DOI: 10.1002/ejoc.200600643

How to Reach Stereogenic Trifluoromethylated Carbon? En Route to the "Grail" of the Asymmetric Trifluoromethylation Reaction

Thierry Billard*[a] and Bernard R. Langlois[a]

Keywords: Trifluoromethylation / Asymmetric synthesis / Enantioselectivity / Diastereoselectivity

The importance of trifluoromethylated molecules has undergone regular growth during the last years, and asymmetric molecules with the CF_3 group borne by a chiral carbon have become more popular. However, methods used to achieve such molecules are still limited. The building block strategy has been the method most employed these last years and stereocontrolled trifluoromethylation reactions have begun to emerge as potential valuable alternatives. Trifluoromethylation of chiral molecules, by using diastereoselective induction, seems promising and already gives good results in certain cases. However, although actively studied to this day, the enantioselective trifluoromethylation of prochiral compounds is still not very efficient even if some interesting results have been already described. Nevertheless, such reactions still present a challenge in terms of efficiency.

1. Introduction

Fluorine occupies a specific place among all of the elements of the periodical classification because of its high electronegativity and its specific properties. This singular nature of the fluorine atom, combined with the unique physical and chemical properties that fluorine imparts to compounds that contain it, explains the importance of organofluorine chemistry.[1] Indeed, the specific physicochemical properties of fluorinated organic compounds are of huge interest in a wide range of applications.[1–2] Consequently, organofluorine chemistry has been steadily growing to become, today, a field of great importance with a distinctive role in highly diverse technological developments (fluoropolymers, pharmaceutical and agrochemical products, material science, etc).[3–4]

Among fluorinated compounds, trifluoromethyl-substituted molecules constitute a particular class of compounds with specific properties, such as polarity, thermal and metabolic stabilities, as well as the high lipophilicity brought by the CF_3 moiety that enhances the compounds bioavailability. Thus, these molecules are very useful, particularly in the pharmaceutical and agrochemical fields.

[a] Laboratoire SERCOF (UMR CNRS 5181), Université Claude Bernard – Lyon 1, Bat Chevreul,
43 Bd du 11 novembre 1918, 69622 Villeurbanne, France
E-mail: billard@univ-lyon1.fr

Thierry Billard was born in Dole (France) in 1971. After studies in various fields, he received a diploma from "Institut de Chimie et Physique Industrielles de Lyon". He then joined Dr B. Langlois' laboratory and then obtained his PhD from the University of Lyon in 1996. After post-doctoral training with Prof. L. Ghosez (Université Catholique de Louvain, Belgium), he was appointed in 1999 as a CNRS permanent researcher in the laboratory of Dr B. Langlois. He is particularly interested in finding new methods for the introduction of a fluorinated moiety into molecules and their application in the synthesis of fluorinated substrates with biological and medical interests.

Bernard R. Langlois was born near Paris (France) in 1947. After receiving his diploma from the "Ecole Supérieure de Physique et Chimie Industrielles de Paris" in 1970, he entered the Rhône–Poulenc Co. where he worked, in different research centers (near Paris and Lyon), on organofluorine chemistry, from bench synthesis to development. In this context, he was involved in fluorinated aromatics and heterocycles, trifluoromethoxy-containing products, trifluoroacetic acid derivatives, triflic acid derivatives, and radical trifluoromethylation reactions. In the meantime, he earned his PhD degree from the University of Lyon in 1984 while studying difluorocarbenes. In 1991, he moved to the University of Lyon where he was appointed as first class Research Director by the CNRS. There, his research group is developing new methodologies for the introduction of fluorine-containing moieties in organic substrates. As far as possible, these methodologies are illustrated by the synthesis of potentially bioactive compounds.

In the last two decades, many reliable methods have been reported for the introduction of a CF_3 moiety into organic compounds[5] and anionic trifluoromethylation has emerged, in recent years, as one of the most powerful strategies. Numerous reagents have been developed to overcome the great instability of the CF_3 anion and to allow nucleophilic trifluoromethylation.[6,7]

Recently, emergence of drugs, such as Befloxatone (antidepressant)[8] (**1**) and Efavirenz (*anti*-HIV)[9] (**2**), in which the CF_3 moiety is located at an asymmetric center, has underlined another important synthetic challenge: how can such chiral compounds be prepared? Many solutions have been developed for this purpose with more or less success. Nevertheless, direct asymmetric trifluoromethylation remains the most "elegant" approach, but this method still represents an important challenge which mobilizes many organofluorine chemists (Figure 1).

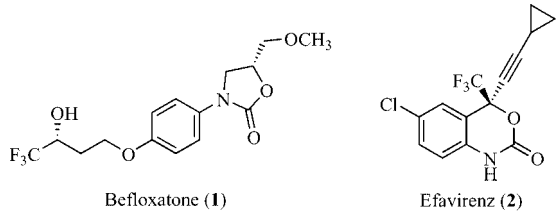


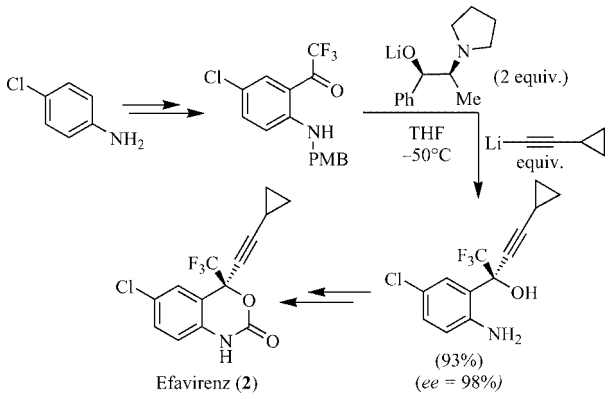
Figure 1. Drugs with CF_3 group at asymmetric carbon.

In this microreview, after a brief overview of the recent developments to circumvent this challenge, we will focus on the most representative results obtained in stereoselective trifluoromethylation with particular attention given to the first attempts in enantioselectivity.

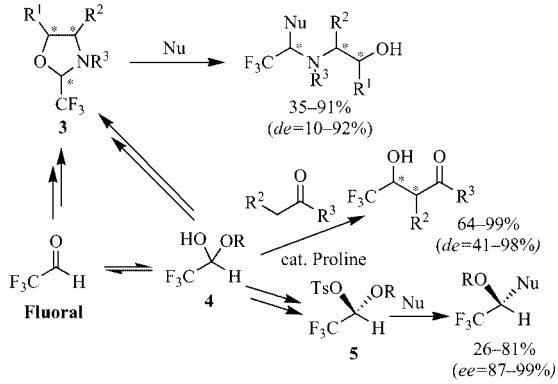
2. The "Indirect Way": α-CF_3 Chemistry

Because of growing interest in asymmetric trifluoromethylated carbons and the difficult challenge of direct enantioselective trifluoromethylation, the first and most used strategies to achieve such structures circumvent the difficulty by stereocontrolled reactions to prochiral trifluoromethylcarbonyl groups. Asymmetric reduction of, or nucleophilic addition to, such moieties have been largely exemplified in the literature.[10] One of the most representative example is the Bristol-Myers Squibb's HIV drug Sustiva (Efavirenz, **2**), which is produced by the asymmetric addition of an organometallic compound to a trifluoromethylcarbonylated substrate (Scheme 1).[11]

The same strategy has also been applied to the synthesis of chiral α-CF_3 amines.[10c,12]More recently, the use of chiral trifluoromethylated oxazolidines (**3**), which arise from fluoral, has also been described to achieve asymmetric trifluoromethylated compounds via an iminium intermediate.[13] Hemiketals (**4**) or ketals (**5**) of fluoral can also be directly involved in the asymmetric aldol reaction or SN_2 processes (Scheme 2).[10c]

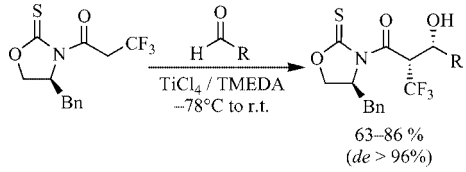


Scheme 1. Asymmetric synthesis of Efavirenz.



Scheme 2. Use of fluoral derivatives.

Very recently, a diastereoselective aldol reaction with α-CF_3 enolates was developed to reach chiral trifluoromethylated compounds with good diastereomeric excess (Scheme 3).[32]



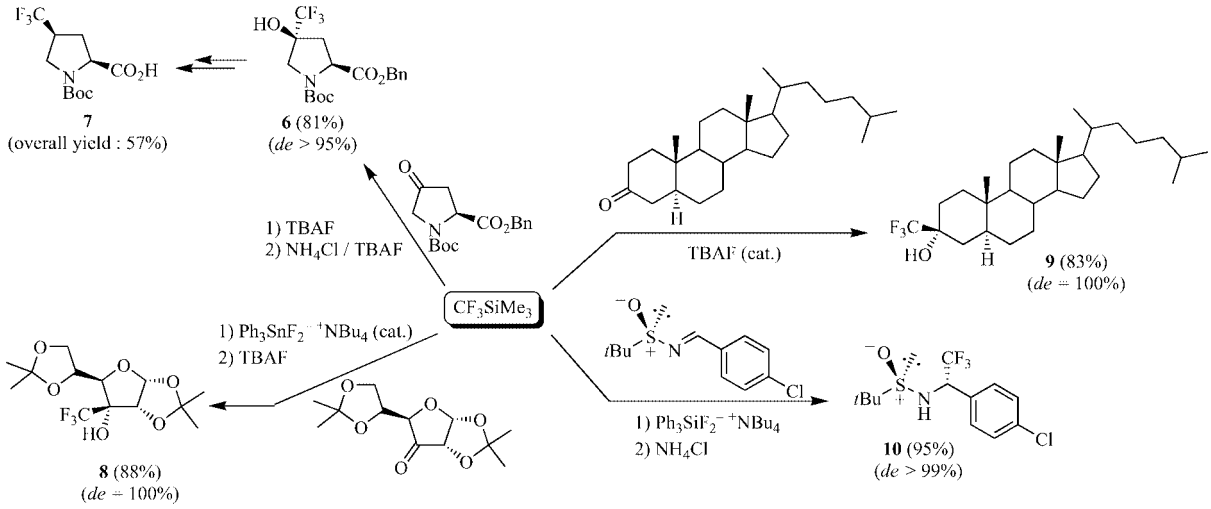
Scheme 3. Diastereoselective aldol reaction of α-CF_3 enolates.

2. The "Direct Way": Stereocontrolled Introduction of the CF_3 Group

2.1. Diastereoselective Strategies

2.1.1. Nucleophilic Trifluoromethylation

Since the emergence of a nucleophilic method for the introduction of a CF_3 group, this strategy has been the most studied. Stereocontrol of the reaction that is most described is the diastereoselective one, which consists of performing the reaction between a "$^-CF_3$" equivalent reagent and a chiral electrophile. This strategy has been largely employed and, generally, gives good results. Because of its commercial availability and its easy handling, the Ruppert–Prakash rea-



Scheme 4. Diastereoselective trifluoromethylation with CF_3SiMe_3.

gent (CF_3SiMe_3) has been largely employed for such a purpose. Thus, for instance, trifluoromethylated amino acids (**7**),[14] sugars (**8**),[15] steroids (**9**),[16] and amines (**10**)[17] have been synthesized with such a strategy (Scheme 4).

Nevertheless, the observed diastereoselection is very dependent on the fluoride sources used. For example, in the synthesis of **10**, the obtained *de* was only 70% when CsF was used instead of TBAT. Furthermore, it is generally noticed that the *de* decreases when the electrophilic site of the molecule moves away from the chiral part. Thus, in trifluoromethylated steroids, if total diastereoselectivity was obtained with **9**, no asymmetric induction was observed in **11** (Figure 2).[18]

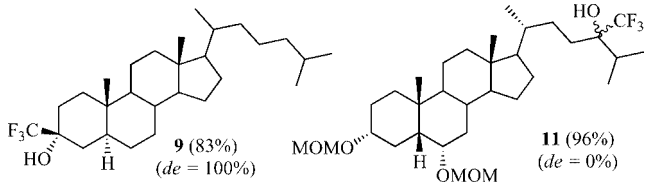
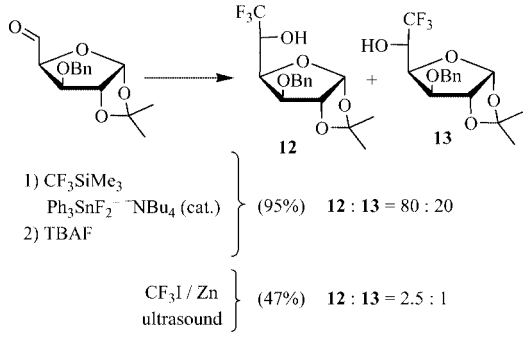
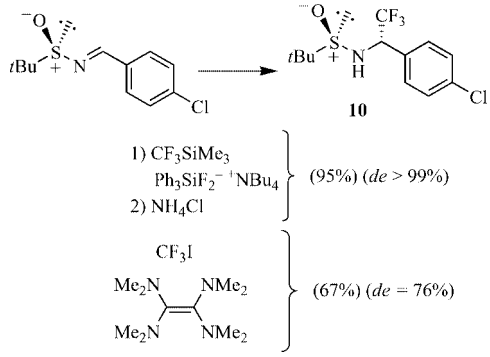


Figure 2. Diastereoselective trifluoromethylation of steroids.



Scheme 5. Diastereoselective trifluoromethylation of sugar with CF_3I.

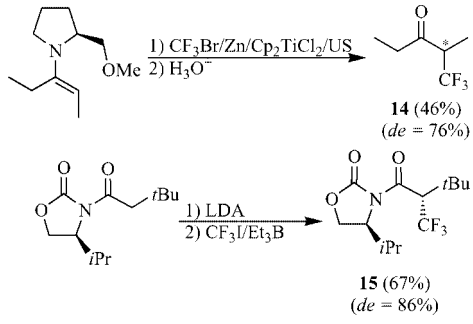
Alternatives to CF_3SiMe_3, based on the use of CF_3I, have been envisaged.[19–20] Nevertheless, the diastereoselectivities are generally lower than those observed with the Ruppert reagent (Schemes 5 and 6). Furthermore, the gaseous form of CF_3I makes these alternatives unsatisfactory.



Scheme 6. Diastereoselective trifluoromethylation of sulfinimide with CF_3I.

2.1.2. Radical Trifluoromethylation

Even if the radical approach, with the use of the electrophilic radical $\cdot CF_3$, is rarely compatible with stereoselectivity, a few diastereoselective inductions have been observed (Scheme 7). The first diastereoselective reaction was de-

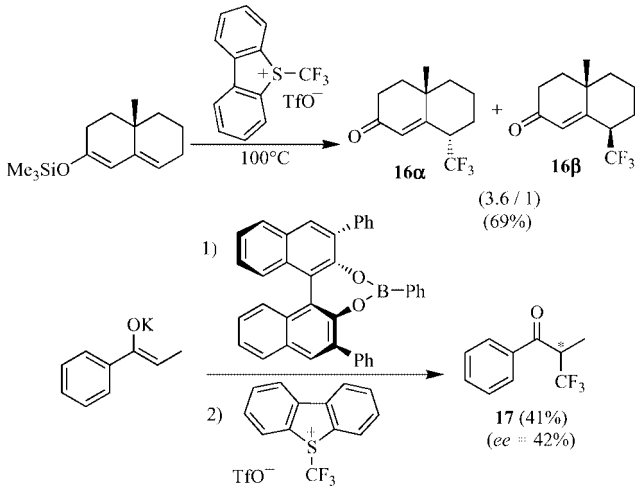


Scheme 7. Diastereoselective radical trifluoromethylation.

scribed by Kitasume and Ishikawa starting from CF_3I or CF_3Br.[21] Even if the mechanism is unknown, a radical process can be reasonably supposed. Starting from CF_3I, lithium enolates of chiral *N*-acyloxazolidinones can also be trifluoromethylated under radical conditions with satisfactory diastereoselectivities.[22] Despite these interesting results, the strategy to achieve chiral trifluoromethylated compounds through this process remains anecdotal and cannot, reasonably, present a general synthetic interest.

2.1.3. Electrophilic Trifluoromethylation

To this day, only a few reagents are able to realize electrophilic trifluoromethylation.[23] Nevertheless, some attempts at diastereoselective trifluoromethylation have already been realized with chiral nucleophilic molecules[24] or by adding chiral Lewis acids to prochiral compounds (Scheme 8).[25] For the moment, these preliminary results are still modest.

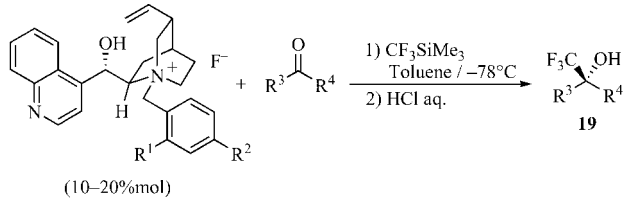


Scheme 8. Diastereoselective electrophilic trifluoromethylation.

2.2. Enantioselective Strategies

At this moment, the lone tentatives of enantioselective trifluoromethylation of prochiral compounds with chiral trifluoromethylating reagents have been realized by a nucleophilic strategy. Indeed, as we said previously, the radical method does not seem very adaptable for such reactions and the low availability of electrophilic trifluoromethylating reagents is still a limitation for such studies. Logically, the Ruppert–Prakash reagent has been the most studied. The first enantioselective trifluoromethylation reaction with CF_3SiMe_3 was published in 1994.[24] The chirality is brought about from a fluoride anion associated to a chiral cation, namely a cinchonium derivative (Table 1). The hypothesis is based on the fact that the chiral ammonium salt should be closely associated with the pentacoordinate species arising from CF_3SiMe_3 and that it is this close coordination that would induce the enantioselectivity.

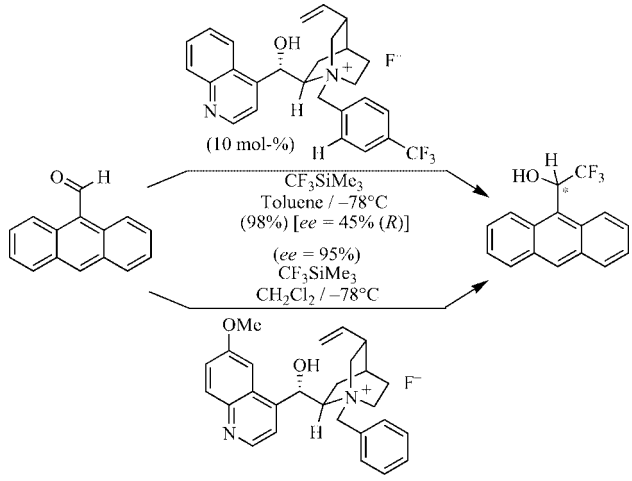
Table 1. Enantioselective trifluoromethylation with cinchonium fluoride catalysis.



Entry	R^1	R^2	R^3	R^4	*ee* [%]	Yield of **19** [%]
1	CF_3	CF_3	Ph	H	46 (*R*)	>99
2	H	CF_3	Ph	Me	48[a]	91
3	H	CF_3	Ph	*i*Pr	51[a]	87
4	H	CF_3	*n*-C_7H_{15}	H	15[a]	>99

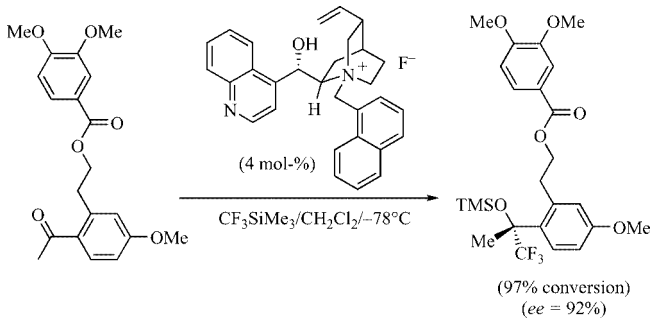
[a] Absolute configuration not determined.

The observed *ee*'s do not exceed 51% (Entry 3) and decrease considerably when non-aromatic carbonyl compounds are used (Entry 4), which leads to the vision that π-π stacking interaction between the carbonyl compound and cinchonium occurs. In unpublished results, Prakash described the highly enantioselective trifluoromethylation (95% *ee*) of 9-anthranaldehyde (unknown yield) by a similar strategy but by using a quinidinium-derived fluoride instead of a cinchonium one; however, the amount of chiral fluoride is not given.[25] The same reaction, conducted with a cinchonium salt, led only to 45% *ee* (Scheme 9).[24]



Scheme 9. Enantioselective trifluoromethylation of 9-anthranaldehyde.

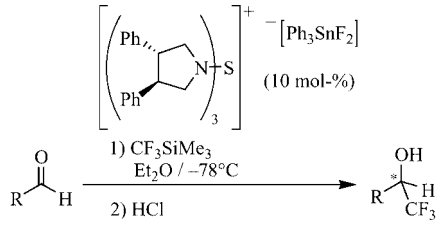
The results are not necessarily so surprising because it is well-known in catalytic reactions that by using quinquina alkaloid derivatives the enantioselectivity is often dependent on the choice of the catalyst for a given reagent. These observations have been confirmed by a Pfizer research group which succeeded to improve enantioselectivity by designing a new cinchonine derivative (Scheme 10).[26] However, this catalyst did not prove to be generally applicable and the same high *ee* with other various carbonyl compounds was not observed.



Scheme 10. Enantioselective trifluoromethylation with optimized cinchonine-derived fluoride.

Another chiral fluoride source has been envisaged by synthesizing chiral TASF analogs.[27] Nevertheless, one more time, the observed *ee* did not exceed 52% (Table 2).

Table 2. Enantioselective trifluoromethylation with chiral TASF analog.



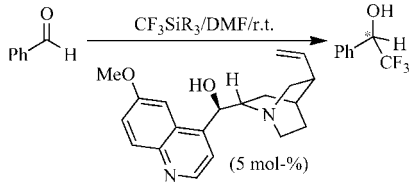
Entry	R	Yield [%]	*ee* [%]
1	Ph	96	52 (*S*)
2	*p*-OMePh	97	37[a]
3	*p*-CF_3Ph	90	24[a]
4	*p*-ClPh	93	30[a]
5	*o*-MePh	98	33[a]
6	1-naphthyl	71	12[a]
7	(*E*)-PhCH=CH	99	18[a]
8	Cyclohexyl	88	10[a]

[a] Absolute configuration not determined.

Other "chiral activations" of CF_3SiMe_3 have been tested by using Lewis base. Thus, attempts to enantioselectively trifluoromethylate benzaldehyde with quinine activation have been realized.[28] However, only modest yields and low *ee*'s were observed (Table 3). The best observed *ee* is only 21% and required a more hindered trifluoromethylated reagent (Entry 4).

With the same idea, activations of the Ruppert–Prakash reagent with $(DHQD)_2PHAL$ or BINAP have also been tried. However, if the obtained yields are better, no *ee* have been observed.[29] Recently, a new class of nucleophilic trifluoromethylating reagents have been described, namely trifluoroacetamides and trifluoromethanesulfinylamides of *gem* amino alcohols.[7] Because such compounds arise from chiral amino alcohols, their use in enantioselective reactions has been studied. Since benzaldehyde seems to be a "challenging compound" to be stereoselectively trifluoromethylated, studies have been conducted with it.[30] A lot of trifluoroacetamides of various silylated chiral *gem* amino

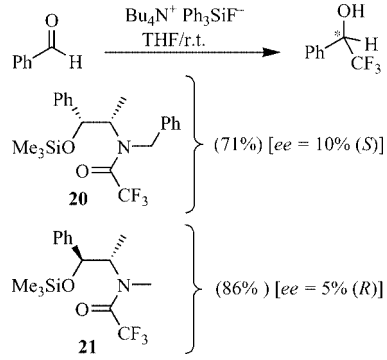
Table 3. Enantioselective trifluoromethylation with chiral Lewis base.



Entry	CF_3SiR_3	Yield [%]	*ee* [%]
1	CF_3SiMe_3	49	9[a]
2	$CF_3SiPhMe_2$	39	6[a]
3	$CF_3SiMePh_2$	35	12[a]
4	CF_3SiEt_3	24	21[a]

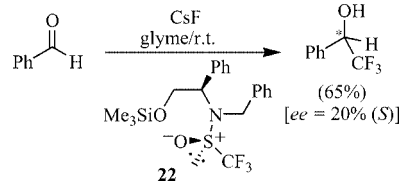
[a] Absolute configuration not determined.

alcohols have been synthesized and tested for enantioselective trifluoromethylations, but only two of them gave modest *ee* (Scheme 11).



Scheme 11. Enantioselective trifluoromethylation with trifluoroacetamides of chiral amino alcohols.

The addition of a third stereocenter, directly bearing the CF_3 group, brought only slight ameliorations (Scheme 12).



Scheme 12. Enantioselective trifluoromethylation with trifluoromethanesulfinamides of chiral amino alcohols.

To this day, the best *ee* that has been obtained with this family of reagents is only 30% by employing trifluoromethanesulfinamide **22** with *N*-benzylcinchoninium fluoride activation, but the yield decreases to 49%.

3. Conclusion

To this day, the best manner to build a chiral carbon center bearing a CF_3 group remains the asymmetric reaction of prochiral trifluoromethylated molecules. Neverthe-

less, the diastereoselective introduction of a trifluoromethyl moiety into chiral molecules has shown some interesting results and is under constant progress and development. Such an alternative could become the new efficient strategy in the future.

Enantioselective trifluoromethylation is always a great challenge in organofluorine chemistry. Some interesting results have been already obtained by a nucleophilic strategy, but the overall results present an important lack of generality and they remain for the moment substrate-dependent. However, this strategy remains pertinent and further developments are under study in our laboratory and others.

The recent work of Togni et al.[23e] in the field of electrophilic trifluoromethylation has opened the way to a new promising alternative for the success of the enantioselective trifluoromethylation of nucleophilic compounds. Togni says, at the end of his article, that they are studying the possible asymmetric development of their method.

Finally, we cannot present the recent progress in asymmetric trifluoromethylation without citing the strange results that have been observed, which includes the potential self-disproportionation of trifluoromethylated enantiomers that was recently described by Soloshonok.[31] Such an unusual phenomenon should be taken into consideration for further research in enantioselective trifluoromethylation.

Since the first *ee* published in 1994, no real advances have been obtained, despite the efforts of the researchers. Thus, the enantioselective trifluoromethylation reaction will become the new "Grail quest" for chemists!

[1] a) U. Groß, S. Rüdiger "Organofluorine Compounds" in *Houben-Weyl: Methods of Organic Chemistry* (Eds.: B. Baasner, H. Hagemann, J. C. Tatlow), Thieme, Stuttgart, **1999**, vol. E10a, pp. 18–26; b) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11; c) T. Hiyama, *Organofluorine Compounds: Chemistry and Properties*, Springer, Berlin, **2000**; d) J. D. Dunitz, *ChemBioChem* **2004**, *5*, 614–621; e) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622–627.

[2] a) R. Filler, Y. Kobayashi, L. M. Yagulpolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**; b) R. E. Banks, B. E. Smart, J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, **1994**; c) T. Hiyama, *Organofluorine Compounds: Chemistry and Properties*, Springer, Berlin, **2000**, ch. 5, pp.137–182; d) A. Becker, *Inventory of Industrial Fluoro-Biochemicals*, Eyrolles, Paris, **1996**.

[3] W. R. Dolbier Jr, *J. Fluorine Chem.* **2005**, *126*, 157–163.

[4] H. Schofield, *J. Fluorine Chem.* **1999**, *100*, 7–11.

[5] M. A. McClinton, D. A. McClinton, *Tetrahedron* **1992**, *48*, 6555–6666.

[6] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786; b) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613–7632; c) G. K. S. Prakash, M. Mandal, *J. Fluorine Chem.* **2001**, *112*, 123–131; d) B. R. Langlois, T. Billard, *Synthesis* **2003**, *2*, 185–194; e) L. Jablonski, J. Joubert, T. Billard, B. R. Langlois, *Synlett* **2002**, *2*, 230–232; f) D. Inschauspe, J.-B. Sortais, T. Billard, B. R. Langlois, *Synlett* **2002**, *2*, 233–235; g) L. Jablonski, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2003**, *44*, 1055–1057.

[7] a) J. Joubert, S. Roussel, C. Christophe, T. Billard, B. R. Langlois, T. Vidal, *Angew. Chem. Int. Ed.* **2003**, *42*, 3133–3136; b) S. Roussel, T. Billard, B. R. Langlois, L. Saint-Jalmes, *Synlett* **2004**, 2119–2122.

[8] a) X. Rabasseda, L. A. Sorbera, J. Castaner, *Drugs Fut.* **1999**, *24*, 1057–1067; b) J. Wouters, F. Moureau, G. Evrard, J.-J. Koenig, S. Jegham, P. George, F. Durant, *Bioorg. Med. Chem.* **1999**, *7*, 1683–1693.

[9] a) J. Ren, J. Milton, K. L. Weaver, S. A. Short, D. I. Stuart, D. K. Stammers, *Structure* **2000**, *8*, 1089–1094; b) O. S. Pedersen, E. B. Pedersen, *Synthesis* **2000**, 479–495.

[10] a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**; b) *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions* (Ed.: P. V. Ramachandran), ACS Symposium Series 746, American Chemical Society, Washington, **2000**; c) T. Kataagiri, K. Uneyama in *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS symposium series 911, American Chemical Society, Washington, **2005**, pp. 318–341; d) K. Mikami, Y. Itoh, M. Yamanaka in *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS Symposium Series 911, American Chemical Society, Washington, **2005**, pp. 356–367; e) G. Resnati, *Tetrahedron* **1993**, *49*, 9385–9445.

[11] M. E. Pierce, R. L. Parsons Jr, L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C.-Y. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, P. J. Reider, *J. Org. Chem.* **1998**, *63*, 8536–8543.

[12] D. Bonnet-Delpon, J.-P. Bégué, B. Crousse in *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS Symposium Series 911, American Chemical Society, Washington, **2005**, pp. 412–428.

[13] a) T. Billard, B. R. Langlois, *J. Org. Chem.* **2002**, *67*, 997–1000; b) N. Lebouvier, C. Laroche, F. Huguenot, T. Brigaud, *Tetrahedron Lett.* **2002**, *43*, 2827–2830; c) K. Higashiyama, A. Ishii, K. Mikami, *Synlett* **1997**, 1381–1382; d) A. Ishii, F. Miyamoto, K. Higashiyama, K. Mikami, *Tetrahedron Lett.* **1998**, *39*, 1199–1202; e) F. Gosselin, A. Roy, P. D. O'Shea, C.-Y. Chen, R. P. Volante, *Org. Lett.* **2004**, *6*, 641–644; f) F. Huguenot, T. Brigaud, *J. Org. Chem.* **2006**, *71*, 2159–2162.

[14] X. L. Qiu, F. L. Qing, *J. Org. Chem.* **2002**, *67*, 7162–7164.

[15] a) J. Kozak, C. R. Johnson, *Nucleosides Nucleotides* **1998**, *17*, 2221–2239; b) C. R. Johnson, D. R. Bhumralkar, E. De Clercq, *Nucleosides Nucleotides* **1995**, *14*, 185–194; c) P. Munier, D. Picq, D. Anker, *Tetrahedron Lett.* **1993**, *34*, 8241–8244; d) S. Lavaire, R. Plantier-Royon, C. Portella, *Tetrahedron: Asymmetry* **1998**, *9*, 213–226; e) C. Schmit, *Synlett* **1994**, 241–242; f) S. Lavaire, R. Plantier-Royon, C. Portella, *J. Carbohydr. Chem.* **1996**, *15*, 361–370; g) U. Eilitz, C. Böttcher, L. Hennig, K. Burger, A. Haas, S. Gockel, J. Sieler, *J. Heterocycl. Chem.* **2003**, *40*, 329–335; h) P. Munier, M. B. Giudicelli, D. Picq, D. Anker, *J. Carbohydr. Chem.* **1994**, *13*, 1225–1230; i) P. Munier, M. B. Giudicelli, D. Picq, D. Anker, *J. Carbohydr. Chem.* **1996**, *15*, 739–762; j) A. P. Kozikowski, V. I. Ognyanov, A. H. Fauq, R. A. Wilcox, S. R. Nahorski, *J. Chem. Soc., Chem. Commun.* **1994**, 599–600.

[16] G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

[17] a) G. K. S. Prakash, M. Mandal, G. A. Olah, *Angew. Chem. Int. Ed.* **2001**, *40*, 589–590; b) G. K. S. Prakash, M. Mandal, G. A. Olah, *Org. Lett.* **2001**, *3*, 2847–2850; c) G. K. S. Prakash, M. Mandal, *J. Am. Chem. Soc.* **2002**, *124*, 6538–6539.

[18] Z. Wang, B. Ruan, *J. Fluorine Chem.* **1994**, *69*, 1–3.

[19] Y. Hanzawa, J.-I. Uda, Y. Kobayashi, Y. Ishido, T. Taguchi, M. Shiro, *Chem. Pharm. Bull.* **1991**, *39*, 2459–2461.

[20] W. Xu, W. R. Dolbier Jr, *J. Org. Chem.* **2005**, *70*, 4741–4745.

[21] T. Kitazume, N. Ishikawa, *J. Am. Chem. Soc.* **1985**, *107*, 5186–5191.

[22] a) K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.* **1993**, *34*, 2169–2170; b) K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron: Asymmetry* **1994**, *5*, 961–974.

[23] a) L. M. Yagupol'skii, N. V. Kondratenko, G. N. Timofeeva, *J. Org. Chem. USSR* **1984**, *20*, 103–105; b) T. Umemoto, *Chem.*

Rev. **1996**, *96*, 1757–1777; c) T. Umemoto in *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS Symposium Series 911, American Chemical Society, Washington, **2005**, pp. 1–15; d) J.-J. Yang, R. L. Kirchmeier, J. M. Schreeve, *J. Org. Chem.* **1998**, *63*, 2656–2660; e) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586.

[24] K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 3137–3138.

[25] G. K. S. Prakash, J. Hu in *Fluorine-Containing Synthons* (Ed.: V. A. Soloshonok), ACS Symposium Series 911, American Chemical Society, Washington, **2005**, pp. 16–56.

[26] S. Caron, N. M. Do, P. Arpin, A. Larivée, *Synthesis* **2003**, 1693–1698.

[27] Y. Kuroki, K. Iseki, *Tetrahedron Lett.* **1999**, *40*, 8231–8234.

[28] a) T. Hagiwara, T. Kobayashi, T. Fuchikami, *Main Group Chem.* **1997**, *2*, 13–15; b) K. Iseki, Y. Kobayashi, *Rev. Heteroat. Chem.* **1995**, *12*, 211–237.

[29] a) S. Roussel, T. Billard, B. R. Langlois, Unpublished Results; b) S. Roussel, PhD Dissertation, Université Claude Bernard – Lyon 1, **2004**.

[30] S. Roussel, T. Billard, B. R. Langlois, L. Saint-Jalmes, *Chem. Eur. J.* **2005**, *11*, 939–944.

[31] V. A. Soloshonok, *Angew. Chem. Int. Ed.* **2006**, *45*, 766–769.

[32] X. Franck, B. Seon-Michel, B. Figadère, *Angew. Chem. Int. Ed.* **2006**, *45*, 5174–5176.

Received: July 25, 2006
Published Online: November 6, 2006

