

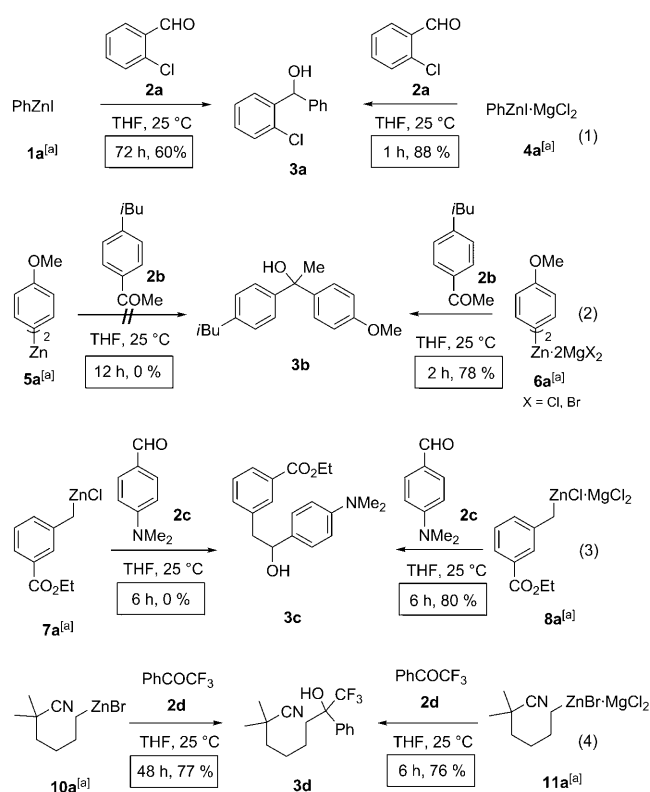
MgCl₂-Accelerated Addition of Functionalized Organozinc Reagents to Aldehydes, Ketones, and Carbon Dioxide**

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Organozinc compounds are important organometallic reagents for organic synthesis, since they tolerate a broad range of functional groups.^[1] Their intrinsic moderate reactivity towards electrophiles can be dramatically increased by transmetalation with catalytic amounts of various transition-metal complexes of Pd,^[2] Ni,^[3] Cu,^[4] Fe,^[5] Co,^[6] and other metal salts.^[7] However, such transmetalations are less appropriate for reactions with ketones or aldehydes. In these cases, Lewis acid complexation^[8] of the carbonyl group is usually a more suitable means of activation.^[9] Herein, we report a practical and highly effective MgCl₂-accelerated addition of various organozinc reagents to aldehydes and ketones as well as to CO₂ under mild conditions.^[10]

The addition of PhZnI (**1a**), which was prepared by the insertion of zinc into the C–I bond of iodobenzene in the presence of LiCl,^[11] to 2-chlorobenzaldehyde (**2a**) required 72 h at 25 °C to reach completion and afforded (2-chlorophenyl)(phenyl)methanol (**3a**) in 60% yield. In contrast, by using PhZnI·MgCl₂ (**4a**), which was prepared by the reaction of iodobenzene with magnesium turnings, ZnCl₂, and LiCl,^[12] complete conversion was reached within 1 h at 25 °C, and the desired alcohol **3a** was obtained in 88% yield [Eq. (1), Scheme 1; see also entries 1–3 in Table 1].^[13] The presence of MgCl₂ (1.0 equiv) is responsible for this dramatic rate acceleration.

Diorganozinc compounds are more reactive than organozinc halides,^[1,14] and thus these reagents are particularly well suited for addition reactions to ketones. The reaction of bis(4-methoxyphenyl)zinc (**5a**), prepared from 4-bromoanisole (*n*BuLi, –78 °C, 2 h; then ZnCl₂ (0.5 equiv)), to 4-isobutylacetophenone (**2b**) did not proceed (25 °C, 12 h). However, the corresponding diarylzinc reagent **6a**^[15] containing MgX₂ (X: Cl, Br; 2.0 equiv) underwent smooth addition to the ketone **2b** within 2 h at 25 °C, and both aryl groups were transferred to the ketone [Eq. (2), Scheme 1; see also entries 4–10 in Table 1]. Functionalized benzylic zinc reagents show the same



Scheme 1. Reactivity of organozinc reagents **1**, **5**, **7**, **10** (without MgCl₂) and **4**, **6**, **8**, **11** (with MgCl₂) with aldehydes and ketones. [a] Complexed LiCl has been omitted for clarity.

behavior, and the addition of the ester-substituted benzylic zinc reagent **7a**, prepared by zinc insertion in the presence of LiCl,^[16] to the aldehyde **2c** did not proceed at 25 °C. Heating the reaction mixture at 50 °C for 14 h led to a conversion of only 60%. In strong contrast, the same zinc reagent complexed with MgCl₂ (**8a**), which was prepared by the reaction of (3-ethoxycarbonyl)benzyl chloride with magnesium turnings in the presence of ZnCl₂ and LiCl,^[17] gave full conversion within 6 h at 25 °C, and the secondary alcohol **3c** was isolated in 80% yield [Eq. (3), Scheme 1; see also entries 1–5 in Table 2].

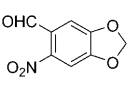
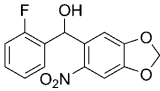
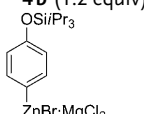
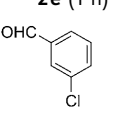
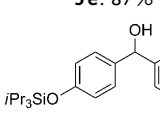
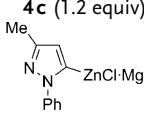
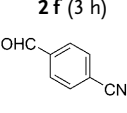
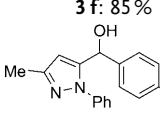
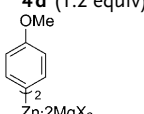
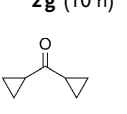
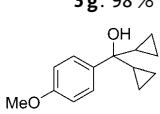
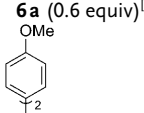
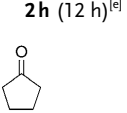
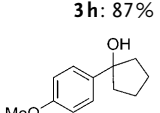
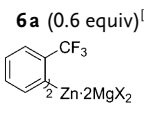
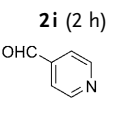
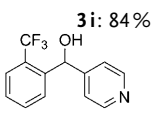
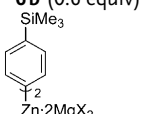
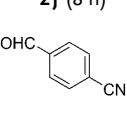
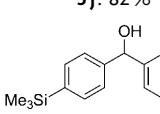
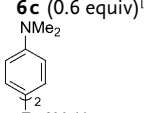
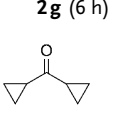
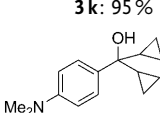
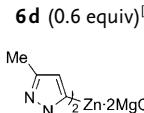
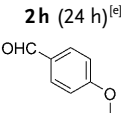
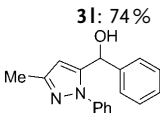
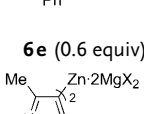
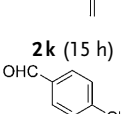
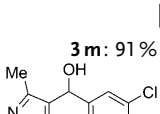
Dibenzylzinc reagents (ArCH₂)₂Zn·2MgCl₂ **9** can also be prepared and used for efficient addition reactions (see also entry 6 in Table 2). Finally, the functionalized alkylzinc reagent **10a** (no MgCl₂ present) and **11a** (complexed with MgCl₂) show a similar difference in reactivity. Thus, the reaction of **10a** with trifluoromethyl phenyl ketone (**2d**) required 48 h at 25 °C, whereas when **11a** was used, complete conversion was reached within 6 h at 25 °C leading to the

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Table 1: Addition of aryl- and heteroarylzinc reagents **4** and **6** complexed with MgCl_2 to aldehydes and ketones.

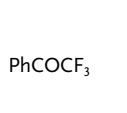
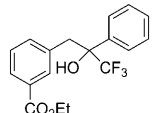
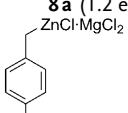
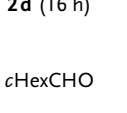
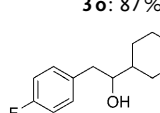
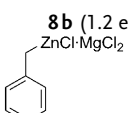
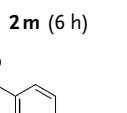
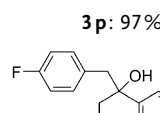
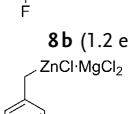
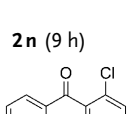
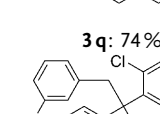
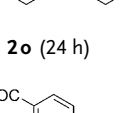
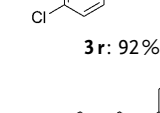
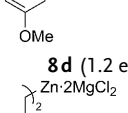
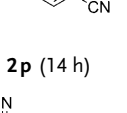
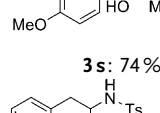
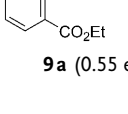
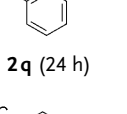
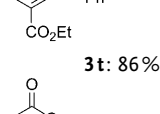
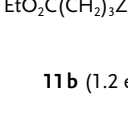
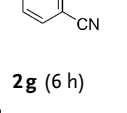
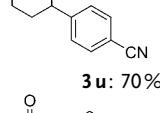
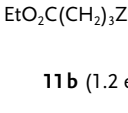
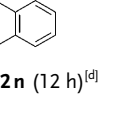
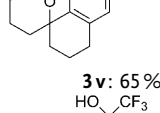
Entry	Arylzinc reagent ^[a]	Electrophile (<i>t</i>) ^[b]	Product ^[c]
1	 4b (1.2 equiv)	 2e (1 h)	 3e : 87 %
2	 4c (1.2 equiv)	 2f (3 h)	 3f : 85 %
3	 4d (1.2 equiv)	 2g (10 h)	 3g : 98 %
4	 6a (0.6 equiv) ^[d]	 2h (12 h) ^[e]	 3h : 87 %
5	 6a (0.6 equiv) ^[d]	 2i (2 h)	 3i : 84 %
6	 6b (0.6 equiv) ^[d]	 2j (8 h)	 3j : 82 %
7	 6c (0.6 equiv) ^[d]	 2g (6 h)	 3k : 95 %
8	 6d (0.6 equiv) ^[d]	 2h (24 h) ^[e]	 3l : 74 %
9	 6e (0.6 equiv)	 2k (15 h)	 3m : 91 %
10	 6f (0.6 equiv) ^[d]	 2l (24 h)	 3n : 83 %

[a] Complexed LiCl has been omitted for clarity. [b] 1.0 equiv of electrophile was used. All reactions were performed at 25 °C unless otherwise indicated. [c] Yield of isolated, analytically pure product. [d] X = Cl, Br. [e] Reaction performed at 50 °C.

tertiary alcohol **3d** in 76–77% yield [Eq. (4), Scheme 1; see also entries 7–9 in Table 2).

These MgCl_2 -mediated addition reactions have an excellent substrate scope (Tables 1 and 2). Thus, the electron-poor 2-fluorophenylzinc iodide- MgCl_2 (**4b**) added to aldehyde **2e** at 25 °C within 1 h to afford the alcohol **3e** in 87% yield

Table 2: Addition of benzyl- and alkylzinc reagents of **8**, **9**, and **11** complexed with MgCl_2 to aldehydes, aldimines, and ketones.

Entry	Zinc reagent ^[a]	Electrophile (<i>t</i>) ^[b]	Product ^[c]
1	 8a (1.2 equiv)	 2d (16 h)	 3o : 87 %
2	 8b (1.2 equiv)	 2m (6 h)	 3p : 97 %
3	 8b (1.2 equiv)	 2n (9 h)	 3q : 74 %
4	 8c (1.2 equiv)	 2o (24 h)	 3r : 92 %
5	 8d (1.2 equiv)	 2p (14 h)	 3s : 74 %
6	 9a (0.55 equiv)	 2q (24 h)	 3t : 86 %
7	 11b (1.2 equiv)	 2g (6 h)	 3u : 70 %
8	 11b (1.2 equiv)	 2n (12 h) ^[d]	 3v : 65 %
9	 11c (1.2 equiv)	 2d (24 h)	 3w : 60 %

[a] Complexed LiCl has been omitted for clarity. [b] 1.0 equiv of electrophile was used. All reactions were performed at 25 °C unless otherwise indicated. [c] Yield of isolated, analytically pure product. [d] The reaction was performed at 50 °C.

(entry 1 in Table 1). Electron-rich arylzinc reagents such as (4-triisopropoxyphenyl)zinc bromide- MgCl_2 (**4c**) and the 5-pyrazolylzinc chloride **4d** added to benzaldehydes **2fg** to furnish secondary alcohols **3fg** in 85% and 98% yield, respectively (entries 2 and 3 in Table 1).

As indicated above [Eq. (2), Scheme 1], it is advantageous to use diarylzinc compounds **6** ($\text{Ar}_2\text{Zn} \cdot 2\text{MgX}_2 \cdot 2\text{LiCl}$; 0.6 equiv). In these cases, both Ar groups are transferred in the carbonyl addition reaction. Thus, the addition of bis(4-methoxyphenyl)zinc-2 MgX_2 (**6a**) to aliphatic ketones such

dicyclopentyl ketone (**2h**) and cyclopentanone (**2i**) proceeded in 2 h and 12 h, respectively, leading to the alcohols **3h,i** in 84 % and 87 % yield (entries 4 and 5 in Table 1).^[18] Bis(2-trifluoromethylphenyl)zinc-2MgX₂ (**6b**) reacted smoothly with a heterocyclic aldehyde such as **2j** furnishing the pyridyl alcohol **3j** in 82 % yield (entry 6 in Table 1). The electron-rich arylzinc reagent bis(4-trimethylsilylphenyl)-zinc-2MgX₂ (**6c**) added to 4-cyanobenzaldehyde (**2g**) in almost quantitative yield giving the benzhydryl alcohol **3k** (entry 7 in Table 1). Also, bis(4-*N,N*-dimethylaminophenyl)-zinc-2MgX₂ (**6d**) reacted with the ketone **2h** in 24 h leading to the desired product **3l** (74 %; entry 8 in Table 1). The bis(5-pyrazolyl)zinc species^[19] **6e** as well as the bis(1,2-oxazol-4-yl)zinc compound **6f** added to substituted benzaldehydes **2k,l** providing heterocyclic secondary alcohols **3m,n** in 83 % and 91 % yield, respectively (entries 9 and 10 in Table 1).

Benzylic zinc reagents are similarly activated by the presence of MgCl₂. Thus, the ester-substituted benzylic zinc reagent **8a** smoothly added within 16 h to trifluoromethyl phenyl ketone (**2d**) leading to the tertiary alcohol **3o** in 87 % yield (entry 1 in Table 2). Various electron-poor benzylic zinc reagents such as **8b,c** added to cyclohexanecarbaldehyde (**2m**), α -tetralone (**2n**), and benzophenone **2o** providing the products **3p-r** in 74–97 % yield (entries 2–4 in Table 2). 4-Methoxybenzylzinc chloride-MgCl₂ (**8d**) reacted well with 4-acetylbenzonitrile (**2p**) furnishing the benzylic alcohol **3s** in 74 % yield (entry 5 in Table 2).

Instead of benzylic zinc chlorides of type **8** (ArCH₂ZnCl·MgCl₂; 1.2 equiv) it is also beneficial to use dibenzylzinc compounds of type **9** ((ArCH₂)₂Zn·2MgCl₂; 0.6 equiv). Usually both benzylic groups are transferred to the electrophile. Recently, it has been reported by Arrayas, Carretero,^[20a] and Charette^[20b] that both aryl *N*-(2-pyridyl-sulfonyl)aldimines and Cu^{II} catalysis are required for the addition of various zinc reagents. However, the presence of MgCl₂ allows direct addition of organozincs to *N*-tosylimines. Thus, the reaction of the benzylic zinc reagent **9a** with the *N*-tosylimine **2q** afforded the expected *N*-tosylamine derivative **3t** in 86 % yield within 24 h at 25 °C (entry 6 in Table 2).^[20c] As already shown in Equation (4) of Scheme 1, functionalized alkylzinc bromides prepared by the Mg/ZnCl₂/LiCl method^[12] readily add to aldehydes and ketones. Thus, EtO₂C-(CH₂)₃ZnBr·MgCl₂ (**11b**) added to the aldehyde **2g** and α -tetralone (**2n**) in 6 h and 12 h, respectively, leading to the lactones **3u,v** in 65 % and 70 % yield (entries 7 and 8 in Table 2). The related zinc reagent EtO₂C(CH₂)₅ZnBr·MgCl₂ (**11c**) added to the trifluoromethyl ketone **2d** within 24 h at 25 °C leading to the tertiary alcohol **3w** in 60 % yield (entry 9 in Table 2).

Remarkably, the presence of MgCl₂ allows the addition of aryl and benzylic zinc reagents to CO₂ (1 bar) at 25–50 °C in THF without the use of a polar solvent.^[21] It is advantageous to use diorganozinc reagents of type **6** (Ar₂Zn·2MgX₂) and **9** ((ArCH₂)₂Zn·2MgCl₂). With these reagents, both organic groups are transferred to CO₂. Thus, bis(4-methoxyphenyl)-zinc-2MgX₂ (**6a**) added in THF to CO₂ (1 bar, 25 °C, 3 h) providing 4-methoxybenzoic acid (**12a**) in 84 % yield (entry 1 in Table 3).^[22] Similarly, bis(4-trimethylsilylphenyl)-zinc-2MgX₂ (**6c**) was carboxylated within 6 h at 25 °C leading

Table 3: Addition of aryl- and benzylic zinc reagents complexed with MgCl₂ to carbon dioxide.

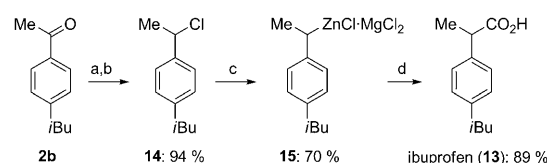
Entry	Zinc reagent ^[a]	Product ^[b,c]
1	(<i>p</i> -MeOC ₆ H ₄) ₂ Zn·2MgX ₂ 6a ^[d]	<i>p</i> -MeOC ₆ H ₄ CO ₂ H 12a : 84 % (25 °C, 3 h)
2	(<i>p</i> -Me ₃ SiC ₆ H ₄) ₂ Zn·2MgX ₂ 6c ^[d]	<i>p</i> -Me ₃ SiC ₆ H ₄ CO ₂ H 12b : 73 % (25 °C, 6 h)
3	(<i>p</i> -MeOC ₆ H ₄ CH ₂) ₂ Zn·2MgCl ₂ 9b	<i>p</i> -MeOC ₆ H ₄ CH ₂ CO ₂ H 12c : 98 % (25 °C, 2 h)
4	(<i>m</i> -CF ₃ C ₆ H ₄ CH ₂) ₂ Zn·2MgCl ₂ 9c	<i>m</i> -CF ₃ C ₆ H ₄ CH ₂ CO ₂ H 12d : 86 % (50 °C, 12 h)
5	(<i>o</i> -FC ₆ H ₄ CH ₂) ₂ Zn·2MgCl ₂ 9d	<i>o</i> -FC ₆ H ₄ CH ₂ CO ₂ H 12e : 98 % (25 °C, 12 h)

[a] Complexed LiCl has been omitted for clarity. [b] Yield of isolated, analytically pure product. [c] The reaction conditions with CO₂ are indicated. [d] X = Cl, Br.

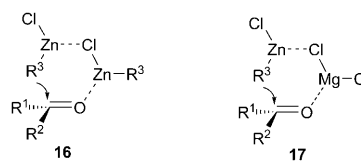
to the benzoic acid **12b** in 73 % yield (entry 2 in Table 3). Dibenzylzinc reagents of type **9** reacted especially well and smoothly provided the corresponding phenylacetic acids **12c–e** in 86–98 % yield (entries 3–5 in Table 3).

Substituted phenylacetic acids often have useful pharmaceutical properties.^[23] As an application of our method, we report a short four-step synthesis of ibuprofen (**13**)^[24] from the commercially available ketone **2b** without transition-metal catalysis and purification steps (Scheme 2). Thus, the reduction of **2b** with NaBH₄ followed by chlorination using thionyl chloride provided the benzylic chloride **14** in 94 % yield over two steps. The corresponding benzylic zinc reagent **15** was readily obtained in 70 % yield. This secondary benzylic zinc halide of type **8** was sufficiently reactive to undergo addition to CO₂ to produce ibuprofen (**13**) in 89 % yield.^[25]

The acceleration effect of MgCl₂ may be rationalized by assuming that the usual six-membered transition-state **16** is modified by the presence of MgCl₂.^[26] Thus, R³ZnCl, which complexes the carbonyl group, is replaced by MgCl₂ (see transition-state **17**; Scheme 3). Since MgCl₂ is a stronger Lewis acid than R³ZnCl, more effective activation of the carbonyl group towards the addition of the zinc reagent is expected. Our results show that the addition of an organo-



Scheme 2. Synthesis of ibuprofen (**13**) by carboxylation of the benzylic-zinc reagent **15**. Reagents and conditions: a) NaBH₄ (1.5 equiv), MeOH, reflux, 2 h; b) SOCl₂ (1.0 equiv), CH₂Cl₂, 25 °C, 12 h; c) Mg turnings (2.5 equiv), LiCl (1.25 equiv), ZnCl₂ (1.1 equiv), THF, 25 °C, 2 h; d) CO₂ (1 bar), THF, 25 °C, 12 h then 50 °C, 12 h.



Scheme 3. Tentative MgCl₂-modified six-membered transition state for the addition of R³ZnCl to a carbonyl substrate R¹R²CO.

metallic reagent to a carbonyl group depends not only on the reactivity of the carbon–metal bond, but also on the Lewis acid activation of this carbonyl group. Both of these effects should be considered for predicting the addition rates of organometallic reagents. Similar synergetic effects have been reported.^[27,28]

In summary, we have shown that the sluggish reactivity of organozinc reagents towards aldehydes, ketones, and CO₂ can be dramatically improved by the addition of MgCl₂ (usually generated during the preparation of the zinc reagents). This practical procedure considerably extends the reactivity scope of organozinc reagents. In particular, the direct reaction with CO₂ allows the expeditious preparation of various phenylacetic acids, as shown in a short synthesis of ibuprofen. Further applications are currently underway in our laboratories.

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