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Efficient Asymmetric Synthesis of α-Trifluoromethyl-Substituted Primary Amines via Nucleophilic 1,2-Addition to Trifluoroacetaldehyde SAMP– or RAMP–Hydrazone

Dieter Enders* and Kazumasa Funabiki†

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Strasse 1, 52074 Aachen, Germany

enders@rwth-aachen.de

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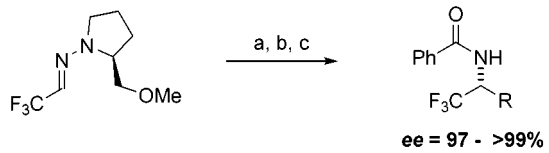
ABSTRACT



***ee* = 97 - >99%**

a) RLi, Et_2O, −78 °C, b) benzoylation, c) SmI_2,THF-DMPU, rt

An efficient asymmetric synthesis of α-trifluoromethyl-substituted primary amines via nucleophilic 1,2-addition of alkyllithium reagents to trifluoroacetaldehyde SAMP– or RAMP–hydrazone followed by benzoylation and SmI_2-promoted nitrogen–nitrogen single bond cleavage is described.

The development of novel methods for the asymmetric synthesis of fluorine-containing molecules is one of the most challenging topics in organofluorine chemistry.[1] Many successful procedures for the enantioselective synthesis of α-trifluoromethylated alcohols have hitherto appeared.[2] In contrast, there have been only a few reports on the asymmetric synthesis of α-trifluoromethyl-substituted primary amines. In these reports, where there still remain unsatisfactory enantioselectivities, chemical yields, and/or diversity.[3] Because of their importance in pharmaceutical research based on the special electronic properties of the trifluoromethyl group,[4] it is of particular interest to develop more general, efficient, and enantioselective routes to the title compounds.

The 1,2-addition of organometallic reagents to CN double bonds is one of the most efficient routes to α-branched amines.[5] Among them, the asymmetric 1,2-addition reaction using SAMP[6] or RAMP as a chiral auxiliary provides a

† On leave from Department of Chemistry, Faculty of Engineering, Gifu University, 1-1, Yanagido, Gifu 501-1193, Japan.

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(4) (a) Ojima, I.; Kato, K.; Jameison, F. A. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 219. (b) Shirlin, D.; Tarnus, C.; Baltzer, S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 651.

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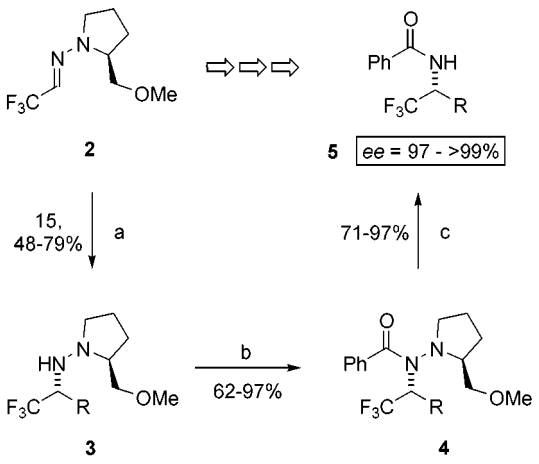
Scheme 1. Asymmetric Synthesis of α-Trifluoromethyl-Substituted Primary Amines[a]

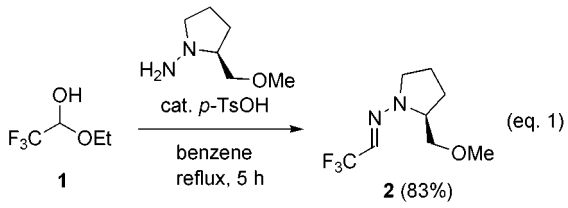


[a] (a) RLi, −78 °C; (b) catalytic DMAP, Et_3N, PhCOCl, rt or *n*-BuLi, PhCOCl, −78 °C to rt; (c) SmI_2, THF−DMPU, rt.

promising synthetic route to enantioenriched amines, which has been successfully applied for the asymmetric synthesis of natural products.[7]

Herein we describe the highly enantioselective synthesis of α-trifluoromethylated amines via nucleophilic 1,2-addition of alkyl- or phenyllithium reagents to trifluoroacetaldehyde SAMP− or RAMP−hydrazone, followed by benzoylation and SmI_2-promoted nitrogen−nitrogen single bond cleavage, as described in Scheme 1.

Trifluoroacetaldehyde SAMP−hydrazone **2** was readily obtained in 83% yield from commercially available trifluoroacetaldehyde ethyl hemiacetal **1** and SAMP in the presence of a catalytic amount of *p*-TsOH in benzene (eq 1).[8]



Trifluoroacetaldehyde RAMP−hydrazone was prepared in the same manner in 66% yield.

When 3 equiv of *n*-BuLi was added slowly to an Et_2O solution of **2** at −78 °C and the reaction mixture was gradually warmed to room temperature, a low yield (36%) of the product **3a** was obtained together with a complex mixture, probably due to the low stability of trifluoromethylated lithium hydrazide (Table 1, entry 1).

Table 1. Screening of the Reaction Conditions of Nucleophilic 1,2-Addition

entry[a]	*n*-BuLi (equiv)	solvent	yield (%)[b]	de (%)[c]
1[d]	3	Et_2O	36	>96 (>98)
2	1.5	Et_2O	63	>96 (>98)
3	3	Et_2O	79	>96 (>98)
4	1.5	THF	43 (37)	82 (>98)
5	3	THF	45 (39)	82 (>98)

[a] The reactions were carried out with trifluoroacetaldehyde SAMP−hydrazone **2** at −78 °C for 1 h. [b] Yields of isolated products. Values in parentheses are for the major diastereomer. [c] Measured by ^{19}F NMR before isolation. Values in parentheses after column chromatography. [d] After *n*-BuLi was added at −78 °C, the reaction mixture was warmed to room temperature overnight.

Treatment of **2** with 1.5 equiv of *n*-BuLi in Et_2O at low temperature (−78 °C) for a shorter reaction time (1 h) gave trifluoromethylated hydrazine **3a** in 63% yield (entry 2). The use of 3 equiv of *n*-BuLi gave a higher yield (entry 3). Employing THF as reaction solvent resulted in unsatisfactory yields of **3a** with decrease in diastereoselectivities (entries 4 and 5). The major diastereoisomer was readily separated by flash column chromatography.

The results of the reaction of **2** with various alkyllithium reagents as well as PhLi are summarized in Table 2.[9]

Table 2. Reaction of Trifluoroacetaldehyde SAMP− or RAMP−Hydrazone **2** with RLi

entry[a]	R	product	yield (%)[b]	de (%)[c]	$[\alpha]_D$ (*c*, $CHCl_3$)[d]
1	*n*-Bu	**3a**	79	>96 (>98)	−39.7 (0.88)
2[e]	*n*-Bu	**3a′**	74	>96 (>98)	+43.5 (0.95)
3	Et[f]	**3b**	48	>96 (>98)	−42.3 (0.90)
4	*n*-Pr[f]	**3c**	65	>96 (>98)	−45.9 (1.15)
5	*n*-Hex	**3d**	68	>96 (>98)	−39.7 (0.90)
6	*t*-Bu	**3e**	58 (50)	72 (>98)	−33.8 (1.25)
7	Ph	**3f**	15[g]	86 (88)	−38.2 (1.20)

[a] The reactions were carried out with trifluoroacetaldehyde SAMP−hydrazone **2** and RLi (3 equiv) in Et_2O at −78 °C for 1 h. [b] Yields of isolated products. Values in parentheses are for the major diastereomer. [c] Measured by ^{19}F NMR before isolation. Values in parentheses after column chromatography. [d] All optical rotations were measured in Uvasol grade $CHCl_3$ at 26 °C. [e] Trifluoroacetaldehyde RAMP−hydrazone was used instead of **2**. [f] Prepared from *t*-BuLi and the corresponding RI according to ref 10. [g] There were many unidentified byproducts in the ^{19}F NMR of the crude reaction mixture.

Commercially available alkyllithiums, such as *n*-BuLi and *n*-hexyllithium, reacted well in the nucleophilic 1,2-addition to give the corresponding trifluoromethylated hydrazines **3a**,**a′**,**d** in good yields with excellent diastereoselectivity

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(7) For a review on the synthesis of alkaloids, see: Enders, D.; Thiebes, C. *Pure Appl. Chem.* In press.

(8) Trifluoroacetaldehyde SAMP−hydrazone is much more stable than trifluoroacetaldehyde imines. Therefore in contrast the hydrazone can be purified by flash column chromatography.

(entries 1, 2, and 5). Ethyllithium and *n*-propyllithium, easily prepared from *t*-BuLi and the corresponding alkyl iodide,[10] also reacted with hydrazone **2** to provide the corresponding hydrazines **3c**,**d** in 48 and 65% yields, respectively (entries 3 and 4). Treatment of of **2** with *t*-BuLi gave a moderate yield of **3e** in moderate de (entry 6). However, the diastereomer could be readily separated by column chromatography, affording diastereomerically pure **3e**. When hydrazone **2** was treated with PhLi under the same conditions, 15% of the product **3f** was obtained in 86% de along with a complex mixture of byproducts (entry 7). Unfortunately, even in the presence of the trifluoromethyl group, the reaction of **2** with 3 equiv of MeLi in Et_2O or toluene at −78 °C did not proceed efficiently, giving only a small amount of the product together with recovery of **2** (58−75%). Raising the reaction temperature from −78 °C to room temperature in analogy to fluorine-free hydrazones as well as using MeMgI at −20 °C or $MeCeCl_2$ at −78 °C in place of MeLi did not improve the reaction.

The absolute configuration of the stereogenic center generated by the 1,2-addition using SAMP was established unambiguously as *R* by X-ray crystallography of **3e**.[11]

Significantly, after benzoylation, the chiral auxiliary was easily cleaved by treatment of **4** with 3 equiv of SmI_2[12] in the presence of 1,3-dimethyltetrahydro-2(1*H*)-pyrimidone (DMPU)[13] in THF at room temperature for 30 min, affording the (*R*)-*N*-benzoyl α-trifluoromethylated amines **5** without detectable epimerization or racemization (Table 3).[14]

Table 3. SmI_2 Cleavage of the N−N Single Bond of Trifluoromethylated SAMP− or RAMP−Hydrazides **4**

entry[a]	R	product	yield (%)[b]	ee (%)[c]	$[\alpha]_D$ (*c*, $CHCl_3$)[d]
1	*n*-Bu	**5a**	87	98	+40.8 (0.80)
2[e]	*n*-Bu	**5a**	4 (90)		
3[f]	*n*-Bu	**5a′**	95	97	−40.2 (0.95)
4	*n*-Pr	**5b**	83	98	+29.6 (0.82)
5	*n*-Hex	**5c**	97	98	+43.6 (0.90)
6	*t*-Bu	**5d**	71	>99	+22.9 (0.85)
7	Ph	**5e**	73	*g*	−2.58 (0.66)

[a] The reactions were carried out with hydrazide **4** and SmI_2 (3 equiv) in the presence of DMPU in THF at room temperature for 30 min. [b] Isolated yields. Values in parentheses refer to the recovery of **4**. [c] Measured by HPLC analysis using a chiral stationary phase column (DAICEL OD or (*S*,*S*)-Whelk-O, 1-heptane/2-propanol = 9/1 or 95/5). [d] All optical rotations were measured in Uvasol grade $CHCl_3$ at 25 or 27 °C. [e] MeOH was used as a solvent in the absence of DMPU. [f] RAMP−hydrazide **4a′** was used. [g] The ee could not be determined yet.

As shown in Table 3, various SAMP− or RAMP−hydrazides **4** participated successfully in the reaction to provide the corresponding amides **5** in good to excellent yields with excellent ee (up to >99%).[15] The reaction in MeOH gave a trace amount of the product **5a**, together with recovery of the starting hydrazide (90%).

In summary, we have succeeded in the highly enantioselective synthesis of α-trifluoromethylated amines through the 1,2-addition of various organolithium species to trifluoroacetaldehyde SAMP− or RAMP−hydrazone and subsequent SmI_2-promoted cleavage of the nitrogen−nitrogen single bond.

Further studies toward the asymmetric synthesis of trifluoromethylated bioactive compounds are now in progress.

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(9) **General Procedure of 1,2-Addition to Trifluoroacetaldehyde SAMP−Hydrazone.** A solution of *n*-BuLi (1.6 M) in hexane (3.08 mmol) was slowly added to a dry Et_2O (1 mL) solution of trifluoroacetaldehyde SAMP−hydrazone **2** (1.03 mmol) at −78 °C. After being stirred at that temperature for 1 h, the reaction mixture was quenched with a mixture of crushed ice, a saturated $NaHCO_3$ solution (50 mL), and Et_2O (30 mL). The aqueous portion was extracted with Et_2O (30 mL × 3), and the combined organic layers weredried over anhydrous Na_2SO_4 and concentrated in vacuo. After the isomer ratio was determined, flash column chromatography of the residue on silica gel eluting with pentane−Et_2O (10/1) gave **3a** in 79% yield.

(10) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(11) Details of X-ray structure analysis will be described in a full paper.

(12) SmI_2 (0.1 M in THF) was purchased from Aldrich Chemical Co. Inc. The purity of SmI_2 is very important for high yields. For the pioneering work for SmI_2-induced cleavage of the nitrogen−nitrogen single bond of hydrazines, see: (a) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227. For examples in MeOH or *t*-BuOH, see: (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (c) Atkinson, S. R.; Kelly, B. J.; Williams, J. *Tetrahedron* **1992**, *48*, 7713. (d) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (e) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (f) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. For examples in THF in the presence of HMPA, see: (g) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447. (h) Kadota, I.; Park, J.-Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 841. (i) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329.

(13) DMPU was distilled over CaH_2 in vacuo. Beck, A. K.; Seebach, D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Eds.; John Wiley & Sons: Chichester, 1995; Vol. 3, p 2123.

(14) **General Procedure.** A THF solution of SmI_2 (0.9 mmol, 8.8 mL of a 0.1 M THF solution) was added dropwise to a THF solution (2 mL) of SAMP−hydrazide **4a** (0.29 mmol) and DMPU (0.5 mL) at room temperature under argon. After 30 min at room temperature, the reaction mixture was quenched with a mixture of a diluted $NaHCO_3$ solution (50 mL) and CH_2Cl_2 (20 mL), extracted with CH_2Cl_2 (30 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel using pentane−Et_2O (5/1) as the eluent, affording **5a** in 87% yield.

(15) This result is also the first example for SmI_2-induced cleavage of the nitrogen−nitrogen single bond of SAMP− or RAMP−hydrazides in our laboratory. Very recently, Lassaletta and Llera reported the removal of the (*S*)-(−)-1′-methoxy-1′-ethylpropyl)pyrrolidyl group by the use of SmI_2, see: Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem.* **2000**, *112*, 3015; *Angew. Chem., Int. Ed.* **2000**, *39*, 2893.