$LaCl_3$·2LiCl-Catalyzed Addition of Grignard Reagents to Ketones

Albrecht Metzger, Andrei Gavryushin, Paul Knochel*

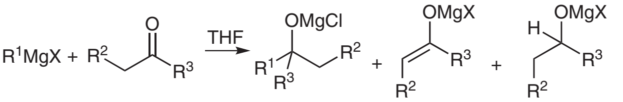
Department Chemie und Biochemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 München, Germany
Fax +49(89)218077680; E-mail: Paul.Knochel@cup.uni-muenchen.de

Received 18 February 2009

Abstract: The addition of Grignard reagents to ketones using substoichiometric amounts of $LaCl_3$·2LiCl was studied. Catalytic amounts of $LaCl_3$·2LiCl (30 mol%) provide, in most cases, yields similar to those obtained using a stoichiometric amount.

Key words: 1,2-addition, lanthanides, Grignard reagents, functionalized organometallics, lanthanum trichloride

The addition of Grignard reagents **1** to ketones **2** leading to tertiary alcohols of type **3** is a standard transformation in organic synthesis (Scheme 1).[1]

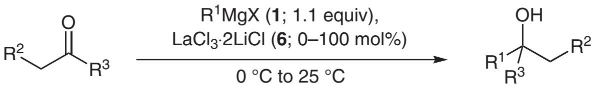


1 **2** **3** **4** **5**

Scheme 1 Possible products of the reaction of a Grignard reagent with a ketone

Such 1,2-addition is often complicated if sterically hindered or unreactive Grignard reagents are used. In these cases, several side reactions such as enolization (leading to **4**) or β-hydride transfer (leading to secondary alcohols **5**) are observed. The formation of byproducts **4** and **5** can be considerably reduced by using a Lewis acid activation of the ketone **2**. Lanthanide halides such as $CeCl_3$ introduced by Imamoto have proven to be especially effective.[2] However, the low solubility of $CeCl_3$ in THF requires the use of a stoichiometric amount of these relatively expensive salts.

Recently, we have reported the preparation of THF-soluble $LaCl_3$·2LiCl complex (**6**, 0.52–0.6 M in THF)[3] which has been found highly efficient for improving of the addition of various Grignard reagents to ketones and imines.[4] This method was later applied for the synthesis of tryptamines.[5] However, $LaCl_3$·2LiCl (**6**) has been used so far only in stoichiometric amounts, while a catalytic version of this reaction should also be possible.[6] Herein, we report the comparative study of the stoichiometric and catalytic 1,2-addition reaction of various Grignard reagents[7] to ketones using 30 mol% of $LaCl_3$·2LiCl (**6**) (Scheme 2 and Table 1).



2 **3**

Scheme 2 Reaction of Grignard reagents with ketones mediated by $LaCl_3$·2LiCl (**6**)

Thus, the reaction of cyclohexylmagnesium bromide (**1a**) with the readily enolizable ketone **2a** in the presence of one equivalent of $LaCl_3$·2LiCl (**6**) provided the tertiary alcohol **3a** in 93% yield (entry 1 of Table 1). By using 30 mol% of $LaCl_3$·2LiCl (**6**) a similar yield (87%) was achieved. Without the addition of $LaCl_3$·2LiCl (**6**) only 33% of the alcohol **3a** was isolated.

The reaction of the secondary alkylmagnesium reagent (*i*-PrMgCl; **1b**) with 1,3-diphenylacetone (**2b**) was strongly influenced by the addition of $LaCl_3$·2LiCl (**6**). Thus, the alcohol **3b** was obtained in 86% with stoichiometric amount of **6** and in 65% yield in the presence of 30 mol% of **6** (entry 2). In the absence of $LaCl_3$·2LiCl (**6**), only traces of the alcohol **3b** were obtained due to the occurrence of competing reduction and enolization reactions. With MeMgCl (**1c**) which does not possess β-hydrogen atoms, similar yields were obtained regardless of the amount of lanthanum salts added (entry 3). Reaction of phenylmagnesium chloride (**1d**) with enolizable ketone **2b** led to the desired alcohol **3d** in 93–97% yield in the presence of either 30 mol% or 100 mol% of $LaCl_3$·2LiCl (**6**; entry 4). Without $LaCl_3$·2LiCl (**6**), a yield of 67% was achieved. In the reaction of naphthylmagnesium chloride (**1e**) with less sterically hindered cyclohexyl methyl ketone (**2d**), the influence of $LaCl_3$·2LiCl (**6**) was relatively strong (entry 5). The uncatalyzed reaction afforded the product in 22% yield; in the presence of 30 mol% of $LaCl_3$·2LiCl (**6**) a yield of 66% was obtained. Using stoichiometric amounts of $LaCl_3$·2LiCl (**6**) led to the product **3e** in 76% yield. In the absence of a catalyst, sterically hindered Grignard reagents did not react satisfactorily with ketones bearing acidic protons. Thus, reaction of 2-(trifluoromethyl)phenylmagnesium chloride (**1f**) and acetophenone (**2e**) furnished the corresponding alcohol **3f** in 72% yield only in the presence of $LaCl_3$·2LiCl (**6**), regardless of whether 100 mol% or 30 mol% were used (entry 6). A poor yield of **3f** (13%) was observed in the absence of $LaCl_3$·2LiCl (**6**). Treatment of dicyclopropyl ketone (**2f**), cyclopropyl methyl ketone (**2g**) and cyclohexane (**2h**) with various organomagnesium reagents **1g**–**i** led to the desired alcohols **3g**–**i** in similar yields almost independent of the

SYNLETT 2009, No. 9, pp 1433–1436
Advanced online publication: 18.05.2009
DOI: 10.1055/s-0029-1217169; Art ID: G07109ST

$LaCl_3·2LiCl$ (**6**) amount (entries 7–9). However, the positive influence of $LaCl_3·2LiCl$ (**6**) was well demonstrated in the case of heteroaromatic organomagnesium compounds such as the thiophenylmagnesium reagent **1j** and especially 2-pyridylmagnesium chloride (**1k**; entries 10 and 11). Reaction with ketones **2d** and **2a** led to the desired alcohols **3j** and **3k** in 71–86% yield only in the presence of $LaCl_3·2LiCl$ (**6**). Using electron-rich arylmagnesium reagents **1e** and **1l** and enolizable ketones **2i** and **2j** the alcohols **3l** and **3m** (entries 12 and 13) were obtained in lower yields with $LaCl_3·2LiCl$ (**6**) than without the use of **6**. These results show that for the addition of electron-rich organomagnesium species the influence of $LaCl_3·2LiCl$ (**6**) on the product yield can be negative.

Table 1 Reaction of Grignard Reagents of Type **1** with Different Ketones of Type **2** in the Presence of $LaCl_3·2LiCl$ (**6**)[8,9]

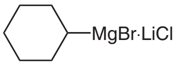
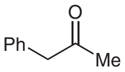
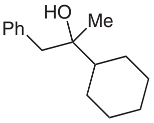
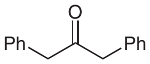
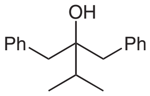
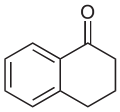
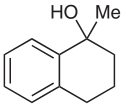
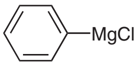
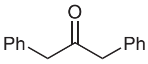
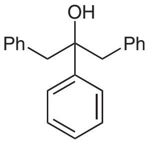
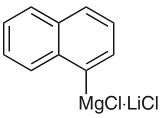
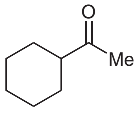
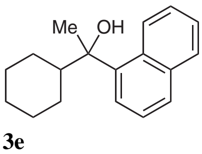
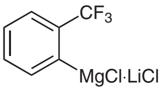
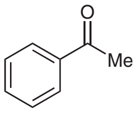
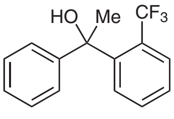
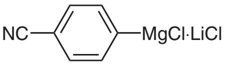
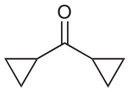
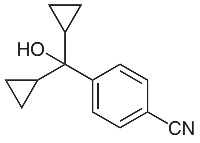
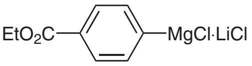
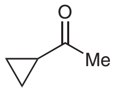
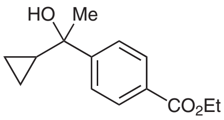
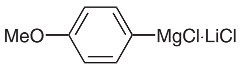
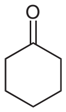
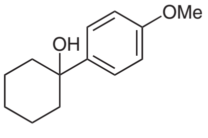
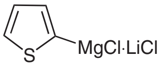
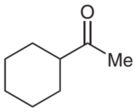
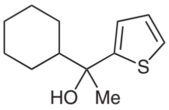
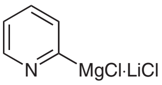
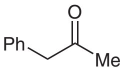
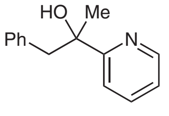
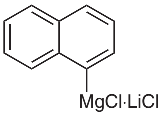
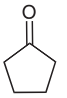
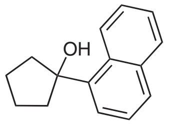
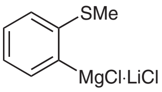
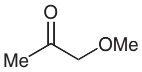
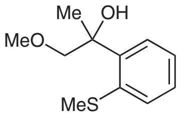
Entry	Grignard reagent of type **1**	Ketone of type **2**	Product of type **3**	Yield (%)[a] [$LaCl_3·2LiCl$ (**6**; 100 mol%)]	Yield (%)[a] [$LaCl_3·2LiCl$ (**6**; 30 mol%)]	Yield (%)[a] [$LaCl_3·2LiCl$ (**6**; 0 mol%)]
1	 **1a**[c]	 **2a**	 **3a**	93	87	33[b]
2	*i*-PrMgCl **1b**[d]	 **2b**	 **3b**	86	65	<3
3	MeMgCl **1c**[d]	 **2c**	 **3c**	95	94	69
4	 **1d**[d]	 **2b**	 **3d**	97	93	67[b]
5	 **1e**[e]	 **2d**	 **3e**	76	66	22
6	 **1f**[e]	 **2e**	 **3f**	72	72	13
7	 **1g**[e]	 **2f**	 **3g**	77	84	87
8	 **1h**[e]	 **2g**	 **3h**	76	83	81

Table 1 Reaction of Grignard Reagents of Type **1** with Different Ketones of Type **2** in the Presence of LaCl$_3$·2LiCl (**6**)[8,9] (continued)

Entry	Grignard reagent of type **1**	Ketone of type **2**	Product of type **3**	Yield (%)[a] [LaCl$_3$·2LiCl (**6**; 100 mol%)]	Yield (%)[a] [LaCl$_3$·2LiCl (**6**; 30 mol%)]	Yield (%)[a] [LaCl$_3$·2LiCl (**6**; 0 mol%)]
9	 **1i**[e]	 **2h**	 **3i**	73	74	84
10	 **1j**[e]	 **2d**	 **3j**	54	86	65
11	 **1k**[e]	 **2a**	 **3k**	71	67	22
12	 **1e**[e]	 **2i**	 **3l**	59	65	75
13	 **1l**[e]	 **2j**	 **3m**	55	62	70

[a] Isolated yields.

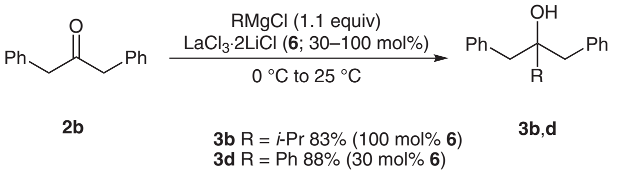
[b] Yields determined by ^{1}H NMR.

[c] Grignard reagent prepared by direct magnesium insertion in the presence of LiCl according to ref. 7a.

[d] Grignard reagent is commercially available by Chemetall GmbH (Frankfurt).

[e] Grignard reagent prepared by halogen–magnesium exchange reaction using *i*-PrMgCl·LiCl according to ref. 7b.

An upscaling of the above described procedure gave satisfactory results (Scheme 3). Reaction of ketone **2b** either with secondary alkylmagnesium reagent **1b** in the presence of LaCl$_3$·2LiCl (**6**; 100 mol%) or with arylmagnesium reagent **1d** in the presence of LaCl$_3$·2LiCl (**6**; 30 mol%) furnished the expected alcohols **3b** and **3d** in 83–88% yield.



Scheme 3 Upscaled reaction (20 mmol) of ketone **2b** with either *i*-PrMgCl (**2b**) using 100 mol% of **6** or PhMgCl (**3d**) using 30 mol% of **6**.

In conclusion, we have shown that it is possible to perform the addition of alkyl-, aryl- and heteroarylmagnesium reagents to various ketones in satisfactory yields using catalytic amount of LaCl$_3$·2LiCl (**6**). Further studies to improve the scope of this catalytic activation of ketones with LaCl$_3$·2LiCl (**6**) is underway in our laboratory.

Acknowledgment

We thank the Fonds der Chemischen Industrie, and the DFG for financial support. We thank Chemetall GmbH (Frankfurt) for the generous gift of Grignard reagents and LaCl$_3$·2LiCl solution.

References and Notes

(1) For recent reviews, see: (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (b) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727.
(2) (a) Imamoto, T.; Sugiyura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747. (c) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568. (d) Wang, Q.; Chen, C. *Org. Lett.* **2008**, *10*, 1223.
(3) LaCl$_3$·2LiCl solution in THF is commercially available from Chemetall GmbH, Frankfurt (Germany).
(4) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
(5) Nicolaou, K. C.; Krasovskiy, A.; Trepanier, V. E.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2008**, *47*, 4217.

(6) The addition of Grignard reagents to imines requires only 10 mol% of $LaCl_3 \cdot 2LiCl$(**6**). An isolated example of the addition of PhMgBr to camphor using 10 mol% of $LaCl_3 \cdot 2LiCl$ has also been reported (ref. 4).

(7) (a) For the preparation of Grignard reagents via direct magnesium insertion into aromatic halides in the presence of LiCl, see: Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. (b) For the preparation of Grignard reagents via halogen–magnesium exchange reaction, see: Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.

(8) **Typical Procedure 1 [30 mol% $LaCl_3 \cdot 2LiCl$ (6)]; Preparation of 1-Phenyl-1-[2-(trifluoromethyl)-phenyl]ethanol (3f)**: In a flame-dried flask, flushed with argon, acetophenone (**2e**; 240 mg, 2.00 mmol) was added followed by $LaCl_3 \cdot 2LiCl$ (**6**; 1.15 mL, c = 0.52 M in THF, 30 mol%) and the mixture was stirred for 1 h. Then, THF (2.5 mL) was added. Into another flame-dried and argon-flushed flask 2-(trifluoromethyl)bromobenzene (495 mg, 2.20 mmol) was added followed by *i*-PrMgCl·LiCl (1.32 mL, c = 1.64 M in THF, 2.16 mmol). After GC analysis of a hydrolyzed aliquot showed full conversion, the resulting aromatic Grignard reagent **1f** was added to the ketone at 0 °C. The reaction mixture was stirred at this temperature until full conversion was achieved. Then, sat. NH_4Cl solution (50 mL) was added and the layers were separated followed by extraction using Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane–Et_2O = 7:1 + 1.0 vol% Et_3N) furnished the alcohol **3f** as a pale yellow liquid (381 mg, 72%). ^{1}H NMR (600 MHz, $C_4D_{10}O$): δ = 7.80 (d, J = 7.6 Hz, 1 H), 7.69 (d, J = 7.6 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.35 (t, J = 7.6 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 2 H), 7.18 (t, J = 7.6 Hz, 2 H), 7.11 (t, J = 7.4 Hz, 1 H), 4.31 (s, 1 H), 1.93 (s, 3 H). ^{13}C NMR (150 MHz, $C_4D_{10}O$): δ = 149.9 (q, $^5J_{CF}$ = 1.6 Hz), 148.4 (q, $^3J_{CF}$ = 1.4 Hz), 131.6 (q, $^4J_{CF}$ = 1.1 Hz), 129.9, 129.5 (q, $^2J_{CF}$ = 31.6 Hz), 128.8 (q, $^3J_{CF}$ = 6.7 Hz), 128.4, 127.7, 127.1, 126.5 (q, $^4J_{CF}$ = 0.8 Hz), 125.4, (q, $^1J_{CF}$ = 273.4 Hz), 76.7, 33.0 (q, $^5J_{CF}$ = 1.7 Hz). MS (70 eV, EI): m/z (%) = 266 (2) [M$^+$], 251 (100), 231 (61), 211 (29), 183 (6), 169 (5), 121 (5). HRMS (EI): m/z calcd for $C_{15}H_{13}F_3O$: 266.0918; found: 266.0905. IR (ATR): 3463 (vw), 2983 (vw), 1602 (w), 1494 (w), 1446 (m), 1304 (vs), 1271 (s), 1164 (s), 1122 (vs), 1095 (s), 1032 (vs), 928 (m), 910 (m), 765 (vs), 754 (s), 698 (vs) cm^{-1}.

(9) **Typical Procedure 2 [100 mol% $LaCl_3 \cdot 2LiCl$ (6)]: Preparation of 1-Methyl-1,2,3,4-tetrahydronaphthalen-1-ol (3c)**: In a flame-dried flask, flushed with argon, α-tetralone (**2c**; 292 mg, 2.00 mmol) was added followed by $LaCl_3 \cdot 2LiCl$ (**6**; 3.85 mL, c = 0.52 M in THF, 100 mol%) and the reaction mixture was stirred for 1 h. Then, MeMgCl (**1c**; 0.74 mL, c = 2.99 M in THF, 2.20 mmol) was added at 0 °C. The ice-bath was removed. After GC analysis of a hydrolyzed aliquot showed full conversion sat. NH_4Cl solution (50 mL) was added and the layers were separated followed by extraction using Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (pentane–Et_2O = 9:1 + 1.0 vol% Et_3N) furnished the alcohol **3c** as a white solid (307 mg, 95%); mp 92–94 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.52–7.58 (m, 1 H), 7.04–7.11 (m, 1 H), 6.98–7.04 (m, 1 H), 6.84–6.90 (m, 1 H), 2.39–2.60 (m, 2 H), 1.42–1.70 (m, 5 H), 1.39 (s, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 143.7, 136.2, 128.8, 127.1, 126.9, 126.5, 70.2, 40.0, 31.1, 30.2, 20.7. MS (70 eV, EI): m/z (%) = 162 (1) [M$^+$], 147 (100), 129 (56), 119 (17), 91 (32), 84 (34), 44 (6). HRMS (EI): m/z calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1040. IR (ATR): 3313 (m), 2969 (w), 2933 (m), 2865 (w), 1487 (m), 1440 (m), 1366 (m), 1337 (m), 1284 (m), 1230 (w), 1184 (m), 1152 (m), 1103 (s), 1066 (m), 1048 (m), 990 (m), 949 (m), 930 (s), 854 (m), 761 (vs), 728 (s), 686 (s) cm^{-1}.