

Radicals

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Preparation of Primary and Secondary Dialkylmagnesiums by a Radical I/Mg-Exchange Reaction Using *s*Bu₂Mg in Toluene

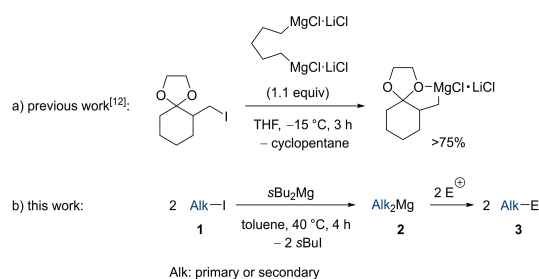
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Abstract: The treatment of primary or secondary alkyl iodides with *s*Bu₂Mg in toluene (25–40 °C, 2–4 h) provided dialkylmagnesiums that underwent various reactions with aldehydes, ketones, acid chlorides or allylic bromides. 3-Substituted secondary cyclohexyl iodides led to all-*cis*-3-cyclohexylmagnesium reagents under these exchange conditions in a highly stereoconvergent manner. Enantiomerically enriched 3-silyloxy-substituted secondary alkyl iodides gave after an exchange reaction with *s*Bu₂Mg stereodefined dialkylmagnesiums that after quenching with various electrophiles furnished various 1,3-stereodefined products including homo-aldol products (99% dr and 98% *ee*). Mechanistic studies confirmed a radical pathway for these new iodine/magnesium-exchange reactions.

Organomagnesium reagents are indispensable organometallic reagents with numerous synthetic applications.^[1] They combine the inherent high reactivity of the carbon-magnesium bond with a good functional group tolerance^[2] and an excellent compatibility with Lewis acid catalysts.^[3] Magnesium organometallics are prepared by a direct insertion of magnesium turnings into organic halides^[1] or by a directed magnesiation of aromatic and heterocyclic derivatives^[4] triggered by magnesium bases such as TMPMgCl·LiCl^[5] or TMP₂Mg·2LiCl^[6] (TMP = 2,2,6,6-tetramethylpiperidyl). Recently, *s*Bu₂Mg in toluene was used for directed magnesiations^[7] allowing the preparation of various diaryl- and diheteroaryl-magnesium reagents in toluene, an industrially friendly solvent.^[8] A further preparation of organomagnesium reagents involves a halogen/magnesium exchange of aryl iodides or bromides.^[9] In contrast to the insertion of magnesium turnings, this reaction is of high industrial relevance and more practical for many synthetic applications due to its homogeneous nature. *i*PrMgCl·LiCl^[10] or *s*Bu₂Mg·2LiOR^[11] are highly efficient

exchange reagents broadly used for the preparation of unsaturated aryl-, heteroaryl- and alkenylmagnesium reagents. However, the preparation of alkylmagnesium derivatives using an I/Mg-exchange is scarcely described in literature and suffers from a highly narrow substrate scope limited to primary alkyl iodides bearing a remote oxygen-coordinating group on the alkyl iodide (Scheme 1a).^[12] A more general protocol for preparing alkylmagnesium reagents was therefore highly desirable. Herein, we wish to report a *s*Bu₂Mg mediated I/Mg-exchange reaction of various primary or secondary alkyl iodides of type **1** in toluene providing dialkylmagnesiums of type **2** under mild reaction conditions. Trapping with various electrophiles (E⁺) provided a range of polyfunctional products of type **3** (Scheme 1). Furthermore, we have found that this new exchange reaction proceeded via a radical mechanism.^[13] Applied to secondary alkyl iodides, the new method allowed the stereoconvergent preparation of diastereomerically and enantiomerically enriched secondary dialkylmagnesiums.

Thus, in preliminary experiments, we have examined the reaction of octyl iodide (**1a**) with *i*PrMgCl·LiCl in THF and have obtained mostly the corresponding substitution product (2-methyldecane in 71% yield) with little amount of desired Oct₂Mg **2a** (<5%).^[14] Quenching **2a** with allyl bromide in the presence of 5 mol% CuCN·2LiCl^[15] furnished 1-undecene (**3a**) which yield was easily determined by GC-analysis. Furthermore, switching from THF to toluene as solvent provided **2a** in 21% GC-yield.^[14] These results led us to look for alternative exchange reagents and we found that *s*Bu₂Mg gave the best results.^[14] *s*Bu₂Mg was conveniently prepared by treating *s*BuMgCl with *s*BuLi in a cyclohexane:ether mixture. Evaporation of the solvent and replacement with toluene produced 0.43–0.48 M homogeneous solutions of *s*Bu₂Mg.^[7a] Furthermore, variation of the



Scheme 1. Preparation of dialkylmagnesium reagents **2** from primary or secondary alkyl iodides **1** via an I/Mg-exchange in toluene using *s*Bu₂Mg leading after quenching reactions with electrophiles to products of type **3**.

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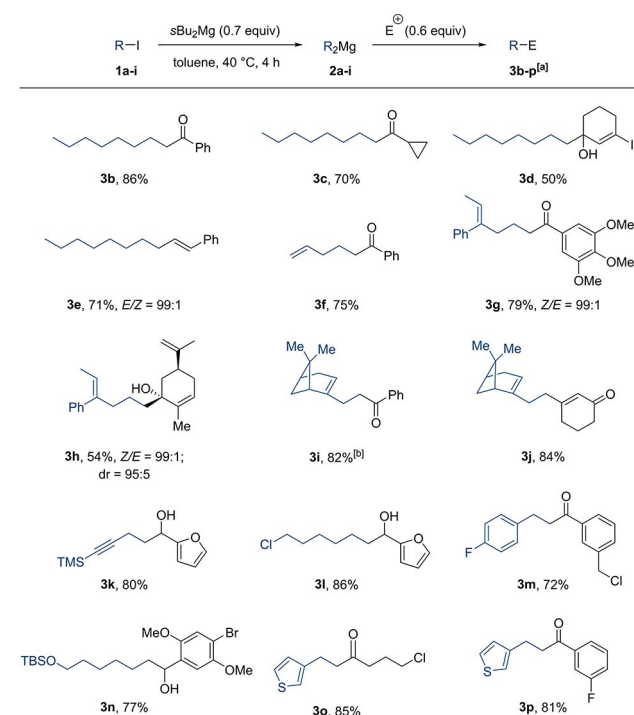
solvent at 25 °C showed that running the reaction in pure toluene without any coordinating co-solvent led to superior yields of **3a** (entries 1–3 of Table 1).^[16] Performing the reaction at 40 °C further increased the yield of **3a** to 65 % (entry 4). By using 0.7 equiv. of the exchange reagent *s*Bu₂Mg, **3a** was formed in 81 % yield (entry 5).

With these optimized results in hand, we treated magnesium reagent **2a** with various electrophiles and investigated the reaction scope (Scheme 2). Thus, acylation of the copper derivative of **2a** obtained by adding CuCN·2LiCl (as 1 M solution in THF; 1 equiv)^[15] and further reaction with benzoyl chloride or cyclopropanecarbonyl chloride (0.6 equiv, –40 °C, 3 h) furnished the corresponding ketones **3b–c** in 70–86 % isolated yield. Addition

Table 1: Optimization of the reaction of octyl iodide (**1a**) with *s*Bu₂Mg leading after allylation to undecene (**3a**).

| Entry | Equiv of <i>s</i> Bu ₂ Mg | Solvent | T [°C] | Yield of 3a [%] ^[a] |
|-------|--------------------------------------|-------------------|--------|---------------------------------------|
| 1 | 0.6 | THF | 25 | 3 |
| 2 | 0.6 | Bu ₂ O | 25 | traces |
| 3 | 0.6 | toluene | 25 | 55 |
| 4 | 0.6 | toluene | 40 | 65 |
| 5 | 0.7 | toluene | 40 | 81 |

[a] All reactions were performed on a 0.5 mmol scale. Yields were determined by GC-analysis using undecane as internal standard.



[a] Isolated yield of analytically pure products. [b] This experiment was performed on 5 mmol scale.

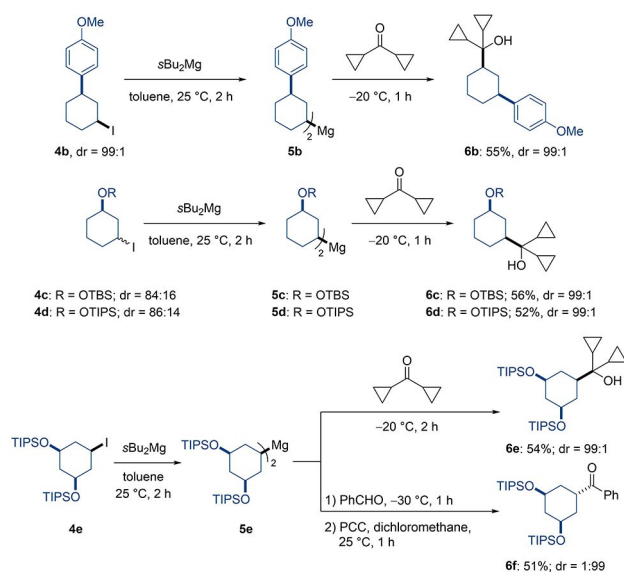
Scheme 2. Preparation of various primary dialkylmagnesiums (**2a–2i**) from the corresponding iodides (**1a–1i**)^[14] using *s*Bu₂Mg in toluene and quenching with various electrophiles leading to products **3b–3p**.

of **2a** to 3-iodo-2-cyclohexanone (0.6 equiv, 0 °C, 1 h) provided the tertiary alcohol **3d** in 50 % yield. Fe-catalyzed cross-coupling (5 % Fe(acac)₃, 20 % TMEDA)^[17] with (*E*)-3-styryl bromide (0.6 equiv, 0 °C, 0.5 h) gave (*E*)-1-phenyl-1-undecene (**3e**) in 71 % yield (*E:Z* = 99:1). Unsaturated 1-iodo-4-pentene (**1b**) gave after I/Mg-exchange di(4-pentenyl)magnesium (**2b**). After transmetalation with CuCN·2LiCl and reaction with benzoyl chloride, ketone **3f** was obtained in 75 % yield. (*Z*)-4-Phenyl-4-hexenyl iodide (**1c**)^[18] reacted similarly and the corresponding dialkylmagnesium **2c** was benzoylated with 3,4,5-trimethoxybenzoyl chloride (–40 °C, 3 h) giving the ketone **3g** (*Z:E* = 99:1) in 79 % yield. A diastereoselective addition of **2c** to (*S*)-carvone in toluene gave the tertiary alcohol **3h** in 54 % yield (*Z:E* = 99:1; *dr* = 95:5).^[19] The terpenic iodide derived from (*R*)-nopol (**1d**) gave the expected diorganomagnesium species **2d** which after a Cu-transmetalation underwent a smooth acylation with benzoyl chloride as well as an addition-elimination with 3-iodo-2-cyclohexen-1-one^[20] leading to the corresponding ketones **3i–j** in 82–84 % yield. Homopropargylic iodide **1e**^[14] and the chloro-substituted iodide **1f** were selectively converted with *s*Bu₂Mg under the standard conditions to the dialkylmagnesiums **2e** and **2f** which afforded after addition of furfural the corresponding alcohols **3k** and **3l** in 80–86 % yield. 2-(4-Fluorophenyl)ethyl iodide (**1g**)^[14] furnished after I/Mg-exchange, transmetalation with CuCN·2LiCl and acylation with 3-(chloromethyl)benzoyl chloride ketone **3m** in 72 % yield. Silyl-substituted iodides such as 6-*tert*-butyldimethylsilyloxycyclohexane (**1h**)^[14] gave after I/Mg-exchange the corresponding dialkylmagnesium **2h** which was added to a functionalized benzaldehyde leading to alcohol **3n** in 77 % yield. Heterocyclic iodides such as 3-(2-iodoethyl)thiophene (**1i**)^[14] underwent cleanly the I/Mg-exchange with *s*Bu₂Mg and after transmetalation and acylation with 4-chlorobutyryl chloride or 3-fluorobenzoyl chloride gave the ketones **3o–p** in 81–85 % yield.

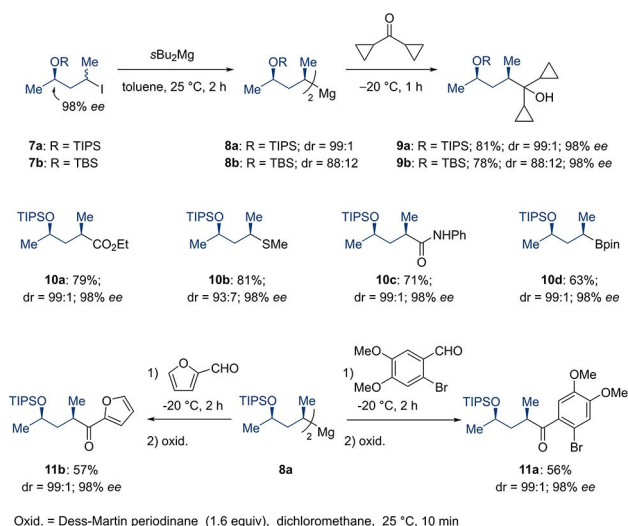
Then we turned our attention to secondary alkyl iodides and chose cyclohexyl iodide (**4a**) as a model substrate.^[14] We have found again that the best exchange was obtained at 25 °C in toluene using *s*Bu₂Mg (0.6 equiv) affording dicyclohexylmagnesium (**5a**) after only 2 h reaction time in 42 % GC-yield. In contrast to primary alkyl iodides, no heating was required. Quenching with allyl bromide gave 2-propenyl cyclohexane **6a** in 48 % isolated yield.^[14] Although a higher conversion could not be reached, these promising results led us to examine some substituted iodocyclohexane derivatives such as **4b–4e**. Although, we realize that this radical reaction may result in an absolute stereochemistry loss of the carbon-iodine bond, a good relative stereoselectivity may still be reached in favourable equilibration processes. Therefore, we have chosen the secondary alkyl iodides **4b–4e** bearing a bulky substituent in position 3.^[21] These cyclohexyl iodides used as *cis-trans* mixtures reacted with *s*Bu₂Mg (0.6 equiv) at 25 °C within 2 h and provided the corresponding dicyclohexylmagnesium species **5b–5e** (optimum conversion of 75 %) tentatively written as *cis*-isomers. Accordingly, quenching reactions of **5b–5e** with dicyclopentyl ketone provided only the diastereomerically pure *cis*-

tertiary alcohols **6b–6e** in 52–56 % yield showing that the exchange reaction proceeded in a stereoconvergent way (Scheme 3). In the case of the TIPSO-substituted dicyclohexylmagnesium **5e**, quenching with benzaldehyde followed by PCC-oxidation (PCC=pyridinium chlorochromate)^[22] led to an epimerization and provided the diastereomerically pure *trans*-ketone **6f** in 51 % yield (dr = 1:99).

With these results in hand, we turned our attention to silylated oxygenated derivatives of commercially available optically enriched (*R,R*)-pentanediol (98 % *ee*).^[23] We anticipated that the presence of a closely located silyl-ether function would improve the conversion of these I/Mg-



Scheme 3. Stereoconvergent I/Mg-exchange on cyclohexyl iodides **4b–4e** leading to dialkylmagnesium reagents **5b–5e** and subsequent addition to dicyclopropyl ketone providing the diastereomerically pure *cis*-alcohols **6b–6e** and the *trans*-ketone **6f**.



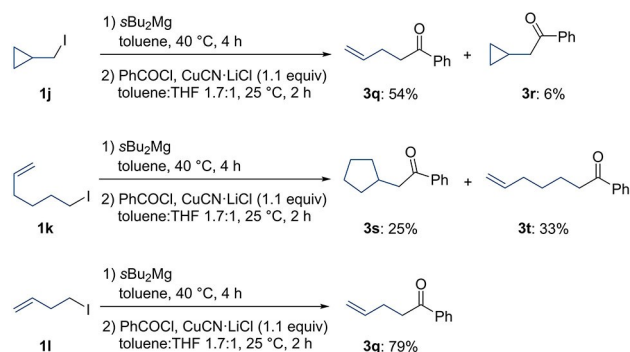
Scheme 4. Preparation of enantiomerically and diastereomerically enriched dialkylmagnesium reagents **8a** and **8b** followed by trapping with various electrophiles.

exchanges. Thus, epimeric mixtures of iodides **7a** or **7b** were submitted to the usual I/Mg-exchange protocol using $s\text{Bu}_2\text{Mg}$ (0.6 equiv) in toluene (25 °C, 2 h). As expected a stereoconvergent I/Mg-exchange^[23] provided diastereomerically enriched Grignard reagents **8a** and **8b** as shown by subsequent quenching reactions with dicyclopropyl ketone affording the tertiary alcohol **9a** (dr = 99:1) and **9b** (dr = 88:12). These results indicated that the stereoconvergence of the formation of Grignard reagent **8** is highest with the TIPS-protected substrate (**7a**). Thus, we have treated **8a** with various electrophiles such as ethyl cyanofornate, *S*-methyl benzenethiosulfonate, phenyl isocyanate and methyl pinacolyl borate leading to the corresponding products **10a–10d** with high enantiomeric and diastereomeric purity (98 % *ee* and dr up to 99:1; Scheme 4).

The relative stereochemistry of products of type **10** was confirmed by treating **10a** with $\text{CF}_3\text{SO}_3\text{H}$ in dichloromethane, 25 °C, 2 h affording the corresponding *trans*-2,4-dimethylbutyrolactone in 79 % yield.^[14,23] Additionally, we have reacted **8a** with 3,4-dimethoxybenzaldehyde or furfural (-20 °C, 2 h) producing intermediate alcohols which were oxidized using the Dess-Martin periodinane^[24] affording the valuable homo-aldol products **11a** and **11b** in 56–57 % overall yields (dr = 99:1; 98 % *ee*).

Preliminary mechanistic studies were undertaken to demonstrate the radical nature of this I/Mg-exchange. Thus, the treatment of radical clock probes^[25] such as alkyl iodides **1j**, **1k** and **1l** provided evidence of a radical pathway, since cyclopropylmethyl iodide **1j** gave, after quenching with PhCOCl , mostly the open-chain product **3q** with less than 10 % of the non-rearranged ketone **3r**. On another hand, treatment of 5-hexenyl iodide (**1k**) under the I/Mg-exchange conditions afforded after benzoylation a significant amount of ring closure product cyclopentylmethyl phenyl ketone (**3s**) as well as open-chain product **3t**. As expected 3-butenyl iodide (**1l**) furnished under the same conditions only the open-chain ketone **3q** in 79 % yield (Scheme 5).

The cyclic iodo-acetal **12**^[26] was subjected to the I/Mg-exchange under various conditions. We have observed the formation of products **13**, **14** and **15** in various proportions,^[14] but could optimize the reaction to produce the cyclic iodide **13** in 67 % yield (dr = 95:5) by using commercial $n\text{Bu}_2\text{Mg}$ or $s\text{Bu}_2\text{Mg}$ in THF in the presence of



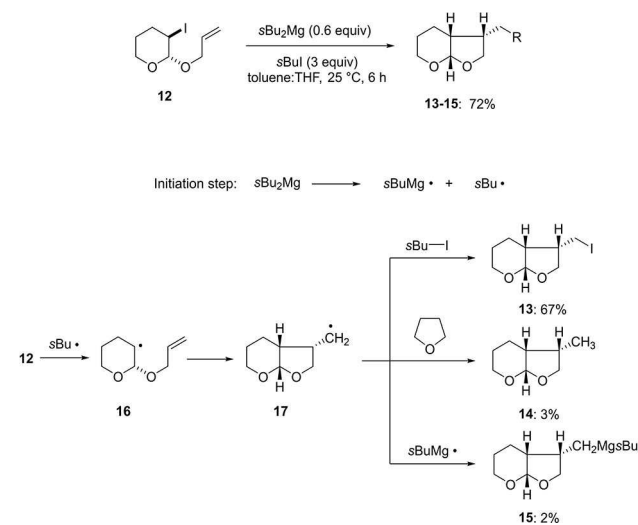
Scheme 5. Radical clock experiments using alkyl iodides **1j**, **1k** and **1l** for I/Mg-exchanges and subsequent benzoylations.

*s*BuI (3 equiv). Interestingly, the addition of styrene inhibited the reaction completely showing the radical character of this reaction.^[14] This cyclization may be rationalized by an atom-transfer mechanism^[27] (Scheme 6). Thus, we assumed that the initiation step was a homolytic cleavage of *s*Bu₂Mg,^[1b] followed by a radical chain reaction induced by a *s*-butyl radical producing the radical **16** from the iodide **12**. After cyclization, the new radical **17** was produced and trapped by *s*BuI affording the major product **13** in 67% yield. Reaction of **17** with THF gave the bicyclic acetal **14**. Recombination of **17** with the *s*BuMg radical will provide **15**, which was detected in 2% yield. These observations supported an atom-transfer mechanism for the I/Mg-exchange.

In conclusion, we have reported a new preparation of various primary dialkylmagnesiums in toluene using *s*Bu₂Mg as an exchange reagent. This exchange reaction allowed the preparation of various primary dialkylmagnesiums in toluene and was extended to several secondary cyclohexyl iodides providing the thermodynamically most favored Grignard reagents. The diastereomeric ratio of these I/Mg-exchanges on secondary iodides could be further improved by using secondary alkyl iodides bearing a TIPSO-group at the 3-position. Thus, chiral secondary dialkylmagnesiums were prepared from 3-substituted silyl enol ethers and gave after various quenching reactions with electrophiles, highly enantiomerically and diastereomerically enriched products (up to dr=99:1 and 98% *ee*). Mechanistic investigations supported an atom-transfer mechanism.

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Scheme 6. Atom-transfer cyclization of **12** triggered by *s*Bu₂Mg providing selectively the bicyclic iodide **13**.

chemicals. We also thank C. Ober and Dr. D. Stephenson for performing NMR experiments. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Atom-Transfer Reaction • Diastereoselectivity • Iodine • Magnesium • Radical Cyclizations

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