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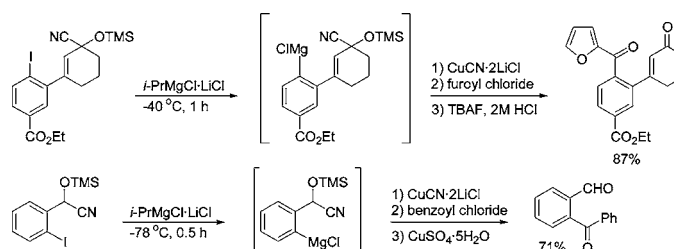
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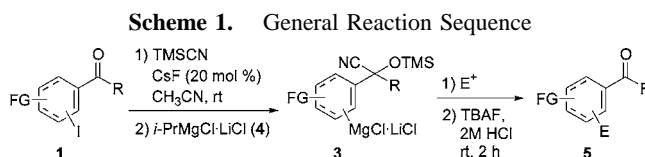
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ABSTRACT

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 cyano-

hydrins[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]

(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.

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_3CN (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]
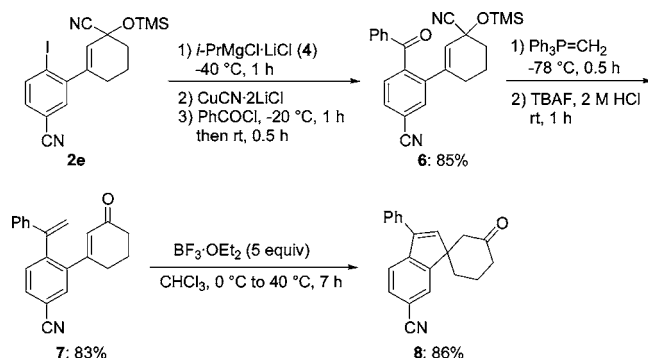
Starting from the silylated cyanohydrin **2d**, we performed after magnesiation a Negishi cross-coupling with methyl 2-iodoacrylate. The usual deprotection led to the dienic ketone **9** in 81% yield. A solution of **9** in mesitylene was heated (220 °C, 72 h) and underwent an electrocyclic ring closing 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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(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.
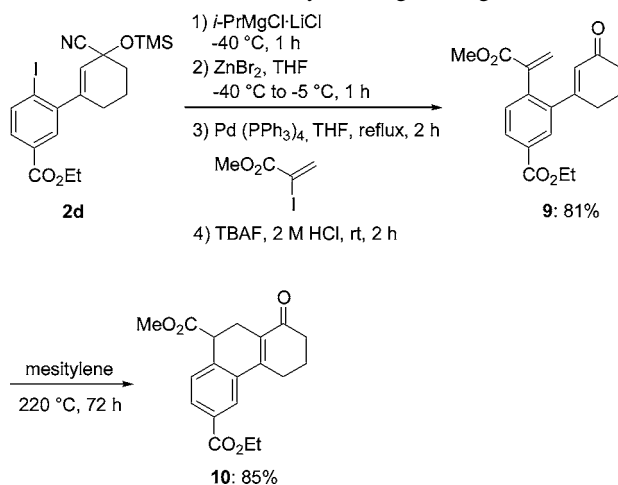
(7) Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055.

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

1) *i*-PrMgCl·LiCl (**4**)
-40 °C, 1 h
2) CuCN·2LiCl
3) PhCOCl, -20 °C, 1 h
then rt, 0.5 h

2e → **6**: 85%

1) Ph₃P=CH₂
-78 °C, 0.5 h
2) TBAF, 2 M HCl
rt, 1 h

BF₃·OEt₂ (5 equiv)
CHCl₃, 0 °C to 40 °C, 7 h

7: 83% → **8**: 86%

of CuCN·2LiCl, allylations and acylations proceed smoothly. We have found that the deprotection of the resulting silylated cyanohydrins is best performed with $CuSO_4 \cdot 5H_2O$ (1 equiv)

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

1) *i*-PrMgCl·LiCl
-40 °C, 1 h
2) ZnBr₂, THF
-40 °C to -5 °C, 1 h
3) Pd (PPh₃)₄, THF, reflux, 2 h

MeO₂C

4) TBAF, 2 M HCl, rt, 2 h

2d → **9**: 81%
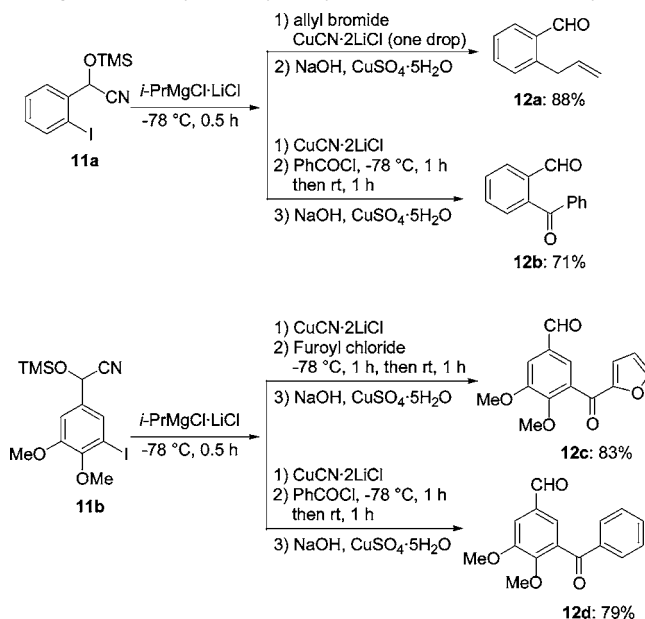
mesitylene
220 °C, 72 h

10: 85%

and 1 M NaOH (room temperature, 2 h), leading to the desired aldehydes **12a−d** in 71−88% yield (Scheme 4).

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

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

1) allyl bromide
CuCN·2LiCl (one drop)
2) NaOH, CuSO₄·5H₂O

12a: 88%

1) CuCN·2LiCl
2) PhCOCl, -78 °C, 1 h
then rt, 1 h
3) NaOH, CuSO₄·5H₂O

12b: 71%

11a
i-PrMgCl·LiCl
-78 °C, 0.5 h

1) CuCN·2LiCl
2) Furoyl chloride
-78 °C, 1 h, then rt, 1 h
3) NaOH, CuSO₄·5H₂O

12c: 83%

1) CuCN·2LiCl
2) PhCOCl, -78 °C, 1 h
then rt, 1 h
3) NaOH, CuSO₄·5H₂O

12d: 79%

11b
i-PrMgCl·LiCl
-78 °C, 0.5 h

Grignard reagents bearing silylated cyanohydrins under very mild conditions. Extensions of this methodology are currently underway in our laboratories.

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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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 NH₃ (2 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), 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 (Na₂SO₄), and concentrated in vacuo. The concentrated organic fraction is dissolved in ethanol (2 mL). An aqueous solution of NaOH (1 M, 1 mL) and CuSO₄·5H₂O (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 (Na₂SO₄), 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.

(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