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Grignard Reagents: Alkoxide-Directed Iodine–Magnesium Exchange at sp^3 Centers

Fraser F. Fleming,*,† Subrahmanyam Gudipati,† Viet Anh Vu,†
Robert J. Mycka,† and Paul Knochel‡

Department of Chemistry and Biochemistry, Duquesne University,
Pittsburgh, Pennsylvania 15282-1530 and Department Chemie,
Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377, München, Germany

flemingf@duq.edu

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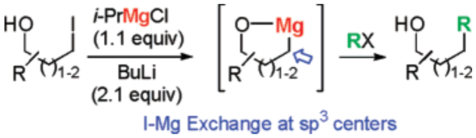
ABSTRACT



Sequential addition of *i*-PrMgCl and BuLi to sp^3 hybridized iodoalcohols triggers a facile iodine–metal exchange. Intercepting the resulting cyclic Grignard reagents with a slight excess of an electrophile leads to a diverse range of substituted alcohols. The iodine–magnesium exchange strategy is effective with 3-carbon iodoalcohols bearing alkyl substitutents on the carbinol or adjacent carbons and with the chain-extended homolog 4-iodobutan-1-ol.

Grignard reagents have remained among the most important organometallic reagents since their discovery over 100 years ago.[1] The centrality of Grignard reagents stems from their high reactivity toward a vast array of electrophiles and their facile synthesis through magnesium insertion.[1] Recently, a renaissance in the chemistry of Grignard reagents has ensued following the discovery of magnesium exchange reactions at low temperatures.[2] The significance of this transformation lies in providing Grignard reagents capable of incorporating an array of otherwise incompatible functionality.[3]

Halogen−magnesium[2] and sulfoxide−magnesium[4] exchange strategies provide efficient routes to a diverse range of sp^2 hybridized Grignard reagents. By contrast, the use of exchange processes for synthesizing sp^3 hybridized Grignards is significantly more challenging.[5] A few ingenious strategies[5] have arisen for accessing sp^3 hybridized Grignard reagents, driven in part by a desire for increased functional group tolerance and in part by the potential for generating chiral Grignard reagents.[6]

A conceptually appealing route to sp^3 hybridized Grignard reagents is via an intramolecular halogen−metal exchange in which a pendant alkoxy group facilitates reagent delivery.[7] Related lithium−halogen,[8] −sulfur,[9] and −tellurium[10] exchange processes with haloalcohols generate nucleophilic reagents and avoid the requirement for hydroxyl protection.[11]

[†] Duquesne University.

[‡] Ludwig-Maximilians-Universität.

(1) (a) *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000. (b) *Handbook of Grignard Reagents*; G. S. Silverman, G. S., Rakita, P. E., Eds.; Dekker: New York, 1996.

(2) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4303.

(3) *Handbook of Functionalized Organometallics: Applications in Synthesis*; Knochel, P., Ed.; Wiley-VCH: Chichester, 2005.

(4) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557.

(5) (a) Stoll, A. H.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 606. (b) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351. (c) Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651. (d) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072. (e) Schulze, V.; Hoffmann, R. W. *Chem.−Eur. J.* **1999**, *5*, 337. (f) Avolio, S.; Malan, C.; Marek, I.; Knochel, P. *Synlett* **1999**, 1820. (g) Satoh, T.; Tokano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557. (h) Hoffmann, R. W.; Nell, P. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 338.

(6) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, *32*, 225.

(7) For a summary of related functionalized organolithiums, see: Najera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867. For a first report of Mg insertion with pendant magnesium alkoxides, see: Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.

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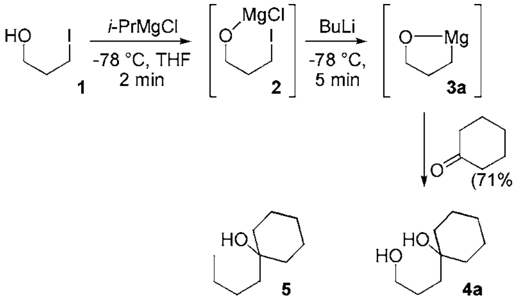
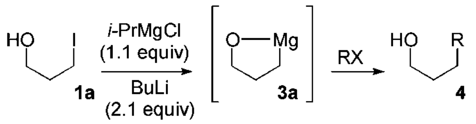
Exploring the viability of an alkoxide-directed halogen−magnesium exchange employed iodopropanol as a prototype because of the proven utility of the resulting nucleophiles.[12] Screening numerous organolithium and Grignard reagent combinations revealed a distinct benefit in first generating the magnesium alkoxide **2** (Scheme 1) rather than the corresponding lithium alkoxide. Apparently, the magnesium alkoxide is less succeptable toward cyclization to the oxetane than the corresponding lithium alkoxide. Intensive optimization led to a procedure in which addition of *i*-PrMgCl to a −78 °C THF solution of iodopropanol is followed by 2 equiv of butyllithium, by far the most effective organolithium reagent[13] for promoting the halogen−metal exchange (Scheme 1). Intercepting the resulting organometallic reagent **3a** with a slight excess (1.4 equiv) of cyclohexanone provided the diol **4a** in 71% yield. Remarkably, the clean reaction is accompanied by only a small amount of the alcohol **5** resulting from resulting from butyl addition. The selective nucleophilic addition of the alkoxypropyl group is consistent with formation of the cyclic Grignard reagent **3a**.

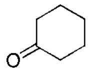
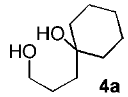
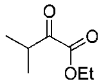
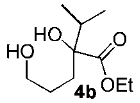
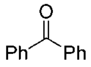
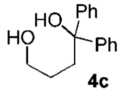
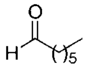
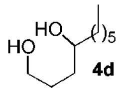
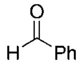
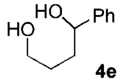
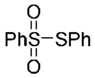
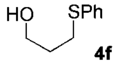
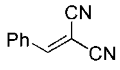
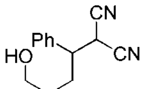
Scheme 1. Intramolecular Exchange Route to sp^3 Hybridized Grignard Reagents



Intercepting the Grignard reagent **3a** with a variety of electrophiles effectively provides a diverse array of functionalized alcohols (Table 1). Aliphatic and aromatic ketones and aldehydes smoothly react with **3a** to afford the corresponding diols (Table 1, entries 1−5) with ethyl 2-methyl-3-oxobutyrate generating the alcohol **4b** resulting from selective addition to the more electrophilic ketone carbonyl (Table 1, entry 2). Sulfenylation of the intermediate Grignard is the only case requiring an excess of the electrophile, affording the corresponding sulfide **4g** and phenylbutyl sulfide (Table 1, entry 6). An efficient and selective conjugate addition ensues in the reaction of **3a** with benzylidene malononitrile to afford **4g** (Table 1, entry 7).

Table 1. Sequential Mg−I Exchange and Alkylation of 3-Iodopropan-1-ol



entry	electrophile	alcohol	yield (%)
1		 **4a**	71
2		 **4b**	71
3		 **4c**	64
4		 **4d**	73
5		 **4e**	48[a]
6		 **4f**	64[b]
7		 **4g**	70

[a] Accompanied by 41% of 1-phenylpentan-1-ol resulting from butyl addition. [b] Required 2.5 equiv of $PhSO_2SPh$.

The intramolecular iodine−magnesium exchange strategy is equally applicable in generating several homologous sp^3 hybridized Grignard reagents (Table 2). Iodine−magnesium exchange with the chain-extended 4-carbon iodoalcohol **5a** provides an intermediate capable of effectively intercepting carbon and sulfur electrophiles (Table 2, entries 1−3). Substituents are tolerated within the propanol scaffold at the carbinol carbon or on the adjacent carbon, although the efficiency of the reaction is diminished relative to the unsubstituted parent system (compare Table 2, entries 4−7 with Table 1, entries 1, 5, and 6). Control experiments indicate that substituents facilitate internal iodide displacement to oxiranes and oxetanes,[14] consistent with the known propensity of alkyl substitution to promote cyclization.[15]

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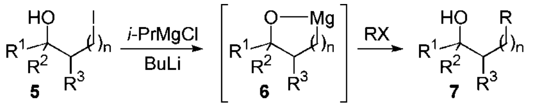
(11) Several recent protocols describe the formation of sp^2 hybridized organometallics containing hydroxyl or carboxyl functionality: (a) Kopp, F.; Wunderlich, S.; Knochel, P. *Chem. Commun.* **2007**, 2075. (b) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404. (c) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288. (d) Kato, S.; Nonoyama, N.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2002**, *43*, 7315.

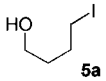
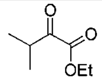
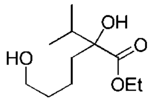
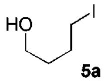
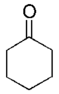
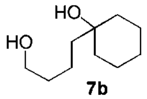
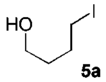
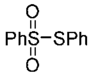
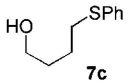
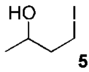
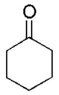
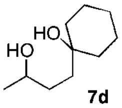
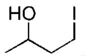
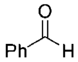
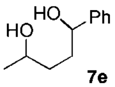
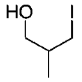
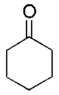
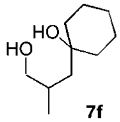
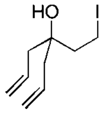
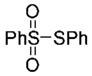
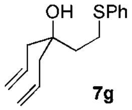
(12) Oshima, K. *Sci. Synth.* **2004**, *7*, 573.

(13) Phenyllithium and MeLi are unable to promote the reaction whereas EtLi and *t*-BuLi were significantly inferior to the use of BuLi. Employing 2 equiv of ethylhexyllithium, trimethylsilylmethyllithium, or hexyllithium or 1 equiv and an additional equivalent of BuLi and alkylating with cyclohexanone as a test electrophile affords **4a** in 34−50% yield.

(14) Sequential deprotonation and protonation of **1**, **5b**, and **5c** at −78 °C leads to diminishing recovery with 1-iodo-2,2,4-trimethylpentan-3-ol affording only 2-isopropyl-3,3-dimethyloxetane.

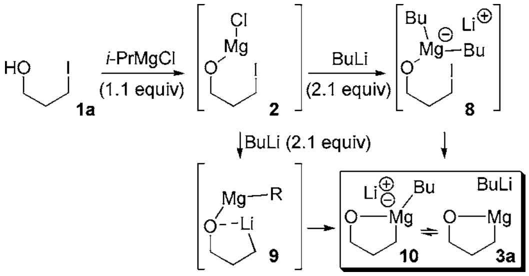
Table 2. Mg−I Exchange and Alkylation of Substituted Iodoalcohols



entry	alkyliodide	electrophile	alcohol	yield (%)
1	 **5a**		 **7a**	46
2	 **5a**		 **7b**	60[a]
3	 **5a**		 **7c**	57[a]
4	 **5b**		 **7d**	55
5	 **5b**		 **7e**	57[b]
6	 **5c**		 **7f**	45[c]
7	 **5d**		 **7g**	54

[a] Required 2.5 equiv of electrophile. [b] Accompanied by 33% of 1-phenylpentan-1-ol resulting from butyl addition. [c] Accompanied by 31% of 1-butylcyclohexanol resulting from butyl addition.

Scheme 2. I−Mg Exchange of sp^3 Hybridized Alkyliodides



Mechanistically the exchange is envisaged to proceed through the magnesium alkoxide **2** (Scheme 2). Sequential chlorine−butyl exchange[16] and butyl addition could afford the electron rich magnesiate **8** from which an iodine−butyl exchange would directly generate the cyclic magnesiate **10**.[17] Alternatively, iodide activation through internal complexation to magnesium could facilitate a directed iodine−lithium exchange[18] to afford the organolithium **9** prior to reorganization to the magnesium ate complex **10**.[17]

Conceptually, the more basic butyl group in the ate complex **10** might be selectively consumed by engaging the co-generated butyliodide in an E$_2$ elimination. Alternatively, an equilibrium between the magnesiate **10** and cyclic Grignard **3a** might be displaced in favor of **3a** by consumption of iodobutane by the butyllithium released from the ate complex. Intercepting the intermediate Grignard reagents with electrophiles is, in some cases, compromised by competitive butyl addition to the electrophile (Table 1, entries 5 and 6, and Table 2, entries 2, 3, 5, and 6), suggesting incomplete consumption of butyllithium prior to alkylation with the electrophile (Scheme 2). The use of only 1 equiv of BuLi leads to incomplete iodine−metal exchange.

Alkoxide-directed iodine−magnesium exchange of iodoalchohols provides a valuable strategy for accessing sp^3 hybridized Grignard reagents. The exchange proceeds rapidly at −78 °C affording cyclic alkylmagnesium alkoxides that selectively intercept a range of electrophiles to afford functionalized alcohols. Conceptually, the alkoxide-directed exchange strategy provides a valuable synthesis of sp^3 hybridized Grignard reagents of direct relevance in synthesizing functionalized and chiral Grignard reagents.

Acknowledgment. Financial support from the National Science Foundation (CHE 0515715, 0421252 HRMS, and 0614785 for NMR facilities) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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