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Communications

Stereoselective Preparation of Functionalized Alkenylmagnesium Reagents via an Iodine−Magnesium Exchange Reaction

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Organomagnesium reagents are versatile organometallic reagents that have found wide applications.[1] The high reactivity of the carbon−magnesium bond precludes the presence of many functionalities in these organometallics. However, low-temperature Grignard syntheses should allow the generation of polyfunctional organomagnesium reagents since they do not react to a great extent at −78 °C with functional groups such as esters, amides, or nitriles.[2] Unfortunately, the low-temperature insertion of activated magnesium (Rieke-Mg) is inhibited by these functionalities.[3] Recently,[4] we have shown that polyfunctional aryl iodides bearing an ester or nitrile function undergo a low-temperature iodine−magnesium exchange[5] in the presence of i-PrMgBr or i-Pr_2Mg. However, typical alkenyl iodides are inert under these reaction conditions. Herein, we wish to report reaction conditions allowing the stereoselective generation of alkenylmagnesium reagents as well as applications of this exchange reaction in solid-phase synthesis. In strong contrast to functionalized aryl iodides for which the iodine−magnesium exchange was complete using a stoichiometric amount of i-PrMgBr at −20 to −40 °C, alkenyl iodides proved to be far less reactive. No exchange reaction was observed with i-PrMgBr under these conditions. The reaction of (E)-iodooctene (**1a**) with i-Pr_2Mg (1.1 equiv) requires a reaction time of 18 h at 25 °C for complete conversion to the corresponding (E)-octenylmagnesium derivative (**2a**). After treatment with tosyl cyanide (−78 °C, 5 h), the corresponding nitrile **3a** was obtained in 71% isolated yield as only one stereoisomer showing that the iodine−magnesium exchange on alkenyl iodides proceeds with complete retention of configuration of the double bond (Scheme 1 and Table 1). Similarly, the reaction of **2a** with benzaldehyde provides only (E)-1-phenyl-2-nonenol (**3b**; entry 2 of Table 1) in 60% isolated yield. The reaction of a functionalized alkenyl iodide like (E)-5-chloro-1-iodopentene (**1b**) with i-Pr_2Mg is complete after 7 h at 25 °C, furnishing after respective treatment with tosyl cyanide or benzaldehyde the stereochemically pure (E)-products **3c** and **3d** in 72% and 62%

Scheme 1

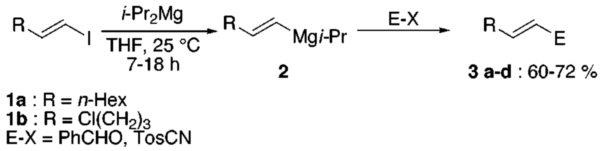
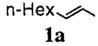
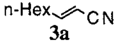
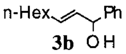
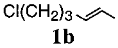
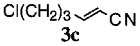
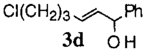
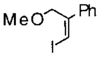
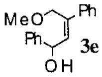
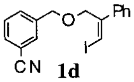
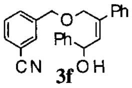
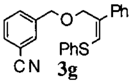
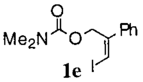
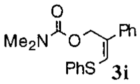
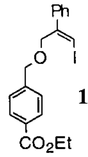
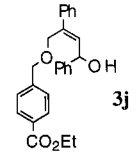
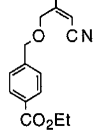


Table 1. Products of Type 3 Obtained after Quenching Functionalized Alkenylmagnesium of Type 2 Prepared via an Iodine−Magnesium Exchange of the Iodoalkenes of Type 1 with i-PrMgBr or i-Pr_2Mg

entry	alkenyl iodide of type **1**	(°C, h)[a]	E-X[b]	product of type **3**	yield (%)[c]
1	 **1a**	25,18	A	 **3a**	71
2	**1a**	25,18	B	 **3b**	60
3	 **1b**	25,7	A	 **3c**	72
4	**1b**	25,7	A	 **3d**	62
5	 **1c**	-70,12	B	 **3e**	95
6	 **1d**	-70,12	B	 **3f**	81
7	**1d**	-70,12	C	 **3g**	79
8	**1d**	-70,12	A	 **3h**	91
9	 **1e**	-70,12	C	 **3i**	64
10	 **1f**	-70,12	B	 **3j**	79
11	**1f**	-70,12	A	 **3k**	87

[a] Reaction conditions for the iodine−magnesium exchange reaction with i-PrMgBr or i-Pr_2Mg. [b] Key: (A) tosyl cyanide; (B) benzaldehyde; (C) diphenyl disulfide. [c] Isolated yields of analytically pure product showing a stereomeric purity of the double bond >99%.

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[‡] Ecole Supérieure de Chimie Organique et Minérale.

[1] (a) Silverman, G. S.; Rakita, P. E., Eds. *Handbook of Grignard-Reagents*; Marcel Dekker: **1996**. For recent applications, see: (b) Klos, A. M.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758. (c) Taber, D. F.; Green, J. H.; Geremia, J. M. *J. Org. Chem.* **1997**, *62*, 9342. (d) Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63. (e) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205. (f) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.

[2] Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109.

[3] Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.

[4] Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.

[5] For a few examples of halogen−magnesium exchange reactions: (a) Villieras, J. *Bull. Soc. Chim. Fr.* **1967**, 1520. (b) Paradies, H. H.; Görbing, M. *Angew. Chem.* **1969**, *81*, 293; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 279. (c) Smith, C. F.; Moore, G. J.; Tamborski, C. *J. Organomet Chem.* **1971**, *33*, C21. (d) Cahiez, G.; Bernard, D.; Normant, J. F. *J. Organomet. Chem.* **1976**, *113*, 107. (e) Seyferth, D.; Lambert, R. L. *J. Organomet. Chem.* **1973**, *54*, 1234. (f) Redwane, N.; Moreau, P.; Commeyras, A. *J. Fluorine Chem.* **1982**, *20*, 699. (g) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845. (h) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407. (i) Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, *38*, 7349.

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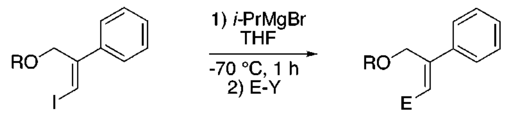
Scheme 2



1c-f **3e-k** : 64-97 %

R = Me, 3-cyanobenzyl, N,N-dimethylcarbamoyl, 4-carbethoxybenzyl
E-Y = PhCHO, TosCN, $(PhS)_2$

isolated yields (>99% *E*). The presence of an oxygen-functionalized directing group[6] should facilitate the iodine–magnesium exchange. Therefore, we have examined the reaction of polyfunctional 3-iodoallylic ethers such as **1c**–**f** (Scheme 2 and Table 1). The readily available (*Z*)-3-iodoallylic ether[7] **1c** was treated at −70 °C with *i*-PrMgBr for 12 h leading to a quantitative iodine–magnesium exchange reaction. The resulting alkenylmagnesium derivative was quenched with benzaldehyde, affording the expected (*Z*)-unsaturated alcohol **3e** (95% yield; >99% *Z*). Remarkably, the related iodoallylic ethers **1d** and **1f** bearing a functional group like a cyanide or ethyl ester and the iodoallylic carbamate **1e** undergo a clean formation of the corresponding polyfunctional alkenylmagnesium reagents. After being quenched with electrophiles such as benzaldehyde, diphenyl disulfide, or tosyl cyanide, the desired products **3f**–**k** were obtained in 64–91% yield (>99% *Z*)[8] (see Table 1). The iodine–magnesium exchange also opens the way for the preparation of alkenylmagnesium reagents for solid-phase synthesis.[9] Thus, the treatment of the resin-attached (*Z*)-alkenyl iodides **1g** and **1h** with *i*-PrMgBr (10 equiv) in a 40:1 THF/NMP mixture at −40 °C for 1 h followed by the addition of benzaldehyde (ca. 15 equiv) furnished after cleavage from the resin (1:9 TFA/CH_2Cl_2, rt, 15 min) the 2,5-dihydrofuranes **3l** and **3m** with 98 and 97% purity (Scheme 3).[10] In the absence of NMP, a reaction time of 2.5 days was required to complete the exchange reaction for **1g** and 4 h for **1h**.[11]

Scheme 3

1g : R = H
1h : R = Br

3l : R = H : 98 % purity
3m : R = Br : 97 % purity

In summary, we have shown that highly functionalized alkenylmagnesium halides can be prepared at low temperature via an iodine–magnesium exchange performed with *i*-PrMgBr or *i*-Pr_2Mg. Under these conditions, functional groups such as a cyanide, a carbamate, or even an ethyl ester are tolerated, and reactions with electrophilic functionalities such as an aldehyde, tosyl cyanide, or diphenyl disulfide proceed in good yields.[12] This method is also suitable for solid-phase organic synthesis and should find applications in combinatorial chemistry.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (SFB 260, Leibniz program), the BMBF program (03 D 0056 2), and BASF AG for generous support.

Supporting Information Available: Characterization data of compounds **3a**–**m**.

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[6] Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

[7] Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.

[8] The retention of the double bond is proven by the iodinolysis of the alkenylmagnesium reagent derived from the iodoallylic ether **1c**, which gave exclusively the starting material back (>99% *Z*).

[9] (a) Balkenhohl, F.; v. d. Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.* **1996**, *108*, 2437; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (b) Früchtel, J. S.; Jung, G. *Angew. Chem.* **1996**, *108*, 19; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

[10] HPLC-purity (UV, 254 nm, RP 18, CH_3CN/H_2O (0.1% TFA) gradient 5–100% CH_3CN). Chemical yield 85% based on loading of the resin.

[11] For theoretical studies on the origin of solvent acceleration in metal–halogen exchange reactions: Jedlicka, B.; Crabtree, R. H.; Siegbahn, P. E. M. *Organometallics* **1997**, *16*, 6021.

[12] Typical Procedure for the Preparation of a Polyfunctional Alkenylmagnesium Intermediate and Its Reaction with Benzaldehyde. Preparation of (*Z*)-4-(4-carbethoxybenzyloxy)-1,3-diphenyl-2-butenol (**3j**). To a stirred solution of (*Z*)-3(4-carbethoxybenzyloxy)-2-phenyl-1-iodopropene (**1f**; 700 mg, 1.66 mmol) in THF (4 mL) was added a solution of *i*-PrMgBr in THF (3.90 mL, 3.32 mmol; 0.85 M) at −85 °C. The reaction mixture was allowed to warm to −70 °C and was stirred overnight. Benzaldehyde (0.48 mL, 4.65 mmol) was added in THF (1.5 mL), and the reaction mixture was worked up after 4 h at −50 °C. The crude product obtained after evaporation of the solvent was purified by flash chromatography (CH_2Cl_2/ether 95:5), affording **3j** (528 mg, 79% yield) as a colorless oil.