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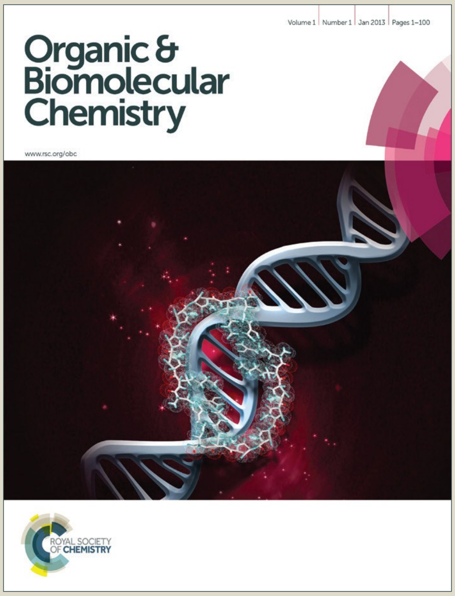

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Magnesium Salt Promoted Tandem Nucleophilic Addition-Oppenauer Oxidation of Aldehydes with Organozinc Reagents

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A magnesium salt promoted synthesis of ketones via tandem nucleophilic addition-Oppenauer oxidation of aldehydes using organozinc chemistry was demonstrated. Magnesium salts concomitantly generated via magnesium metal mediated organohalides zincation exhibit high efficacy for nucleophilic addition of organozinc reagents to aromatic aldehydes and thereafter Oppenauer oxidation whereby ketones were formed in high to excellent yields.

Tandem reaction is widely recognized as a promising protocol for C-C bond formation, functional group implantation and transformation in a one-pot operation.[1] In this respect, strategies involving reactive organometallics are still rare.[2] The nucleophilic addition/Oppenauer oxidation of aldehydes[3] has proven to be a practical and straightforward protocol for ketone synthesis. Among them, the Mg-Oppenauer protocol[3g] provided by Knochel et al. was considered to be the most advantageous as the in situ formed magnesium alkoxides are intrinsically powerful promoters for the forthcoming hydride transference, thus allowing THF, the most commonly used solvent for Grignards albeit a poor solvent for Oppenauer oxidation,[3b-3d] can be directly used without apparent inhibition to hydride transference. Besides, the environmental friendly benzaldehyde instead of carcinogenic chromium salts, enormous reagent excess (MnO_2) or explosively exothemic reagents (oxalyl chlorides/DMSO) was employed as oxidant. However, as we[4] previously mentioned, Grignard reagents should be accurately titrated beforehand and transferred carefully in case over- or less-loading will lead significant side reactions such as Aldol condensation and Tishchenko esterifications.[5] Additionally, routes starting from Grignard reagents demand low reaction temperatures, and sensitive functional groups are still found difficult to be tolerated.[6] To circumvent these problems, we believe that reactive Grignards should be transmetalated to a weaker organometallic reagent or, more directly, use a milder organometallic reagent. In this respect, organozinc reagents arise as an ideal candidate owing to their mild reactivity and wide range of functional groups tolerance.[7] Based on our interests on organozinc reagents,[8] we are interested to employ organozinc reagents as nucleophiles in the nucleophilic addition/Oppenauer oxidation of aldehydes whereby highly functionalized ketones could be expediently produced.

At the beginning, pivaldehyde[9] was selected as the hydride acceptor owing to its low dielectric constant and high oxidation potential (E_0 = 211 mV).[10] Thus, reaction of Et_2Zn **1a** and 4-methoxybenzaldehyde **2a** was first examined to evaluate the efficiency of organozinc reagents (Table 1). Undoubtedly, this reaction did not occur without any additive[11] (entry 1). Metallic salts such as LiX,[12] $MgCl_2$[13], $CoBr_2$,[14] $NiCl_2$[15] etc. have significant positive effect on both organometallics formation and their reactivity. LiCl, for example, have been extensively explored by Knochel et al. as a key additive for organometallic reagents, such as Grignard reagents,[6] organozinc,[16] organoindium[17] and organoaluminum[18] reagents formation. In our reaction system, however, LiCl alone was tested as an inert additive and no reaction were detected at all (entry 2). $MgCl_2$ has been frequently used as a key promoter in a plethora organozinc reagents involving reactions.[19] Unfortunately, it is still an invalid additive here, probably because of its bad solubility in THF.[20] Gratifyingly, one equivalent addition of $MgBr_2$ promptly initiated and completed this transformation within 2 hours, giving ketone **3a** in nearly quantitative yield and excellent chemoselectivity (**3a:4a** = 20:1) (entry 4). MgI_2 too, is a powerful additive, delivering **3a** in 90% yield (82% isolated yield, entry 5). Combination an equal amount of LiCl and $MgCl_2$ made a clear solution in THF, allowing addition reaction completed in 6 h, albeit the desired ketone **3a** was obtained in only 57% isolated yield together with a significant amount of secondary alcohol **4a** remained (entry 6). An equal molar mixture of LiCl and $MgBr_2$ also cleanly converted aldehyde **2a**

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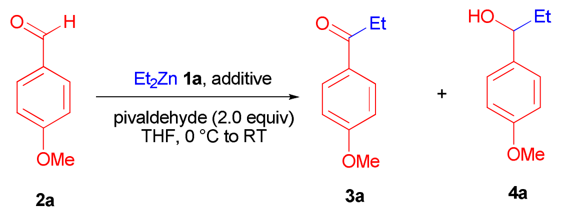
into ketone **3a** in a similar yield as with $MgBr_2$ alone (entry 7). These experimental facts implied that LiCl did not perform any pivotal role besides increase the solubility of magnesium salts in THF (entries 2-7). Other metallic salts screened such as CsF, $CoCl_2$, $NiCl_2$ and CH_3OLi, $Al(OiPr)_3$ are all failed in promoting this type of transformation.

Table 1 Optimization of reaction conditions[a]



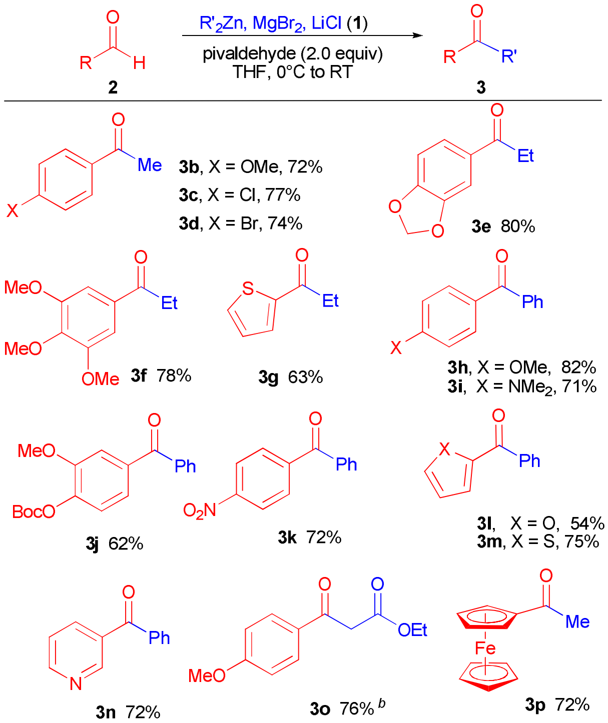
Entry	Additive[b]	3a (%)[c]	3a/4a[c]
1		n. r.[e]	/
2	LiCl	n. r.	/
3	$MgCl_2$	n. r.	/
4	$MgBr_2$	92(84)[d]	20:1
5	MgI_2	90(82)[d]	15:1
6	$MgCl_2{\cdot}LiCl$	57	2:1
7	$MgBr_2{\cdot}LiCl$	90(82)[d]	18:1

[a] The reaction was performed with **1a** (4.0 mmol), **2a** (2.0 mmol), pivaldehyde (4.0 mmol) in THF (10 mL) under 0 °C and then stirred at room temperature. [b] Additive (4.0 mmol). [c] Yields and the products ratios were determined by crude ^{1}H NMR. [d] isolated yield of **3a**. [e] n. r. = no reaction.

With this optimized condition in hand, we first examined the applicability of organozinc reagents. As summarized in Table 2, a wide range of aromatic or heteroaromatic aldehydes could be successfully converted into corresponding ketones using diorganozinc reagents such as Me_2Zn (**3b-3d**, **3p**), Et_2Zn (**3e-3g**) and Ph_2Zn (**3h-3n**). Neither electron donating nor electron accepting substituents appear to influence the reaction course. Various heteroaromatic ketones, such as thiophenyl (**3g**, **3m**), furyl (**3l**) and pyridyl (**3n**) ketones are easily prepared in good yields from corresponding aldehydes. Notably, in the presence of 2 equiv of pivaldehydes, zinc, LiCl and $MgBr_2$, Reformatsky type reaction of 4-methoxybenzaldehyde with ethyl 2-bromopropionate give the desired ketone **3o** in good yield. Importantly, ferrocenyl ketone **3p** was obtained from ferrocenecarbaldehyde in 72% yield.

Although diorganozinc reagents are effective organometallic species here, highly functionalized diorganozinc reagents are not easily available.[21] It is advantageous to employ functionalized organozinc halides as which can be easily prepared from cheap bromides by $ZnCl_2$ mediated magnesium insertion.[22] Most interestingly, magnesium salts concomitantly generated during organozinc halides formation offer an immediate promoter for this type transformation. Thus, treatment of $PhZnBr{\cdot}MgCl_2{\cdot}LiCl$ **5a**, prepared by in situ magnesiation of phenyl bromide in the presence of $ZnCl_2$ and LiCl, with a mixture of piperonyl aldehyde and two equivalents of pivaldehyde at room temperature yielded ketone **6a** in 79% isolated yield (Table 3). Notably, only less than 7% byproducts, mainly derived from nucleophilic addition-Oppenauer oxidation of organozinc reagent **5a** to pivaldehyde were detected according to GC-MS analysis. This promising result encouraged us to further examine the efficacy of other aromatic aldehydes. Gratifyingly, aromatic aldehydes bearing both electro-donating groups such as methyl(**6b**), methoxyl (**6c**) and electro-withdrawing groups, such as fluoro (**6d**), chloro (**6e**, **6f**), nitro (**6g**), nitrile (**6h**) and ester (**6i**) produced the desired ketones in good to excellent results. Steric hindered aromatic aldehyde, such as 2-methyl, 2-methoxyl and 2-chlorobenzaldehydes are applicable with corresponding ketones (**6b**, **6c**, **6f**) obtained in satisfactory yields. Heteroaromatic organozincs as represented by 2-furanyl, 2- and 3-thiophenylzinc halides were well applied, giving corresponding heteroaomatic ketones (**6k-6m**) in acceptable yields. Sensitive functional groups such as nitro (**6g**), nitril (**6h**) and ester (**6i**) are well tolerated with corresponding functionalized ketones obtained in good yields. Again,

Table 2. Reaction of aldehydes with organozinc reagents[a]



[a] The reaction was performed with R'_2Zn **1** (4.0 mmol), aldehyde **2** (2.0 mmol), pivaldehyde (4.0 mmol), $MgBr_2$ (4.0 mmol) and LiCl (4.0 mmol) in THF (10 mL) under ice-water bath and then stirred at room temperature. [b] Zn (4.0 mmol) and $BrCH_2CO_2Et$ (4.0 mmol) was used instead of $BrZnCH_2CO_2Et$.

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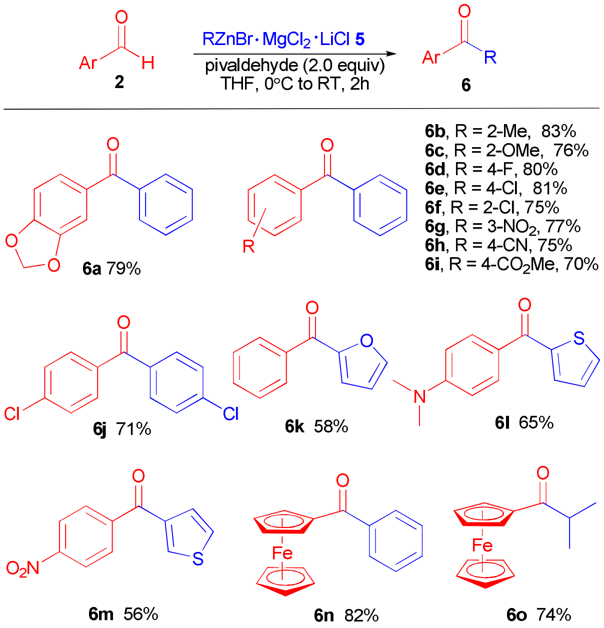
ferrocenyl ketone **6n** and **6o** were efficiently prepared from ferrocenecarbaldehyde in high yields.

LiCl mediated magnesium-halogen exchange reactions is now widely accepted as a common method for highly functionalized Grignards reagents preparation,[23] which, in the presence of $ZnCl_2$, converted into corresponding organozinc reagents.[21] In order to examine the efficiency of highly functionalized organozinc reagents thus prepared, ethyl 4-idobenzoate **7a** was first magnesiated *via* I/Mg exchange with *i*-PrMgCl·LiCl[24] and was then treated with $ZnCl_2$ to give the desired organozinc reagents which, exhibited excellent reactivity that the highly functionalized diaryl ketones **9a-9c** were obtained in high yields (Table 4). Iodobenzene bearing an electron-withdrawing CF_3 substituent found difficulty in direct magnesium insertion.[25] Nevertheless, treatment of 3-iodotrifluorobenzene by Turbo Grignards (*i*-PrMgCl·LiCl) and then transmetalated with $ZnCl_2$ afforded the corresponding organozinc reagents, which reacted with methyl 4-formylbenzoate and 3,4,5-trimethoxybenzaldehyde in the presence of 2 equivlents of pivaldehyde, giving functionalized diaryl ketone **9d** and **9e** in 80% and 84% yields respectively (Table 4). Similarly, organozinc reagents derivated from 4-fluoroiodobenzene **7c** and 4-iodobenzonitrile **7d** reacted with 4-fluorobenzaldehyde and 3,4,5-trimethoxybenzaldehyde respectively to give functionalized benzophenones **9f** and **9g** in good yields.

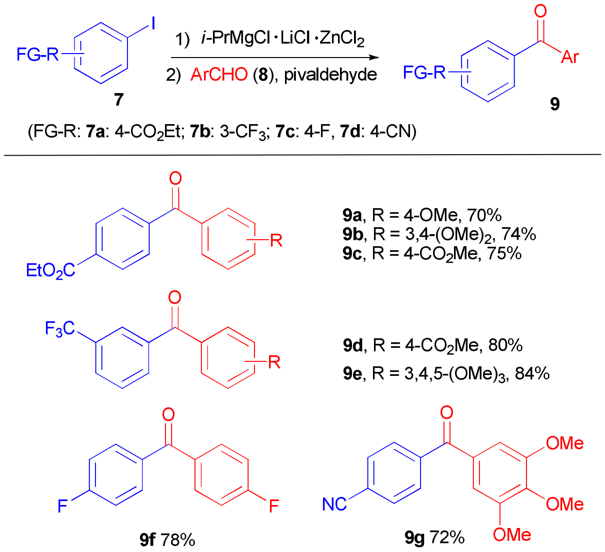
Table 3 Reaction of aldehydes with organozinc halides[a]



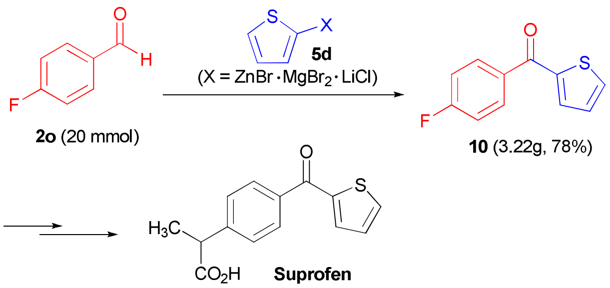
[a] Organozinc reagents were added to a mixture of aldehyde (2.0 mmol) and pivaldehyde (4.0 mmol) under icer-water bath and were then stirred at room temperature for 2h.

The excellent efficiency of the present reaction system was further highlighted by a 20 mmol scale synthesis of 2-(4-fluorobenzoyl)thiophene **10**, a key intermediate of a well-known medicine Suprofen[25] (Scheme 1). Thus 2-thienylzinc bromide **5d**, readily prepared from 2-bromothiophene (30 mmol) *via* LiCl promoted zincation, underwent complete conversion of 4-fluorobenzaldehyde (20 mmol) within 2h to afford the 2-(4-fluorobenzoyl)thiophene in 78% isolated yield.

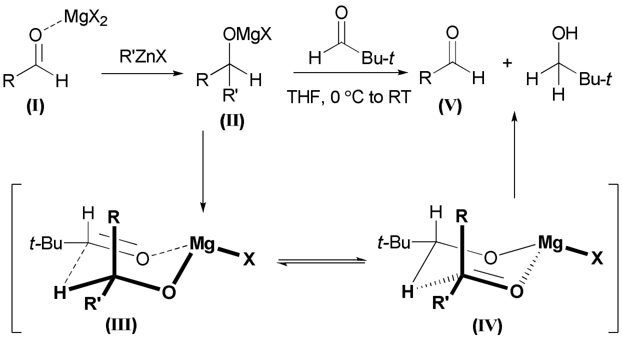
Table 4 Reaction of organozinc reagents prepared by $ZnCl_2$ mediated I/Mg exchange reaction.[a]



[a] Organozinc reagents generated from I/Mg exchange (about 4 mmol) were added to a mixture of aldehyde (2.0 mmol) and pivaldehyde (4.0 mmol) under icer-water bath and were then stirred at room temperature for 2h.



Scheme 1 Gram scale synthesis of 2-(4-fluorobenzoyl)thiophene



Scheme 2 Proposed reaction mechanism

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Mechanistically, magnesium salt plays a pivotal role both in addition reaction of organozinc reagents towards aromatic aldehydes and Oppenauer oxidation. So we proposed that the reaction proceeds as shown in Scheme 2. Initially, magnesium salts act as Lewis acid to complex and activate aldehyde carbonyl (**I**) which further react with organozinc reagent to give a magnesium alkoxide (**II**). Pivaldehyde then coordinates to the magnesium complex (**III**) and a hydride transfer occurred through complex (**IV**) to generate ketone (**V**).

In conclusion, a magnesium salt promoted synthesis of aromatic ketones via a tandem nucleophilic addition-Oppenauer oxidation of aldehydes using organozinc chemistry was demonstrated. Magnesium salts concomitantly generated via magnesium mediated organohalides zincation exhibit high efficacy for nucleophilic addition of organozinc reagents to aldehydes and thereafter Oppenauer oxidation whereby ketones were formed in high to excellent yields. This transformation offers an green and facile procedure for highly functionalized aryl and alkyl ketones preparation. The usefulness of this practical and efficient method was demonstrated in gram-scale synthesis of 2-(4-fluorobenzoyl)thiophene, a key intermediate to non-steroidal anti-inflammatory drug Suprofen.

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Notes and references

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