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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] and Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

jmchong@uwaterloo.ca

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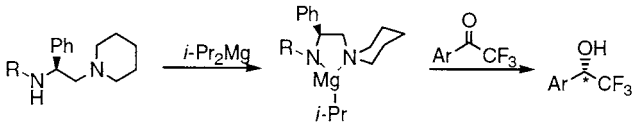
ABSTRACT



Chiral organomagnesium amides (COMAs), readily prepared from dialkylmagnesiums and chiral secondary amines, can reduce trifluoromethyl ketones to form secondary alcohols with excellent enantioselectivities (up to 98:2 er) and chemical yields (typically >95% conversion, >85% isolated yields). These MPV-type reductions use an achiral hydride source, and the chiral amine is readily recovered.

Enantioselective reductions of ketones to chiral alcohols have been studied extensively, and there are many excellent methods available for reducing a wide variety of ketones with high selectivities.[1] A particularly attractive approach to such reductions is the use of a recoverable chiral catalyst or reagent in conjunction with an achiral hydride source. Thus, the use of oxazaborolidine catalysts (i.e., CBS-type reductions) is more appealing than the use of stoichiometric reagents such as DIP−Cl where the borane is consumed in the reaction.[2]

We recently introduced chiral organomagnesium amides (COMAs, $RMgNR^*_2$) as reagents for the enantioselective alkylation of aldehydes.[3] In the course of our studies, it was observed that transfer of hindered alkyl groups such as *i*-Pr was often accompanied by competing reduction. It is probable that such reductions arise from β-hydride transfer via a Meerwein−Ponndorf−Verley (MPV)-type mechanism;[4] it is well-known that reduction is often competitive with alkyl transfer when some Grignard reagents are reacted with carbonyl compounds.[5] In fact, Grignard reagents derived from chiral alkyl halides have been used as asymmetric reducing agents, although selectivities are typically moderate.[6] Since reductions using COMAs likely proceed with the hydride coming from an achiral source (i.e., R_2Mg), the chiral ligand should be recoverable and recyclable, and hence, in principle, COMAs might be very desirable chiral reducing agents. We report herein our initial findings in this area.

In testing a new chiral reducing agent, the standard substrate appears to be acetophenone.[1] However, treatment of acetophenone with various COMA reagents, prepared from dialkylmagnesiums (R_2Mg) and amine **1a**, gave only trace amounts of phenethyl alcohol (Scheme 1). Deuteration experiments with MeOD suggested that enolization was a major competing pathway. Thus, it seemed that only ketones without α-protons might be suitable substrates.

One such class of compounds are aryl trifluoromethyl ketones. Asymmetric reduction of such ketones would furnish chiral nonracemic trifluoromethyl carbinols. There is cur-

(1) For recent reviews, see: (a) Itsuno, S. *Org. React.* **1998**, *52*, 395−576. (b) Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3−16.

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

(3) Yong, K. H.; Taylor, N. J.; Chong, J. M. *Org. Lett.* **2002**, *4*, 3553−3556.

(4) The reagent *s*-$BuMgN(TMS)_2$ has been shown to reduce benzophenone, although incompletely, likely by β-hydride transfer: Henderson, K. W.; Allan, J. F.; Kennedy, A. R. *J. Chem. Soc., Chem. Commun.* **1997**, 1149−1150.

(5) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995, p 249.

(6) Falorni, M.; Lardicci, L.; Giacomelli, G. *J. Org. Chem.* **1989**, *54*, 2383−2388.

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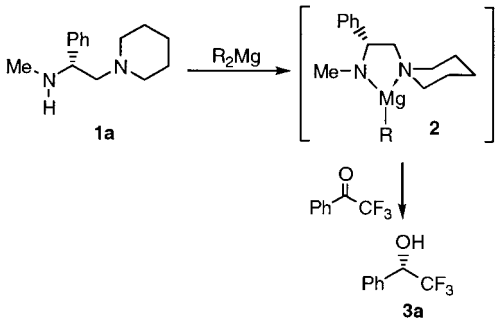
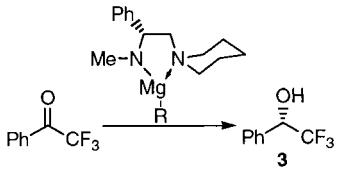
Scheme 1



rently considerable interest in asymmetric syntheses of fluorinated organics, particularly as potential pharmaceuticals.[7] In addition, asymmetric reductions of trifluoromethyl ketones have received relatively little attention (compared to other carbonyl compounds). We were thus very pleased to find that treatment of 2,2,2-trifluoroacetophenone with COMA reagents **2** rapidly (−78 °C, 1 h) and efficiently (>95% GC yields, >85% isolated yields) afforded the desired alcohol **3a** (Scheme 1). A survey of different alkyl groups showed that the enantioselectivity depended on the alkyl group used as a hydride source (Table 1). The best

Table 1. Reactions of COMA **2** with Trifluoroacetophenone



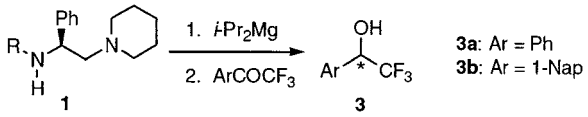
entry	R	yield[a]	er[b] R:S
1	*n*-Bu	86	34:66
2	*i*-Bu	93	33:67
3	*i*-Pr	92	29:71
4	*t*-Bu	88	49:51

[a] Percent isolated yields of chromatographed alcohol. [b] Determined by HPLC analysis on a Chiralcel OD column.

selectivities were observed with R = *i*-Pr, so *i*-Pr_2Mg was used for all further studies.

Enantioselective reductions of trifluoroacetophenone often proceed with relatively low selectivities (compared to acetophenone). This is likely due to the similar size of trifluoromethyl and phenyl groups.[8] Nonetheless, some good selectivities have been reported,[9] and in some cases, reductions of trifluoromethyl ketones proceed with much higher selectivities than their methyl analogues.[10] Therefore, to probe reductions with COMA reagents further, we assessed a number of ligand/*i*-Pr_2Mg combinations for their ability to reduce trifluoroacetophenone and 1-naphthyl trifluoromethyl ketone (Table 2).

Table 2. Effect of Ligand Structure on Stereoselectivity



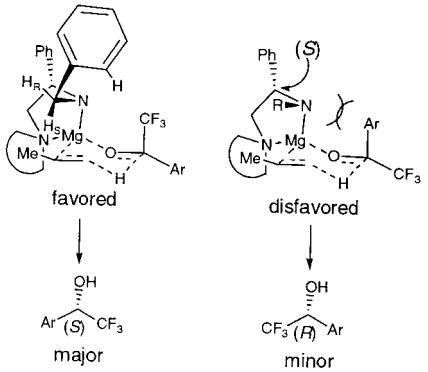
	ligand		Ar = Ph		Ar = 1-Nap	
entry	R	no.	yield[a]	er[b] R:S	yield[a]	er[b] R:S
1	Me	**1a**	93	71:29	97	16:84
2	Et	**1b**	87	76:24	86	31:69
3	*i*-Pr	**1c**	86	54:46	92	11:88
4	*t*-Bu	**1d**	94	21:79	94	21:79
5	Ph	**1e**	**84**[c]	**13:87**	87	46:54
6	$PhCH_2$	**1f**	89	66:34	**92**	**7:93**
7	(*R*)-PhCH(Me)	**1g**			**93**	**9:91**
8	(*S*)-PhCH(Me)	**1h**			92	24:76

[a] Percent isolated yields of chromatographed alcohol. [b] Determined by HPLC analysis with a Chiralcel OD column. [c] Ether was used as the only solvent. Selectivities were lower under standard conditions.

In all cases, good to excellent yields of the desired alcohol were isolated. For 1-naphthyl trifluoromethyl ketone, reductions using COMAs with (*S*)-ligands consistently provided the (*S*)-carbinol as the major product. There is no obvious relationship between the size of the *N*-alkyl/aryl (R) group and the observed selectivity. However, it is noteworthy that *N*-benzyl ligand **1f** gave high selectivities (entry 6). Since both diastereomers of the α-methylbenzyl analogues (**1g** and **1h**) were readily available, they were also tested. As expected, they behaved differently. One isomer gave results essentially identical to those of the nor-methyl case, while the other isomer gave noticeably lower selectivity.

Results may be rationalized in terms of six-membered chairlike transition states (Scheme 2). One would expect that

Scheme 2. Proposed transition states for reduction of $ArC(O)CF_3$ with *i*-Pr_2Mg/**1f**



(7) For leading references, see: Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207−7219.

(8) Note, however, that a CF_3 group is similar to a *tert*-butyl group in reductions using DIP−Cl: Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075−1086.

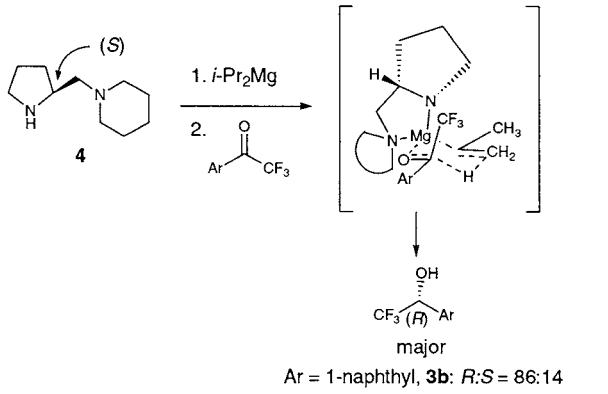
the diamine ligand would chelate the Mg atom and that the phenyl and *N*-alkyl groups would be preferentially oriented anti to each other on the resulting five-membered ring. Approach of the ketone to this reagent from the less hindered face could then take place with the CF_3 group oriented axial or equatorial in a six-membered ring transition state. Since relatively large aryl groups would prefer to be equatorial, the transition state with an axial CF_3 group is energetically more favorable and gives rise to the major product. On the basis of this model, ligands of the (*S*)-configuration should afford (*S*)-carbinol as the major product. This is what is observed.

The enhanced selectivity observed with *N*-benzyl ligand **1f** compared to ligands with smaller or larger *N*-alkyl groups can also be explained using this model if one invokes a stabilizing effect on one of the possible transition states by the benzyl group. Specifically, an Ar−H···F−C interaction may help to stabilize the transition state where the CF_3 is axial. Such interactions, although known to be very weak, have been observed in the solid state.[11] In our case, the presence of such interactions helps to explain the differences in selectivities observed for ligands **1f**, **1g**, and **1h**. Thus, using the model shown in Scheme 2, it would be expected that replacement of the benzylic pro-(*R*) hydrogen in **1f** (to give **1g**) should have little influence on selectivity but that replacement of the pro-(*S*) hydrogen (to give **1h**) should give decreased selectivity since steric interactions would make it difficult for the favorable conformation shown to be attained. The experimental evidence, namely, that **1f** and **1g** give essentially identical selectivities while **1h** gives significantly lower selectivity (Table 2, entries 6−8), is consistent with these expectations.

With trifluoroacetophenone, the major product formed using ligands **1a**−**f** (all of the (*S*)-configuration) was sometimes *R* and sometimes *S*. In general, ligands with smaller *N*-alkyl groups (e.g., Me, Et, $PhCH_2$) were (*R*)-selective, while ligands with larger groups (e.g., *t*-Bu, Ph) were (*S*)-selective. This may be because ligands with smaller *N*-alkyl groups can adopt conformations in which the *N*-alkyl group and the phenyl group of the phenylglycine-derived ligand are cis. Approach of the ketone to the reagent would then be on the opposite face to that depicted in Scheme 2, and the opposite (*R*)-enantiomer would predominate. Thus, with trifluoroacetophenone, larger N-substituents were needed to obtain good selectivities, and the best numbers were observed with ligand **1e** (R = Ph, Table 2, entry 5).

The idea that the relative orientation of the N-alkyl group and the phenyl (side-chain) group is important in determining the absolute configuration of the product is supported by results using derivatives of proline as ligands. With such ligands, the "side-chain" and N-alkyl group are confined in a five-membered ring and may be considered cis-oriented in a COMA complex. An analysis of possible transition states similar to that shown in Scheme 2 leads to the conclusion that ligands of (*S*)-configuration should give products of (*R*)-configuration. In fact, reductions of 1-naphthyl trifluoromethyl ketone using COMAs derived from (*S*)-proline (e.g., **4**, Scheme 3) consistently gave rise to (*R*)-**3b** as the major product.

Scheme 3



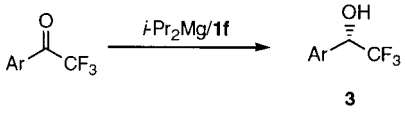
While the arguments presented above explain the differences in enantioselectivities observed with different ligands and trifluoroacetophenone, they do not explain why there are differences between aryl groups. Perhaps with acyclic ligands, the orientation of the N-alkyl group is always anti and the transition states shown in Scheme 2 pertain. Thus, larger aryl groups will show a stronger preference for adopting an equatorial orientation and be more likely to show high (*S*)-selectivity. With trifluoroacetophenone, the two groups (Ph and CF_3) are relatively similar in size, and thus the selectivity may be more sensitive to changes in ligand structure. However, the changes in enantioselectivities observed, particularly reversals, with different N-alkyl groups on the ligand are difficult to accommodate with this model. Thus, neither explanation is completely satisfactory.

Other aryl trifluoromethyl ketones were also reduced with the *i*-Pr COMA derived from **1f** (Table 3). In general, selectivities were excellent, particularly with larger aryl groups. Product **3e**, derived from aryl = 9-anthryl, is especially interesting since it is a useful chiral auxiliary and it is known that enrichment to high enantiomeric purity is easily achieved by recrystallization.[12] The selectivity observed with COMA *i*-Pr_2Mg/**1f** (96% ee) compares favorably with results reported for other established chiral reducing agents: BINAL-H, 92−98% ee;[12] DIP−Cl, 82% ee;[13] CBS-catecholborane, 94% ee.[14]

When an alkynyl trifluoromethyl ketone was reduced with *i*-Pr_2Mg/**1f**, only moderate selectivity was observed and the major isomer was the (*R*)-enantiomer (Table 3, entry 6), reflecting the relatively small size of an alkynyl group

(9) (a) Bradshaw, C. W.; Hummel, W.; Wong, C.-H.; *J. Org. Chem.* **1992**, *57*, 1532−1536. (b) Kanth, J. V. B.; Brown, H. C. *Tetrahedron* **2002**, *58*, 1069−1074.
(10) Kuroki, Y.; Sakamaki, Y.; Iseki, K. *Org. Lett.* **2001**, *3*, 457−459.
(11) (a) Shimoni, L.; Glusker, J. P. *Struct. Chem.* **1994**, *5*, 383−397. (b) Parsch, J.; Engels, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 5664−5672.
(12) (a) Chong, J. M.; Mar, E. K. *J. Org. Chem.* **1991**, *56*, 893−896.
(13) Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725−1738.
(14) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.

Table 3. Reduction of Various Ketones with COMA Reagents



3

entry	Ar	product	yield[a]	er[b] R:S
1[c,d]	Ph	**3a**	84	13:87
2	1-naphthyl	**3b**	92	7:93
3	2-Me-1-Naph	**3c**	95	7:93
4	mesityl	**3d**	89	3:97
5	9-anthryl	**3e**	**95**	**2:98**
6[c]	Bu-≡-	**3f**	88	61:39

[a] Percent isolated yields of chromatographed alcohol. [b] Determined by HPLC analysis on a Chiralcel OD column. [c] Lower isolated yield reflects the slightly volatile product. [d] Ligand **1e** used under standard conditions.

compared to a CF_3 group. Overall, results can be explained by relative sizes aryl > CF_3 > alkynyl, consistent with A values for these groups.[15]

While stoichiometric amounts of COMA reagents are used in these reductions, it is important to note that the hydride is transferred from an achiral source and that the chiral ligand is easily recovered by acid−base extraction. Reactions proceed under very mild conditions, with high yields, and with selectivities up to 98:2 er. These attributes suggest that COMAs are very useful reducing agents in select cases. Work to improve the range of substrates and increase selectivities is in progress.

A typical experimental procedure is as follows. A solution of *i*-Pr_2Mg[16](0.50 mmol) was added to a precooled (−78 °C) solution of diamine (0.51 mmol) in ether (12 mL) under argon. The resultant solution was then stirred at ambient temperature for 30 min. THF (1.5 mL) was added, and the *i*-Pr−COMA solution was cooled to −78 °C. A solution of trifluoromethyl ketone (ca. 0.25−0.3 mmol) in ether (1 mL) was added, and the reaction was stirred at −78 °C and allowed to warm to rt slowly (5−6 h). The reaction was quenched with saturated aqueous NH_4Cl, and the layers were separated. Standard extractive workup followed by silica gel column chromatography (10→20% Et_2O in hexanes) gave the desired alcohol. The enantiomeric ratio of the product was determined by chiral-phase HPLC.

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Supporting Information Available: Experimental details for the preparation of ligands **1a**−**h** and reductions and details for determinations of enantiomeric ratios and absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026901P

(15) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−697.

(16) See Supporting Information for the preparation of *i*-Pr_2Mg.