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Authors: Aurelien Honraedt, Arie Van Der Lee, Jean-Marc Campagne, and Eric Leclerc

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α,α-Difluoro-α-(trimethylsilyl)acetamides as Versatile Reagents for the Preparation of Difluorinated Aldol and Mannich Adducts

Aurélien Honraedt,[a] Arie Van Der Lee,[b] Jean-Marc Campagne[a] and Eric Leclerc*[a]

[a] Dr. A. Honraedt, Pr. J.-M. Campagne, E. Leclerc
Institut Charles Gerhardt UMR 5253 CNRS-UM2-UM1-ENSCM
Ecole Nationale Supérieure de Chimie de Montpellier
8, rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France.
E-mail: eric.leclerc@enscm.fr

[b] Dr. A. Van Der Lee
Institut Européen des Membranes, ENSCM/UMII/UMR-CNRS 5635
Pl. Eugène Bataillon, CC 047, 34095 Montpellier, Cedex 5, France.

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Abstract. The very efficient addition of α,α-difluoro-α-(trimethylsilyl)acetamides to aldehydes, ketones and *N*-(*tert*-butanesulfinyl)imines is described. The reaction is promoted by a catalytic amount of TBAT and high yields, as well as very high stereoselectivities in the case of *N*-(*tert*-butanesulfinyl)imines, are achieved. The synthetic potential of this method is illustrated by the conversion of the resulting products to β-hydroxyketones, diols and β-aminoalcohols by addition of various Grignard reagents or reduction of the amide moiety.

Keywords: fluorine; aldol reaction; Mannich reaction; Grignard reagent; diastereoselectivity

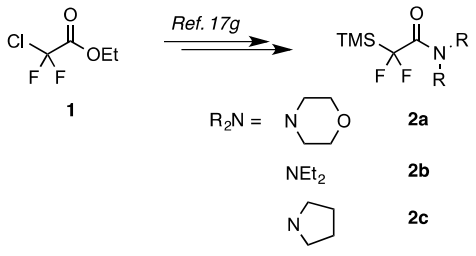
Introduction

The tremendous interest that have generated fluorinated molecules in the last few years finds its origin in the peculiar properties that fluorine atoms bestow to the bioactivity of drug-like molecules. Indeed, the electronic and stereoelectronic features of the fluorine atom and of the C–F bond has often major consequences on the lipophilicity, the pKa, the metabolic stability and, of course, the binding with a receptor.[1] As a result, the pharmacodynamic or pharmacokinetic properties of drugs featuring fluorine atoms in judicious positions may be considerably improved. This is illustrated by the ever-increasing occurrence of fluorinated molecules among the list of marketed drugs and agrochemicals.[2] If most synthetic strategies concentrate on fluorination and trifluoromethylation reactions, the direct introduction of CF_2Y (Y ≠ F) group is also the subject of an increasing number of studies.[3,4] This is of course a more widespread and diffuse topic since the nature and the role of the Y substituent may vary widely. Indeed, as far as difluoromethylation is concerned, Y can be hydrogen atom for the direct introduction of CF_2H but also a reducible, heteroatom-centered group for an indirect reaction (Y = SR, SO_2R, …).[5],[6] But various heteroatom or carbon-centered functional groups can also be introduced (Y = $P(O)(OR)_2$, C(O)X, alkyl, aryl, …), either for structural requirements or for post-functionalization purposes.[7] For that matter, the carbonyl function constitutes an interesting starting point for further synthetic elaboration as well as a stabilizing group for the addition of a nucleophilic difluoromethylating agent. Consequently, the preparation of difluorinated aldol and Mannich products, either through direct aldol, Reformatsky-type or Mukaiyama-type reactions, has known considerable developments.[8,9] However, most of these approaches either suffer from the use of strong bases or overstoichiometric amounts of metallic salts, or imply the sometimes delicate preparation of difluorinated silyl enol ethers.[10] Alternatives to these classical approaches have been recently devised, such as the elegant trifluoroacetate release strategy pioneered by Colby and Wolf, or a one-pot one-catalyst procedure relying on a Brook rearrangement/fluoride elimination sequence recently reported by us.[11,12] Both methods have indeed allowed the mild *in situ* release of difluoroenolates and their addition to carbonyl electrophiles and imines. We wish to present herein a study demonstrating that α,α-difluoro-α-(trimethylsilyl)acetamides can act as stable difluoroenoxysilane surrogates that can successfully

be added to aldehydes, ketones and *N*-(*tert*-butanesulfinyl)aldimines in a high-yielding and highly selective process. Moreover, it is shown that the amide group of the resulting adducts can easily be converted to useful functional groups such as a primary alcohol and aliphatic or aromatic ketones.

Results and Discussion

During the study of a one-pot three-component tetra-*n*-butylammonium diphenyltrifluorosilicate (TBAT)-catalyzed Mannich reaction starting from Ruppert-Prakash reagent, acylsilanes and various activated imines, we noticed that the ammonium difluoroenolate, which is supposedly generated during the one-pot process, was unreactive towards *N*-(*tert*-butanesulfinyl)imines.[13] A careful examination of the litterature indeed shows that the addition to sulfinylimines has been mostly accomplished either from difluoroenol ethers, under Lewis or Brønsted acid activation,[8g,11d,14] or *via* imino-Reformatsky reactions.[9a,9c,9k] The addition of difluoroenoxysilanes to sulfinylimines promoted only by a Lewis base, without any activation of the electrophile, has never been reported. In contrast, the Lewis base-promoted addition of $TMSCH_2CO_2Et$ and $TMSCF_2P(O)(OEt)_2$ to *N*-(*tert*-butanesulfinyl)imines has been reported, suggesting a marked difference in reactivity between these silyl carbon nucleophiles and *O*-silyl enol ethers.[15] Reagents of the general type $TMSCF_2COX$ thus appeared as interesting alternatives to difluoroenolates and enoxysilanes. Esters $TMSCF_2CO_2R$ can be prepared by electroreduction of the corresponding chlorodifluoroacetate or trifluoroacetate and their nucleophilic addition to aldehydes and imines has been fragmentarily described in a handful of reports.[16] On the other hand, α,α-difluoro-α-(trimethylsilyl)acetamides can be easily prepared in large scale in a two-step sequence from ethyl chlorodifluoroacetate. Such reagents have been used in cross-coupling or radical addition reactions but, to the best of our knowledge, their Lewis base-promoted addition to carbonyl derivatives and imines is almost ignored.[17,18] We thus embarked on an exhaustive study of their reactivity towards carbonyl electrophiles and imines.



Scheme 1. α,α-Difluoro-α-(trimethylsilyl)acetamides **2a-c**.

α,α-Difluoro-α-(trimethylsilyl)acetamides **2a-c** were thus prepared from **1** according to the two-step method reported by Hartwig.[17g] The addition of **2a** to 4-bromobenzaldehyde was first studied and representative efforts in the optimization process are depicted in table 1. The standard reaction conditions used for the one-pot aldol and Mannich reactions (TBAT 0.1 equiv., THF, – 30°C, entry 1) immediately allowed us to isolate the desired aldol-type product in 83% yield. The reaction time was however a bit long and could be reduced to 3h by running the reaction at 0°C without erosion of the yield (table 1, entry 2). However, these conditions remained unsatisfactory for two reasons: (i) a mixture of OH and OTMS products (**3** and **4**) was systematically obtained when the reaction was worked-up with a simple evaporation or a mild hydrolysis with saturated NH_4Cl; (ii) a residual amount of unreacted aldehyde could be detected at the end of these reactions while **2a** was totally consumed, leaving only its protodesilylated derivative **2'a** as a by-product. A short survey allowed us to optimize our conditions (table 1, entry 3): the use of 1.2 equivalent of **2a** allowed full conversion of the aldehyde, performing the reaction at rt and using a higher concentration shortened the reaction time to 1h while an acidic work-up allowed the isolation of only the free alcohol. Aldol **3** was thus obtained in an excellent yield of 92%. Interestingly, we were able to obtain only the OTMS product **4** in 75% yield by using *N*,*O*-*bis*(trimethylsilyl)acetamide (BSA) as an additive (table 1 entry 4). This very reactive silylating agent had also an accelerating effect since the reaction could be performed at –30°C in only 2h, even if lowering the temperature to –78°C resulted in a sluggish reaction. This point will be discussed below but this accelerating effect highlight one of the few drawbacks of using nucleophiles such as **2** instead of difluoroenoxysilanes, meaning the catalyst turnover and the initiation of a new catalytic cycle.

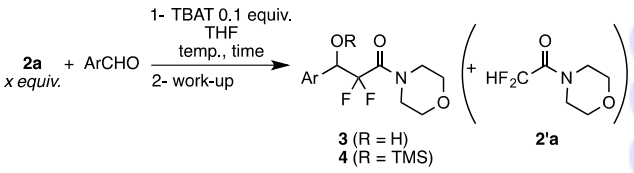


Table 1. Optimization of the aldol-type reaction.[a]

Entry	Temp. [°C]	x	Time [h]	Work-up	**3** + **4** [%][b]
1[c]	–30	1	20	evaporation	83 + 6
2[c]	0	1	3	evaporation	80 + 7
3[d]	rt	1.2	1	aq. HCl/MeOH	92 + 0
4[e,f]	–30	1.2	2	sat. NH_4Cl	0 + 75
5[e,f]	–78	1.2	2	sat. NH_4Cl	0 + 34

[a] Ar = 4-BrC_6H_4. [b] Isolated yields of **3** and **4**. [c] Concentration of the reaction medium was c = 0.2M. [d] Concentration of the reaction medium was c = 1M. [e] Concentration of the reaction medium was c = 0.1M. [f] BSA was used as an additive (1 equiv.).

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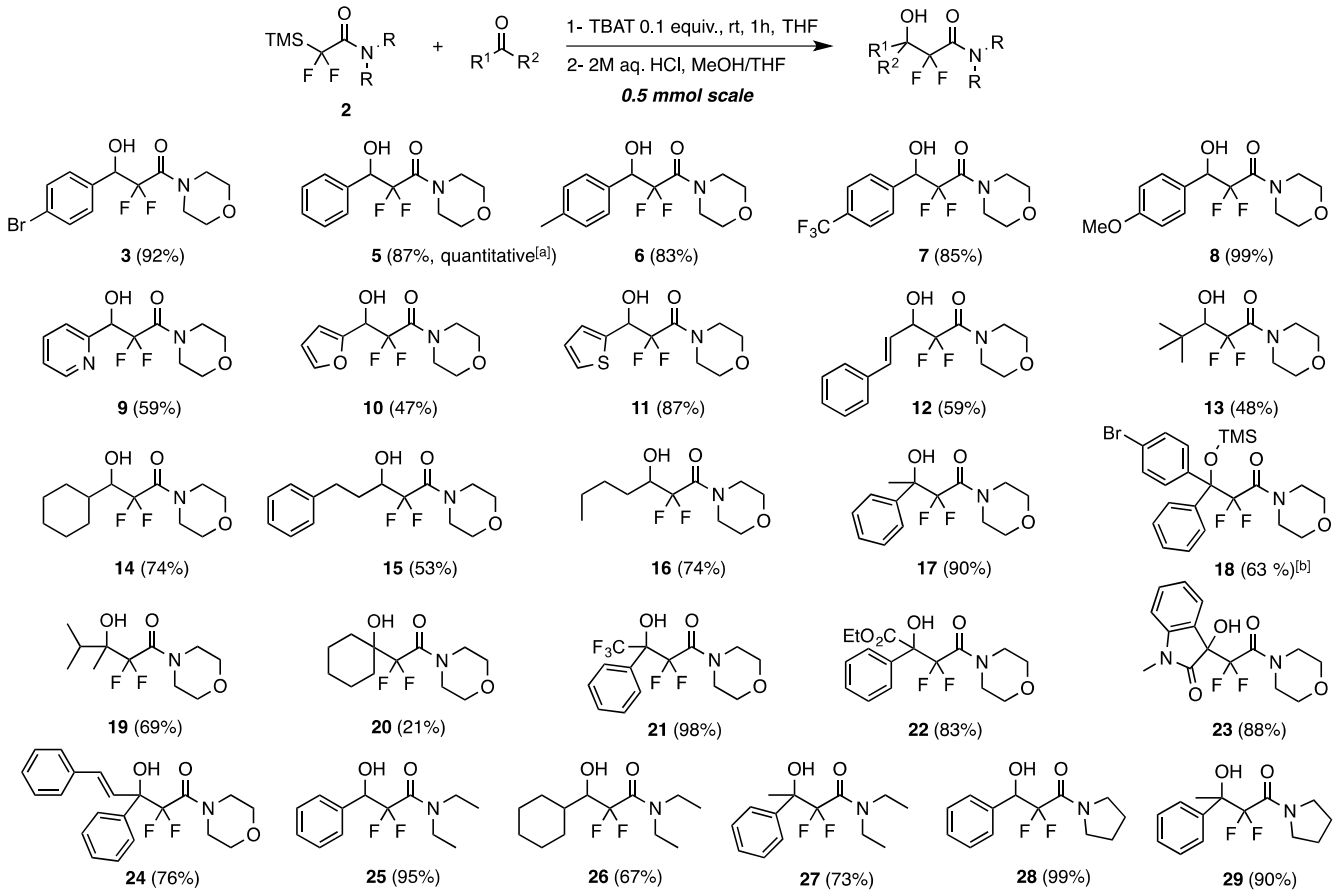

Scheme 2. Scope of the aldol reaction. [a] Isolated yield on 4 mmol scale. [b] Hydrolysis was performed using aq. sat. NH_4Cl.

The optimized conditions depicted in table 1, entry 3 were applied to a wide range of carbonyl electrophiles, first using **2a** as the nucleophile. Good to excellent yields were obtained in the addition to various aromatic aldehydes bearing electron-withdrawing or electron-donating groups (compounds **3**-**8**, 83 to 99% yield). Lower but still practical yields are obtained with heteroaromatic aldehydes (compounds **9**-**11**, 47 to 87% yield). To our delight, the reaction was also effective with non-aromatic aldehydes, which was not the case in our previous studies of one-pot aldol reactions. Cinnamaldehyde but also linear or branched aliphatic aldehydes are efficiently converted to aldols **12**-**16** in fair to good yields (48-74%). More interestingly, ketones are also suitable electrophiles that lead to compounds **17**-**23** in moderate to excellent yields. If the reaction with cyclohexanone affords compound **20** in a disappointing 21% yield, other aromatic (**17**-**18**, 63 to 90%), aliphatic (**19**, 69%), and activated ketones (**21**-**23**, 83 to 98%) give satisfactory results. Interestingly, if the addition to *p*-bromobenzophenone was efficient, the resulting TMS ether was surprisingly stable. The standard HCl hydrolysis was totally uneffective and so was an attempt of tetra-*n*-butylammonium fluoride (TBAF)-mediated deprotection. It was thus decided to isolate this addition product as its TMS ether **18** (reaction quenched with sat. NH_4Cl) in 63 % yield. The use of enones as electrophiles was also investigated. The reaction with pent-3-ene-2-one as the electrophile afforded a messy crude reaction mixture from which the 1,2-addition product appeared as the major compound while only traces of the 1,4-adduct could be detected. However, the addition onto chalcone afforded exclusively the 1,2-addition product **24** in a good 76% yield. The reaction is also quite insensitive to the nature of the nitrogen substituents of **2**. **2b** and **2c** indeed react with aldehydes and ketones with a similar efficiency (**25**-**29**, 67 to 95 %). Finally, this methodology appears to be quite robust since a small scale-up to 4 mmol resulted in a substantial increase of the isolated yield (**5**, quantitative).

Having assessed the reactivity of **2** with a wide range of carbonyl electrophiles, our next move was to examine the addition to sulfinylimines. As mentioned above, *in situ*-generated difluoroenoxysilanes failed to react with these electrophiles. Our first attempts in the addition of **2a** onto sulfinylimine **30** failed as long as the reactions were performed at temperatures below 0°C. However, a first attempt at room temperature allowed us to observe a sluggish but workable reaction (table 2, entry 1). A 54% conversion was indeed

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observed for the sulfinamide after 18h of reaction and addition product **31** could be detected in the crude mixture along with a substantial amount of the protodesilylation product **2'a**. A short solvent survey was therefore conducted in order to enhance the rate of the reaction and limit the hydrolysis of **2a**. However, the use of less polar solvents such as CH_2Cl_2 or $CHCl_3$ (entries 2 and 3) totally inhibits the reaction while MeCN and DMF only led to complex mixtures that were devoid of **31** (entries 4 and 5). As for our previous reports, THF appeared to be the sole operative solvent. If the use of tetramethylammonium fluoride (TMAF) as the promoter did not improve our first result (entry 6), performing the reaction at higher concentration was eventually sufficient to fully convert **30** (entry 7). **31** was in that case obtained in 78% isolated yield and, most remarkably, as only one diastereomer detectable by ^1H and ^{19}F NMR analysis of the crude mixture.

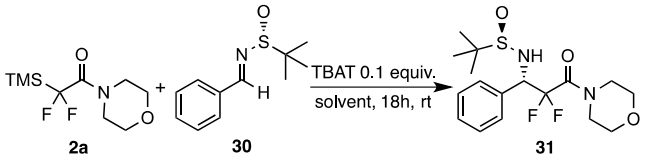
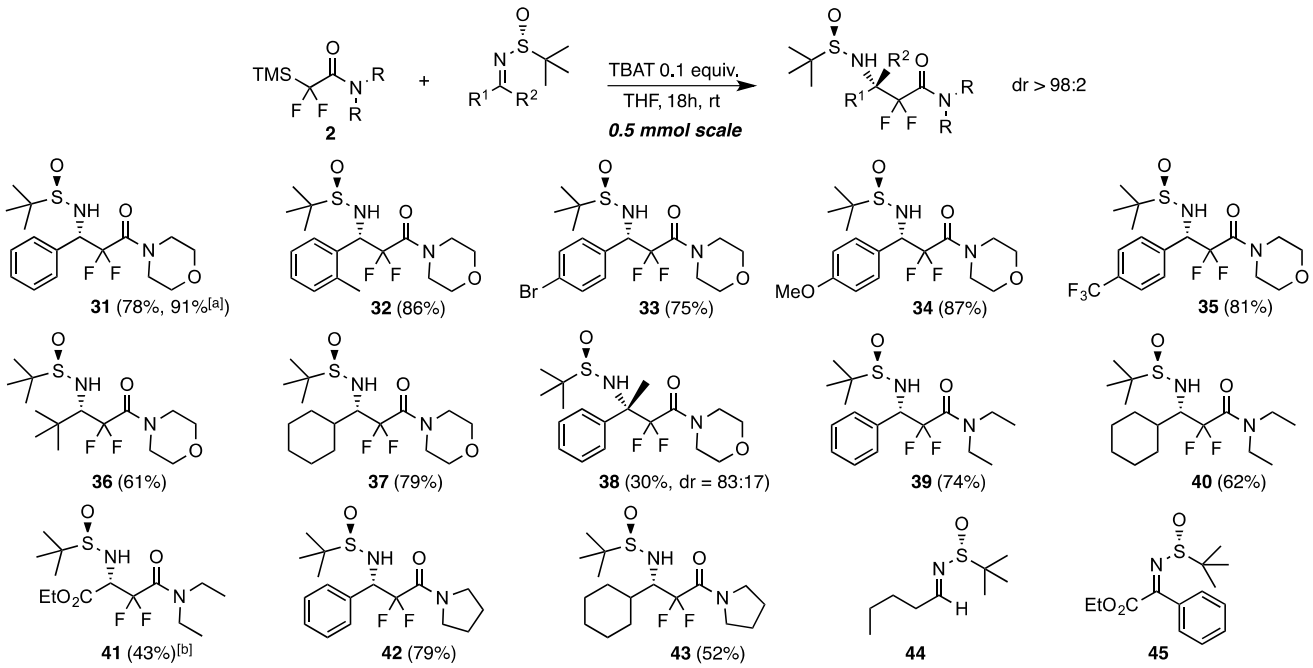


Table 2. Optimization of the Mannich-type reaction.[a]

Entry	Solvent	Concentration	Conversion [%][b]
1	THF	0.1M	54
2	CH_2Cl_2	0.1M	<5
3	$CHCl_3$	0.1M	0
4	MeCN	0.1M	n.d.
5	DMF	0.1M	n.d.
6	THF[c]	0.1M	24
7	THF	1M	100[d]

[a] The reaction was performed using 1.2 equiv. of **2a**. [b] Conversion of **30** assessed by ^1H NMR analysis of the crude mixture. [c] 0.1 equiv. of TMAF was used instead of TBAT. [d] **31** was isolated in 78% yield

The scope and limitations of this Mannich reaction was afterwards examined on the basis of these optimized conditions. A small range of aldimines were tested and, as for aldehydes, aromatic as well as aliphatic substrates were quite effective in this reaction. The remarkable stereoselectivity observed for **31** appeared to be general, at least for aldimines, since only one diastereomer could be detected by ^1H and ^{19}F NMR analysis of the crude mixture for compounds **31**-**37**. As for the aldol reaction, a small scale-up resulted in an increase of the yield from 78 to 91% for **31**. The reaction is also comparably efficient using substrates **2b** and **2c** (products **39**-**43**). The first limitation appeared when the ketimine derived from acetophenone was used as the electrophile. Compound **38** was obtained in low yield (30%) and with moderate stereoselectivity (83:17 in the crude mixture). Surprisingly, while the reaction was efficient on aliphatic imines derived from pivalaldehyde and cyclohexanecarboxaldehyde, no product could be detected using linear imine **44**. Finally, the use "activated" imines derived from ethyl glyoxylate and ethyl phenylglyoxylate was not as straightforward as anticipated. Indeed, we were able to isolate α-aminoester **41** in 43% yield and as a single diasteromer but complete conversion required the use of a stoichiometric amount of TBAT. However, even under these conditions, ketimine **45** remained totally unreactive. Nonetheless, the preparation of product **41** paves the way for an efficient stereoselective access to β-amino-α,α-difluoroaminoacids.



Scheme 3. Scope of the Mannich reaction. [a] Isolated yield on 1 mmol scale. [b] 1.2 equivalent of TBAT was used.

The relative configuration of the major diasteromer was assigned on the basis of an X-Ray diffraction study performed with compound **33**.[19] As illustrated in the ORTEP drawing (figure 1), the (R_S,*S*) configuration was assigned to **33** and, by analogy, to the other products. This stereochemical outcome is perfectly consistent with literature precedents.[15,20] Indeed, in the absence on any chelating species, an open transition state in which the imine adopts the more stable *s-cis* conformation should be favored (figure 1). This is of course in contrast with Reformatsky reactions that affords the opposite diastereomer through a chelated transition state.[9a,9c,9k]

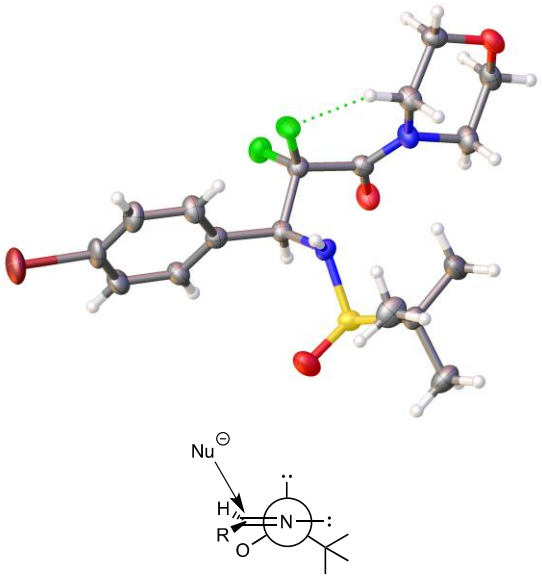
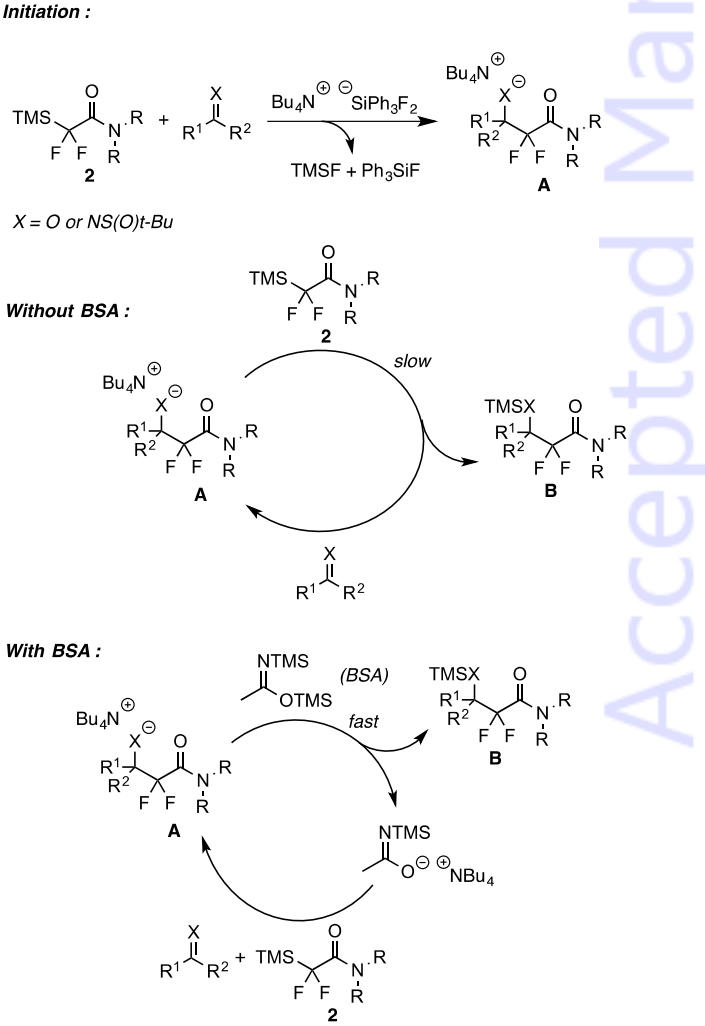


Figure 1. ORTEP drawing of **32** and transition state for the addition.

The lack of reactivity with ketimines and electron-poor imines may be another outward sign of the problem of catalyst turnover when using **2** as the pronucleophile. Indeed, in the absence of any additive, a new catalytic cycle can begin only if the anion **A** resulting from the TBAT-mediated addition to the electrophile is able to activate another molecule of **2** (scheme 4, pathway a). The reaction product is thus silylated to produce **B** and another addition can proceed. This silyl transfer is probably much slower in the case of α,α-difluoro-α-(trimethylsilyl)acetamides **2** than in the case of difluoroenoxysilanes. This hypothesis is illustrated by the reaction temperature used for the aldol reaction: a workable conversion can only be achieved at room temperature with pronucleophiles **2** while the reaction with *in situ*-generated difluoenoxysilane were performed at –30°C. In contrast, the use of BSA as an additive allows the reaction to work at –30°C. The role of BSA in that case is dual: it allows a very fast silylation of **A**, releasing at the same time a strong Lewis base that can efficiently activate the pronucleophile (scheme 4, pathway b). This results in a global enhancement of the reaction rate. The turnover issue in the absence of additive might also explain the difference in reactivity between carbonyl electrophiles and sulfinylimines. While reactions with the first, including moderately reactive ketones, are complete within 1h, the second require 18h for a full conversion. The difference in electrophilicity between these two classes of reagents can hardly account for such a difference. On the other hand, the poor Lewis basicity and the steric hindrance of the resulting amide product **A** in the case of addition to sulfinylimines might considerably slow down the silyl transfer compared to the alkoxide intermediate of the aldol reaction.



Scheme 4. Reaction intermediate and catalyst turnover.

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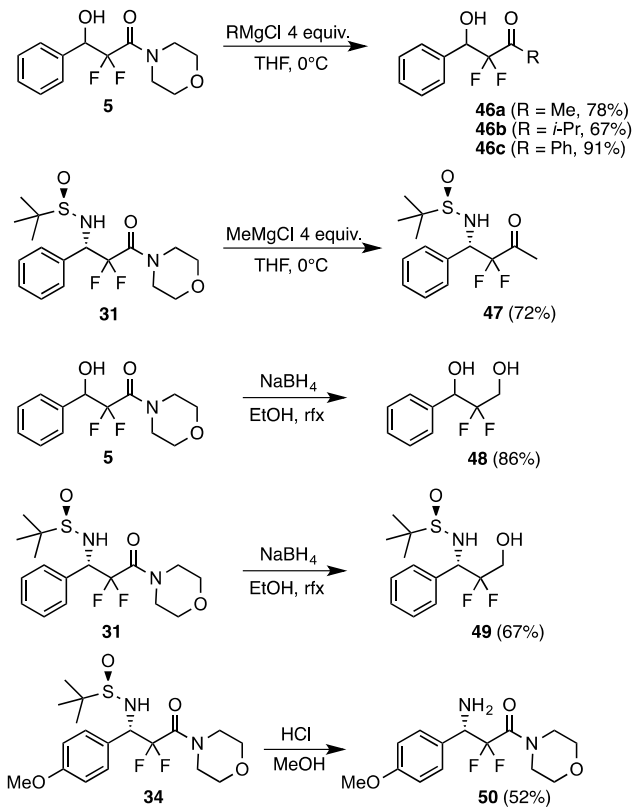
Our next move was to explore the functionalization of the amide residue and demonstrate that our aldol and Mannich adducts could serve as versatile intermediates for the synthesis of difluorinated building-blocks. Morpholinoamides generally exhibits a reactivity similar to Weinreb amides thanks to a stabilization of the tetrahedral intermediate resulting from an organometallic addition by an internal chelation. In the case of difluorinated amide, this stabilization is reinforced by the electron-withdrawing effect of the CF_2 moiety that slows down the collapse of the tetrahedral intermediate. Consequently, the addition of an excess of Grignard reagents to aldol **5** and sulfinamide **31** cleanly affords the corresponding ketones **46** and **47** (scheme 5).[17g] An important feature is the facile access to aliphatic ketone derivatives that cannot be directly prepared through Mukaiyama-type reaction, as mentioned earlier, and that have never been reported through imino-Reformatsky approach.[9a] Our two-step process is an efficient route to such compounds that therefore still competes with our former one-pot procedure or with direct Reformatsky reactions. Complete reduction of the amide group is also possible and affords 1,3-diols or 1,3-aminoalcohols **48** and **49** in good yields (scheme 5). Other transformations were described by Hartwig for α-aryl-α,α-difluoroacetamides and should be applicable to our aldol and Mannich products.[17g] Finally, and as widely described in the literature, the sulfinamide group of **34** could be converted to the free amine (**50**, 52%) using HCl in methanol (scheme 5).



Scheme 5. Derivatization of aldol and Mannich adducts.

Conclusion

We have thus described the very efficient TBAT-catalyzed addition of α,α-difluoro-α-(trimethylsilyl)acetamides to aldehydes, ketones and *N*-(*tert*-butanesulfinyl)aldimines. The addition to carbonyl electrophiles is fairly general as good to excellent yields are obtained with a wide range of aromatic and aliphatic aldehydes and ketones. The addition to sulfinylaldimines allows the preparation of β-amino-α,α-difluoroamides with very high diastereoselectivities while ketimines appeared to be more reluctant substrates. Finally, these aldol and Mannich products can be easily converted to ketones, diols and aminoalcohols thanks to very efficient addition of Grignard reagents or to the complete reduction of the amide function. Overall, the efficiency of α,α-difluoro-α-(trimethylsilyl)acetamides as stable and easily accessible surrogates to difluoroenoxysilanes was clearly demonstrated, as well as their versatility in terms of reactivity and synthetic potential. A catalytic asymmetric addition of **2** to carbonyl electrophiles is currently under investigation in our group and results will be reported in due course.

Experimental Section

General procedure for the aldol reaction.

To a solution of the aldehyde/ketone (0.5 mmol) and trimethyl silyl α,α-difluoroacetamide **2a-c** (0.6 mmol, 1.2 eq) in dry THF (0.5 mL, C=1) at room temperature was added TBAT (27.0 mg, 10 mol%). The mixture was stirred for one hour and then diluted with methanol (1.0 mL, EtOH was used in presence of ethyl ester derivatives). A 2M HCl aqueous solution (1.0 mL) was added and the stirring continued for 1h. The mixture was carefully quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were successively washed with brine (10 mL), dried on Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by Biotage Isolera (25 g SNAP Ultra cartridge, EtOAc/pentane mixture) to afford the title compound.

General procedure for the Mannich reaction.

To a solution of the (*R*S)-*tert*-butanesulfinylaldimine/ketimine (0.5 mmol) and trimethyl silyl α,α-difluoroacetamide **2a-c** (0.6 mmol, 1.2 eq) in dry THF (0.5 mL, C=1) at room temperature was added TBAT (27.0 mg, 10 mol%). The mixture was stirred for 18 hours at room temperature and then quenched with a saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were successively washed with brine (10 mL), dried on Na_2SO_4, filtered and concentrated in vacuo. Diastereomeric ratios were determined by NMR 1H. The crude reaction mixture was purified by Biotage Isolera (25 g SNAP Ultra cartridge, EtOAc/pentane mixture) to afford the title compound.

General procedure for the Grignard addition to 5 and 30.

To a solution of **5** or **31** (0.5 mmol) in dry THF (5.0 mL, C=0.1) at –40°C was added the Grignard reagent solution (2.0 mmol). The mixture was allowed to warm up to r.t. for one hour (4h at 0°C for the addition of PhMgCl). The solution was cooled to 0°C and then quenched with a 1M HCl aqueous solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were successively washed with brine (10 mL), dried on Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by Biotage Isolera (25 g SNAP Ultra cartridge, EtOAc/pentane mixture) to afford the title compound.

General procedure for the reduction of 5 and 31.

To a solution of of **5** or **30** (0.5 mmol) in EtOH (C= 0.025) was added $NaBH_4$ (7.5 mmol). The mixture was heated at reflux for four hours. The mixture was cooled down to 0°C then quenched with a 1M HCl aqueous solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were successively dried on Na_2SO_4, filtered and concentrated in vacuo. The crude reaction mixture was purified by Biotage Isolera (25 g SNAP Ultra cartridge, EtOAc/pentane mixture) to afford the title compound.

Supporting Information Available.

Detailed experimental procedures, analytical data of compounds **3** and **5**-**50** as well as copies of their ^{1}H, ^{13}C and ^{19}F NMR spectra are presented in the Supporting Information. Crystallographic data and the CIF file relative to **32** are also included.

Acknowledgements

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FULL PAPER

α,α-Difluoro-α-(trimethylsilyl)acetamides as Versatile Reagents for the Preparation of Difluorinated Aldol and Mannich Adducts

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Aurélien Honraedt,[a] Arie Van Der Lee,[b] Jean-Marc Campagne[a] and Eric Leclerc*[a]