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Highly diastereoselective addition of organometallic reagents to a trifluoroacetaldehyde hydrazone derived from (*R*)-*N*-benzylphenylglycinol

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This article is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—Organolithium and Grignard reagents add efficiently with very high stereoselectivity (>98% de) to a trifluoroacetaldehyde hydrazone derived from (*R*)-*N*-benzylphenylglycinol. The addition proceeds on the *re* face of the chelated hydroxyhydrazone providing the (*R*)-α-trifluoromethylated amine after hydrogenolysis.

Chiral amines are very important substructures of bioactive compounds and their asymmetric synthesis is a major objective of organic synthesis. To this purpose, nucleophilic addition of organometallic reagents to the CN double bond is one of the most widely used method.[1] Generally the stereoselectivity of the reaction is controlled by a stereogenic *N*-substituent which can be removed in the last step in order to give the free amino compounds. Because of their large availability, arylethylamines, β-amino alcohols and their *O*-substituted derivatives are some of the most frequently used auxiliaries. Unfortunately, these chiral auxiliaries are generally lost during the removal step. The addition of organometallic reagents to the CN double bond of hydrazones constitutes a major improvement of this strategy. In this case, the N–N bond can be cleaved under reductive conditions to give the optically active amine and the chiral auxiliary can be recovered.[2]

The incorporation of fluorine atoms or fluorine-containing groups into a molecule often drastically perturbs its physical, chemical and biological properties.[3] It has been shown that very often fluorinated analogues of biologically active compounds exhibit unique physiological activities. Therefore there is an increasing interest in the stereoselective synthesis of fluorinated compounds.[4] For instance, the nucleophilic addition of organometallic reagents to the CN double bond is the subject of considerable interest for the synthesis of α-fluoromethylamino compounds. Several groups reported the stereoselective addition of organometallic species on chiral trifluoromethylated aldimines[5] and ketimines.[6]

Recently, Enders et al. reported the stereoselective preparation of α-trifluoromethylated amines by addition of organolithium reagent to SAMP- and RAMP-hydrazones derived from fluoral hemiacetal.[7] This methodology allowed an efficient recovery of the chiral auxiliary but the reactivity of Grignard reagents was not mentioned. In the course of our study concerning the synthesis of enantiopure α-fluoromethylamino compounds,[8] we were interested in the development of the stereoselective addition of Grignard reagents to a fluoral based hydrazone. Since the pioneering work of Takahashi et al.[9] and more recent one of Brown and co-workers,[10] the addition of Grignard reagents to hydrazones derived from amino alcohols showing a free hydroxyl group is known to occur with a very high stereoselectivity. However, this reaction appears to be limited to aryl hydrazones. Therefore, in order to expand the scope of the hydrazone methodology in the fluorinated series, we decided to evaluate the stereoselectivity of the addition

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Table 1. Synthesis of hydrazone **2**

1 **2** **3**

Entry	Catalyst (equiv)	Time	Ratio **2**:**3**[a]	Yield (%)[b]
1	PPTS (0.1)	1.5 h	76:24	72
2	APTS (0.1)	2 h	71:29	98
3	No catalyst	35 min	100:0	96

[a] Measured by ^{19}F NMR spectroscopy of the crude reaction mixture. Compound **3** was obtained as a 75:25 mixture of diastereomers.
[b] Yields of isolated products.

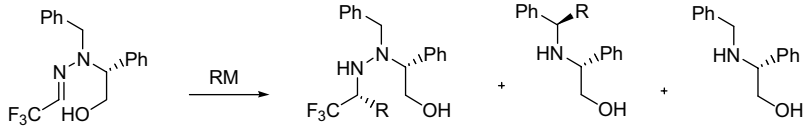
of organometallics to a (*R*)-phenylglycinol derived trifluoromethylhydrazone.

The hydrazone **2**[11] was readily prepared in high yield by condensation of trifluoroacetaldehyde ethyl hemiacetal and hydrazine **1**[12] in toluene at reflux with azeotropic removal of water and ethanol (Table 1). Under acidic catalysis (entries 1 and 2), the ring closure of the hydroxyhydrazone **2** into **3** occurred as a side reaction. This undesired side reaction could easily be avoided with short reaction time under neutral conditions (entry 3).

The results of the reactions of **2** with various organometallic reagents are summarized in Table 2. The addition of *n*-butyllithium to hydrazone **2** in THF at −78 °C gave the hydrazine **4a** in low yield (37%) but with excellent stereoselectivity (>98% de)[13] (Table 2, entry 1). Because of the deprotonation of the free hydroxyl group, at least 2 equiv of organometallic reagent were necessary for the reaction to occur. The addition of *n*-butylmagnesium and vinylmagnesium chloride (1.8 M in THF) proceeded at room temperature to give the expected hydrazines **4a** in 44–58% yield and **4b** in 23–47% yield as a single diastereomer[13] (Table 2, entries 2–5). The trifluoromethyl hydrazone is thus much more reactive than its aromatic analogues which required reflux temperature and tenfold molar excess of Grignard reagents to give the corresponding hydrazine.[10] Modification of the reactions conditions and the amount of organometallic reagent in THF failed to improve significantly the yield of hydrazines **4**. Two unexpected side products were identified. The (*R*)-*N*-benzylphenylglycinol **6** should result from the N–N bond cleavage. The unfluorinated benzylamine **5c**[14] (Table 2, entry 6) should arise from the stereoselective addition of benzylmagnesium chloride on the *re* face of an intermediate imine obtained by elimination of the electron withdrawing fluorinated fragment (Fig. 1).

A significant improvement of the CN 1,2-addition selectivity was noticed when the reaction was performed in Et_2O as the solvent. The addition of 3 equiv of *n*-butyllithium proceeded selectively at −30 °C and the hydrazine **4a**[15] was obtained as a single diastereomer in 65% yield (Table 2, entry 7). In a similar manner vinylmagnesium chloride (1.8 M in THF, 3 equiv) and benzylmagnesium chloride (1.35 M in THF, 3 equiv) were added smoothly to the hydrazone **2** at room temperature. The corresponding hydrazine **4b** and **4c** were obtained in 75% and 68% yields with complete stereoselectivity[13]

Table 2. RM addition to hydrazone **2**



2 **4** (> 98%de) **5** **6**

Entry	RM (equiv)	Solvent	Conditions	Yield of **4** (%)[a]	Yield of **5** (%)[a]	Yield of **6** (%)[a]
1	*n*-BuLi (2.2)	THF	−78 °C, 2 h	**4a** (37)		
2	*n*-BuMgCl (2.2)	THF	−78 °C, 2 h, then rt, 12 h	**4a** (44)		
3	*n*-BuMgCl (3.3)	THF	−40 °C, 3 h, then rt, 3 h	**4a** (58)		**6** (16)
4	VinylMgCl (4)	THF	−78 °C, 30 min, then rt, 3 h	**4b** (23)		**6** (50)
5	VinylMgCl (3.3)	THF	−50 °C, 2 h, then rt, 4 h	**4b** (47)		
6	BnMgCl (4)	THF	0 °C to rt, 4 h		**5c** (34)[b]	
7	*n*-BuLi (3)	Et_2O	−30 °C, 4 h	**4a** (65)		
8	VinylMgCl (3)	Et_2O	0 °C to rt, 4 h	**4b** (75)		
9	BnMgCl (3)	Et_2O	0 °C to rt, 4 h	**4c** (68)		

[a] Yields of isolated products.
[b] One single diastereomer.

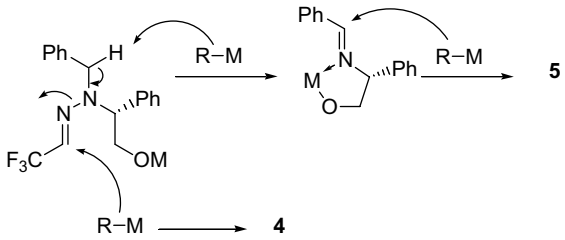
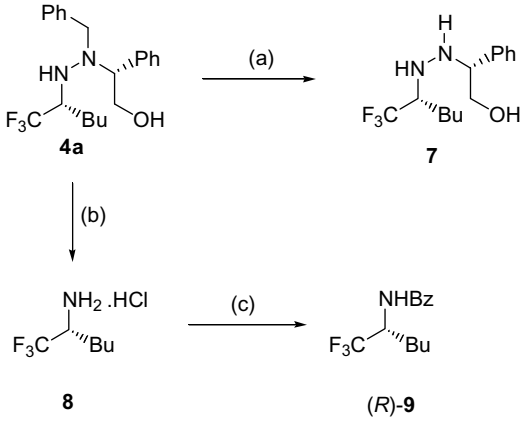


Figure 1. Competitive reactions occurring in THF.

(Table 2, entries 8 and 9). However a poor conversion of **2** (<15%) was obtained with phenyllithium (2 M in dibutylether, 3 equiv) in Et_2O.

We next focused our attention on the removal of the chiral auxiliary and the assignment of the absolute configuration of the newly formed chiral centre. To this purpose, hydrazine **4a** resulting from *n*-butyllithium or *n*-butylmagnesium chloride addition to hydrazone **2** was submitted to hydrogenolysis (Scheme 1). In the presence of $Pd(OH)_2$ the selective debenzylation of nitrogen gave hydrazine **7** without any detectable epimerization. The complete reduction was achieved in more drastic conditions by treatment of **4a** with H_2 (6 bar), 10% Pd/C, in MeOH–concd HCl at 60 °C for 12 h. In these conditions the expected trifluoromethylated amine hydrochloride **8** was quantitatively obtained but the chiral auxiliary was not recovered. The (*R*) configuration was assigned by comparison of the optical rotation value of the corresponding benzoate **9** with the literature values.[16] We assume that the hydrazines **4b**,**c** also present the (*R*) configuration.

This result confirmed that the stereochemical outcome of the reaction was consistent with the *re* face attack of the hydrazone. The high level of stereoselectivity can be explained by a six member ring intermediate involving a chelation of both the hydroxyl group and a nitrogen atom of the hydrazone (Fig. 2).



Scheme 1. Configuration assignment of **4a**. Reagents, yields: (a) H_2 6 bar, $Pd(OH)_2$, MeOH–HCl 3 N, rt, 24 h, 41% (>98% de); (b) H_2 6 bar, 10% Pd/C, MeOH–concd HCl, 60 °C, 12 h, quantitative; (c) PhCOCl, Et_3N, DMAP, CH_2Cl_2, 12 h, 25%.

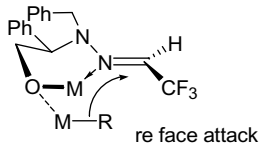


Figure 2. Postulated transition state for diastereoselective addition to hydrazone **2**.

In conclusion, we have developed a highly stereoselective method for the synthesis of α-trifluoromethyl amines. Grignard reagents proved to add as efficiently as organolithium reagents to the hydroxyhydrazone provided that the reaction was performed at room temperature in Et_2O. Further experiments are in progress to enlarge the scope of this reaction.

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Supplementary data

Experimental procedure and characterization data for compounds **4b**, **4c**, **7**, **8** and **9** are available. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.040.

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11. *Synthesis of hydrazone* **2**. In a 250 ml round bottom flask equipped with a Dean–Stark apparatus, hydrazine **1** (2.62 g, 10.8 mmol) was dissolved in toluene (150 ml). Trifluoroacetaldehyde ethylhemiacetal (1.68 g, 13 mmol) was added dropwise and the solution was heated to reflux for 35 min. After this time, the reaction was cooled down to room temperature and evaporated under reduced pressure. The hydrazone **2** was obtained as a colourless oil (3.33 g, 96% yield). IR (film): 3412, 3065, 3031, 2928, 1592, 1265, 1131 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 2.86 (dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 3.87 (ddd, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 4.24–4.32 (m, 3H), 4.62 (dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 6.36 (q, J_{HF} = 3.8 Hz, 1H), 7.03–7.34 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 54.2, 66.1, 75.4, 116.3 (q, $^2J_{CF}$ = 38.3 Hz), 119.6 (q, $^1J_{CF}$ = 269.0 Hz), 126.3, 127.5, 127.9, 128.0, 128.1, 128.6, 128.8, 133.8, 137.8, 138.2. ^{19}F NMR (235 MHz, $CDCl_3$) δ: −64.7 (d, $^3J_{HF}$ = 3.8 Hz). $[\alpha]_D^{20}$ +89.1 (*c* 0.68, $CHCl_3$). GC/MS: *m/z* (%) 322 (M^+) (3), 291 (78), 121 (8), 91 (100).
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15. *Hydrazine* **4a**. In a 50 ml Schlenk round bottom flask filled with argon, **2** (684 mg, 2.12 mmol) was dissolved in dry diethyl ether (30 ml). The solution was cooled down to −30 °C and *n*-butyllithium (2.95 ml, 2.15 M, 6.4 mmol) was added dropwise. The dark yellow solution was stirred for 4 h at this temperature and quenched with NH_4Cl (saturated solution 20 ml). The reaction was extracted twice with diethyl ether, dried on magnesium sulfate and evaporated under reduced pressure to afford a yellow oil which was purified by chromatography (petroleum ether/diethyl ether 70/30) to provide **4a** as a pale yellow oil (524 mg, 65% yield). IR (film): 3408, 3030, 2960, 1602, 1455, 1275 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.79 (m, 3H), 1.09–1.33 (m, 5H), 1.46 (m, 1H), 2.62 (s, 1H), 3.04 (q, $^3J_{HF}$ = 6.8 Hz, 1H), 3.24 (d, $^2J_{HH}$ = 13.8, 1H), 3.45 (dd, $^3J_{HH}$ = 11.5 Hz, $^2J_{HH}$ = 2.9 Hz, 1H), 3.74 (dd, $^3J_{HH}$ = 9.2 Hz, $^2J_{HH}$ = 2.9 Hz, 1H), 3.92 (d, $^2J_{HH}$ = 13.8, 1H), 4.10 (dd, $^3J_{HH}$ = 11.5 Hz, $^3J_{HH}$ = 9.2 Hz, 1H), 7.01–7.25 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 13.9, 22.8, 28.0, 28.5, 60.2 (q, $^2J_{CF}$ = 34.3 Hz), 60.8, 65.9, 69.9, 126.5 (q, $^1J_{CF}$ = 282.8 Hz), 127.4, 128.0, 128.3, 128.8, 136.7, 138.2. ^{19}F NMR (235 MHz, $CDCl_3$) δ: −73.6 (d, $^3J_{HF}$ = 6.8 Hz). $[\alpha]_D^{20}$ −20.1 (*c* 0.44, $CHCl_3$). GC/MS: *m/z* (%) 380 (M^+) (6), 349 (19), 259 (73), 121 (14), 91 (100). Anal. Calcd for $C_{21}H_{27}F_3N_2O$: C, 66.30; H, 7.15; N, 7.36. Found: C, 66.47; H, 7.33; N, 7.25.
16. $[\alpha]_D^{20}$ +35.0 (*c* 0.50, $CHCl_3$) (lit.[7a] 98% ee $[\alpha]_D^{20}$ +40.8 (*c* 0.80, $CHCl_3$)).