ORGANIC LETTERS

2002
Vol. 4, No. 21
3553−3556

Enantioselective Alkylation of Aldehydes with Chiral Organomagnesium Amides (COMAs)

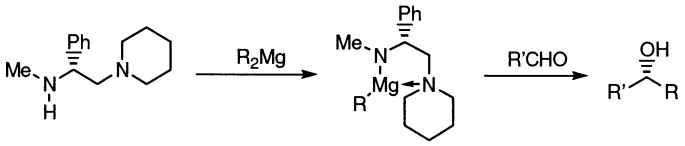
Kelvin H. Yong, Nicholas J. Taylor, and J. Michael Chong*

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

Received March 4, 2002 *(Revised Manuscript Received August 29, 2002)*

ABSTRACT



Dialkylmagnesiums react with chiral secondary amines to form chiral organomagnesium amides (COMAs). These reagents alkylate aldehydes to form secondary alcohols with enantioselectivities up to 91:9 er.

The enantioselective addition of organometallic reagents to carbonyl compounds to prepare alcohols has been the subject of intense scrutiny over the past few decades. Significant advances have been made, particularly with organozinc reagents,[1] to enable such reactions to be carried out with high degrees of stereoselectivity. However, although considerable attention has been paid to modifying more traditional organometallics such as organolithiums and magnesiums with chiral ligands, these metals have enjoyed only limited success.[2] This limited success is due, at least in part, to the intrinsic high reactivity of these organometallics to carbonyl compounds coupled with decreased reactivity upon complexation with chiral ligands. This combination has meant that modifications with chiral complexing agents have typically given fairly low selectivities except where very low temperatures or large excesses of ligand are employed. Despite these disadvantages, the ready availability of organomagnesium (Grignard) reagents makes them extremely attractive targets for enantioselective modification.[3] We now report that by directly linking a chiral ligand to Mg in the form of organomagnesium amides, good enantioselectivities in the alkylation of aldehydes may be achieved.[4]

Achiral organomagnesium amides ($RMgNR'_2$) have been known for over 20 years,[5] but there have been no reports of chiral versions of these reagents.[6−8] This is somewhat surprising given the tremendous variety of chiral amines that have been successfully used in other asymmetric transformations. On the other hand, perhaps the lack of interest in these reagents for alkylations is to be expected given their known propensity to enolize[5] and reduce (via β-hydride transfer)

(1) Review: Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

(2) Reviews: (a) Solladié, G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 157−199. (b) Huryn, D. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. I, part I, pp 49−75.

(3) Recent examples: (a) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128. (b) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751−9758. (c) Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969−3975.

(4) Disclosed, in part, in: Chong, J. M.; Yong, K. H. *Asymmetric Alkylation of Aldehydes with Chiral Organomagnesium Amides*; PacifiChem 2000, Honolulu, HI, 2000.

(5) Ashby, E. C.; Willard, G. F. *J. Org. Chem.* **1978**, *43*, 4094−4098.

(6) It was suggested that the use of alkyl(amido)magnesium compounds as "asymmetric induction reagents" would be studied, but results have not been reported: Henderson, K. W.; Allan, J. F.; Kennedy, A. R. *J. Chem. Soc., Chem. Commun.* **1997**, 1149−1150.

(7) Very recently, the enantioselective 1,4-addition of organomagnesium amides derived from bisoxazolines to enamidomalonates was described: Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708−9709.

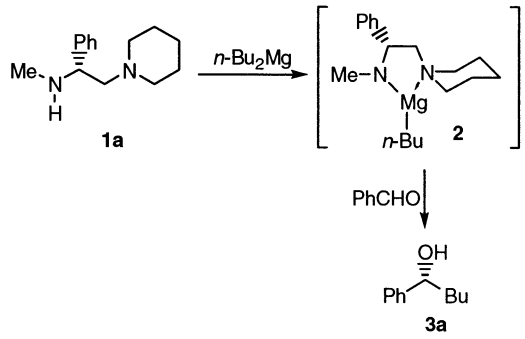
(8) Related chiral magnesium bisamides have been reported to be effective for enantioselective deprotonations: (a) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *J. Chem. Soc., Chem. Commun.* **2000**, 479−480. (b) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Tetrahedron* **2002**, *58*, 4573−4587.

10.1021/ol0258132 CCC: $22.00
Published on Web 09/19/2002

ketones.[6] Notwithstanding these possible limitations, we reasoned that direct linkage of an amine ligand as a metal amide, as in organomagnesium amides, would be more successful than the use of external coordinating agents. We therefore prepared some chiral organomagnesium amides and investigated their reactivity with carbonyl compounds.

Ashby has shown that admixture of Me_2Mg with secondary amines R_2NH in Et_2O at room temperature results in a rapid acid−base reaction to provide $MeMgNR_2$.[5] Therefore we allowed *n*-Bu_2Mg to react with amine **1a**, a compound that has been shown to be an effective chiral ligand in organocopper chemistry,[9] under the same conditions. The reagent so formed, represented as **2** on the basis of stoichiometry, reacted smoothly with PhCHO (Et_2O, −78 °C) to give a single product, the desired alcohol **3**. There was no evidence of reduction or other competing side reactions. The selectivity observed (80:20 er) was encouraging enough to examine this reaction further. Addition of THF or other Lewis bases (e.g., THP, pyridine, Et_3N, PPh_3) increased the selectivity slightly. Best selectivities were observed with THF at −78 °C (89:11 er, 76% yield). Lowering the reaction temperature to −90 °C increased the selectivity somewhat but at the expense of yield (91:9 er, 70% yield). Reactions in neat THF (−78 °C) gave comparable selectivities (87:13 er) but in much lower yield.

Scheme 1

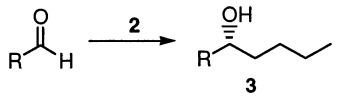


Thus chiral organomagnesium amide (COMA) **2** was treated with other aldehydes (Table 1) in Et_2O−THF. In general, reasonable levels of enantioselectivity were obtained, with highest selectivities observed for various benzaldehydes. It is noteworthy that even aliphatic aldehydes (Table 1, entries 6 and 7) gave good induction, albeit with only modest yields. However, chemical yields based on recovered aldehyde were quite high. Quenching experiments with MeOD suggest that competing enolization may be a problem with aliphatic aldehydes.

To probe the effects of structural variations of the ligand on the stereoselectivity of alkylation, other diamines were prepared and evaluated for the butylation of benzaldehyde (Table 2). In each case, alcohol **3a** was isolated in good yield

(9) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heinis, D. *Tetrahedron* **1993**, *49*, 965−986.

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



entry	R	product	yield[a]	er[b]
1	Ph	**3a**	76	89:11
2[c]	Ph	**3a**	70	91:9
3	4-$CH_3C_6H_4$	**3b**	57	88:12
4	4-ClC_6H_4	**3c**	50	83:17
5	1-naphthyl	**3d**	71	77:23
6	$MOMO(CH_2)_8$	**3e**	34[d]	82:18
7	$BnO(CH_2)_7$	**3f**	41[e]	84:16

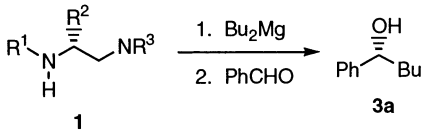
[a] Percent isolated yields of chromatographed **3**. [b] Determined by HPLC analysis on a Chiralcel OD column. [c] Reaction carried out at −90 °C. [d] The yield based on recovered starting material was 89%. [e] The yield based on recovered starting material was 88%.

(66−80%) and its enantiomeric purity was determined. Changing the ring size of the tertiary amine (entries 1−3) showed that a six-membered ring (diamine **1a**) gave highest selectivities and an acyclic analogue (entry 4) decreased the selectivity.

Variation of the size of R^1 (entries 1, 5−7) showed that a methyl group was best. Finally, changes in R^2 (by using valine, phenylalanine, and *tert*-leucine in place of phenylglycine in the synthesis of diamine **1**, entries 8−10) suggested that a phenyl group (as in **1a**) performs better than alkyl groups. Somewhat ironically, after probing these simple structural variations, the first ligand examined, namely, **1a**, has thus far given the highest selectivities.

The absolute configuration of **3a** was determined by comparison of observed rotations with literature values.[10] In general, for ligands **1a**−**j**, ligands with *R* configuration gave

Table 2. Effect of Ligand Structure on Stereoselectivity



	ligand[a]				er of **3**[b]
entry	R^1	R^2	R^3	no.	*R*:*S*
1	Me	Ph	$(CH_2)_5$	**1a**	89:11
2	Me	Ph	$(CH_2)_4$	**1b**	73:27
3	Me	Ph	$(CH_2)_6$	**1c**	74:26
4	Me	Ph	Et_2	**1d**	67:33
5	Et	Ph	$(CH_2)_5$	**1e**	43:57
6	H	Ph	$(CH_2)_5$	**1f**	39:61
7	*t*-Bu	Ph	$(CH_2)_5$	**1g**	46:54
8	Me	*i*-Pr	$(CH_2)_5$	**1h**	36:64
9	Me	$PhCH_2$	$(CH_2)_5$	**1i**	28:72
10	Me	*t*-Bu	$(CH_2)_5$	**1j**	25:75

[a] Ligands **1a**−**d** had *R* configuration; **1e**−**j** had *S* configuration. [b] Determined by HPLC analysis with a Chiralcel OD column.

(*R*)-**3a** as the major isomer while (*S*)-ligands produced (*S*)-**3a** preferentially. In addition, for alcohols **3b**−**e** prepared using ligand **1a** (which has *R* configuration, Table 1), the absolute configuration of the major enantiomer formed was always *R*.[11] Thus the absolute configuration of the major product may be reliably predicted.

In an effort to better understand this reaction, crystals of COMA **2** were grown and analyzed by X-ray crystallography (Figure 1). Structures of a few simple organomagnesium

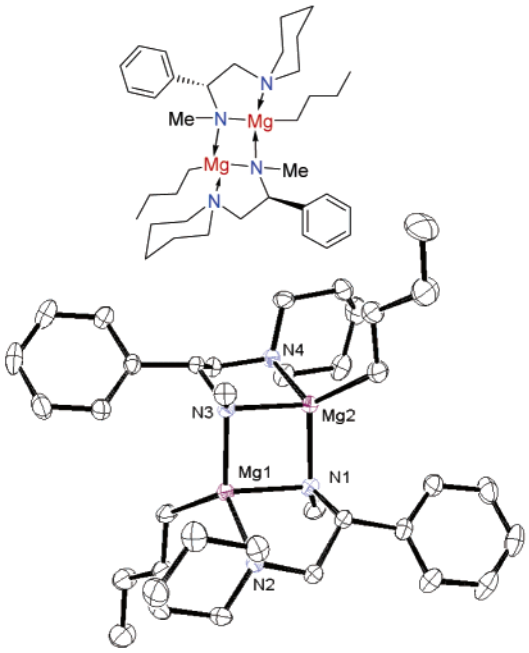
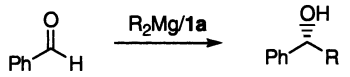


Figure 1. ORTEP drawing of COMA reagent **2**.

amides (e.g., $Me_2Mg/MeHNCH_2CH_2NMe_2$) are known[12] and are also dimeric, but this is the first X-ray structure of a chiral organomagnesium amide. The structure is very similar to previously reported structures of dialkylzinc−amino alcohol complexes, materials that are catalyst precursors for extremely effective enantioselective alkylating agents.[13] While mechanistic arguments cannot be made on the basis of a single X-ray structure, the absolute configurations of major products in these COMA additions can be rationalized by invoking arguments of least hindered approach of aldehydes to a dimeric reagent.

Other alkyl groups could also be transferred using COMA reagents. Thus reaction of a series of dialkylmagnesiums R_2-

Table 3. Alkylation of PhCHO with COMA Reagents



3a: R = *n*-Bu
4a-4e

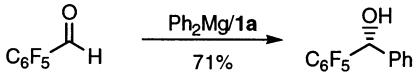
entry	R	product	yield[a]	er[b]
1	Me	**4a**	34[c]	86:14
2	Et	**4b**	70	84:16
3	*n*-Bu	**3a**	76	89:11
4	n-C_7H_{15}	**4c**	77	89:11
5	n-$C_{10}H_{21}$	**4d**	76	88:12
6	*i*-Pr	**4e**	44[d]	72:28

[a] Percent isolated yields of chromatographed alcohol. [b] Determined by HPLC analysis on a Chiralcel OD column. [c] Reaction carried out in THF. Low yield due to incomplete reaction and volatility of product. [d] Benzyl alcohol also formed.

Mg with **1a** produced COMA reagents, which could alkylate PhCHO with good levels enantioselectivity (Table 3). Straight chain alkyl groups of varying lengths all gave similar selectivities and yields. However, a branched alkyl group (*i*-Pr) gave a low yield of the desired secondary alcohol along with considerable amounts of benzyl alcohol.

This chemistry is not limited to alkyl groups. Ph_2Mg could be used to arylate a substituted benzaldehyde to form a chiral diaryl carbinol with reasonable selectivity (Scheme 2). Such

Scheme 2



5
er = 85:15

asymmetric arylations have, until recently, been very difficult to achieve with good selectivities.[14]

Because the group to be transferred may be more valuable than *n*-Bu, we investigated the possibility of preparing COMAs without sacrificing one of the alkyl groups of the dialkylmagnesium. When amine **1a** was allowed to react with 0.5 equiv of Me_2Mg, a clear solution, presumably the diamidomagnesium was formed. Addition of 0.5 equiv of Bu_2Mg and THF to this solution gave a solution that reacted with PhCHO in a manner identical to that with the reagent prepared from the amine and 1 equiv of Bu_2Mg (i.e., 73% yield of **3a**, 89:11 er). This method for forming COMAs, although less convenient, offers the distinct advantage of sacrificing the readily available Me_2Mg as a base rather than losing a more important alkyl group.

In addition, the amine ligand is easily recovered at the end of the reaction by simple acid−base extraction followed by distillation. The recovered ligand has been reused in COMA reactions without affecting the yield or the er.

(10) (*R*)-(+)-**3a** shows $[\alpha]^{25}_D = 45.9$ (*c* 6, C_6H_6): Mukaiyama T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455−1460.

(11) See Supporting Information for details.

(12) (a) Henderson, K. W.; Mulvey, R. E.; Clegg, W.; O'Neil, P. A. *J. Organomet. Chem.* **1992**, *439*, 237−250. (b) Magnuson, V. R.; Stucky, G. D. *Inorg. Chem.* **1969**, *8*, 1427−1433. (c) Olmstead, M. M.; Grigsby, W. J.; Chacon, D. R.; Hascall, T.; Power, P. P. *Inorg. Chim Acta* **1996**, *251*, 273−284.

(13) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842.

(14) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222−4223.

Overall, we have shown that chiral organomagnesium amides (COMAs) can be easily prepared from dialkylmagnesiums and chiral amines. The first alkylations of aldehydes using these reagents have been achieved, and good levels of stereoinduction are observed. The ready accessibility of dialkylmagnesiums (from Grignard reagents) and the facile recovery of the amine ligand suggest that this approach to asymmetrically alkylate aldehydes offers considerable promise. Studies to develop more selective reagents are underway.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support and the Ontario Ministry of Training, Colleges, and Universities for a postgraduate scholarship (to K.H.Y.)

Supporting Information Available: Experimental details for the preparation of and spectral data for compounds **3**−**5**, procedures for preparation and titration of R_2Mg solutions, details for determinations of enantiomer ratios and absolute configurations, and X-ray crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0258132