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Stereoselective metal-free catalytic synthesis of chiral trifluoromethyl aryl and alkyl amines†

Andrea Genoni, Maurizio Benaglia,* Elisabetta Massolo and Sergio Rossi

The enantioselective organocatalytic reduction of trifluoromethyl aryl and alkyl ketoimines afforded the corresponding fluorinated amines with high chemical and stereochemical efficiency. The Lewis base catalyzed reaction with trichlorosilane led to chiral products with a trifluoromethyl group directly linked to the newly generated stereocenter typically in >90% yield and up to 98% e.e.

Organofluorine compounds find applications in several fields of scientific research, like pharmaceuticals, agrochemicals and veterinary, but also in materials science.[1] In particular, fluorinated molecules have lately gained extraordinary importance as drug candidates.[2] Special attention has been recently devoted to the preparation of chiral molecules featuring stereocenters bearing directly a fluorine atom or a trifluoromethyl group.[3] Despite the great interest in the last years in the topic, the highly stereochemically efficient synthesis of chiral organofluorine compounds still represents a challenge for synthetic chemists.[4] Two approaches have been followed so far: in one case the direct introduction of a fluorine atom or a fluorinated residue is involved;[5] the second methodology, that has been preferred so far, is based on the stereoselective transformation of a fluorine-containing building block.

In this context enantiopure trifluoromethylated compounds are attracting extraordinary attention due to their increasing occurrence in numerous biologically active molecules, but also their use as fundamental components in materials for optoelectronic devices.[6] Among others, chiral amines play a fundamental role in medicinal chemistry (Fig. 1).

Considering that trifluoromethyl ketones are readily accessible, the catalytic enantioselective reduction of the corresponding keto imine derivatives offers a viable approach for the synthesis of enantiomerically pure trifluoromethylated amines. Indeed only very few enantioselective hydrogenations have been reported on those substrates;[7] but in one case the Pd catalyzed reduction is limited to fluorinated iminoesters,[7a] while in the second case, although the enantioselectivities are good to high, the use of relatively high pressures of hydrogen and of an expensive and toxic transition-metal catalyst is a significant drawback.[7b] Lately a highly enantioselective organocatalyzed procedure has been reported, but it is limited to trifluoromethyl aryl ketones, involves the use of a consistent amount of a quite expensive sterically hindered phosphoric acid and relies on the use of stoichiometric amounts of benzothiazolines as reducing agents.[8] More recently the stereoselective synthesis of amines, *via* catalytic isomerization of imines, either derived from trifluoromethyl aryl or alkyl ketones, has been described.[9]

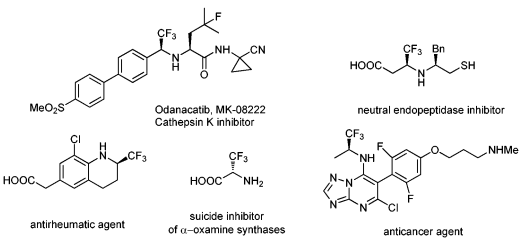

Fig. 1 Biologically active trifluromethylated chiral amines.

The catalytic highly stereoselective synthesis of such compounds remains a challenge, especially relatively to chiral trifluoromethyl alkyl amines, documented only in two works.[7b,9]

We have decided to investigate the use of trichlorosilane in the presence of a chiral catalyst to perform stereoselectively that specific transformation.[10] The reaction with trichlorosilane in the presence of catalytic amounts of a chiral Lewis base is a well-established.[11] In the last decade different classes of enantiomerically pure Lewis bases have been developed.[12]

We started our investigation by screening different typologies of chiral activators, developed by us and other groups. The catalysts, shown in Fig. 2, were employed to promote the enantioselective reduction of ketoimines derived from the trifluoromethyl phenyl ketone, selected as model compounds to identify the catalyst and the experimental conditions of choice.

Chiral picolinamides derived from ephedrine (catalyst **A**),[13] binaphthyl diamine (catalyst **C**)[14] and from prolinol (catalyst **B**)[15] were employed, as well other Lewis bases like (*S*)-prolinol-derived phosphoroamides (catalyst **D**)[16] and chiral biphosphine oxides, like compound **E**.[17]

Dipartimento di Chimica, Università di Milano, Via Golgi 19, 20133, Milano, Italy. E-mail: maurizio.benaglia@unimi.it; Fax: +39 0250314159; Tel: +39 0250314171

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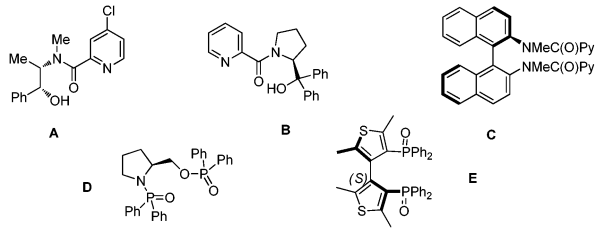
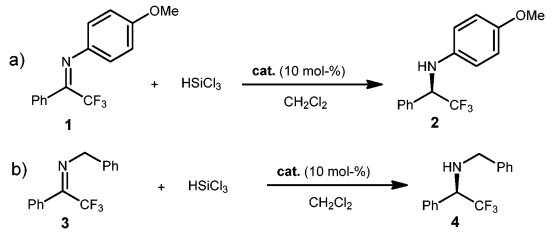


Fig. 2 Chiral catalysts employed in the $HSiCl_3$-mediated reduction of fluorinated ketoimines.



Scheme 1 Enantioselective reduction of trifluoromethyl phenyl ketone-derived imines.

In a typical procedure the reaction was performed at 0 °C in dichloromethane for 12 hours in the presence of 10 mol% amount of a chiral Lewis base (Scheme 1).

From preliminary investigations it emerged that *N*-aryl protected imines behaved better than *N*-benzyl derived substrates (see entries 1–4 of Table 1). Ephedrine-derived picolinamide **A** was able to promote the reduction of *N*-4-methoxyphenyl imine of 2,2,2-trifluoroacetophenone in 83% yield after 15 hours at 0 °C in dichloromethane and 87% e.e.‡

In further studies different experimental parameters were investigated (Table 2). Chlorinated solvents afforded the most reliable and interesting results, therefore dichloromethane was selected as the preferred reaction medium.

Regarding the yields, we often observed a discrepancy among the conversion value determined by NMR and the isolated yield after chromatographic purification. Therefore different quench and work up procedures were attempted (a few selected results are reported in Table 2). Those studies led us to identify a methodology involving the quench with a limited and controlled amount of NaOH solution that allowed isolation of the chiral amine **2** in 91% yield (quantitative conversion by NMR on the crude reaction mixture) and 91% e.e. (entry 6).

Table 1 Enantioselective imine reduction catalyzed by **A–E** catalysts

Entry[a]	Catalyst	Imine	Yield[b] (%)	Yield[b] (%) (isolated)	e.e.[c] (%)
1	**A**	**1**	83	25	87
2	**A**	**3**	15	n.d.	n.d.
3	**B**	**1**	71	51	53[d]
4	**B**	**3**	67	65	15[d]
5	**C**	**1**	99	77	73
6	**D**	**1**	47	n.d.	35
7	**E**	**1**	75	61	25

[a] Reaction run for 15 hours in dry DCM at 0 °C. [b] Yields determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification. [c] Enantiomeric excess determined by HPLC on the chiral stationary phase. [d] The enantiomer with opposite absolute configuration was obtained.

Table 2 Reduction of 2,2,2-trifluoroacetophenone-derived imine **1**

Entry[a]	Catalyst	Temp. (°C)	Yield[b] (%)	Yield[b] (%) (isolated)	e.e.[c] (%)
1	**A** (10%)	0	83	25	87
2	**A** (10%)	−50	61	57	77[d]
3	**A** (10%)	20	77	51	85
4	**B** (10%)	−50	67	55	45[d]
5	**A** (10%)	0	93	83	89[e]
6	**A** (10%)	0	99	91	91[f]
7	**A** (10%)	0	98	51	90[g]
8	**A** (5%)	0	99	90	91[f]
9	**A** (1%)	0	73	53	89[f]

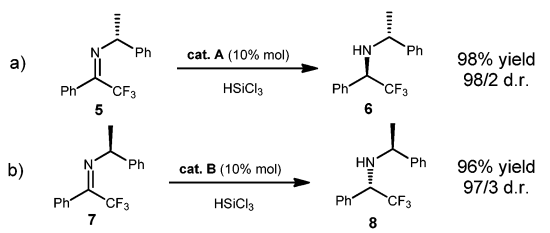
[a] Reaction run for 15 hours in dry DCM at 0 °C. [b] Yields determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification. [c] Enantiomeric excess determined by HPLC on the chiral stationary phase. [d] Reaction run for 40 hours in dry DCM. [e] Reaction quench: stoichiometric amount of $NaHCO_3$ sat. sol. [f] Reaction quench: stoichiometric amount 10% sol. NaOH. [g] Reaction quench: 10% HCl then 10% sol. NaOH.

Finally, operating under the best experimental conditions, it was attempted to lower the catalyst loading; we were happy to see that the catalyst still worked efficiently at 5 mol%, leading to the product in quantitative yield and 90% e.e.; however, also at 1% chiral Lewis base **A** catalyzed the reaction with 89% e.e. albeit in a lower yield. It is worth mentioning that, by performing the reaction with 5 mol% of the chiral base, the ACE (Asymmetric Catalyst Efficiency) of catalyst **A** is 14.3. But ACE reaches the value of 55.65 for the reaction performed with 1 mol% of the catalyst (values calculated on the basis of data of entries 8 and 9, Table 2). The definition of ACE was recently proposed[18] in the attempt to compare and evaluate the efficiency of different catalysts, taking into consideration not only the level of enantioselectivity and the yield guaranteed by the catalyst, but also the molecular weight of the product and of the catalyst itself. Noteworthy, picolinamide **A** favourably compares both with chiral phosphoric acids (ACE value 4)[8] and even with organometallic catalysts[7b] (ACE value 15.7).[19]

A further improvement in the stereoselectivity of the process was obtained by performing the reduction of fluorinated chiral ketoimine **5** in the presence of catalyst **A** (Scheme 2).[20]

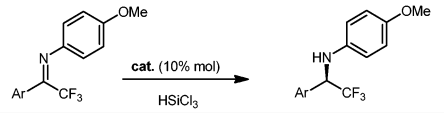
Therefore (*R*)-1-phenylethylamine and trifluoromethyl phenyl ketone were reacted to synthesize imine **5** that was reduced in the presence of catalyst **A** to give chiral amine **6** in almost quantitative yield and 98/2 diastereoisomeric ratio.§ [21] Noteworthy, the enantiomeric ketoimine **7** led to amine **8** with the opposite absolute configuration in 97/3 d.r. by performing the reaction in the presence of catalytic amounts of **B**.¶

The general applicability of the methodology was then investigated (Table 3). High yields and enantioselectivities were generally obtained, independently of the electronic nature of the aromatic ring substituents.



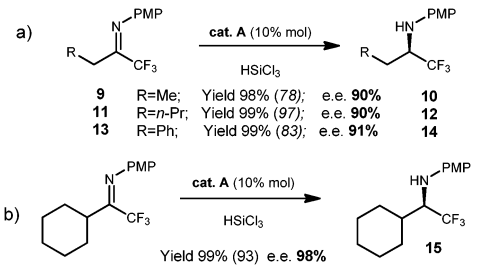
Scheme 2 Enantioselective reduction of trifluoromethyl phenyl ketone-derived chiral imines.

Table 3 Enantioselective reduction of *N*-PMP imines of different trifluoromethyl aryl ketones



Entry[a]	Cat.	Ar group	Yield[b] (%)	Yield (%) (isolated)	e.e.[c] (%)
1	**A**	Ph	99	91	91
2	**A**	4-ClPh	99	93	90
3	**C**	4-ClPh	90	65	65
4	**A**	4-FPh	83	77	89
5	**A**	4-CFsPh	99	90	90
6	**A**	3-MePh	99	87	91
7	**A**	4-OmePh	99	90	91
8	**A**	4-MePh	80	70	90
9	**A**	4-NMe_2Ph	80	70	75
10	**A**	4-OCH_2COOR-Ph	99	75	67

[a] Reaction run for 15 hours in dry DCM at 0 °C. [b] Yields determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification. [c] Enantiomeric excess determined by HPLC on the chiral stationary phase (see ESI for chromatographic details).



Scheme 3 Reduction of trifluoromethyl alkyl ketone-derived imines.

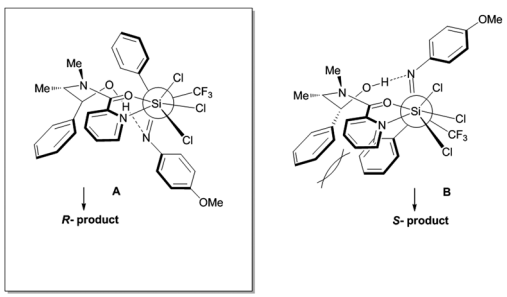


Fig. 3 Proposed model of stereoselection.

Even more interestingly, the methodology was successfully employed in the reduction of imines derived from trifluoromethyl alkyl ketones. In performing the reduction of 1,1,1-trifluoro-2-butanone-derived imine in the presence of picolinamide **A**, chiral amine (R)-**10** was isolated in 98% yield and 90% e.e. (Scheme 3). A branched alkyl fluorinated ketoimine was also considered: chiral amine **15** was obtained with 98% e.e.

In a tentative model of stereoselection the pyridine nitrogen and the CO amidic group of the picolinamide activate trichlorosilane by coordination.[20] In the proposed stereoselection model **A**, leading to the observed major enantiomer, the steric interaction between the pyridine ring and the aryl group is much less significant than that observed in adduct **B**, and is thus disfavored (Fig. 3).

In conclusion, the enantioselective organocatalytic reduction of imines derived both from aryl and alkyl trifluoromethyl ketones, in good yields and high enantioselectivities, typically of 90% e.e. and up to 98% e.e., was successfully realized. With an ACE value of about 55, picolinamide **A** established itself as one of the most efficient and versatile catalysts for the reduction of a wide range of fluorinated imines. The well documented possibility of easy removal of the *N*-PMP residue[22] or the benzyl group[23] makes the present method a viable and attractive synthesis also for chiral fluorinated primary amines.

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Notes and references

‡ The absolute configuration was established by comparison of the optical rotation value with data reported in the literature.
§ The reduction of **7** (enantiomer of **5**) with trichlorosilane in the presence of **A** led to the product in 98% yield and 82/18 diastereoisomeric ratio (match and mismatch combination).
¶ The reduction of **5** (or **7**) with trichlorosilane in the presence of DMF led to the product in 73% yield and 70/30 diastereoisomeric ratio.

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