Enantioselective Reduction of Trifluoromethyl Ketones with Chiral Organomagnesium Amides (COMAs)

Kelvin H. Yong and J. Michael Chong*

*Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, (GWC)²
Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada
N2L 3G1*

Supporting Information

A. General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether and THF were freshly distilled from Na/benzophenone. ¹H and ¹³C NMR spectra were recorded in CDCl₃ at 300 and 75 MHz, respectively. Optical rotations were recorded in cells with 10 cm path length on a Perkin-Elmer 241 digital polarimeter. The known diamine **1a**¹ was prepared from (*R*)-phenylglycine and diamines **1b**,² **1c**,³ **1d**,⁴ **1e**,⁴ **1f**,⁵ **1g**,³ and **1h**³ were prepared from (*R*)-2-phenyl-2-(1-piperidinyl)ethanol⁵ as previously described. Enantiomeric ratios of the carbinols were determined either directly or indirectly (as benzoate) by HPLC using a 4.6 mm x 150 mm Chiralcel OD column, eluting with 5-10% isopropanol in hexanes or 100% hexanes (for benzoate).

Trifluoromethyl ketones were prepared according to procedures described previously.^{6,7}

¹ Rossiter, B. E.; Eguchi, M.; Hernandez, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heinis, D. *Tetrahedron Lett.* **1991**, 32, 3973-3976.

² Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; *Tetrahedron*, **1993**, 49, 965-986.

³ Curthbertson, E.; O'Brien, P.; Towers, T. D. *Synthesis*, **2001**, 693-695.

⁴ Saraavanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, 39, 167-170.

⁵ Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483-1492.

⁶ a) Chong, J. M.; Mar, E. K. *J. Org. Chem.* **1991**, 56, 893-896; b) Mar, E. K. Ph. D. Dissertation, Ch. 6, University of Waterloo, 1990.

Chiral carbinols **3a**, **3b**, **3c**, **3d** and **3e** were reported by our laboratory previously.⁶
Chiral carbinol **3f** was reported by Brown.⁸

Preparation of diisopropylmagnesium solution.⁹

1,4-Dioxane (18 mL, 0.22 mole) was added slowly to a mechanically stirred 1 M solution of *i*-propylmagnesium chloride (200 mL, 0.2 mole). The resultant heterogeneous mixture was stirred at ambient temperature overnight (8-12 h). The suspension was then transferred *via* cannula to centrifuge tubes and centrifuged (2500 rpm, 30 min) to give a clear and colorless diisopropylmagnesium solution. A few drops of 1,4-dioxane were added to the solution to confirm the complete precipitation of magnesium dichloride, and the clear supernatant was then transferred *via* cannula into a Schlenk tube and the concentration was determined by titration before use.

Titration of dialkylmagnesium solution.

The following procedure is an extension of the titration procedure reported by Love¹⁰ for Grignard reagents. The dialkylmagnesium solution (~0.5 M) was added dropwise to a stirred solution of accurately weigh salicylaldehyde phenylhydrazone (~ 1 mmol) in THF (15 mL) under argon at room temperature. The solution turned yellow initially and the end point is indicated by the bright golden orange color. The exact amount of dialkylmagnesium solution needed to reach the end point was recorded. Each mole of

⁷ Linderman, R. J.; Lonikar, M. S. *J. Org. Chem.* **1988**, 53, 6013-6022.

⁸ Ramachandran, P. V.; Teodorović, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, 5, 1061-1074.

⁹ Wakefield, B. J. "Organomagnesium Methods in Organic Synthesis" Academic Press, **1995**, 65-67.

¹⁰ Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, 64, 3755-3756.

dialkylmagnesium will react with two moles of indicator and the concentration was calculated by:

$$M = \text{mmol of indicator} / (2 \times \text{volume of } R_2Mg \text{ in mL})$$

Preparation of *i*-Pr-COMA (2) solution using ligand **1f**.

A solution of 0.52 M *i*-Pr₂Mg (0.95 mL, 0.494 mmol) was added to a solution of precooled (−78 °C) diamine **1f** (150 mg, 0.51 mmol) in ether (12 mL) under argon. The resultant solution was then stirred at ambient temperature for 0.5 h to form a cloudy solution. Then THF (1.5 mL) was added to the reaction and stirred for 0.5 h to form the a clear *i*-Pr-COMA reagent. The resultant COMA solution was used directly in the next reaction.

B. COMA for Enantioselective MPV Reductions

2,2,2-Trifluoro-1-phenylethanol (**3a**)

Carbinol **3a** was prepared using a number of different COMAs and the yields and er are shown in Table 2. The following is a typical procedure used

for enantioselective reduction of ketones:

The *i*-Pr-COMA solution (0.5 mmol) (from *i*-Pr₂Mg and diamine **1e**) was cooled to −78 °C and a solution of trifluoromethyl acetophenone (44 mg, 0.25 mmol) in ether (1 mL) was added and the reaction was stirred at −78 °C and allowed to warm up to rt slowly (5-6 h). The reaction was quenched with saturated aqueous NH₄Cl (5 mL) and the layers were separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined

organic phase was washed with 0.5 M HCl to remove the diamine **1f** (2 x 3 mL). The diamine can be recovered by acid-base extraction (see below). The organic phase was dried (Na₂SO₄), filtered and concentrated under reduced pressure to give the crude **3a**. The product was purified by silica gel column chromatography (10% Et₂O in hexanes) to give the desired alcohol as a pale yellow oil (40 mg, 89%, er = 13:87). The enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, 5% isopropanol in hexanes, 1.0 mL/min *S*: 25.3min, *R*: 27.0 min). [α]_D²⁵ = +21.6 (c = 0.52, CHCl₃); Lit.¹¹ (*S*-isomer), [α]_D²⁵ = +30.4 (c = 1.56, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.5-7.3 (5H, m), 4.99 (1H, br q, *J* = 6.1 Hz), 2.74 (1H, br s); ¹³C NMR (75 MHz, CDCl₃) δ 134.0, 129.7, 128.7, 127.5, 124.3 (q, *J*_{C-F} = 282 Hz), 74.6 (q, *J*_{C-F} = 32.0 Hz); MS (EI) *m/z* 176 (M⁺, 31), 107 (100), 79 (84).

Recovery of diamine :

The acidic aqueous phase was washed once with ether (1 mL), then basified with 5 M KOH. The diamine was then extracted into ether (3 x 5 mL). The organic layer was dried (Na₂SO₄), filtered and evaporated under reduced pressure to give a light yellow oil. Kugelrohr distillation (0.5 mm Hg) gave the recovered amine as colorless oil (~80% recovery).

2,2,2-Trifluoro-1-(1-naphthyl)ethanol (3b)

Alcohol **3b** was prepared using a number of different COMAs and the yields and er are shown in Table 2. The following represents the data for one of the reactions.

¹¹ Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **2000**, 65, 157-163.

Carbinol **3b** was prepared using *i*-Pr-COMA (0.5 mmol) (from *i*-Pr₂Mg and diamine **1f**) and the corresponding trifluoromethyl ketone (58 mg, 0.26 mmol). The product was purified by silica gel column chromatography (10→20% Et₂O in hexanes) to give **3b** as a colourless oil (56 mg, 96%, er = 7:93). The enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, 10% isopropanol in hexanes, 1.0 mL/min *R*: 10.4 min, *S*: 35.9 min). $[\alpha]_{\text{D}}^{25} = +17.5$ (*c* = 1.01, EtOH); Lit.¹² (*R*-isomer), $[\alpha]_{\text{D}}^{25} = -21.1$ (*c* = 1, EtOH). ¹H NMR (300 MHz, CDCl₃) δ 8.05 (1H, d, *J* = 8.3 Hz), 8.0-7.9 (2H, m), 7.82 (1H, d, *J* = 7.2 Hz), 7.6-7.4 (3H, m), 5.89 (1H, q, *J* = 6.3 Hz), 2.61 (1H, br s); ¹³C NMR (75 MHz, CDCl₃) δ 133.6, 131.0, 130.1, 129.9, 129.0, 126.8, 125.9, 125.8, 125.2, 124.8 (q, *J*_{C-F} = 284 Hz), 122.7, 74.6 (q, *J*_{C-F} = 32.0 Hz); MS (EI) *m/z* 226 (*M*⁺, 54), 157 (81), 129 (100).

2,2,2-Trifluoro-1-[1-(2-methylnaphthyl)]ethanol (**3c**)

Carbinol **3c** was prepared according the general procedure described for **3a** using *i*-Pr-COMA (0.5 mmol) (from *i*-Pr₂Mg and diamine **1f**) and the corresponding trifluoromethyl ketone (60 mg, 0.25 mmol). The product was purified by silica gel column chromatography (10→20% Et₂O in hexanes) to give **4-77** as a colourless oil (58 mg, 95%, er = 7:93). The enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, 10% isopropanol in hexanes, 1.0 mL/min *R*: 9.2 min, *S*: 23.8 min). $[\alpha]_{\text{D}}^{25} = +36.1$ (*c* = 1.07, CHCl₃); Lit.⁶ (*R*-isomer), $[\alpha]_{\text{D}}^{25} = -36$ (*c* = 0.634, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.68 (1H, br s), 7.8-7.7 (2H, m), 7.6-7.4 (2H, m), 7.30 (1H, d, *J* = 8.4 Hz), 5.89 (1H, br s), 2.76 (1H, br s), 2.57 (3H, br s);

¹² Bucciarelli, M.; Fomi, A.; Moretti, I.; Torre, G. *Synthesis*, **1983**, 897-899.

^{13}C NMR (75 MHz, CDCl_3) δ 136.3 (br), 133.2 (br), 131.8 (br), 130.1 (br), 129.0 (br), 128.6 (br), 126.3 (br, 2C), 125.4 (q, $J_{\text{C-F}} = 284$ Hz) 125.1, 70.9 (m), 21.1 ; MS (EI) m/z 240 (M^+ , 60), 171 (100), 143 (84), 128 (92).

2,2,2-Trifluoro-1-(2,4,6-trimethylphenyl)ethanol (**3d**)

Carbinol **3d** was prepared according the general procedure described for **3a** using *i*-Pr-COMA (0.5 mmol) (from *i*-Pr₂Mg and diamine **1f**) and the corresponding trifluoromethyl ketone (61 mg, 0.27 mmol). The product was purified by silica gel column chromatography (10% Et₂O in hexanes) to give **3d** as a colourless oil (55 mg, 89%, er = 3:97). The enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, 5% isopropanol in hexanes, 1.0 mL/min *R*: 10.1 min, *S*: 13.7 min). $[\alpha]_{\text{D}}^{25} = +26.64$ ($c = 1.22$, CHCl_3); Lit.⁶ (*R*-isomer), $[\alpha]_{\text{D}}^{25} = -30$ ($c = 0.544$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 6.86 (2H, s), 5.51 (1H, q, $J = 8.1$ Hz), 2.42 (7H, br s), 2.25 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 138.8, 138.2 (br), 131.0 (br), 126.9, 125.6 (q, $J_{\text{C-F}} = 283$ Hz), 70.2 (q, $J_{\text{C-F}} = 32.2$ Hz), 20.9 (3C); MS (EI) m/z 226 (M^+ , 54), 157 (81), 129 (100).

2,2,2-Trifluoro-1-(9-anthryl)ethanol (**3e**)

Carbinol **3e** was prepared according the general procedure described for **3a** using *i*-Pr-COMA (0.5 mmol) (from *i*-Pr₂Mg and diamine **1f**) and the corresponding trifluoromethyl ketone (72 mg, 0.26 mmol). The ketone was introduced directly to the reaction as a solid. The product was purified by silica gel column chromatography (10→20% Et₂O in hexanes) to give **3d** as a

pale yellow solid (69 mg, 95%, er = 2:98). The enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, 10% isopropanol in hexanes, 1.0 mL/min *R*: 12.1 min, *S*: 29.2 min). $[\alpha]_{\text{D}}^{25} = +28.6$ ($c = 1.05$, CHCl_3); Lit.⁶ (*S*-isomer), $[\alpha]_{\text{D}}^{25} = +31$ ($c = 1.015$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 8.94 (1H, br s), 8.52 (1H, s), 8.12 (1H, br s), 8.01 (2H, br d, $J = 8.3$ Hz), 7.6-7.4 (4H, m), 6.63 (1H, q, $J = 8.0$ Hz), 2.90 (1H, br s); ^{13}C NMR (75 MHz, CDCl_3) δ 131.7 (br), 130.7 (br), 129.2 (br), 127.3 (br, 2C), 126.2 (br), 125.2 (q, $J_{\text{C-F}} = 284$ Hz), 124.9 (br, 2C), 123.7, 70.0 (q, $J_{\text{C-F}} = 32.8$ Hz); MS (EI) m/z 276 (M^+ , 54), 207 (65), 178 (100).

1,1,1-Trifluoro-oct-3-yn-2-ol (**3f**)

Alcohol **3f** was prepared according the general procedure described for **3a** using *i*-Pr-COMA (0.5 mmol) (from *i*-Pr₂Mg and diamine **1f**) and the corresponding trifluoromethyl ketone (47 mg, 0.29 mmol). The product was purified by silica gel column chromatography (10% Et₂O in hexanes) to give **3f** as a colourless oil (42 mg, 88%, er = 61:39). $[\alpha]_{\text{D}}^{25} = +2.5$ ($c = 0.86$, CHCl_3); Lit.⁸ (*S*-isomer), $[\alpha]_{\text{D}}^{25} = -13.2$ ($c = 3.1$, CHCl_3). The alcohol was derivatized to the benzoate and enantiomeric ratio of the product was determined by chiral phase HPLC (ChiralCel-OD, hexanes, 1.0 mL/min *R*: 9.7 min, *S*: 10.8 min). ^1H NMR (300 MHz, CDCl_3) δ 4.7-4.5 (1H, m), 2.53 (1H, d, $J = 8.1$ Hz), 2.23 (1H, dt, $J = 1.6, 6.9$ Hz), 1.6-1.3 (4H, m), 1.89 (1H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 122.8 (q, $J_{\text{C-F}} = 282$ Hz), 89.6, 72.1, 62.5 (q, $J_{\text{C-F}} = 36.2$ Hz), 30.0, 21.8, 18.2, 13.5; MS (EI) m/z 165 ($[\text{M-Me}]^+$, 1.3), 147 (23), 120 (23), 111 (100).