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Lewis Base Activation of Grignard Reagents with *N*-Heterocyclic Carbenes. Cu-Free Catalytic Enantioselective Additions to γ-Chloro-α,β-Unsaturated Esters

Yunmi Lee and Amir H. Hoveyda*

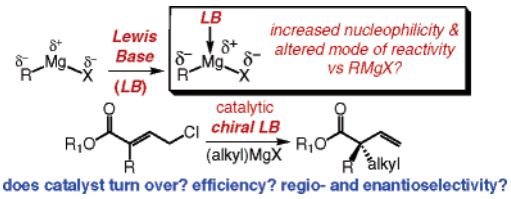
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received October 18, 2006; E-mail: amir.hoveyda@bc.edu

Catalytic asymmetric additions of alkylmetals to allylic halides[1] or phosphates[2] and α,β-unsaturated carbonyls[3] are effective methods of enantioselective C−C bond formation. Such processes are carried out in the presence of a metal salt, which is nearly always Cu-based.[4] Attributes of the in-situ-formed Cu reagent govern reactivity and selectivity. Development of Cu-free protocols[5] is a critical step toward achieving reactivity and selectivity profiles that are inaccessible by organocopper systems.

We have introduced amino acid-[2] and *N*-heterocyclic carbene (NHC)-based ligands for asymmetric allylic alkylations (AAA);[6] these are all Cu-catalyzed reactions with organozinc reagents. We recently set out to develop transformations of the more readily available allylic chlorides (vs phosphates[2]) with alkylmagnesium halides that generate the difficult-to-access all-carbon quaternary stereogenic centers.[7] Grignard reagents, although less functional group tolerant compared to dialkylzinc reagents, are more atom economical and user friendly as well as less expensive and easier to prepare.[8] Our goal is to explore modes of reactivity that do *not* involve Cu catalysis. We have thus probed the concept of altering and enhancing the reactivity of Grignard reagents with a substoichiometric amount of a chiral Lewis base, whereby the resulting complex induces high enantioselectivity. Herein, we report the results of studies leading to Cu-free catalytic AAA reactions of α-alkyl-γ-chloro-α,β-unsaturated esters.[9] Products bear an all-carbon quaternary stereogenic center flanked by modifiable alkene and ester groups.[10] To the best of our knowledge, this is the first catalytic AAA method that involves Grignard reagents and affords all-carbon quaternary stereogenic centers (Cu-catalyzed protocols included) (Scheme 1).[7]

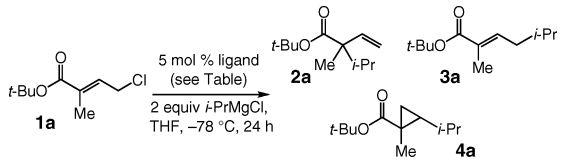
Scheme 1. Activation of Grignard Reagents by a Lewis Base

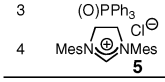


Our approach is based on the principle that association of a Lewis base to an alkylmagnesium halide may cause distribution of electron density, affording a Lewis base·RMgX complex that exhibits enhanced nucleophilicity[11] and perhaps a different mode of reactivity (vs the original alkylmetal). The possibility of elevated nucleophilicity is supported by an increase in C−Mg bond lengths of the derived Et_2O complexes (vs alkylmetal),[12] which is also observed in the X-ray structure of an NHC·$MgEt_2$.[13]

The effect of a representative number of simple Lewis basic agents on the reaction of *i*-PrMgCl with allylic chloride **1a** is summarized in Table 1. Without a Lewis base (entry 1), only 28% **4a** is generated (<2% allylic alkylation). The presence of 5 mol % PPh_3 (entry 2) has no effect, and (O)PPh_3 (entry 3) gives <10% allylic alkylation (>98% **3a**). However, with 5 mol % imidazolinium salt **5**, conversion is doubled, and, along with ∼30% **4a**, allylic alkylation products **2a** and **3a** are formed (30% of product mixture). The latter change in reactivity, albeit modest, indicated that an NHC can enhance (30−60% conversion) and alter reactivity (S_N2' addition product only obtained with **5**).

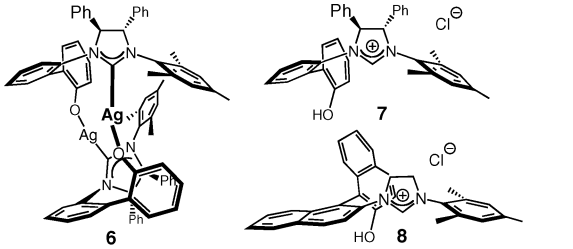
Table 1. Activation of *i*-PrMgCl by Catalytic Amounts of Simple Lewis Bases[a]



entry	Lewis Base	conv (%)[b]	2+3 (%)[c]	2:3[c]	4 (%)[c]
1	none	28	–	–	28
2	PPh_3	25	–	–	25
3	(O)PPh_3	30	7	<2:>98	23
4	 **5**	60	30	1:1	30

[a] Reactions run under N_2 atm. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra and chiral GLC. [c] Determined by chiral GLC (see the Supporting Information for details).

Table 2. Initial Studies with Chiral Heterocyclic Complexes[a]



entry	R	chiral ligand	conv (%)[b]	% **2**[b]	**2**:**3**[b]	ee **2** (%)[c]	% **4**[b]	% **9**[b]
1	*t*-Bu	**6**	87	7	1:2.9	89	18	42
2	*t*-Bu	**7**	>98	56	3.5:1	93	28	<2
3	*t*-Bu	**8**	59	5	1:4.9	−12	29	<2
4	Me	**7**	***>98***	***82***	***9:1***	***97***	***9***	***<2***

[a−c] See Table 1.

Next, we examined the effect of chiral Lewis base systems. As shown in entry 1 of Table 2, with 2.5 mol % Ag(I) complex **6**,[6b] reaction of **1a** with *i*-PrMgCl proceeds to 87% conversion (vs 30−60% in Table 1). Cyclopropane **4a** and unsaturated ester **9a**[14] are the major products; nonetheless, **2** is generated in 89% ee. With

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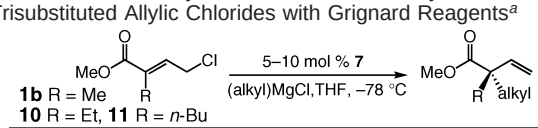
Table 3. NHC-Catalyzed Enantioselective Alkylations of Trisubstituted Allylic Chlorides with Grignard Reagents[a]



1b R = Me
10 R = Et, **11** R = *n*-Bu

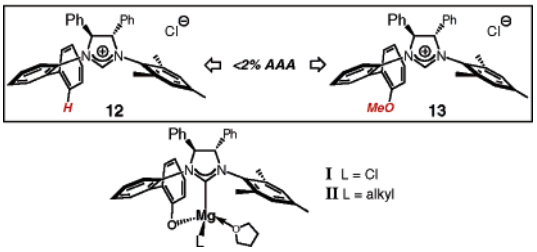
entry	R	(alkyl)MgCl	mol % **7**	conv (%)[b]; time (h)	$S_N2':S_N2$[b]	cycloprop. (%)[b]	S_N2' yield (%)[c]	ee (%)[d]
1	Me	*i*-PrMgCl	5	>98; 24	9.0:1	9	80	97
2	Me	*c*-pentMgCl	5	95; 48	4.3:1	12	57	75
3	Me	*c*-hexMgCl	5	95; 24	11.5:1	27	63	94
4	Me	*n*-BuMgCl	8	93; 48	6.1:1	28	34	63
5	Et	*i*-PrMgCl	5	>98; 24	10.1:1	7	73	97
6	*n*-Bu	*i*-PrMgCl	5	>98; 24	10.1:1	7	75	98
7	Et	*c*-pentMgCl	10	>98; 48	7.3:1	8	66	90
8	*n*-Bu	*c*-pentMgCl	10	>98; 60	3.5:1	13	59	85
9	Et	*c*-hexMgCl	10	>98; 48	13.3:1	19	60	96
10	*n*-Bu	*c*-hexMgCl	10	84; 48	11.5:1	13	57	96
11	Et	*n*-BuMgCl	10	>98; 60	7.3:1	26	35	79

[a] Reactions run under N_2 atm; 2 equiv RMgCl in entries 1−5, 3 equiv for entries 6−11. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra and chiral GLC. [c] Isolated yields of pure S_N2' products. [d] Determined by chiral GLC (see Supporting Information for details).

5 mol % imidazolinium chloride **7**[6b] the reaction proceeds to >98% conversion, generating **2** as 56% of the mixture (vs 7% with **6**), as the major regioisomer (3.5:1 vs 1:2.9 with **6**), and in 93% ee (entry 2). In the presence of **7** (NHC formed in situ through deprotonation by *i*-PrMgCl), **4** is generated (28%) but **9a** is not detected. Chiral salt **8**[6a] is less efficient (59% conversion, entry 3) and does not promote a highly enantioselective reaction. With methyl ester **1b** (entry 4, Table 2) as the substrate (vs *t*-Bu ester **1a**), catalytic AAA proceeds to >98% conversion to afford **2b** in 97% ee, 9:1 regioselectivity (**2b**/**3b**) along with only 9% cyclopropane **4b**.[14]

As the data summarized in Table 3 indicate, Cu-free catalytic AAA of alkyl-based Grignard reagents and a range of allylic chlorides bearing trisubstituted olefins proceed to >98% conversion with 3.5:1−13.3:1 regioselectivity, in 63−98% ee and in up to 80% isolated yield of S_N2' products. Reactions with secondary alkylmagnesiums are more enantioselective (cf. entries 4 and 11). In some instances, more of the undesired cyclopropane is generated (e.g., entries 3, 4, 11). This may be due to the relatively slow rate of asymmetric alkylation (vs uncatalyzed addition). Consistent with this hypothesis, slow addition of **1b** (syringe pump; 17 h) delivers the AAA product in 91% ee along with only 15% of the derived cyclopropane (vs 27% in entry 3). These findings suggest that a more sterically accessible chiral NHC could give rise to more efficient AAA reactions. In addition to being more user friendly and atom economical, the present method complements the related protocol involving dialkylzinc reagents,[9b] where secondary alkylmagnesium halides participate in catalytic AAA with low enantioselectivity (<50% ee). Reactions can be performed with commercial Grignard reagents; use of alkylmagnesium bromides leads to less efficient and less selective processes (see the Supporting Information for more details).[15]

The inactivity of chiral salts **12** and **13** (<2% AAA) underline the significance of the phenolic OH in **7**. Loss of activity, presumably owing to the bulk of the chiral ligand, is therefore more than regained by the presence of the hydroxyl unit (**12** and **13** vs **5**, Table 1). Catalytic AAA involving **7** is likely initiated by the formation of an O−Mg bond, facilitating the generation of a NHC·Mg complex such as **I** (or its diastereomer; metal center is stereogenic[6b] in **I** and **II**), which can be converted to alkylmagnesium complex **II**.[16] The inefficiency of Ag salt **6** may be the result of energetically unfavorable Ag−Mg exchange. Specific models regarding the identity of the Mg complex and the origin of enantioselectivity are difficult to propose at the present time. Initial studies do indicate that catalytic AAA does not involve addition of the carbene to allylic chlorides (to give enantiomerically enriched electrophiles).[17]



Design of more efficient chiral NHC and application of the principles of Lewis base catalysis to reactions with Grignard reagents that are out of the realm of Cu-based catalysis are in progress.[18]

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Supporting Information Available: Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439.
(2) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779−1785.
(3) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236.
(4) For Zr-catalyzed AAA with alkylmagnesium halides, see: (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997−6998. For Ni-catalyzed AAA with Grignard reagents, see: (b) Indolese, A. F.; Consiglio, G. *Organometallics* **1994**, *13*, 2230−2234. (c) Nomura, N.; Rajanbabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713−1716. (d) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650.
(5) For a rare non-Cu-catalyzed asymmetric conjugate addition of Et_2Zn to acyclic enones (chiral *o*-phenoxyketimine ligands), see: Bräse, S.; Höfener, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7879−7881.
(6) (a) Larsen, A. O.; Leu, W.; Nieto-Oberhuber, C.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130−11131. (b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877−6882. See also: (c) Lee, K. S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7184.
(7) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds.; Wiley−VCH: Weinheim, Germany, 2006.
(8) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995−3022.
(9) For related Cu-catalyzed AAA method with amino acid-based chiral ligands and involving dialkylzinc reagents, see: (a) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691. (b) Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 1255−1258.
(10) Products obtained can be used to access enantiomerically enriched tertiary alcohols and amines. See: Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627−4831.
(11) Lewis base activation of Lewis acids in synthesis has been pioneered by Denmark. See: Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789. For enantioselective alkylmetal additions (noncatalytic) that might involve Lewis base activation, see: Denmark, S. E.; Nicaise, O. J. C. *Chem. Commun.* **1996**, 999−1004.
(12) Ehlers, A. W.; van Klink, G. P. M.; van Eis, M. J.; Bickelhaupt, F.; Nederkoorn, P. H. J.; Lammertsma, K. *J. Mol. Model.* **2000**, *6*, 186−194.
(13) Arduengo, A. J., III; Dias, R.; Davidson, F.; Harlow, R. L. *J. Organomet. Chem.* **1993**, *462*, 13−18.
(14) Byproducts **4** and **9** are formed in <2% ee (see the Supporting Information for details).
(15) Cu-catalyzed variants (**6** and $CuCl_2·2H_2O$) are more efficient (0.5 mol %, >98% in 1 h) but less selective. For example, reaction of **1b** with *i*-PrMgCl delivers **2b** with 5.5:1 regioselectivity (vs 9:1 with **7**) and in 89% ee (vs 97% with **7**). Details will be reported in a separate account.
(16) Catalytic AAA of **1a** with $(i\text{-Pr})_2Mg$ affords **2a** in 94% ee and 4:1 regioselectivity (95% conversion, 24% **4**; Table 1 conditions).
(17) For example, reaction of allylic chloride **1a** with 1.0 equiv **7** and 2.0 equiv *i*-PrMgCl leads to <2% conversion.
(18) Similar arguments can account for high activity of NHC·Cu complexes (e.g., ref 6). It is direct complexation/activation of a *non*transition, and especially an early, metal by an NHC that has not been previously utilized.

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