

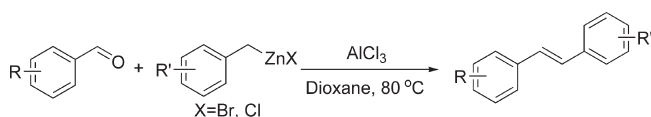
Lewis Acid Promoted Carbon–Carbon Double-Bond Formation via Organozinc Reagents and Carbonyl Compounds

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Using cheap and readily available AlCl_3 as Lewis acid, functionalized aldehydes react with organozinc reagents to give (*E*)-alkenes stereoselectively in high yields.

Carbon–carbon double bond formation is one of the useful and fundamental reactions in synthetic organic chemistry, particularly in the synthesis of complex natural products with biological activities. Since the pioneering work of Wittig,¹ the synthesis of alkenes by the olefination of carbonyl compounds has received considerable attention due to the simplicity, convenience, and efficiency of this methodology.² In addition to phosphorus ylides,³ other

related processes involving sulfur⁴ and silicon⁵ ylides have been developed. Furthermore, olefination of carbonyl group using transition metals, such as titanium⁶ and chromium,⁷ or using metal carbene complexes, including Re,⁸ Ru,⁹ Fe,¹⁰ and Rh,¹¹ have also been reported. Organozinc reagents have been widely used in organic synthesis.¹² Compared with organomagnesium and organolithium reagents, organozincs are relatively stable yet active, more selective, and tolerant to ester and amide functional groups. Generally, the reaction of organozinc reagents and aldehydes represents one of the most reliable methods to prepare secondary alcohols,¹³ while *gem*-dizinc species reacts with a carbonyl group to give olefination products.¹⁴

Wang has reported a useful procedure to make alkenes by transition-metal-catalyzed olefination of benzylzinc halides and carbonyl compounds,¹⁵ in which Co, Ni, or Pd was used to catalyze the reaction between organozinc reagents and carbonyl groups. A reaction involving a transition-metal-catalyzed formation of secondary silyl ethers, followed by the loss of Me_3SiOH to give (*E*)-alkenes, was proposed (Scheme 1). One feature associated with this mechanism is that it is well established that organozinc reagents react with

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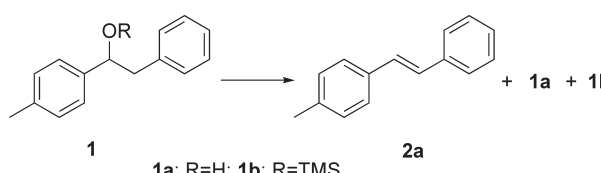
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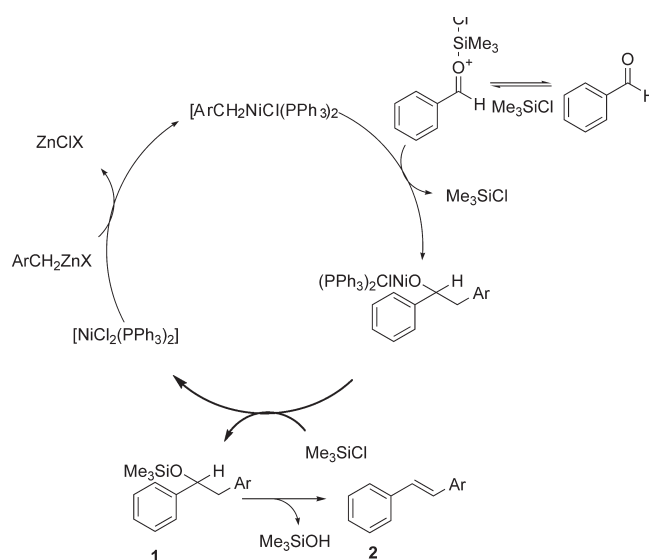
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TABLE 1. Olefination of Secondary Alcohol and Silyl Ether^a


entry	1	NiCl ₂ (PPh ₃) ₂ (mol %)	TMSCl (equiv)	ZnCl ₂ (equiv)	product (2a/1a/1b) ^b
1	1a	3	2	1.5	58/7/35
2	1b	3	2	1.5	63/3/34
3	1a	0	2	0	0/92/8
4	1b	0	2	0	0/0/100
5	1a	0	0	1.5	0/100/0
6	1b	0	0	1.5	0/0/100
7	1a	3	0	0	0/100/0
8	1b	3	0	0	0/0/100
9	1a	3	2	0	0/92/8
10	1b	3	2	0	0/0/100
11	1a	3	0	1.5	0/100/0
12	1b	3	0	1.5	0/0/100
13	1a	0	2	1.5	69/12/19
14	1b	0	2	1.5	68/6/26
15	1a	0	2	1.5	100/0/0 ^c
16	1b	0	2	1.5	100/0/0 ^c

^a Reaction conditions: **1** (0.5 mmol), THF (2.0 mL), at 25 °C under N₂ for 8 h. ^b Detected by GC. ^c Reaction temperature: 50 °C.

SCHEME 1. Transition-Metal-Involved Mechanism by Wang



aldehydes to give secondary alcohols under mild reaction conditions. Although mechanistically this reaction does not necessarily need a transition-metal salt, one can envision that this reaction might be accelerated by the addition of Lewis acids as promoters. Our recent research also proved that Lewis acids play a profound role in asymmetric hydrogenation reactions.¹⁶ Another item to note is that the conversion of silyl ether (**1**) to alkene (**2**) without any promoters is

difficult to obtain, as it is known that the silyl ether is labile to hydrolysis rather than elimination.

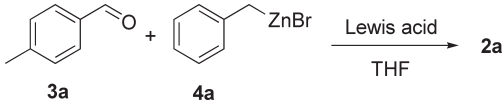
We reinvestigated this reaction and found that transition metal was not necessary in this reaction. Herein, we report the Lewis acid promoted olefination of benzylzinc halides and carbonyl compounds under transition-metal-free conditions.

To make it clear how the transformation of secondary silyl ethers to alkenes occurred, **1a** and **1b** were employed as substrates for the control reactions. Under standard reaction conditions reported by Wang et al.,^{15a} both **1a** and **1b** can be converted to the desired product **2a**, indicating a combination of transition metal–TMSCl–ZnCl₂ is workable (Table 1, entries 1 and 2). When we ran the reaction in the presence of only NiCl₂(PPh₃)₂ (3 mol %), or TMSCl (2 equiv) or ZnCl₂ (1.5 equiv), no elimination product was detected (Table 1, entries 3–8); when we ran the reaction with a binary combination, different results were obtained: NiCl₂(PPh₃)₂–TMSCl or NiCl₂(PPh₃)₂–ZnCl₂ gave no products (Table 1, entries 9–12), while the TMSCl–ZnCl₂ combination gave products with fair yields, accompanying recovered starting material, and corresponding protection/deprotection products (Table 1, entries 13 and 14). When the reaction temperature was increased from 25 to 50 °C, the starting material was completely converted to the desired alkene (Table 1, entries 15 and 16).

The results in Table 1 clearly illustrated that this olefination reaction does not need the catalysis of a transition metal; the combination of TMSCl and ZnCl₂ plays the key role. We then repeated the reaction with or without NiCl₂(PPh₃)₂ by reacting *p*-tolualdehyde and benzylzinc(II) bromide¹⁷ under the reported reaction conditions,^{15a} and the reactions

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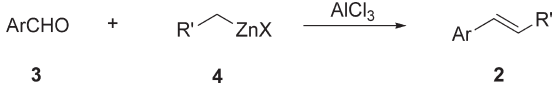
TABLE 2. Optimization of the Lewis Acid Promoted Olefination of Benzylzinc Bromide and *p*-Tolaldehyde^a


entry	<i>T</i> (°C)	Lewis acid (equiv)	solvent	yield (%)
1	25	TMSCl (2)	THF	67 ^{b, c}
2	25	TMSCl (2)	THF	61 ^c
3	50	TMSCl (2)	THF	77
4	50	LiCl (2)	THF	76 ^d
5	50	CeCl ₃ (2)	THF	58 ^d
6	50	ZnCl ₂ (2)	THF	0 ^c
7	50	FeCl ₃ (2)	THF	0 ^c
8	50	Cu(OAc) ₂ (2)	THF	0 ^c
9	50	BF ₃ ·Et ₂ O (2)	THF	56 ^c
10	50	AlCl ₃ (2)	THF	82
11	50	AlCl ₃ (1)	THF	38 (37)
12	50	AlCl ₃ (0.5)	THF	0 (56)
13	50	AlCl ₃ (3)	THF	87
14	50	AlCl ₃ (3)	NMP	78 ^d
15	50	AlCl ₃ (3)	DMF	67 ^d
16	50	AlCl ₃ (3)	acetonitrile	62 ^c
17	50	AlCl ₃ (3)	toluene	74 ^c
18	50	AlCl ₃ (3)	dioxane	83
19	80	AlCl ₃ (3)	dioxane	89

^a Reaction conditions: aldehyde (1.0 mmol), benzylzinc bromide (1.5 mmol), and Lewis acid in a solvent (3.0 mL) at a specified temperature under N₂ for 8 h. ^b 3 mol % of NiCl₂(PPh₃)₂ was added. ^c Unreacted aldehyde recovered. ^d 2-Phenyl-1-*p*-tolylethanol was obtained.

proceeded almost equally well; (*E*)-alkene **2a** was obtained stereoselectively. Both of the reactions did not reach completion after 8 h at room temperature, and the secondary silyl ether and unreacted aldehyde were detected (Table 2, entries 1 and 2). If the reaction was carried out in the absence of NiCl₂(PPh₃)₂ at a higher temperature (50 °C), silyl ether disappeared and (*E*)-stilbene was obtained in good yield (Table 2, entry 3). To clarify whether the elimination occurred via silyl ether or directly via alcohol, we tried other Lewis acids. When LiCl or CeCl₃ were used as Lewis acids, only secondary alcohol was isolated, while when ZnCl₂, FeCl₃, or Cu(OAc)₂ was used as Lewis acid, typically no reaction occurred and most of the aldehyde was recovered (Table 2, entries 4–8). Gratifyingly, when BF₃·Et₂O or AlCl₃ was employed, olefination occurred to give the (*E*)-alkenes stereoselectively in fair to good yields (Table 2, entries 9 and 10). Reducing the amount of AlCl₃ to 1 molar equiv gave a lower yield accompanied by secondary alcohol; reducing the amount of AlCl₃ to 0.5 molar equiv gave only secondary alcohol; increasing the amount of AlCl₃ to 3 molar equiv gave higher yields (Table 2, entries 11–13).

With cheap and readily available AlCl₃ as Lewis acid, we tested the reaction in different solvents. When *N,N*-dimethylformamide (DMF) or *N*-methyl-2-pyrrolidone (NMP) was used as solvent, olefination did not proceed; only secondary alcohol was separated in fair yields. Olefination product was obtained in medium to good yield, respectively, with acetonitrile, toluene, or dioxane as solvent (Table 2, entries 14–18). When we performed the reaction in dioxane at 80 °C, a better yield was obtained, and the reaction time was reduced from 8 to 2 h (Table 2, entry 19).

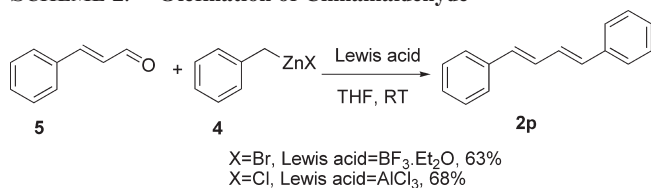
TABLE 3. Lewis Acid Promoted Olefination of Aldehydes with Organozinc Reagents^a


entry	3 Ar	4 R', X	product	yield (%)
1	3a , <i>p</i> -CH ₃ C ₆ H ₄	4a , Ph, Br	2a	89
2	3b , <i>o</i> -CH ₃ C ₆ H ₄	4a , Ph, Br	2b	81
3	3c , <i>m</i> -CH ₃ C ₆ H ₄	4a , Ph, Br	2c	83
4	3d , C ₆ H ₅	4a , Ph, Br	2d	93
5	3e , <i>o</i> -FC ₆ H ₄	4a , Ph, Br	2e	94
6	3f , <i>p</i> -ClC ₆ H ₄	4a , Ph, Br	2f	91
7	3g , <i>p</i> -BrC ₆ H ₄	4a , Ph, Br	2g	90
8	3h , 2,4-Di-ClC ₆ H ₃	4a , Ph, Br	2h	87
9	3a , <i>p</i> -CH ₃ C ₆ H ₄	4b , Ph, Cl	2a	88
10	3d , C ₆ H ₅	4b , Ph, Cl	2d	83
11	3f , <i>p</i> -ClC ₆ H ₄	4b , Ph, Cl	2f	80
12	3a , <i>p</i> -CH ₃ C ₆ H ₄	4c , 4-Cl-Ph, Cl	2i	89
13	3d , C ₆ H ₅	4c , 4-Cl-Ph, Cl	2f	78
14	3f , <i>p</i> -ClC ₆ H ₄	4c , 4-Cl-Ph, Cl	2j	71
15	3a , <i>p</i> -CH ₃ C ₆ H ₄	4d , <i>n</i> -C ₃ H ₇ , I	2k	41 ^b
16	3a , <i>p</i> -CH ₃ C ₆ H ₄	4e , <i>n</i> -C ₇ H ₁₅ , I	2L	44 ^b
17	3f , <i>p</i> -ClC ₆ H ₄	4d , <i>n</i> -C ₃ H ₇ , I	2m	36 ^b
18	3f , <i>p</i> -ClC ₆ H ₄	4e , <i>n</i> -C ₇ H ₁₅ , I	2n	43 ^b
19	3i , <i>p</i> -CH ₃ OC ₆ H ₄	4a , Ph, Br	2o	86 ^c
20	3d , C ₆ H ₅	4b , Ph, Cl	2d	77 ^d

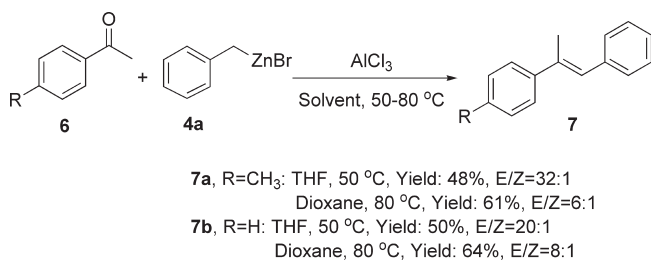
^a Reaction conditions: aldehyde (1.0 mmol), organozinc reagent (1.5 mmol), AlCl₃ (3.0 mmol), dioxane (3.0 mL), at 80 °C under N₂. ^b THF (3.0 mL), reflux. ^c TMSCl (3.0 mmol), THF (3.0 mL), at 65 °C. ^d 100 mmol of substrate was used.

The results are summarized in Table 3 for the reactions that were run under the optimized reaction conditions (AlCl₃ as Lewis acid, in dioxane or THF at 80 °C under N₂) where the olefination reaction was carried out with aromatic aldehydes and organozinc halides. This reaction has a wide scope of substrate tolerance. *o*, *m*, *p*-tolualdehyde, benzaldehyde, and halogenated benzaldehydes are all workable substrates to react with benzylzinc bromide, good to excellent yields were obtained, and no obvious steric effect was observed (Table 3, entries 1–8). However, aryl aldehydes bearing an electron-donating substituent react faster than those bearing an electron-withdrawing substituent. Other benzylzinc reagents, such as benzylzinc chloride (**4b**) and 4-chlorobenzylzinc chloride (**4c**), worked equally well as **4a** (Table 3, entries 9–14). Likewise, without any additive, alkylzinc iodides (**4d**, **4e**) react very slowly with aldehydes even in refluxing THF and at prolonged reaction times to give the corresponding alcohols and recovered aldehydes. Although the addition of AlCl₃ greatly improved the reactivity of alkylzinc reagents and aldehydes, (*E*)-alkenes were obtained in only medium yields accompanied by alcohols (Table 3, entries 15–18) even at prolonged reaction times. When the reaction was performed with *p*-anisaldehyde (**3i**) as substrate, very low yield was obtained; fortunately when AlCl₃ was replaced by TMSCl as Lewis acid, olefination proceeded very well in refluxing THF (Table 3, entry 19). The reaction can be easily performed on a larger scale: when benzaldehyde (**3d**, 100 mmol) was treated with benzylzinc chloride (**4b**) in the presence of AlCl₃, at 80 °C in dioxane for 8 h, after recrystallization from ethanol, (*E*)-stilbene (**2d**) was obtained in 77% yield (Table 3, entry 20).

SCHEME 2. Olefination of Cinnamaldehyde



SCHEME 3. Olefination of Aromatic Ketones



This method can be extended to unsaturated aldehydes. When cinnamaldehyde was reacted with benzylzinc bromide, the corresponding (1*E*,3*E*)-1,4-diphenyl-1,3-butadiene (**2**) was obtained in medium isolated yields; both AlCl₃ and BF₃·Et₂O are suitable Lewis acids for the reaction (Scheme 2).

Aromatic ketones also reacted with benzylzinc bromide in the presence of AlCl₃ to give an (*E*)/(*Z*) mixture as products. Solvents are important in this reaction. With dioxane as solvent, medium yields was obtained with poor selectivities; when THF was used as solvent, good selectivities but lower yields were observed (Scheme 3).

According to our experimental results and other related studies,^{13,14} Lewis acid may play multiple roles in this reaction: (1) it activates carbonyl compound by coordination to carbonyl group; (2) it accelerates the insertion of organozinc reagent to carbonyl compound; and (3) it facilitates the formation of alkene from secondary alcohol or silyl ether.

In conclusion, a highly stereoselective carbon–carbon double-bond-forming reaction was reported. Using cheap and readily available AlCl₃ as Lewis acid, functionalized aldehydes react with organozinc reagents to give (*E*)-alkenes stereoselectively in high yields.

Experimental Section

General Procedure for the Lewis Acid Promoted Olefination of Aldehydes with Organozinc Reagents. AlCl₃ (400 mg, 3.0 mmol) and dry dioxane (3.0 mL) were added into an oven-dried Schlenk tube equipped with a septum and a stirring bar under nitrogen. The mixture was cooled with ice–water, and then *p*-tolualdehyde (120 mg, 1.0 mmol) was added. The reaction mixture was stirred for an additional 5 min before benzylzinc bromide (1.0 mL, 1.5 mmol, 1.5 M in THF) was added via syringe over 5 min. The reaction mixture was moved into an oil bath and stirred at 80 °C for 2 h. The starting materials were completely consumed as determined by GC analysis, the reaction mixture was cooled with ice–water, and ether (10.0 mL) and saturated NH₄Cl solution (3.0 mL) were added. The aqueous layer was separated and extracted with ether (3 × 5.0 mL), and the combined organic extracts were dried over Na₂SO₄ and evaporated. Flash chromatography with hexanes as eluent afforded compound **2a**, which was confirmed by ¹H and ¹³C NMR.

(*E*)-4'-Methylstilbene (Compound 2a, Table 3, Entry 1). Prepared according to the general procedure using hexanes as eluent (173.0 mg, 89%): white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H), 7.07 (d, *J* = 2.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.24–7.27 (m, 1H), 7.34 (m, 2H), 7.41 (m, 2H), 7.50 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 126.6, 126.7, 127.6, 127.9, 128.8, 128.9, 129.6, 134.8, 137.7.

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Supporting Information Available: Experimental procedure and spectroscopic data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.