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Magnesiated Unsaturated Silylated Cyanohydrins as Synthetic Equivalents of Aromatic and Heterocyclic Grignard Reagents Bearing a Ketone or an Aldehyde

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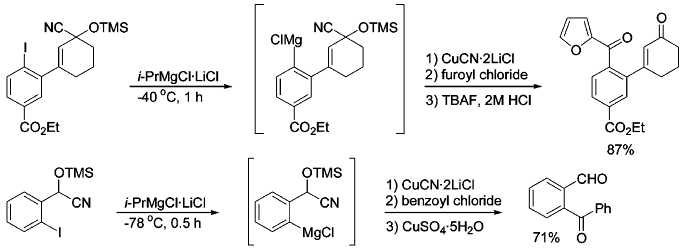
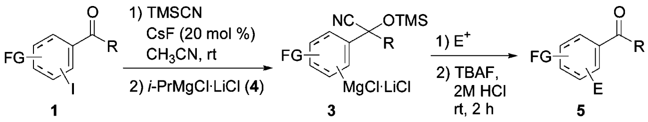
ABSTRACT



The preparation of iodo-substituted aryl, heteroaryl, or cycloalkenyl ketones as silylated cyanohydrins allows the smooth performance of an I/Mg-exchange using *i*-PrMgCl·LiCl. A facile deprotection of the resulting functionalized products obtained by a reaction with electrophiles (acid chlorides, allylic bromide, benzylidene-*p*-toluenesulfonamide, and 3-iodocyclohexenone) produces polyfunctional ketones in good overall yields. This sequence can be extended to aromatic iodoaldehydes. In these cases, the deprotection of the silylated cyanohydrin functionality is best performed with aqueous $CuSO_4$ under basic conditions.

The preparation of Grignard reagents bearing functional groups has become very convenient by the use of the mixed magnesium−lithium complex *i*-PrMgCl·LiCl, which undergoes rapidly a Br/Mg exchange on numerous unsaturated bromides.[1] The preparation of aromatic organomagnesium reagents bearing a reactive functionality such as a ketone[2] or an aldehyde is rather difficult to achieve in the absence of a protecting group.[3] As potential protecting group for iodoketones of type **1**, we envisioned using silylated cyanohydrins[4] of type **2**, which are available by a CsF-catalyzed silylcyanation with trimethylsilyl cyanide (Scheme 1 and Table 1).

Scheme 1. General Reaction Sequence



Herein, we wish to report that the conversion of the silylated cyanohydrins **2** to the corresponding Grignard reagent **3** proceeds well by using the powerful exchange reagent *i*-PrMgCl·LiCl (**4**).[1]

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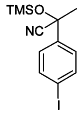
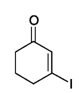
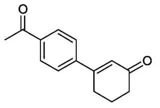
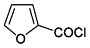
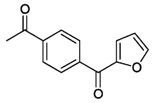
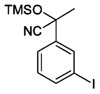
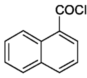
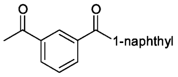
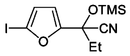
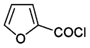
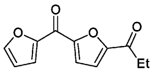
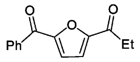
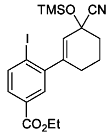
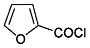
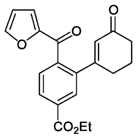
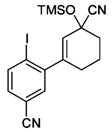
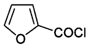
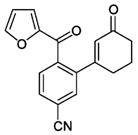
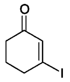
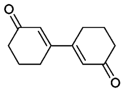
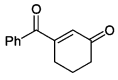
[1] (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215. (c) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288. (d) Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2005**, 543. (e) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (f) Kopp, F.; Sklute, G.; Polborn, K.; Marek, J.; Knochel, P. *Org. Lett.* **2005**, *7*, 3789.

[2] Kneisel, F. F.; Knochel, P. *Synlett* **2002**, 179.

[3] *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley & Sons, Inc.: New York, 1999; pp 293−369.

10.1021/ol052792d CCC: $33.50

Table 1. Polyfunctional Ketones Obtained by the Reaction of the Silylated Cyanohydrins **2** with *i*-PrMgCl·LiCl, Leading to Functionalized Gignard Reagents **3**, Followed by Transmetalation with CuCN·2LiCl and Reaction with an Electrophile and Deprotection

entry	silylated cyanohydrins	T, t (°C, h)[a]	electrophiles	product of type **5**	yield (%)[b]
1	 **2a**	-20, 1		 **5a**	83
2	**2a**	-20, 1		 **5b**	85
3	 **2b**	-20, 1		 **5c**	72
4	 **2c**	-40, 1		 **5d**	71
5	**2c**	-40, 1	PhCOCl	 **5e**	72
6	 **2d**	-40, 1		 **5f**	87
7	 **2e**	-40, 1		 **5g**	81
8	 **2f**	-40, 2		 **5h**	76
9	**2f**	-40, 2	PhCOCl	 **5i**	71

[a] Reaction conditions for performing the I/Mg exchange. [b] Overall yield (being from the cyanohydrin) after reaction with an electrophile and deprotection.

A direct reaction of **3** with various electrophiles (E$^+$) or in the presence of CuCN·2LiCl[5] provides a range of silylated cyanohydrins that are readily converted to the polyfunctional ketones of type **5** in good yields (Scheme 1 and Table 1). Thus, the silylated cyanohydrins were readily prepared by using TMSCN (1.2 equiv) and CsF (20 mol %) in CH$_3$CN (room temperature, 2 h), starting from the corresponding ketones.[4]

The reaction of the silylated cyanohydrins **2a** with *i*-PrMgCl·LiCl (**4**; −20 °C, 1 h) provides the intermediate arylmagnesium reagent **3a**, which is stable at low temperature.[6] Its transmetalation with CuCN·2LiCl allows a smooth cross-coupling with 3-iodocyclohexenone, leading to the diketone **5a** in 83% yield (entry 1). The removal of the transient silylated cyanohydrin is carried out by adding TBAF (1.5 equiv, 1 M solution in THF). After 0.5 h, a 2 M HCl solution is added, and the reaction mixture is stirred for 2 h. Alternatively, the Grignard reagent **3a** reacts after transmetalation with CuCN·2LiCl with furoyl chloride, furnishing the diketone **3b** in 85% yield (entry 2). The same behavior is observed with the silylated cyanohydrin **2b** derived from 3-iodoacetophenone. After a copper-mediated acylation with 1-naphthoyl chloride, the expected diketone **5c** is isolated after deprotection in 72% yield (entry 3). Heterocyclic ketones can be used as well. Thus, the resulting silylated cyanohydrin **2c** is converted at −40 °C to the corresponding heteroarylmagnesium derivative **3c**. Acylation with various acid chlorides furnishes the diketones **5e,f** in 71−72% yield (entries 4 and 5). Unsaturated 3-iodocyclohexenones can be readily converted to the expected silylated cyanohydrins **2d,e** in almost quantitative yield. Their reactions with *i*-PrMgCl·LiCl (**4**) in THF at −40 °C for 1 h produce the Grignard reagents **3d,e** in high yields. Copper(I)-catalyzed acylation with furoyl chloride affords after standard deprotection (TBAF, 2 M HCl) the unsaturated diketones **5g** and **5h** in 81−87% yield (entries 6 and 7). A similar reactivity pattern is observed with the silylated cyanohydrin **2f** that reacts with 3-iodocyclohexenone or PhCOCl, leading to diketones **5i,j** in 71−76% yield (entries 8 and 9).

Interestingly, the silylated cyanohydrin **2e** reacts after magnesiation with PhCOCl, leading to the ketone **6**, which after Wittig olefination and deprotection furnishes dienic ketone **7** in 83% yield. The treatment of the functionalized diene **7** with BF$_3$·OEt$_2$ (5 equiv; 0 to 40 °C, 7 h) triggers an intramolecular Michael addition, providing the annelated spiroketone **8** in 83% yield (Scheme 2).[7]

Starting from the silylated cyanohydrin **2d**, we performed after magnesiation a Negishi cross-coupling with methyl 2-iodoacrylate. The usual deprotection led to the dienic ketone **9** in 81% yield. A solution of **9** in mesitylene was heated (220 °C, 72 h) and underwent an electrocyclic ring closing followed by a double bond isomerization, affording the tricyclic ketone **10** in 85% yield (Scheme 3).

The use of silylated cyanohydrins as protecting group can be also successfully applied to aldehydes. Thus, the magnesiation of the silylated cyanohydrins **11a,b** occurs rapidly with *i*-PrMgCl·LiCl (**4**) at −78 °C (0.5 h). In the presence

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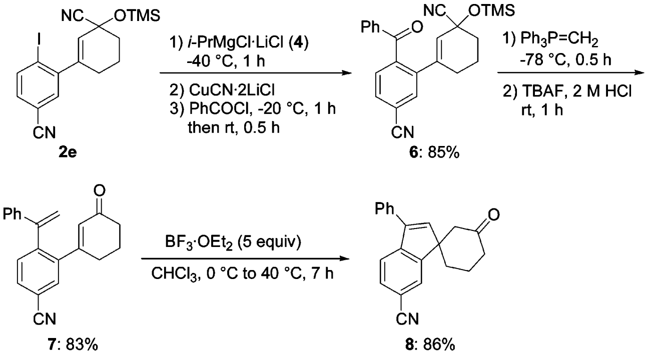
(4) (a) Kim, S. S.; Rajagopal, G.; Song, D. H. *J. Organomet. Chem.* **2004**, *689*, 1734. (b) North, M. *Synlett* **1993**, 807. (c) Deng, H.; Ister, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3333. (d) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (e) Hayashi, M.; Miyamoto, Y.; Inoue, S.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515. (f) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537. (g) Hanashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805. (h) Tian, S. K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900.

(5) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(6) (a) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Org. Lett.* **2002**, *4*, 659. (b) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Org. Lett.* **2002**, *4*, 2493.

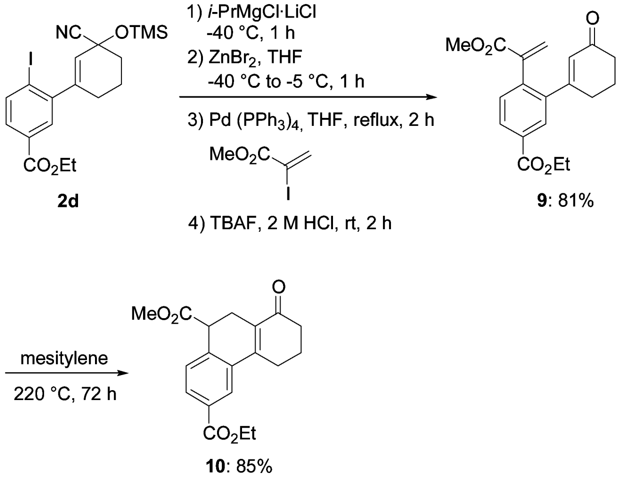
(7) Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055.

Scheme 2. Synthesis of Annelated Spiroketone **8**



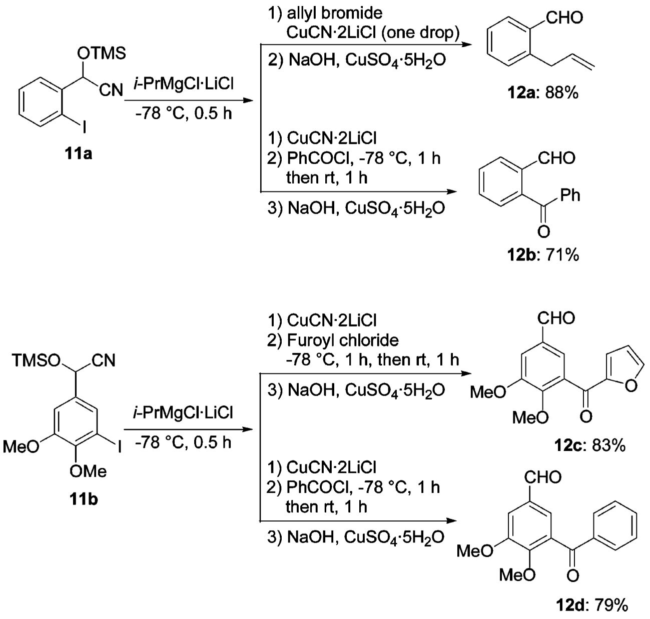
of CuCN•2LiCl, allylations and acylations proceed smoothly. We have found that the deprotection of the resulting silylated cyanohydrins is best performed with $CuSO_4$•$5H_2O$ (1 equiv) and 1 M NaOH (room temperature, 2 h), leading to the desired aldehydes **12a−d** in 71−88% yield (Scheme 4).

Scheme 3. Electrocyclic Ring Closing of **9**



In summary, we have prepared polyfunctionalized aryl-, heteroaryl-, and cycloalkenyl-magnesium derivatives bearing silylated cyanohydrins as masked ketones and aldehydes. These functionalized Grignard reagents react with a range of electrophiles in satisfactory yields, leading to polyfunctional ketones and aldehydes after simple deprotection procedures. The use of the powerful I/Mg exchange reagent *i*-PrMgCl•LiCl (**4**)[1,8] allows generation of the intermediate Grignard reagents bearing silylated cyanohydrins under very mild conditions. Extensions of this methodology are currently underway in our laboratories.

Scheme 4. Preparation of Functionalized Aldehydes via Magnesiated Silylated Cyanohydrins Derived from Aldehydes



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Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) *i*-PrMgCl•LiCl is commercially available from Chemetall GmbH, Frankfurt, Germany.

(9) **Typical Procedure 1. Preparation of Diketone 5f.** To a solution of **2d** (217 mg, 0.46 mmol) in THF (0.35 mL) was slowly added *i*-PrMgCl•LiCl (0.26 mL, 0.51 mmol, 2.0 M in THF) at −40 °C. The reaction mixture was stirred at −40 °C for 1 h. A complete conversion to the Grignard reagent was observed as indicated by GC analysis of hydrolyzed reaction aliquots. CuCN•2LiCl (0.45 mmol, 0.45 mL, 1.0 M in THF) was added dropwise at −40 °C, and then the reaction mixture was slowly warmed to −30 °C over 40 min. Furoyl chloride (92 mg, 0.70 mmol) in THF (0.10 mL) was added, and the mixture was stirred at −30 °C for 1 h, then warmed to room temperature, and stirred again for 1 h. TBAF (0.7 mL, 1.0 M in THF) was added. After 30 min, HCl (0.45 mL, 2.0 M) was added, and the reaction mixture was stirred for 2 h before the addition of aqueous NH_3 (2 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (pentane/ether = 2:3) yielded the pure product **5f** (135 mg, 87%) as a yellow solid, mp 79.8−80.4 °C.

(10) **Typical Procedure 2. Preparation of 12c.** A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of **11b** (196 mg, 0.5 mmol) in dry THF (0.5 mL). *i*-PrMgCl•LiCl (2.0 M in THF, 0.55 mmol) was added slowly at −78 °C, and the resulting reaction mixture was stirred at this temperature for 0.5 h. A complete conversion to the Grignard reagent was observed as indicated by GC analysis of hydrolyzed reaction aliquots. THF (1.0 mL) and the solution of CuCN•2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added, and the reaction mixture was stirred at −78 °C for 1 h, then warmed to room temperature and stirred for 1 h before it was quenched with aqueous ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The organic fractions were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The concentrated organic fraction is dissolved in ethanol (2 mL). An aqueous solution of NaOH (1 M, 1 mL) and $CuSO_4$•$5H_2O$ (0.5 mmol, 125 mg) were added to the ethanolic solution, and the reaction mixture was stirred at room temperature for 2 h. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The organic fractions were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (eluent, pentane/ether = 3:1) yielded the pure product **12c** (108 mg, 83%) as a solid, mp 103.6−104.0 °C.