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Unprecedented Catalytic Asymmetric Reduction of N–H Imines

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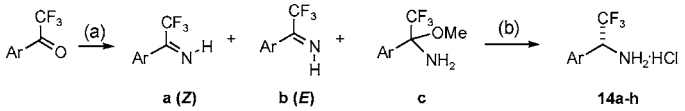
ABSTRACT



(a) $LiN(SiMe_3)_2$, toluene; then MeOH, rt; (b) catBH, 5 mol% (*S*)-Bu-OAB, toluene, -15 °C; HCl.

Addition of lithium bis(trimethylsilyl)amide to perfluorinated ketones 1a–j affords (*E*)-*N*-TMS-ketimines 2a–j that are reduced in situ to afford racemic perfluoromethylated amine hydrochloride salts 3a–j in 54–97% yields. Solvolysis of the N–Si bond in MeOH leads to formation of bench-stable, isolable N–H imine *Z*/*E* isomer mixtures along with a methanol adduct. Enantioselective reduction of these three-component mixtures provides the first catalytic asymmetric synthesis of trifluoromethylated amines in 72–95% yields and 75–98% ee.

The asymmetric synthesis of enantiomerically enriched chiral amines continues to be an area of interest because of their ubiquity as core constituents of clinically relevant pharmaceutical compounds.[1] Chiral fluorinated amines have received attention from medicinal chemists because of the unusual and often profound effects on physical properties imparted by the introduction of the fluorine atom into organic molecules, as well as their potential use as amide bond surrogates in peptide mimics.[2−4] Herein we wish to report a simple protocol for the one-pot reductive amination of trifluoromethyl ketones along with the discovery of an unprecedented catalytic asymmetric reduction of N−H imines and its application to the enantioselective synthesis of trifluoromethylated amines.

The reductive amination of aldehydes and ketones is a classical chemical transformation that proceeds readily with a wide range of substrates.[5] In stark contrast, perfluoromethylated ketones generally perform poorly under reductive amination conditions. This is due to the formation of stable

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(2) (a) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposia-in-Print No 58; *Tetrahedron* **1996**, *52*, 1−330. (b) *Fluorine Containing Amino Acids: Synthesis and Properties*; Kuhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (c) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661−692. (d) Iseki, K. *Tetrahedron* **1998**, *54*, 13887−13914. (e) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16.

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(4) (a) Volonterio, A.; Bravo, P.; Zanda, M. *Org. Lett.* **2000**, *2*, 1827−1830. (b) Molteni, M.; Volonterio, A.; Zanda. M. *Org. Lett.* **2003**, *5*, 3887−3890.

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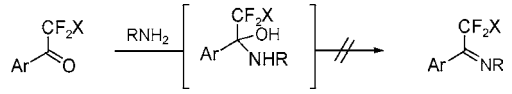
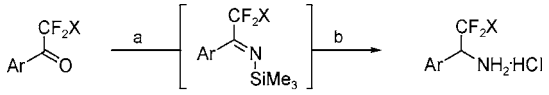
hemiaminal adducts that often fail to undergo dehydration to afford the required imine (Scheme 1). The use of $TiCl_4$ as a potent dehydrating agent has been reported to overcome this problem with trifluoromethyl ketones.[6]

Scheme 1. Imine Formation with Perfluorinated Ketones



Inspired by literature precedent for the formation of *N*-trimethylsilyl imines from diaryl ketones[7] and aldehydes,[8] we found that addition of lithium bis(trimethylsilyl)amide as an ammonia equivalent to prepared[9] trifluoromethyl ketones **1a**−**h** in toluene at 20−25 °C proceeded smoothly within 15 min to form stable, isolable *N*-trimethylsilyl-*E*-ketimines **2a**−**h**. The isolated imine **2c** was determined to be a single *E*-isomer by ^{1}H NOE experiments in d_8-toluene. Irradiation of the trimethylsilyl resonance showed NOE to both aromatic resonances. The formation of a strong oxygen−silicon bond in the form of lithium trimethylsilanolate is believed to be the driving force for this reaction. *N*-TMS-imines **2a**−**h** were reduced in situ with BH_3·Me_2S at 20−25 °C to yield the corresponding racemic amines **3a**−**h**, which were conveniently purified and isolated as their hydrochloride salts in 64−97% yield over 3 steps (Table 1, entries 1−8).[10] Extension of this one-pot reductive amination protocol to difluoromethyl and pentafluoroethyl ketones **1i** and **1j** was also successful and gave the corresponding amines **3i** and **3j** in unoptimized yields of 70% and 54%, respectively (Table 1, entries 9 and 10).

Table 1. One-Pot Racemic Reductive Aminations[a]



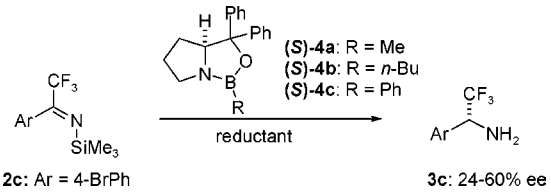
1a-j **2a-j** **3a-j**

entry	Ar	X	1	3	yield (%)[b]
1	Ph	F	**1a**	**3a**	92
2	3-BrC_6H_4	F	**1b**	**3b**	78
3	4-BrC_6H_4	F	**1c**	**3c**	97
4	2-MeSC_6H_4	F	**1d**	**3d**	94
5	3-MeSC_6H_4	F	**1e**	**3e**	97
6	2-PhC_6H_4	F	**1f**	**3f**	75
7	2-naphthyl	F	**1g**	**3g**	86
8	9-phenanthryl	F	**1h**	**3h**	64
9	4-BrC_6H_4	H	**1i**	**3i**	70
10	Ph	CF_3	**1j**	**3j**	54

[a] Reagents and conditions: (a) $LiN(SiMe_3)_2$, toluene, THF, rt; (b) BH_3·Me_2S, toluene, then HCl in Et_2O. [b] Isolated yields of amine hydrochloride salts.

Next we sought to expand the scope of the reaction to provide access to enantiomerically enriched trifluoromethylated amines. The commercial availability, favorable economics, and well-precedented scalability of their reactions prompted us to begin our investigation with oxazaborolidine (OAB) catalysts.[11,12] Our initial attempts to perform an OAB-catalyzed reduction of *N*-TMS-ketimine **2c** under a variety of conditions led to high yields of **3c** but with enantioselectivities of 24−60% ee at best (Scheme 2).[13]

Scheme 2. Enantioselective Reduction of *N*-TMS Imines



It is reasonable to assume that the low to moderate asymmetric induction could be related to poor substrate binding to the Lewis acid OAB catalyst due to steric hindrance at ketimine nitrogen. Therefore, we envisioned that formation of a less sterically congested imine substrate might improve the enantioselectivity of the reduction. Minimization of unfavorable steric interactions between catalyst and ketimine substrate should be attained with the corresponding N−H imine (*N*-unsubstituted) substrate and should closely mimic the steric requirements of a ketone. Perusal of the

(6) Barney, C. L.; Huber, E. V.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 5547−5550.

(7) Kruger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132.

(8) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem* **1983**, *48*, 289−294.

(9) Perfluorinated ketones were prepared according to: Creary, X. *J. Org. Chem.* **1987**, *52*, 5026−5030.

(10) **Representative Procedure.** 2,2,2-Trifluoromethyl acetophenone **1a** (491 mg, 2.82 mmol) was dissolved in toluene (10 mL) at room temperature. A solution of lithium bis(trimethylsilylamide) (3.15 mL, 3.15 mmol, 110 mol %, 1 M in THF) was added over a 10 min period. The reaction was stirred at room temperature for 15 min, and BH_3·Me_2S (2.82 mL, 5.73 mmol, 2 M in toluene) was added. The reaction mixture was stirred at room temperature for 20 min. After cooling to 0 °C, aqueous 2 N NaOH (4 mL) was carefully added dropwise over 5 min (*caution: gas evolution!*). The mixture was stirred at room temperature for 90 min. The layers were separated, and the organic layer was washed with aqueous 2 N NaOH (5 mL) and water (5 mL), dried with $MgSO_4$, and filtered. To the solution of crude free amine in toluene was added a solution of hydrogen chloride (1 mL of 4 M in 1,4-dioxane or 2 mL of 2 M in diethyl ether). A white precipitate formed. After standing at room temperature for 1 h, the slurry was filtered, and the solids were washed with MTBE (10 mL) to afford (*R*,*S*)-1-phenyl-2,2,2-trifluoroethylamine hydrochloride **3a** as a white powder (549 mg, 92% yield): ^{1}H NMR (CD_3OD) δ 7.52−7.58 (m, 5H), 5.37 (q, J = 7.5, 1H); ^{13}C NMR (CD_3OD) δ 132.0, 130.6, 129.8, 129.5, 124.8 (q, J = 281), 56.7 (q, J = 33); ^{19}F NMR (CD_3OD) δ −72.0.

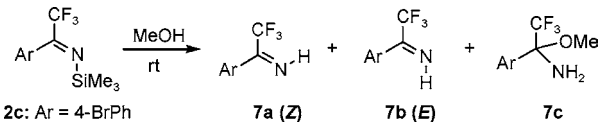
(11) Reviewed in: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(12) Oxazaborolidine catalysts were prepared according to: Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751−762

(13) For oxazaborolidine-mediated stoichiometric reductions of *N*-TMS imines: Ortiz-Marciales, M.; Tirado, L. M.; Colón, R.; Ufret, M. L.; Figueroa, R.; Lebrón, M.; Dejesús, M.; Martínez, J.; Malavé, T. *Synth. Commun.* **1998**, *28*, 4067−4075. For oxazaborolidine-mediated stoichiometric reductions of CF_3-substituted oxime ethers: (b) Demir, A. S.; Sesenoglu, Ö.; Gerçek-Arkin, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 2309−2313.

literature revealed that N−H imines have received scant attention as synthetic intermediates. With a few exceptions, N−H imines have been reported as inherently unstable, leading to difficulties in their preparation and isolation, and often exist as mixtures of *E*/*Z* isomers.[14] Thus, we were delighted to find that solvolysis of *N*-TMS-ketimine **2c** in MeOH proceeded readily and led to cleavage of the nitrogen−silicon bond and isolation of a stable N-H imine **7** (Scheme 3).

Scheme 3. Synthesis of N−H Imines



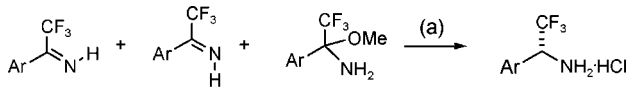
2c: Ar = 4-BrPh **7a (*Z*)** **7b (*E*)** **7c**

This represents one of the few reported examples of stable, readily isolable N−H ketimines.[14] A comprehensive study of imine **7** (Ar = 4-BrPh) by ^{1}H NMR spectroscopy in d_8-toluene determined that it existed as a mixture of *Z*/*E* isomers **7a**/**7b** along with variable amounts of a methanol adduct **7c**. The existence of a dynamic equilibrium between the imine isomers was demonstrated when irradiation of the aromatic resonance of one isomer (in an NOE experiment) led to transfer of magnetization to the corresponding resonance in the other imine isomer. Further proton NOE experiments were used to prove the geometry of the imines, as NOE enhancements were observed from the N−H to the aromatic protons in the minor *E*-isomer. The same NOE was absent in the major *Z*-isomer.

Enantioselective additions to imines are often complicated by the existence of imine isomerization equilibrium that can lead to plural transition states and correspondingly low ee's.[1c] Therefore, we were gratified to find that treatment of a crude three-component mixture of **7a**:**7b**:**7c** [65:19:16] with 5 mol % (*S*)-Bu-OAB [(*S*)-**4b**] and 150 mol % catecholborane in toluene at −15 °C gave amine (*R*)-**14c** in 91% ee and 95% isolated yield (Table 2, entry 3). To the best of our knowledge, the catalytic asymmetric reduction of N−H imines is unprecedented in the literature. After optimization of reaction parameters, we directly applied this procedure to other aryl trifluoromethyl N−H ketimines.[15] As illustrated in Table 2, the enantioselectivities (75−98% ee) and yields (72−95%) were consistently high with imines bearing substituents in either the ortho, meta, or para positions. Notably, similar levels of enantioselectivity were observed with commercially available methyl-OAB catalyst **4a**.[16] However, use of phenyl-OAB **4c** as catalyst led to poor enantioselectivity.

The sense of stereochemical induction was found to be the same as that observed with OAB-catalyzed reductions of trihalomethyl ketones.[17] Thus, the stereochemical outcome of the reduction is consistent with a boatlike transition state

Table 2. Enantioselective Reductions of N−H Imine Mixtures[a]



a (*Z*) **b (*E*)** **c** **14a-h**

entry	Ar	**5**−**12** [a:b:c][b]	**14**	yield (%)[c]	% ee[d]
1	Ph	**5** [18:8:74]	**a**	87	86[e]
2	3-BrC$_6$H$_4$	**6** [41:15:44]	**b**	72	86 (91)
3	4-BrC$_6$H$_4$	**7** [65:19:16]	**c**	95	91[e]
4	2-MeSC$_6$H$_4$	**8** [68:32:0]	**d**	93	88 (99)
5	3-MeSC$_6$H$_4$	**9** [57:23:20]	**e**	84	85
6	2-PhC$_6$H$_4$	**10** [76:24:0]	**f**	88	98 (99)
7	2-naphthyl	**11** [45:15:46]	**g**	86	75[e]
8	9-phenanthryl	**12** [65:19:16]	**h**	84	97 (99)

[a] Reagents and conditions: (a) 5 mol % (*S*)-Bu-OAB [(*S*)-**4b**], 150 mol % catecholborane, toluene, −15 °C, then HCl in Et$_2$O. [b] Isomer ratios determined by 500 MHz ^{1}H NMR spectroscopy in $CDCl_3$ at 25 °C. [c] Isolated yields of hydrochloride salts. [d] % ee determined by chiral HPLC analysis of crude free amine, values in parentheses for isolated hydrochloride salts. [e] (*R*)-configuration assigned on the basis of comparison with literature values for optical rotations (see ref 3g).

structure **A** involving coordination of boron with the sterically more accessible nitrogen lone pair *anti* to the CF_3 group of *Z*-imine, similar to that proposed by Corey and coworkers.[17] Alternatively, a chairlike transition state structure **B** involving coordination of boron with the nitrogen lone pair *syn* to the CF_3 group of *E*-imine may also be plausible on the basis of stereoelectronic arguments. Since high enantioselectivity is observed, we presume that N−H imine *E*/*Z* isomers and methanol adduct may all converge to

(14) Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217−4218 and references therein.

(15) **Representative Procedure.** (*S*)-2,2,2-Trifluoro-1-(4-bromophenyl)-ethylamine hydrochloride [(*S*)-**14c**]: A solution of (*R*)-*B*-butyl-diphenylpyrrolidino-oxazaborolidine (*R*)-**4b** (3.14 mL, 0.94 mmol, 2.5 mol %, 0.3 M in toluene) was dissolved in toluene (10 mL) and cooled to −15 °C, and catecholborane (6.01 mL, 56.5 mmol, 150 mol %) was added to the solution. A solution of 1-(4-bromophenyl)-2,2,2-trifluoroethylimine **7** (10.0 g, 37.6 mmol) in toluene (40 mL) was added dropwise via syringe pump over a period of 2.5 h. After the addition was complete, the reaction mixture was stirred at −15 °C for 18 h. The reaction was quenched with aqueous 1 N HCl (50 mL) and allowed to warm to room temperature, and the layers were separated. The aqueous layer was basified with 10 N NaOH to pH 12. The aqueous layer was extracted with MTBE (1 × 50 mL). The layers were separated, and the organic layer was washed with aqueous 2 N NaOH (2 × 50 mL) and water (50 mL). The organic layer was treated with Amberlite IRC-50S ion-exchange resin (5 g) for 40 min to remove (*R*)-diphenylprolinol and filtered. The organic layer was dried and filtered. A solution of hydrogen chloride (40 mL, 2 M in diethyl ether) was added to the crude solution of amine. A white precipitate formed. After aging at room temperature for 1 h, the slurry was filtered, and the solids were washed with MTBE (10 mL) to afford (*S*)-2,2,2-trifluoro-1-(4-bromophenyl)-ethylamine hydrochloride (*S*)-**14c** as a white powder (10.9 g, 95% yield, 91% ee HPLC): ^{1}H NMR (CD_3OD) δ 7.73 (d, 2H, J = 8.5), 7.51 (d, 2H, J = 8.5), 5.42 (q, 1H, J = 7.4); ^{13}C NMR (CD_3OD) δ 133.8, 131.6, 128.7, 126.3, 124.6 (q, J = 280), 55.9 (q, J = 33); ^{19}F NMR (CD_3OD) δ −72.1. HRMS calcd for $C_8H_8NF_3Br$ [M + H] 253.9792, found 253.9790. Enantioselective reduction with (*S*)-butyl-OAB (*S*)-**4b** as catalyst gave amine (*R*)-**14c** in 95% yield and 91% ee HPLC (method A, AD column: $t_{R_{major}}$ = 6.9 min; $t_{R_{minor}}$ = 7.9 min; see Supporting Information) with identical spectral characterictics; $[\alpha]^{23}_D$ = −13.7 (c = 0.75, MeOH). lit.[3g] $[\alpha]^{25}_D$ = +11.2 (c = 1.5, MeOH).

(16) For example enantioselective reduction of N−H imine **7** with 5 mol % of commercially available (*R*)-methyl-OAB afforded amine (*S*)-**14c** in 90−91% ee on a 10 g scale. See Supporting Information.

(17) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107−7110.

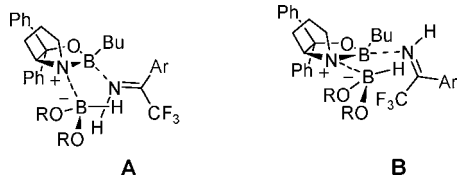


Figure 1. Transition state rationale for enantioselectivity.

product through the intermediacy of a single imine−OAB complex **A** or **B** that undergoes hydride transfer to the *si* face of the imine.[18]

In conclusion, we have developed a novel one-pot reductive amination for the formation of perfluoroalkylamines. We have reported the first examples of an enantioselective synthesis of trifluoromethylated amines that features an unprecedented asymmetric reduction of N−H imines. The reaction proceeds with good to high enantioselectivity and yield. Further investigations into the scope and mechanism of this reaction are ongoing and will be reported in due course.

Acknowledgment. We thank Dr. Thomas J. Novak for HRMS data.

Supporting Information Available: Experimental details and characterization for compounds **2a**−**h**, **3i**−**j**, **5**−**12**, and **14a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) In a single unoptimized experiment we observed that isolated methanol adduct **7c** containing less than 5% N−H imine underwent enantioselective reduction with (*S*)-methyl-OAB and catecholborane in toluene at −15 °C to afford amine **14c** in 72% yield and 78% ee.