanamine **11** (18.9 mg, 0.09 mmol, 1 eq.) and 2,6-dichloroisonicotinaldehyde (17.6 mg, 0.1 mmol, 1.2 eq.) were dissolved in MeOH (3 mL) and refluxed for 7 h until the reaction went to completion (monitoring by ^{19}F NMR analysis). The reaction mixture was allowed to cool down to room temperature and portionwise treated with NaBH_4 (34 mg, 0.9 mmol, 10 eq.). Then, the mixture was quenched with NH_4Cl solution and extracted with ethyl acetate. The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 10:1) to give (*R*)-1-(4-chlorophenyl)-*N*-((2,6-dichloropyridin-4-yl) methyl)-2,2,2-trifluoro ethanamine **12** (27.3 mg, 82%) as white solid.

K. Nobuyuki, K. Yuichi, N. Yoshitaka, WO 2006/004062, PCT/JP2005/012247

(*R*)-1-(4-Chlorophenyl)-*N*-((2,6-dichloropyridin-4-yl)methyl)-2,2,2-trifluoroethanamine (12) (xyd 357)



CAS number : [872705-52-7] (racemic)

Formula : $\text{C}_{14}\text{H}_{10}\text{Cl}_3\text{F}_3\text{N}_2$

M.W. : 369.6 g/mol

Yield : 82%

ee : 90%

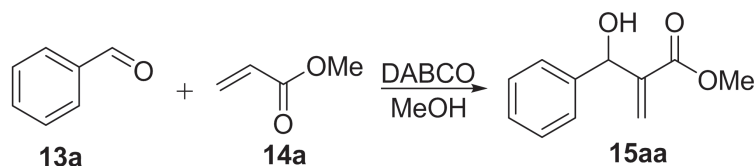
Aspect : white solid; mp: 93 °C

^1H NMR (CDCl_3 , 300 MHz): δ 7.32-7.41 (m, 4H), 7.22 (s, 2H), 4.11 (q, $J = 7.1$ Hz, 1H), 3.75 (q, $J = 12.9$ Hz, 2H), 2.14 (s, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 154.4, 150.9, 135.6, 131.9, 129.9, 129.4, 124.9 (q, $^1J_{\text{CF}} = 279.8$ Hz), 121.9, 63.4 (q, $^2J_{\text{CF}} = 29.2$ Hz), 49.1; ^{19}F NMR (CDCl_3 , 282 MHz): -74.5 (d, $J = 7.1$ Hz); IR (neat) ν cm^{-1} ; HRMS Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{F}_3\text{Cl}_3$ ($[\text{M}+\text{H}]^+$): 368.9940, Found: 368.9944; HPLC (Daicel CHIRALCEL OD-H column, Heptane : Isopropanol = 99:1, flow rate = 0.4 mL/min, $\lambda = 210$ nm): $\tau_{\text{R}} = 37.2$ min (major enantiomer), $\tau_{\text{R}} = 41.3$ min (minor enantiomer).

6.4 Nucleophilic trifluoromethylthiolation of Morita-Baylis-Hillman derivatives

6.4.1 Synthesis of Morita-Baylis-Hillman Adducts

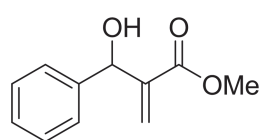
Typical procedure for the synthesis of Morita-Baylis-Hillman Alcohols (15)



To a mixture of benzaldehyde (1.03 mL, 10 mmol) and DABCO (112 mg, 1 mmol) in MeOH (5 mL) was added methyl acrylate (2.72 mL, 30 mmol). The solution was stirred at r.t. until the reaction was complete (monitored by TLC). The mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and dried over MgSO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 5:1) to give methyl 2-(hydroxy(phenyl)methyl)acrylate **15aa** (699 mg, 36%) as colorless oil.

D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, 349, 281-286.

Methyl 2-(hydroxy(phenyl)methyl)acrylate (15aa) (xyd 457)



CAS number : [18020-59-2]

Formula : $\text{C}_{11}\text{H}_{12}\text{O}_3$

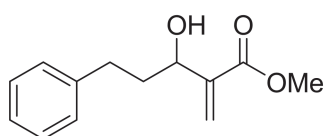
M.W. : 192.2 g/mol

Yield : 36%

Aspect : colorless oil

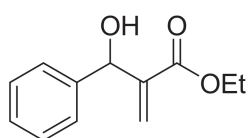
¹H NMR (CDCl_3 , 300 MHz): δ 7.28-7.40 (m, 5H), 6.34 (s, 1H), 5.84 (s, 1H), 5.56 (d, J = 5.4 Hz, 1H), 3.72 (s, 3H), 3.06 (d, J = 5.2 Hz, OH); **¹³C NMR** (CDCl_3 , 75 MHz): δ 166.9, 142.0, 141.3, 128.6, 128.0, 126.7, 126.3, 73.4, 52.1.

For a complete characterization see 1) D. Seebach, R. Henning, T. Mukhopadhyay, *Chem. Ber.* **1982**, 115, 1705-1720; 2) T. Tsuda, T. Yoshida, T. Saegusa, *J. Org. Chem.* **1988**, 53, 1037-1040; 3) D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, 349, 281-286.

Methyl 3-hydroxy-2-methylene-5-phenylpentanoate (15 ap) (xyd 505)**CAS number** : [115204-95-0]**Formula** : C₁₃H₁₆O₃**M.W.** : 220.3 g/mol**Yield** : 55%**Aspect** : colorless oil

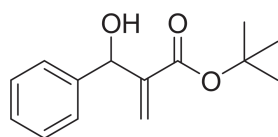
¹H NMR (CDCl₃, 300 MHz): δ 7.30-7.41 (m, 5H), 6.34 (s, 1H), 5.91 (s, 1H), 4.52 (q, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 2.75-2.97 (m, 3H), 2.04-2.14 (m, 2H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.9, 142.0, 141.3, 128.6, 128.0, 126.7, 126.3, 73.4, 52.1.

For a complete characterization see a) W. Poly, D. Schomburg, H. M. R. Hoffmann, *J. Org. Chem.* **1988**, *53*, 3701-3710; b) I. Shiina, Y. Yamai, T. Shimazaki, *J. Org. Chem.* **2005**, *70*, 8103-8106.

Ethyl 2-(hydroxy(phenyl)methyl)acrylate (15aq) (xyd 536-1)**CAS number** : [37442-45-8]**Formula** : C₁₂H₁₄O₃**M.W.** : 206.2 g/mol**Yield** : 29%**Aspect** : colorless oil

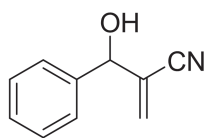
¹H NMR (CDCl₃, 300 MHz): δ 7.28-7.37 (m, 5H), 6.34 (s, 1H), 5.82 (s, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.08-3.10 (m, OH), 1.24 (t, *J* = 6.9 Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.5, 142.3, 141.5, 128.5, 127.9, 126.7, 126.0, 73.5, 61.1, 14.2.

For a complete characterization see Y. Fort, M. C. Berthe, P. Caubere, *Tetrahedron* **1992**, *48*, 6371-6384.

***tert*-Butyl 2-(hydroxy(phenyl)methyl)acrylate (15ar) (xyd 536-2)****CAS number** : [135513-98-3]**Formula** : C₁₄H₁₈O₃**M.W.** : 234.3 g/mol**Yield** : 50%**Aspect** : colorless oil

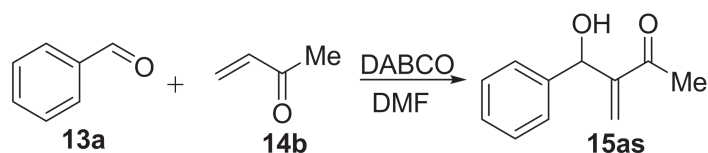
¹H NMR (CDCl₃, 300 MHz): δ 7.30-7.36 (m, 5H), 6.26 (s, 1H), 5.72 (s, 1H), 5.50 (d, *J* = 5.5 Hz, 1H), 3.12 (d, *J* = 5.6 Hz, OH), 1.40 (s, 9H); **¹³C NMR** (CDCl₃, 75 MHz): δ 165.8, 143.5, 141.7, 128.5, 127.8, 126.6, 125.5, 81.8, 73.7, 28.1.

For a complete characterization see Y. Fort, M. C. Berthe, P. Caubere, *Tetrahedron* **1992**, *48*, 6371-6384.

2-(Hydroxy(phenyl)methyl)acrylonitrile (15at) (xyd 565)**CAS number** : [19362-96-0]**Formula** : C₁₀H₉NO**M.W.** : 159.2 g/mol**Yield** : 86%**Aspect** : colorless oil

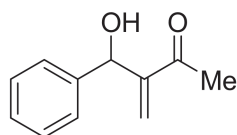
¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.39 (m, 5H), 6.05 (s, 1H), 5.97 (s, 1H), 5.22 (d, *J* = 3.6 Hz, 1H), 3.12 (d, *J* = 3.9 Hz, OH); ¹³C NMR (CDCl₃, 75 MHz): δ 139.3, 130.0, 130.0, 129.0, 126.6, 126.3, 117.1, 74.2.

For a complete characterization see a) J. Cai, Z. Zhou, G. Zhao, C. Tang, *Org. Lett.* **2002**, *4*, 4723-4725; b) D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, *349*, 281-286..

Synthesis of 3-(hydroxy(phenyl)methyl)but-3-en-2-one (15as)

To a solution of DABCO (56 mg, 0.5 mmol) and benzaldehyde (0.5 mL, 5 mmol) in DMF (2.5 mL) was added methylvinyl ketone (0.42 mL, 5 mmol). The reaction mixture was stirred at r.t. for 90h. Then, the mixture was extracted by DCM and washed with water. The organic layer was dried over MgSO₄ and concentrated in vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 5:1) to give 3-(hydroxy(phenyl)methyl)but-3-en-2-one **15as** (290.7 mg, 33%) as colorless oil.

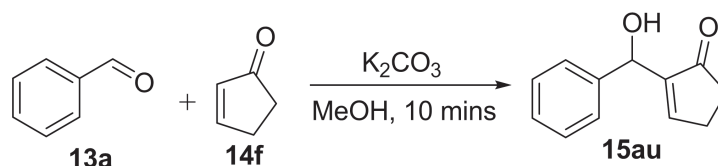
M. Shi, C.-Q. Li, J.-K. Jiang, *Tetrahedron* **2003**, *59*, 1181-1189.

3-(Hydroxy(phenyl)methyl)but-3-en-2-one (15as) (xyd 556)**CAS number** : [73255-39-7]**Formula** : C₁₁H₁₂O₂**M.W.** : 176.2 g/mol**Yield** : 33%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.28-7.37 (m, 5H), 6.19 (s, 1H), 5.97 (d, *J* = 1.0 Hz, 1H), 5.61 (d, *J* = 5.1 Hz, 1H), 3.14 (brs, OH), 2.34 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 200.5, 150.1, 141.6, 128.5, 127.8, 126.8, 126.6, 73.0, 26.6.

For a complete characterization see M. Shi, C.-Q. Li, J.-K. Jiang, *Tetrahedron* **2003**, *59*, 1181-1189.

Synthesis of 2-(hydroxy(phenyl)methyl)cyclopent-2-enone (15au)



To the mixture of K_2CO_3 (345 mg, 2.5 mmol) and benzaldehyde (0.5 mL, 5 mmol) in methanol (7mL) was added cyclopent-2-enone (0.63 mL, 7.5 mmol). The mixture was stirred for 10 mins until the reaction was complete (monitored by TLC). The reaction was quenched with 1M HCl and extracted with ethyl acetate. The combined organic layer was subsequently washed with NaHCO_3 aq., brine and dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 5:1) to give 2-(hydroxy(phenyl)methyl)cyclopent-2-enone **15au** (376 mg, 40%) as colorless oil.

S. Luo, X. Mi, H. Xu, P. G. Wang, J.-P. Cheng, *J. Org. Chem* **2004**, *69*, 8413-8422.

2-(Hydroxy(phenyl)methyl)cyclopent-2-enone (15au) (xyd 522)

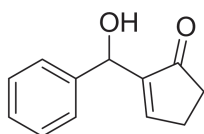
CAS number : [122617-89-4]

Formula : $\text{C}_{12}\text{H}_{12}\text{O}_2$

M.W. : 188.2 g/mol

Yield : 40%

Aspect : colorless oil

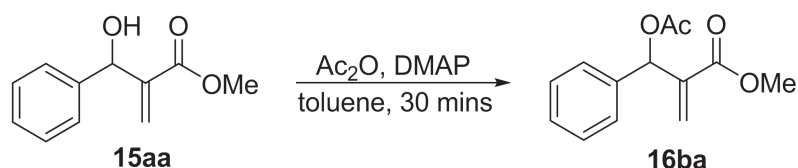


$^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.32-7.38 (m, 6H), 5.57 (s, 1H), 3.45-3.46 (m, OH), 2.59 (m, 2H), 2.46-2.48 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 209.8, 159.5, 147.8, 141.4, 128.6, 128.0, 126.5, 70.1, 35.4, 26.8.

For a complete characterization see K. P. Guerra, C. A. M. Afonso, *Eur. J. Org. Chem.* **2011**, 2372-2379.

6.4.2 Synthesis of Morita-Baylis-Hillman acetates and carbonates

Synthesis of methyl 2-(acetoxymethyl)cyclopent-2-enone (16ba)



Acetic anhydride (0.4 mL, 4.4 mmol) was added dropwise into a mixture of methyl 2-(hydroxy(phenyl)methyl)acrylate (699 mg, 3.6 mmol) and DMAP (44 mg, 0.36 mmol) in toluene (5mL) for 30 mins at 0 °C. The resulting solution was allowed to warm to r.t. for 1 hour. Then, the reaction mixture was cooled to 0 °C, and washed with 2 M HCl, water, saturated NaHCO₃ and dried over MgSO₄. The organic layer was concentrated to afford methyl 2-(acetoxymethyl(phenyl)methyl)acrylate **16ba** (829 mg, 98%) as colorless oil.

Y. Guo, G. Shao, L. Li, W. Wu, R. Li, J. Li, J. Song, L. Qiu, M. Prashad, F. Y. Kwong, *Adv. Synth. Catal.* **2010**, 352, 1539-1553.

Methyl 2-(acetoxymethyl(phenyl)methyl)acrylate (**16ba**) (xyd 464)

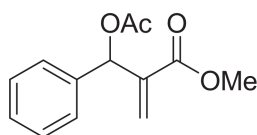
CAS number : [124957-36-4]

Formula : C₁₃H₁₄O₄

M.W. : 234.2 g/mol

Yield : 98%

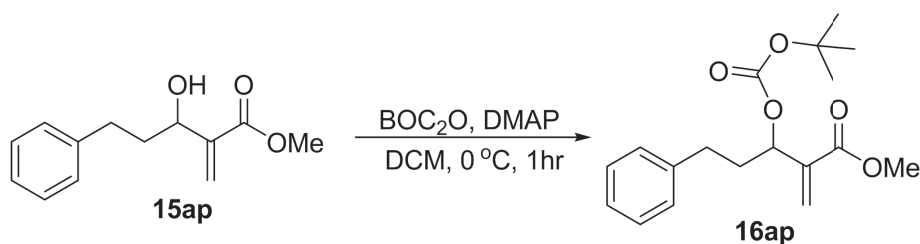
Aspect : colorless oil



¹H NMR (CDCl₃, 300 MHz): δ 7.30-7.40 (m, 5H), 6.68 (s, 1H), 6.40 (s, 1H), 5.86-5.87 (m, 1H), 3.71 (s, 3H), 2.11 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 169.6, 165.6, 139.8, 137.9, 128.6, 128.5, 127.8, 125.9, 73.2, 52.1, 21.2.

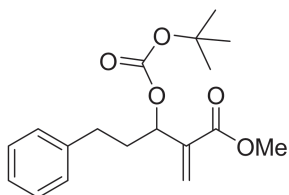
For a complete characterization see P. H. Mason, N. D. Emslie, *Tetrahedron*, **1994**, 50, 12001-12008.

Typical procedure for the synthesis of Morita-Baylis-Hillman carbonate (**16**)



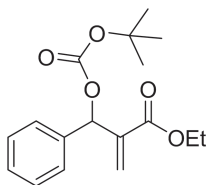
Di-*tert*-butyl dicarbonate (0.72 mL, 3.1 mmol) was added into a mixture of methyl 3-hydroxy-2-methylene-5-phenylpentanoate (660 mg, 3 mmol) and DMAP (36.6 mg, 0.3 mmol) in DCM (2mL) for 1 hour at 0 °C. The resulting solution was washed with 2 M HCl, water and saturated NaHCO₃ and dried over MgSO₄. The organic layer was concentrated in vacuum and the residue was purified by column chromatography on silica gel (petroleum ether/ ethyl acetate: 5:1) to afford methyl 3-(*tert*-butoxycarbonyloxy)-2-methylene-5-phenylpentanoate **16ap** (404 mg, 42%) as colorless oil.

D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, 349, 281-286.

Methyl 3-((*tert*-butoxycarbonyloxy)-2-methylene-5-phenylpentanoate (16ap) (xyd 507)**CAS number** : [1330066-94-8]**Formula** : C₁₈H₂₄O₅**M.W.** : 320.4 g/mol**Yield** : 42%**Aspect** : colorless oil

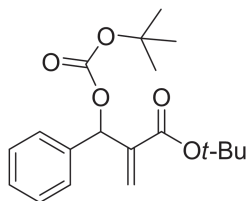
¹H NMR (CDCl₃, 300 MHz): δ 7.26-7.36 (m, 5H), 6.39 (s, 1H), 5.94 (s, 1H), 5.52-5.55 (m, 1H), 3.82 (s, 3H), 2.71-2.87 (m, 2H), 2.01-2.16 (m, 2H), 1.56 (s, 9H); **¹³C NMR** (CDCl₃, 75 MHz): δ 165.8, 152.8, 141.3, 140.3, 128.5, 128.5, 126.1, 125.3, 82.6, 74.3, 52.1, 36.3, 31.9, 27.9.

For a complete characterization see W. Sun, X. Ma, L. Hong, R. Wang, *J. Org. Chem.* **2011**, *76*, 7826-7833.

Ethyl 2-((*tert*-butoxycarbonyloxy)(phenyl)methyl)acrylate (16aq) (xyd 542-1)**CAS number** : [736931-10-5]**Formula** : C₁₇H₂₂O₅**M.W.** : 306.4 g/mol**Yield** : 29%**Aspect** : white solid

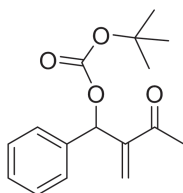
¹H NMR (CDCl₃, 300 MHz): δ 7.31-7.41 (m, 5H), 6.48 (s, 1H), 6.40 (s, 1H), 5.89 (s, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 1.46 (s, 9H), 1.22 (t, *J* = 6.9 Hz, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 165.1, 152.6, 140.0, 137.7, 128.5, 127.8, 125.7, 82.7, 76.0, 61.1, 27.9, 14.1.

For a complete characterization see a) Y. Du, X. L. Han, X. Lu, *Tetrahedron Lett.* **2004**, *45*, 4967-4971; b) J. Feng, X. Lu, A. Kong, X. Han, *Tetrahedron* **2007**, *63*, 6035-6041.

***tert*-Butyl 2-((*tert*-butoxycarbonyloxy)(phenyl)methyl)acrylate (16ar) (xyd 542-2)****CAS number** : [956833-13-9]**Formula** : C₁₉H₂₆O₅**M.W.** : 334.4 g/mol**Yield** : 61%**Aspect** : white solid

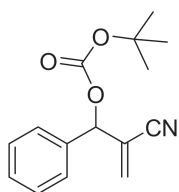
¹H NMR (CDCl₃, 300 MHz): δ 7.33-7.37 (m, 5H), 6.42 (s, 1H), 6.33 (s, 1H), 5.79 (s, 1H), 1.46 (s, 9H), 1.36 (s, 9H); **¹³C NMR** (CDCl₃, 75 MHz): δ 164.3, 152.6, 141.2, 137.9, 128.5, 128.0, 124.7, 82.6, 81.6, 76.3, 28.0, 27.9.

For a complete characterization see S. Zheng, X. Lu, *Org. Lett.* **2008**, *10*, 4481-4484.

tert-Butyl 2-methylene-3-oxo-1-phenylbutyl carbonate (16as) (xyd 560)**CAS number** : [736931-22-9]**Formula** : C₁₆H₂₀O₄**M.W.** : 276.3 g/mol**Yield** : 58%**Aspect** : colorless oil

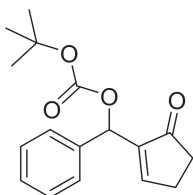
¹H NMR (CDCl₃, 300 MHz): δ 7.30-7.40 (m, 5H), 6.56 (s, 1H), 6.22 (s, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 2.31 (s, 3H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 197.4, 152.5, 148.0, 138.2, 128.6, 128.4, 127.5, 125.5, 82.7, 75.2, 27.9, 26.3.

For a complete characterization see C.-K. Pei, X.-C. Zhang, M. Shi, *Eur. J. Org. Chem.* **2011**, 4479-4484.

tert-Butyl 2-cyano-1-phenylallyl carbonate (16at) (xyd 576)**CAS number** : [1005193-04-3]**Formula** : C₁₅H₁₇NO₃**M.W.** : 259.3 g/mol**Yield** : 56%**Aspect** : yellow solid

¹H NMR (CDCl₃, 300 MHz): δ 7.40-7.43 (m, 5H), 6.10 (s, 1H), 6.08 (s, 1H), 6.04 (d, *J* = 1.1 Hz, 1H), 1.48 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 152.2, 135.6, 131.8, 129.4, 129.1, 127.1, 123.4, 116.3, 83.7, 27.8.

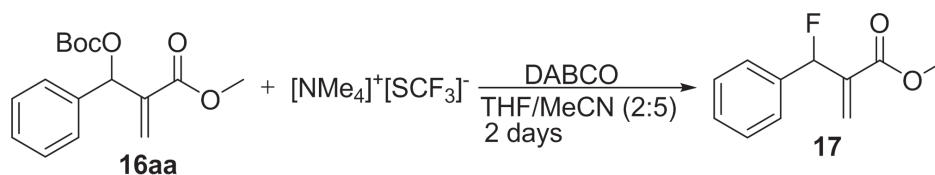
For a complete characterization see D. J. V. C. van Steenis, T. Marcelli, M. Lutz, A. L. Spek, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2007**, 349, 281-286.

Methyl 3-(tert-butoxycarbonyloxy)-2-methylene-5-phenylpentanoate (16au) (xyd 507)**CAS number** : [1316313-04-8]**Formula** : C₁₇H₂₀O₄**M.W.** : 288.3 g/mol**Yield** : 48%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.54 (s, 1H), 7.32-7.42 (m, 5H), 6.34 (s, 1H), 2.61 (m, 2H), 2.42-2.44 (m, 2H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 206.6, 159.3, 152.6, 145.6, 138.1, 128.7, 128.4, 127.0, , 82.8, 73.2, 35.0, 27.9, 26.8.

For a complete characterization see M. Kamlar, S. Hybelbauerová, I. Císařová, J. Vesely, *Org. Biomol. Chem.* **2014**, 12, 5071-5076.

6.4.3 Synthesis of monofluorine product



To a stirred solution of methyl 2-((*tert*-butoxycarbonyloxy)(phenyl)methyl) acrylate **16aa** (29.2 mg, 0.1 mmol) and DABCO (1.12 mg, 0.01 mmol) in dry THF (0.4 mL) was added the solution of $[\text{Me}_4\text{N}]^+[\text{SCF}_3]^-$ (32 mg, 0.2 mmol) in MeCN (1 mL) at room temperature. After 2 days, the reaction went to completion (monitoring by ^{19}F NMR analysis and TLC). The reaction mixture was concentrated in *vacuo* and purified by silica gel column chromatography (petroleum ether/ethyl acetate: 30/1) to give methyl 2-(fluoro(phenyl)methyl)acrylate **17** (9.7 mg, 50%) as colorless oil.

Methyl 2-(fluoro(phenyl)methyl)acrylate (**17**) (xyd 417)

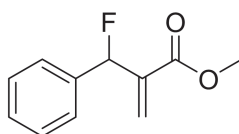
CAS number : [203392-27-2]

Formula : $\text{C}_{11}\text{H}_{11}\text{FO}_2$

M.W. : 194.2 g/mol

Yield : 50%

Aspect : colorless oil

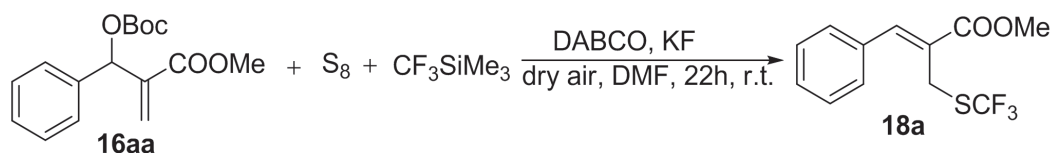


^1H NMR (CDCl_3 , 300 MHz): δ 7.35-7.40 (m, 5H), 6.46 (d, $J = 2.6$ Hz, 1H), 6.12 (d, $J = 55.2$ Hz, 1H), 6.02 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 165.4 (d, $^3J_{\text{CF}} = 6.3$ Hz), 139.4 (d, $^2J_{\text{CF}} = 22.7$ Hz), 137.4 (d, $^2J_{\text{CF}} = 20.2$ Hz), 129.1 (d, $^3J_{\text{CF}} = 2.7$ Hz), 128.6, 127.2 (d, $^3J_{\text{CF}} = 5.6$ Hz), 126.2 (d, $^3J_{\text{CF}} = 8.8$ Hz), 90.9 (d, $^1J_{\text{CF}} = 172.7$ Hz), 52.2; ^{19}F NMR (CDCl_3 , 282 MHz): -171.5.

For a complete characterization see L. Bernardi, B. F. Bonini, M. Comes-Franchini, M. Fochi, M. Folegatti, S. Grilli, A. Mazzanti, A. Ricci, *Tetrahedron: Asymmetry* **2004**, *15*, 245-250.

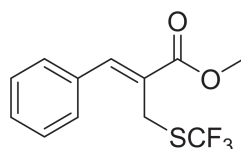
6.4.4 Use of the combination of S₈/CF₃SiMe₃/KF

Typical procedure for combination of S₈/CF₃SiMe₃/KF for trifluoromethylthiolation of MBH derivatives (18)



In an oven-dried tube, sulfur (19.2 mg, 0.6 mmol) and KF (58.1 mg, 1 mmol) in dry DMF (2 mL) were stirred at room temperature under dry air for 15 minutes. Me₃SiCF₃ (71 mg, 0.5 mmol) was then added to the mixture followed by addition of methyl 2-((*tert*-butoxycarbonyloxy)(phenyl)methyl)acrylate (29.2 mg, 0.1 mmol) and DABCO (1.12 mg, 0.01 mmol). After 22 hours, the reaction went to completion (monitoring by ¹⁹F NMR analysis). The reaction was quenched with water and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 40/1) to give the corresponding (*Z*)-methyl 3-phenyl-2-((trifluoromethylthio)methyl)acrylate **18a** (25.7 mg, 93%) as colorless oil.

(*Z*)-Methyl 3-phenyl-2-((trifluoromethylthio)methyl)acrylate (18a) (xyd 476-2, 554)



CAS number : unknown

Formula : C₁₂H₁₁F₃SO₂

M.W. : 276.3 g/mol

Yield : 93%

Aspect : colorless oil

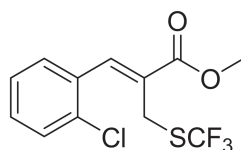
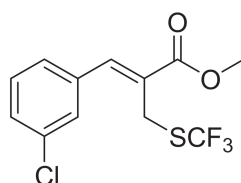
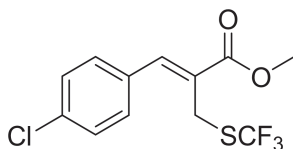
¹H NMR (CDCl₃, 300 MHz): δ 7.90 (s, 1H), 7.41-7.46 (m, 5H), 4.07 (s, 2H), 3.87 (s, 3H);

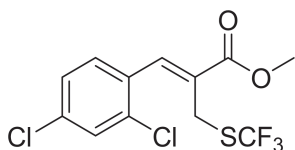
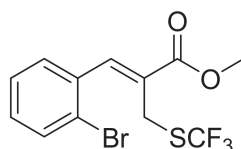
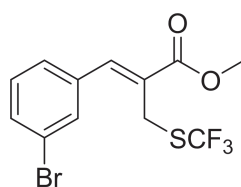
¹³C NMR (CDCl₃, 75 MHz): δ 167.0, 143.8, 134.2, 130.7 (q, ¹J_{CF}=305.2 Hz), 129.7, 129.4,

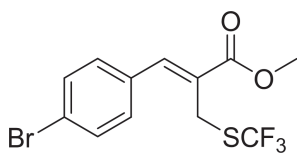
129.0, 126.0, 52.7, 27.2 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3; **IR** (neat) ν

2955, 1713, 1631, 1494, 1437, 1364, 1270, 1104, 1081, 976, 783, 755, 696 cm⁻¹; **HRMS**

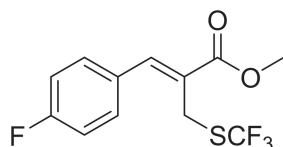
Calcd for C₁₂H₁₁F₃O₂S [M]⁺: 276.0432, Found: 276.0446.

(Z)-Methyl 3-(2-chlorophenyl)-2-((trifluoromethylthio)methyl)acrylate (18b) (xyd 520)**CAS number** : unknown**Formula** : C₁₂H₁₀ClF₃SO₂**M.W.** : 310.7 g/mol**Yield** : 79%**Aspect** : colorless oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.94 (s, 1H), 7.34-7.46 (m, 4H), 3.91 (s, 2H), 3.89 (s, 3H);**¹³C NMR** (CDCl₃, 75 MHz): δ 166.4, 140.5, 134.2, 133.0, 130.7, 130.7 (q, ¹J_{CF}=305.5 Hz),130.0, 129.9, 128.6, 127.0, 52.7, 27.0 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.4;**IR** (neat) ν 2960, 1716, 1635, 1467, 1434, 1362, 1288, 1266, 1150, 1106, 1081, 976, 782, 755 cm⁻¹; **HRMS** Calcd for C₁₂H₁₀ClF₃O₂S [M]⁺: 310.0042, Found: 310.0035.**(Z)-Methyl 3-(3-chlorophenyl)-2-((trifluoromethylthio)methyl)acrylate (18c) (xyd 524)****CAS number** : unknown**Formula** : C₁₂H₁₀ClF₃SO₂**M.W.** : 310.7 g/mol**Yield** : 80%**Aspect** : colorless oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.81 (s, 1H), 7.33-7.42 (m, 4H), 4.02 (s, 2H), 3.87 (s, 3H);**¹³C NMR** (CDCl₃, 75 MHz): δ 166.6, 142.0, 136.0, 135.0, 130.3, 130.6 (q, ¹J_{CF}=305.3 Hz),129.6, 129.2, 127.6, 127.2, 52.8, 27.0 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3;**IR** (neat) ν 2955, 1714, 1630, 1568, 1437, 1362, 1281, 1203, 1151, 1104, 1079, 881, 787, 756 cm⁻¹; **HRMS** Calcd for C₁₂H₁₀ClF₃O₂S [M]⁺: 310.0042, Found: 310.0033.**(Z)-Methyl 3-(4-chlorophenyl)-2-((trifluoromethylthio)methyl)acrylate (18d) (xyd 521)****CAS number** : unknown**Formula** : C₁₂H₁₀ClF₃SO₂**M.W.** : 310.7 g/mol**Yield** : 86%**Aspect** : colorless oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.82 (s, 1H), 7.37-7.44 (m, 4H), 4.03 (s, 2H), 3.87 (s, 3H);**¹³C NMR** (CDCl₃, 75 MHz): δ 166.7, 142.4, 135.8, 132.7, 130.7, 130.6 (q, ¹J_{CF}=302.9 Hz),129.3, 126.6, 52.7, 27.1 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3; **IR** (neat) ν2960, 1709, 1635, 1585, 1501, 1433, 1317, 1265, 1183, 1145, 1109, 1011, 831, 789, 758 cm⁻¹;**HRMS** Calcd for C₁₂H₁₀ClF₃O₂S [M]⁺: 310.0042, Found: 310.0046.

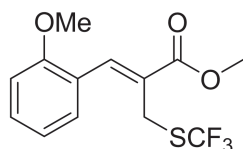
(Z)-Methyl 3-(2,4-dichlorophenyl)-2-((trifluoromethylthio)methyl)acrylate (18e) (xyd 525)**CAS number** : unknown**Formula** : C₁₂H₉Cl₂F₃SO₂**M.W.** : 345.2 g/mol**Yield** : 93%**Aspect** : pale yellow oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.86 (s, 1H), 7.49 (s, 1H), 7.32-7.37 (m, 2H), 3.89 (s, 5H);**¹³C NMR** (CDCl₃, 75 MHz): δ 166.2, 139.2, 136.1, 135.1, 131.4, 130.6 (q, ¹J_{CF}=305.3 Hz),130.6, 130.0, 129.2, 127.5, 52.8, 27.0 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3;**IR** (neat) ν 2955, 1717, 1635, 1585, 1469, 1440, 1378, 1284, 1150, 1103, 1080, 1053, 981, 864, 820, 769, 756 cm⁻¹; **HRMS** Calcd for C₁₂H₉Cl₂F₃O₂S [M]⁺: 343.9652, Found: 343.9639.**(Z)-Methyl 3-(2-bromophenyl)-2-((trifluoromethylthio)methyl)acrylate (18f) (xyd 515)****CAS number** : unknown**Formula** : C₁₂H₁₀BrF₃SO₂**M.W.** : 355.2 g/mol**Yield** : 86%**Aspect** : colorless oil at 25 °C**¹H NMR** (CDCl₃, 300 MHz): δ 7.88 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.38-7.39 (m, 2H),7.26-7.29 (m, 1H), 3.89 (s, 5H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.4, 142.6, 134.8, 133.2,130.8, 130.7 (q, ¹J_{CF}=305.4 Hz), 129.9, 128.4, 127.6, 124.1, 52.7, 27.4 (q, ³J_{CF}=2.4 Hz); **¹⁹F****NMR** (CDCl₃, 282 MHz): -42.3; **IR** (neat) ν 2955, 1716, 1635, 1468, 1434, 1362, 1287,1205, 1150, 1106, 1081, 1027, 976, 903, 824, 753 cm⁻¹; **HRMS** Calcd for C₁₁H₇⁸¹BrF₃O₂S [M(⁸¹Br)-OCH₃]: 324.9333, Found: 324.9321.**(Z)-Methyl 3-(3-bromophenyl)-2-((trifluoromethylthio)methyl)acrylate (18g) (xyd 516)****CAS number** : unknown**Formula** : C₁₂H₁₀BrF₃SO₂**M.W.** : 355.2 g/mol**Yield** : 69%**Aspect** : pale yellow oil**¹H NMR** (CDCl₃, 300 MHz): δ 7.80 (s, 1H), 7.52-7.58 (m, 2H), 7.29-7.38 (m, 2H), 4.02 (s,2H), 3.87 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.6, 141.9, 136.3, 132.6, 132.1, 130.6 (q,¹J_{CF}=305.4 Hz), 130.5, 127.7, 123.1, 52.7, 27.4 (q, ³J_{CF}=2.4 Hz); **¹⁹F NMR** (CDCl₃, 282MHz): -42.2; **IR** (neat) ν 2955, 1714, 1635, 1563, 1440, 1362, 1279, 1201, 1151, 1105, 1078,864, 785 cm⁻¹; **HRMS** Calcd for C₁₂H₁₀⁸¹BrF₃O₂S [M(⁸¹Br)]⁺: 355.9516, Found: 355.9508.

(Z)-Methyl 3-(4-bromophenyl)-2-((trifluoromethylthio)methyl)acrylate (18h) (xyd 469)**CAS number** : unknown**Formula** : C₁₂H₁₀BrF₃SO₂**M.W.** : 355.2 g/mol**Yield** : 99%**Aspect** : white solid; mp= 61 °C

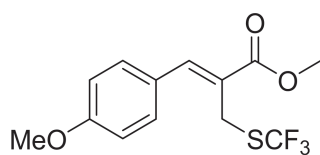
¹H NMR (CDCl₃, 300 MHz): δ 7.80 (s, 1H), 7.56-7.59 (m, 2H), 7.29-7.32 (m, 2H), 4.02 (s, 2H), 3.87 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.7, 142.4, 133.1, 132.3, 130.8, 130.6 (q, ¹J_{CF}=305.2 Hz), 126.7, 124.1, 52.8, 27.0 (q, ³J_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3; **IR** (neat) ν 2955, 1713, 1635, 1591, 1496, 1434, 1278, 1151, 1103, 1073, 1009, 920, 831 cm⁻¹; **HRMS** Calcd for C₁₂H₁₀BrF₃O₂S [M]⁺: 353.9537, Found: 353.9535.

(Z)-Methyl 3-(4-fluorophenyl)-2-((trifluoromethylthio)methyl)acrylate (18i) (xyd 484)**CAS number** : unknown**Formula** : C₁₂H₁₀F₄SO₂**M.W.** : 294.3 g/mol**Yield** : 94%**Aspect** : colorless oil

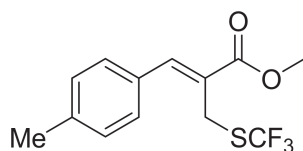
¹H NMR (CDCl₃, 300 MHz): δ 7.84 (s, 1H), 7.42-7.47 (m, 2H), 7.11-7.16 (m, 2H), 4.04 (s, 2H), 3.87 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.8, 163.4 (d, ¹J_{CF}=249.8 Hz), 142.6 (d, ⁴J=2.4 Hz), 131.5 (d, ³J_{CF}=8.4 Hz), 130.7 (q, ¹J_{CF}=305.2 Hz), 130.4 (d, ⁵J_{CF}=3.4 Hz), 125.8, 116.3 (d, ²J_{CF}=21.6 Hz), 52.7, 27.1 (q, ³J_{CF}=2.6 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.4, -110.6; **IR** (neat) ν 2955, 1712, 1634, 1437, 1270, 1228, 1157, 1104, 1079, 977, 834, 776, 755 cm⁻¹.

(Z)-Methyl 3-(2-methoxyphenyl)-2-((trifluoromethylthio)methyl)acrylate (18j) (xyd 590)**CAS number** : unknown**Formula** : C₁₃H₁₃F₃SO₃**M.W.** : 306.3 g/mol**Yield** : 64%**Aspect** : colorless oil

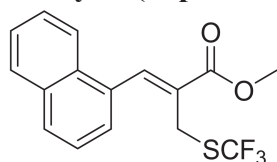
¹H NMR (CDCl₃, 300 MHz): δ 8.02 (s, 1H), 7.36-7.41 (m, 2H), 6.92-7.04 (m, 2H), 4.00 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 167.0, 157.7, 140.0, 131.2, 130.9 (q, ¹J_{CF}=305.1 Hz), 129.7, 126.2, 123.4, 120.7, 110.9, 55.7, 52.5, 27.5 (q, ³J_{CF}=2.6 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.4; **IR** (neat) ν 2949, 1711, 1602, 1488, 1464, 1437, 1272, 1247, 1050, 1105, 1081, 1050, 1025, 830, 783, 752 cm⁻¹.

(Z)-Methyl 3-(4-methoxyphenyl)-2-((trifluoromethylthio)methyl)acrylate (18k) (xyd 529)**CAS number** : unknown**Formula** : C₁₃H₁₃F₃SO₃**M.W.** : 306.3 g/mol**Yield** : 88%**Aspect** : white solid; mp < 50 °C

¹H NMR (CDCl₃, 300 MHz): δ 7.84 (s, 1H), 7.46 (d, *J*=7.8 Hz, 2H), 6.97 (d, *J*=7.8 Hz, 2H), 4.12 (s, 2H), 3.86 (s, 6H); **¹³C NMR** (CDCl₃, 75 MHz): δ 167.3, 161.0, 143.7, 131.7, 130.7 (q, ¹*J*_{CF}=309.0 Hz), 126.7, 123.1, 114.5, 52.6, 27.4 (q, ³*J*_{CF}=2.4 Hz), 21.5; **¹⁹F NMR** (CDCl₃, 282 MHz): -42.4; **IR** (neat) ν 2960, 2843, 1717, 1599, 1510, 1440, 1258, 1288, 1165, 1150, 1103, 1078, 1031, 960, 833, 755 cm⁻¹; **HRMS** Calcd for C₁₃H₁₃F₃O₃S [M]⁺: 306.0538, Found: 306.0531.

(Z)-Methyl 3-*p*-tolyl-2-((trifluoromethylthio)methyl)acrylate (18l) (xyd 526)**CAS number** : unknown**Formula** : C₁₃H₁₃F₃SO₂**M.W.** : 290.3 g/mol**Yield** : 93%**Aspect** : colorless oil

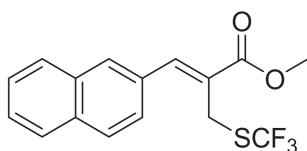
¹H NMR (CDCl₃, 300 MHz): δ 7.86 (s, 1H), 7.35-7.38 (m, 2H), 7.24-7.26 (m, 2H), 4.09 (s, 2H), 3.86 (s, 3H), 2.39 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 167.1, 144.0, 140.2, 131.4, 130.8 (q, ¹*J*_{CF}=305.2 Hz), 129.8, 129.6, 124.8, 52.6, 27.4 (q, ³*J*_{CF}=2.4 Hz), 21.5; **¹⁹F NMR** (CDCl₃, 282 MHz): -42.4; **IR** (neat) ν 2955, 1711, 1630, 1610, 1437, 1320, 1270, 1150, 1104, 1080, 980, 918, 810, 755 cm⁻¹; **HRMS** Calcd for C₁₃H₁₃F₃O₂S [M]⁺: 290.0588, Found: 290.0574.

(Z)-Methyl 3-(naphthalen-1-yl)-2-((trifluoromethylthio)methyl)acrylate (18m) (xyd 517)**CAS number** : unknown**Formula** : C₁₆H₁₃F₃SO₂**M.W.** : 326.3 g/mol**Yield** : 95%**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 8.40 (s, 1H), 7.89-7.92 (m, 3H), 7.50-7.56 (m, 4H), 3.94 (s, 5H); **¹³C NMR** (CDCl₃, 75 MHz): δ 166.7, 142.2, 133.6, 131.6, 131.4, 130.7 (q, ¹*J*_{CF}=305.2 Hz), 129.9, 129.0, 128.8, 126.9, 126.6, 126.4, 125.4, 124.5, 52.7, 27.3 (q, ³*J*_{CF}=2.5 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -42.3; **IR** (neat) ν 2955, 1713, 1629, 1507, 1434, 1339, 1281,

1261, 1148, 1106, 1091, 970, 898, 778 cm^{-1} ; **HRMS** Calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2\text{S}$ $[\text{M}]^+$: 326.0588, Found: 326.0579.

(Z)-Methyl 3-(naphthalen-2-yl)-2-((trifluoromethylthio)methyl)acrylate (18n) (xyd 514)



CAS number : unknown

Formula : $\text{C}_{16}\text{H}_{13}\text{F}_3\text{SO}_2$

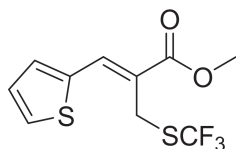
M.W. : 326.3 g/mol

Yield : 94%

Aspect : white solid

^1H NMR (CDCl_3 , 300 MHz): δ 8.05 (s, 1H), 8.00 (s, 1H), 7.85-7.92 (m, 3H), 7.52-7.55 (m, 3H), 4.17 (s, 2H), 3.90 (s, 3H); **^{13}C NMR** (CDCl_3 , 75 MHz): δ 167.0, 143.9, 133.6, 133.2, 131.7, 130.8 (q, $^1J_{\text{CF}}=308.2$ Hz), 129.7, 128.8, 128.7, 127.8, 127.5, 126.9, 126.4, 126.0, 52.7, 27.4 (q, $^3J_{\text{CF}}=2.4$ Hz); **^{19}F NMR** (CDCl_3 , 282 MHz): -42.2; **IR** (neat) ν 2960, 1715, 1635, 1440, 1339, 1259, 1154, 1101, 1079, 953, 824, 752 cm^{-1} ; **HRMS** Calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2\text{S}$ $[\text{M}]^+$: 326.0588, Found: 326.0591.

(Z)-Methyl 3-(thiophen-2-yl)-2-((trifluoromethylthio)methyl)acrylate (18 $^{\circ}$) (xyd 535)



CAS number : unknown

Formula : $\text{C}_{10}\text{H}_9\text{F}_3\text{S}_2\text{O}_2$

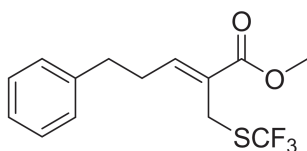
M.W. : 282.3 g/mol

Yield : 88%

Aspect : white solid; mp= 68 $^{\circ}\text{C}$

^1H NMR (CDCl_3 , 300 MHz): δ 7.98 (s, 1H), 7.60-7.62 (m, 1H), 7.39 (m, 1H), 7.15 (m, 1H), 4.26 (s, 2H), 3.86 (s, 3H); **^{13}C NMR** (CDCl_3 , 75 MHz): δ 167.0, 137.0, 135.6, 133.9, 131.4, 130.7 (q, $^1J_{\text{CF}}=309.0$ Hz), 128.0, 121.8, 52.7, 27.4 (q, $^3J_{\text{CF}}=2.4$ Hz); **^{19}F NMR** (CDCl_3 , 282 MHz): -42.0; **IR** (neat) ν 2960, 1708, 1614, 1434, 1417, 1271, 1207, 1096, 836, 711 cm^{-1} ; **HRMS** Calcd for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_2\text{S}_2$ $[\text{M}]^+$: 281.9996, Found: 281.9997.

(Z)-Methyl 5-phenyl-2-((trifluoromethylthio)methyl)pent-2-enoate (18p) (xyd 534)



CAS number : unknown

Formula : $\text{C}_{14}\text{H}_{15}\text{F}_3\text{SO}_2$

M.W. : 304.3 g/mol

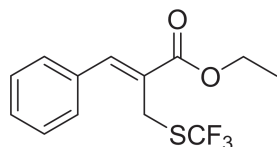
Yield : 20%

Aspect : pale yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.33-7.29 (m, 2H), 7.18-7.22 (m, 3H), 7.00 (t, $J=7.6$ Hz, 1H), 3.78 (s, 3H), 3.72 (s, 2H), 2.77-2.82 (m, 2H), 2.54-2.62 (m, 2H); **^{13}C NMR** (CDCl_3 , 75 MHz): δ 166.4, 145.9, 140.6, 131.0 (q, $^1J_{\text{CF}}=301.1$ Hz), 128.8, 128.5, 127.5, 126.5, 52.4, 34.7, 30.9,

25.7 (q, $^3J_{CF}=2.3$ Hz); ^{19}F NMR (CDCl_3 , 282 MHz): -42.1; IR (neat) ν 2955, 1715, 1647, 1501, 1454, 1438, 1276, 1199, 1147, 1100, 1053, 968, 781, 750, 698 cm^{-1} .

(Z)-Ethyl 3-phenyl-2-((trifluoromethylthio)methyl)acrylate (18q) (xyd 547)



CAS number : unknown

Formula : $\text{C}_{13}\text{H}_{13}\text{F}_3\text{SO}_2$

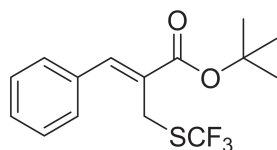
M.W. : 290.3 g/mol

Yield : 84%

Aspect : colorless oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.89 (s, 1H), 7.44 (m, 5H), 4.33 (q, $J=7.0$ Hz, 2H), 4.07 (s, 2H), 1.37 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 166.5, 143.5, 134.4, 130.8 (q, $^1J_{CF}=305.2$ Hz), 129.6, 129.4, 129.0, 126.4, 61.7, 27.2 (q, $^3J_{CF}=2.5$ Hz), 14.3; ^{19}F NMR (CDCl_3 , 282 MHz): -42.4; IR (neat) ν 2988, 1708, 1635, 1451, 1367, 1268, 1150, 1106, 1083, 1019, 864, 791, 755 cm^{-1} ; HRMS Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_2\text{S}$ $[\text{M}]^+$: 290.0588, Found: 290.0577.

(Z)-tert-Butyl 3-phenyl-2-((trifluoromethylthio)methyl)acrylate (18r) (xyd 561)



CAS number : unknown

Formula : $\text{C}_{15}\text{H}_{17}\text{F}_3\text{SO}_2$

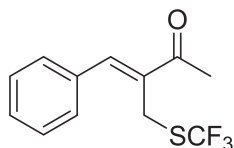
M.W. : 318.4 g/mol

Yield : 28%

Aspect : pale yellow oil

^1H NMR (CDCl_3 , 300 MHz): δ 7.80 (s, 1H), 7.42-7.44 (m, 5H), 4.01 (s, 2H), 1.56 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 165.5, 142.7, 134.6, 130.9 (q, $^1J_{CF}=305.0$ Hz), 129.4, 129.3, 128.9, 127.8, 82.1, 28.2, 27.3 (q, $^3J_{CF}=2.6$ Hz); ^{19}F NMR (CDCl_3 , 282 MHz): -42.4; IR (neat) ν 2977, 1706, 1635, 1456, 1369, 1285, 1150, 1108, 849, 785, 754 cm^{-1} .

(Z)-4-Phenyl-3-((trifluoromethylthio)methyl)but-3-en-2-one (18s) (xyd 562)



CAS number : unknown

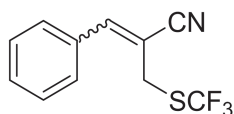
Formula : $\text{C}_{12}\text{H}_{11}\text{F}_3\text{SO}$

M.W. : 260.3 g/mol

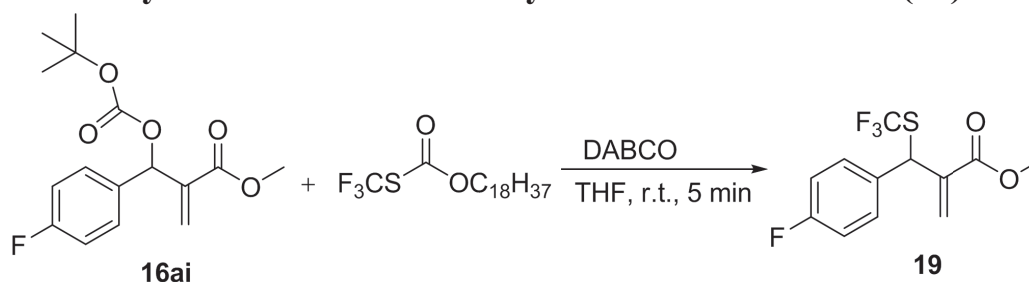
Yield : 65%

Aspect : yellow oil

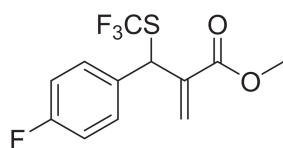
^1H NMR (CDCl_3 , 300 MHz): δ 7.71 (s, 1H), 7.47-7.48 (m, 5H), 4.02 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 198.0, 143.8, 135.7, 134.3, 130.8 (q, $^1J_{CF}=305.1$ Hz), 129.9, 129.4, 129.1, 25.8, 25.6 (q, $^3J_{CF}=2.6$ Hz); ^{19}F NMR (CDCl_3 , 282 MHz): -42.5; IR (neat) ν 2960, 1668, 1624, 1384, 1258, 1216, 1104, 1027, 965, 742, 695 cm^{-1} .

(E+Z)-3-Phenyl-2-((trifluoromethylthio)methyl)acrylonitrile (18t) (xyd 582)**CAS number** : unknown**Formula** : C₁₁H₈F₃SN**M.W.** : 243.2 g/mol**Yield** : 79%; *E/Z*=82:18**Aspect** : yellow oil

¹H NMR (CDCl₃, 300 MHz, *E* isomer): δ 7.75-7.78 (m, 2H), 7.44-7.46 (m, 3H), 7.15 (s, 1H), 3.85 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz, *E* isomer): δ 146.6, 132.6, 131.3, 130.3 (q, ¹J_{CF}=305.9 Hz), 129.3, 129.2, 117.2, 106.4, 35.4 (q, ²J_{CF}=2.5 Hz), 29.0 (q, ²J_{CF}=2.7 Hz, *Z* isomer); ¹⁹F NMR (CDCl₃, 282 MHz): -41.1 (*E* isomer), -41.7 (*Z* isomer); IR (neat) ν 2960, 2222, 1621, 1445, 1257, 1217, 1154, 1099, 1031, 933, 753, 689 cm⁻¹.

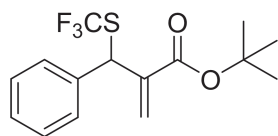
6.4.5 Use of Zard's reagent**Typical procedure for the use of Zard's reagent for trifluoromethylthiolation of Moita-Baylis-Hillman carbonate (19)**

In an oven-dried tube, methyl 2-((*tert*-butoxycarbonyloxy)(4-fluorophenyl)methyl)acrylate **16ai** (31 mg, 0.1 mmol) and DABCO (1.12 mg, 0.01 mmol) were dissolved in THF (2 mL) and followed by the addition of *O*-octadecyl *S*-trifluoromethyl carbonothioate (35.9 mg, 0.09 mmol). After 5 minutes, the reaction was quenched with 1M HCl and extracted with Et₂O. The combined organic layer was dried over MgSO₄ and concentrated in *vacuo*. The residue was purified by preparative TLC (petroleum ether/ethyl acetate: 20/1) to give methyl 2-((4-fluorophenyl)(trifluoromethylthio)methyl)acrylate **19** as colorless oil.

Methyl 2-((4-fluorophenyl)(trifluoromethylthio)methyl)acrylate (19) (xyd 580)**CAS number** : unknown**Formula** : C₁₂H₁₀F₄SO₂**M.W.** : 294.3 g/mol**Yield** : 78% (¹⁹F NMR)**Aspect** : colorless oil

¹H NMR (CDCl₃, 300 MHz): δ 7.32-7.37 (m, 2H), 7.00-7.06 (m, 2H), 6.55 (s, 1H), 6.10 (d, *J*=0.8 Hz, 1H), 5.55 (s, 1H), 3.74 (s, 3H); **¹³C NMR** (CDCl₃, 75 MHz): δ 165.5, 162.6 (d, ¹*J*_{CF}=246.2 Hz), 139.1, 133.4 (d, ³*J*_{CF}=3.1 Hz), 130.0 (d, ³*J*_{CF}=8.3 Hz), 129.9 (q, ¹*J*_{CF}=309.8 Hz), 128.7, 115.9 (d, ²*J*_{CF}=21.7 Hz), 52.6, 48.2 (q, ³*J*_{CF}=2.2 Hz); **¹⁹F NMR** (CDCl₃, 282 MHz): -41.8, -114.1. (Product contaminated with C₁₈H₃₇OH)

***tert*-Butyl 2-(phenyl(trifluoromethylthio)methyl)acrylate (20) (xyd 581)**



CAS number : unknown

Formula : C₁₅H₁₇F₄SO₂

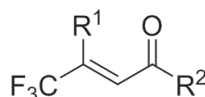
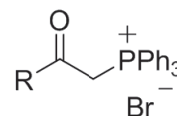
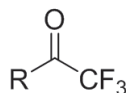
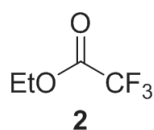
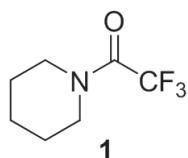
M.W. : 318.4 g/mol

Yield : 52% (¹⁹F NMR)

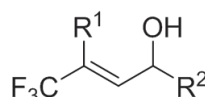
Aspect : white solid

¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.42 (m, 5H), 6.44 (s, 1H), 5.94 (s, 1H), 5.49 (s, 1H), 1.40 (s, 9H); **¹⁹F NMR** (CDCl₃, 282 MHz): -41.8. (mixed with thermodynamic SCF₃ product and C₁₈H₃₇OH)

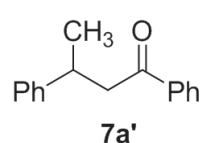
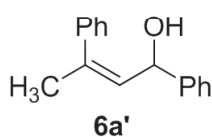
Formulas of molecules



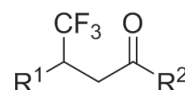
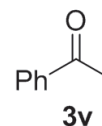
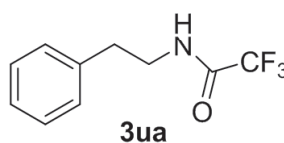
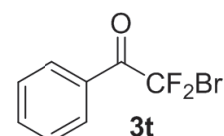
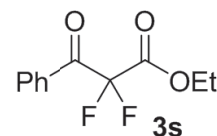
- 5a** R¹ = C₆H₅, R² = C₆H₅
5b R¹ = 4-OMeC₆H₄, R² = C₆H₅
5c R¹ = 4-BrC₆H₄, R² = C₆H₅
5d R¹ = 4-MeC₆H₄, R² = C₆H₅
5e R¹ = 3,4-Me₂C₆H₃, R² = C₆H₅
5f R¹ = 4-CF₃C₆H₄, R² = C₆H₅
5g R¹ = 4-ClC₆H₄, R² = C₆H₅
5h R¹ = C₆H₅, R² = 4-BrC₆H₄
5i R¹ = C₆H₅, R² = 4-ClC₆H₄
5j R¹ = C₆H₅, R² = 3-OMeC₆H₄
5k R¹ = C₆H₅, R² = 2-OMeC₆H₄
5l R¹ = C₆H₅, R² = 4-NO₂C₆H₄
5m R¹ = 4-ClC₆H₄, R² = 4-OMeC₆H₄



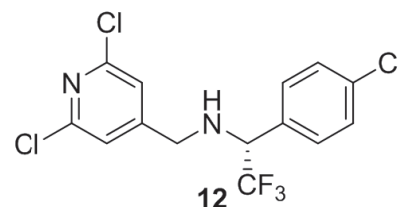
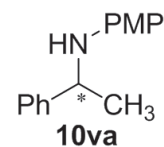
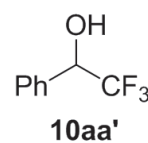
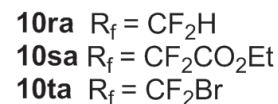
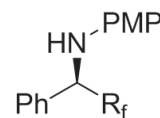
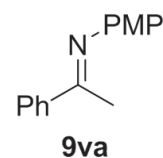
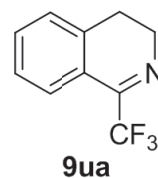
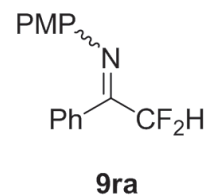
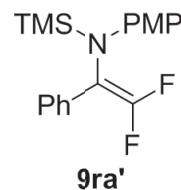
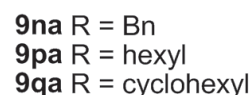
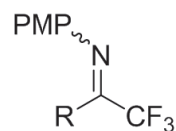
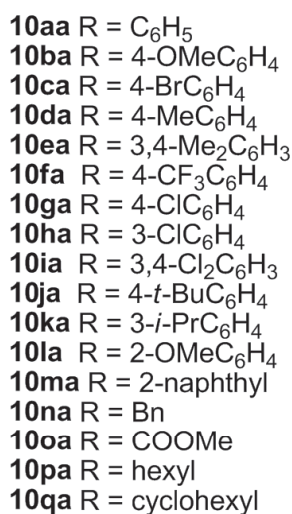
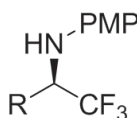
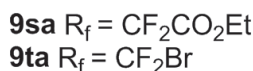
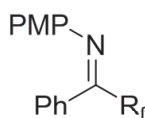
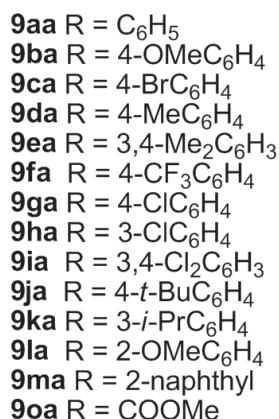
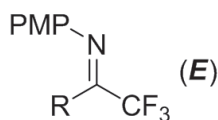
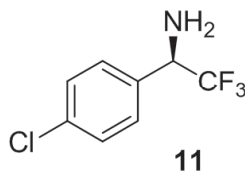
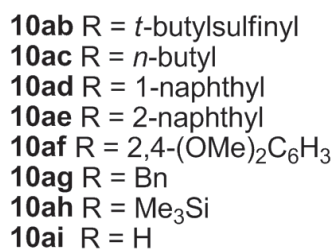
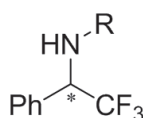
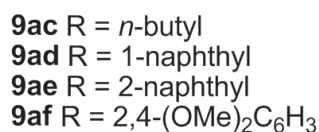
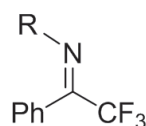
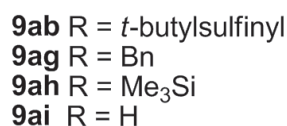
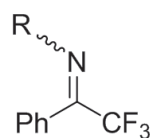
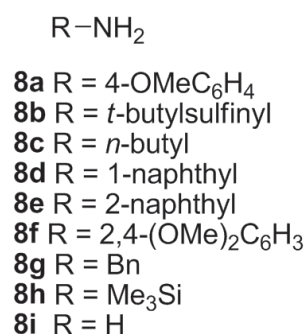
- 6a** R¹ = C₆H₅, R² = C₆H₅
6b R¹ = 4-OMeC₆H₄, R² = C₆H₅
6c R¹ = 4-BrC₆H₄, R² = C₆H₅
6d R¹ = 4-MeC₆H₄, R² = C₆H₅
6e R¹ = 3,4-Me₂C₆H₃, R² = C₆H₅
6f R¹ = 4-CF₃C₆H₄, R² = C₆H₅
6g R¹ = 4-ClC₆H₄, R² = C₆H₅
6h R¹ = C₆H₅, R² = 4-BrC₆H₄
6i R¹ = C₆H₅, R² = 4-ClC₆H₄
6j R¹ = C₆H₅, R² = 3-OMeC₆H₄
6k R¹ = C₆H₅, R² = 2-OMeC₆H₄
6l R¹ = C₆H₅, R² = 4-NO₂C₆H₄
6m R¹ = 4-ClC₆H₄, R² = 4-OMeC₆H₄



- 3a** R = C₆H₅
3b R = 4-OMeC₆H₄
3c R = 4-BrC₆H₄
3d R = 4-MeC₆H₄
3e R = 3,4-Me₂C₆H₃
3f R = 4-CF₃C₆H₄
3g R = 4-ClC₆H₄
3h R = 3-ClC₆H₄
3i R = 3,4-Cl₂C₆H₃
3j R = 4-*t*-BuC₆H₄
3k R = 3-*i*-PrC₆H₄
3l R = 2-OMeC₆H₄
3m R = 2-naphthyl
3n R = Bn
3o R = COOMe
3p R = hexyl
3q R = cyclohexyl



- 7a** R¹ = C₆H₅, R² = C₆H₅
7b R¹ = 4-OMeC₆H₄, R² = C₆H₅
7c R¹ = 4-BrC₆H₄, R² = C₆H₅
7d R¹ = 4-MeC₆H₄, R² = C₆H₅
7e R¹ = 3,4-Me₂C₆H₃, R² = C₆H₅
7f R¹ = 4-CF₃C₆H₄, R² = C₆H₅
7g R¹ = 4-ClC₆H₄, R² = C₆H₅
7h R¹ = C₆H₅, R² = 4-BrC₆H₄
7i R¹ = C₆H₅, R² = 4-ClC₆H₄
7j R¹ = C₆H₅, R² = 3-OMeC₆H₄
7k R¹ = C₆H₅, R² = 2-OMeC₆H₄
7l R¹ = C₆H₅, R² = 4-NO₂C₆H₄
7m R¹ = 4-ClC₆H₄, R² = 4-OMeC₆H₄
7n R¹ = Me, R² = C₆H₅
7o R¹ = Bn, R² = C₆H₅
7p R¹ = H, R² = Bn
7q R¹ = C₆H₅, R² = Me
7r R¹ = C₆H₅, R² = H



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- ¹³¹ We thank Dr. Vitaliy Petrik for the gift of the S₂(CF₃)₂ reagent.
- ¹³² We thank Dr. S. Zard for providing us with a sample of his reagent.

Curriculum Vitae

Educational Background

- 2011-2014 **INSA de Rouen (National Institute for Applied Sciences, Rouen)**, IRCOF, France
Ph.D. in organic chemistry
- 2008-2011 **Shanghai University**, College of Science
Master of Science degree in organic chemistry
 « Studies on the Application of Asymmetric Organocatalyzed Cascade Reaction in Synthesis of Quinolizidines »
 Basic Courses: Progress in Chemistry, Organic Synthesis and Mechanisms, Spectrum Identification of Organic Compounds, Scientific English for Chemistry
 GPA: top 5%
- 2004-2008 **Shanghai University**, College of Science
Bachelor of Engineering degree with several scholarships including special prize in applied chemistry
 Secretary of the information department and art department in students' board
 Basic Courses: Medicinal Chemistry, Biochemistry, Instrumental Analysis, Introduction of Spectroscopy, Analytical Chemistry, Organic Chemistry, Physical Chemistry, Mathematical Statistics for Chemistry,
 GPA: 3.5 (top 5%)

Publications

- Regio- and Stereocontrolled Nucleophilic Trifluoromethylthiolation of Morita-Baylis-Hillman Carbonates
X. Dai, D. Cahard*, *Synlett* (special cluster on organofluorine chemistry) DOI: 10.1055/s-0034-1379162.
- Enantioselective Synthesis of α -CF₃ Arylmethylamines by Ruthenium-Catalyzed Transfer Hydrogenation Reaction
X. Dai, D. Cahard*, *Adv. Synth. Catal.* **2014**, *356*, 1317 (highlighted in *Synfacts* **2014**, *10*, 0732)
- Iron (II) complexes are suitable catalysts for the isomerization of trifluoromethylated allylic alcohols. Synthesis of trifluoromethylated dihydrochalcones
 D. Cahard*, V. Bizet, X. Dai, S. Gaillard, J.L. Renaud*, *J. Fluorine Chem.* **2013**, *155*, 78 invitation to the especial issue for « Ojima's ACS award »
- One-pot three-component syntheses of indoloquinolizidine derivatives using an organocatalytic Michael Addition and subsequent Pictet-Spengler Cyclization
 X. Wu*, X. Dai, H. Fang, J. Chen, W. Cao, G. Zhao, *Chemistry: A European Journal* **2011**, *17*, 10510
- Organocatalyzed enantioselective one-pot three-component access to

indoloquinolizidines

X. Dai, X. Wu*, Y. Zhang, J. Chen, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 3034

- Organocatalyzed enantioselective one-pot three-component access to indoloquinolizidines by Michael addition-Pictet-Spengler sequence
X. Wu*, X. Dai, L. Nie, J. Chen, Z. Ren, W. Cao, G. Zhao, *Chemical Communication* **2010**, *46*, 2733

Communications

- School of Normandy Chemistry Doctor's day (JEDNC), Le Havre, 05/2014
Communication by poster:
Xiaoyang Dai, Dominique Cahard
Nucleophilic trifluoromethylthiolation of Baylis-Hillman Adducts
- 17th European Symposium on Fluorine Chemistry, Paris, 07/2013
Communication by poster:
Xiaoyang Dai, Dominique Cahard
Combination of ruthenium complex, amino alcohol and i-PrOH for enantioselective transfer hydrogenation of CF₃-ketimines

Other Experience

- | | |
|-----------|--|
| 2010 | ticket-service volunteer at Shanghai World Expo |
| 2008-2009 | secretary of Litong Machinery Parts Co., Ltd., Zhejiang |
| 2009 | translator and editor in a student union of Shanghai University, translating several chapters of a book from Chinese into English |
| 2008 | research associate in Shanghai Institute of Organic Chemistry, Chinese academy of Sciences where I improved the capability of searching reference and the sensitivity to the chemical research |

Other skills

Good English speaking and writing skills
Japanese Fair, passed JLPT-3
French Fair
Fluent user of Microsoft office

Résumé

Objectifs de la thèse

Le fluor moléculaire a été isolé en 1886 par le chimiste français Henri Moissan qui reçut le prix Nobel pour cette découverte. Le fluor est le 13^{ème} élément le plus abondant de l'écorce terrestre, il est présent principalement sous forme minérale de fluorure de calcium. Cependant, la nature ne sait pas facilement incorporer le fluor dans des molécules organiques; en effet, il n'existe qu'une dizaine de molécules organiques naturelles fluorées. Par contre, les chimistes ont élaborés des milliers de molécules fluorées par synthèse.

En raison des effets uniques de l'atome de fluor sur les molécules fluorées, effets stériques, électroniques, stéréoélectroniques, l'introduction d'atome(s) de fluor modifie les propriétés des molécules et notamment l'activité biologique. Ainsi, de nos jours, plus en plus de molécules bioactives possèdent un ou plusieurs atomes de fluor.

En particulier, le motif CF₃ existe fréquemment dans les produits pharmaceutiques et agrochimiques, et le motif SCF₃ rencontre un intérêt de plus en plus fort. Le plus souvent, ces motifs sont fixés sur des noyaux aromatiques et des oléfines, plus rarement sur des carbones sp³. Il est donc très utile de développer des nouvelles méthodologies pour la construction de molécules comportant les motifs Csp₃-CF₃ et Csp₃-SCF₃.

Pour la construction de molécules contenant le groupe trifluorométhyle, nous nous sommes concentrés sur la réaction de transfert d'hydrure par catalyse organométallique avec une emphase pour la synthèse asymétrique qui fournit un moyen efficace pour générer des molécules énantiopures. Dans une première partie, nous avons développé deux réactions de transfert d'hydrure catalysées par des complexes de métaux de transition :

- 1) l'isomérisation catalytique d'alcools allyliques trifluorométhylés par des complexes de fer (II) pour synthétiser différentes CF₃ dihydrochalcones (**Schéma 1, éq. a**)
- 2) le transfert d'hydrogène énantiosélectif de céto-imines trifluorométhylées par des complexes chiraux de ruthénium en utilisant l'isopropanol comme source d'hydrure pour

obtenir des amines trifluorométhylées optiquement actives (**Schéma 1, éq. b**)

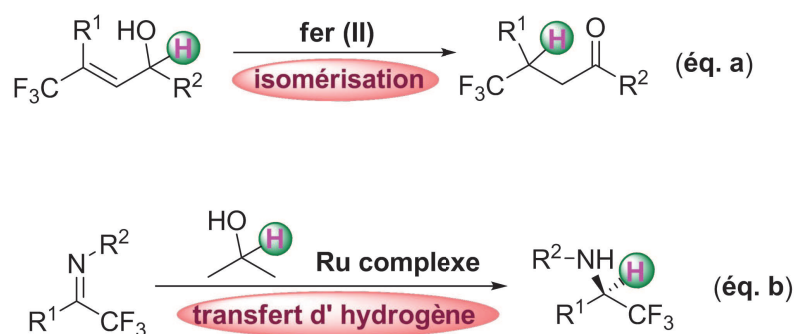


Schéma 1

Grâce à la forte électronégativité et la très forte lipophilie du groupe SCF₃, ce motif est devenu incontournable dans les produits pharmaceutiques et agrochimiques. Dans une seconde partie de la thèse, nous avons étudié la trifluorométhylthiolation allylique nucléophile de dérivés de Morita-Baylis-Hillman. Deux isomères sont anticipés pour la réaction de trifluorométhylthiolation. L'un est le produit thermodynamique portant une double liaison conjuguée avec le cycle aromatique (**Schéma 2, éq. a**). L'autre est le produit cinétique possédant la fonction alcène terminale (**Schéma 2, éq. b**).

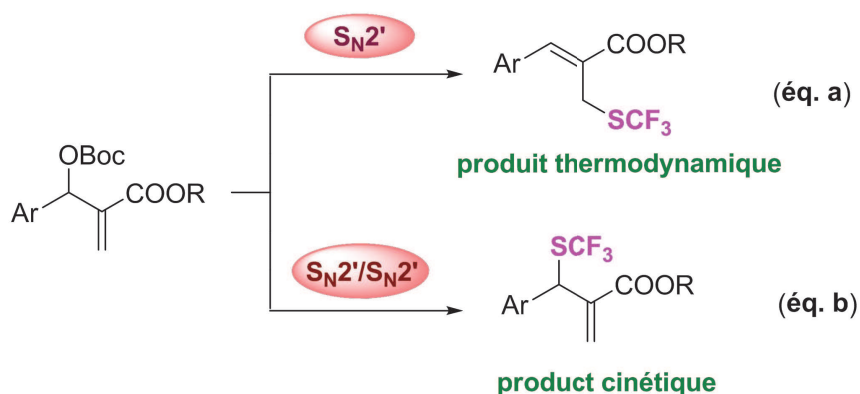


Schéma 2

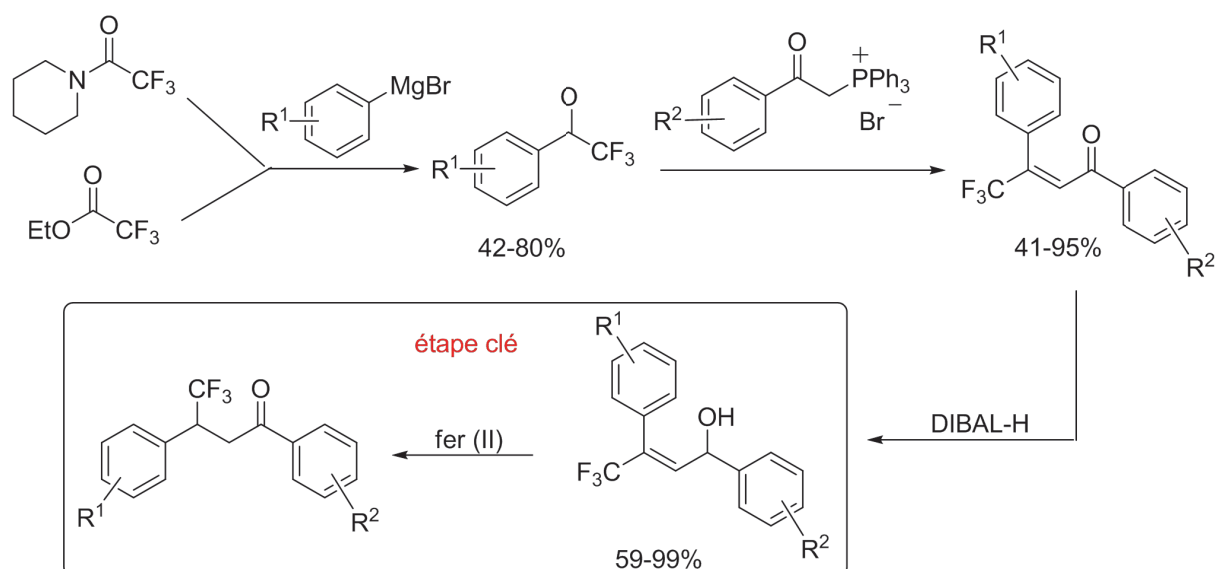
Première partie : Réactions de transfert d'hydrure.

1) Isomérisation d'alcools allyliques trifluorométhylés par des complexes de fer (II).

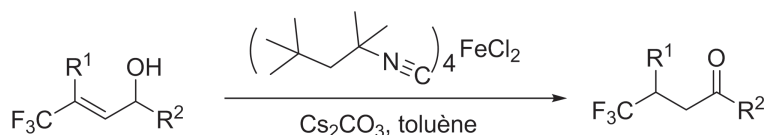
L'isomérisation d'alcools allyliques est un procédé de synthèse efficace, économique en atomes pour convertir des alcools allyliques en des composés carbonylés saturés. Cette

réaction d'isomérisation est équivalente à une réduction suivie d'une oxydation ou vice et versa. Les éléments du groupe 8 (Fe, Ru) et ceux du groupe 9 (Rh, Ir) sont les métaux les plus étudiés dans la réaction d'isomérisation d'alcools allyliques. Notre laboratoire a déjà étudié en détails cette réaction avec des complexes de ruthénium. Pour des raisons de coût, nous nous sommes intéressés à la catalyse par des complexes de fer et en particulier de fer (II) qui n'ont pas encore été rapportés en isomérisation d'alcools allyliques. Dans la littérature, seuls des complexes de fer (0) polycarbonyles, toxique car libérant du monoxyde de carbone, avait été engagé dans cette réaction.

Les substrats nécessaires à l'étude, les alcools allyliques trifluorométhylés, ont été obtenus selon le schéma réactionnel présenté **Schéma 3**.



Après étude des paramètres de la réaction, nous avons trouvé que la réaction fonctionne bien en utilisant un catalyseur de fer (II) tetra(isonitrile) en présence de Cs_2CO_3 comme base dans le toluène à température ambiante. Une série de dihydrochalcones a ainsi pu être préparée avec de bons rendements (**Tableau 1**). Globalement, les composés aromatiques riches ou déficients en électrons, qu'ils soient identiques ou non aux positions R^1 et R^2 , ont donné des bons rendements. Les alcools allyliques ayant un groupement R^1 aliphatique ont aussi donné de bons rendements en isomérisation.



entrée	R ¹	R ²	T (°C)	t (h)	conv. (%)	rdt. (%)
1	Ph	Ph	25	22	100	72
2	4-OMeC ₆ H ₄	Ph	40	22	100	76
3	4-BrC ₆ H ₄	Ph	40	21	100	72
4	4-MeC ₆ H ₄	Ph	40	22	100	75
5	3,4-MeC ₆ H ₃	Ph	40	23	100	69
6	4-CF ₃ C ₆ H ₄	Ph	40	13	100	65
7	4-ClC ₆ H ₄	Ph	40	23	100	74
8	Ph	4-BrC ₆ H ₄	40	23	100	85
9	Ph	4-ClC ₆ H ₄	40	22	100	69
10	Ph	3-OMeC ₆ H ₄	40	22	100	70
11	Ph	2-OMeC ₆ H ₄	100	5 jours	50	28
12	4-ClC ₆ H ₄	4-OMeC ₆ H ₄	40	42	87	49
13	Me	Ph	55	22	100	75
14	Bn	Ph	40	21	100	69

Tableau 1

Pour la première fois, nous avons exploité des complexes de fer (II) dans la réaction d'isomérisation d'alcools allyliques appliquée à la synthèse de dihydrochalcones trifluorométhylées.

2) Transfert d'hydrogène énantiosélectif de céto-imines trifluorométhylées par des complexes chiraux de ruthénium

Comme deuxième exemple de réaction asymétrique de transfert d'hydrure, nous avons développé le transfert d'hydrogène énantiosélectif sur des céto-imines trifluorométhylées avec la volonté d'utiliser une source simple de chiralité et une source d'hydrure pas chère pour obtenir des amines trifluorométhylées optiquement actives.

Les céto-imines trifluorométhylées requises pour notre étude ont été principalement synthétisées avec de bons rendements en utilisant des cétones trifluorométhylées et la

p-méthoxy aniline comme indiqué **Schéma 4**.

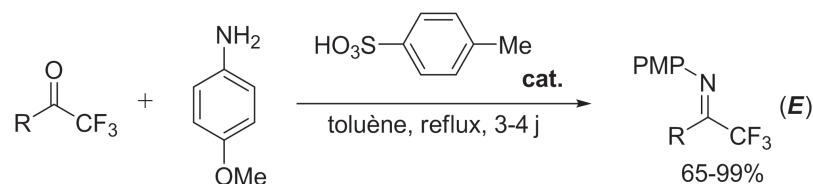


Schéma 4

Nous avons attribué la configuration *E* à l'imine avec le groupement R = 2-naphthyl par diffraction de rayon-X (**Figure 1**), par RMN ^{19}F , ^1H HOESY de l'imine avec le groupement R = phenyl (**Figure 2**) et par calculs DFT. Bien que la connaissance de la configuration de l'imine soit essentielle pour proposer des états de transition, les données de la littérature indiquent parfois l'isomère *E*, parfois le *Z*. Notre étude permet donc l'attribution de cette configuration.

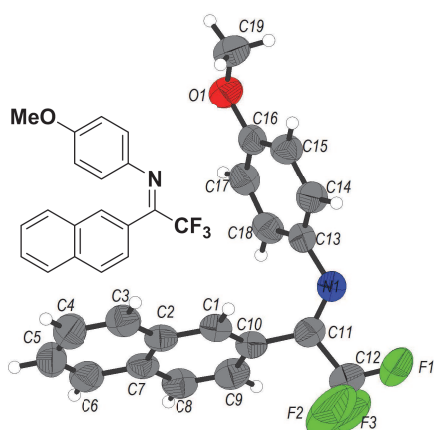


Figure 1 rayon-X

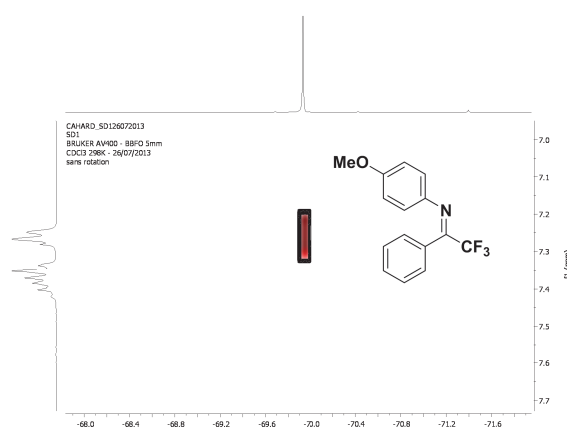
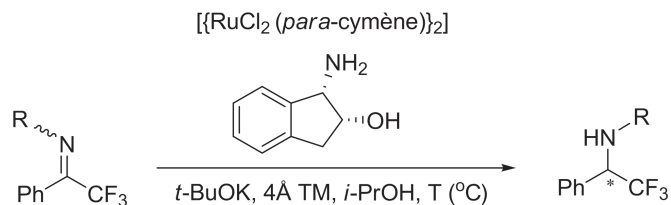


Figure 2 ^{19}F , ^1H HOESY

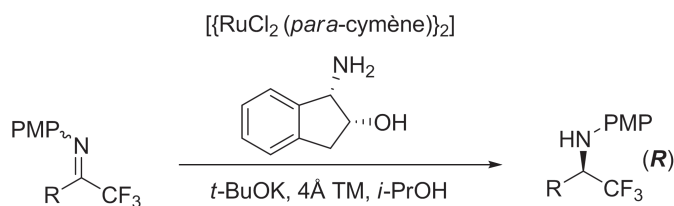
Après optimisation des conditions réactionnelles, nous avons choisi le ligand chiral (1*S*, 2*R*)-1-amino-2-indanol et la source de ruthénium [$\{\text{RuCl}_2(\textit{para}\text{-cymène})\}_2$] pour générer le catalyseur. Aussi, *t*-BuOK a été choisi comme base en présence de tamis moléculaire dans l'isopropanol qui agit en tant que solvant et source d'hydrure. Plusieurs substituants sur l'atome d'azote ont été testés : *p*-méthoxyphenyl (PMP), *t*-butylsulfinyl, *n*-butyl, naphthyl, 2,4-diméthoxyphenyl, benzyl, triméthylsilyl, ainsi que l'imine libre NH. La céto-imine avec le substituant PMP a donné les meilleurs rendements et énantiosélectivités (**Tableau 2**).



entrée	R	température (°C)	t (h)	rdt (%)	ee (%)
1	PMP	25	14	98	93 (<i>R</i>)
2	<i>t</i> -butylsulfinyl	40	14	0	-
3	<i>n</i> -butyl	40	1	0	-
4	1-naphthyl	25	14	99	72 (+)
5	2-naphthyl	25	15	99	84 (-)
6	2,4-(MeO) ₂ C ₆ H ₃	25	22	80	90 (-)
7	Bn	40-80	5 jours	86	0
8	Me ₃ Si	25	13.5	77	32 (nd)
9	H	25	14	99	32 (nd)

Tableau 2

Dans les conditions réactionnelles optimales, nous avons ensuite étudié la généralité de la réaction sur une série d'imines trifluorométhylées avec le substituant PMP sur l'atome d'azote. Différents groupements aromatiques ont été utilisés et ont conduit aux amines CF₃ correspondantes avec des rendements et des énantiosélectivités élevés en général (**Tableau 3**). La configuration absolue des amines CF₃ a été déterminée par polarimétrie et comparaison avec les données de la littérature.



entrée	R	température (°C)	t (h)	rdt (%)	ee (%)
1	C ₆ H ₅	25	14	98	93
2	4-MeOC ₆ H ₄	40	13.5	99	91
3	4-BrC ₆ H ₄	25	14	94	90
4	4-MeC ₆ H ₄	25	14	99	92
5	3,4-Me ₂ C ₆ H ₄	25	14	94	90
6	4-CF ₃ C ₆ H ₄	25	14	99	89
7	4-ClC ₆ H ₄	25	14	98	90
8	3-ClC ₆ H ₄	25	13	99	89
9	3,4-Cl ₂ C ₆ H ₄	25	13.5	81	84
10	4- <i>t</i> -BuC ₆ H ₄	40	14	99	92
11	3- <i>i</i> -PrC ₆ H ₄	25	14	98	91
12	2-MeOC ₆ H ₄	90	16	0	-
13	2-naphthyl	25	14	99	91

Tableau 3

Pour une application en synthèse d'un analogue de produit pour l'agrochimie, nous avons ciblé une molécule connue et utilisée comme agent de lutte contre les maladies agricoles et horticoles (Schéma 5).

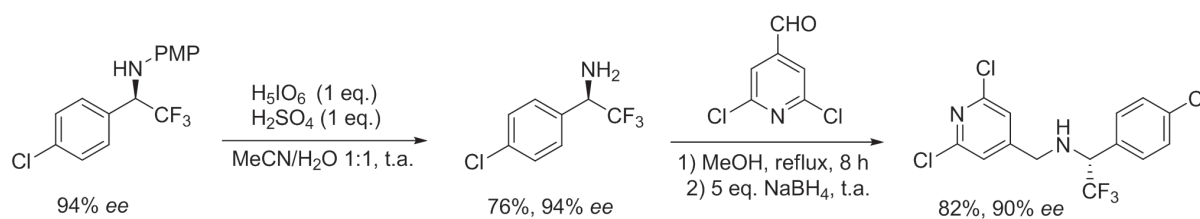
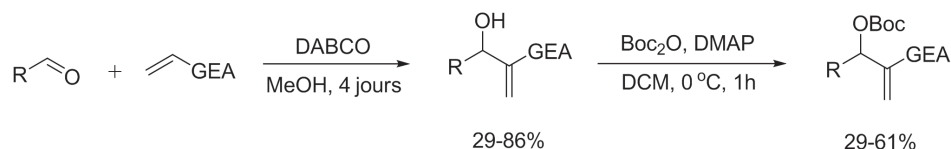


Schéma 5

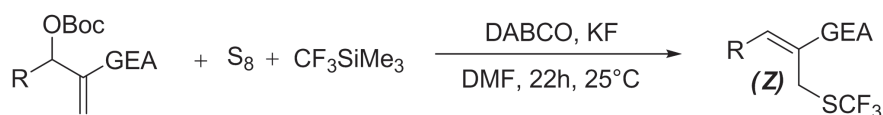
Deuxième partie : Trifluorométhylthiolation nucléophile d'adduits de Morita-Baylis-Hillman.

Dans la deuxième partie de ma thèse, nous avons étudié la trifluorométhylthiolation

nucléophile d'adduits de Morita-Baylis-Hillman pour la construction de motif Csp³-SCF₃. Les carbonates de Morita-Baylis-Hillman ont été obtenus par réaction de dicarbonate di-*tert*-butyle et les adduits de Morita-Baylis-Hillman qui ont été préparés par réaction d'aldéhydes avec des acrylates, l'acrylonitrile ou la méthyl vinyl cétone en présence de DABCO dans le méthanol (**Schéma 6**).

**Schéma 6**

Après différents tests de réactifs de trifluorométhylthiolation nucléophile et de conditions réactionnelles, nous avons décidé de choisir la combinaison de S₈/CF₃SiMe₃/KF pour générer l'anion SCF₃. Le DABCO a été choisi comme catalyseur dans le DMF.



GEA = ester, cétone, nitrile

entrée	R	GEA	rdt (%)	entrée	R	GEA	rdt (%)
1	Phenyl	CO ₂ Me	93	11	4-OMeC ₆ H ₄	CO ₂ Me	88
2	2-ClC ₆ H ₄	CO ₂ Me	79	12	4-MeC ₆ H ₄	CO ₂ Me	93
3	3-ClC ₆ H ₄	CO ₂ Me	80	13	1-naphthyl	CO ₂ Me	95
4	4-ClC ₆ H ₄	CO ₂ Me	86	14	2-naphthyl	CO ₂ Me	94
5	2,4-Cl ₂ C ₆ H ₃	CO ₂ Me	93	15	2-thienyl	CO ₂ Me	88
6	2-BrC ₆ H ₄	CO ₂ Me	86	16	PhCH ₂ CH ₂	CO ₂ Me	20
7	3-BrC ₆ H ₄	CO ₂ Me	69	17	Phenyl	CO ₂ Et	84
8	4-BrC ₆ H ₄	CO ₂ Me	99	18	Phenyl	CO ₂ <i>t</i> -Bu	28
9	4-FC ₆ H ₄	CO ₂ Me	94	19	Phenyl	COMe	65
10	2-OMeC ₆ H ₄	CO ₂ Me	64	20	Phenyl	CN	79

Tableau 4

Les carbonates de Morita-Baylis-Hillman avec des groupements aromatiques soit électroattracteurs (chloro, bromo, fluoro) soit électrodonneurs (méthyl, méthoxy) donnent des rendements bons à excellents après 22 heures de réaction (**Tableau 4**). Il en est de même pour

les groupes naphtyles et hétéro aromatiques. Par contre, les produits SCF₃ substitués avec des groupements R alkyles qui n'ont pas de conjugaison donnent de faibles rendements. Tous les esters et l'énone évalués ont donné lieu à un seul isomère *Z* alors que le nitrile a donné un mélange 82:18 d'isomères *E/Z* avec 79% rendement. En plus des carbonates de MBH, nous avons évalué un acétate, mais le rendement chute à 34% car nous avons dans ce cas un moins bon groupe partant (**Tableau 4**).

Les produits SCF₃ thermodynamiques entièrement conjugués obtenus dans ces conditions sont intéressants; néanmoins, il serait bon aussi de trouver un moyen efficace pour la synthèse des produits SCF₃ cinétiques présentant un centre stéréogène. Dans cet objectif, nous avons testé d'autres conditions sans métal en évaluant le réactif de Zard, F₃CSCO₂C₁₈H₃₇. La réaction s'est avérée très rapide et en opérant en un temps court, il a été possible d'isoler le produit cinétique SCF₃ sous catalyse par le DABCO avec 78% de rendement (**Schéma 7**).

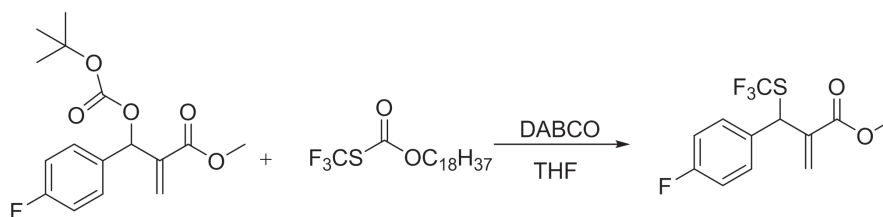


Schéma 7

Nous avons ainsi réalisé la trifluorométhylthiolation nucléophile sans métal de dérivés de Morita-Baylis-Hillman afin d'accéder de façon regio- et stéréocontrôlée à des produits soit thermodynamiques soit cinétiques (**Schéma 8**).

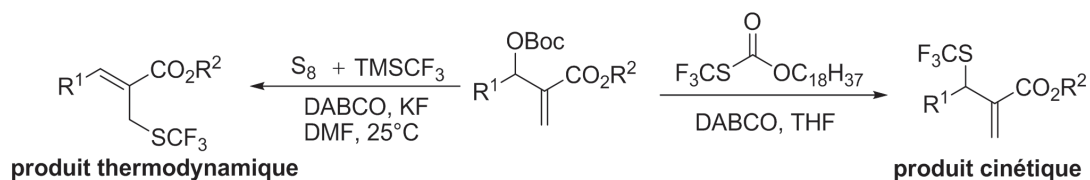
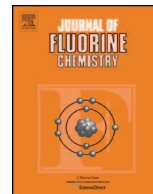


Schéma 8

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Iron(II) complexes are suitable catalysts for the isomerization of trifluoromethylated allylic alcohols. Synthesis of trifluoromethylated dihydrochalcones



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ARTICLE INFO

Article history:

Received 6 May 2013

Received in revised form 27 May 2013

Accepted 29 May 2013

Available online 15 June 2013

Keywords:

Iron

Fluorinated compounds

Catalysis

Isomerization

Dihydrochalcone

ABSTRACT

We demonstrated that iron(II) complexes can substitute platinum metals as well as iron(0) carbonyls for the isomerization of γ -trifluoromethylated allylic alcohols into β -trifluoromethylated ketones. In particular, iron(II)-tetra(isonitrile) complexes were employed for the synthesis of a series of trifluoromethylated dihydrochalcones variously decorated on each aromatic ring.

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1. Introduction

The isomerization of allylic alcohols into the corresponding saturated carbonyl compounds, often referred to as redox isomerization is an efficient, selective, redox- and atom-economical, one-pot isomerization process [1]. Second- and third-row transition metals, such as Ru, Rh, and Ir, have been widely used in isomerization of allylic alcohols [2]. Faced with an ever-increasing demand for precious metal, their replacement by abundant, less expensive and environmentally benign first-row transition metals is eagerly sought after. In this context, iron salts, which are very abundant on Earth and usually non-toxic, are the subject of current intense research [3]. It has been demonstrated that various iron(0) carbonyls that include homoleptic $[\text{Fe}(\text{CO})_5]$ [4], $[\text{Fe}_2(\text{CO})_9]$ [5], $[\text{Fe}_3(\text{CO})_{12}]$ [6] as well as heteroleptic $[(\text{bda})\text{Fe}(\text{CO})_3]$ ($\text{bda} = \text{trans-benzylideneacetone}$) [7] and $[(\text{COT})\text{Fe}(\text{CO})_3]$ ($\text{COT} = \text{cyclooctatetraene}$) [7] are catalytically active in the isomerization of allylic alcohols under irradiation conditions. Good evidence was provided that photodissociation of these complexes gave $[\text{Fe}(\text{CO})_3]$ that would act as the true catalytic species [8]. However, as a source of

carbon monoxide, iron(0) carbonyls are toxic and not really appropriate for the development of an asymmetric variant of the isomerization reaction. Consequently, we focused our attention on iron(II) catalysts which we could not find precedence in the literature as far as isomerization of allylic alcohols is concerned. In addition, a number of chiral iron(II)-catalysts have been successfully applied in asymmetric transfer hydrogenation and would be definitely evaluated in the isomerization reaction that is also a hydride transfer reaction [9,10,11]. We recently reported the first involvement of trifluoromethylated allylic alcohols in ruthenium-catalyzed isomerization [12]. The presence of the CF_3 group is beneficial to accelerate the hydride insertion step and thus allows higher reactivity in particular for trisubstituted $\text{C}=\text{C}$ bond of allylic alcohols which isomerizations are conducted under mild conditions. We and others demonstrated that a ruthenium hydride intermediate is generated from an allylic alcohol and a ruthenium complex in basic medium with concomitant formation of the corresponding α,β -unsaturated carbonyl derivative [13]. Thus, we hypothesized that: (i) such a discrete metal hydride might be an intermediate in iron-catalyzed allylic alcohol isomerization and (ii) iron complexes, able to catalyze transfer hydride reduction, might also be active in isomerization of allylic alcohols. For this study, we focused on three types of iron(II) complexes. One of the most efficient and easily amenable to structural modification type of iron complexes are the modular Morris complexes **C1–C3** (Fig. 1)

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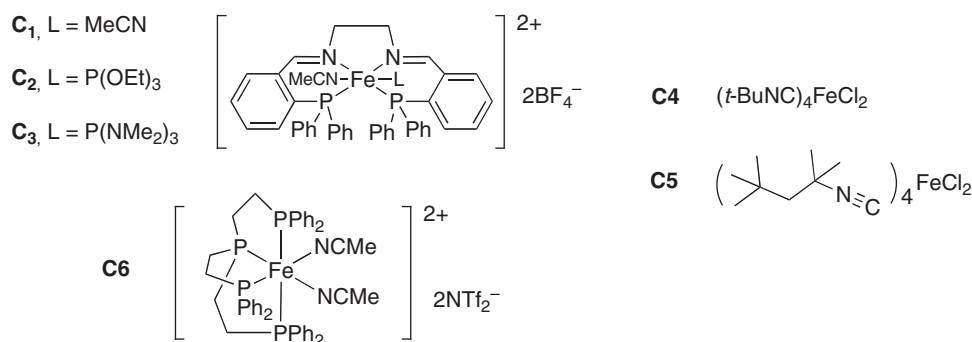


Fig. 1. Iron(II) catalysts.

[10]. Such complexes are able to reduce carbonyl functions through hydride transfer hydrogenation in high yields. Moreover, it is worth mentioning that reduction of enones in the presence of such iron complexes led to the corresponding saturated alcohols through reduction of the activated C=C double bond [10d,e]. Variation of the apical ligand nature (L = MeCN, P(OEt)₃, P(NMe₂)₃...) can also modify the reactivity of the iron complex. The second family of iron complexes are achiral analogues of the chiral iron-tetra(isonitrile) complexes reported by Reiser and coworkers (complexes **C**₄–**C**₅, Fig. 1) [11]. We also evaluated the complex [(PP₃)Fe(NCMe)₂][NTf₂]₂ (PP₃ = P(CH₂CH₂PPh₂)₃) **C**₆ [14].

Obviously, switching from ruthenium to iron in isomerization of allylic alcohols would create a fully cost-effective reaction. In order to demonstrate the ability of iron(II) complexes to catalyze the isomerization reaction, we targeted trifluoromethylated dihydrochalcones as fluoro analogues of these members of the flavonoid family [15]. Indeed, dihydrochalcones are key intermediates for the synthesis of bioactive molecules that possess a wide range of properties including anticancer, antiviral, antibacterial, antioxydant among others [16]. The search for novel substitution patterns for dihydrochalcones also included fluorinated motifs. Towards this goal, Surya Prakash, Mathew and coworkers have recently described a synthetic route to CF₃-dihydrochalcones through intermolecular Friedel-Crafts acylation and alkylation of 4,4,4-trifluorocrotonic acid with various arenes in the presence of excess triflic acid (Fig. 2, top) [17]. However, this methodology is limited in that only CF₃-dihydrochalcones bearing identically substituted aryls at C₁ and C₃ positions can be synthesized. Moreover, in this synthetic approach, dihydrochalcones are sometimes accompanied by other regioisomers. Konno and coworkers obtained some CF₃-dihydrochalcones through asymmetric rhodium-catalyzed 1,4-conjugate arylation

of 4,4,4-trifluoro-1-phenyl-2-buten-1-one, and hence aryl variety was generated only at C₃ (the aryl at C₁ was constantly a phenyl group) [18]. We herein propose an alternative route to single regioisomers of CF₃-dihydrochalcones that feature variously decorated aromatic rings through iron(II)-catalyzed isomerization of γ-CF₃ allylic alcohols (Fig. 2, bottom).

2. Results and discussion

In a first series of experiments, we examined the reaction conditions optimized for the ruthenium-catalyzed isomerization: 1 mol% catalyst and 1 equivalent of Cs₂CO₃ in toluene (0.5 M) at 25–50 °C. Under these conditions in the presence of allylic alcohol **1a**, the isomerization took place in the presence of iron(II) catalysts **C**₁–**C**₅ but failed with **C**₆ (Table 1). With catalyst **C**₆, we recovered the starting material quantitatively without any isomerized product. With Morris type catalysts **C**₁–**C**₃, the isomerization required a temperature of 50 °C to obtain full conversion of **1a**. The isomerization performed best with the tetra(isonitrile) catalysts **C**₄ and **C**₅ at 25 °C for 22 h providing the desired β-trifluoromethylated ketone **2a** in up to 72% yield after silica gel column chromatography (Table 1, entry 5). When the reaction was run at 50 °C with **C**₅, full conversion was reached within 7 h, albeit in a much lower isolated yield due to the concomitant formation of ketolisation byproducts that were favoured at higher temperature (Table 1, entry 6). Advantageously, catalysts **C**₄ and **C**₅ are easily synthesized by treatment of the corresponding isocyanides with FeCl₂·4H₂O in methanol. We selected the iron(II)-tetra(isonitrile) catalyst **C**₅ for further investigation of reaction parameters and substrate scope.

The solvent effect was evaluated next (Table 2, entries 1–6). The reaction failed in CHCl₃ and MeOH but the isomerization reaction

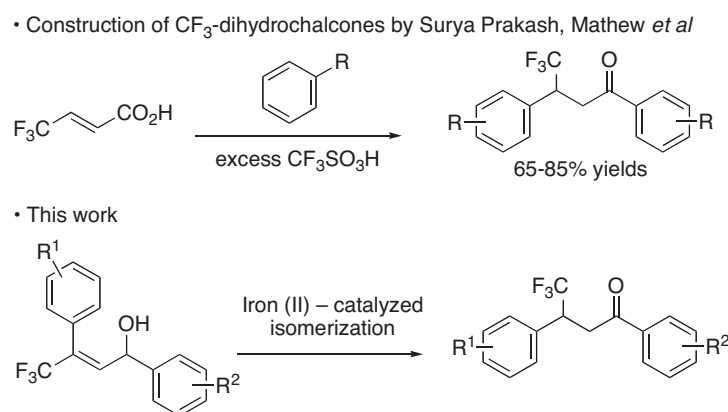
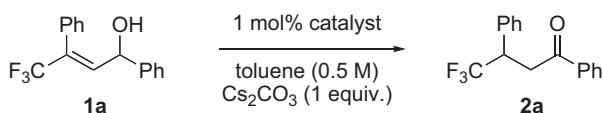


Fig. 2. Proposed investigation.

Table 1
Catalyst screening.

Entry	Catalyst	T ($^\circ\text{C}$)	Time (h)	Conv. (%) ^a	2 (Yield %) ^b
1	C1	50	18	93	70
2	C2	50	22	67	24
3	C3	50	22	88	40
4	C4	25	21	100	69
5	C5	25	22	100	72
6	C5	50	7	100	35
7	C6	50	27	0	–

^a Conversion was determined by ^{19}F NMR using trifluorotoluene as internal standard.

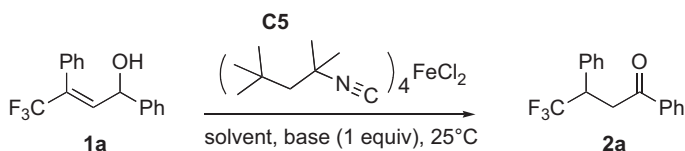
^b Yield of isolated product by column chromatography.

took place in toluene, CH_2Cl_2 , THF and CH_3CN with preference for toluene that afforded the β -trifluoromethylated ketone **2a** in the highest isolated yield. The isomerization was conducted with and without base and we found that base-free conditions are not appropriate for the isomerization process (Table 2, entry 7). This observation may indicate that the reaction proceeds through iron alkoxide intermediate by displacement of a chloride ligand. The conversions were not complete with *t*-BuOK and K_2CO_3 whereas full conversion was obtained in the presence of Cs_2CO_3 (Table 2, entries 8,9 vs 1). The molar ratio of catalyst **C5** could be reduced to 0.1 mol% (Table 2, entry 10); however, although full conversion was reached, the reaction yield is lower compared to the reaction run with 1 mol% of catalyst. A test experiment without catalyst but with Cs_2CO_3 confirmed that the catalyst is required for the isomerization; nevertheless, with *t*-BuOK alone the reaction, although very messy, produced ca. 15% of **2** [19].

Under the optimal conditions, the substrate scope was investigated by employing a variety of bis-aryl allylic alcohols in order to synthesize β - CF_3 dihydrochalcones that feature diversely decorated Ar^1 and Ar^2 aryl groups. The results are summarized in Table 3. Substrates featuring Ar^1 substituted with electron-donating, electron-neutral, and electron-withdrawing groups gave the dihydrochalcones in a similar range of yield 65–76%. Halogen and electron-donating substituents on Ar^2 are suitable with the

exception of the 2-methoxy substituent (substrate **1j**, Table 3, entry 10) that gave only 28% yield. This poor yield might result of steric hindrance or, more likely, a chelation between the oxygen atom of the methoxy group and the iron alkoxide. In addition, a 4-nitro substituent (substrate **1l**, Table 3, entry 12) did not react at all. In this latter case, the strong electron-withdrawing NO_2 group renders more acidic the hydrogen atom at C_1 . In other words, this hydrogen atom has a lower hydride character and could be responsible for the poor reactivity of substrate **1l**.

The stereocontrol of $\text{C}(\text{sp}^3)\text{-CF}_3$ stereogenic centres at the β -position of the carbonyl function in dihydrochalcone motif would be of great added value to the method [18,20]. Towards this goal, we have applied our recently published approach consisting in the enantiospecific *syn*-specific 1,3-hydride transfer starting from optically enriched allylic alcohols **1a** [12a]. The tetra(isonitrile) catalysts **C4** and **C5** gave the isomerized product in only 34% ee with 36% enantiospecificity, but Morris complex **C1** afforded the β - CF_3 dihydrochalcone **2a** in 84% ee and 89% es (Table 4). These results demonstrate that the iron(II)-catalyzed isomerization could proceed enantiospecifically through *syn*-specific 1,3-hydride shift. In addition, we attempted the enantioselective isomerization from racemic allylic alcohol **1a** and a chiral Morris-type catalyst featuring an enantiopure diamine (*R,R*)-1,2-diphenylethylenediamine. Unfortunately however, the result was a very poor ee value

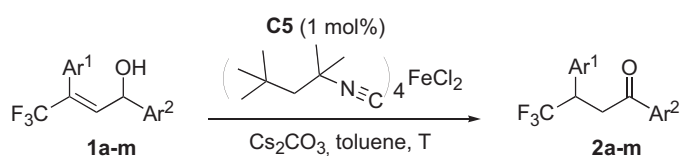
Table 2
Screening of reaction parameters.

Entry	Solvent	Base	C5 (x mol%)	Time (h)	2 (Yield %) ^a
1	Toluene	Cs_2CO_3	1	22	72
2	CH_2Cl_2	Cs_2CO_3	1	47	60
3	CHCl_3	Cs_2CO_3	1	28	–
4	THF	Cs_2CO_3	1	52	42
5	MeOH	Cs_2CO_3	1	25	–
6	MeCN	Cs_2CO_3	1	25	60
7	Toluene	Without	1	24	–
8	Toluene	K_2CO_3	1	22	16 ^b
9	Toluene	<i>t</i> -BuOK	1	22	58 ^b
10	Toluene	Cs_2CO_3	0.1	18	56

^a Yield of isolated product by column chromatography.

^b Conversion determined by ^{19}F NMR.

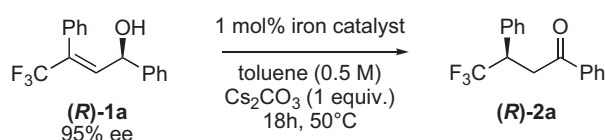
Table 3
β-CF₃ Dihydrochalcone syntheses through iron(II)-catalyzed isomerization.



Entry	Ar ¹	Ar ²	T (°C)	Time (h)	2	2 (Yield %) ^a
1	Ph	Ph	25	22	2a	72
2	4-OMeC ₆ H ₄	Ph	40	22	2b	76
3	4-BrC ₆ H ₄	Ph	40	21	2c	72
4	4-MeC ₆ H ₄	Ph	40	22	2d	75
5	3,4-Me ₂ C ₆ H ₃	Ph	40	23	2e	69
6	4-CF ₃ C ₆ H ₄	Ph	40	13	2f	65
7	4-ClC ₆ H ₄	Ph	40	23	2g	74
8	Ph	4-BrC ₆ H ₄	40	23	2h	85
9	Ph	4-ClC ₆ H ₄	40	22	2i	69
10	Ph	2-OMeC ₆ H ₄	100	120	2j	28
11	Ph	3-OMeC ₆ H ₄	40	22	2k	70
12	Ph	4-NO ₂ C ₆ H ₄	40–80	48	2l	–
13	4-ClC ₆ H ₄	4-OMeC ₆ H ₄	40	42	2m	49

^a Yield of isolated product by column chromatography.

Table 4
Isomerization of enantioenriched allylic alcohol **1a**.



Entry	Catalyst	Yield (%) ^a	Ee (%) ^b	Es (%) ^c
1	C4 or C5	75	34	36
2	C1	86	84	89

^a Yield of isolated product.

^b Enantiomeric excess measured by HPLC using OD-H column.

^c Enantiospecificity: Es = 100 × (ee product)/(ee reactant).

(<10% ee). This outcome may indicate that a similar mechanism underpins both ruthenium and iron catalysts. Further investigations are required in order to gain mechanistic insights.

3. Conclusion

We have demonstrated for the first time the potential of iron(II)-catalysts, in particular dichlorotetra(isonitrile) iron(II) in the isomerization of a series of trifluoromethylated allylic alcohols. Indeed, iron(II) catalysts appear to represent a cost-effective replacement of platinum metal catalysts and an environmentally friendly substitute for toxic iron(0) complexes. A series of β-CF₃ dihydrochalcones diversely decorated on each aromatic rings have been synthesized in yields ranging from 28 to 85%. The mechanism of this transformation in the presence of iron catalyst remains elusive, but we have demonstrated a high enantiospecific process from enantioenriched allylic alcohol leading to optically enriched β-CF₃ dihydrochalcone in up to 84% ee. Further applications and mechanistic investigations are in progress in our laboratories.

4. Experimental

4.1. General remarks

¹H (300 MHz), ¹³C (75.5 MHz) and ¹⁹F (282 MHz) NMR spectra were recorded on Bruker AVANCE 300. Chemical shifts in NMR

spectra are reported in parts per million from TMS or CFCl₃ resonance as the internal standard. IR spectra were recorded on a Perkin-Elmer IRFT 1650 spectrometer. The conversions were determined by ¹⁹F NMR. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. Toluene was distilled from sodium benzophenone under a positive pressure of nitrogen and degassed before use. The allylic alcohols were prepared using literature methods [12a].

4.2. Representative procedure for the isomerization

In a Schlenk tube under inert atmosphere, were added the (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-ol **1a** (278.27 mg, 1 mmol), degassed toluene (2 mL), caesium carbonate (325.8 mg, 1 mmol), and iron catalyst **C5** (6.84 mg, 1 mol%). The reaction was conducted at 25 °C for 22 h until the signal of starting allylic alcohol disappeared by ¹⁹F NMR analysis. Then, the reaction mixture was filtered through a pad of celite, concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 99/1) to give the desired 4,4,4-trifluoro-1,3-diphenylbutan-1-one **2a**. Yield: 72%; white solid (mp = 66 °C). ¹H NMR (CDCl₃) δ 3.52 (dd, 1H, *J* = 17.8 Hz, *J* = 4.3 Hz), 3.64 (dd, 1H, *J* = 17.8 Hz, *J* = 8.8 Hz), 4.11–4.25 (m, 1H), 7.18–7.87 (m, 10H); ¹³C NMR (CDCl₃) δ 38.4 (q, *J* = 2.0 Hz), 44.9 (q, *J* = 27.4 Hz), 127.1 (q, *J* = 279.5 Hz), 128.2, 128.4, 128.8,

128.9, 129.2, 133.7, 134.7 (q, $J = 1.9$ Hz), 136.4, 195.4; ^{19}F NMR (CDCl_3) δ -70.2 (d, $J = 9.7$ Hz); HRMS Calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}$ (M^+), 278.0918, Found 278.0920; IR (neat) ν 3068, 1680, 1300, 1250, 1187, 1153, 1103 cm^{-1} .

Acknowledgments

This work is promoted by the Interregional CRUNCH Network. V.B. thanks the Région Haute-Normandie for a PhD fellowship. X.D. thanks the China Scholarship Council for a PhD fellowship.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jfluchem.2013.05.028>.

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Enantioselective Synthesis of α -Trifluoromethyl Arylmethylamines by Ruthenium-Catalyzed Transfer Hydrogenation Reaction

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Received: December 10, 2013; Published online: March 27, 2014

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201301115>.

Abstract: A simple combination of dichloro(*para*-cymene)ruthenium(II) dimer, a chiral amino alcohol and isopropyl alcohol allowed for *in-situ* generation of the bifunctional catalyst responsible for the transfer hydrogenation reaction of trifluoromethyl ketimines in excellent yields with high enantioselectivi-

ties (up to 93% *ee*). Herein, we describe the optimization, scope, limitations, and applications of the method.

Keywords: amines; enantioselectivity; fluorine; ruthenium; transfer hydrogenation

Introduction

The trifluoromethyl group has been increasingly employed in the organic synthesis of pharmaceutical and agrochemical compounds, and outstanding results have recently emerged for the trifluoromethylation of arenes and heteroarenes.^[1] Concurrently, innovation in methods for the construction of *sp*³ carbons featuring a CF₃ group is steadily progressing.^[2] In this context, and emphasizing chiral species, α -trifluoromethyl amines hold great potential in diversifying the family of chiral amines. Indeed, chiral amines have a broad application, being prevalent motifs in natural products and in synthetic biologically active compounds. Chiral amines also find widespread application in asymmetric synthesis as chiral auxiliaries, organocatalysts, and as chiral bases.^[3] In addition, the trifluoroethylamine motif RCH(CF₃)NH has emerged as a remarkable surrogate of the natural peptide bond in the area of peptide mimics.^[4] Peptide analogues featuring this fluorinated motif display both retarded proteolytic degradation and enhanced permeability through biological barriers. Furthermore, a number of drug candidates feature the trifluoroethylamine motif such as the cathepsin K inhibitor Odanacatib,^[5] the anticancer agent CF₃-Ac-Docetaxel,^[6] as well as others.^[7] Several characteristic effects of fluorine can account for the importance of biologically active α -trifluoromethyl amino compounds. Indeed, the trifluoromethyl group reduces the basicity of an adjacent amine function

while retaining its ability to act as an H-bond donor. The C–N–C bond angle of (CF₃)CH–NH–CH is close to the 120° observed with an amide, and the C–CF₃ bond is isopolar with a carbonyl function.^[8] In addition, the replacement of the planar amide bond by the CH(CF₃)NH motif presents structural analogy with the tetrahedral proteolytic transition state associated with peptides.

The asymmetric construction of the stereogenic carbon centre in α -trifluoromethyl amines has been achieved through three key disconnections as depicted in Figure 1. In view of the simple preparation of ketimines from the corresponding trifluoromethyl ketones, it is not surprising that several approaches were based on the C=N bond reduction. Notably, this was achieved by enantioselective palladium-catalyzed hydrogenation of either α -trifluoromethyl imino esters,^[9]

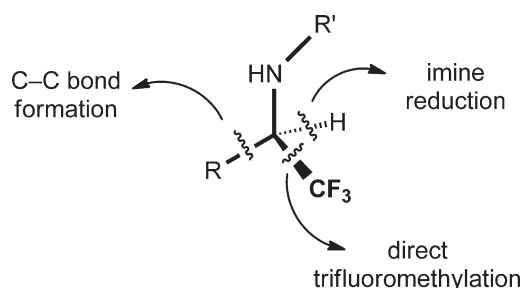


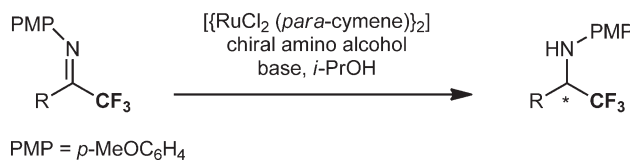
Figure 1. Key disconnections to access enantioenriched α -trifluoromethyl amines.

or from aryl and alkyl ketimines^[10] under high pressure of hydrogen in up to 91 and 94% *ee*, respectively. To avoid handling high pressure H₂ gas, Akiyama's group reported a highly enantioselective Brønsted acid-organocatalyzed transfer hydrogenation of aromatic and heteroaromatic trifluoromethyl ketimines (up to 98% *ee*). This group used benzothiazoline as a source of hydride and chiral phosphoric acid as a source of chirality.^[11] More recently, Benaglia's group proposed the enantioselective Lewis base-organocatalyzed hydrosilylation of not only aryl but also alkyl ketimines by means of trichlorosilane in up to 98% *ee*.^[12] Diastereoselective reductive aminations were also reported exploiting either simple amino acids^[13] or *N*-*tert*-butanesulfonamide^[14] as chiral auxiliaries to get high *dr* values. In addition, *N*-benzyl trifluoromethyl ketimines were catalytically isomerized into α -trifluoromethyl amines with the aid of chiral bases.^[15] As an alternative, the C–C bond disconnection has also been investigated through direct nucleophilic trifluoromethylation of aldimines with the Rupprecht–Prakash reagent.^[16] The other C–C bond could be constructed starting from trifluoroacetaldehyde imines, hydrazones, or *N,O*-acetals of trifluoroacetaldehyde;^[17] for example, the reaction of the acetal with arylboroxines and a Pd(II)/chiral pyridine-oxazolidine complex afforded enantioenriched secondary α -trifluoromethyl amines.^[18] Although some of these methods allowed high stereoselectivities, some drawbacks still limit scalability and transfer to other applications (of concern are the use of toxic reagents, and expensive sources of chirality). In addition, a method applicable to non-fluorinated substrates may prove ineffective on fluorinated analogues as observed in the hydrogenation of *N*-arylimines catalyzed by iridium bis(phosphine) complexes.^[19]

Of the different approaches for the reduction of imines, the asymmetric transfer hydrogenation (ATH) has attracted considerable attention due to its operational simplicity in not requiring the handling of hazardous hydrogen gas, metallic hydrides, or silanes. Other advantages are that a low loading of metal catalyst can be used, and purification of products is facilitated thanks to the formation of volatile by-products, such as acetone or carbon dioxide. In this context, Akiyama's pioneering work on chiral phosphoric acid-catalyzed transfer hydrogenation paved a new route for chiral α -trifluoromethyl amines.^[11] Recently, our group illustrated an efficient ruthenium-catalyzed hydride transfer in the isomerization of trifluoromethyl allylic alcohols.^[20] As a new example of hydride transfer applied to fluorinated molecules, we herein disclose the first enantioselective ruthenium-catalyzed transfer hydrogenation of trifluoromethyl ketimines that has the advantage of both using isopropyl alcohol as a simple source of hydride and an inexpensive amino alcohol as a source of chirality (Scheme 1).

This work:

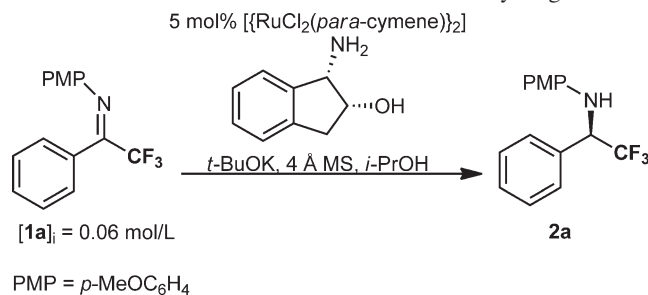
- enantioselective approach
- ruthenium-catalyzed transfer hydrogenation
- chiral amino alcohol as source of chirality
- isopropyl alcohol as source of hydrogen donor



Scheme 1. Our approach towards optically enriched α -trifluoromethyl amines.

Results and Discussion

The first series of experiments examined the asymmetric transfer hydrogenation of ketimine **1a** (Scheme 1, R = C₆H₅) in a 5:2 formic acid-triethylamine azeotropic mixture with $\{[\text{RuCl}[(S,S)\text{-TsDPEN}](\eta^6\textit{-para-cymene})]\}$ (TsDPEN = *N*-*para*-tosyl-1,2-diphenylethylenediamine) under Noyori's conditions.^[21] The reaction proceeded in moderate to good enantioselectivities (*ee* up to 81%); however, the yield of the expected chiral α -CF₃ amine **2a** did not exceed 58% because of the formation of 2,2,2-trifluoro-1-phenylethanol as a side product. To avoid the ketimine hydrolysis we modified the reaction parameters, in particular the ratio formic acid:triethylamine and the use of isopropyl alcohol as an alternative hydrogen source; however, again, the yield in **2a** was not enhanced. Thus, we turned our attention to a catalytic transfer hydrogenation system using *N,O*-type ligands to perform the reduction of the trifluoromethyl ketimine **1a**. For this purpose, we were inspired by the independent works of Noyori,^[22] Wills,^[23] Püntener,^[24] and Guijarro and Yus^[25] on related ATH of non-fluorinated ketones and ketimines. Specifically, this latter work described the diastereoselective transfer hydrogenation of optically pure *N*-(*tert*-butylsulfinyl)imines in the presence of an achiral amino alcohol ligand, or a chiral ligand with matched effect.^[25a,b] With regard to this work, we decided to examine an enantioselective version by means of prochiral ketimines and chiral ruthenium complexes featuring an optically pure amino alcohol ligand. Because *N,O*-type ligands are incompatible with the formic acid-triethylamine reduction system,^[26] we used isopropyl alcohol as hydrogen donor. We first selected a simple achiral ligand, 2-amino-2-methylpropan-1-ol, in combination with $\{[\text{RuCl}_2(\textit{para-cymene})]_2\}$ at room temperature in isopropyl alcohol. Pleasingly, the expected α -trifluoromethyl amine was obtained in 88% yield without 2,2,2-trifluoro-1-phenylethanol side product. The next step was obviously to evaluate a chiral non-racemic amino alcohol ligand; to this end, we selected (1*S*,2*R*)-1-amino-2-in-

Table 1. Optimization of reaction conditions for the enantioselective transfer hydrogenation of ketimine **1a**.


Run	Base	Ratio Ru dimer/L ^[a] /base	Temperature [°C]	Time [h]	Yield ^[b] [%]	<i>ee</i> [%]
1	KOH	1:2:5	25	14	> 98	92
2	<i>t</i> -BuOK	1:2:5	25	14	> 98	93
3	<i>i</i> -PrONa	1:2:5	25	14	> 98	93
4	Cs ₂ CO ₃	1:2:5	25	14	0	-
5	K ₂ CO ₃	1:2:5	25	14	0	-
6	<i>t</i> -BuOK	1:2:5	0	21	59	94
7	<i>t</i> -BuOK	1:2:5	40	5	> 98	93
8	<i>t</i> -BuOK	1:2:5	80	5	> 98	92
9	<i>t</i> -BuOK	1:2:5 ^[c]	25	14	79	93
10	<i>t</i> -BuOK	1:2:5 ^[c]	40	14	> 98	91
11	<i>t</i> -BuOK	1:4:5	25	22	87	93
12	<i>t</i> -BuOK	1:2:10	25	14	> 98	93
13	<i>t</i> -BuOK	1:2:5 ^[d]	25	14	> 98	87
14	<i>t</i> -BuOK	1:2:5 ^[e]	25–90	18	0 ^[f]	-

^[a] L = ligand.

^[b] Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

^[c] 3 mol% of ruthenium dimer was used.

^[d] $[\{\text{RuCl}_2(\text{benzene})\}_2]$ was used.

^[e] $[\text{RuCp}^*(\text{ACN})_3]^+\text{PF}_6^-$ was used.

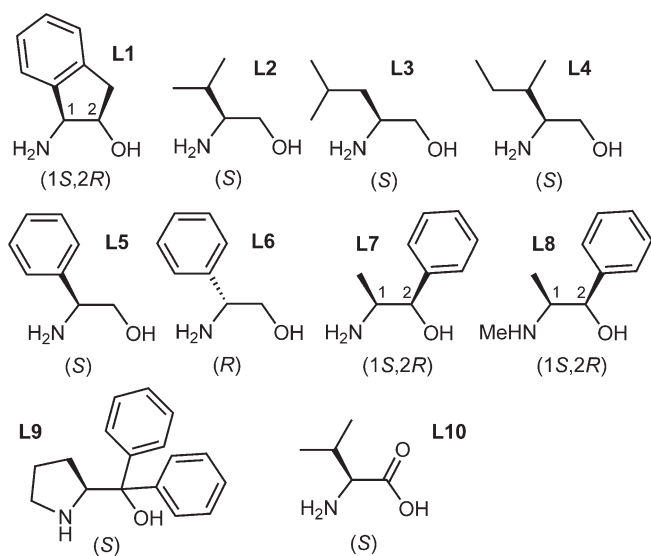
^[f] Only 2,2,2-trifluoro-1-phenylethanol was obtained.

danol that gave an excellent 93% *ee* value. With these suitable conditions in hand, we next conducted the optimization of the reaction conditions by scrutinizing the nature of the base, the ratio of the reagents, the imine concentration, the temperature, and the source of ruthenium (Table 1).

A base was essential for the reaction and its nature appeared crucial for the reactivity with a strong requirement for alkoxides over carbonates; indeed, K₂CO₃ and Cs₂CO₃ did not allow the reaction whereas KOH, *i*-PrONa and *t*-BuOK gave full conversions of the starting ketimine **1a** (Table 1, runs 1–5). We chose to keep *t*-BuOK as the base to study the effect of the temperature on the course of the reaction. At 0 °C, the reaction was not complete, even after a prolonged reaction time, whereas an increase of the temperature allowed us to significantly reduce the reaction time without impacting the enantioselectivity; in the range 0–60 °C the *ee* value difference was only 2% (Table 1, runs 6–8). The optimal amount of catalyst was established at 5 mol% with a ratio Ru dimer/ligand/base of 1:2:5. A lower loading of catalyst had the effect of lowering the conversion for a fixed reaction time. The same tendency was also observed when

the quantity of ligand was doubled. Moreover, twice the amount of base did not improve the reaction. It is important to note that these changes had a very small impact on the enantioselectivities (Table 1, runs 9–12). The concentration of ketimine **1a** in isopropyl alcohol was fixed at 0.06 M and variations were conducted in the range 0.01–0.2 M; but, here again, no perceptible effect was observed on the enantioselectivity. These experiments were conducted with the aid of a catalyst prepared *in-situ* by heating, at reflux, a mixture of $[\{\text{RuCl}_2(\textit{para}\text{-cymene})\}_2]$, (1*S*,2*R*)-1-amino-2-indanol, and 4 Å molecular sieves in isopropyl alcohol. We found that changing the ruthenium source to $[\{\text{RuCl}_2(\text{benzene})\}_2]$, showing a less bulky arene moiety, lowered the *ee* value of **2a** to 87% (Table 1, run 13). Alkylated η^6 -arene such as the η^6 -*para*-cymene enhanced stabilization of the transition state due to the increased π -donation of the arene as well as contributing to a favourable secondary C(*sp*³)-H/ π interaction with the aryl moiety of the substrate.^[27] The use of $[\text{RuCp}^*(\text{ACN})_3]^+\text{PF}_6^-$ (Cp* = η^5 -pentamethylcyclopentadienyl, ACN = CH₃CN) showed no efficiency, yielding the 2,2,2-trifluoro-1-phenylethanol as the sole product (Table 1, run 14).

Table 2. Screening of chiral ligands in the transfer hydrogenation of **1a**.^[a]



Run	Ligand	Yield [%] ^[b]	<i>ee</i> [%] (Configuration) ^[c]
1	L1	> 98	93 (<i>R</i>)
2	L2	53	42 (<i>S</i>)
3	L3	92	26 (<i>S</i>)
4	L4	96	48 (<i>S</i>)
5	L5	85	23 (<i>R</i>)
6	L6	69	20 (<i>S</i>)
7	L7	> 98	67 (<i>R</i>)
8	L8	72	69 (<i>R</i>)
9	L9	0	-
10	L10	0	-

^[a] Reactions were run under optimized conditions (see Table 1, run 2).

^[b] Yields were determined by ¹⁹F NMR using trifluorotoluene as internal standard.

^[c] The absolute configuration was determined by comparison with data reported in the literature.^[11,16f]

Ethanol was also examined as an alternative source of hydrogen donor but the reaction resulted only in a moderate yield.

The effect of the β -amino alcohol ligand was addressed by evaluating various structures having either one or two stereogenic centres. A series of ten ligands **L1–L10** was studied and the results are reported in Table 2. At first sight, ruthenium complex with **L1** ligand, (1*S*,2*R*)-1-amino-2-indanol, was the most efficient and stereodiscriminating catalyst; however, the results obtained with other ligands also deserved special attention. In the literature, it was reported that the outcome of asymmetric induction in asymmetric transfer hydrogenation of ketones is determined primarily by the configuration of the hydroxy-bearing carbon.^[22,24,28] These studies also reported that the amine-substituted carbon affects the enantioselection but to a lesser extent and mainly through steric ef-

fects. In the major part, our results were in agreement with these previous observations. Surprisingly, however, we observed an inversion of the main enantiomer configuration caused by a simple change in the nature of the substituent, alkyl or aryl at the amine-substituted carbon, while keeping the same absolute configuration at this carbon (Table 2, runs 2–6). Indeed, with **L5**, (*S*)-2-amino-2-phenylethanol, the (*R*) enantiomer of **2a** was obtained, in an identical way to the use of **L1**, but the use of **L2**, **L3**, or **L4**, which have the 2-phenyl group replaced by a 2-alkyl chain, gave the opposite (*S*) enantiomer of **2a**. This is a quite unique observation for which we could not find a precedent in the literature. A case was reported in ATH of ketoisophorone with ligands having both a 2-alkyl chain: (*S*)-prolinol gave the (*R*) alcohol while (*S*)-*tert*-leucinol gave the (*S*) alcohol. Unfortunately, the required data were not detailed.^[24] Otherwise, **L5** and **L6** provided opposite enantiomers of **2a**, as expected. Reversing the position of alkyl and aryl groups on the ligands, while retaining the same absolute configurations at the two centres such as in **L7** compared to **L1**, led to a lower enantioselectivity for the *R* enantiomer of **2a** (Table 2, runs 1 and 7). *N*-Alkylated derivative **L8**, having a secondary amino group, exhibited a lower reactivity and a slightly increased enantioselectivity by comparison with **L7**. (*S*)-Diphenylprolinol **L9** as ligand was unsuccessful in the reaction, possibly due to bulkiness.^[29] We also considered a ruthenium aminocarboxylate complex with the amino acid **L10** that has found application in the transfer hydrogenation of ketones^[30] but not of ketimines; however, no reaction occurred.

After having demonstrated that the ruthenium complex bearing **L1** as ligand was the most efficient in terms of reactivity and stereodiscrimination, we then went on to a series of ketimines in the enantioselective transfer hydrogenation reaction. This work included aryl and alkyl ketimines with various protecting groups (PG) for the nitrogen atom (Table 3). It is important to mention that all the aryl ketimines described hereafter were obtained as a single *E* isomer. It was essential that the ketimine geometry was clearly established because it has a strong impact on the stereochemical course of the reaction (see later in the text). For aryl ketimines **1a–m**, excellent yields and high *ee* values were obtained, irrespective of the electronic nature and position of the substituents on the benzene ring, except for the 2-MeO substituted ketimine **1l** (Table 3, runs 1–13). This substrate did not react, even at 90 °C, possibly because of the steric demand next to the imine function. The absolute configuration of the amine **2a** was determined by polarimetry and comparison with published data.^[11,16f] The absolute configurations of the other aryl methylamines were assigned by analogy. The scope of the reaction was further explored with benzyl and *n*-hexyl

Table 3. Variation of substrates and protecting groups.

5 mol% $\{[RuCl_2(\textit{para-cymene})]_2\}$

$[1]_i = 0.06 \text{ mol/L}$

Run	R	PG	2	Yield [%] ^[a]	<i>ee</i> [%]
1	C ₆ H ₅	PMP	2a	98	93 (<i>R</i>)
2	4-BrC ₆ H ₄	PMP	2b	94	90 (<i>R</i>)
3	4-MeOC ₆ H ₄	PMP	2c	99	91 (<i>R</i>)
4	4-ClC ₆ H ₄	PMP	2d	98	90 (<i>R</i>)
5	4-MeC ₆ H ₄	PMP	2e	99	92 (<i>R</i>)
6	4- <i>t</i> -BuC ₆ H ₄	PMP	2f	99	92 (<i>R</i>)
7	3-ClC ₆ H ₄	PMP	2g	99	89 (<i>R</i>)
8	4-CF ₃ C ₆ H ₄	PMP	2h	99	89 (<i>R</i>)
9	3- <i>i</i> -PrC ₆ H ₄	PMP	2i	98	91 (<i>R</i>)
10	3,4-Cl ₂ C ₆ H ₃	PMP	2j	81	84 (<i>R</i>)
11	3,4-Me ₂ C ₆ H ₃	PMP	2k	94	90 (<i>R</i>)
12	2-MeOC ₆ H ₄	PMP	2l	0	–
13	2-naphthyl	PMP	2m	99	91 (<i>R</i>)
14	Bn	PMP ^[b]	2n	–	–
15	hexyl	PMP ^[c]	2o	52	22 (nd ^[e])
16	C ₆ H ₅	<i>t</i> -BuSO ^[c]	2p	– ^[d]	–
17	C ₆ H ₅	Bn	2q	86	0
18	C ₆ H ₅	1-naphthyl	2r	99	72 (+)
19	C ₆ H ₅	2-naphthyl	2s	99	84 (–)
20	C ₆ H ₅	2,4-(MeO) ₂ C ₆ H ₃	2t	80	90 (–)
21	C ₆ H ₅	H ^[c]	2u	99	32 (nd ^[e])

^[a] Yields of isolated pure products.

^[b] Mixture of imine–enamine tautomers (1:1).

^[c] Mixture of diastereoisomers.

^[d] Only 2,2,2-trifluoro-1-phenylethanol was obtained.

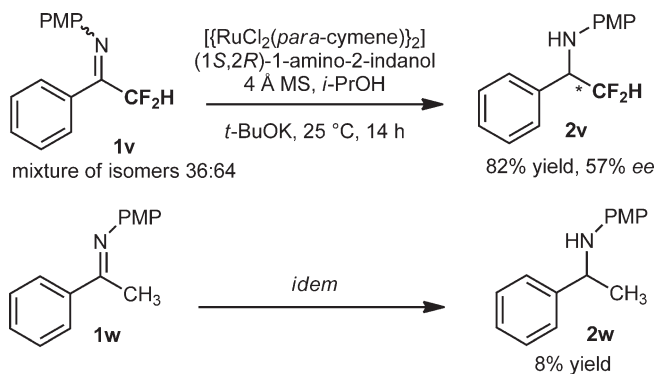
^[e] nd = not determined.

ketimines. Ketimine **1n** with a benzyl group showed imine–enamine tautomerization (1:1) and failed to react under our ATH conditions. In the case of *n*-hexyl ketimine **1o**, the desired amine was obtained in a moderate yield and a low *ee* value of 22% (Table 3, run 15). Apart from the PMP group, other protecting groups were also examined to evaluate their steric and electronic effects on reactivity and enantioselectivity. The ketimine **1p**, with *N*-(*tert*-butylsulfinyl) protecting and activating group, is significantly more electrophilic than its *N*-PMP analogue, albeit with a greater instability and tendency to hydrolysis. Hence, **1p** was fully converted into 2,2,2-trifluoro-1-phenylethanol under our ATH conditions (Table 3, run 16). This result indicated that the conditions reported by Guijarro, Yus and co-workers^[25a] could not be transposed to trifluoromethyl aryl ketimines.^[31]

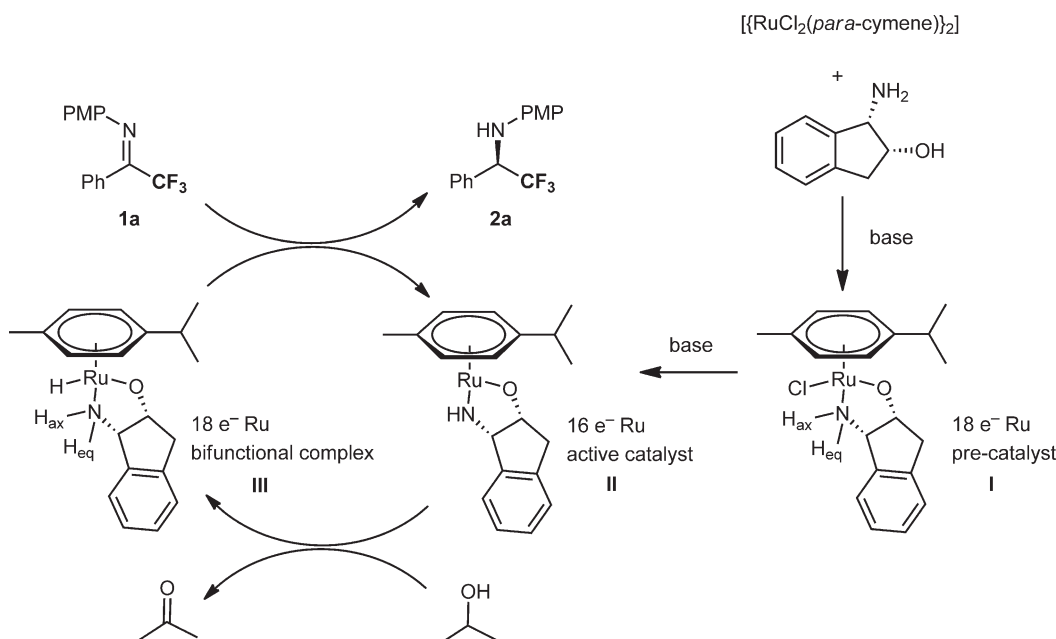
Benzyl-protected ketimine **1q** gave the desired amine in the form of a racemic compound because of

a base-mediated 1,3-hydrogen shift. Indeed, this isomerization reaction led to the regioisomeric imine, which, after transfer hydrogenation, gave an amine not possessing a stereogenic centre (Table 3, run 17).^[32] In addition, three bulky *N*-aryl-protected ketimines **1r**, **1s**, and **1t** were employed in the ATH reaction; in outcomes, we got the corresponding imines in high yields but lower *ee* values were obtained compared the *N*-PMP ketimines (Table 3, runs 18–20). A step-economic synthetic plan would be to utilize N–H imines to avoid a deprotection step after ATH reaction.^[33] By chance the 2,2,2-trifluoro-1-phenylethan-amine **1u** was reported to be a stable, readily isolable N–H ketimine existing as a dynamic mixture of *Z* and *E* isomers.^[34] However, the existence of two imine geometries could cause the multiplication of transition states and a poor enantiodiscrimination during the course of enantioselective additions to these imines. In our study, ketimine **1u** gave full conversion into the expected free amino product **2u** but with only 32% *ee* (Table 3, run 21). Although the investigation of N–H ketimines is a very important area to explore, no attempt was done to screen other amino alcohol ligands.

The difluoromethyl group has received less attention than the CF₃ group due to synthetic difficulties associated with this motif. Nevertheless, it is a motif of great interest in modern organofluorine chemistry.^[35] Difluoromethyl ketimine **1v** was prepared following a literature procedure that gave a mixture of inseparable geometric isomers in a ratio 36:64.^[10,36] This mixture was subjected to our ATH conditions. Amine **2v** was obtained in a good yield and a moderate *ee* value that we reasonably ascribed to the starting mixture of stereoisomers (Scheme 2, *top*). In order to provide a comparison of the behaviour of fluorinated *versus* non-fluorinated ketimines and to highlight the effect of fluorine, we conducted the ATH reaction on phenyl methyl ketimine **1w** (*E* isomer). We only obtained an 8% yield of the expected amine **2w** (Scheme 2, *bottom*), clearly indicating



Scheme 2. A comparative study with α -difluoromethylated amine **1v** and non-fluorinated ketimine **1w**.



Scheme 3. Catalytic cycle for the ATH reaction of ketimine **1a**.

that the presence of the electron-withdrawing CF_3 group in **1a** significantly enhanced the electrophilic character of the iminic carbon and thus the ketimine reactivity. This result confirmed, one more time, that the chemistry developed for fluorinated substrates cannot be simply transposed to non-fluorinated molecules and *vice versa*.^[31]

The mechanism of ATH reaction as well as the origin of the stereoselectivity are well documented in the literature, although the $\text{C}=\text{N}$ bond reduction was less investigated than the $\text{C}=\text{O}$ bond reduction.^[25d,28,37] The pre-catalyst **I** was generated by reaction of the ruthenium dimer with the amino alcohol and further reacted, in presence of the base, to provide the active catalyst **II** (Scheme 3). This 16 electron deficient ruthenium complex dehydrogenated the isopropyl alcohol to form the ruthenium hydride complex **III** with the release of acetone. The bifunctional complex **III** transferred a hydride to the ketimine, together with a proton, in a stepwise process to end up with the amine and regeneration of the active catalyst **II**.

Upon formation of the pre-catalyst, the complex became chiral-at-metal with the possibility of formation of diastereomers owing to the chirality of the amino alcohol ligand. An X-ray diffraction study along with NMR spectroscopic data showed that the pre-catalyst exists as a single diastereoisomer.^[38] In order to rationalize the enantiofacial discrimination of the prochiral ketimines, we needed to know their precise structures that is, *E* or *Z* configuration. Although the geometry of the trifluoromethyl ketimines is a parameter of prime importance, it was not often properly taken into account in the literature for tran-

sition state models of the enantiodiscriminating step. Indeed, in reactions involving ketimine **1a**, mechanisms were proposed employing either the *E* or the *Z* configuration of the ketimine $\text{C}=\text{N}$ bond.^[10–12,39] We therefore conducted a comprehensive study to ascertain the geometry of aryl trifluoromethyl ketimines. Imine **1m** featuring a 2-naphthyl moiety was crystallized and studied by X-ray diffraction to show the *E* configuration.^[40] Next, the ^{19}F , ^1H -HOESY NMR spectrum of ketimine **1a** was recorded; it showed an interaction with an aromatic $\text{C}-\text{H}$ of the phenyl group but not with the aromatic $\text{C}-\text{H}$ of the PMP group, confirming the *E* configuration. In addition, DFT calculations were realized. The geometries of the *E* and *Z* isomers were first optimized at the B3LYP/6-311++G(d,p) level of theory. As stacking interactions could stabilize the *E* isomer, we also performed calculations at the $\omega\text{B97X-D}/6-311++\text{G(d,p)}$ level of theory. The use of the latter functional indicated that the *E* isomer was $4.5 \text{ kcal mol}^{-1}$ more stable than the *Z* isomer whereas the difference was only 2 kcal mol^{-1} with the widespread B3LYP functional. In the light of our own observations together with published information this led us to propose a transition state to deduce the origin of the enantioselectivity (Figure 2). Transfer of the hydride to the iminic carbon took place through the *Si*-face of the ketimine, followed by a proton transfer to the iminic nitrogen, to produce the *R* enantiomer of the amine.

As an illustration of the utility of these chiral trifluoromethyl amines, (*R*)-**2d** was readily converted into the corresponding free amine **3d** without loss of the stereochemical integrity at the stereogenic centre.

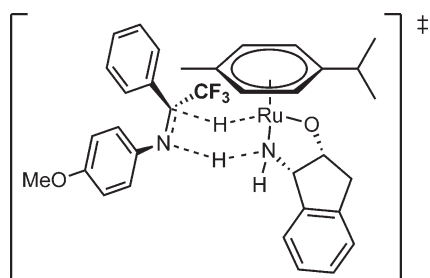
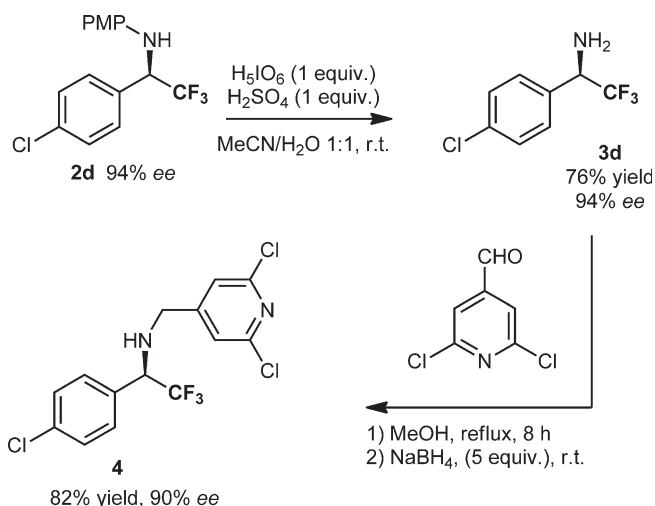


Figure 2. Transition state for hydrogen transfer *via* metal-ligand bifunctional catalysis.

Next, the imine formation with 2,6-dichloroisonicotin-aldehyde followed by reduction by means of sodium borohydride provided compound **4** that is a trifluoro analogue of a potent plant disease control agent (Scheme 4).^[41] Erosion of the *ee* value was noticed but will hopefully be avoided by testing other conditions for the reductive amination step. We believe that our asymmetric transfer hydrogenation reaction should be readily applicable to compounds such as Odanacatib or CF₃-Ac-Docetaxel (see earlier in the text).



Scheme 4. Synthesis of the trifluoro analogue of a plant disease control agent.

Conclusions

We have investigated an enantioselective ruthenium-catalyzed transfer hydrogenation of CF₃ ketimines that allows the synthesis of optically enriched α -trifluoromethyl amines in high yields and enantioselectivities. Aryl ketimines led to high *ee* values for the corresponding aryl trifluoromethyl amines; however, the most challenging aliphatic ketimines gave much lower enantioselectivities, presumably caused by diastereomeric mixtures of the starting ketimines. The

method is remarkable for its simplicity using isopropyl alcohol and an inexpensive chiral amino alcohol. It contributes a suitable alternative to asymmetric hydrogenation using molecular hydrogen and chiral ruthenium-bisphosphine catalysts. Furthermore, the *E*-configuration of aryl trifluoromethyl ketimines was ascertained and the origin of the enantioselectivity was rationalized. Finally, we showed how the PMP protecting group could be easily cleaved and the free amine engaged in the synthesis of a trifluoro analogue of an active compound.

Experimental Section

General Information

¹H (300 MHz), ¹³C (75.5 MHz) and ¹⁹F (282 MHz) NMR spectra were recorded on a Bruker AVANCE 300. Chemical shifts in NMR spectra are reported in parts per million from TMS or CFCl₃ resonance as the internal standard. IR spectra were recorded on a Perkin-Elmer IR-FT 1650 spectrometer. The wave numbers (ν) of recorded IR signals are quoted in cm⁻¹. The conversion and ratio of the corresponding products were determined by ¹⁹F NMR analysis adopting α,α,α -trifluorotoluene as internal standard with D1 value = 5 s. The enantiomeric excesses were determined by HPLC analysis. HPLC analysis were performed on Agilent HPLC 1100 Series system, column Daicel Chiralcel OD-H, OJ-H or AD-H, mobile phase *n*-heptane/isopropyl alcohol, UV detector at 254 or 210 nm. High-resolution mass spectrometry was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. Unless otherwise noted, all reagents were purchased from commercial sources and were used without further purification. Isopropyl alcohol was dried over molecular sieves under an argon atmosphere. Trifluoromethyl ketimines **1a–u** were prepared through the corresponding trifluoromethyl ketones^[42] according to literature procedures.^[11,43] Some of the ketimines employed in this work are known: **1a**,^[39b,44] **1b**,^[39b,45] **1c**,^[10] **1d**,^[39b] **1e**,^[39b] **1h**,^[39b] **1i**,^[39b] **1m**,^[11,39a] **1n** (mixture of tautomers),^[12,46] **1o**,^[39b] **1p**,^[14,47] **1q**,^[32] **1s**,^[44] **1u**,^[34] **1v**,^[10,39a,46] **1w**.^[48]

Typical Procedure for the Synthesis of CF₃ Ketimines (**1**)

(*E*)-*N*-[1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1f**):** To a 50-mL round-bottom flask fitted with a Dean–Stark water trap and reflux condenser were added 1-(4-*tert*-butylphenyl)-2,2,2-trifluoroethanone (2.30 g, 10 mmol) and *p*-anisidine (1.48 g, 12 mmol), along with dry toluene (25 mL) and *p*-toluenesulfonic acid (51.66 mg, 0.3 mmol). The mixture was refluxed until the theoretical amount of water had collected into the trap. The reaction was also monitored by ¹⁹F NMR. After completion, the reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ and extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated under vacuum. The residue was purified by silica gel column chromatography to give the ketimine as a yellow oil; yield: 99%. ¹H NMR (CDCl₃): δ = 7.31–7.34 (m, 2H),

7.15–7.18 (m, 2H), 6.70–6.78 (m, 4H), 3.76 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (CDCl_3): δ = 157.7, 155.6 (q, J_{CF} = 33 Hz), 153.6, 140.1, 128.6, 127.5, 125.8, 123.4, 120.3 (q, J_{CF} = 277 Hz), 114.1, 55.5, 35.0, 31.2; ^{19}F NMR (CDCl_3): δ = -70.2; IR (neat): ν = 2965, 1602, 1503, 1463, 1329, 1233, 1189, 1124, 1033, 971, 830 cm^{-1} ; HR-MS: m/z = 336.1569, calcd. for $\text{C}_{19}\text{H}_{21}\text{NF}_3\text{O}$ ($[\text{M} + \text{H}]^+$): 336.1575.

(E)-N-[1-(3-Chlorophenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1g): Yellow oil; yield: 65%. ^1H NMR (CDCl_3): δ = 7.28–7.29 (m, 1H), 7.17–7.20 (m, 2H), 7.28–7.29 (m, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.67 (m, 4H), 3.68 (s, 3H); ^{13}C NMR (CDCl_3): δ = 158.2, 153.6 (q, J_{CF} = 33.8 Hz), 139.2, 135.0, 132.5, 130.5, 130.3, 128.6, 127.0, 123.6, 120.0 (q, J_{CF} = 277 Hz), 114.3, 55.5; ^{19}F NMR (CDCl_3): δ = -70.4; IR (neat): ν = 2958, 1602, 1503, 1293, 1231, 1193, 1125, 982, 835, 759 cm^{-1} ; HR-MS: m/z = 314.0552, calcd. for $\text{C}_{15}\text{H}_{12}\text{NF}_3\text{O}^{35}\text{Cl}$ ($[\text{M} + \text{H}]^+$): 314.0560.

(E)-N-[1-(3-Isopropylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1i): Yellow oil; yield: 99%. ^1H NMR (CDCl_3): δ = 7.28–7.31 (m, 2H), 7.15 (d, J = 7.0 Hz, 1H), 7.07 (s, 1H), 6.74–6.80 (m, 4H), 3.78 (s, 3H), 2.85 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (CDCl_3): δ = 157.8, 156.0 (q, J_{CF} = 33 Hz), 149.4, 140.1, 130.5, 128.8, 128.5, 127.1, 126.0, 123.3, 120.2 (q, J_{CF} = 277.5 Hz), 114.1, 55.5, 34.0, 23.8; ^{19}F NMR (CDCl_3): δ = -70.2; IR (neat): ν = 2963, 1602, 1503, 1465, 1325, 1237, 1186, 1125, 1118, 1033, 988, 835, 763, 700 cm^{-1} ; HR-MS: m/z = 322.1413, calcd. for $\text{C}_{18}\text{H}_{19}\text{NF}_3\text{O}$ ($[\text{M} + \text{H}]^+$): 322.1419.

(E)-N-[1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1j): Yellow oil; yield: 99%. ^1H NMR (CDCl_3): δ = 7.39–7.42 (m, 2H), 7.01–7.04 (m, 1H), 6.72–6.79 (m, 4H), 3.76 (s, 3H); ^{13}C NMR (CDCl_3): δ = 158.4, 152.5 (q, J_{CF} = 34.5 Hz), 139.0, 135.0, 133.6, 131.1, 130.6, 130.5, 128.2, 123.5, 119.8 (q, J_{CF} = 276.8 Hz), 114.4, 55.5; ^{19}F NMR (CDCl_3): δ = -70.3; IR (neat): ν = 2967, 1601, 1503, 1470, 1326, 1247, 1195, 1126, 1033, 984, 839, 763, 732 cm^{-1} ; HR-MS: m/z = 348.0176, calcd. for $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{F}_3\text{NO}$ ($[\text{M} + \text{H}]^+$): 348.0170.

(E)-N-[1-(3,4-dimethylphenyl)-2,2,2-trifluoroethylidene]-4-methoxyaniline (1k): Yellow oil; yield: 89%. ^1H NMR (CDCl_3): δ = 7.03–7.08 (m, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.71–6.78 (m, 4H), 3.75 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (CDCl_3): δ = 157.7, 155.8 (q, J_{CF} = 33.8 Hz), 140.1, 139.2, 137.3, 130.0, 129.5, 128.1, 126.3, 123.4, 120.3 (q, J_{CF} = 276.8 Hz), 114.1, 55.4, 19.9; ^{19}F NMR (CDCl_3): δ = -70.3; IR (neat): ν = 2954, 1651, 1602, 1503, 1442, 1328, 1239, 1203, 1153, 1123, 1032, 980, 871, 766, 733 cm^{-1} ; HR-MS: m/z = 308.1264, calcd. for $\text{C}_{17}\text{H}_{17}\text{NF}_3\text{O}$ ($[\text{M} + \text{H}]^+$): 308.1262.

(E)-N-(1-Phenyl-2,2,2-trifluoroethylidene)naphthalen-1-amine (1r): Yellow oil; yield: 45%. ^1H NMR (CDCl_3): δ = 8.01–8.04 (m, 1H), 7.81–7.84 (m, 1H), 7.52–7.58 (m, 3H), 7.28–7.32 (m, 1H), 7.15–7.24 (m, 5H), 6.46 (d, J = 7.3 Hz, 1H); ^{13}C NMR (CDCl_3): δ = 157.9 (q, J_{CF} = 34.5 Hz), 143.9, 133.9, 130.5, 130.1, 128.6, 128.3, 128.2, 127.0, 126.7, 126.4, 123.3, 120.0 (q, J_{CF} = 277.5 Hz), 114.1; ^{19}F NMR (CDCl_3): δ = -70.0; IR (neat): ν = 3065, 1661, 1392, 1328, 1190, 1127, 968, 780, 772, 696 cm^{-1} ; HR-MS: m/z = 300.0988, calcd. for $\text{C}_{18}\text{H}_{13}\text{NF}_3\text{O}$ ($[\text{M} + \text{H}]^+$): 300.1000.

(E)-N-(1-Phenyl-2,2,2-trifluoroethylidene)-2,4-dimethoxyaniline (1t): Yellow solid; mp 87°C; yield: 80%. ^1H NMR (CDCl_3): δ = 7.22–7.37 (m, 5H), 6.55–6.58 (m, 1H), 6.34–6.36 (m, 1H), 6.27–6.31 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H);

^{13}C NMR (CDCl_3): δ = 158.8, 157.3, 150.7, 131.4, 130.1, 128.4, 128.1, 122.0, 120.1 (q, J_{CF} = 276.8 Hz), 104.2, 99.4, 55.5; ^{19}F NMR (CDCl_3): δ = -69.9; IR (neat): ν = 2966, 1601, 1438, 1333, 1311, 1211, 1129, 1030, 971, 856 cm^{-1} ; HR-MS: m/z = 310.1057, calcd. for $\text{C}_{16}\text{H}_{13}\text{NF}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$): 310.1055.

General Procedure for the Synthesis of CF_3 Imines (2) by ATH of CF_3 Ketimines (1)

A mixture of $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (6.1 mg, 0.01 mmol), (1*S*,2*R*)-1-amino-2-indanol (3 mg, 0.02 mmol), 4 Å molecular sieves and anhydrous isopropyl alcohol (0.5 mL) was heated at 90°C for 20 min. During this heating period, the initially orange reaction mixture turned dark red in colour. The reaction was then cooled to room temperature and a solution of trifluoromethyl ketimine (0.2 mmol) in isopropyl alcohol (2 mL) and a solution of *t*-BuOK (5.5 mg, 0.05 mmol) in 0.5 mL isopropyl alcohol were successively added. After 14 h, the reaction went to completion (monitoring by ^{19}F NMR). The reaction mixture was filtered through a small amount of silica gel and washed with ethyl acetate. The combined organic phase was concentrated under reduced pressure and purified by column chromatography on silica gel (petroleum ether/ethyl acetate: 30:1) to give the corresponding trifluoromethylamine 2.

(R)-N-(1-Phenyl-2,2,2-trifluoroethyl)-4-methoxyaniline (2a):^[11] Colorless oil; yield: 99%; 93% *ee*; $[\alpha]_{\text{D}}^{20}$: -64.5 (c 1.40, CHCl_3); ^1H NMR (CDCl_3): δ = 7.37–7.46 (m, 5H), 6.71–6.77 (m, 2H), 6.58–6.63 (m, 2H), 4.78–4.83 (m, 1H), 4.08 (d, J = 7.1 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (CDCl_3): δ = 153.9, 140.1, 134.9, 129.6, 129.5, 128.5, 125.7 (q, J_{CF} = 280.5 Hz), 116.3, 115.4, 62.3 (q, J_{CF} = 29.2 Hz), 56.2; ^{19}F NMR (CDCl_3): δ = -74.6 (d, J = 7.3 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_{R} = 16.0 min (*S*), τ_{R} = 16.8 min (*R*).

(R)-N-[1-(4-Bromophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2b):^[11] White solid; yield: 94%; 90% *ee*; ^1H NMR (CDCl_3): δ = 7.50–7.54 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.72–6.77 (m, 2H), 6.54–6.59 (m, 2H), 4.73–4.83 (m, 1H), 4.06 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (CDCl_3): δ = 153.6, 139.1, 133.4, 132.2, 129.8, 124.9 (q, J_{CF} = 280.0 Hz), 123.4, 115.9, 115.0, 61.4 (q, J_{CF} = 29.5 Hz), 55.8; ^{19}F NMR (CDCl_3): δ = -74.7 (d, J = 7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_{R} = 25.2 min (minor enantiomer), τ_{R} = 29.2 min (major enantiomer).

(R)-N-[1-(4-Methoxyphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2c):^[11] White solid; yield: 99%; 91% *ee*; ^1H NMR (CDCl_3): δ = 7.38 (d, J = 8.6 Hz, 2H), 6.91–6.94 (m, 2H), 6.74–6.79 (m, 2H), 6.59–6.65 (m, 2H), 4.76–4.81 (m, 1H), 4.08 (d, J = 6.5 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (CDCl_3): δ = 160.0, 153.2, 139.6, 129.1, 126.2, 125.2 (q, J_{CF} = 279.8 Hz), 115.7, 114.8, 114.3, 61.0 (q, J_{CF} = 29.2 Hz), 55.6, 55.2; ^{19}F NMR (CDCl_3): δ = -74.8 (d, J = 7.4 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_{R} = 27.8 min (major enantiomer), τ_{R} = 30.4 min (minor enantiomer).

(R)-N-[1-(4-Chlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2d):^[11] White solid; yield: 98%; 90% *ee*; ¹H NMR (CDCl₃): δ = 7.35–7.42 (m, 4H), 6.73–6.77 (m, 2H), 6.55–6.61 (m, 2H), 4.76–4.86 (m, 1H), 4.09 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.5, 139.2, 135.2, 132.8, 129.4, 129.2, 125.0 (q, J_{CF} = 279.8 Hz), 115.9, 115.0, 61.0 (q, J_{CF} = 29.2 Hz), 55.6, 55.2; ¹⁹F NMR (CDCl₃): δ = -74.1 (d, J = 7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 23.6 min (minor enantiomer), τ_R = 27.5 min (major enantiomer).

(R)-N-(1-*para*-Tolyl-2,2,2-trifluoroethyl)-4-methoxyaniline (2e):^[11] Colourless oil; yield: 99%; 92% *ee*; ¹H NMR (CDCl₃): δ = 7.38 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.73–6.78 (m, 2H), 6.60–6.65 (m, 2H), 4.75–4.84 (m, 1H), 4.08 (d, J = 7.3 Hz, 1H), 3.73 (s, 3H), 2.36 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.3, 139.7, 139.1, 131.4, 129.7, 127.9, 125.3 (q, J_{CF} = 279.8 Hz), 115.8, 114.9, 61.6 (q, J_{CF} = 29.2 Hz), 55.7, 21.3; ¹⁹F NMR (CDCl₃): δ = -74.6 (d, J = 7.4 Hz); HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 52.5 min (minor enantiomer), τ_R = 58.7 min (major enantiomer).

(R)-N-[1-(4-*tert*-Butylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2f): Colourless oil; yield: 99%; 92% *ee*; [α]_D²⁰: -85.6 (c 1.22, CHCl₃); ¹H NMR (CDCl₃): δ = 7.37–7.44 (m, 4H), 6.75–6.79 (m, 2H), 6.63–6.67 (m, 2H), 4.77–4.86 (m, 1H), 4.08 (d, J = 7.5 Hz, 1H), 3.74 (s, 3H), 1.34 (s, 9H); ¹³C NMR (CDCl₃): δ = 153.3, 152.2, 139.8, 131.4, 127.6, 125.4 (q, J_{CF} = 280.5 Hz), 126.0, 115.7, 114.9, 61.4 (q, J_{CF} = 29.2 Hz), 55.7, 34.7, 31.4; ¹⁹F NMR (CDCl₃): δ = -74.5 (d, J = 7.4 Hz); IR (neat): ν = 3394, 2968, 1513, 1233, 1182, 1177, 1118, 1028, 825, 684 cm⁻¹; HR-MS: m/z = 337.1653, calcd. for C₁₉H₂₂NF₃O (M⁺): 337.1653; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 13.4 min (minor enantiomer), τ_R = 15.2 min (major enantiomer).

(R)-N-[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2g): Pale yellow oil; yield: 99%; 89% *ee*; [α]_D²⁰: -52.7 (c 0.84, CHCl₃); ¹H NMR (CDCl₃): δ = 7.47 (s, 1H), 7.32–7.38 (m, 3H), 6.73–6.78 (m, 2H), 6.56–6.61 (m, 2H), 4.75–4.85 (m, 1H), 4.10 (d, J = 7.1 Hz, 1H), 3.72 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.5, 139.1, 136.4, 135.0, 130.3, 129.5, 128.3, 126.3, 124.9 (q, J_{CF} = 280.5 Hz), 115.8, 115.8, 61.4 (q, J_{CF} = 30 Hz), 55.7; ¹⁹F NMR (CDCl₃): δ = -74.5 (d, J = 7.2 Hz); IR (neat): ν = 3372, 2936, 1575, 1512, 1233, 1172, 1119, 1033, 818, 785, 697 cm⁻¹; HR-MS: m/z = 315.0635, calcd. for C₁₅H₁₃NF₃O (M⁺): 315.0638; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 26.0 min (minor enantiomer), τ_R = 29.5 min (major enantiomer).

(R)-N-[1-[4-(Trifluoromethyl)phenyl]-2,2,2-trifluoroethyl]-4-methoxyaniline (2h):^[11] Pale yellow oil; yield: 99%; 89% *ee*; ¹H NMR (CDCl₃): δ = 7.66 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 6.73–6.78 (m, 2H), 6.55–6.60 (m, 2H), 4.85–4.95 (m, 1H), 4.14 (d, J = 7.0 Hz, 1H), 3.72 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.7, 139.0, 138.4, 131.5 (q, J_{CF} = 32.2 Hz), 128.6, 126.0 (q, J_{CF} = 3.8 Hz), 124.9 (q, J_{CF} = 280.5 Hz), 124.0 (q, J_{CF} = 270.8 Hz), 115.9, 115.0, 61.6 (q, J_{CF} = 29.2 Hz), 55.7; ¹⁹F NMR (CDCl₃): δ = -63.3, -74.4 (d, J = 7.2 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm):

τ_R = 21.6 min (minor enantiomer), τ_R = 28.0 min (major enantiomer).

(R)-N-[1-(3-Isopropylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2i): Yellow oil; yield: 98%; 91% *ee*; [α]_D²⁰: -55.7 (c 1.08, CHCl₃); ¹H NMR (CDCl₃): δ = 7.21–7.32 (m, 4H), 6.72–6.76 (m, 2H), 6.60–6.63 (m, 2H), 4.73–4.83 (m, 1H), 4.05 (d, J = 7.3 Hz, 1H), 3.70 (s, 3H), 2.83–2.97 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.3, 149.7, 139.8, 134.4, 129.0, 127.2, 126.4, 125.3, 125.4 (q, J_{CF} = 280.5 Hz), 115.8, 114.9, 61.9 (q, J_{CF} = 29.2 Hz), 55.7, 34.2, 24.0; ¹⁹F NMR (CDCl₃): δ = -74.4 (d, J = 7.3 Hz); IR (neat): ν = 3379, 2961, 1608, 1512, 1443, 1347, 1234, 1164, 1118, 1118, 1035, 818, 708 cm⁻¹; HR-MS: m/z = 324.1568, calcd. for C₁₈H₂₁NF₃O ([M + H]⁺): 324.1575; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 20.2 min (minor enantiomer), τ_R = 24.5 min (major enantiomer).

(R)-N-[1-(3,4-Dichlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2j): Yellow oil; yield: 81%; 84% *ee*; [α]_D²⁰: -42.4 (c 1.12, CHCl₃); ¹H NMR (CDCl₃): δ = 7.57–7.58 (m, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.30–7.33 (m, 1H), 6.73–6.79 (m, 2H), 6.54–6.59 (m, 2H), 4.74–4.83 (m, 1H), 4.09 (d, J = 6.5 Hz, 1H), 3.73 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.7, 138.8, 134.6, 133.6, 133.3, 131.0, 130.1, 127.4, 124.7 (q, J_{CF} = 280.5 Hz), 115.9, 115.0, 60.9 (q, J_{CF} = 30 Hz), 55.7; ¹⁹F NMR (CDCl₃): δ = -74.6 (d, J = 7.1 Hz); IR (neat): ν = 3378, 2941, 1512, 1470, 1401, 1347, 1234, 1175, 1122, 1032, 917, 816, 769, 711 cm⁻¹; HR-MS: m/z = 350.0322, calcd. for C₁₅H₁₃NF₃Cl₂O ([M + H]⁺): 350.0326; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 27.8 min (minor enantiomer), τ_R = 34.1 min (major enantiomer).

(R)-N-[1-(3,4-Dimethylphenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2k): Colourless oil; yield: 94%; 90% *ee*; [α]_D²⁰: -85.8 (c 1.50, CHCl₃); ¹H NMR (CDCl₃): δ = 7.14–7.20 (m, 3H), 6.73–6.79 (m, 2H), 6.60–6.66 (m, 2H), 4.70–4.80 (m, 1H), 4.07 (d, J = 6.5 Hz, 1H), 3.73 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.3, 139.8, 137.8, 137.3, 131.8, 130.2, 129.2, 125.4, 125.4 (q, J_{CF} = 280.5 Hz), 115.7, 114.9, 61.6 (q, J_{CF} = 29.2 Hz), 55.8, 20.0, 19.6; ¹⁹F NMR (CDCl₃): δ = -74.6 (d, J = 7.4 Hz); IR (neat): ν = 3372, 2923, 1511, 1455, 1348, 1233, 1179, 1158, 1115, 1035, 816, 757, 689 cm⁻¹; HR-MS: m/z = 310.1411, calcd. for C₁₇H₁₉NF₃O ([M + H]⁺): 310.1419; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 36.8 min (minor enantiomer), τ_R = 49.1 min (major enantiomer).

(R)-N-[1-(Naphthalen-2-yl)-2,2,2-trifluoroethyl]-4-methoxyaniline (2m):^[11] White solid; yield: 99%; 91% *ee*; ¹H NMR (CDCl₃): δ = 7.70–7.81 (m, 4H), 7.35–7.44 (m, 3H), 6.60–6.63 (m, 2H), 6.51–6.54 (m, 2H), 4.82–4.92 (m, 1H), 4.09 (d, J = 6.4 Hz, 1H), 3.57 (s, 3H); ¹³C NMR (CDCl₃): δ = 153.5, 139.6, 133.6, 133.3, 131.8, 129.0, 128.2, 127.8, 126.8, 126.7, 125.4 (q, J_{CF} = 280.3 Hz), 115.9, 115.0, 62.0 (q, J_{CF} = 29.4 Hz), 55.7; ¹⁹F NMR (CDCl₃): δ = -74.2 (d, J = 7.3 Hz); HPLC (Chiralcel AD-H column, heptane/isopropyl alcohol = 95:5, flow rate = 0.5 mL min⁻¹, λ = 254 nm): τ_R = 26.4 min (major enantiomer), τ_R = 30.3 min (minor enantiomer).

N-(1,1,1-Trifluorooctan-2-yl)-4-methoxyaniline (2o): Yellow oil; yield: 52%; 22% *ee*; ¹H NMR (CDCl₃): δ = 6.76–6.81 (m, 2H), 6.60–6.65 (m, 2H), 3.75 (s, 3H), 3.65–3.72 (m,

1H), 3.26 (d, $J=9.0$ Hz, 1H), 1.81–1.92 (m, 1H), 1.11–1.59 (m, 8H), 0.87–0.92 (m, 4H); ^{13}C NMR (CDCl_3): $\delta=151.7$, 139.9, 125.4 (q, $J_{\text{C,F}}=282$ Hz), 113.8, 113.7, 55.8 (q, $J_{\text{C,F}}=28.5$ Hz), 54.6, 50.9, 30.7, 28.3, 26.6, 21.3, 12.8; ^{19}F NMR (CDCl_3): $\delta=-76.6$ (d, $J=6.9$ Hz); IR (neat): $\nu=3389$, 2957, 1619, 1511, 1465, 1234, 1167, 1130, 1037, 818, 691 cm^{-1} ; HR-MS: $m/z=290.1724$, calcd. for $\text{C}_{15}\text{H}_{23}\text{NF}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 290.1732; HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=15.3$ min (minor enantiomer), $\tau_{\text{R}}=16.7$ min (major enantiomer).

***N*-Benzyl-1-phenyl-2,2,2-trifluoroethanamine (2q)**^[49]
Yellow oil; yield: 86%; 0% *ee*; ^1H NMR (CDCl_3): $\delta=7.40$ –7.45 (m, 5H), 7.29–7.35 (m, 5H), 4.11–4.19 (m, 1H), 3.85 (d, $J=13.4$ Hz, 1H), 3.68 (d, $J=13.4$ Hz, 1H), 2.06 (br s, 1H); ^{13}C NMR (CDCl_3): $\delta=139.1$, 134.3, 129.2, 128.9, 128.8, 128.7, 128.3, 127.5, 125.6 (q, $J_{\text{C,F}}=284.2$ Hz), 63.5 (q, $J_{\text{C,F}}=28.5$ Hz), 51.1; ^{19}F NMR (CDCl_3): $\delta=-74.4$ (d, $J=7.4$ Hz); HPLC (Chiralcel OJ-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=17.3$ min, $\tau_{\text{R}}=23.5$ min.

(+)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)naphthalen-1-amine (2r)
Pale yellow oil; yield: 99%; 72% *ee*; $[\alpha]_{\text{D}}^{20}$: +171.7 (c 0.82, CHCl_3); ^1H NMR (CDCl_3): $\delta=7.90$ –7.93 (m, 1H), 7.75–7.78 (m, 1H), 7.42–7.50 (m, 4H), 7.31–7.38 (m, 3H), 7.26–7.29 (m, 1H), 7.15–7.20 (m, 1H), 6.47 (d, $J=7.5$ Hz, 1H), 5.03–5.13 (m, 1H), 4.98 (d, $J=6.6$ Hz, 1H); ^{13}C NMR (CDCl_3): $\delta=140.6$, 134.4, 133.9, 129.3, 129.1, 129.0, 128.0, 126.2, 125.6, 124.2, 125.3 (q, $J_{\text{C,F}}=280.5$ Hz), 119.9, 119.7, 107.3, 60.8 (q, $J_{\text{C,F}}=29.2$ Hz); ^{19}F NMR (CDCl_3): $\delta=-74.4$ (d, $J=7.0$ Hz); IR (neat): $\nu=3425$, 3064, 1583, 1527, 1407, 1245, 1168, 1119, 888, 766 cm^{-1} ; HR-MS: $m/z=302.1159$, calcd. for $\text{C}_{18}\text{H}_{15}\text{NF}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 302.1157; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=15.3$ min (major enantiomer), $\tau_{\text{R}}=19.3$ min (minor enantiomer).

(-)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)naphthalen-2-amine (2s)
White solid; mp 83 °C; yield: 99%; 84% *ee*; $[\alpha]_{\text{D}}^{20}$: -14.8 (c 1.14, CHCl_3); ^1H NMR (CDCl_3): $\delta=7.53$ –7.58 (m, 2H), 7.38–7.46 (m, 3H), 7.22–7.32 (m, 4H), 7.10–7.15 (m, 1H), 6.83 (dd, $J=8.8$ Hz, 2.4 Hz, 1H), 6.70–6.71 (m, 1H), 4.91–5.00 (m, 1H), 4.39 (d, $J=7.4$ Hz, 1H); ^{13}C NMR (CDCl_3): $\delta=143.2$, 134.8, 134.0, 129.4, 129.3, 129.1, 128.3, 128.0, 127.7, 126.7, 126.4, 125.2 (q, $J_{\text{C,F}}=280.5$ Hz), 123.1, 118.0, 106.9, 60.6 (q, $J_{\text{C,F}}=29.2$ Hz); ^{19}F NMR (CDCl_3): $\delta=-74.3$ (d, $J=7.2$ Hz); IR (neat): $\nu=3397$, 2923, 1722, 1632, 1497, 1248, 1169, 1121, 844, 800, 747 cm^{-1} ; HR-MS: $m/z=302.1171$, calcd. for $\text{C}_{18}\text{H}_{15}\text{NF}_3$ ($[\text{M}+\text{H}]^+$): 302.1157; HPLC (Chiralcel AD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=18.0$ min (minor enantiomer), $\tau_{\text{R}}=28.9$ min (major enantiomer).

(-)-*N*-(1-Phenyl-2,2,2-trifluoroethyl)-2,4-dimethoxyaniline (2t)
White solid; mp 86 °C; yield: 80%; 90% *ee*; $[\alpha]_{\text{D}}^{20}$: -31.4 (c 0.55, CHCl_3); ^1H NMR (CDCl_3): $\delta=7.37$ –7.48 (m, 5H), 6.43–6.47 (m, 2H), 6.30–6.32 (m, 1H), 4.80–4.89 (m, 1H), 4.73 (d, $J=6.2$ Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (CDCl_3): $\delta=153.2$, 148.5, 134.6, 129.7, 129.1, 128.9, 128.1, 125.4 (q, $J_{\text{C,F}}=279.8$ Hz), 112.1, 103.8, 99.4, 61.4 (q, $J_{\text{C,F}}=29.2$ Hz), 55.8; ^{19}F NMR (CDCl_3): $\delta=-74.6$ (d, $J=7.2$ Hz); IR (neat): $\nu=3408$, 2957, 1598, 1512, 1457, 1268, 1206, 1119, 1025, 840, 762 cm^{-1} ; HR-MS: $m/z=312.1217$, calcd. for $\text{C}_{16}\text{H}_{17}\text{NF}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 312.1211; HPLC (Chiralcel AD-H

column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=12.0$ min (minor enantiomer), $\tau_{\text{R}}=15.2$ min (major enantiomer).

(*R*)-1-Phenyl-2,2,2-trifluoroethanamine (2u)^[15c,16f]
Yellow oil; yield: 99%; 32% *ee*; ^1H NMR (CDCl_3): $\delta=7.38$ –7.44 (m, 5H), 4.36–4.43 (m, 1H), 1.78 (br s, 2H); ^{13}C NMR (CDCl_3): $\delta=135.6$, 131.4, 129.1, 128.8, 125.8 (q, $J_{\text{C,F}}=279.8$ Hz), 58.1 (q, $J_{\text{C,F}}=30$ Hz); ^{19}F NMR (CDCl_3): $\delta=-77.2$ (d, 7.5 Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=210$ nm): $\tau_{\text{R}}=22.4$ min (minor enantiomer), $\tau_{\text{R}}=26.7$ min (major enantiomer).

***N*-(1-Phenyl-2,2-difluoroethyl)-4-methoxyaniline (2v)**^[50]
Pale yellow oil; yield: 82%; 57% *ee*; ^1H NMR (CDCl_3): $\delta=7.34$ –7.44 (m, 5H), 6.70–6.76 (m, 2H), 6.55–6.60 (m, 2H), 5.99 (td, $J=55.9$ Hz, 3.2 Hz, 1H), 4.63 (td, $J=13.2$ Hz, 2.9 Hz, 1H), 4.16 (br s, 1H), 3.71 (s, 3H); ^{13}C NMR (CDCl_3): $\delta=153.0$, 140.1, 135.7, 129.0, 128.7, 127.9, 116.0 (t, $J_{\text{C,F}}=245.2$ Hz), 115.6, 114.9, 61.3 (t, $J_{\text{C,F}}=21$ Hz), 55.8; ^{19}F NMR (CDCl_3): $\delta=-126.4$ (d, $J=7.5$ Hz); HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=254$ nm): $\tau_{\text{R}}=26.6$ min (minor enantiomer), $\tau_{\text{R}}=31.2$ min (major enantiomer).

(*R*)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanamine (3d)^[11]

(*R*)-*N*-[1-(4-Chlorophenyl)-2,2,2-trifluoroethyl]-4-methoxyaniline **2d** (52.6 mg, 0.17 mmol) was dissolved in 4 mL of MeCN/H₂O (1:1). Periodic acid (38 mg, 0.17 mmol) and concentrated H₂SO₄ (16.7 mg, 0.17 mmol) were subsequently added into the solution. After 24 h, the reaction went to completion (monitoring by ^{19}F NMR analysis). The aqueous solution was made alkaline by adding 10% aqueous NaOH to pH 8 and then extracted with ethyl acetate. The combined organic solution was washed with brine and dried over MgSO₄. The solvent was removed under vacuum and the residue purified by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to afford the chiral primary amine **3d** as a pale yellow oil; yield: 76%; 94% *ee*; ^1H NMR (CDCl_3): $\delta=7.34$ –7.40 (m, 4H), 4.37–4.40 (m, 1H), 1.76 (br s, 2H); ^{13}C NMR (CDCl_3): $\delta=135.1$, 134.0, 129.3, 129.0, 125.5 (q, $J_{\text{C,F}}=279.8$ Hz), 57.5 (q, $J_{\text{C,F}}=29.1$ Hz); ^{19}F NMR (CDCl_3): $\delta=-77.3$ (d, $J=7.3$ Hz); IR (neat): $\nu=3402$, 1598, 1494, 1257, 1116, 1091, 1015, 889, 830 cm^{-1} ; HR-MS: $m/z=210.0294$, calcd. for $\text{C}_8\text{H}_8\text{NF}_3\text{Cl}$ ($[\text{M}+\text{H}]^+$): 210.0297; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol=95:5, flow rate=0.5 mL min^{-1} , $\lambda=210$ nm): $\tau_{\text{R}}=22.5$ min (minor enantiomer), $\tau_{\text{R}}=24.2$ min (major enantiomer).

(*R*)-1-(4-Chlorophenyl)-*N*-[(2,6-dichloropyridin-4-yl)methyl]-2,2,2-trifluoroethanamine (4)

(*R*)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanamine **3d** (18.9 mg, 0.09 mmol) and 2,6-dichloroisonicotinaldehyde (17.6 mg, 0.1 mmol) were dissolved in MeOH (3 mL) and refluxed for 7 h until the reaction went to completion (monitoring by ^{19}F NMR analysis). The reaction mixture was allowed to cool down to room temperature and was then treated with NaBH₄ portionwise (34 mg, 0.9 mmol, 10 equiv.). Then, the mixture was quenched with NH₄Cl so-

lution and extracted with ethyl acetate. The combined organic phase was dried over MgSO_4 , concentrated under reduced pressure and the residue purified by column chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to give the desired product **4** as white solid; mp 93 °C; yields: 82%; 90% ee; $^1\text{H NMR}$ (CDCl_3): δ = 7.32–7.41 (m, 4H), 7.22 (s, 2H), 4.11 (q, J = 7.1 Hz, 1H), 3.75 (q, J = 12.9 Hz, 1H), 2.14 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3): δ = 154.4, 150.9, 135.6, 131.9, 129.9, 129.4, 124.9 (q, J_{CF} = 279.8 Hz), 121.9, 63.4 (q, J_{CF} = 29.2 Hz), 49.1; $^{19}\text{F NMR}$ (CDCl_3): δ = -74.5 (d, J = 7.1 Hz); IR (neat): ν = 3352, 1544, 1492, 1365, 1258, 1164, 1121, 1015, 813, 610 cm^{-1} ; HR-MS: m/z = 312.1211, calcd. for $\text{C}_{16}\text{H}_{17}\text{NF}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$): 312.1211; HPLC (Chiralcel OD-H column, heptane/isopropyl alcohol = 99:1, flow rate = 0.4 mL min^{-1} , λ = 210 nm): τ_{R} = 37.2 min (major enantiomer), τ_{R} = 41.3 min (minor enantiomer).

Acknowledgements

X.D. thanks the China Scholarship Council for a PhD fellowship. This work was supported by Normandie Université, CNRS, CRUNCH and LABEX SYNORG (ANR-11-LABX-0029). The authors thank Professor Georges Dupas for DFT calculations on ketimine geometries.

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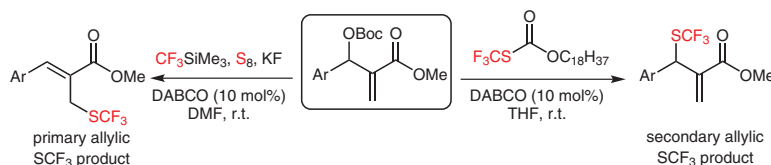
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Regio- and Stereocontrolled Nucleophilic Trifluoromethylthiolation of Morita–Baylis–Hillman Carbonates

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Received: 09.07.2014

Accepted after revision: 25.08.2014

Published online: 15.10.2014

DOI: 10.1055/s-0034-1379162; Art ID: st-2014-b0579-c

Abstract Reactions of Morita–Baylis–Hillman carbonates with metal-free sources of trifluoromethylthio anion have been studied. The combination of $\text{CF}_3\text{SiMe}_3/\text{S}_8/\text{KF}/\text{DMF}$ gave the primary allylic SCF_3 products through apparent $\text{S}_{\text{N}}2'$ reaction whereas the use of Zard's reagent, $\text{CF}_3\text{SCO}_2\text{C}_{18}\text{H}_{37}$, allowed us to intercept the fleeting secondary allylic SCF_3 product.

Key words fluorine, sulphur, Morita–Baylis–Hillman adduct, substitution, stereocontrol

Organofluorine chemistry has become, more than ever, an area of tremendous expansion. It is not only because fluorinated compounds play a key role in pharmaceutical, agrochemical, and material sciences, but also because fluorine is a fascinating atom revealing subtle effects.¹ Fluorine has sparked the imagination of chemists for the synthesis of a plethora of novel architectures featuring fluorine atom(s). Among the fluorinated motifs in vogue, the trifluoromethylthio group occupies a place of choice owing to its exceptional lipophilicity that it confers to molecules (Hansch hydrophobic parameter: $\pi = 1.44$ versus 0.88 for CF_3 and 1.04 for OCF_3)² and its high electron-withdrawing character (Hammett substituent constants: $\sigma_{\text{m}} = 0.40$, $\sigma_{\text{p}} = 0.50$ versus 0.43, 0.54, respectively for the CF_3 group).³ Indeed, the SCF_3 group is very appealing for the conception of new drugs with enhanced capacity to pass cell membranes.⁴ Several synthetic routes to SCF_3 -bearing compounds have been elaborated including the direct introduction of the SCF_3 group, the trifluoromethylation of sulfur compounds, and various functional group interconversions.⁵ Many of the direct approaches involved $\text{C}(\text{sp}^2)\text{--S}$ bond-forming reactions because aryl- and heteroaryl- SCF_3 compounds are predominant in biologically active compounds bearing a SCF_3 group such as Toltrazuril,^{6a} Tiflorex,^{6b} and Vaniliprole⁷ (Figure 1). Much less evaluated were the compounds featuring the $\text{C}(\text{sp}^3)\text{--SCF}_3$ sequence, as encountered in Cefazafur⁸ (Figure 1). The reason for this relative lack of $\text{C}(\text{sp}^3)\text{--SCF}_3$ compounds is due to the paucity of synthetic methods despite the growing interest for SCF_3 chemistry.

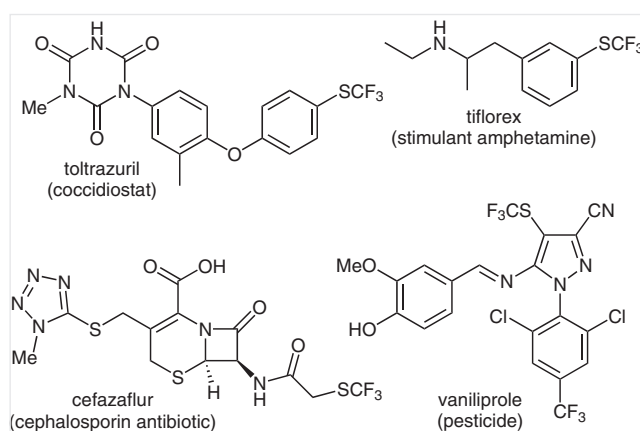
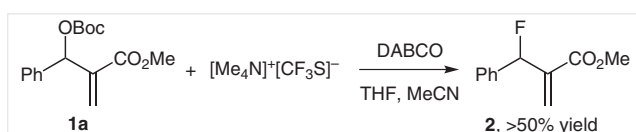


Figure 1 Examples of SCF_3 bioactive compounds

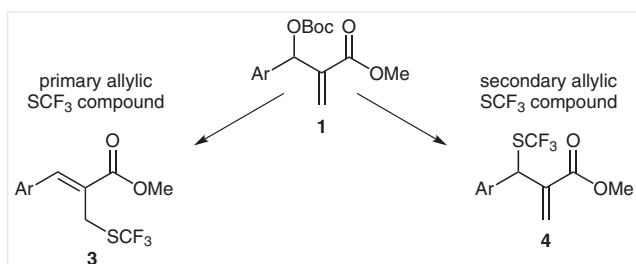
Recently, several laboratories reported on electrophilic trifluoromethylthiolation at sp^3 carbons thanks to the availability of easy-to-handle reagents,⁹ including asymmetric reactions.¹⁰ Regarding the nucleophilic trifluoromethylthiolation, reactions of alkyl, benzyl, allyl, and propargyl halides with trifluoromethylthio metal compounds (Hg , Ag , Cu , Cs)^{11,12a} or organic SCF_3 salts [NMe_4 , $\text{S}(\text{NMe}_2)_3$, TDAE]¹² were reported. In addition, the displacement of bromide in α -bromoketones was described.^{13,14} Transformation of alcohols into trifluoromethyl sulfides through phosphitylation and reaction with bis(trifluoromethyl) disulfide was also reported.¹⁵ Various α -diazo compounds reacted with AgSCF_3 in copper-mediated trifluoromethylthiolations to form $\text{C}(\text{sp}^3)\text{--SCF}_3$ bonds.¹⁶ For a cheap and storable crystalline source of SCF_3 anion, Li and Zard reported the synthesis of *O*-octadecyl-*S*-trifluorothiolarcarbonate, $\text{CF}_3\text{SCO}_2\text{C}_{18}\text{H}_{37}$, and reactions with gramines and α -bromoketones and -ester in the presence of KF and pyrrolidine.¹⁴ Except these nucleophilic substitutions, there is no report of other types of substitution reactions. In order to complement the toolbox for the construction of new SCF_3 derivatives, we herein describe the regio- and stereocontrolled direct introduction of the nucleophilic SCF_3 group onto Morita–Baylis–Hillman (MBH) carbonates.

Among the sources of SCF_3^- anion, we firstly selected the tetramethylammonium trifluoromethylthiolate $[\text{NMe}_4]^+[\text{SCF}_3]^-$, a metal-free reagent prepared from Me_4NF , S_8 , and Ruppert–Prakash reagent (CF_3SiMe_3).^{12a} Treatment of the MBH adduct **1a** with $[\text{NMe}_4]^+[\text{SCF}_3]^-$ in the presence of 10 mol% of DABCO in a mixture THF–MeCN (2:5) gave only a trace amount of a new SCF_3 compound as evidenced by its ^{19}F NMR spectrum ($\delta = -42.3$ ppm). Instead, the monofluorinated secondary allylic fluoride **2** was formed as the major product ($\delta = -171.0$ ppm) (Scheme 1).



Attempts to favor the SCF_3 compound were unsuccessful: these included the evaluation of MBH carbonate **1a** in various solvents, the use of additives such as CuI or KF, as well as the handling of silver trifluoromethylthiolate, AgSCF_3 . Although monofluorinated compound **2** was not the expected target, it is nevertheless interesting because **2** is otherwise difficult to prepare. Indeed, MBH adducts reacted with DAST (diethylaminosulfur trifluoride) to give a mixture of primary and secondary allylic fluorides.¹⁷ In our case, only the secondary allylic fluoride **2** was obtained; however, this method to install a single fluorine atom, which makes use of $[\text{NMe}_4]^+[\text{SCF}_3]^-$, is far from atom-economical. The decomposition of $[\text{NMe}_4]^+[\text{SCF}_3]^-$ into thiocarbonyl fluoride (F_2CS) and fluoride was a major obstacle in our quest for SCF_3 compounds.¹⁸

In order to solve this problem, we next investigated another metal-free approach to generate the SCF_3 anion by means of the combination of $\text{CF}_3\text{SiMe}_3/\text{S}_8/\text{KF}/\text{DMF}$ by analogy to the oxidative trifluoromethylthiolation of terminal alkynes described by Qing and co-workers.¹⁹ We anticipated the two possible SCF_3 products depicted in Scheme 2. The primary allylic SCF_3 product **3** having the alkene double bond conjugated with the aromatic ring is the result of an apparent $\text{S}_{\text{N}}2'$ reaction whereas the secondary allylic SCF_3 product **4** retains the terminal alkene motif in an overall process that may be viewed as a simple S_{N} reaction.



Scheme 2

The addition of Me_3SiCF_3 to a DMF solution of sulfur and KF followed by the successive addition of the MBH carbonate and DABCO, gave after 22 hours the primary allylic SCF_3 product **3** as the main product without detection of **4**. It is worth noting that **3** (^{19}F NMR: $\delta = -42.3$ ppm) was the product obtained in trace amounts in the reaction with $[\text{NMe}_4]^+[\text{SCF}_3]^-$. The order of addition of the reagents as well as the quantity of KF (10 equiv) were revealed to be important in reaching high yields of **3**. Further optimization of the reaction conditions was performed with MBH carbonate **1i** for easy monitoring by ^{19}F NMR. We were pleased to obtain the SCF_3 product **3i** in DMF at 20 °C in the presence of 10 mol% of DABCO in 84% isolated yield (Table 1, entry 1) and even in 94% yield in a more concentrated medium. The assignment of configuration was done by NOESY NMR experiment. Interestingly, **3i** was obtained as a single *Z*-isomer with a *trans* arrangement of the Ar function and the methyl ester. Other solvents were tested (Table 1, entries 3–6), leading either to no product formation in CH_2Cl_2 , toluene, and acetonitrile or to a poor yield in THF. We also evaluated DBU, DMAP and PCy_3 as alternative Lewis bases, but lower yields were obtained compared to those obtained with the use of DABCO (Table 1, entries 1 and 7–9). Moreover, without Lewis base, **3i** was obtained in 69% yield (Table 1, entry 10), indicating that the active SCF_3 anion could directly add

Table 1 Screening of Reaction Parameters^a

Table 1 provides a screening of reaction parameters for the synthesis of primary allylic SCF_3 compound **3i** from MBH adduct **1i** (where Ar = 4- FC_6H_4). The reaction involves CF_3SiMe_3 , S_8 , a solvent, and a fluoride source with a Lewis base.

Entry	Solvent	Fluoride source	Lewis base	Temp (°C)	Yield (%)
1	DMF	KF	DABCO	20	84 (94) ^b
2	DMF	KF ^c	DABCO	20	58
3	CH_2Cl_2	KF	DABCO	20	0
4	toluene	KF	DABCO	20	0
5	THF	KF	DABCO	20	5
6	MeCN	KF	DABCO	20	0
7	DMF	KF	DBU	20	46
8	DMF	KF	DMAP	20	36
9	DMF	KF	PCy_3	20	75
10	DMF	KF	–	20	69
11	DMF	KF	DABCO	50	75
12	DMF	Me_4NF	DABCO	20	0

^a The reactions were performed with 10 mol% of Lewis base, 10 equiv of fluoride source and with a combination of $\text{CF}_3\text{SiMe}_3/\text{S}_8/\text{KF} = 5:6:10$ in solvent (4 mL) for 22 h under dry air.

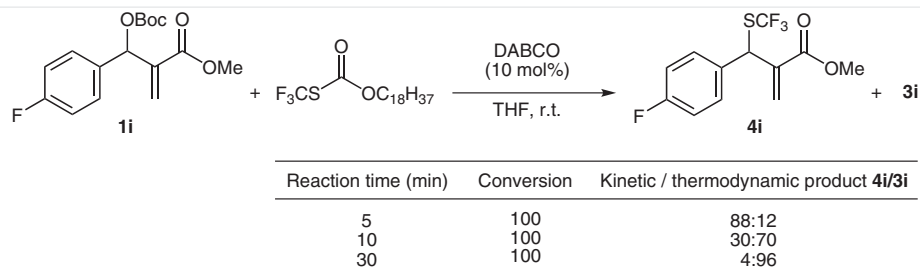
^b The reaction was run in DMF (2 mL).

^c The amount of KF used was 2 equiv.

to the MBH carbonate through a S_N2' addition–elimination mechanism. Running the reaction at higher temperature (50 °C) did not contribute to enhance the yield of the reaction (Table 1, entry 11). The use of Me_4NF as fluoride source instead of KF was detrimental to the reaction (Table 1, entry 12).

Encouraged by these promising results, we examined the substrate scope for the regio- and stereoselective allylic trifluoromethylthiolation of other MBH carbonates and acetates, aryl and alkyl derivatives, conjugated esters, ketone, and nitrile (Table 2). First, the reaction with MBH acetate **1a'** was realized but **3a** was isolated only in 34% yield as compared to the 93% of the corresponding carbonate **1a**; this might be due to the difficulty of elimination of the acetoxy group (Table 2, entries 1 and 2). Hence, the carbonates were chosen as starting material for screening the impact of both R and EWG groups. For aryl esters, either electron-withdrawing (Cl, Br, F) or electron-donating (Me, MeO) substituents on the aromatic ring provided good to excellent yields of **3** after 22 hours (Table 2, entries 3–13). The metal-free approach is particularly suitable to avoid undesired reactions with halogen substituents on the aromatic ring that sometimes occur when transition metals are used. Sterically more demanding naphthyl groups and the 2-thienyl heteroaromatic also led to high yields (Table 2, entries 14–16). The trifluoromethylthiolation worked as well with the alkyl MBH carbonate **1p** but in a much lower yield probably caused by the absence of conjugation with the phenyl ring (Table 2, entry 17). The impact of the steric hindrance of the ester moiety was examined and it was found that increasing the size of the alkyl group tended to reduce the yield of the reaction (Table 2, entries 18 and 19). MBH carbonates derived from the methylvinylketone **1s** and acrylonitrile **1t** were well tolerated in the trifluoromethylthiolation reaction giving the corresponding SCF_3 products **3s** and **3t**, respectively, in good yields (Table 2, entries 20 and 21). In contrast to ester and ketone products, which were obtained as single *Z*-isomers, nitrile **3t** was produced with a *E/Z* ratio of 82:18.²⁰

Although we have found appropriate conditions to prepare the primary allylic SCF_3 products **3** through a regio- and stereoselective allylic trifluoromethylthiolation, the access to secondary allylic SCF_3 products **4**, which contain a stereogenic carbon, would be of high interest as well.



Scheme 3

Table 2 Substrate Scope

Entry	Substrate	R	LG	EWG	Product	Yield (%) ^a
1	1a	Ph	OBoc	CO ₂ Me	3a	93
2	1a'	Ph	OAc	CO ₂ Me	3a	34
3	1b	2-ClC ₆ H ₄	OBoc	CO ₂ Me	3b	79
4	1c	3-ClC ₆ H ₄	OBoc	CO ₂ Me	3c	80
5	1d	4-ClC ₆ H ₄	OBoc	CO ₂ Me	3d	86
6	1e	2,4-Cl ₂ C ₆ H ₃	OBoc	CO ₂ Me	3e	93
7	1f	2-BrC ₆ H ₄	OBoc	CO ₂ Me	3f	86
8	1g	3-BrC ₆ H ₄	OBoc	CO ₂ Me	3g	69
9	1h	4-BrC ₆ H ₄	OBoc	CO ₂ Me	3h	99
10	1i	4-FC ₆ H ₄	OBoc	CO ₂ Me	3i	94
11	1j	2-OMeC ₆ H ₄	OBoc	CO ₂ Me	3j	64
12	1k	4-OMeC ₆ H ₄	OBoc	CO ₂ Me	3k	88
13	1l	4-MeC ₆ H ₄	OBoc	CO ₂ Me	3l	93
14	1m	1-naphthyl	OBoc	CO ₂ Me	3m	95
15	1n	2-naphthyl	OBoc	CO ₂ Me	3n	94
16	1o	2-thienyl	OBoc	CO ₂ Me	3o	88
17	1p	PhCH ₂ CH ₂	OBoc	CO ₂ Me	3p	20
18	1q	Ph	OBoc	CO ₂ Et	3q	84
19	1r	Ph	OBoc	CO ₂ t-Bu	3r	28
20	1s	Ph	OBoc	COMe	3s	65
21	1t	Ph	OBoc	CN	3t	79 ^b

^a Yield of the isolated pure product as single *Z*-isomer.

^b *E/Z* ratio = 82:18.

As mentioned earlier in the text, Zard demonstrated that *O*-octadecyl-*S*-trifluorothiolcarbonate, $\text{CF}_3\text{SCO}_2\text{C}_{18}\text{H}_{37}$, could be used as an efficient SCF_3 anion donor by activation with the aid of an amine.¹⁴ We surmised that DABCO could play a dual role in activating both the nucleophilic reagent and the MBH carbonate. The trifluoromethylthiolation was examined with Zard's reagent and DABCO at room tem-

perature in THF (Scheme 3). The reaction was very fast and full conversion was reached within five minutes. ^{19}F NMR monitoring of the reaction revealed the kinetic formation of the secondary allylic SCF_3 product **4i** that rapidly isomerized to the primary allylic SCF_3 product **3i** (thermodynamic product) when the reaction time was extended. Compared to the combination of $\text{CF}_3\text{SiMe}_3/\text{S}_8/\text{KF}/\text{DMF}$, Zard's reagent allowed to catch the fleeting secondary allylic SCF_3 (kinetic product) during its brief existence. Indeed, by quenching the reaction mixture after five minutes and purification on silica gel, we were pleased to isolate the kinetic product **4i** in 78% yield although with some contamination by the long chain alcohol side product. Interestingly, the reaction only required a catalytic amount of DABCO to activate Zard's reagent.

In summary, we have found the appropriate conditions for the regio- and stereocontrolled trifluoromethylthiolation of MBH carbonates: the thermodynamically more stable primary allylic SCF_3 derivatives were synthesized by means of the metal-free combination of $\text{CF}_3\text{SiMe}_3/\text{S}_8/\text{KF}/\text{DMF}$ whereas the kinetic secondary allylic SCF_3 derivatives were obtained by using Zard's reagent.²¹ Further studies that include mechanistic investigation, asymmetric variant, and chemical transformations of these novel SCF_3 products are underway in our laboratory.²²

Acknowledgment

We thank the China Scholarship Council for a PhD grant to Xiaoyang Dai, and Chuan-Le Zhu for the preparation of some MBH adducts. Mr Shi-Guang Li and Dr Samir Zard are thanked for the gift of $\text{CF}_3\text{SCO}_2\text{C}_{18}\text{H}_{37}$ reagent and for fruitful discussions.

Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1379162>.

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- (21) **General Procedure for the Preparation of Compounds 3:** Caution! This reaction should be conducted with a gas pressure regulator and in a well-ventilated hood to avoid exposure to

toxic bis(trifluoromethyl)sulfide and higher analogues. In an oven-dried tube, sulfur (19.2 mg, 0.6 mmol) and KF (58.1 mg, 1 mmol) in anhydrous DMF (2 mL) were stirred at r.t. under dry air for 30 min. Me_3SiCF_3 (71 mg, 0.5 mmol) was then added to the mixture followed by addition of the MBH carbonate (0.1 mmol) and DABCO (1.12 mg, 0.01 mmol). After 22 h, the reaction went to completion (monitored by ^{19}F NMR analysis). The reaction was quenched with H_2O and extracted with Et_2O . The

combined organic layers were dried over MgSO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether– EtOAc , 40:1) to give the corresponding primary allylic SCF_3 compound.

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This article differs from the e-first online version only in its layout; no content has been changed.

Abstract

In this thesis, we have developed new accesses for the construction of molecules featuring Csp₃-CF₃ and Csp₃-SCF₃ motifs.

For the construction of Csp₃-CF₃ motif, two atom-economical hydride transfer reactions of trifluoromethylated compounds by transition-metal catalysis were realized: 1) the isomerization of trifluoromethylated allylic alcohols by iron (II) complexes for the synthesis of trifluoromethylated dihydrochalcones (up to 85% yield); 2) the enantioselective transfer hydrogenation of trifluoromethylated ketimines by a chiral complex of ruthenium and isopropanol as hydride source for the preparation of optically pure trifluoromethylated amines in high yields (up to 99%) and high enantioselectivities (up to 93%).

For the construction of Csp₃-SCF₃ motif, the nucleophilic allylic trifluoromethylthiolation of Morita-Baylis-Hillman derivatives was investigated. The regio- and stereoselective access to thermodynamic trifluoromethylthiolated products has been achieved by combination of S₈/KF/Me₃SiCF₃/DMF in good yields (up to 99% yield). The kinetic trifluoromethylthiolated products were obtained by using Zard's trifluoromethylthiolating reagent.

Key words: fluorine, hydride transfer, isomerization, trifluoromethylthiolation enantioselective synthesis

Résumé

Dans ce manuscrit, nous avons développé de nouveaux accès pour la construction de molécules comportant les motifs Csp₃-CF₃ et Csp₃-SCF₃.

Pour la construction du motif Csp₃-CF₃, deux réactions de transfert d'hydrure sur des composés trifluorométhylés par catalyse avec des métaux de transition ont été réalisées : 1) l'isomérisation catalytique d'alcools allyliques trifluorométhylés par des complexes de fer(II) pour synthétiser différentes CF₃ dihydrochalcones (rendement jusqu'à 85%) ; 2) le transfert d'hydrogène énantiosélectif de céto-imines trifluorométhylées par des complexes chiraux de ruthénium en utilisant l'isopropanol comme source d'hydrure pour obtenir des amines trifluorométhylées optiquement actives avec de hauts rendements (jusqu'à 99%) et de hautes énantiosélectivités (jusqu'à 93%).

Pour la construction du motif Csp₃-SCF₃, la trifluorométhylthiolation allylique nucléophile de dérivés de Morita-Baylis-Hillman a été étudiée. L'accès régio- et stéréosélectif aux produits SCF₃ thermodynamiques a été réalisé par la combinaison de S₈/CF₃SiMe₃/KF/DMF avec de bons rendements (jusqu'à 99%). Le produit cinétique a été obtenu en utilisant le réactif de Zard.

Mots-clés : fluor, transfert d'hydrure, isomérisation, trifluorométhylthiolation, synthèse énantiosélective