Radical Reactions

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Transition-Metal-Free Alkoxycarbonylation of Aryl Halides**

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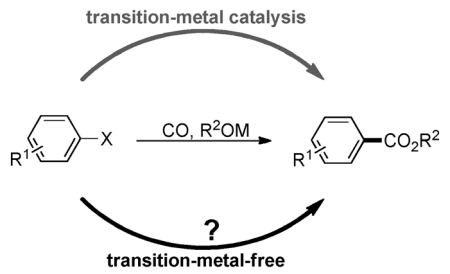
Transition-metal-catalyzed carbonylation involving CO gas is a very important and fundamental chemical transformation, which not only extends the carbon chain length, but also introduces a synthetically versatile carbonyl group. Since the pioneering work of Heck and co-workers,[1,2] transition-metal-catalyzed alkoxycarbonylation of organic halides with CO to afford esters has shown synthetic potential, and been applied in some chemical syntheses during the past several decades (Scheme 1).[3–7] Besides, transition metals, especially palladium- and manganese-catalyzed radical alkoxycarbonylation of alkyl iodides under photoirradiation conditions have also been developed to be an efficient approach towards the synthesis of carboxylic acid esters.[8–13] However, there are still some challenges such as the turnover numbers and turnover frequencies, which hinder its wide industrial application. Generally, low-valent-metal catalysts such as palladium(0) are required to activate the C–X bond, whereas the strong binding ability of CO towards low-valent metals deactivate the catalyst, which present a challenge in this transformation. Therefore, discovering a practical alternative to transition-metal-catalyzed carbonylation and opening a new avenue for the carbonylation by utilizing CO gas is highly desirable.



Scheme 1. Approach to alkoxycarbonylation.

Transition-metal-free processes have recently attracted more and more attention from the synthetic community, and we thought that it might serve as an alternative route to addressing the above-mentioned challenge (Scheme 1). The key challenge of this idea is to determine how to activate C–X without the help of transition-metal catalysts. Radical activation could be an option. Recently, transition-metal-free coupling reactions of aryl halides with arenes and alkenes have been developed, and the combination of MO*t*Bu and bidentate nitrogen ligands was employed to initiate the aryl radical by single-electron transfer (SET).[14–22] Obviously, if aryl radicals were formed, the insertion of CO would produce the acyl radical and further generate a carboxylic derivative. Although known since the 1950s,[23] the potential of radical carbonylation in chemical synthesis has not received a great deal of attention, and in fact, only a few nice results have been reported to date. These results usually involve a xenon photolytic system or AIBN/tin hydride mediated radical-chain reaction employing alkyl iodides as substrates.[24–30] To the best of our knowledge, there is no example of employing a transition-metal-free process in alkoxycarbonylation of aryl halides. Herein, we disclose a protocol for accessing *tert*-butyl benzoates through the transition-metal-free alkoxycarbonylation of aryl halides.

Our experiment was initiated by treating 4-iodotoluene (**1a**) with KO*t*Bu in the presence of a high pressure CO (Table 1). By optimizing various reaction parameters, the best results were obtained with the combination of 40 mol% 1,10-phenanthroline and 4 equivalents of KO*t*Bu in benzene at 90°C under 60 atm CO (Table 1, entry 1). With these reaction conditions, a 75% yield of *tert*-butyl-4-methylbenzoate (**2a**) was obtained after 24 hours with a biaryl by-product originating from C–H arylation with the solvent (benzene). The choice of base was essential for the reaction. NaO*t*Bu and LiO*t*Bu were inefficient for this transformation (Table 1, entries 2 and 3). Using 1,10-phenanthroline as additive gave the highest yield, whereas other additives such as 2,9-dimethyl-1,10-phenanthroline, DMEDA, and TMEDA showed less or no efficiency in terms of chemical yields (Table 1, entries 4–6). The use of 1,4-dioxane or DME as a solvent decreased the yield dramatically (Table 1, entries 7 and 8). When benzene was replaced by DMF, only 7% yield of **2a** was obtained (Table 1, entry 9). A lower loading of the additive led to a decreased yield whereas no reaction occurred in the absence of 1,10-phenanthroline (Table 1, entries 10 and 11). Lowering the CO pressure decreased the yield, whereas higher CO pressures showed no improvement (Table 1, entry 12 and 13).

With the above optimized reaction conditions, a variety of aryl iodides were tested (Table 2). Aryl iodides substituted with a methyl group afforded the corresponding esters in moderate to good yields (Table 2, entries 1–3). The position of

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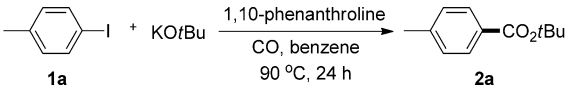
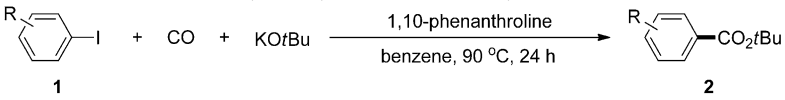
Table 1: Transition-metal-free alkoxycarbonylation of **1a**: Effects of reaction parameters.[a]

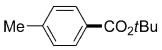
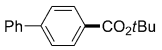
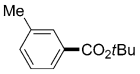
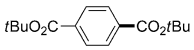
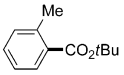
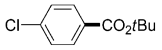
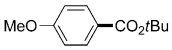
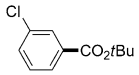
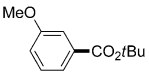
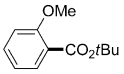
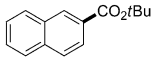
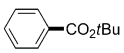
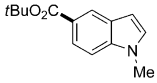
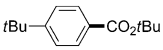
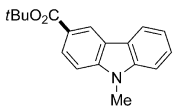


Entry	Variation from standard conditions[a]	Yield [%][b]
1	none	75
2	NaO*t*Bu, instead of KO*t*Bu	2
3	LiO*t*Bu, instead of KO*t*Bu	0
4	**L1**, instead of 1,10-phenanthroline	1
5	DMEDA, instead of 1,10-phenanthroline	27
6	TMEDA, instead of 1,10-phenanthroline	3
7	1,4-dioxane, instead of benzene	27
8	DME, instead of benzene	29
9	DMF, instead of benzene	7
10	20 mol% 1,10-phenanthroline	57
11	without 1,10-phenanthroline	0
12	40 atm CO	49
13	80 atm CO	75

[a] Standard reaction conditions: **1a** (0.5 mmol), 1,10-phenanthroline (40 mol%), KO*t*Bu (4 equiv), 60 atm CO, benzene (2.0 mL), 90 °C, 24 h. [b] The yield was determined by GC analysis by using dibenzofuran as an internal standard. **L1** = 2,9-dimethyl-1,10-phenanthroline. DME = 1,2-dimethoxyethane, DMEDA = *N*,*N*′-dimethylethanediamine, DME = *N*,*N*′-dimethylformamide, TMEDA = tetramethylethylenediamine.

Table 2: Transition-metal-free alkoxycarbonylation of different aryl iodides.[a]



Entry	2	Product	Yield [%][b]	Entry	2	Product	Yield [%][b]
1	**2a**		72	9	**2i**		65[c]
2	**2b**		65	10	**2j**		53[c]
3	**2c**		77	11	**2k**		54[c]
4	**2d**		81[c]	12	**2l**		36[c]
5	**2e**		63[c]	13	**2m**		80[c]
6	**2f**		60[c]	14	**2n**		62[c]
7	**2g**		58[c]	15	**2o**		65[c]
8	**2h**		63[c]	16	**2p**		75[c]

[a] Reaction conditions: 1 (0.5 mmol), 1,10-phenanthroline (40 mol%), KO*t*Bu (4 equiv), 60 atm CO, benzene (2.0 mL), 90 °C, 24 h. [b] Yield of isolated product. [c] Benzotrifluoride (2.0 mL), 105 °C.

substituent seems to have no influence on the product yield. However, when aryl iodides bearing other substituents were employed while using benzene as solvent, the corresponding esters were obtained in poor yields along with high yields of biaryl by-products.

According to the previous published results, electron-deficient benzene derivatives are less-reactive nucleophiles in transition-metal-free C–H arylation reactions.[15] After further optimization, we found that the replacement of benzene with benzotrifluoride at higher temperature could address the aforementioned problem. Furthermore, we investigated the carbonylation of a range of aryl iodides using benzotrifluoride as the solvent. In general, substrates bearing both electron-donating and electron-withdrawing substituents worked well under the modified reaction conditions. The alkoxycarbonylation of aryl iodides bearing methoxy groups produced the esters in moderate to good yields (Table 2, entries 4–6). Iodobenzene reacted well, thus giving the desired ester in a satisfying yield (Table 2, entry 7). The reaction of aryl iodides containing *tert*-butyl and phenyl groups produced the esters **2h** and **2i** in 63% and 65% yield, respectively (Table 2, entries 8 and 9). Surprisingly, an ester group was tolerated under the basic conditions (Table 2, entry 10). Halogen substituents such as Cl could also be tolerated, and provide the possibility for additional product functionalization (Table 2, entries 11 and 12). In a similar manner, α-naphthyl and β-naphthyl esters were obtained in moderate to good yields (Table 2, entries 13 and 14). To our delight, heteroaryl iodides could also be carbonylated to form the corresponding heterocyclic esters (Table 2, entries 15 and 16). We also employed 4-bromotoluene (**3**) in this transition-metal-free alkoxycarbonylation, and **2a** was obtained in 20% yield (Scheme 2).

To gather further insight into our novel transition-metal-free alkoxycarbonylation, radical scavengers, such as TEMPO and 1,1-diphenylethylene, were employed in the reaction of **1a** (Table 3). As a result, the reactions were completely shut down, which could indicate that this transformation involved radical intermediates.

Moreover, electron paramagnetic resonance (EPR) experiments were conducted to reveal some insight into the mechanism. When the benzotrifluoride solvent alone was tested, no signals were observed (see Figure S1 in the Supporting Information). KO*t*Bu or 1,10-phenanthroline in benzotrifluoride also did not show a signal in the EPR spectra (Figures 1a and b). No EPR signal was observed for the mixture of **1a** and KO*t*Bu in benzotrifluoride (Figure 1c), and the EPR spectrum of the mixture of **1a**, KO*t*Bu, and 1,10-phenanthroline displayed

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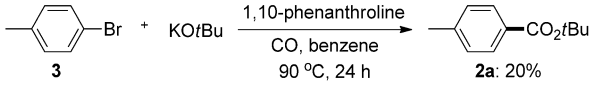
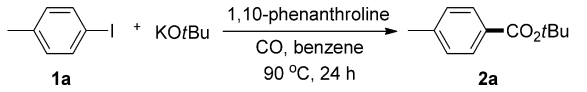


Scheme 2. Transition-metal-free alkoxycarbonylation of aryl bromide.

Table 3: Radical-trapping experiments.[a]



Scavenger	Yield [%][b]
none	75
TEMPO (1 equiv)	0
1,1-diphenylethylene (1 equiv)	0

[a] Reaction conditions: **1a** (0.5 mmol), 1,10-phenanthroline (40 mol%), KO*t*Bu (4 equiv), scavenger (1 equiv), 60 atm CO, benzene (2.0 mL), 90 °C, 24 h. [b] Yield determined by GC analysis. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

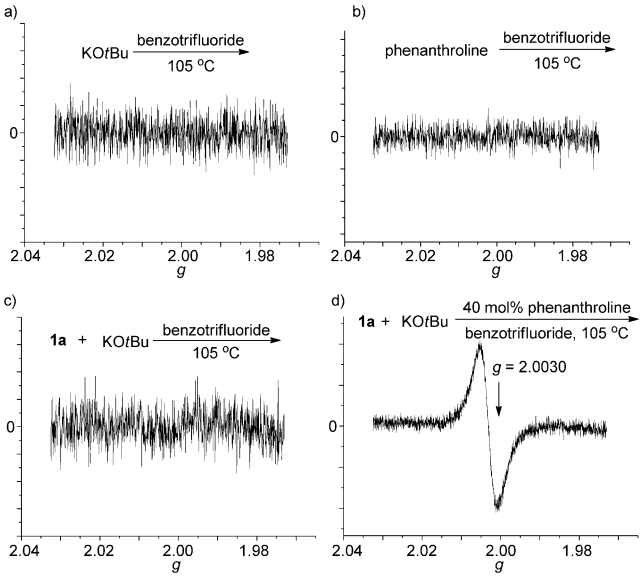
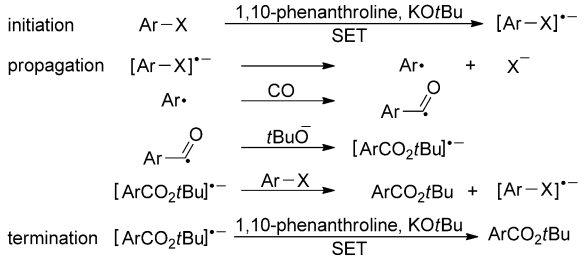


Figure 1. EPR spectra (X band, 9.4 GHz, RT).

a resonance characteristic of an organic radical with an absorption maximum at $g = 2.0030$ (Figure 1 d). The obtained EPR results confirmed the participation of radicals in the reaction system.

According to the previous reports and above results, a radical-chain reaction mechanism is proposed (Scheme 3).[31–33] An aryl halide radical anion is generated from Ar–X by SET in the presence of 1,10-phenanthroline/KO*t*Bu and converted into an aryl radical upon elimination of X^-. The aryl radical reacts with CO to afford an acyl radical, which further reacts with tBuO$^-$ to give the ester radical anion. Then, another SET from the ester radical anion to Ar–X gives product and regenerates an aryl halide radical anion. The reaction is terminated by the formation of product from the ester radical anion by SET in the presence of 1,10-phenanthroline/KO*t*Bu.



Scheme 3. Proposed mechanism.

In conclusion, we have developed the first transition-metal-free alkoxycarbonylation of aryl halides. Moreover, a variety of functional groups were tolerated and heteroaryl iodides were suitable substrates. This transformation provides an effective and practical protocol towards the synthesis of *tert*-butyl benzoates. Preliminary mechanism studies revealed the participation of radicals in the reaction system. Additional exploration of the substrate scope and mechanistic studies, especially EPR investigations, are currently underway and will be reported in due course.

Experimental Section

General procedure: In an oven-dried autoclave tube, 1,10-phenanthroline (40 mol%), KO*t*Bu (4 equiv), and **1** (0.5 mmol) were combined. Benzene (or benzotrifluoride; 2.0 mL) was added to the tube, which was then put in the autoclave. The system was evacuated and refilled with CO three times, and the system pressure was retained at 60 atm. The autoclave was stirred at 90 °C (105 °C for benzotrifluoride) for 24 h and then cooled to room temperature and depressurized. The reaction mixture was quenched by water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with petroleum and ethyl acetate (100:1).

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