Preparation of cyclic alkenylmagnesium reagents *via* an iodine/magnesium exchange†

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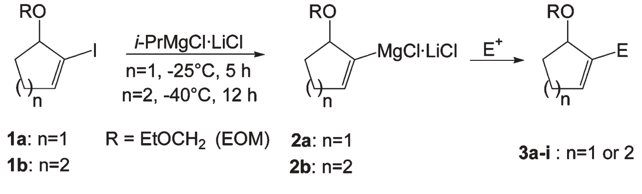
Received (in Cambridge, UK) 8th October 2004, Accepted 8th November 2004
First published as an Advance Article on the web 6th December 2004
DOI: 10.1039/b415588b

The reaction of various cyclic alkenyl iodides with *i*-PrMgCl·LiCl produces the corresponding alkenylmagnesium reagents under mild conditions. After reaction with various electrophiles, like allylic halides, disulfides, aldehydes and acid chlorides, the expected products are obtained in 53–91% yield. Remarkably, the mild conditions of the I/Mg-exchange tolerate the presence of sensitive diene functionalities.

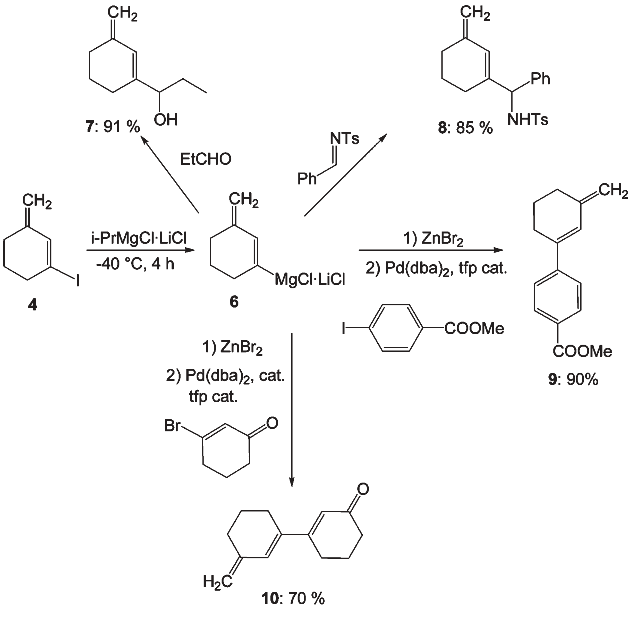
The preparation of functionalized organometallics is an important synthetic task, since these reagents allow the preparation of polyfunctional molecules.[1] In recent years, it was found that the iodine–magnesium exchange reaction[2] is an excellent method for the preparation of various aryl and heteroaryl Grignard reagents.[3] It was found that the rate of the I/Mg-exchange was dependent on the electron-density of the aromatic or the heterocyclic ring. The more electron-poor the ring, the faster was the halogen–magnesium exchange. Interestingly, the I/Mg-exchange of alkenyl iodides was much slower and had to be performed at 25 °C with *i*-Pr$_2$Mg in order to obtain synthetically useful results.[4] Recently, we have found that the rate of the halogen/magnesium exchange can be dramatically increased by using the complex reagent *i*-PrMgCl·LiCl.‡[5] This reagent may be viewed as a magnesiate reagent *i*-PrMgCl$_2^-$Li$^+$ and is therefore much more reactive compared to *i*-PrMgCl.[6] We have demonstrated that chiral 2-iodocycloalkenyl alcohol derivatives of type **1** undergo readily substitution reactions with zinc–copper reagents (if OR is a leaving group) giving chiral cycloalkene derivatives with good to excellent ee.[7] We have now found that *i*-PrMgCl·LiCl reacts at low temperature with **1a** (−25 °C, 5 h) and **1b** (−40 °C, 12 h) leading to the corresponding alkenylmagnesium species **2a** and **2b**. The reaction with various electrophiles (E$^+$) provides the corresponding chiral products **3a–i**§ in good to excellent yield (see Table 1 and Scheme 1).



Scheme 1

Thus, the allylation of **2a** with allyl bromide proceeds readily in the absence of copper additives leading to the protected cyclopentanol **3a** in 91% yield (entry 1 of Table 1). Similarly, the reaction of the cyclohexenol derivative **2b** with allyl bromide furnishes the allylated product **3g** in 81% yield (entry 7). All reactions proceed with complete retention of chirality (proved for allyl cyclohexenol derivative **3g**, ee >98%). Diphenyl disulfide reacts with **2a,b** providing the thioethers **3b** and **3h** in 82 and 80% yield respectively (entries 2 and 8). After the transmetalation with CuCN·2LiCl,[8] the addition–elimination with 3-iodo-2-cyclohexen-1-one leads to the dienone **3c** in 61% yield (entry 3). Aldehydes like benzaldehyde lead to 1,3-diol derivatives such as **3d** (89%) and **3i** (84%) as a mixture of diastereomers (for **3d** and **3i**: dr = 80 : 20). The acylation of the copper derivative of **2a** proceeds in moderate yields affording the unsaturated enone **3e** in 53% yield (entry 5). The opening of *N*-tosylaziridine[9] provides the amino-alcohol derivative **3f** in 63% yield (entry 6).

Interestingly, this approach can be extended to the cyclic *exo*-methylene dienes **4** and **5**.¶ The iododiene **4** is converted smoothly to the corresponding magnesium derivative **6** (−40 °C, 4 h) in high yield. Its reaction with propionaldehyde furnishes the dienic alcohol **7** in 91% yield. The addition to *N*-tosylbenzaldimine gives the diene sulfonamide **8** in 85% yield. After transmetalation with ZnBr$_2$, a Negishi cross-coupling reaction with methyl 4-iodobenzoate or 3-bromocyclohexenone in the presence of Pd(dba)$_2$



Scheme 2

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† Electronic supplementary information (ESI) available: Experimental details and NMR spectra of the compounds. See http://www.rsc.org/suppdata/cc/b4/b415588b/

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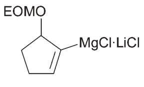
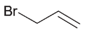
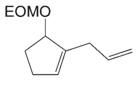
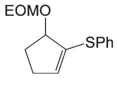
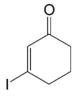
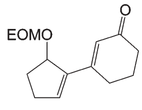
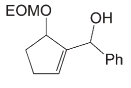
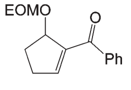
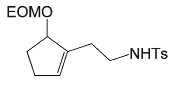
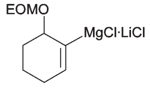
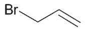
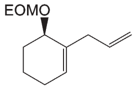
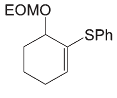
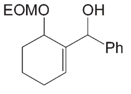
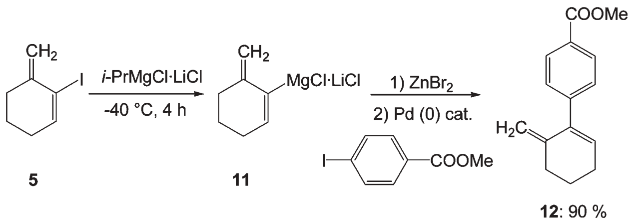
Table 1 2-Magnesiated cycloalkenol derivatives and their reaction with electrophiles

Entry	Grignard reagent	Electrophile	Product of type **3**	Yield (%)[a]
1	 **2a**		 **3a**	91
2	**2a**	PhSSPh	 **3b**	82
3	**2a**		 **3c**	61
4	**2a**	PhCHO	 **3d**	89
5	**2a**	PhCOCl	 **3e**	53
6	**2a**		 **3f**	63
7	 **2b**		 **3g**	81
8	**2b**	PhSSPh	 **3h**	80
9	**2b**	PhCHO	 **3i**	84

[a] Isolated yields of analytically pure products.

(5 mol%), tri(2-furyl)phosphine (tfp, 10 mol%) provides the aryl-substituted diene **9** in 90% yield and the conjugated trienone **10** in 70% yield (Scheme 2).



Scheme 3

A similar behaviour is observed with the diene **5**. Its reaction with *i*-PrMgCl·LiCl (−40 °C, 4 h) provides the corresponding dienic Grignard reagent **11** which undergoes after transmetalation with $ZnBr_2$, a Pd-catalyzed cross-coupling with methyl 4-iodobenzoate leading to the expected product **12** in 90% yield (Scheme 3).

In summary, we have reported that various cyclic alkenyl and dienyl Grignard reagents can be readily prepared *via* an I/Mg-exchange using the new reagent *i*-PrMgCl·LiCl. Further extensions of this method are currently underway in our laboratory.

We thank the Fonds der Chemischen Industrie and for generous financial support. We thank the BASF AG (Ludwigshafen), Wacker-Chemie and Merck (MSD) for the gift of chemicals.

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Notes and references

‡ **Preparation of the reagent *i*-PrMgCl·LiCl:** Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask and THF (25 mL) was added. A solution of *i*-PrCl (100 mmol) in THF (25 mL) was slowly added at rt. The reaction starts within a few minutes. After the addition, the reaction mixture was stirred for 12 h at rt. The grey solution of *i*-PrMgCl·LiCl was transferred via cannula to another flask under Ar and removed in this way from the excess of magnesium. A yield of *ca.* 95–98% of *i*-PrMgCl·LiCl is obtained.

§ **Typical procedure.** Preparation of the allylated product **3a** (entry 1 of Table 1): To a THF solution of the cyclopentenyl iodide (**1a**) (268 mg, 1 mmol in THF (0.3 mL)) was slowly added *i*-PrMgCl·LiCl (0.51 mL, 1.1 mmol, 2.16 M in THF) at −25 °C. After 5 h, a complete conversion to the Grignard reagent (**2a**) was observed as indicated by GC-analysis of hydrolyzed reaction aliquots. Allyl bromide (133 mg, 1.1 mmol, in 1.0 ml of THF) was added and the reaction mixture was warmed to 25 °C and quenched as usual. Purification by flash chromatography (hexane : diethyl ether = 100 : 1) yielded the pure product **3a** (165 mg, 91% yield).

¶ These dienes are readily obtained by the Wittig-olefination of respectively 3-iodo- and 2-iodo-cyclohexenone with CH_2=PPh_3 (rt, 12 h) in variable yields (84% for **4** and 10% for **5**).

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