The chemistry of trifluoromethyl imines and related acetals derived from fluoral

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Trifluoromethylated nitrogen-containing molecules have been shown to have important biological effects and their synthesis is in the focus of the pharmaceutical industry. In the last few years, simple nitrogen derivatives of fluoral, *i.e.* imines, acetals and oxazolidines, have emerged as powerful building blocks to synthesize these target molecules and relevant precursors. This review summarizes the chemistry of these ''N-derivatives of fluoral'', with special highlight on the syntheses of peptidomimetic units (amino alcohols, amino acids…) and heterocycles (piperidines, β-lactams…).

1 Introduction

The substitution of hydrogen by fluorine in organic molecules often induces deep modification of physical, chemical and thus, biological properties of the parent compounds.[1,2] As a consequence, the synthesis of selectively fluorinated compounds, and especially nitrogen-containing ones as biological relevant targets, might be of particular interest.[2] This concerns in particular trifluoromethylated compounds, as shown by the number of CF_3-containing drugs and drug-candidates which are clinically used or in development.[2] The synthesis of such compounds can be realized either by the trifluoromethylation techniques,[3] or through the ''building block'' path from a readily available trifluoromethylated material. Despite the recent progresses in the earlier route, the building block strategy remains the most powerful route to structurally elaborated molecules. The basic question in this approach is the choice of the starting CF_3-containing chemical: this compound has to be readily available at an industrial scale, inexpensive, non-toxic and environmentally compatible. Moreover, it should have a large scope of reactivity, allowing the synthesis of molecules with wide structural and functional diversities. Since trifluoroacetic acid (TFA) is one of the main industrial intermediate in the fluorine area, the chemistry of its derivatives (trifluoroacetic anhydride, esters, imidoyls,…) has been widely developed.[1] The corresponding aldehyde, the fluoral CF_3CHO, can also be considered as a highly useful starting chemical. Indeed, the strong electron-withdrawing character of the trifluoromethyl moiety reinforces the electrophilicity of the carbonyl group and, consequently, fluoral has an emphasized reactivity compared to other aldehydes. Whereas the fluoral itself is an unstable gas difficult to prepare and to use, its hydrate and hemi-acetal derivatives ($CF_3CH(OH)_2$ and $CF_3CH(OH)(OR)$, respectively) are very

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Jean-Pierre Bégué was born in Paris (France) in 1938. He is emeritus Director of Research at the CNRS. After his PhD in 1968 in the Faculty of Sciences-Orsay (Prof. M. Fétizon), he moved to the CNRS group GR12, founded by Dr Bianca Tchoubar. With M. Charpentier-Morize, he was interested in the synthetic application of destabilized carbocations. He turned then to organofluorine chemistry. Since 1993 his group has been located at the Faculty of Pharmacy of Paris-South University (Châtenay-Malabry) where he has developed new methodologies in organofluorine chemistry, medicinal chemistry, fluoro-analogues of natural products, and fluorous chemistry.

Danièle Bonnet-Delpon

Danièle Bonnet-Delpon was born in Commentry (France) in 1949. She is Director of Research at the CNRS. After her PhD in 1982 in the CNRS group GR12, under the supervision of Dr M. Charpentier-Morize, on long range functionalizations, and reactivity of destabilized carbocations, she then progressed from the study of CF_3-substituted carbenium ions to synthetic organofluorine chemistry. In this field she developed with Jean-Pierre Bégué new trifluoromethylated synthons and the use of fluorous phase. She is also strongly involved in the synthesis of fluorinated bioactive compounds: specific ligands of receptors, enzyme inhibitors, and anti-malarials. Since 2003, she has been director of the Laboratory of Fluorinated Molecules at the Faculty of Pharmacy-Paris South (Châtenay-Malabry).

stable and commercially available in bulk at reasonable costs. With amines, they readily provide the corresponding *N,O*-acetals **1** and oxazolidines **2** in the presence of *p*-toluene sulfonic acid (TsOH) or of molecular sieves at room temperature (Fig. 1). Aldimines **3** can also be obtained by using nucleophilic amines and, generally, at toluene reflux with a Dean–Stark apparatus (Fig. 1). However, in many reactions their preparation is not required, since they can be generated *in situ* from *N,O*-acetals **1** and oxazolidines **2** (by means of Lewis acids for example). Moreover, in some cases compounds **1** and **2** have been shown to react directly, as well as **3**. The recent developments in the synthesis of trifluoromethyl nitrogen-containing molecules starting from **1**, **2** and **3** encouraged us to summarize their chemistry in this review, with a special focus on the synthesis of peptidomimetic units and heterocycles, and on some interesting developments. Relevant articles on the topic are compiled on the basis of reaction types. They mainly concern addition and cycloaddition reactions. ''Aminals of fluoral'', usually synthesized by aminolysis of the halon HCFC-123 (dichlorotrifluoroethane), will not be considered here.[4]

The use of hemiaminals of fluoral as innovative and powerful nucleophilic trifluoromethylating agents, developed by Billard and Langlois, has recently been reviewed,[3] and is regarded as out of the scope of this paper. However, it is worthwhile noting that this unique ambivalent feature of ''N-derivatives of fluoral'' makes them an extremely rich source of trifluoromethyl molecules.

2 Addition reactions with organometallics and related reagents

The addition of organometallics to imines is a common approach to amines, including optically active ones. However, these substrates are generally poor electrophiles and the use of external promoters (Lewis or Brønsted acids) is often required. In contrast, the electron withdrawing effect of the CF_3 group

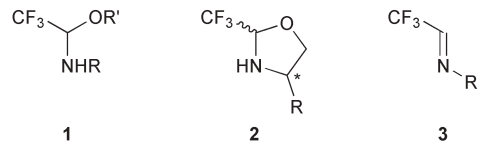

Fig. 1 *N,O*-acetals (**1**), oxazolidines (**2**) and imines (**3**) derived from fluoral.

can often favour the addition of nucleophiles on C=N bonds, without the need of additives, or N-activated substrates.

Alkylation and arylation reactions of **1–3** have been early studied, in an asymmetric manner. Higashiyama and Mikami investigated the reactivity of the amino hemi-acetal **1a** towards organomagnesium reagents. After its generation, **1a** reacted *in situ* with excess of Grignard reagents to afford amines **4** with high de (>90% de) and good yields (Scheme 1).[5]

Funabiki and Enders reported the asymmetric alkylation of **3a** with alkyllithium, using the SAMP-/RAMP-methodology, with excellent diastereoselectivities for primary alkyl groups (>96% de) (Scheme 2).[6]

Unfortunately, this methodology afforded poor yields of product with PhLi as nucleophile (15%). For this latter purpose, Gosselin reported that when the oxazolidine **2a** (R = *i*-Bu, 33% de) was converted *in situ* to the corresponding enantiopure imine by basic treatment, this latter was able to react in a diastereoselective manner with a broad array of aryl lithium reagents (Ar = EWG-C_6H_4, EDG-C_6H_4, pyridyl, furyl,…), yielding the corresponding arylated amino alcohols in high yields (60–95%) and de (60–89%).[7]

Homoallyl and allyl amines are useful synthons on which various modifications can further be introduced. In the first case, allylation reaction of aldimines and of parent compounds is a powerful tool to synthesize these molecules. In the last five years, various research groups have been involved in the application of this methodology in trifluoromethylated series. For example, Kumadaki reported the ene reaction between

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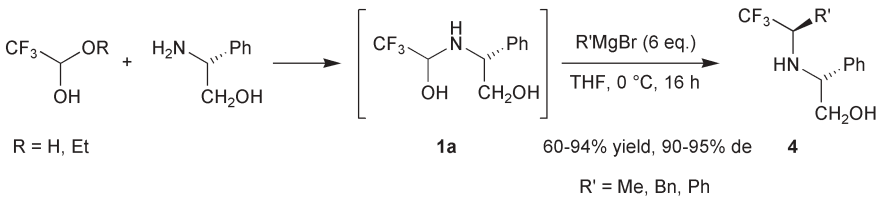
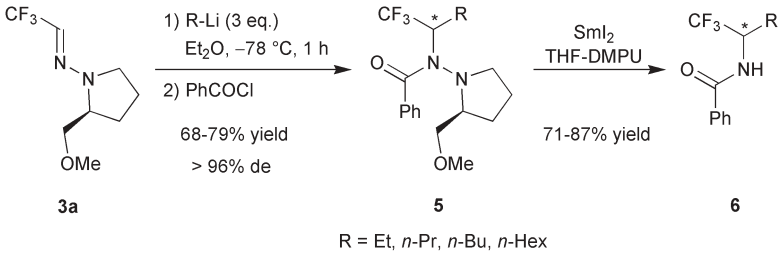
Benoit Crousse was born in 1967 in Issoudun (France). He graduated from the University of Paris VI, and received his PhD degree in 1995 under the supervision of Dr G. Linstrumelle. Then, he joined the group of Prof. P. E. Kündig (University of Geneva, Switzerland) for two years of postdoctoral training. Since 1998, he has been a CNRS permanent Junior Research Scientist in the laboratory of Drs Jean-Pierre Bégué and Danièle Bonnet-Delpon. In 2001, he was promoted Senior Research Scientist. He is particularly interested in finding new methodologies for the preparation of fluorinated compounds, new processes using fluorinated alcohols, and the preparation of fluorinated biological compounds.

Julien Legros

Julien Legros was born in 1974 near to Paris, France. He graduated from the Universities of Paris XII-Créteil and Paris XI-Orsay and obtained his MSc degree in 1999. He did his doctoral studies in the field of organofluorine chemistry under the guidance of Drs Bégué and Bonnet-Delpon at the Faculty of Pharmacy of Paris XI in Châtenay-Malabry, and received his PhD degree in 2002. Subsequently, he joined Professor Bolm's group at the RWTH-Aachen (Germany) as an Alexander von Humboldt postdoctoral fellow, working on iron-catalyzed oxidations (2002–2004). Since the fall of 2004, he has been a permanent CNRS Junior Research Scientist in the group of Dr Bonnet-Delpon.



Scheme 1



Scheme 2

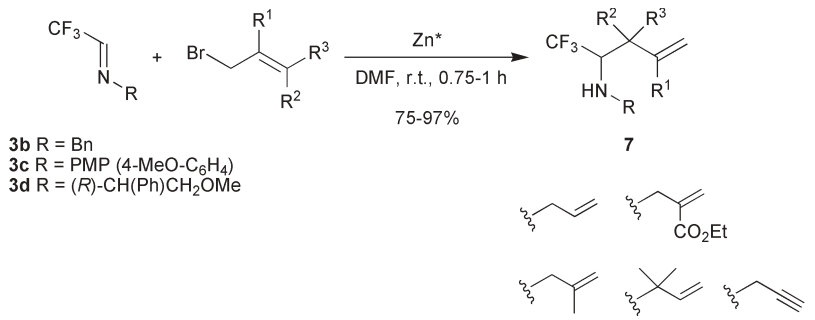
N,O-acetal **1b** ($CF_3C(OEt)NHTs$) in basic medium and/or with a Lewis acid,[8] while Billard and Langlois focused on the use of allyltrimethylsilylane as allyl partner with aldimines.[9] Of particular interest is the development of asymmetric allylation reactions. In 2002, Funabiki reported an allylation reaction of the substrate **3a**.[10] While the diastereoselectivity was very good (>96% de), the tedious conditions (tetra-allyltin as allylation agent in the presence of 12 eq. of PhLi) and the limited reagent scope (only one) made the system unattractive for larger scale applications. The same year, Brigaud reported that the oxazolidine **2b** (R = Ph; 24% de) reacted with allyl trimethylsilane giving the homoallyl amines in high yield, albeit with a poor de (40%).[11] It should be noted that the de of the product is superior to the one of the starting material. It can be supposed that the corresponding imine is generated in the medium by means of the Lewis acid. For the same purpose, we recently addressed a powerful method for the allylation of aldimines **3b–d** under very simple conditions and affording a broad array of homoallylic amines (Scheme 3).[12]

The reaction was performed under Barbier conditions, and as it involved simple allyl bromides as nucleophile precursor, a number of allylating agents can be used. The reaction provided high yields of products (75–97%). Using the methyl ether of (*R*)-phenyl glycinol as chiral auxiliary (**3d**), the corresponding product could be obtained with an excellent 98% de. Interestingly, this methodology also led to homopropargyl amines by using propargyl bromide instead of allyl bromides (Scheme 3).[13]

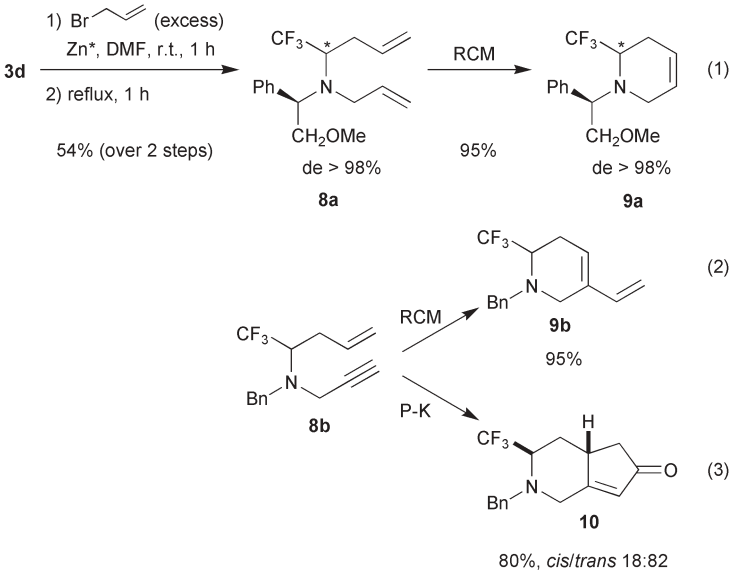
Further studies have shown that when an excess of the allyl (or propargyl) partner was used with aldimines under forced conditions, a *C*-/*N*-allylation sequence occurred, leading to di-unsaturated amines (eqn. (1) in Scheme 4).[13] Moreover, two different allyl groups (or allyl/propargyl) could be introduced by this one-pot method. The obtained adducts are versatile synthons to access to dehydropiperidine derivatives by ring closing metathesis (RCM; eqn. (1) and (2)) or, in the case of allylation/propargylation, to bicycles by Pauson–Khand reaction (P-K; eq. (3)).[13] An asymmetric example of *C*-/*N*-allylation followed by RCM is given in eqn. (1).

Prior to this work, Billard and Langlois reported a route to racemic α-trifluoromethyl nitrogen heterocyles of very varied sizes (6- to 14-membered cycles) *via* RCM.[14] Among them, trifluoropipecoline and a macrolactam were obtained.

The synthesis of allyl amines through vinylation of imines has also been addressed in a single report.[15] The addition of vinyl magnesium bromide on **3b–d** in Et_2O or toluene proceeded efficiently (86–95% yield). In the case of enantiopure imine **3d**, the reaction affords the allyl amine **11** with a 98% de. Acyl protection of the nitrogen, followed by treatment with bromine and then water, yielded a bromhydrine. This



Scheme 3



Scheme 4

latter was further converted to the *syn*-homochiral oxirane **12** (*R*,*R* configuration) under basic conditions, with complete chiral induction (98% de; Scheme 5).[15]

Opening of the β-amino epoxide **12** could offer a promising route to 1,3-diamino-2-alcohols, a central unit present in many protease inhibitors such as HIV-1 protease inhibitors (Saquinavir, Ritonavir) or plasmepsins.[15]

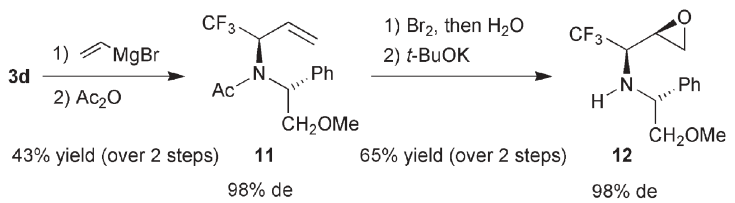
Propargylation reaction has been studied. Brigaud used bis(trimethylsilyl)acetylene with oxazolidine **2b** affording the propargylation product in moderate yield (63%) and almost as a racemate (8% de).[11] We found that lithium acetalides were efficient alkynyl partners with imines **3b–d** as substrates (60–98%) (Scheme 6). In the case of chiral imine **3d**, the diastereoselectivities were remarkable (de > 98%).[16]

Under basic conditions, the propargyl product of the imine **3c** (R′ = PMP) underwent a deprotonation, and subsequent defluorination occurred. Reduction of the compound led to difluoropropargyl amines.

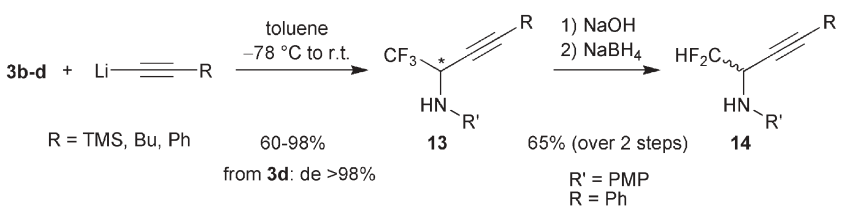
3 Aza-aldol reactions and related processes

The addition of enolates to aldimines (Mannich reaction) is a powerful method for C–C bond formation. In the case of trifluoromethylated substrates **1–3**, this reaction should lead to β-CF_3 β-amino ketones. For this purpose, Akiyama reported the $GaCl_3$-catalysed addition of silyl enolates onto *N,O*-hemiacetal **1c**, leading to the aza-aldol products in good yields (Scheme 7).[17]

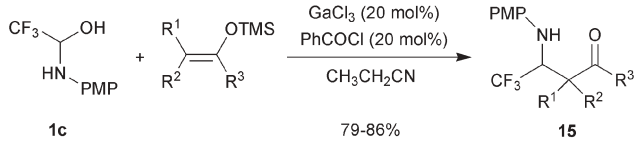
While the reaction was initially performed under stoichiometric conditions, it was shown that when adding benzoyl chloride (20 mol%) to the medium, only catalytic quantities of the gallium salt were required (20 mol%).



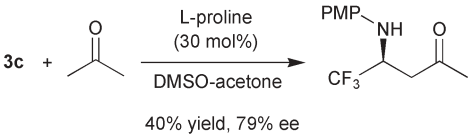
Scheme 5



Scheme 6



Scheme 7



Scheme 11

The development of the Mannich reaction in an asymmetric fashion has also been in the focus of investigations. For example, Brigaud reported that oxazolidine **2b**, in the presence of a Lewis acid, reacted with enoxysilane **16** and ketene silyl acetal **17** affording **18** and **19** diastereoselectively (92% and 68% de, respectively; Scheme 8).[11]

The product **19** is highly interesting, as it leads to the β-CF_3 β-amino acid **20** after deprotection and saponification. An interesting application of the Mannich reaction, with esters as nucleophile source, is the possible access to β-lactams (*vide infra*). Indeed, Ishihara reported that the lithium thioester enolate **21** reacted with the imine **3b** to afford the Mannich product **22** which subsequently underwent cyclisation to yield **23** (Scheme 9).[18]

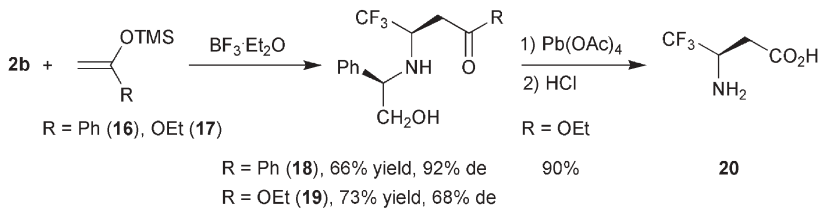
Soloshonok and Avilov previously described an access to the β-CF_3 α,β-diaminoacid **24** by a related process. The non-racemic complex **25** reacted, under basic conditions, with **3c** to yield **26** in excellent yields and diastereoselectivity (91% yield, 98% de; see Scheme 10).[19] It was shown that LiCl was essential for the diastereoselectivity: without this additive, the de of the Mannich-type product was only 32%. Subsequent hydrolysis of **26** led to amino acid **24**.

In recent years, organocatalysed aldol reaction and related processes have emerged powerful tools for asymmetric transformations. In the same line, Funabiki recently addressed a proline-catalysed asymmetric direct Mannich reaction between **3c** and acetone (Scheme 11).[20]

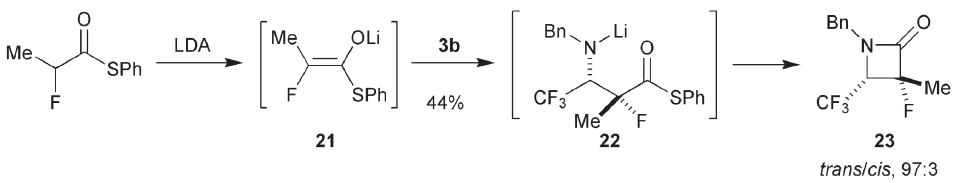
Unfortunately, yields were relatively low (<44%), and to obtain high ee (75–96%), sub-stoichiometric amounts of proline were required (30–50 mol%).

The vinylogous Mannich reaction on aldimines **3b,c,e** (**3e**: R = allyl) has also been described (Scheme 12).[21] This Lewis acid-promoted reaction led to butenolides **29** in high yields (80–92%) and good to excellent *anti*/*syn* ratio (90:10 for R = PMP, 99:1 for others).

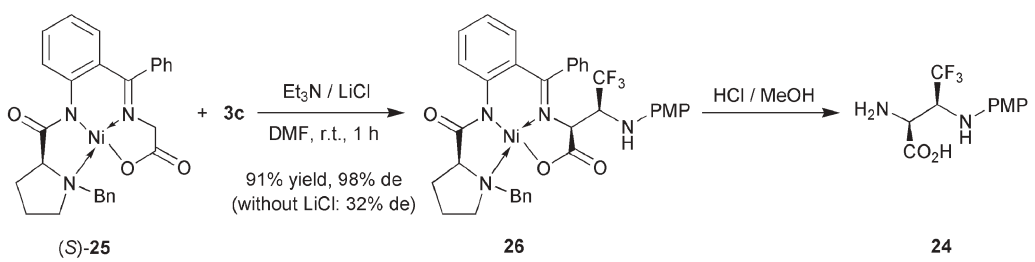
Interestingly, the addition products can lead to α-CF_3 β-hydroxy piperidines **30**, offering so an alternative to other methods, such as RCM (*vide supra*) and cycloaddition reactions (*vide infra*).



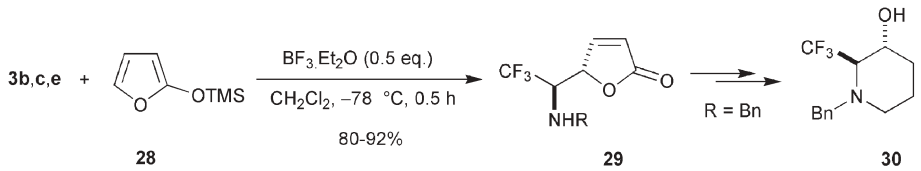
Scheme 8



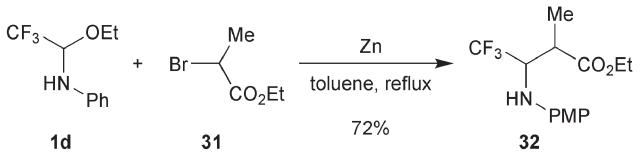
Scheme 9



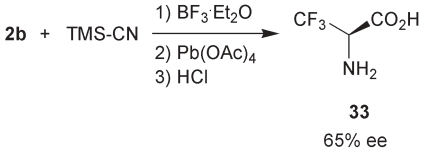
Scheme 10



Scheme 12



Scheme 13



Scheme 14

4 Other types of addition reactions

Other types of additions of functionalised moieties on aldimines have also been reported. For example, Gong and Kato described the Reformatsky reaction on **1d**, affording the β-CF_3 β-amino ester **32** in 72% yield (Scheme 13).[22] It should also be noted that the same authors also reported the addition of malonates onto hemi-acetal, as well as on aldimines, yielding β-CF_3 β-amino diacids.[22]

The addition of TMS-CN is also a powerful method to introduce a carboxylic functionality onto a molecule. In this connection, Brigaud reported that Strecker reaction on oxazolidine **2b** afforded the cyano group addition product, from which enantio-enriched trifluoroalanine **33** (65% ee) could be obtained after deprotection and hydrolysis (Scheme 14).[11] Due to conjugated electronic effects of CF_3 and COOH, the amino acid quickly racemises at pH > 6 and, consequently, particular attention must be paid onto the work-up and purification conditions.

Chiral sulfinyl groups are powerful auxiliaries for asymmetric processes. In this line, Bravo, Zanda and Soloshonok reported the addition of a lithium derivative of the enantiopure sulfoxides **34** and **35** on the imine **3c**.[23] The adducts **36** and **37** were obtained with a good 72% de. After isolation of diastereopure compounds, subsequent transformations led to enantiopure α-trifluoromethyl amines **38** and **39** and amino alcohol **40** (Scheme 15).

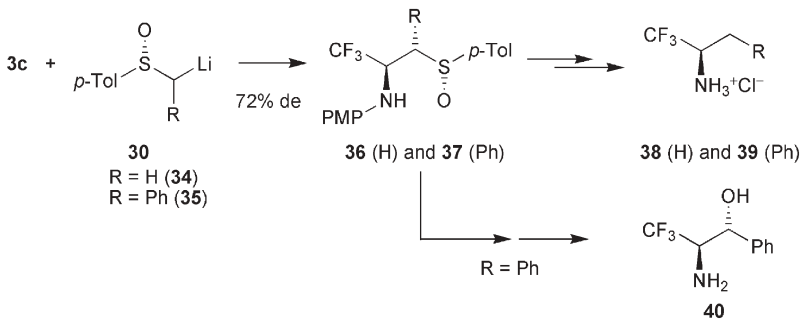
5 Friedel–Crafts-type reactions

The reaction of aromatic compounds with imines, by Friedel–Crafts type reaction, can provide an interesting entry to benzylamine analogues, alternatively to the use of organometallic reagents. In this connection, Kato addressed the synthesis of α-CF_3 α-aryl methylamines from imines of fluoral **3** and electron-rich arenes (phenol, *N*,*N*-dimethylaniline) or heteroarenes (pyrrole, indole, thiophene) in the presence of $BF_3{\cdot}Et_2O$ (0.5–1 eq.) (eqn. (4) in Scheme 16).[24] As exemplified in eqn. (5), starting from aldimines, such as **3f**, products were afforded with excellent de (98%).[25]

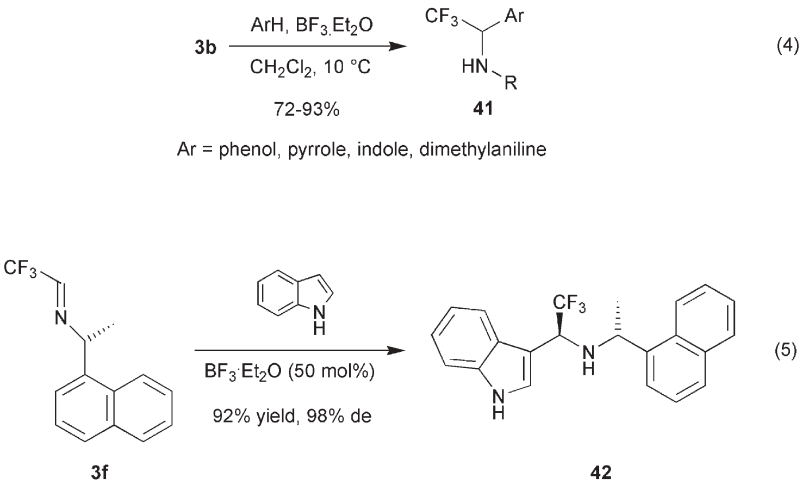
6 Substitution by hetero-elements

The substitution of the hydroxyl or the alkoxy group of *N,O*-acetals of fluoral has been in the focus of many investigations since the pioneer work of Steglich in the sixties.[26] For example the chloro derivative **43–45**, prepared by treatment with PCl_5 of the *N*-protected *N,O*-acetal,[27] reacted with O-, N- and S- nucleophiles as well as with carbon-nucleophiles (anions of malonate, dithiane, nitromethane, *etc.*) (Scheme 17).[28]

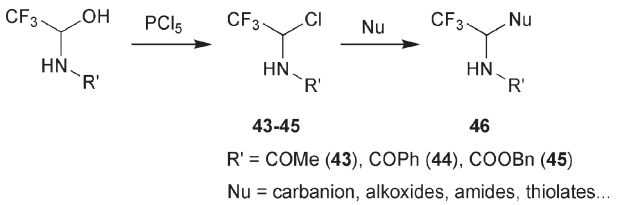
A very interesting application of this methodology has recently been reported by Gagosz and Zard.[29] Xanthates **47** prepared from the chloro-derivative **43**, further generated in the presence of lauroyl peroxide, an amido trifluoroethyl radical. This radical species could then be trapped by a large



Scheme 15



Scheme 16



Scheme 17

scope of olefins providing new radicals and hence xanthate derivatives **49** in high yields (62–95%) (eqn. (6) in Scheme 18). Depending on the structure of the olefin, they could be reduced or converted into useful synthons. Surprisingly, when the radical **48** was generated without a radical olefinic trap, an homodimerisation occurred, leading to bis-trifluoroethylamine **50** (1/1 mixture of *meso* and *dl* isomers) a class of potential metal ligands (eqn. (7)).

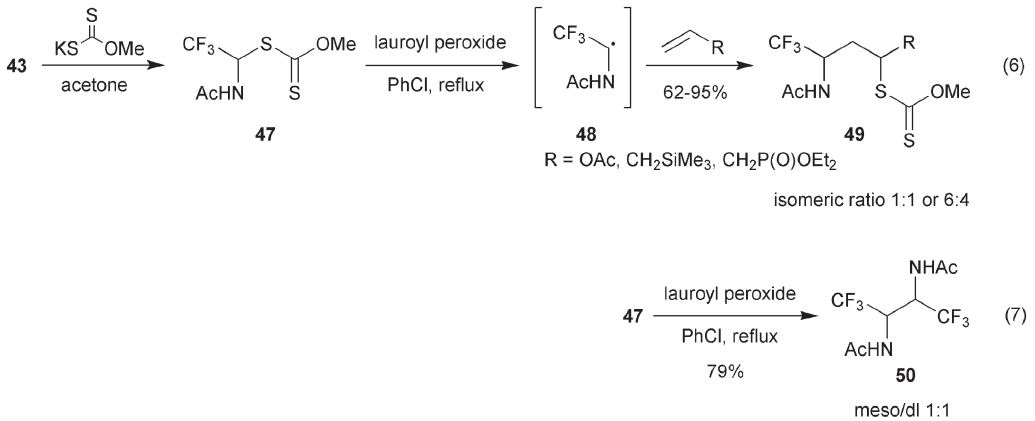
Very recently, the direct substitution of *N*,*O*-acetals **1e** by various phosphite derivatives, leading to trifluoromethyl aminophosphonic acid **52**, has been reported by Ingrassia (Scheme 19).[30] These latter are precursors of β-trifluoromethyl phosphonamidic acids and could represent a stable transition state analogue of bacterial transpeptidases.

7 Cycloaddition reactions

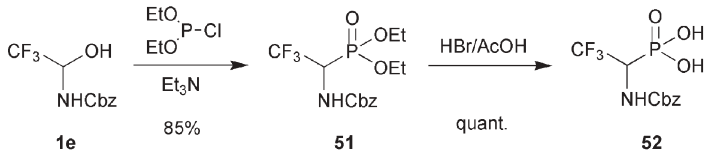
The utilisation of imines as substrates in cycloaddition processes is a direct way to nitrogen-containing cyclic molecules. In this line, imines **3** have been involved in [2 + 1], [2 + 2] and [4 + 2] cycloadditions, affording very interesting aziridine, β-lactam and piperidine derivatives. In the presence of Lewis acid catalysts, ($BF_3{\cdot}Et_2O$ or $Yb(OTf)_3$) trifluoromethyl aldimines **3b,c** reacted with ethyl diazoacetate (EDA) to afford *cis* CF_3-aziridine-2-carboxylates **53** in high yields and with high diastereoselectivities (Scheme 20).[31]

It is worthy of note that it is possible to access to CF_3-aziridine-2-carboxylates directly from fluoral hemi-acetal by a one-pot reaction. The reaction between the hemi-acetal, the amine and the catalyst in HFIP (hexafluoroisopropanol) as solvent, led to the product in good yield albeit with low diastereoselectivies.[32]

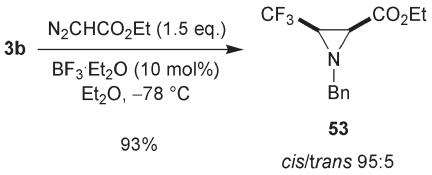
In 2003, Akiyama showed that *cis*- and *trans*-aziridines could be obtained selectively, according to the nature of the diazoacetate (for example, using N_2CHCO_2Ar led preferentially to the *trans*-product). Interestingly, the same group also described the synthesis of a diastereoenriched *cis*-aziridine **55** (94% de) by using a chiral diazoacetate derived from (*R*)-pantolactone **54** (Scheme 21).[33]



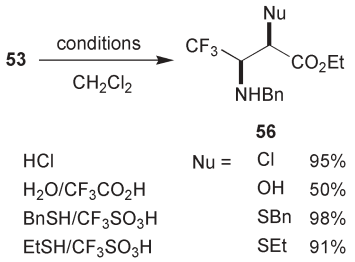
Scheme 18



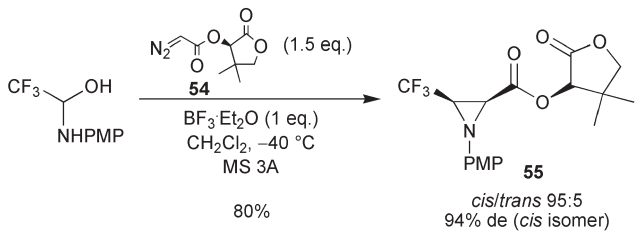
Scheme 19



Scheme 20



Scheme 22



Scheme 21

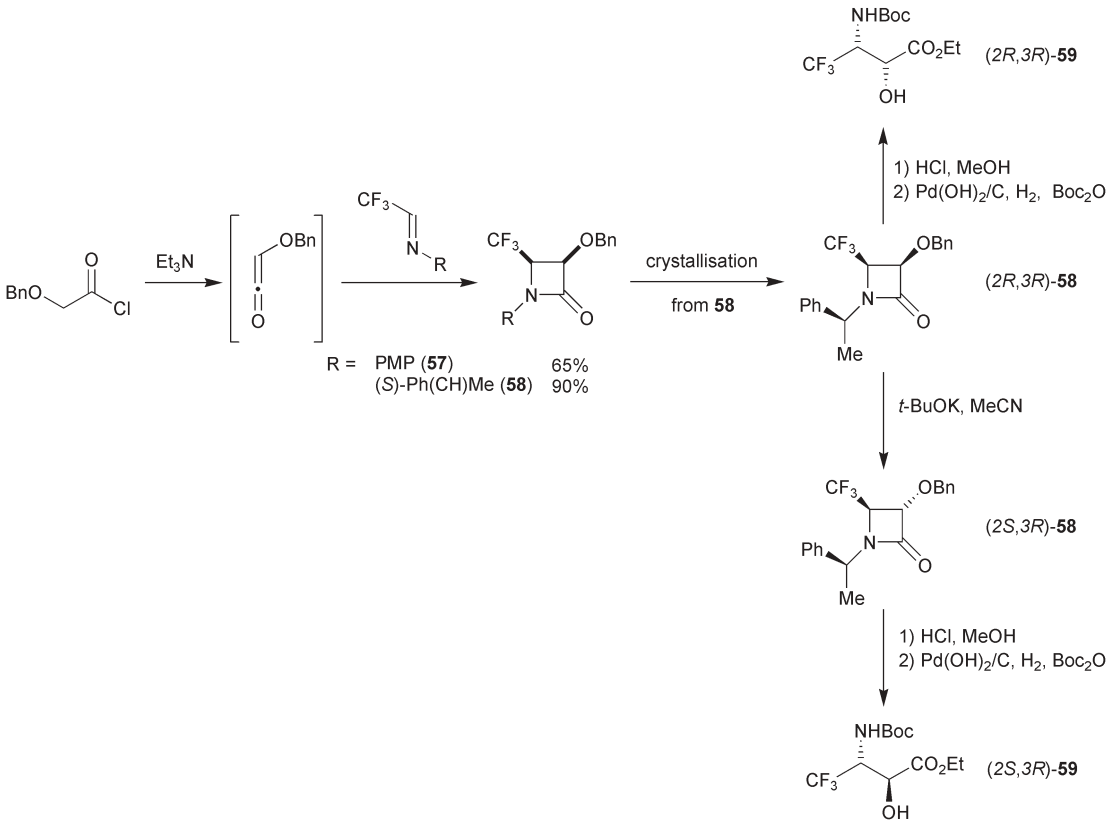
Due to the fact that aziridine-2-carboxylates are potentially useful as precursors of non proteogenic α- and β-amino acids, their reactivity has been widely studied in nonfluorinated series. In this context, it is surprising that only little attention has been devoted to the ring opening of CF_3-aziridine-2-carboxylates. From the *cis*-aziridine **53**, the opening reactions could be performed with HCl, H_2O/CF_3CO_2H, or thiols in the presence of triflic acid, providing stereoselectively the *syn* β-chloroamine, β-amino alcohol or β-amino sulfide, respectively, in high yields (Scheme 22). Conversely to the non-fluorinated analogues, the nucleophilic attack occurred only at C-2, highlighting the high energy required to develop a positive charge in α of a CF_3 moiety. As usually observed in the displacement of aziridine carboxylates, the acid-catalysed ring-opening occurred with complete inversion of configuration of C-2 and provided a single diastereomer of the β-amino ester, despite of the acidic catalysis.[31]

The [2 + 2] ketene-imine cycloaddition (Staudinger reaction) has turned as a classical tool to synthesize β-lactams, from which various peptidomimetic units can further be obtained. With a view to preparing fluoroalkyl analogues of isoserinates, the Staudinger reaction between benzyloxyketene and imines **3** has been performed in our laboratory, providing stereoselectively the *cis*-azetidinones **57–58** (Scheme 23).[34] Unfortunately, all attempts to perform the cycloaddition in an asymmetric manner failed. No chiral induction was observed when a chiral auxiliary (R = (*S*)-Ph(CH)Me) was present on the aldimine (**3f**). The alternative cyclocondensation of lithium ketene silyl acetal of chiral alcohols also gave disappointing results. As an alternative, it was found that the *cis* isomers of **58** were easily separated by spontaneous crystallisation, allowing the isolation of the two diastereomers of the azetidinone (only the enantiomer with 2*R*,3*R* configuration is shown in Scheme 23). Further debenzylation afforded the two enantiomers of the *syn*-CF_3-isoserinate **59**.[35] The isomerisation of the *cis*-β-lactams in basic medium provided the *trans*-β-lactams, offering the access to pure enantiomers of *anti*-CF_3-isoserinates (Scheme 23).[36]

Docetaxel (Taxotere®) has been proven to be one of the most efficient drugs in the fight against cancer.[37] Having in hand a stereoselective access to *cis*-β-lactams, precursors of isoserinates, it was planned to synthesize a fluorinated analogue of docetaxel where the phenyl moiety (stemming from the phenyl isoserinate side chain) would be replaced by a CF_3 substituent in C-3′. To this end, in collaboration with Ojima, the racemic β-lactam **60** has been coupled with the acetyl baccatine III, yielding the desired fluoromethylated docetaxel analogue. During the reaction, a high level kinetic resolution of the racemic β-lactam **60** occurred, and led to the taxoid with desired configurations at the C-2′ and C-3′ positions (2′*R*,3′*R*). The evaluation of the biological activity of **61** showed that this one had a very much higher *in vitro* cytotoxicity towards human cell lines than docetaxel or paclitaxel, in particular towards resistant cell lines MCF7-R (Scheme 24).[37] This is a remarkable example of the positive influence of fluoroalkyl groups on the biological activity of drugs.

Finally, aza-Diels–Alder reactions have also been investigated. Aldimine **3c** reacted as dienophile with Danishefsky's diene in the presence of Lewis acid ($BF_3{\cdot}Et_2O$ or $Yb(OTf)_3$) affording the corresponding dihydropyridinone as a sole regioisomer (Scheme 25).[38]

It is of importance to note that aldimine **3c** could also be used as dienes when reacted with electron rich dienophiles (vinyl ethers, vinyl sulfides, vinyl amides and carbamates) or even styrene, in the presence of $BF_3{\cdot}Et_2O$ or $Yb(OTf)_3$, providing CF_3-substituted alkoxy tetrahydroquinolines in excellent yields and in high to moderate *cis* stereoselectivity.

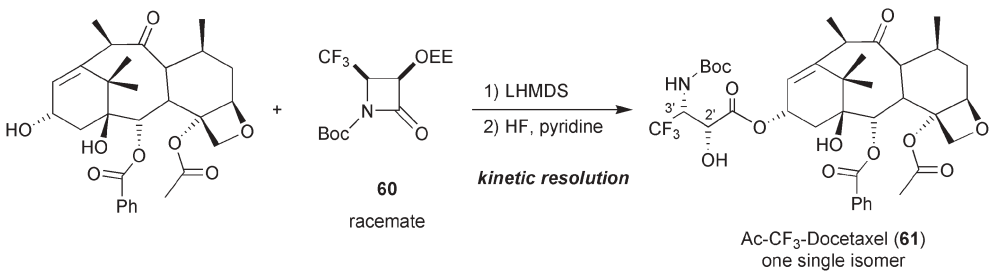


Scheme 23

All these cycloadducts could then be converted under acidic conditions to the corresponding quinolines (Scheme 26).

Interestingly, the tetrahydrocyclopentaquinoline **67** was obtained with cyclopentadiene as dienophile (Scheme 27).

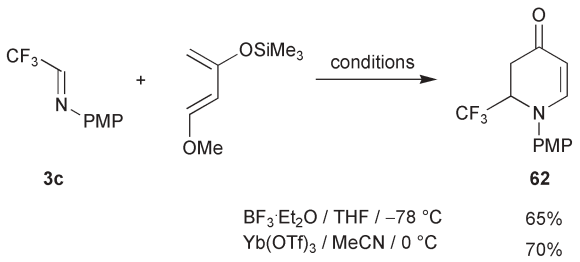
These [4 + 2] reactions highlight the very interesting and vast reactivity of CF_3-aldimines, offering an easy access to various CF_3-derivatives of potential biologically active nitrogenated cycles: piperidinones, quinolines and tetrahydroquinolines.



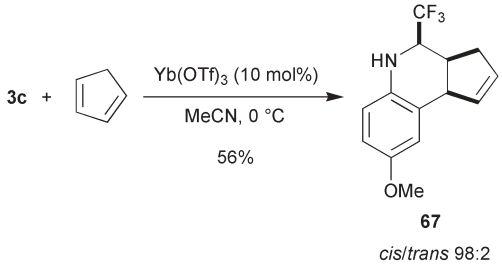
In vitro cytotoxicity on tumoral human cells lines: (IC50 nM)

	Paclitaxel	Docetaxel	Ac-CF_3-Docetaxel
A121 (ovarian)	6.3	1.2	0.3
A549 (NSCLS)	3.6	1.0	0.2
HT-29 (colon)	3.6	1.2	0.4
MCF7 (breast)	1.7	1.0	0.2
MCF7-R (breast)	200	350	17

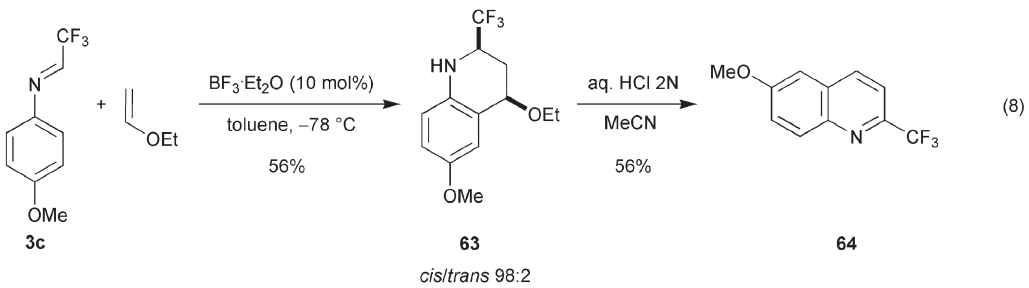
Scheme 24

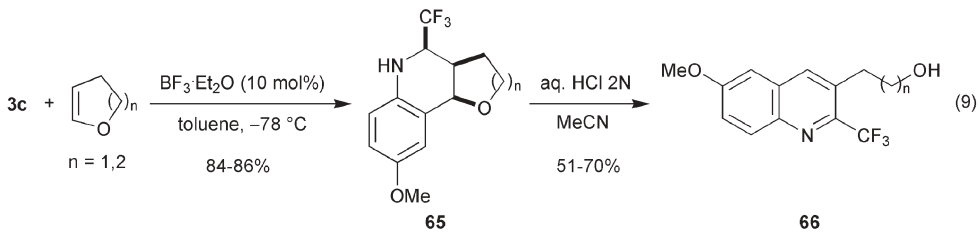


Scheme 25



Scheme 27





Scheme 26

8 Conclusion

During the last decade, the synthesis of nitrogenated molecules with CF_3 substituent has been considered of high importance, especially for pharmaceutical applications. Among all the possible methods, the transformation of readily available "N-derivatives of fluoral" (imines, *N,O*-acetals and oxazolidines) is certainly the most straightforward route to nitrogen-containing building blocks substituted with an α-CF_3 group. In the last years, their reactivity has been largely studied in cycloadditions, and as electrophiles in addition reactions. The setup of these methodologies has led to simple and powerful processes for the synthesis of fluoro-compounds, including optically active ones. Among them, heterocycles (β-lactams, piperidines, quinolines,...) amino alcohols, amino acids,... constitute very attractive synthons, as exemplified by their use as patterns in drugs which has already begun with success. While an increase of the reaction scope is expected in the forthcoming years, "N-derivatives of fluoral" already constitute a rich source of available scaffolds "ready to use" for parallel chemistry.

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References

1 For some general reviews on fluorinated compounds: (*a*) *Organofluorine Chemistry: Principles and Commercial Applications*, eds. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum, New York, 1994; (*b*) *Chemistry of Organic Fluorine Compounds II*, eds. M. Hudlicky and A. E. Pavlath, ACS, Washington, 1995.
2 For some general reviews on biological effects of fluorinated compounds: (*a*) *Biomedical Frontiers of Fluorine Chemistry*, eds. I. Ojima, J. R. McCarthy and J. T. Welch, ACS, Washington, 1996; (*b*) J.-P. Bégué and D. Bonnet-Delpon, *Chimie Bioorganique et Médicinale du Fluor*, Edisciences-CNRS Publishers, 2005.
3 For a recent review: B. R. Langlois and T. Billard, *Synthesis*, 2003, 185.
4 Y. Xu, W. R. Dolbier, Jr. and X. X. Rong, *J. Org. Chem.*, 1997, **62**, 1576.
5 A. Ishii, K. Higashiyama and K. Mikami, *Synlett*, 1997, 1381.
6 D. Enders and K. Funabiki, *Org. Lett.*, 2001, **3**, 1575.
7 F. Gosselin, A. Roy, P. D. O'Shea, C.-y. Chen and R. P. Volante, *Org. Lett.*, 2004, **6**, 641.
8 S. Jonoshita, A. Harada, M. Omote, A. Ando and I. Kumadaki, *Chem. Pharm. Bull.*, 1999, **47**, 656.
9 T. Billard and B. R. Langlois, *J. Org. Chem.*, 2002, **67**, 997.
10 K. Funabiki, M. Nagamori, M. Matsui and D. Enders, *Synthesis*, 2002, 2585.
11 N. Lebouvier, C. Laroche, F. Huguenot and T. Brigaud, *Tetrahedron Lett.*, 2002, **43**, 2827.
12 (*a*) J. Legros, F. Meyer, M. Colibœuf, B. Crousse, D. Bonnet-Delpon and J.-P. Bégué, *J. Org. Chem.*, 2003, **68**, 6444; (*b*) D. Bonnet-Delpon, J.-P. Bégué, J. Legros, B. Crousse and

F. Meyer, (Rhodia Chimie, Fr.) PCT Int. Appl., WO 2003095415, 2003.
13 G. Magueur, J. Legros, F. Meyer, M. Ourévitch, B. Crousse and D. Bonnet-Delpon, *Eur. J. Org. Chem.*, 2005, DOI: 10.1002/ejoc.200400719.
14 S. Gille, A. Ferry, T. Billard and B. R. Langlois, *J. Org. Chem.*, 2003, **68**, 8932.
15 N. T. Ngoc Tam, G. Magueur, M. Ourévitch, B. Crousse, J.-P. Bégué and D. Bonnet-Delpon, *J. Org. Chem.*, 2005, **70**, 699 and references therein.
16 G. Magueur, B. Crousse and D. Bonnet-Delpon, *Tetrahedron Lett.*, 2005, **46**, 2219.
17 J. Takaya, H. Kagoshima and T. Akiyama, *Org. Lett.*, 2000, **2**, 1577.
18 T. Ishihara, K. Ichihara and H. Yamanaka, *Tetrahedron*, 1996, **52**, 255.
19 V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, L. Van Meervelt and N. Mischenko, *Tetrahedron Lett.*, 1997, **38**, 4671.
20 K. Funabiki, M. Nagamori, S. Goushi and M. Matsui, *Chem. Commun.*, 2004, 1928.
21 M. V. Spanedda, M. Ourévitch, B. Crousse, J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron Lett.*, 2004, **45**, 5023.
22 Y. Gong and K. Kato, *J. Fluorine Chem.*, 2001, **111**, 77.
23 P. Bravo, M. Guidetti, F. Viani, M. Zanda, A. L. Markovsky, A. E. Sorochinsky, I. V. Soloshonok and V. A. Soloshonok, *Tetrahedron*, 1998, **54**, 12789.
24 Y. Gong, K. Kato and H. Kimoto, *Bull. Chem. Soc. Jpn*, 2002, **75**, 2637 and references therein.
25 Y. Gong and K. Kato, *Tetrahedron: Asymmetry*, 2001, **12**, 2121.
26 F. Weygand, W. Steglich, I. Lengyel and F. Fraunberger, *Chem. Ber.*, 1966, **99**, 1932.
27 F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer and W. Oettmeier, *Chem. Ber.*, 1966, **99**, 1944.
28 T. Tanaka, Y. Ishiguro and K. Mitsuhashi, *Bull. Chem. Soc. Jpn*, 1993, **66**, 661 and references therein.
29 F. Gagosz and S. Z. Zard, *Org. Lett.*, 2003, **6**, 2655.
30 P. de Medina, L. S. Ingrassia and M. E. Mulliez, *J. Org. Chem.*, 2003, **68**, 8424.
31 B. Crousse, S. Narizuka, D. Bonnet-Delpon and J.-P. Bégué, *Synlett*, 2001, 679.
32 M. V. Spanedda, S. Narizuka, B. Crousse, D. Bonnet-Delpon and J.-P. Bégué, *Collect. Czech. Chem. Commun.*, 2002, **67**, 1359.
33 T. Akiyama, S. Ogi and K. Fuchibe, *Tetrahedron Lett.*, 2003, **44**, 4011.
34 A. Abouabdellah, J.-P. Bégué and D. Bonnet-Delpon, *Synlett*, 1996, 399.
35 A. Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon and T. T. Thanh Nga, *J. Org. Chem.*, 1997, **62**, 8826.
36 A. Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon, A. Kornilov, I. Rodrigues and T. T. Thanh Nga, in *Asymmetric Fluoroorganic Chemistry, Synthesis, Application and Future Directions*, ed. P.V. Ramachandran, ACS Symposium Series 746: Washington, 2000, p. 84.
37 I. Ojima, J. C. Slater, P. Pera, J. M. Veith, A. Abouabdellah, J. P. Bégué and R. J. Bernacki, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 133 and references therein.
38 (*a*) B. Crousse, J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron Lett.*, 1998, **39**, 5765; (*b*) B. Crousse, J.-P. Bégué and D. Bonnet-Delpon, *J. Org. Chem.*, 2000, **65**, 5009.

