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Oxazolidine Ring Opening and Isomerization to (*E*)-Imines. Asymmetric Synthesis of Aryl-α-fluoroalkyl Amino Alcohols

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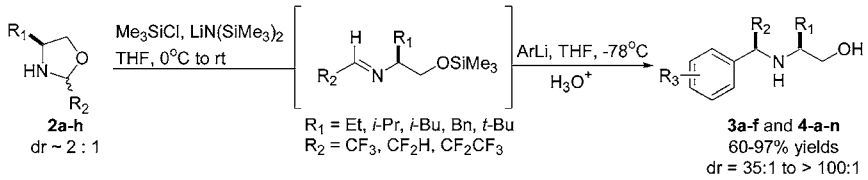
ABSTRACT



A base-induced ring opening/imine isomerization/diastereoselective organometallic addition sequence on 4-substituted 2-perfluoroalkyl-1,3-oxazolidines has been developed for the asymmetric synthesis of aryl α-perfluoroalkylamine derivatives. This practical method provides chiral amino alcohols in 60–95% yield with uniformely high diastereoselectivities ranging from 35:1 to >100:1.

The development of practical methods for the preparation of chiral organofluorine compounds continues to challenge and attract synthetic chemists. Introduction of the fluorine atom can confer unusual chemical reactivity to organic molecules and often exert profound effects on the physical properties of biologically active compounds.[1,2] In particular, the asymmetric synthesis of perfluoroalkylamines has received much attention due to their potential use as components of pharmaceutical agents.[3]

A practical approach to the asymmetric synthesis of α-alkyl phenethylamines involves addition of organometallics to 1,3-oxazolidines formed by condensation of the appropriate aldehyde and chiral amino alcohol.[4] Diastereromeric 2-alkyl and 2-aryl-1,3-oxazolidines are known to exist as solvent-dependent mixtures of imine−oxazolidine tautomers[4c,5] and organometallic addition to these mixtures provides the

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(1) For reviews on the biological significance of organofluorine compounds see: (a) Resnati, G., Soloshonok, V. A., Eds.; Tetrahedron Symposia-in-Print No 58; Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards. *Tetrahedron* **1996**, *52*, 1−330. (b) *Fluorine Containing Amino Acids*: *Synthesis and Properties*; Kuhar, V. P., Soloshonok, V. A. Eds.; Wiley: Chichester, UK, 1994. (c) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, The Netherlands, 1993.

(2) For reviews on asymmetric synthesis of organofluorine compounds see: (a) Iseki, K. *Tetrahedron* **1998**, *54*, 13887−13914. (b) Bravo, P.; Resnati, G. *Tetrahedron*: *Asymmetry* **1990**, *1*, 661−692.

(3) Asymmetric syntheses of perfluoroalkylamines include the following: (a) Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589−590. (b) Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847−2850. (c) Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575−1577. (d) Soloshonok, V. A.; Ono, T. *J. Org. Chem.* **1997**, *62*, 3030−3031. (e) Ishii, A.; Higashiyama, K.; Mikami, K. *Synlett* **1997**, 1381−1382. (f) Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**, *32*, 987−990. (g) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436−2439. For reviews on organometallic additions to imines and their derivatives see: Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. Enders, D.; Reinhold: U. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1895−1946.

(4) (a) Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull.* **1983**, *31*, 2183−2191. (b) Takahashi, H.; Chida, Y.; Yoshii, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 2071−2077. (c) Wu, M-. J.; Pridgen, L. M. *J. Org. Chem.* **1991**, *56*, 1340−1344. (d) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237−1241.

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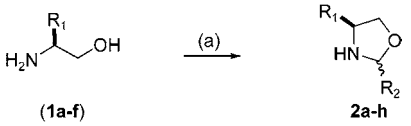
expected adducts in moderate to excellent yields and diastereoselectivities. A related approach has been reported for the asymmetric synthesis of trifluoroethylamines.[3e] We were interested in applying a similar methodology to the asymmetric synthesis of aryl α-fluoroalkyl amino alcohols.

A series of 4-substituted 2-perfluoroalkyl-1,3-oxazolidines **2a**−**h** were readily prepared on multigram scale by heating commercially available chiral amino alcohols (**1a**−**f**) with the corresponding perfluorinated aldehyde hemiacetal or aldehyde hydrate in toluene with azeotropic removal of water/alcohol (Table 1). The crude diastereomeric oxazolidines **2a**−**h** were isolated in 57−99% yield (unoptimized). In contrast to 2-alkyl and 2-aryl-1,3-oxazolidines, ^{1}H NMR spectra of 2-perfluoroalkyl-1,3-oxazolidines in $CDCl_3$ and d_8-THF showed that **2a**−**h** existed solely as the oxazolidine tautomers.

Table 1. Synthesis of 2-Perfluoroalkyl 1,3-Oxazolidines **2a**−**h**[a]

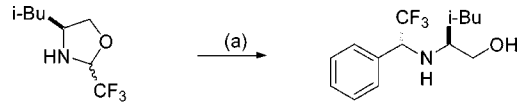


(**1a-f**) **2a-h**

entry	no.	R_1	R_2	product	yield (%)[b]	dr[c]
1	**1a**	Et	CF_3	**2a**	61	2.3:1
2	**1b**	*i*-Pr	CF_3	**2b**	68	2.6:1
3	**1c**	*i*-Bu	CF_3	**2c**	87	2.0:1
4	**1d**	$PhCH_2$	CF_3	**2d**	93	1.5:1
5	**1e**	*t*-Bu	CF_3	**2e**	64	1.4:1
6	**1f**	$(CH_2)_2SMe$	CF_3	**2f**	99	1.2:1
7	**1c**	*i*-Bu	CF_2CF_3	**2g**	82	1.7:1
8	**1c**	*i*-Bu	CF_2H	**2h**	57	2.0:1

[a] Conditions: (a) $F_3CC(OMe)OH$ or $F_3CF_2C(OH)_2$, or $F_2CHC(OH)OEt$, ppts, $PhCH_3$. [b] Isolated yield. [c] Determined by 500 MHz ^{1}H NMR spectroscopy ($CDCl_3$).

Scheme 1. Organometallic Addition to Trifluoromethyl Oxazolidine **2c**[a]



2c **3c**: dr = 2:1 to 5:1

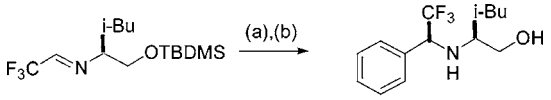
[a] Reagents and conditions: (a) PhLi or PhMgBr, THF, −78 °C.

alcohol adduct **3c** in variable yields and poor diastereomeric ratios (dr) ranging from 2:1 to 5:1. Modification of solvent composition and addition of Lewis acids failed to improve significantly the stereoselectivity of the addition.[6]

(5) Miao, C. K.; Sorcek, R.; Jones, P.-J. *Tetrahedron Lett.* **1993**, *34*, 2259−2262.

To verify that the putative imine intermediates generated from oxazolidines **2a**−**h** would undergo diastereoselective addition with organometallic reagents we prepared *O*-TBDMS protected trifluoroethylimine **4**. Treatment of imine **4** with phenyllithium at −78 °C followed by deprotection of the TBDMS ether gave adduct **3c** in ∼75% yield over 2 steps and dr 40:1 as determined by HPLC (Scheme 2).[7]

Scheme 2. Diastereoselective Organometallic Addition to Trifluoroethylimine[a]



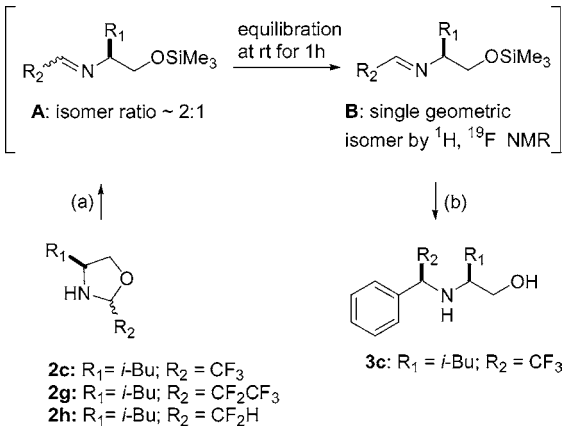
4 **3c**

[a] Reagents and consitions: (a) PhLi, THF, −78 °C. (b) TBAF, THF, 0 °C to rt.

Having verified that imine **4** underwent highly diastereoselective addition of organolithium reagents, we next focused our attention on developing a bench-stable surrogate of imine **4** that would avoid tedious chromatographic separations[3e,6] and circumvent separate protection/deprotection steps.

We reasoned that treatment of oxazolidines **2a**−**g** with a suitable base should induce, after deprotonation, ring opening to generate the corresponding imine **A** or **B** (Scheme 3). In situ trapping of the resulting alkoxide, followed by addition of an organometallic reagent would then provide the desired amino alcohol adducts. We chose to examine this protocol by variable-temperature ^{1}H NMR spectroscopy. Addition of Me_3SiCl and $LiN(SiMe_3)_2$ to a solution of oxazolidine **2c**

Scheme 3. Base-Induced Oxazolidine Ring Opening, Imine Isomerization, and Organometallic Addition[a]



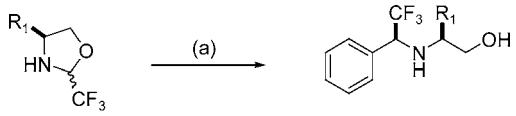
[a] Reagents and conditions: (a) Me_3SiCl, $LiN(SiMe_3)_2$, d_8-THF, −60 °C, then warm to rt. (b) PhBr, *n*-BuLi, THF, −78 °C, H_3O^+.

(6) See ref 3e. As noted by these authors, chromatographic separation of diastereoisomers of (*R*)-phenylglycinol-derived 2-trifluoromethyl-1,3-oxazolidine prior to organometallic addition was required to obtain adducts with diastereomeric ratios up to ∼8:1.

(dr ~2:1) in d_8-THF at −60 °C gave immediate and complete deprotonation and ring opening to provide a stable 2:1 mixture of (*E*)- and (*Z*)-imines **A**. Addition of PhLi to this mixture at −60 °C gave the expected adduct **3c** with a similar dr of ~2:1. The ratio of imines **A** remained unchanged from −60 to 0 °C; however, upon warming to room temperature, the (*Z*)-imine methine resonance at 7.71 ppm gradually disappeared and was concomitantly converted over ~1 h to a single (*E*)-imine **B** methine signal at 7.78 ppm. Addition of PhLi in THF at −78 °C gave amino alcohol **3c** in 64% yield and diastereomeric ratio >40:1 as determined by HPLC. By using this procedure, amino alcohol **3c** could be generated by a simple one-pot base-mediated oxazolidine ring opening/imine isomerization/organometallic addition process (Scheme 3).[8]

We explored the scope of this procedure with respect to the nature of the chiral amino alcohol (Table 2). Treatment

Table 2. Diastereoselective Organometallic Addition to Imine[a]



2a-e **3a-e**

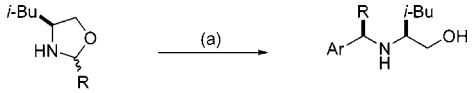
entry	no.	R_1	product	yield (%)[b]	dr[c]
1	**2a**	Et	**3a**	97	49:1
2	**2b**	*i*-Pr	**3b**	97	>100:1
3	**2c**	*i*-Bu	**3c**	64	44:1
4	**2d**	$PhCH_2$	**3d**	81	40:1
5	**2e**	*t*-Bu	**3e**	88	35:1
6	**2f**	$(CH_2)_2SMe$	**3f**	86	38:1

[a] Conditions: (a) Me_3SiCl, $LiN(SiMe_3)_2$, THF, 0 °C to rt; PhBr, *n*-BuLi, THF, −78 °C; H_3O^+. [b] Isolated yield after column chromatography. [c] Diastereomeric ratios determined by HPLC analysis of the crude products.

of diastereomeric oxazolidines **2a**−**f** with Me_3SiCl and $LiN(SiMe_3)_2$ in THF at 0 °C and warming to room temperature over 1 h gave single imine (*E*)-isomer **B** in all cases as ascertained by ^1H and ^{19}F NMR spectroscopy. Subsequent addition of phenyllithium at −78 °C gave amino alcohol products **3a**−**f** in 63−97% yields, with diastereomeric ratios ranging from 35:1 to >100:1.[9−11]

We then investigated the scope of this methodology with respect to the nature of the aryllithium nucleophile. As

Table 3. Diastereoselective Organometallic Addition to Imine[a]



2c, 2g, 2h **4a-n**

entry	no.	R	Ar	product	yield (%)[b]	dr[c]
1	**2c**	CF_3	1-naphthyl	**4a**	89	40:1
2	**2c**	CF_3	4-bromophenyl	**4b**	82	40:1
3	**2c**	CF_3	4-methoxyphenyl	**4c**	89	40:1
4	**2c**	CF_3	3-trifluoromethylphenyl	**4d**	95	40:1
5	**2c**	CF_3	2-methylthiophenyl	**4e**	74	69:1
6	**2c**	CF_3	3-fluoro-4-methoxy	**4f**	89	40:1
7	**2c**	CF_3	3-pyridyl	**4g**	76	36:1
8	**2c**	CF_3	2-furyl	**4h**	60	40:1
9	**2g**	CF_2CF_3	phenyl	**4i**	89	77:1
10	**2g**	CF_2CF_3	3-trifluoromethylphenyl	**4j**	94	40:1
11	**2g**	CF_2CF_3	2-methylthiophenyl	**4k**	92	69:1
12	**2h**	CF_2H	phenyl	**4l**	75	40:1
13	**2h**	CF_2H	3-trifluoromethylphenyl	**4m**	78	40:1
14	**2h**	CF_2H	2-methylthiophenyl	**4n**	82	40:1

[a] Conditions: (a) Me_3SiCl, $LiN(SiMe_3)_2$, THF, 0 °C to rt; ArLi, THF, −78 °C; H_3O^+. [b] Isolated yield after column chromatography. [c] Diastereomeric ratios determined by HPLC analysis of the crude products.

illustrated in Table 3, a variety of aryllithium reagents[10] added smoothly to the imine derived from 4-isobutyl-2-trifluoromethyl-1,3-oxazolidine **2c** (entries 1−8). Nonsubstituted, mono- and disubstituted including para-, meta-, and ortho-substituted aryllithium, and heteroaryllithium reagents added in 60−95% yields and diastereoselectivities ranging from dr 36:1 to 69:1. The procedure was extended to 2-pentafluoroethyl-1,3-oxazolidine **2g**, which behaved similarly to oxazolidine **2c**, affording amino alcohol adducts **4i**−**k** in 89−94% yields without erosion in stereoselectivity (dr 40:1 to 77:1). The use of 2-difluoromethyl-1,3-oxazolidine **2h** also proved successful. However, in this case ^1H NMR analysis in $CDCl_3$ showed that imine **A** ($R_2 = CF_2H$ in Scheme 3), generated by treatment of oxazolidine **2h** with Me_3SiCl and $LiN(SiMe_3)_2$, existed as a 2:1 mixture of geometric isomers

(7) Imine **4** was prepared in 2 steps and 80% yield by protection of commercially available (*S*)-leucinol (**1c**) with TBDMSCl, followed by reaction with trifluoroacetaldehyde methyl hemiacetal (ppts, $PhCH_3$, Δ). ^1H NMR spectroscopic analysis confirmed that imine **4** was a single geometric isomer.

(8) During the course of our work, a conceptually related method for opening acetals and oxazolidines was reported: Iwata, A.; Tang, H.; Kunai, A.; Ohshita, J.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* **2002**, *67*, 5170−5175.

(9) The minor diastereomer was quantified by HPLC, using enriched samples prepared by direct organolithium addition to oxazolidines **2a**−**g** that typically gave ~2:1 diastereomeric ratios.

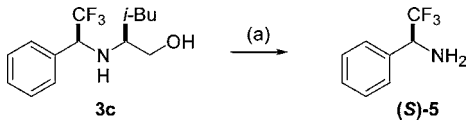
(10) Solutions of aryllithium species were freshly generated from the corresponding aryl bromides via halogen−metal exchange with *n*-BuLi or by deprotonation of the corresponding hydrocarbon in the case of furan.

(11) **Representative procedure**: To a solution of oxazolidine **2c** (247.2 mg, 1 mmol) in THF (2 mL) at 0−5 °C was added Me_3SiCl (152 μL, 1.20 mmol, 1.2 equiv) and $LiN(SiMe_3)_2$ (1.20 mL, 1.20 mmol, 1.2 equiv, 1 M in THF). The solution was stirred for 30 min, the cooling bath was removed, and the mixture was warmed to room temperature for 1 h. In a separate flask 3-bromobenzotrifluoride (418 μL, 3 mmol, 3.0 equiv) was charged in THF (6 mL). The solution was cooled to −78 °C and *n*-BuLi (1.88 mL, 3 mmol, 3.0 equiv, 1.6 M in hexanes) was added. After being stirred for 15 min, the solution of imine was transferred via cannula and the mixture was stirred at −78 °C for 2 h. The reaction was quenched with 1 N HCl (2 mL) then warmed to room temperature for 30 min, NaOH (5 mL, 2.5 N) was added, and the solution was extracted with MTBE (15 mL). The layers were separated and the organic layer was washed with brine (2 mL), dried with $MgSO_4$, and concentrated under vacuum. Chromatography of the residue (20% EtOAc in hexanes) gave amino alcohol **4d**: colorless oil, 370 mg, 95% yield, dr 40:1; $[\alpha]^{20}_D$ +48.3 (*c* 6.9, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.60 (m, 1H), 7.53 (m, 1H), 4.40 (dd, 1H, J = 15.7, 11.9 Hz), 3.50 (dd, 1H, J = 10.9, 3.5 Hz), 3.29 (dd, 1H, J = 10.8, 7.3 Hz), 2.55 (m, 1H), 2.06 (br s, 2H), 1.54 (m, 1H), 1.31 (m, 1H), 1.20 (m, 1H), 0.88 (d, 3H, J = 6.6 Hz), 0.75 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 132.2, 131.1 (q, J = 33 Hz), 129.3, 125.9, 125.8, 123.8 (q, J = 272 Hz), 119.1 (dt, J = 287, 36 Hz), 114.3 (qt, J = 258, 34 Hz), 64.7, 60.0 (app t, J = 22 Hz), 54.8, 40.3, 24.8, 23.2, 22.2; LRMS calcd for $C_{16}H_{19}F_8NO$ 393.32, found 393.9 [M+1].

at room temperature (Scheme 3). Heating to 60 °C for 1 h completed the isomerization and gave imine **B** as a single (*E*)-isomer that underwent organometallic addition at −78 °C to provide amino alcohols **4*l*−n** in 75−82% yields and consistently high diastereoselectivities (dr 40:1).[11]

Oxidative cleavage of the amino alcohol moiety from adduct **3c** with $Pb(OAc)_4$ gave 2,2,2-trifluoro-1-phenethylamine (*S*)-**5** (Scheme 4).[12] The (*S*)-stereochemistry was assigned by comparison of optical rotation values with literature ($[\alpha]^{20}_D$ +22.2 (*c* 0.75, MeOH) [lit.[3a] $[\alpha]^{20}_D$ +28.6 (*c* 0.65, MeOH)]). This result confirmed that the stereochemical outcome of the organometallic addition was consistent with preferential attack on the *si* face of the (*E*)-imine intermediate.

Scheme 4. Determination of Stereochemistry[a]



3c (*S*)-5

[a] Reagents and conditions: (a) $Pb(OAc)_4$, MeOH, CH_2Cl_2, 0 °C, then aq HCl, EtOH.

In conclusion, we have developed a practical method for the asymmetric synthesis of aryl α-fluoroalkyl amino alcohols using a one-pot base-induced oxazolidine ring opening/imine isomerization/diastereoselective organometallic addition sequence.

Acknowledgment. The authors thank Dr. Laird Trimble for assistance in performing variable-temperature ^1H NMR and ^{19}F spectroscopy experiments.

Supporting Information Available: Experimental procedures and characterization for compounds **2a−h**, **3a−f**, and **4a−n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Mokhallalati, M. K.; Pridgen, L. N. *Synth. Commun*. **1993**, *23*, 2055−2064.