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### Permalink

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### Journal

Tetrahedron Letters, 56(5)

### ISSN

0040-4039

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### Publication Date

2015

### DOI

10.1016/j.tetlet.2014.12.066

Peer reviewed

# FULL PAPER

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DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

# Reduction of Weinreb Amides to Aldehydes under Ambient Conditions with Magnesium Borohydride Reagents

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*Dedicated to the memory of Professor Sheldon Shore*

**Keywords:** Synthetic methods / Aminoborohydride / Weinreb Amide / Partial Reduction / Aldehyde

Chloromagnesium dimethylaminoborohydride (ClMg<sup>+</sup>[H<sub>3</sub>BNMe<sub>2</sub>]<sup>-</sup>, MgAB) is an analogue of the versatile lithium dialkylaminoborohydrides (LAB reagents), prepared by the reaction of dimethylamine-borane with methylmagnesium chloride. Solutions of MgAB are stable in solution, remaining active at least three months. MgAB is a partial reducing agent for Weinreb amides under ambient reaction conditions and is complementary to the

commonly utilized lithium aluminum hydride (LiAlH<sub>4</sub>) and diisobutylaluminum hydride (DIBAL) reagents. To prevent over-reduction, the aldehyde products are readily isolated in good yields by forming the sodium bisulfite adducts. Aldehyde products can both be stored and later used as the bisulfite adducts, or can be regenerated from the bisulfite adducts by treatment with aqueous formaldehyde.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.xxxxxxxx>.

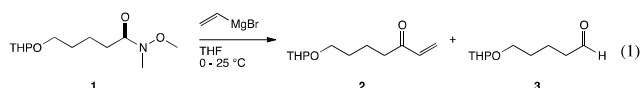
## Introduction

Reduction of amides with metal hydride reagents to the corresponding alcohol and amine is not unusual.<sup>[1]</sup> However, the reduction of amides to the corresponding aldehydes represents a challenge and only a few methods are available to do this transformation. The partial reduction of amides to aldehydes is often substrate specific, being highly dependent upon the nature of the substituent on the amide nitrogen atom, with bulkier substituents affording higher yields of aldehydes.<sup>[2-4]</sup> In most cases, this transformation is carried out with aluminum hydrides such as LiAlH<sub>4</sub>,<sup>[5]</sup> DIBAL,<sup>[6]</sup> and their derivatives.<sup>[7]</sup> The general reduction of amides to aldehydes with commercially available metal hydride sources result in poor yields of aldehydes.<sup>[8]</sup> These reductions often require cryogenic reaction conditions followed by exothermic workups, resulting in over-reduction to amines or alcohols. Borohydrides reduce tertiary amides, but are not as reactive as aluminum hydrides.<sup>[9]</sup>

One synthetic strategy to prevent over-reduction employs specialized amide derivatives such as *N*-acylcarbazoles<sup>[10]</sup> (acylimidazoles<sup>[11]</sup> and acylaziridines<sup>[12]</sup>), and morpholine amides.<sup>[13]</sup> Of particular note are the *N*-methoxy-*N*-methylamides (Weinreb amides).<sup>[4]</sup> Weinreb amides are readily prepared from carboxylic acids<sup>[14-16]</sup> and their derivatives, such as acid chlorides,<sup>[4]</sup> esters,<sup>[17]</sup> lactones, and anhydrides.<sup>[14]</sup> Since their discovery, these amides have been utilized extensively as acylating agents in synthesis.<sup>[14,18-21]</sup> The presence of the methoxy group on the *N*-atom allows the formation of stable chelates of the tetrahedral intermediate following one equivalent of organometallic nucleophile, preventing further nucleophilic addition. Reaction of Weinreb amides with Grignard and organolithium reagents is one of the best ways to generate ketones. However, controlled reduction of Weinreb amides to the corresponding aldehydes typically uses very strong reducing agents such as DIBAL and LiAlH<sub>4</sub>.<sup>[22]</sup>

Recent work towards the partial reduction of amides has resulted in the reported use of transition metal hydrides, such as titanium and zirconium hydrides.<sup>[23,24]</sup> Buchwald reported that the combination of titanium(IV) isopropoxide and diphenylsilane can reduce *N,N*-disubstituted amides to the corresponding aldehydes.<sup>[25]</sup> However, this method is limited to  $\alpha$ -enolizable substrates via an enamine intermediate. Georg reported a promising reduction of tertiary amides, including Weinreb amides, to the corresponding aldehydes using Cp<sub>2</sub>Zr(H)Cl.<sup>[26,27]</sup>

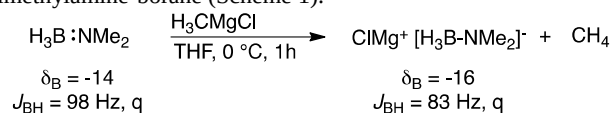
A recent observation prompted this study: during the synthesis of vinyl ketone **2**, Weinreb amide **1** was treated with an aged commercial solution of vinylmagnesium bromide. A mixture of the desired product **2** and aldehyde **3** was isolated (Eq 1).



Using freshly prepared vinylmagnesium bromide, only the desired  $\alpha,\beta$ -unsaturated ketone **2** was formed, indicating the presence of a hydride reducing agent contaminant in the commercial sample of Grignard reagent. To verify this hypothesis, the older commercial vinylmagnesium bromide was added to benzaldehyde. <sup>1</sup>H NMR analysis of the product revealed a 2:1 mixture of the allylic alcohol, 1-phenyl-2-propen-1-ol, and benzyl alcohol. Similar observations of reduction products from Grignard reactions with Weinreb amides have been reported in the literature,<sup>[17]</sup> thus warranting an investigation into the reduction of Weinreb amides using magnesium-based hydrides. We have recently synthesized chloromagnesium dimethylaminoborohydride (ClMg<sup>+</sup>[H<sub>3</sub>BNMe<sub>2</sub>]<sup>-</sup>, MgAB), using the reaction of Grignard reagents with dimethylamine-borane.<sup>[28]</sup> Herein is a study of the ability of MgAB to reduce Weinreb amides to the corresponding aldehydes.

## Results and Discussion

Chloromagnesium dimethylaminoborohydride (MgAB) was quantitatively synthesized from methylmagnesium chloride and dimethylamine-borane (Scheme 1).<sup>[28b]</sup>



Scheme 1. Synthesis of MgAB

In the  $^{11}\text{B}$  NMR spectrum in THF, the MgAB species appears as a quartet at  $\delta_{\text{B}}$  -16 ppm, while the starting amine-borane has a chemical shift of  $\delta_{\text{B}}$  -14 ppm. The starting material and the product can be further distinguished by their coupling constants; dimethylamine-borane is a quartet with  $J_{\text{BH}} = 98$  Hz, while the product chloromagnesium dimethylaminoborohydride has  $J_{\text{BH}} = 83$  Hz (Figure 1).

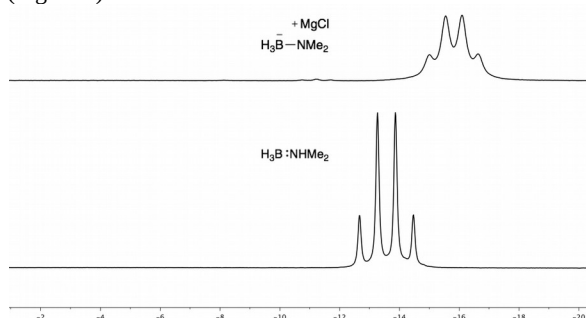


Figure 1. Reaction of dimethylamine-borane with MeMgCl in THF: (top)  $^{11}\text{B}$  NMR of  $\text{ClMg}^+ [\text{H}_3\text{BNMe}_2]^-$ ; (bottom)  $^{11}\text{B}$  NMR of dimethylamine-borane.

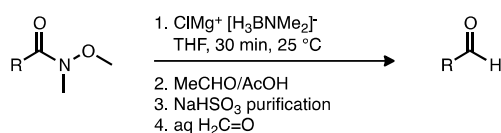
When synthesizing MgAB, chloride-based methyl or ethyl Grignard reagents give complete conversion. However bromide-based Grignard reagents afford mixtures due to Schlenk disproportionation.<sup>[29]</sup> MgAB can be stored under inert atmosphere at room temperature for at least three months without any disproportionation as monitored by  $^{11}\text{B}$  NMR.

Previously, we have reported that various lithium aminoborohydrides ( $\text{Li}^+ [\text{H}_3\text{BNR}_2]^-$ , LAB reagents) reduce both aliphatic and aromatic amides to give either the corresponding alcohols or amines, depending on both the steric environments of the tertiary amide and the LAB reagent.<sup>[30]</sup> Controlled reduction of Weinreb amides using either LAB reagents or 9-borabicyclo[3.3.1]nonane (9-BBN) was not demonstrated.<sup>[31]</sup>

The controlled reduction of *N*-methoxy-*N*-methylbenzamide to benzaldehyde using MgAB was investigated as a model substrate. One equivalent of MgAB reduced *N*-methoxy-*N*-methylbenzamide to benzaldehyde in 30 minutes at 25 °C, as evidenced by TLC analysis. However, after acidic quench and aqueous work up,  $^1\text{H}$  NMR analysis of the crude mixture revealed the presence of benzyl alcohol in addition to benzaldehyde. We speculated that an inexpensive sacrificial aldehyde, such as acetaldehyde, could be used as a hydride scavenger during the quench. Indeed, dropwise transfer of the reduction mixture to a pentane solution of acetaldehyde and acetic acid prevented the over-reduction, but contamination was observed. Attempted purification of the crude benzaldehyde by silica gel column chromatography resulted in the isolation of almost pure benzyl alcohol. Dimethylaminoborane ( $\text{Me}_2\text{N-BH}_2$ ), the by-product from MgAB, exists as a stable dimer and is usually unreactive to aldehydes.<sup>[32]</sup> Evidently, activation of the aldehyde carbonyl by silica gel results in the reduction of benzaldehyde, similar to that observed for the silica gel-promoted reduction by *N*-heterocyclic carbene boranes.<sup>[33]</sup>

Even though MgAB is an excellent reducing agent to achieve the controlled reduction of Weinreb amides to aldehydes, convenient isolation of pure aldehyde products proved to be a challenge. Purification of aldehydes by addition of bisulfite is a well-established procedure; ketones and aldehydes form insoluble solid bisulfite adducts.<sup>[34]</sup> Separating bisulfite adducts from the crude reaction mixture, followed by the regeneration of the aldehyde, proved to be convenient and practical. The aldehydes are readily regenerated by treatment with either aqueous acid<sup>[35]</sup> or base.<sup>[36]</sup> Regeneration of the aldehyde by treatment of the bisulfite adduct with aqueous formaldehyde was straightforward, allowing for the isolation of various aldehydes from the organic layer (Table 1).<sup>[37]</sup>

Table 1. Reduction of Weinreb Amides<sup>[a]</sup>

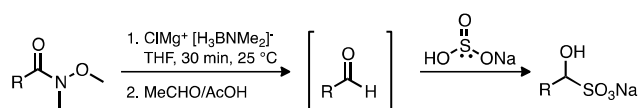


| Entry | Amide | Product | Yield <sup>[b]</sup> (%) |
|-------|-------|---------|--------------------------|
| 1     |       |         | 75                       |
| 2     |       |         | 74                       |
| 3     |       |         | 81                       |
| 4     |       |         | 82                       |
| 5     |       |         | 70                       |
| 6     |       |         | 81                       |
| 7     |       |         | 74                       |
| 8     |       |         | 70                       |
| 9     |       |         | 75                       |
| 10    |       |         | 89                       |
| 11    |       |         | 80 <sup>[c]</sup>        |

[a] Reagents and conditions:  $\text{ClMg}^+ [\text{H}_3\text{BNMe}_2]^-$  (1 M, 2 mmol), THF (1.5 mL), argon, 25 °C, 30 min. [b] Isolated yield of aldehyde after liberation from bisulfite adduct. [c] 60 min.

The bisulfite adducts of aldehydes are stable crystalline solids, and are amenable to long term storage or use in situ.<sup>[38]</sup> Thus reduction of Weinreb amides to directly provide the robust bisulfite adducts was explored (Table 2).

Table 2. Reduction of Weinreb Amides to Aldehydes Isolated as Bisulfite Adducts<sup>[a]</sup>

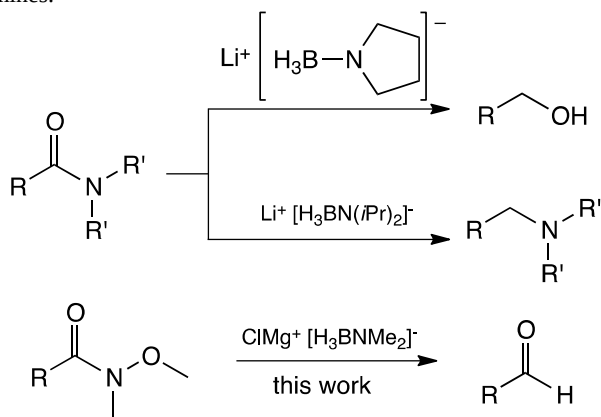


| Entry | Amide | Product | Yield <sup>[b]</sup> (%) |
|-------|-------|---------|--------------------------|
| 1     |       |         | 70                       |
| 2     |       |         | 70                       |
| 3     |       |         | 67                       |

[a] Reagents and conditions:  $\text{ClMg}^+ [\text{H}_3\text{BNMe}_2]^-$  (1M), THF (1.5 mL), argon, 25 °C, 30 min. [b] Isolated yield of solid bisulfite adduct.

Isolating the bisulfite adducts in lieu of liberating the free aldehyde allowed expansion of the study to include adducts of water-soluble aldehydes (Table 2, entries 1 through 3).

The controlled reduction of Weinreb amides to aldehydes with MgAB expands the versatility of amide reduction by aminoborohydrides (Scheme 2). LAB reagents developed in the Singaram lab can be used to reduce both aliphatic and aromatic amides to give either the corresponding alcohols or amines.<sup>[30]</sup> Reduction of amides with lithium pyrrolidinoborohydride yield the corresponding alcohols, whereas reaction with sterically crowded lithium diisopropylaminoborohydride yield the corresponding amines.



Scheme 2. Reaction of tertiary amides with aminoborohydride reagents

## Conclusions

In summary, a mild, simple and efficient method for the reduction of Weinreb amides to aldehydes under ambient conditions has been developed using a new reducing agent, chloromagnesium dimethylaminoborohydride (MgAB). This reagent can be prepared by the reaction of methylmagnesium chloride with dimethylamine-borane at 0 °C. The aldehyde product is effectively isolated as the corresponding bisulfite adduct, which can be stored, or unveiled to provide pure aldehydes. This methodology should be particularly attractive for applications in industry. MgAB is milder, safer, and complementary to reducing agents typically used to convert Weinreb amides to aldehydes.

## Experimental Section

All reactions were performed in oven-dried, argon-cooled glassware. The dimethylamine-borane was used as received from

Callery Chemical Company. All Grignard reagents were used as received from Aldrich and were stored at room temperature. All air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. The concentrations of the alkyl Grignard reagents were monitored using the titration method described by Knochel.<sup>[39]</sup> Tetrahydrofuran (THF) was freshly obtained from a solvent purification system (Pure Solv MD, Innovative Technology Inc.). NMR spectra were recorded at 500 MHz (<sup>1</sup>H), 125 MHz (<sup>13</sup>C), and 160.4 MHz (<sup>11</sup>B). All <sup>1</sup>H NMR and <sup>13</sup>C NMR chemical shifts are reported in  $\delta$  units relative to the respective solvent of the NMR sample. <sup>11</sup>B NMR samples are reported relative to the external standard  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  ( $\delta_{\text{B}} = 0$ ). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration.

**General Procedure for the Preparation of Chloromagnesium Dimethylaminoborohydride (MgAB), 1 M Solution in THF:** An oven-dried, Ar-cooled 50-mL round-bottom flask equipped with a stir bar and septa was charged with an ethereal solution of  $\text{MeClMg}$  (10.35 mL, 2.9M, 30 mmol) and cooled to 0 °C (ice bath). A 1.5 M dimethylamine-borane solution in THF (20 mL, 30 mmol) was added with stirring over a period of 40 min. After 1 h of stirring, a 0.4 mL aliquot was taken for <sup>11</sup>B NMR analysis. The <sup>11</sup>B NMR spectrum indicated formation of the chloromagnesium aminoborohydride product ( $-16$ , q,  $J_{\text{BH}} = 83$  Hz). The MgAB solution was then transferred to an oven-dried, Ar-cooled ampoule via a cannula for storage. Note that, although the chemical shift of the corresponding amine-borane complex is close to that of the MgAB, the  $J_{\text{BH}}$  values of dimethylamine-borane are 98 Hz.

**General Procedure for the Reduction of Weinreb Amides to Aldehydes:** The following procedure for the reduction of *N*-methoxy-*N*-methylbenzamide by MgAB is representative. To an oven-dried and argon cooled 25-mL round-bottom flask equipped with a stir bar and septa was added *N*-methoxy-*N*-methylbenzamide (0.305 mL, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (MgAB, 2 mL, 1 M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). After 30 min, the reaction solution was added dropwise to a solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL). The combined organic layers was washed with 1 M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield crude aldehyde as an orange oil. The crude aldehyde (2 mmol) was transferred to a round-bottom flask equipped with a magnetic stir bar followed by EtOH (3 mL) and EtOAc (5 mL) and cooled with an ice bath. A saturated aqueous solution of  $\text{NaHSO}_3$  (1 mL) was added with stirring. After 4 h, the solid bisulfite adduct was isolated by vacuum filtration, washed with  $\text{Et}_2\text{O}$  (3 x 5 mL) and dried under vacuum to yield a white solid. The bisulfite adduct was then added to a round-bottom flask dissolved in  $\text{H}_2\text{O}$  (10 mL) and a 37% formalin solution (2 mL) was added followed by  $\text{Et}_2\text{O}$  (20 mL). The biphasic solution was stirred for 1 h. The aqueous layer was separated and extracted with a 1:1 mixture of THF/ $\text{Et}_2\text{O}$  (3 x 10 mL). The combined organic layers was dried over magnesium sulfate, and concentrated under reduced pressure to give the aldehyde as a pale yellow oil (0.160 g, 1.5 mmol 75% yield). For other aldehydes prepared by this method see Table 1.

**Benzaldehyde:**<sup>[40]</sup> Pale yellow oil (0.160 g, 75% yield). <sup>1</sup>H NMR ( $\text{CDCl}_3$ ):  $\delta$  7.48–7.51 (m, 1H), 7.59–7.61 (m, 1H), 7.84–7.86 (m, 2H), 9.97 (s, 1H). <sup>13</sup>C NMR ( $\text{CDCl}_3$ ):  $\delta$  128.5, 129.0, 130.1, 134.5, 136.4, 192.4 ppm.

***o*-Tolualdehyde:**<sup>[41]</sup> Pale yellow oil (0.178 g, 74% yield). <sup>1</sup>H NMR ( $\text{CDCl}_3$ ):  $\delta$  2.68 (s, 3H), 7.24–7.26 (m, 1H), 7.33–7.36 (m, 1H), 7.44–7.48 (m, 1H), 7.77–7.79 (m, 1H), 10.25 (s, 1H). <sup>13</sup>C NMR ( $\text{CDCl}_3$ ):  $\delta$  19.7, 126.4, 131.8, 132.1, 133.7, 134.2, 140.7, 192.9 ppm.

**3,5-Dimethylbenzaldehyde:**<sup>[42]</sup> Pale yellow oil (0.217 g, 81% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.39 (s, 3H), 7.26–7.27 (m, 1H), 7.48–7.50 (m, 2H), 9.95 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 21.1, 127.6, 136.3, 136.7, 138.8, 192.7 ppm.

**p-Methoxybenzaldehyde:**<sup>[43]</sup> Yellow oil (0.223 g, 82% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.83 (s, 1H), 6.94–6.96 (d, *J* = 8.8 Hz, 2H), 7.78–7.79 (d, *J* = 6.9 Hz, 2H), 9.83 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 55.6, 114.3, 129.9, 132.0, 164.6, 190.8 ppm.

**trans-Cinnamaldehyde:**<sup>[43]</sup> Yellow oil (0.185 g, 70% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.66–6.71 (dd, *J* = 15.9, 7.6 Hz, 1H), 7.39–7.42 (m, 3H), 7.46 (d, *J* = 15.9 Hz, 1H), 7.52–7.54 (m, 2H), 9.67 (d, *J* = 7.6 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 128.5, 129.1, 131.3, 134.0, 152.9, 193.8 ppm.

**3-Bromo-4-methylbenzaldehyde:**<sup>[44]</sup> White solid (0.322 g, 81% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.44 (s, 3H), 7.35–7.37 (d, *J* = 7.7 Hz, 1H), 7.66–7.69 (d, *J* = 7.7 Hz, 1H), 7.99, (s, 1H), 9.87 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 23.5, 125.7, 128.5, 131.4, 133.5, 135.9, 145.2, 190.7 ppm.

**o-Bromobenzaldehyde:**<sup>[45]</sup> Pale yellow oil (0.274 g, 74% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.40–7.47 (m, 2H), 7.64 (m, 1H), 7.89–7.91 (m, 1H), 10.35 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 122.5, 127.2, 128.0, 129.9, 133.5, 134.8, 192.0 ppm.

**p-Chlorobenzaldehyde:**<sup>[42]</sup> White solid (0.197 g, 70% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.49–7.51 (d, *J* = 8.4 Hz, 2H), 7.80–7.82 (d, *J* = 8.4 Hz, 2H), 9.97 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 129.6, 131.0, 134.8, 141.0, 190.9 ppm.

**p-Trifluoromethylbenzaldehyde:**<sup>[43]</sup> Pale yellow oil (0.261 g, 75% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.79–7.81 (d, *J* = 7.8, 2H), 7.99–8.01 (d, *J* = 7.8, 2H), 10.1 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 66.0, 126.2, 130.1, 138.8, 191.3 ppm.

**p-Nitrobenzaldehyde:**<sup>[45]</sup> Yellow solid (0.269 g, 89% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.06–8.08 (d, *J* = 8.0 Hz, 2H), 8.36–8.38 (d, *J* = 8.8 Hz, 2H), 10.1 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 124.4, 130.6, 140.1, 151.2, 190.5 ppm.

**Octanal:**<sup>[46]</sup> Pale yellow oil (0.205 g, 80% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.82–0.85 (t, *J* = 7.0 Hz, 3H), 1.20–1.29 (m, 6H), 1.55–1.60 (m, 4H), 2.36–2.39 (t, *J* = 7.0 Hz, 2H), 9.72 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 14.1, 22.2, 22.6, 29.1, 29.2, 31.7, 44.0, 202.9 ppm.

**General Procedure for the Formation of Aldehyde Bisulfite Adducts:** The following procedure for the formation of the bisulfite adduct of 5-bromonicotinaldehyde is representative. To an oven-dried and argon cooled 25-mL round-bottom flask equipped with a stir bar and septa was added 5-bromo-*N*-methoxy-*N*-methylnicotinamide (0.490 g, 2 mmol) followed by THF (1.7 mL). Chloromagnesium dimethylaminoborohydride (MgAB, 2 mL, 1 M, 2 mmol) was then added dropwise via a syringe. The reaction was monitored by TLC (Hex/EtOAc, 1:1). After 30 min, the reaction solution was added dropwise to a solution of acetaldehyde (2 mmol) and acetic acid (2 mmol) in pentane (10 mL). After 15 min, saturated aqueous NH<sub>4</sub>Cl (2 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et<sub>2</sub>O (2 x 10 mL). The combined organic layers was washed with 1 M HCl (10 mL), dried with magnesium sulfate, and concentrated under reduced pressure to yield orange oil. To a round-bottom flask equipped with a magnetic stir bar was charged the crude aldehyde (2 mmol) followed by EtOH (3 mL) and EtOAc (5 mL) and cooled with an ice bath. A saturated aqueous solution of NaHSO<sub>3</sub> (1 mL) was added with stirring. After 4 h, the solid bisulfite adduct was isolated by vacuum filtration, washed with Et<sub>2</sub>O (3 x 5 mL) and dried under vacuum to yield a white solid (0.407g, 70%). Thermal decomposition of the compounds prohibited melting point measurement,<sup>[38]</sup> and elemental analysis gave unreliable results, as is typical of bisulfite adducts. For other adducts prepared by this method see Table 2.

**Sodium hydroxy(pyridin-2-yl)methanesulfonate:** White solid (0.296 g, 70% yield); mp 150 °C (dec). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 5.66 (br s, 1H), 7.56 (t, *J* = 6.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 8.04 (m, 1H), 8.54 (d, *J* = 5.2 Hz, 1H); <sup>13</sup>C NMR (D<sub>2</sub>O): δ 81.4, 121.4, 122.8, 138.3, 143.3 ppm; MS (ESI): calcd. for C<sub>6</sub>H<sub>6</sub>NNaO<sub>4</sub>S 210.9915; peak not seen due to ion suppression.

**Sodium (5-bromopyridin-3-yl)(hydroxy)methanesulfonate:** White solid (0.407 g, 70% yield); mp 140 °C (dec). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 5.73 (br s, 1H), 8.47 (t, *J* = 2.0 Hz, 1H), 8.76 (d, *J* = 1.9 Hz, 1H), 8.82 (d, *J* = 2.2 Hz, 1H); <sup>13</sup>C NMR (D<sub>2</sub>O): δ 83.7, 121.8, 135.9, 141.5, 146.6, 150.4 ppm; MS (ESI): calcd. for C<sub>6</sub>H<sub>6</sub>BrNNaO<sub>4</sub>S 288.9020; peak not seen due to ion suppression.

**Sodium hydroxy(thiophen-2-yl)methanesulfonate:** White solid (0.290 g, 67% yield); mp 155 °C (dec). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 5.79 (br s, 1H), 7.67–7.77 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.19 (t, *J* = 8.0 Hz, 1H). <sup>13</sup>C NMR (D<sub>2</sub>O): δ 102.0, 126.0, 127.0, 127.4, 146.8 ppm; MS (ESI): calcd. for C<sub>5</sub>H<sub>5</sub>NaO<sub>4</sub>S 215.9527; peak not seen due to ion suppression. C<sub>5</sub>H<sub>5</sub>NaO<sub>4</sub>S: C 27.78, H 2.33, S 29.66; found C 21.99, H 1.18, S 20.94.

**Supporting Information** (see footnote on the first page of this article): General information and procedures, characterization data, and NMR spectra of all compounds.

## Acknowledgments

NP thanks the National Institutes of Health NIGMS Bridges to the Future Program (GM 51765-10). CT thanks the Royal Thai Government for a Higher Education Strategic Scholarship for Frontier Research Network.

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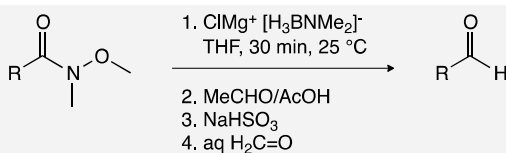
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### Layout 2:



Chloromagnesium dimethylaminoborohydride ( $\text{ClMg}^+ [\text{H}_3\text{BNMe}_2]^-$ , MgAB), prepared by the reaction of dimethylamine-borane with Grignard reagents, allows for the reduction of Weinreb amides to aldehydes under ambient conditions.

Aldehyde products are readily isolated from the crude in good yields by forming the sodium bisulfite adducts. Aldehyde products can both be stored and later used as the bisulfite adducts, or can be regenerated.

### Reduction

Christopher L. Bailey, Jacob W. Clary, Chittreeya Tansakul, Lucas Klabunde, Christopher L. Anderson, Alexander Y. Joh, Alexander T. Lill, Natalie Peer, Rebecca Braslau, and Bakthan Singaram\* ..... Page No. – Page No.

Reduction of Weinreb Amides to Aldehydes under Ambient Conditions with Magnesium Borohydride Reagents

**Keywords:** Synthetic methods / Aminoborohydride / Weinreb Amide / Partial Reduction / Aldehyde