



Palladium-catalyzed and copper-mediated cross-coupling reaction of aryl- or alkenylboronic acids with acid chlorides under neutral conditions: efficient synthetic methods for diaryl ketones and chalcones at room temperature



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ABSTRACT

Palladium-catalyzed cross-coupling reaction of aryl- or alkenylboronic acids with acid chlorides in the presence of copper(I) thiophene-2-carboxylate (CuTC) as an activator in diethyl ether at room temperature under strictly non-basic conditions affords the diaryl ketones or chalcones in moderate to excellent yields. A wide range of substrates bearing an electron-donating or an electron-withdrawing substituent on the aromatic ring are compatible.

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1. Introduction

Unsymmetrical diaryl ketone and chalcone motifs are important building blocks to construct natural products and pharmaceuticals.¹ For example, as shown in Fig. 1, sulisobenzone is an important class of unsymmetrical diaryl ketones used as UV absorbers in some sunscreens that protects the skin from UV lights.^{1a} Optically active (*S*)-ketoprofen is a nonsteroidal anti-inflammatory drug with approximately 160 times the anti-inflammatory potency of aspirin.^{1b} On the other hand, sofalcone is one of the chalcone derivatives, which is used as an anti-ulcer with mucosa protective effect and isolated from the root of the Chinese medicinal plant *Sophora subprostrata*.^{1c} Rottlerin (ROT) is widely used as an inhibitor toward protein kinase C-delta.^{1d}

Since Haddach and McCarthy have reported the palladium-catalyzed cross-coupling reaction of acid chlorides with arylboronic acids under basic conditions for the synthesis of diaryl ketones,² the analogous reactions have been developed for a construction of diaryl ketone³ and chalcone^{4,5} derivatives. These

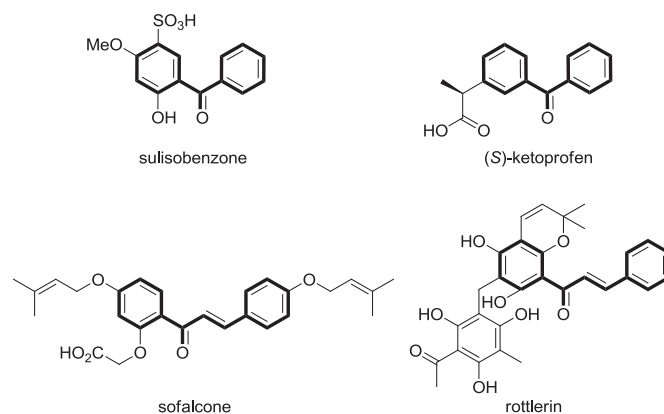


Fig. 1. Examples of representative diaryl ketones and chalcones.

coupling reactions involve several advantageous features relative to Friedel–Crafts acylation⁶ or carbonylative Suzuki–Miyaura⁷ and Mizoroki–Heck type reactions^{8,9} of aryl halides in the presence of carbon monoxide: mild reaction conditions, high regioselectivity, and compatibility with various functional groups. In addition, organoboronic acids are non-toxic and stable toward heat, air, and

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moisture. Although numerous reports described the coupling of organoboron compounds with carboxylic acid derivatives under basic conditions,^{10,11} to the best of our knowledge, there are no reports describing the synthesis of diaryl ketones or chalcones by cross-coupling reaction of organoboronic acids with acid chlorides under neutral conditions. We herein report the Pd-catalyzed cross-coupling reaction of aryl- or alkenylboronic acids with acid chlorides under neutral conditions. We proceed with an assistance of copper(I) thiophene-2-carboxylate (CuTC) under non-basic and mild reaction conditions (room temperature), leading to various diaryl ketones and chalcones.¹²

2. Results and discussion

2.1. Cross-coupling reaction of arylboronic acids **1** with acid chlorides **2**

Our initial investigation started with a cross-coupling reaction of phenylboronic acid (**1a**) with benzoyl chloride (**2a**) as model substrates in the presence of 5 mol % of Pd(dba)₂ plus 10 mol % of PPh₃ as the catalyst and 1 equiv of various copper compounds in THF at 65 °C for 12 h.¹³ The results obtained are shown in Table 1. Benzophenone (**3a**) was obtained in the presence of various copper halides in 39–52% yields (Table 1, entries 1–3). Both Cu(OAc)₂ and CuOAc were found to be inferior (Table 1, entries 4 and 5). To our delight, when we used copper(I) thiophene-2-carboxylate (CuTC), the desired product **3a** was formed in 57% yield (Table 1, entry 6). The similar copper compounds, such as CuFC and CuPC showed low activity. In all cases, the reaction gave rise to the formation of a little amount of 4-chlorobutyl benzoate and biphenyl, presumably derived from homocoupling of **1a**. Formation of 4-chlorobutyl benzoate was attributed to Pd-mediated reaction of **2a** with THF as the reactant.¹⁴ The similar boiling point and polarity of 4-chlorobutyl benzoate would be a drawback for an isolation of the desired **3a**.

Therefore, we screened other solvents for the reaction of **1a** with **2a** by using CuTC as an additive, as shown in Table 2. Reactions proceeded in ethereal solvents, such as 1,2-dimethoxyethane (DME) and Bu₂O in moderate yields (Table 2, entries 2 and 3). Reactions in higher temperature increased the yield (Table 2, entries 4 and 5). Surprisingly, diethyl ether as the solvent significantly suppressed the side reactions and the reaction proceeded at room temperature in 78% yield (Table 2, entry 6). However, the yield of the reaction in less polar toluene decreased to 37% (Table 2, entry 7). Unfortunately,

Table 1
Effect of Cu compounds for cross-coupling reaction of **1a** with **2a**^a

Entry	Copper compound	Yield ^b (%)
1	CuCl	52
2	CuBr	39
3	CuI	45
4	Cu(OAc) ₂	34
5	CuOAc	42
6	CuTC	57
7	CuFC ^c	39
8	CuPC ^d	41

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Pd(dba)₂ (5 mol %), PPh₃ (10 mol %), and copper compound (0.1 mmol) in THF at 65 °C for 12 h.

^b GC yields.

^c CuFC=copper(I) furan-2-carboxylate.

^d CuPC=copper(I) pyridine-2-carboxylate.

Table 2
Solvent effect on cross-coupling reaction of **1a** with **2a**^a

Entry	Solvent	Temp (°C)	Yield ^b (%)
1	THF	65	57
2	DME	65	59
3	Bu ₂ O	65	51
4	THP	80	72
5	1,4-dioxane	100	72
6	Et ₂ O	25	78 (97) ^c
7	toluene	65	37
8	DMF	65	0
9	DMSO	65	0
10	methanol	25	0 ^d

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Pd(dba)₂ (5 mol %), PPh₃ (10 mol %), and CuTC (0.1 mmol) for 12 h.

^b GC yields.

^c A GC yield is shown in parenthesis under the following conditions: ratio of **1a**/**2a**=2:1, reaction time; 3 h.

^d Methyl benzoate was formed in 59% yield.

reactions in DMF or DMSO did not afford **3a** at all (Table 2, entries 8 and 9). When methanol was used as the solvent, methyl benzoate was formed in 59% yield (Table 2, entry 10). Diethyl ether seems to play an important role as the low concentration of CuTC and boronic acid **1a** in the reaction system is favorable to avoid excess amounts of activated organoboron species leading to homocoupling during the reaction, thereby giving rise to biphenyl as a byproduct. Further examination revealed that the reaction was completed within 3 h and **1a**/**2a**=2:1 ratio gave superior yield (97%).

Finally, we explored various catalyst systems and the results are summarized in Table 3. When we employed Pd(PPh₃)₄, **3a** was obtained in lower yield (60%, Table 3, entry 2) presumably due to suppression of catalytic reaction rate by the presence of excess PPh₃ ligands. Although P(OPh)₃ and P(2-furyl)₃ in combination with Pd(dba)₂ gave satisfactory yields (Table 3, entries 3 and 4), P(*t*-Bu)₃ and PMe₃ as the ligand and Pd(dba)₂ alone gave poor results (Table 3, entries 5–7). As the other palladium catalyst precursor, Pd(OAc)₂ with PPh₃ afforded **3a** in 71% yield, albeit along with 8% yield of biphenyl as the byproduct (Table 3, entry 8). Palladium catalyst containing bidentate phosphine ligand, such as PdCl₂(dppf) gave

Table 3
Cross-coupling reaction of **1a** with **2a** using various catalyst systems^a

Entry	Catalyst	Yield ^b (%)
1	Pd(dba) ₂ /2 PPh ₃	97
2	Pd(PPh ₃) ₄	60
3	Pd(dba) ₂ /2 P(OPh) ₃	92
4	Pd(dba) ₂ /2 P(2-furyl) ₃	72
5	Pd(dba) ₂ /2 P(<i>t</i> -Bu) ₃	14
6	Pd(dba) ₂ /2 PMe ₃	0
7	Pd(dba) ₂	6
8	Pd(OAc) ₂ /2 PPh ₃	71
9	PdCl ₂ (dppf) ^c	15
10	Ni(cod) ₂	<1

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), catalyst (5 mol %) and CuTC (0.1 mmol) in Et₂O (3 mL) at room temperature for 3 h.

^b GC yields.

^c dppf=1,1'-bis(diphenylphosphino)ferrocene.

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