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[8] Crystallographic structure determinations were performed on a Bruker SMART Apex CCD diffractometer using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved with Patterson methods and extended by direct methods applied to difference structure factors. Crystallographic data for **2**: $C_{69}H_{109}Al_4B_4NO_8 \cdot (C_6H_6)$, $M_r = 1309.91$, monoclinic, space group $P2_1/n$, $a = 13.8868(6)$, $b = 25.188(1)$, $c = 23.346(1)$ Å, $\beta = 106.805(1)^\circ$, $V = 7817.2(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.113$ g cm^{-3}, $\mu = 1.1$ cm^{-1}, $T = 110$ K. A final refinement on F^2 converged at $wR(F^2) = 0.1789$ for 13782 reflections and $R(F) = 0.0733$ for 7505 reflections with $F_o \geq 4\sigma(F_o)$ and 857 parameters. Crystallographic data for **3**: $[C_{25}H_{41}SZr][C_{65}H_{107}Al_4B_4O_8] \cdot (C_7H_8)_{1.5}$, $M_r = 1770.83$, monoclinic, space group $P2_1/c$, $a = 20.6291(8)$, $b = 20.3125(8)$, $c = 26.301(1)$ Å, $\beta = 110.155(1)^\circ$, $V = 10346.0(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.137$ g cm^{-3}, $\mu = 2.11$ cm^{-1}, $T = 110$ K. A final refinement on F^2 converged at $wR(F^2) = 0.2289$ for 18278 reflections and $R(F) = 0.0808$ for 11143 reflections with $F_o \geq 4\sigma(F_o)$ and 1145 parameters and 16 restraints. One of the toluene molecules in the lattice shows extensive orientational disorder, resulting in unrealistic displacement parameters when allowed to vary anisotropically. The other toluene molecule is disordered over an inversion center, and was described as a single molecule with 0.5 occupancy with geometrical restraints. CCDC-177577 (**2**) and CCDC-177576 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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BuMgN*i*Pr$_2$: A New Base for Stoichiometric, Position-Selective Deprotonation of Cyclopropane Carboxamides and Other Weak CH Acids**

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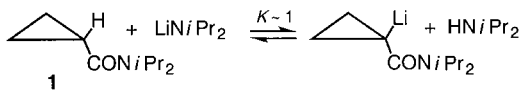
Organolithium (RLi) and -magnesium (R_2Mg) compounds are kinetically poor bases for proton removal from weak carbon acids. If an amine like *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) is added, the barrier is sometimes lowered, but the nucleophility of the organometallic compound remains a problem. This can be ameliorated by using metal amides like lithium diisopropylamide (LDA) and bis(diisopropylamido)magnesium (DA_2Mg). These poor nucleophiles are still kinetically effective bases for deprotonation of weakly acidic CH groups ($pK_a \approx 30 - 35$).[1] However, as the pK_a of the liberated amine and that of the CH acid (e.g. **1**) are similar, such deprotonations are nowhere near stoichiometric (e.g. Scheme 1[2]). This is unsatisfactory.



1

Scheme 1. The equilibrium reaction of LDA with amide **1**.

We now introduce alkylmagnesium amides, here specifically BuMgN*i*Pr$_2$, denoted hereafter as BuMgDA, as an effective solution to this problem.[3] We prepare BuMgDA simply by adding 1.0 equivalent of anhydrous diisopropylamine (DAH) to commercial[4] dibutylmagnesium in heptane (ca. 1.0 M) at room temperature and then stirring the solution for five minutes at 50 °C. BuMgDA[3b] in heptane is quite reactive. Replacing heptane, all or in part, with THF (after the base has been formed) increases this usefully. Unlike Bu_2Mg and many organolithium bases, BuMgDA is stable even in refluxing THF for many hours. BuMgDA, like DA_2Mg, deprotonates/metalates amide-activated[5] cyclopropyl-CH (α, β, or beyond) and cubyl-CH (*ortho*),[6] but the BuMgDA deprotonations are driven to completion by irreversible formation of butane.

It is instructive to compare the metalation of the cyclopropylcarboxamide **2** using Bu_2Mg solutions in heptane treated first with 0, 0.5, or 1.0 equivalent of DAH. Bu_2Mg itself reacted only slowly;[7] mostly starting material was recovered. In the other two cases, when at least some BuMgDA[3b] was present, the overall deprotonation/metalation/carboxylation proceeded in high yield, but the final

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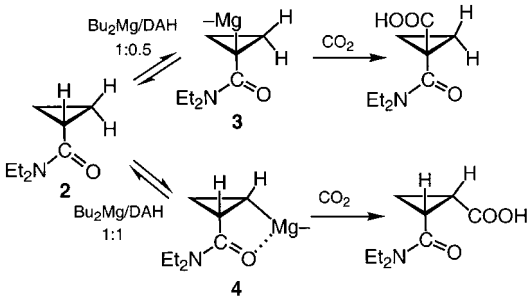
outcome (Scheme 2) depended importantly on the ratio of DAH to Bu_2Mg. When this was 0.5:1.0, α metalation predominated; when it was 1:1, β metalation was favored instead. Looked at simply: when there is an excess of Bu_2Mg it scavengers the DAH generated by the initial α deprotonation;



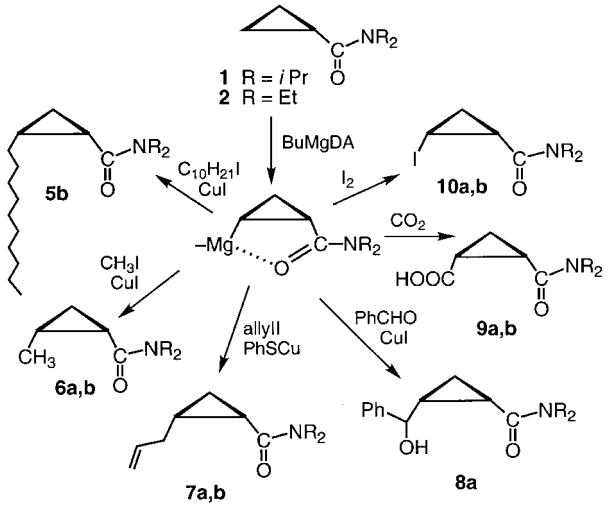
Scheme 2. Predominant position of magnesiation of **2** as a function of Bu_2Mg to DAH ratio. Standard conditions: heptane/THF (1:1); RT; two days; analysis after carboxylation at $-78 \rightarrow 0\,^{\circ}C$.

when there is no excess of Bu_2Mg, free DAH remains and equilibration can occur. Ultimately, equilibration leads mostly to the thermodynamically favored, amide-stabilized β-magnesium compound. Sooner or later, and irreversibly in both cases, butane is formed, all the DAH is consumed, and essentially stoichiometric metalation is achieved.

Whereas the α-lithiated analogues of cyclopropane carbonyl derivatives are excessively nucleophilic and often self-destruct before they can be trapped usefully,[8] the α-amido-Grignard species **3**[3b] provides a convenient and dependable route to α-substituted cyclopropane diethylcarboxamides. We made this amido-Grignard by treating **2** (ca. 0.5 M in 1:1 heptane/THF) with the mixture of bases (BuMgDA + Bu_2Mg)[3b] resulting from reaction of 0.5 equivalent of DAH with 1.05 equivalents[9] of Bu_2Mg. α-Metalation was optimum after 48 h at room temperature (longer times, higher temperature, or more THF led to some β metalation). The α-carboxy (85 % yield of isolated product), α-iodo (70 %), and α-methyl (76 %) compounds were obtained from **3** by reaction with CO_2, I_2, and CH_3I, respectively.

Treatment of the diethylamide **2** (ca. 0.5 M) with 1.05 equivalents[9] of BuMgDA in THF gave in due course mostly the β-metalated material **4**, but optimum conversion required reaction for 8 h at 60 °C. On the other hand, β metalation occurred almost immediately, even at room temperature, when the *N*,*N*-diisopropylcarboxamide **1** was used instead. Probably the larger bulk of the isopropyl group(s) favors an amide conformation with the carbonyl oxygen atom proximate to a β-site.

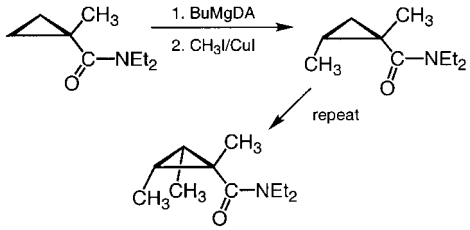
The reactions of the β-metalated compounds (ca. 0.5 M) shown in Scheme 3 were all carried out at room temperature or below, and required 1 to 24 h for completion. The addition of 20 mol % CuI or PhSCu was needed to obtain reasonable rates in the alkylations. When R was ethyl, less than 10 % of the product resulted from α substitution; when R was isopropyl, less than 5 %, often much less. No other base provides such high discrimination for β substitution on a cyclopropane carboxamide having an α proton.



Scheme 3. β Substitutions on cyclopropylamides by BuMgDA metalation. For **a**, R = ethyl; for **b**, R = isopropyl. Yields of isolated products: **5b**: 46 % (single run, 84 % based on unreacted **2**); **6a**: 76 %; **6b**: 66 %; **7a**: 76 %; **7b**: 89 %; **8a**: 43 % (single run); **9a**: 81 %; **9b**: 88 %; **10a**: 70 %; **10b**: 80 %.

These reactions produce stereospecifically the *cis*-to-the-amide isomers.[10] The more favored *trans* isomer can be obtained by purposeful epimerization with base; BuMgDA works well.[11]

Of course, β substitution can also be achieved if the α position is blocked; *cis*-β' substitution can be done as well (Scheme 4, 66 % overall yield).



Scheme 4. The β and β' methylations of the α-methyl derivative of **2** by magnesiation with BuMgDA.

The ability to introduce numerous substituents in controlled fashion onto a readily available cyclopropane provides a new paradigm for the synthesis of complex cyclopropanes, one requiring neither carbene addition nor intramolecular cyclization.

Milnacipran (**11**), a clinically useful antidepressant, is presently prepared from reaction of epichlorohydrin with benzyl cyanide anion followed by an intramolecular displacement to close the cyclopropane ring, then functional group manipulation.[12] We present here an entirely different strategy (Scheme 5) proceeding from cyclopropane carboxylic acid, available in bulk cheaply. α Magnesiation of its diethylcarboxamide **2** with BuMgDA/Bu_2Mg followed by phenylation with iodobenzene and 5 mol % CuI gave **12** in 53 % yield (82 % based on recovered **2**). Further magnesiation, now using stoichiometric BuMgDA, occurred at the β position. The resulting amido-Grignard reacted easily with

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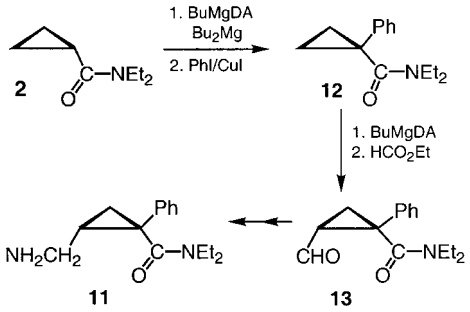
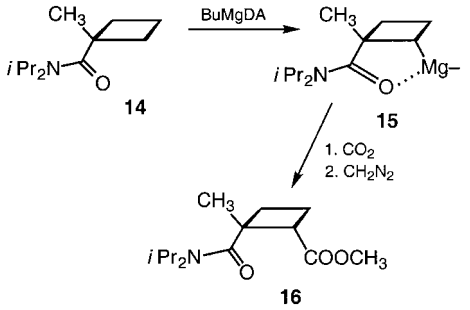


Scheme 5. A new approach to the synthesis of Milnacipran (**11**).

ethyl formate to give **13** (73% yield of isolated product), a known Milnacipran precursor.[12]

Aromatic and benzyl CH groups are more acidic than those of cyclopropanes and cubanes, so it is not surprising that BuMgDA stoichiometrically metalates an amide-activated CH group appropriately positioned thereupon. What if the CH group is less acidic? Cyclobutane CH is kinetically 2500 times more weakly acidic than cyclopropane CH.[13] Under conditions as harsh as most base/solvent combinations can withstand (e.g. LiTMP/THF or LiTMP + $Hg(TMP)_2$/THF at 0° C (TMP = 2,2,6,6-tetramethylpiperidine) or LDA/THF at reflux), there is no observed metalation of **14**. However, under the conditions of our preliminary trials, reaction of **14** with excess BuMgDA in THF at reflux for 5 h gave about 20% conversion[14] to the *cis*-β-metalated compound **15**, identified by formation of ester **16**[10] (17% yield of isolated product, Scheme 6). Although still to be optimized, this β deprotonation/metalation of a cyclobutane amide is extraordinary and unprecedented.



Scheme 6. Deprotonation/magnesiation of an amide-activated cyclobutane using BuMgDA.

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[2] Z. Hantosi, PhD Thesis, The University of Chicago, **1999**.
[3] a) As far as we can determine, amido-Grignards have not been examined elsewhere for their deprotonation/metalation abilities. b) We ignore, for the present, consideration of Schlenk equilibria and/or aggregation of magnesiated species.
[4] Aldrich Chemical sells a mixture of *n*-butyl and *s*-butyl compounds; this generates a mixture of *n*BuMgDA/*s*BuMgDA; this was what we used. The pure compounds behave similarly as bases.
[5] See: V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
[6] The magnesiated products have useful (but reduced) Grignard-like reactivity; cf. ref. [1].
[7] The addition of TMEDA does not improve the proton removal ability of Bu_2Mg.
[8] a) For example: H. W. Pinnick, Y.-H.Chang, S. C. Foster, M. Govindan, *J. Org. Chem.* **1980**, *45*, 4505–4507.
[] b) The α-lithio derivative of **2**, prepared by reaction of **2** with *n*BuLi at −78 °C, is stable only below 0 °C.
[9] A small excess of Bu_2Mg was used to remove adventitious water.
[10] Stereochemical assignments: aq. 30% H_2SO_4 amide hydrolysis (no isomerization; demonstrated by re-amidation) followed (e.g. for **9**) by NMR comparison to the known acid or (e.g. for **10**) by X-ray analysis; for **6** by X-ray analysis of the crystalline dicyclohexylamide analogue; for Scheme 4, ^1H and ^{13}C NMR; for **16**, X-ray single crystal analysis. CCDC-173837 (**10**), CCDC-173837 (**6**), CCDC-173571 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).
[11] Prolonged exposure of the products to the generating conditions also leads to isomerization.
[12] S. Shuto, S. Ono, H. Imoto, K. Yoshii, A. Matsuda, *J. Med. Chem.* **1998**, *41*, 3507–3514, and references therein.
[13] A. Streitwieser, Jr., R. A. Caldwell, W. R. Young, *J. Am. Chem. Soc.* **1969**, *91*, 529.
[14] By NMR: 20% **16**, 80% unreacted starting material.

New Methods for Proteomic Research: Preparation of Proteins with N-Terminal Cysteines for Labeling and Conjugation**

Thomas J. Tolbert and Chi-Huey Wong*

In memory of Sun Fong

Proteins with N-terminal cysteines are useful in a wide range of biotechnological applications ranging from protein semi-synthesis to site-specific N-terminal labeling. Peptides and proteins with N-terminal cysteines undergo native chemical ligation and expressed protein ligation reactions with thioesters to form native peptide bonds.[1, 2] These reactions have been used to extend the size of proteins that can be synthesized chemically and to incorporate synthetic peptides with modifications and labels into expressed proteins.[3–8] In addition, proteins with N-terminal cysteines also react chemoselectively with aldehydes to form thiazolidines, and this reaction has been utilized to label and immobilize peptides and proteins.[9–12] Here we present a novel method (Figure 1) to produce proteins with N-terminal cysteines by

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.