A New Approach to Substituted Cyclobutanes: Direct β-Deprotonation/ Magnesiation of Cyclobutane Carboxamides

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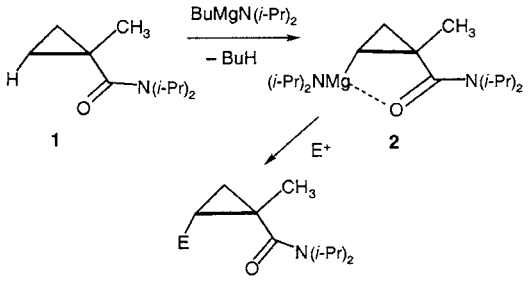
In memoriam: Professor Ray Lemieux, gentleman and scholar.

Abstract: BuMgN(*i*-Pr)$_2$ is shown to be kinetically and thermodynamically efficient for deprotonation/magnesiation *cis* and β to an activating carboxamido group on a cyclobutane ring. The resulting carboxamido-stabilized amido-Grignards are useful reagents. The method provides an entirely new approach to controlled substitution on cyclobutanes. BuMgN(*i*-Pr)$_2$ will also metalate pivaloyl amides.

Key words: metalation, diastereoselective, amido-Grignards, cyclobutanes, substituent effects

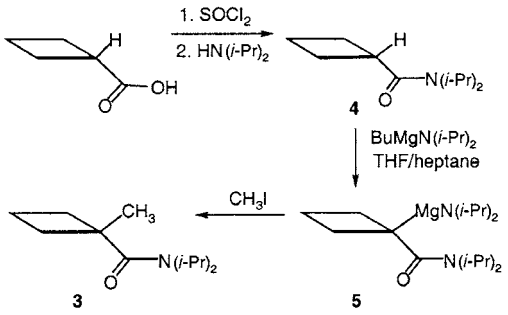
Alkyl magnesium amides, e.g. BuMgN(*i*-Pr)$_2$, deprotonate and magnesiate mildly acidic CH groups near, but not necessarily bearing, a carboxamido group.[1] Thus, phenyl, cyclopropyl **1**, and cubyl carboxamides are converted (e.g. Scheme 1) into synthetically useful carboxamido-stabilized vicinal[2] amido-Grignards **2**.



Scheme 1

How acidic must the hydrogen of the CH group be for a useful rate of deprotonation/magnesiation? Any quantitative answer would require a new scale incorporating the activating and stabilizing effects of the carboxamido group. Qualitatively, we expect (and find) a rough correlation of rate with relative kinetic acidities:[3] benzene, ca. 10^{+8}; cubane, $6 \times 10^{+4}$; cyclopropane, $7 \times 10^{+4}$. On the same scale, the kinetic acidities of cyclopentane and cyclohexane are much less: 5.7 and 1.0, respectively. Under standard conditions (vide infra), BuMgN(*i*-Pr)$_2$ fails to significantly magnesiate 5- or 6-membered rings β to a carboxamido group thereupon, even when the α-position is blocked. Cyclobutane CH (relative kinetic acidity = 28) is only about five times more acidic than cyclopentane and 2,500 times less acidic than cyclopropane. Nonetheless, as we show now, cyclobutyl carboxamides are effectively and usefully deprotonated/magnesiated by BuMgN(*i*-Pr)$_2$.

1-Methyl-1-(*N*,*N*-diisopropylcarboxamido)cyclobutane (**3**) was prepared by α-alkylation of the parent **4**, itself made in standard fashion via the acid chloride from commercially available cyclobutane carboxylic acid (Scheme 2). Although other bases can be used for α-deprotonation/metalation, we chose BuMgN(*i*-Pr)$_2$. It is simple to make,[1] reasonably stable even in refluxing THF, and very effective for stoichiometric deprotonations (butane being formed irreversibly). Reaction of the intermediate α-amido-Grignard **5** with methyl iodide gave **3**, isolated in 88–95% yield as a colorless solid, mp 55.0–55.5 °C.



Scheme 2

BuMgN(*i*-Pr)$_2$ in THF/heptanes will deprotonate/magnesiate the β-position of cyclopropyl amide **1** stoichiometrically at 20 °C. The corresponding cyclobutyl amide **3** is unreactive under these conditions, but treatment with excess BuMgN(*i*-Pr)$_2$ in THF/heptanes at reflux (73 °C) gave a good rate and produced what is taken to be the β-carboxamido stabilized amido-Grignard **6**.[4] Addition of the cooled reaction mixture to a solution of elemental iodine in THF (Scheme 3) gave a mixture of two iodides in an ^{1}H NMR ratio of ca. 10:1.[5] We isolated a 77% yield of the major iodide; its stereochemistry is as shown in **7**, established unambiguously by X-ray crystallography.[6a] The minor isomer is the epimeric iodide.

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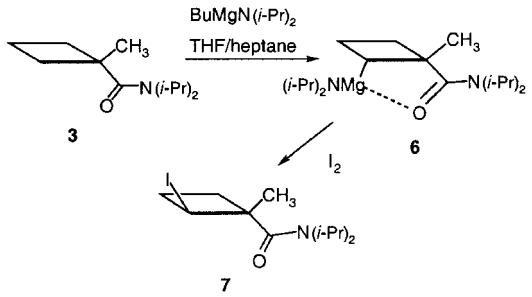
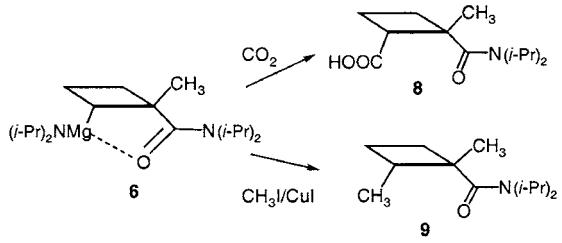


Scheme 3

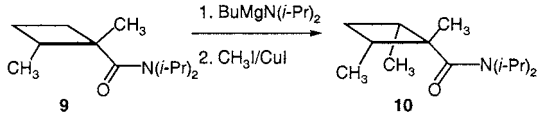
In the major isomer, the iodine has been introduced *trans* to the activating amide group, opposite to the stereospecificity found for deprotonation/magnesiation/iodination of the cyclopropane analog.[1] This may be due to the lesser configurational stability of cyclobutyl radicals and anions relative to the cyclopropyl species.[7] However, exactly as in the cyclopropane series, carboxylation of **5** (Scheme 4) led to the *cis*-acid **8** in 80% isolated yield.[8] The stereochemistry of **8** was assigned unambiguously by X-ray single crystal analysis of the corresponding methyl ester.[6b] Methylation of **6** with CH_3I/CuI gave a solid (mp ca. 41 °C; 64% isolated yield);[8] structure **9** was obtained by X-ray crystallography.[6c] As in the carboxylation, the major product is formed with retention of configuration at the Grignard carbon of **6**.



Scheme 4

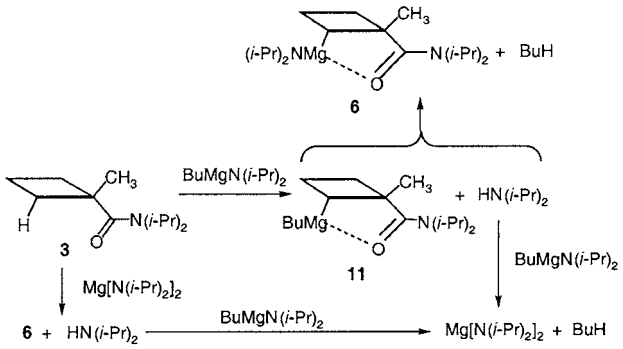
To our knowledge, these are the first examples of 'ortho-metalation' on a cyclobutane. We expect that amido-Grignard **6** will have much the same flexibility and utility in synthesis as its cyclopropane analog in reactions with electrophiles.[1]

To demonstrate the exceptional potential of the method for preparing substituted cyclobutanes, we briefly investigated introduction of another methyl group onto **9**, now in the *cis* β′-position. It soon became clear that **9** is deprotonated/magnesiated more slowly than **3**, presumably a result of statistics as well as steric hindrance. Nonetheless, reaction of **9** with excess BuMgN(*i*-Pr)$_2$ in THF/heptane at reflux for 48 hours followed by methylation with CH_3I/CuI gave the trimethyl compound **10** in 36% isolated yield along with 25% of recovered starting material (Equation 1). The mirror plane symmetry in the assigned structure **10** follows from the ^{1}H- and ^{13}C NMR spectra which show the β- and β′-methyl groups to be magnetically equivalent.



Equation 1

We believe that proton removal from activated CH groups is done by the lone pair of nitrogen in BuMgN(*i*-Pr)$_2$ or Mg[N(*i*-Pr)$_2$]$_2$, the latter present in trace amounts. Carbon-bound metals are kinetically poor at deprotonating CH groups, whereas metal salts of amines are much better. Indeed, we have found that Bu_2Mg is useless in this regard,[1] whereas Mg[N(*i*-Pr)$_2$]$_2$ is effective kinetically (but not thermodynamically). For this reason we show **11** (Scheme 5) as a precursor of **6** (and perhaps a part precursor for **7**, **8**, and **9**). If Mg[N(*i*-Pr)$_2$]$_2$ is the actual proton abstractor, **6** would be formed directly. In all cases the reactions are driven forward by formation of butane.

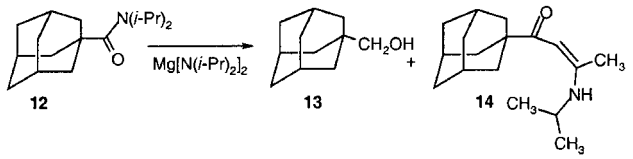


Scheme 5

Deprotonation/magnesiation of cyclopropyl carboxamides is essentially a stoichiometric reaction at room temperature requiring just one equivalent of BuMgN(*i*-Pr)$_2$.[1] This is not so with the corresponding cyclobutane amides. About two equivalents of BuMgN(*i*-Pr)$_2$ are needed for good conversion,[9] even at reflux. This is probably due to the diisopropyl amine liberated in the course of Scheme 5. The freed amine reacts with BuMgN(*i*-Pr)$_2$, slowly at room temperature (the cyclopropyl case), but rapidly above 50 °C, giving butane and Mg[N(*i*-Pr)$_2$]$_2$. As some BuMgN(*i*-Pr)$_2$ is thus destroyed, there is need for an excess.

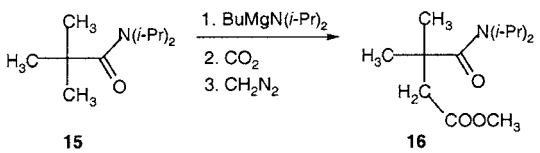
Deprotonation/magnesiation of cyclobutane carboxamides with BuMgN(*i*-Pr)$_2$ opens new synthetically useful paths. As we shown with numerous examples in the cyclopropane series,[1] carboxamido-stabilized amido-Grignards enable stereospecific introduction of a variety of substituents. Permutations and combinations of these reactions provide an entirely new method for the preparation of substituted cyclobutanes. The use of alkyl magnesium homochiral amides should provide for selection between the enantiotopic protons *cis* and β to the carboxamido group as we have shown elsewhere for cyclopropanes.[10]

In theory, were base and solvent completely stable, and were there no destructive side reactions, any CH-group near an appropriately placed carboxamido group would be deprotonated/magnesiated completely by BuMgDA, the conversion taken to completion by formation of butane. In reality, most compounds we have tried with CH kinetic acidities less than that of cyclobutane reacted only very slowly with BuMgN(*i*-Pr)$_2$ at <100 °C. The 1-*N*,*N*-diisopropylcarboxamides of 1-methylcyclopentane, 1-methylcyclohexane, and adamantane gave little if anything derived from the desired deprotonation/magnesiation. Instead, on prolonged treatment, a complex mixture of products was produced, many (and maybe all) from reactions at the carboxamido substituent. Some N-dealkylated carboxamides were found, presumably the result of Hofmann-type eliminations. Mg[N(*i*-Pr)$_2$]$_2$, probably formed by disproportionation of BuMgN(*i*-Pr)$_2$, seems responsible for the other major products, for these were formed much more quickly when pure Mg[N(*i*-Pr)$_2$]$_2$ was used instead of BuMgN(*i*-Pr)$_2$. For example, reaction of the adamantyl carboxamide **12** with four equivalents of Mg[N(*i*-Pr)$_2$]$_2$ in refluxing THF/heptane (Equation 2) gave, amongst other things, the known carbinol **13** and the strange ene-amide **14**, identified by single crystal X-ray analysis.[6d] Spectroscopically similar ene-amides (oils) were formed even from the more acidic compounds **3** and **15** (vide infra) on treatment with Mg[N(*i*-Pr)$_2$]$_2$, but their structures were not identified as conclusively.



Equation 2

The kinetic acidity of a hydrogen on a methyl group is somewhat greater than that of a methylene hydrogen and thus lies between a cyclobutane and a cyclopentane.[11] This enhancement, even with the statistical boost of 3:2, proved insufficient for significant deprotonation/magnesiation of a β-to-the-carboxamide hydrogen on the methyl group of 1-methyl-1-(*N*,*N*-diisopropylcarboxamido)cyclopentane; standard conditions favored other reactions (vide supra). On the other hand, it appears that the statistical boost provided by the 9 hydrogens in the pivaloyl carboxamido **15** is sufficient for useful deprotonation/magnesiation. Reaction of **15** with excess BuMgN(*i*-Pr)$_2$ in THF/heptane at reflux for 8 hours, followed by carboxylation and diazomethane esterification, gave a 56% isolated yield of the succinic acid derivative **16** (Equation 3).



Equation 3

This result gives us hope that we can find a base and reaction conditions for effective deprotonation/magnesiation in still less favorable cases. If, as we suspect, unwanted products like those in Scheme 5 arise from the reducing properties (in the Meerwein–Ponndorff–Verley sense) of Mg[N(*i*-Pr)$_2$]$_2$, it should be better for deprotonation/magnesiation to derive the base instead from a tertiary amine. This and the use of different solvents and higher temperatures are under investigation.

References

(1) (a) Eaton, P. E.; Zhang, M. X. *Angew. Chem. Int. Ed.*; **2002**, 41, 2169. (b) See also: Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Eaton, P. E.; Xiong, Y.; Lee, C. H. *J. Chin. Chem. Soc.* **1991**, *38*, 303.

(2) The activating/stabilizing carboxamido group need not be on the β-carbon, see: Eaton, P. E.; Lukin, K. *J. Am. Chem. Soc.* **1993**, *115*, 11370.

(3) Streitwieser, A. Jr.; Caldwell, R. A.; Young, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 529.

(4) We assign the liganding interaction shown by analogy to that seen in a cyclopropyl example for which we have a single crystal X-ray structure: Eaton, P. E.; Zhang, M. X.; Steele, I., unpublished results

(5) **Typical Procedure.** Dry diisopropylamine (202 mg, 2.0 mmol) was added dropwise to a stirred 1 M solution of Bu_2Mg in heptanes (Aldrich, 2.0 mL, 2.0 mmol) at 0 °C. The mixture was stirred at r.t. for 1.5 h to give a pale yellow BuMgN(*i*-Pr)$_2$ solution. Amide **3** (99 mg, 0.5 mmol) in THF (1.5 mL) was added at r.t. to the base solution so made. The resulting pale yellow solution was taken to reflux (73 °C, bath at 85 °C) for 4 h. Afterwards, the solution was cooled to r.t. and added to I_2 (1 g, 4 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at r.t. for 1.5 h then quenched with aq 10% HCl (5 mL), extracted with $CHCl_3$ (3 × 10 mL) and washed with aq sat. $(NH_4)_2SO_4$ (10 mL). The extract was washed with an aq 10% $Na_2S_2O_3$ (10 mL), then again with aq sat. $(NH_4)_2SO_4$ (2 × 10 mL), dried over Na_2SO_4 and concentrated at r.t. in vacuo. The residual brown liquid was chromatographed (silica gel, CH_2Cl_2) to give **7** (124 mg, 77%) as a colorless solid: mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.96 (dd, *J* = 10 and 9 Hz, 1 H), 3.73 (sept, *J* = 7 Hz, 1 H), 3.27 (sept, *J* = 7 Hz, 1 H), 2.48 (m, 1 H), 2.31–2.42 (m, 2 H), 2.02 (m, 1 H), 1.47 (s, 3 H), 1.39 (d, *J* = 7 Hz, 3 H), 1.38 (d, *J* = 7 Hz, 3 H), 1.17 (d, *J* = 7 Hz, 3 H), 1.15 (d, *J* = 7 Hz, 3 H). ^{13}C NMR (100 MHz): δ = 174.1, 49.7, 47.9, 46.0, 32.6, 28.8, 28.1, 25.7, 20.7, 20.4., Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.97; H, 6.79; N, 4.36. The epimer of **7** was eluted somewhat later from the column: mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (dd, *J* = 6.0 and 5.6 Hz, 1 H), 3.45 (sept, *J* = 6.4 Hz, 1 H), 3.29 (sept, *J* = 6.8 Hz, 1 H), 3.17 (dd, *J* = 20.0 and 11.2 Hz, 1 H), 2.85–2.75 (m, 1 H), 2.09 (m, 1 H), 1.64–1.57 (m, 1 H), 1.53 (s, 3 H), 1.40 (d, *J* = 6.8 Hz, 3 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.35 (d, *J* = 6.4 Hz, 3 H), 1.18 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz): δ = 173.2, 52.0, 48.3, 46.1, 30.8, 30.2, 29.2, 22.2, 21.6, 21.1, 20.5, 20.2. MS (ES): 324.0 [M + 1].

(6) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, e-mail: deposit@ccde.cam.ac.uk, as supplementary publications numbered: (a) 206444; (b) 173571; (c) 209582 (racemate); (d) 205769.

(7) Remarkably little is known about what happens at the magnesiated carbon during Grignard reactions with {E^+}. See: Gawley, R. E. In *Grignard Reagents. New Developments*; Richey, H. G. Jr., Ed.; Wiley: Chichester, **2000**, 139.
(8) We estimate that we would have seen in the NMR spectra of the crudes any other isomer present in >10% yield.
(9) Bu_2Mg as supplied commercially (Aldrich) has a mix of *n*-butyl and *sec*-butyl groups. Thus, two bases result from reaction with HN(*i*-Pr)$_2$: *n*-BuMgN(*i*-Pr)$_2$ and *sec*-BuMgN(*i*-Pr). We have made each separately and have found only small differences in their ability to deprotonate/magnesiate **3**.
(10) Zhang, M. X.; Komiya, N.; Eaton, P. E. *224th ACS National Meeting, Boston*; **2002**, 341-ORGN.
(11) Best value at present for neopentane:cyclohexane relative kinetic acidity is 8.2:1 (per hydrogen) obtained using CsCHA at 50 °C. Private Communication, Prof. A. Streitwieser, March 4, 2003.