Cross-Coupling

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Zinc Chloride Enhanced Arylations of Secondary Benzyl Trifluoroacetates in the Presence of β-Hydrogen Atoms**

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During the past three decades, carbon–carbon bond formation has been one of the central themes in synthetic chemistry. Among the variety of C–C bond-formation reactions, transition-metal-catalyzed coupling reactions have been extensively studied and widely applied.[1–9] However, those transition-metal-catalyzed reactions involving alkyl groups have encountered inherent problems owing to the sluggish reductive elimination and facile β-hydride elimination steps.[10,11] Many efforts have been made to overcome this difficulty with some success.[12–36] However, as shown in Figure 1, the arylation of secondary benzyl derivatives, especially in the presence of β-hydrogen atoms, remains a challenge in this field.

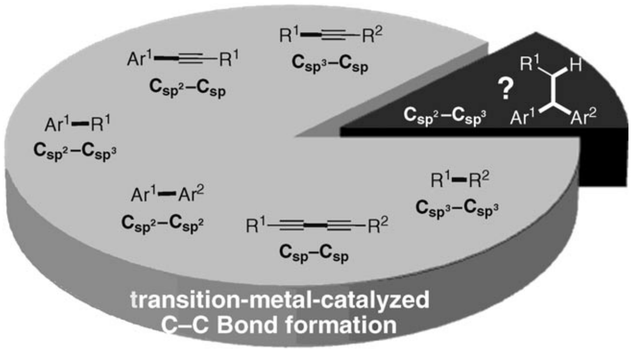


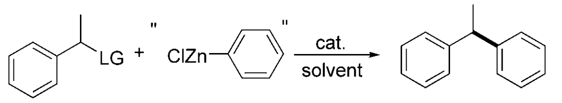
Figure 1. The theme of C–C bond formations.

Diarylalkane fragments are key components of several pharmacologically active compounds, such as Phenindamine and Fluspirilene.[37] Theoretically, an aryl nucleophile could undergo a nucleophilic substitution with primary benzyl derivatives in the traditional manner. However, owing to steric hindrance, it is less effective when the electrophiles are secondary benzyl derivatives. Only a few results have been reported in the literature.[38–40] In fact, even the most simple diarylmethanes, involving a primary benzyl derivative as the electrophile and an aryl nucleophile, were mainly produced using transition-metal-catalyzed reactions.[30,41–53] Beller and co-workers described two elegant benzylation reactions using a Friedel–Crafts arylation strategy of secondary benzyl derivatives with electron-rich arene nucleophiles.[54,55] A cobalt-catalyzed arylation of benzyl chloride derivatives with aryl zinc reagents has also been described.[49,50] In general, there is still a lack of efficient methods to build new C–C bonds between secondary benzyl derivatives and arenes.

In order to investigate the capability of the phosphine-olefin ligands,[56,57] our research interest focused on exploring the potential reaction between secondary benzyl derivatives and aryl zinc reagents. Unexpectedly, all of the reactions employing palladium catalysts failed. Interestingly, the reaction did work without palladium catalysts. After further investigation, we found that $ZnCl_2$ played a key role in the reaction. Herein, we report these observations.

To examine the bond formation between a secondary benzyl electrophile and aryl zinc reagents, we initially tested the reaction of **1** with **2a** (prepared from PhLi with 1.4 equiv of $ZnCl_2$) in the presence of a $Pd(OAc)_2$/dppf catalyst. No conversion of starting material was identified by GC for the reaction of **1a** with **2a** (Table 1, entry 1). The reactions of **1b** and **1c** with **2a** in the presence of $Pd(OAc)_2$/dppf and toluene as the solvent led to consumption of the electrophiles with only trace amounts of the desired arylation product **3aa** observed (Table 1, entries 3 and 4). To our delight, when

Table 1: Arylation of **1** with phenylzinc chloride **2a**.[a]



1 **2a** **3aa**

Entry	LG	Solvent	Catalyst	Conv. **1** [%]	Conv. **3aa** [%]
1	OH **1a**	THF	dppf, $Pd(OAc)_2$	0	0
2	OAc **1d**	toluene	dppf, $Pd(OAc)_2$	0	0
3	OMs **1b**	THF	dppf, $Pd(OAc)_2$	100	trace[b]
4	OTFA **1c**	THF	dppf, $Pd(OAc)_2$	80	<1[c]
5	OTFA **1c**	toluene	dppf, $Pd(OAc)_2$	100	84
6	OH **1a**	toluene	dppf, $Pd(OAc)_2$	0	0
7	OTFA **1c**	toluene	none	100	95
8	OTFA **1c**	THF	none	54	36
9	OAc **1d**	toluene	none	0	0

[a] Reaction conditions: **1** (1.8 mmol), **2a** (2.5 mmol; prepared from PhLi with 1.4 equiv of $ZnCl_2$), solvent (4.0 mL), 50 °C, 24 h; conversion was determined by GC with biphenyl as an internal standard. [b] 1-Chloroethyl-benzene was the major product. [c] Styrene was the major product. LG = leaving group, THF = tetrahydrofuran, Ac = acetyl, TFA = trifluoroacetyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

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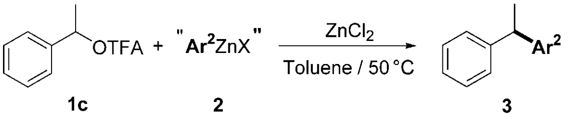
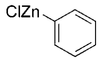
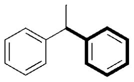
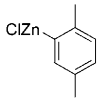
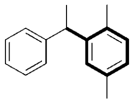
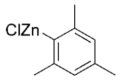
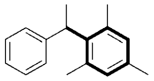
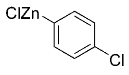
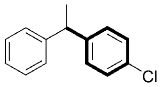
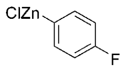
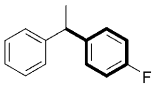
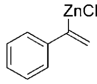
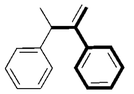
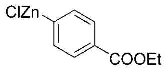
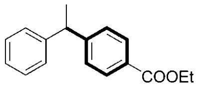
toluene was used as the solvent, the reaction of **1c** with **2a** gave 84 % conversion to **3aa** (Table 1, entry 5). The reactions of **1a** and **1d** with **2a** were then re-examined in toluene; however, no desired product was observed when **1a** and **1d** were employed as electrophilic components (Table 1, entries 6 and 2, respectively). Unexpectedly, the reaction of **1c** with **2a** in toluene produced 95 % arylation of **3aa** without a palladium catalyst (Table 1, entry 7), whilst the reaction of **1c** with **2a** in tetrahydrofuran afforded only 36 % **3aa** (Table 1, entry 8). There was almost no reaction between **1d** and **2a** in toluene without a palladium catalyst (Table 1, entry 9).

Table 2 shows the results of the reactions of **1c** with various organozinc reagents **2** under the same conditions as shown in Table 1, entry 7. Good to excellent yields were obtained from a variety of substituted arylzinc reagents (Table 2, entries 1–5, and 7). Particularly noteworthy was that an alkenylzinc reagent **2f** provided 75 % of the corresponding alkenylation product **3af** (Table 2, entry 6). When optically pure electrophile **1c** was investigated, complete racemization was observed.

Table 2: Arylation of secondary benzyl trifluoroacetate **1c** with different arylzinc reagents **2**.[a]

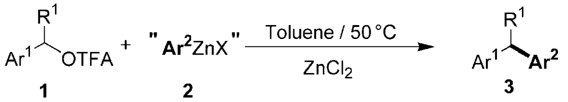


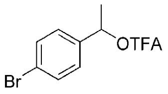
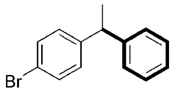
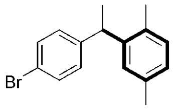
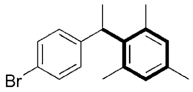
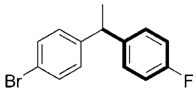
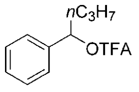
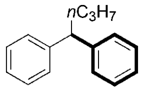
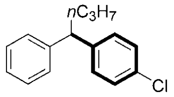
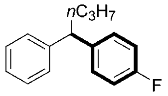
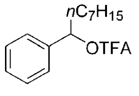
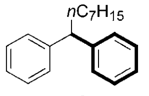
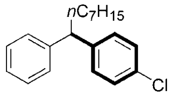
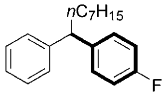
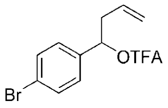
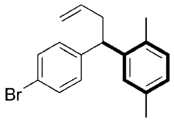
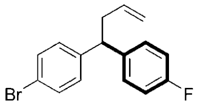
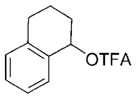
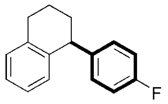
Entry	2		3		Yield [%]
1		**2a**		**3aa**	76
2		**2b**		**3ab**	90
3		**2c**		**3ac**	88
4		**2d**		**3ad**	88
5		**2e**		**3ae**	92
6		**2f**		**3af**	75
7		**2g**		**3ag**	79

[a] Reaction conditions: **1** (1.8 mmol), **2** (2.5 mmol; prepared from the ArLi with 1.4 equiv of ZnCl₂), toluene (4.0 mL), 50 °C, 24 h, yield of isolated product.

The substrate scope was then investigated further, and the arylation reactions of various aryl zinc reagents proceeded smoothly, providing the products in good to high yields (Table 3). Not only CH_3-substituted but also n-C_3H_7 (**1h**)- and n-C_7H_{15} (**1e**)-substituted benzyl derivatives were examined as electrophiles in the reaction, and afforded their corresponding products in high yields. Electron-withdrawing groups were also tolerated. Meanwhile, C–Br bonds on the phenyl ring remained intact, and olefin functional groups were also tolerated under the reaction conditions.

Table 3: Substrate scope of the arylation of benzyl trifluoroacetates.[a]



Entry	1		2	3		Yield [%]
1		**1g**	**2a**		**3ga**	98
2		**1g**	**2b**		**3gb**	77
3		**1g**	**2c**		**3gc**	80
4		**1g**	**2e**		**3ge**	81
5		**1h**	**2a**		**3ha**	92
6		**1h**	**2d**		**3hd**	83
7		**1h**	**2e**		**3he**	75
8		**1e**	**2a**		**3ea**	94
9		**1e**	**2d**		**3ed**	73
10		**1e**	**2e**		**3ee**	84
11		**1f**	**2b**		**3fb**	68
12		**1f**	**2e**		**3fe**	46
13		**1g**	**2e**		**3ge**	80

[a] Reaction conditions: **1** (1.8 mmol), **2** (2.5 mmol; prepared from the ArLi with 1.4 equiv of ZnCl₂), toluene (4.0 mL), 50 °C, 24 h, yield of isolated product.

It is noteworthy that only the arylzinc reagents generated from the reaction of aryllithiums with $ZnCl_2$ afforded the desired arylation products in high yields (Table 4, entry 1). When TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) was added as an additive or the arylzinc reagent was prepared from ArMgX, no arylation reaction took place (Table 4, entries 2–4). Indeed, we recently disclosed the potential differences between the structure and reactivity of "PhZnCl" reagents.[58] If the "PhZnCl" was prepared from PhMgBr with $ZnCl_2$, the co-product $MgCl_2$ would aggregate with PhZnCl in tetrahydrofuran. The detrimental effects of $MgCl_2$ in this reaction probably indicated that the vacant coordination site in "PhZnCl" was important for the arylation of benzyl trifluoroacetate.

Table 4: Arylation of benzyl trifluoroacetate **1c** with phenylzinc reagents prepared by different methods.

$$\mathbf{1c} + \text{"PhZnCl"} \xrightarrow[50\,^{\circ}\mathrm{C}]{\text{Toluene}} \mathbf{3aa}$$

Entry	"PhZnCl"	Yield [%]
1	$PhLi + ZnCl_2$	76
2	$PhLi + TMEDA{\cdot}ZnCl_2$	0
3	$PhMgBr + ZnCl_2$	trace[a]
4	$PhMgBr + TMEDA{\cdot}ZnCl_2$	0

[a] ca. 60% conversion, although a complicated mixture of products was obtained.

The reactions of **1c** with **2e** in the presence of different amounts of $ZnCl_2$ were further monitored by in situ IR spectroscopy (see the Supporting Information); Table 5 and Figure 2 show the critical role of $ZnCl_2$ in this transformation.

Table 5: Effect of salts on the arylation of benzyl trifluoroacetate with arylzinc reagents.

$$\mathbf{1c} + Zn(4\text{-}FC_6H_4)_2 \xrightarrow[\text{Toluene / }50\,^{\circ}\mathrm{C}]{\text{Additive}} \mathbf{3ae}$$

Entry	Additives (equiv)	Yield [%]
1	–	trace
2	LiCl	trace
3	$Zn(OTFA)_2$ (0.4)	6
4	$Zn(OTFA)_2$ (1.2)	2
5	$ZnCl_2$ (0.1)	3
6	$ZnCl_2$ (0.4)	27
7	$ZnCl_2$ (1.2)	88

$Zn(4\text{-}FC_6H_4)_2$ did not react with **1c** to produce **3ae** (Table 5, entry 1). 0.1 or 0.4 equivalents of $ZnCl_2$ did not efficiently promote the reaction (Table 5, entry 5 and 6, respectively).[59] Delightfully, arylation product **3ae** was isolated in 88% yield when $ZnCl_2$ (1.2 equiv) was added to the reaction (Table 5, entry 7). One could reasonably speculate that the reaction of $Zn(4\text{-}FC_6H_4)_2$ with $ZnCl_2$ would spontaneously generate $4\text{-}FC_6H_4ZnCl$. When less than 1.0 equivalent of $ZnCl_2$ reacted with $Zn(4\text{-}FC_6H_4)_2$, only $4\text{-}FC_6H_4ZnCl$ and excess $Zn(4\text{-}FC_6H_4)_2$ was expected to form in the reaction mixture, and no $ZnCl_2$ was present. These important experiments revealed that ArZnCl could not efficiently react with **1c** to form **3ae** under these conditions. The kinetic profiles in Figure 2 clearly showed that the more $ZnCl_2$ was left, the faster the reaction proceeded.

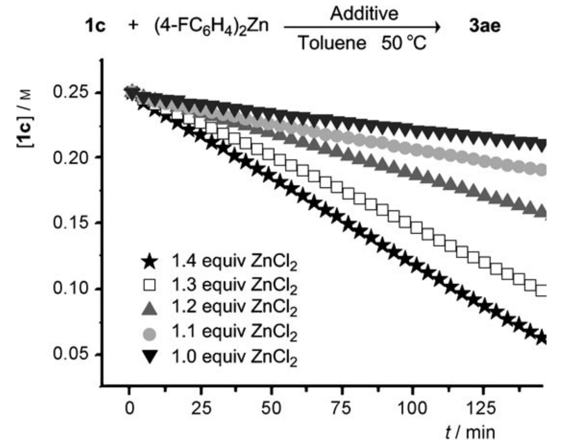


Figure 2. Kinetic profiles of the arylation of **1c** with $(4\text{-}FC_6H_6)_2Zn$ in the presence of different amounts of $ZnCl_2$.

LiCl had no effect on the arylation reaction (Table 5, entry 2); in addition, $Zn(OTFA)_2$ was also not able to facilitate the reactions (Table 5, entry 3 and 4). When the reaction was carried out in polar, coordinating solvents, such as tetrahydrofuran, dimethylacetamide, acetonitrile etc., no arylation reactions were observed (see the Supporting Information).

In addition, the zero-order kinetic profiles indicated that the reaction underwent a $ZnCl_2$-enhanced process, and that the rate-limiting step was the step after the interactions between **1c** and **2e** with the $ZnCl_2$ salt (see the Supporting Information).

In conclusion, a $ZnCl_2$-enhanced arylation of benzyl trifluoroacetate with arylzinc reagents was investigated. The β-hydrogen atoms could be tolerated in the substrates. Both electron-rich and electron-deficient arene substrates were arylated under the mild reaction conditions. Moreover, the role of $ZnCl_2$ was unambiguously identified. The newly developed arylation method could offer a very versatile synthetic route to access a series of diverse diarylalkanes motifs. Detailed mechanistic and kinetic investigations are currently underway in our laboratory.

Experimental Section

General procedure: A Schlenk tube was charged with 4-fluoro bromobenzene (2.5 mmol) and 3.0 mL of THF under an argon atmosphere at room temperature. After cooling to −78 °C, 1.0 mL of *n*BuLi (2.5 M) was slowly added to the reaction mixture, and stirred at −78 °C for 30 min, then 3.5 mL of a $ZnCl_2$ solution (1.0 M in THF) was slowly added at −78 °C. After slowly warming to room temperature, the solution was stirred for one hour, and the solvent was removed under reduced pressure. Toluene (4.0 mL) was added to the residue. After the zinc reagent was dispersed, **1c** (1.8 mmol) was added to the mixture. The resulting solution was stirred at 50 °C for 12 h, then was quenched with 1M HCl, diluted the mixture with 5 mL of diethyl ether.

The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether = 1:200) to afford the desired product in 92 % yield.

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Keywords: arylation · C–C coupling · cross-coupling · diarylalkanes · zinc

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