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Palladium-Catalyzed Decarboxylative Alkoxycarbonylation of Potassium Aryltrifluoroborates with Potassium Oxalate Monoesters

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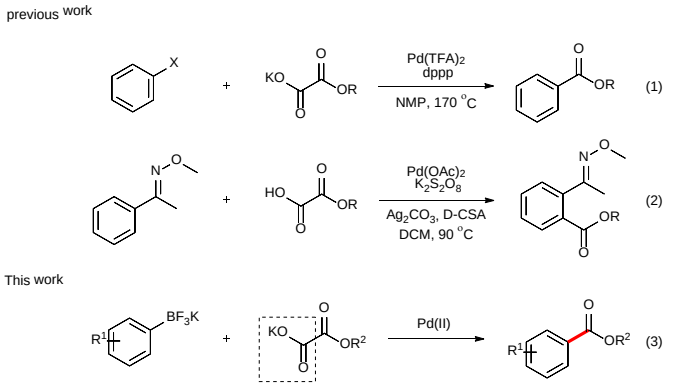
Palladium-catalyzed decarboxylative alkoxycarbonylation of potassium aryltrifluoroborates with potassium oxalate monoesters in the presence of potassium persulfate was performed under mild conditions. A number of benzoyl esters with a wide variety of substituents at different positions were efficiently synthesized with this method. Mechanism of the palladium-catalyzed decarboxylative carbonylation of aryltrifluoroborates was studied, and a radical-mediated Pd(II)/Pd(IV) catalytic cycle was proposed.

Introduction

During the past decade, transition metal-catalyzed cross coupling has been extensively studied as a powerful synthetic tool for selective carbon–carbon (C–C) bond formation.[1] In particular, transition metal-catalyzed decarboxylative coupling has recently attracted more and more attention.[2] Compared with the traditional coupling reactions, this transformation is more environmentally friendly since stoichiometric organometallic waste is replaced by the innocuous CO_2 gas. In addition, as the coupling partners, carboxylic acids are readily available at low cost, fairly stable and easy to handle and store in laboratory. However, although the first decarboxylative cross-coupling reaction was realized with unsatisfactory yield in 1960s,[3] it remained unelaborated until recent years. In 2002, Myers reported the silver-mediated decarboxylation of benzoic acid derivatives, followed by a palladium-catalyzed Heck reaction with alkenes.[4] This discovery opened the door to a new area of synthetic methodology. Later on, the milestone discoveries were reported by Goossen and co-workers,[5] who developed the synthesis of biaryls via palladium/copper-catalyzed decarboxylative coupling of aryl carboxylic acids and aryl halides. Furthermore, alkyl, alkenyl, and alkynyl carboxylic acids were also demonstrated as effective substrates in decarboxylative cross-coupling reactions, turning the methods into highly valuable alternatives to classical reactions for the C–C bond formation.

In 2008, α-oxocarboxylic acids were first utilized as coupling partners by Goossen's group in a Cu/Pd-catalyzed acylation reaction of aryl halides.[6] Alkoxycarbonylation of aryl halides via decarboxylation of oxalate monoesters was later realized by Liu and co-workers (Scheme 1, eq 1).[7] However, high temperature was required for the decarboxylation process in these reports, which limits the substrate scope of these reactions.



Scheme 1 Synthesis of aryl esters with Pd-catalyzed decarboxylative coupling.

Inspired by Minisci's work on peroxydisulfate,[8] we discovered that decarboxylative *ortho*-carbonylation of acetanilides with α-oxocarboxylic acids can be realized at room temperature in the presence of a persulfate.[9] Recently, Wang's group developed the Pd-catalyzed *ortho*-ethoxycarbonylation of *O*-methylketoximes with potassium oxalate monoester using Ag_2CO_3 and $K_2S_2O_8$ as oxidants (eq 2).[10] However, these reactions can be performed only on substrates with a directing group, which limits the potential application of this approach. We envisioned that boronic acids or their derivatives may be utilized in the coupling reactions to broaden the product range of the method. Arylboronic acids and their derivatives are staple substrates in Suzuki-Miyaura coupling reactions.[11] However, the most common pathway of direct transformation from arylboronic acids to carbonyl compounds, the insertion of carbon monoxide,[12] suffers from the use of high pressure of the toxic and flammable CO gas, which diminishes its practical utility. To provide an alternative access to aryl ketones, Goossen

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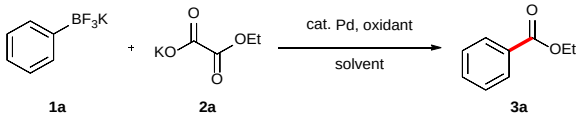
Electronic Supplementary Information (ESI) available: Data table of the time-yield curve and copies of ^1H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/x0xx00000x

and Yamamoto developed the Pd-catalyzed decarboxylative cross-coupling reactions of arylboronic acids with anhydrides, carboxylic acids, and α-oxocarboxylic acids, in which the requirement for high temperature or stoichiometrical expensive metal reagents or strong bases is avoided.[13] Inspired by these results, our group realized the decarboxylative acylation and aminocarbonylation of potassium aryltrifluoroborates with α-oxocarboxylic acids and oxamic acids.[14] Herein, as a supplement to the previous methods, we report the Pd-catalyzed decarboxylative alkoxycarbonylation of potassium aryltrifluoroborates with potassium oxalate monoesters under mild conditions.

Results and Discussion

On the basis of our success on decarboxylative cross coupling of aryltrifluoroborates with α-oxocarboxylic acids and oxamic acids,[14] we investigated the decarboxylative coupling reaction between potassium phenyltrifluoroborate and potassium 2-ethoxy-2-oxoacetate (Table 1). The ethyl benzoate was obtained with 10 mol% $Pd(OAc)_2$ and 2 equiv. $K_2S_2O_8$ in a mixture of DMSO and water at room temperature (entry 1). Further screening of solvent showed that the mixture of MeCN/DMSO/H_2O was the best (entries 2–5). Although $(NH_4)_2S_2O_8$ was also effective, $K_2S_2O_8$ was found to be the optimal oxidant (entries 6 and 7). Gratifyingly, the product yield was improved when the reaction was heated at 70 °C for 5 min and then cooled to room temperature (entry 8). Finally, a high yield was acquired by increasing the amount of the $K_2S_2O_8$ to 3 equiv (entry 9). It was noted that $Pd(OAc)_2$ was the most efficient catalyst in this reaction (entries 9–12). Furthermore, the desired coupling product was not observed in the absence of a palladium catalyst (entry 13).

Table 1 Optimization of reaction conditions[a]



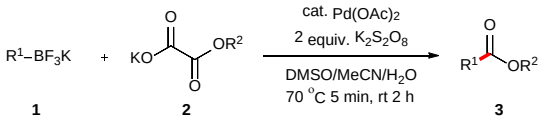
1a 2a 3a

Entry	Pd catalyst	Oxidant	Solvent (v:v)	Yield(%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO/H_2O (4:1)	21
2	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/H_2O (4:1)	<5
3	$Pd(OAc)_2$	$K_2S_2O_8$	DME/H_2O (4:1)	0
4	$Pd(OAc)_2$	$K_2S_2O_8$	diglyme//H_2O (4:1)	0
5	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	30
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	18
7	$Pd(OAc)_2$	H_2O_2	MeCN/DMSO/H_2O (2:2:1)	0
8[c]	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	72
9[c,d]	$Pd(OAc)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	84(82)
10[c,d]	Pd(TFA)2	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	60
11[c,d]	Pd(acac)2	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	39
12[c,d]	$Pd(MeCN)_2(BF_4)_2$	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	68
13[c,d]	-	$K_2S_2O_8$	MeCN/DMSO/H_2O (2:2:1)	0

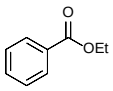
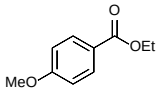
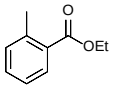
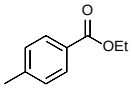
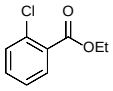
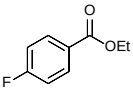
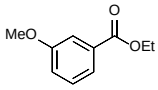
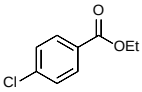
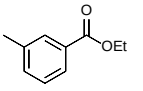
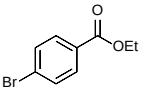
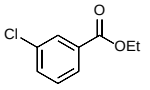
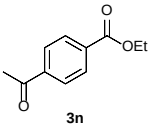
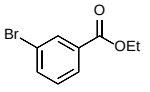
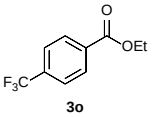
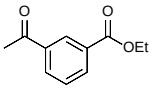
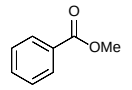
[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), PdX_2, oxidant (0.6 mmol), 6 mL solvent, rt, overnight. [b] Yields and conversions are based on **1a**, determined by ^{1}H-NMR using dibromomethane as the internal standard. Isolated yield is in parenthesis. [c] Preheated at 70 °C for 5 min, and then rt for 1h. [d] With 3.0 eq. (0.6 mmol) $K_2S_2O_8$.

With the optimized conditions in hand, we then investigated the substrate scope of the alkoxycaronylation reaction. As shown in Table 2, a variety of aryl esters were synthesized under the standard conditions. Potassium phenyltrifluoroborates with a methyl group at the *meta*- or *para*-position of the phenyl ring (Table 2, **3e** and **3j**) gave comparable yields to that of **3a**. The *ortho*-methyl phenyltrifluoroborate gave a lower yield than those of the counterparts with a *meta*- or *para*- methyl group (**3b** vs. **3e**, **3j**), presumably due to the steric effect. Ester **3k**, which has a fluoro group at the *para*-postion of the phenyl ring, could be produced in a good yield from the corresponding substrate (**3k**). Methoxy-, chloro-, and bromo-substituted phenyltrifluoroborates gave moderate yields (**3c**, **3d**, **3f**, **3g**, **3i**, **3l** and **3m**), while lower yields were observed with the electron-withdrawing groups on the phenyl ring (**3h**, **3n**, **3o**). In addition, potassium 2-methoxy-2-oxoacetate (**7b**) was demonstrated as a feasible substrate, affording a satisfying yield (**3p**).

Table 2 Alkoxycarbonylation of potassium aryltrifluoroborates[a]



1 2 3

Product	Yield[b] (%)	Product	Yield[b] (%)
 **3a**	82	 **3i**	44
 **3b**	52	 **3j**	76
 **3c**	60	 **3k**	79
 **3d**	43	 **3l**	67
 **3e**	81	 **3m**	63
 **3f**	58	 **3n**	35
 **3g**	63	 **3o**	35
 **3h**	57	 **3p**	76

[a] Conditions: **1** (0.3 mmol), **2a** or **2b** (0.6 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.030 mmol, 10 mol%), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), DMSO/MeCN/H_2O (4:4:2, v/v/v, 6 mL), preheated at 70 °C for 5 min, then at rt for 1h. [b] Isolated yields based on **1**.

Mechanistic study

As mentioned above and in our previous reports[14], the alkoxycarbonylation and aminocarbonylation reactions require heating at the beginning of the reaction. To illustrate the function of increased temperature and thereby to provide some insights of the catalytic process, time courses for acylation, aminocarbonylation, and alkoxycarbonylation of potassium phenyltrifluoroborate were examined (Figures 1 and 2). Not surprisingly, the reaction rates for production of the ketone and the amide at room temperature were comparatively high at the beginning, as most of the product was accumulated in the first 2 hours (Figure 2, red and purple). In the case of heated reactions, the early reaction rates were extraordinarily fast (Figure 2, blue and green). Remarkably, the alkoxycarbonylation process was almost completed within 2 min at 70 °C (Figure 1, pink).

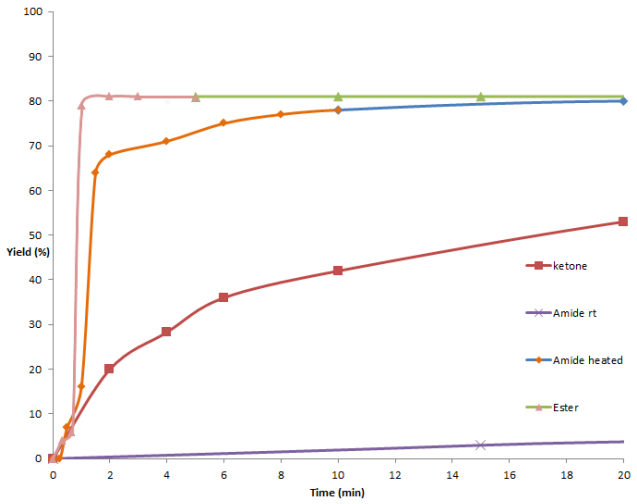


Fig. 1. Time courses of the cross-coupling reactions. 0–20 min.

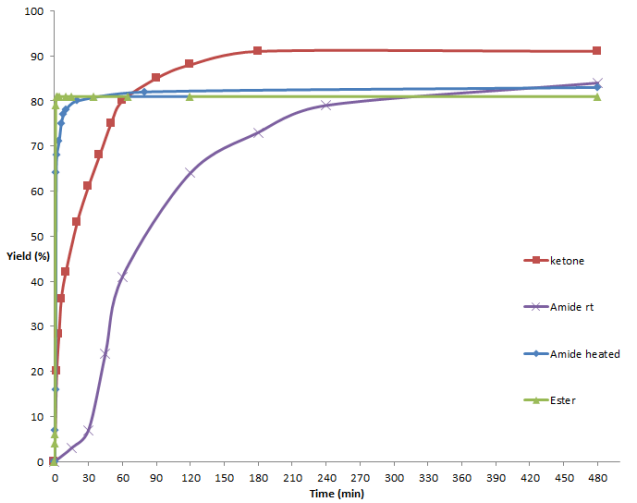
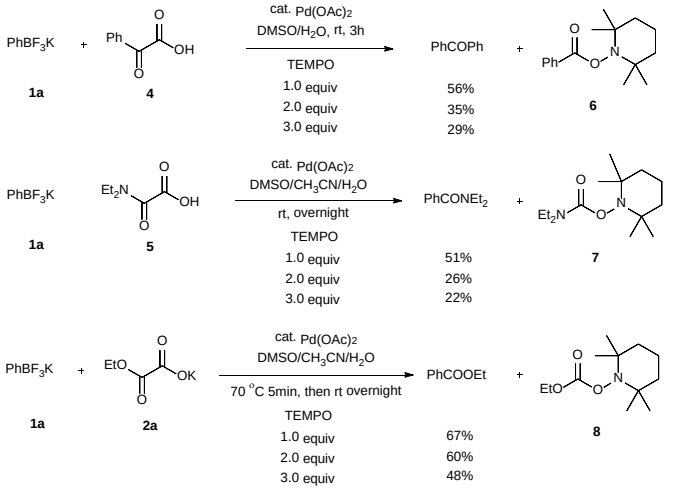


Fig. 2 Time Courses of the cross-coupling reactions. 0–480 min.

To further study the mechanistic aspects of the catalytic decarboxylative cross-coupling, TEMPO was introduced to the reactions under standard conditions as a radical trapping reagent (Scheme 2). It was found that the formation of the decarboxylative coupling products was suppressed, while TEMPO- aldehyde, amide, and ester adducts were detected by LC-MS respectively. The decarboxylative coupling reactions were not completely inhibited, which is consistent with the reaction rate study since the coupling reactions were so fast at the beginning that they could overwhelm the competing reactions. In addition, the yields of the coupling products were reduced by increasing the amount of TEMPO in the reaction systems. Furthermore, the TEMPO adducts were isolated from the control experiments under the similar conditions in the absence of $PhBF_3K$ and $Pd(OAc)_2$ (see experimental section). Thus, all the results suggest that radical intermediates are likely formed and involved in these coupling reactions, which indicates a different reaction pathway from the previously proposed ligand exchange process of direct decarboxylative acylation of acetanlides.[9]



Scheme 2 Control experiments with TEMPO.

Based on the above observations and previous literature reports,[15] a tentative mechanism for the cross coupling is proposed (Figure 3). The reaction is initiated by the transmetallation between the Pd(II) catalyst and the boronic intermediates derived from hydrolysis of the aryltrifluoroborate to afford the Pd(II) intermediate **A**. Oxidation of **A** in the presence of the carbonyl radical **C**, which is formed by the decarboxylation of an α-oxocarboxylic or oxamic acid, generates the Pd(IV) intermediate **B**. The desired carbonyl product is then produced via reductive elimination of **B**, while the Pd(II) species is reproduced. It's noteworthy that a dimeric Pd(III) mechanism cannot be excluded.[16]

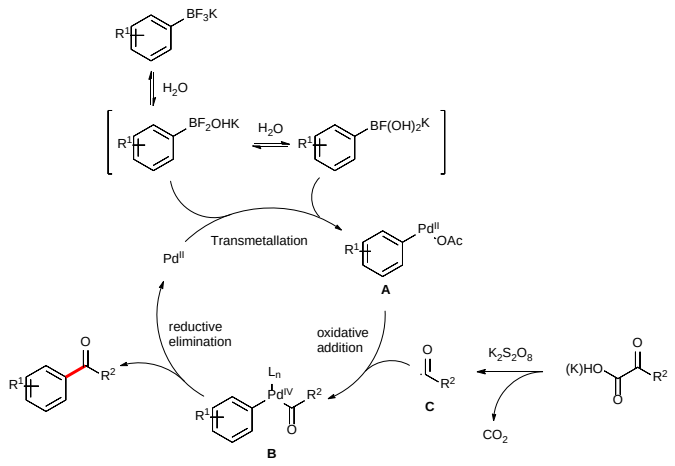


Fig. 3 Plausible Reaction Mechanism. L = Ligand.

Conclusions

In summary, we have demonstrated that a handy and efficient palladium-catalyzed alkoxycarbonylation of potassium aryltrifluoroborates with the decarboxylation of potassium oxalate monoester could be performed under mild and compatible conditions. This unprecedented reaction provides a promising pathway towards a variety of aryl esters. Additionally, the mechanistic study suggests that radicals should be involved in this process, constituting the possible Pd(II)/Pd(IV) catalytic cycle.

Experimental

General Methods

All reactions were carried out in oven-dried glassware. Pd (II) catalysts, Ag_2CO_3, $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were purchased and used directly. All other solvents and commercially available reagents (boronic acids, KHF_2, amines and potassium oxalate monoester) were purchased and used directly. For TLC analysis, precoated plates (0.25 mm thick) were used; for air-flashed column chromatography, flash silica gel (32–63 μm) was used. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz), using $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard at room temperature. ^{1}H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm).

Starting Materials

Potassium aryltrifluoroborates (**1a**, **1i, 1j** and **1l**) and potassium oxalate monoesters (**2a, 2b)** were purchased and used directly. Other potassium aryltrifluoroborates were prepared from boronic acids with KHF_2 according to the reported procedure.[17] *N*,*N*-diethyloxamic acid (**5**) was prepared from diethyl oxalate with *N*,*N*-diethylamine according to the reported procedure.[18]

General Procedure for the synthesis of Aryl esters (3)

An 8 mL vial was charged with magnetic bar, $ArBF_3K$ (**1**, 0.3 mmol), potassium oxalic acid monoesters (**2**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.6 mmol, 2.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.03mmol/2.4mL, 10 mol%, 2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction mixture was stirred at 70 °C for 5 min, and then cooled down to room temperature and stirred for 1h. The reaction was quenched by the addition of 3 mL of water and the resulting mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was dried over Na_2SO_4, and then concentrated under vacuum. The desired product was obtained after purification by flash chromatography column on silica gel (gradient eluent of EtOAc in Hexanes: 0 ~ 30%, v/v).

Ethyl benzoate (3a) (CAS No. 93-89-0). Colorless oil, 36.9 mg, 82% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.36 (t, *J* = 7.0 Hz, 3 H), 4.35 (q, *J* = 7.0 Hz, 2 H), 7.36–7.42 (m, 2 H), 7.51 (t, *J* = 7.5 Hz, 1 H), 8.03 (d, *J* = 7.5 Hz, 2 H).

Ethyl 2-methylbenzoate (3b) (CAS No. 87-24-1). Colorless oil, 26.1 mg, 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.39 (t, *J* = 7.0 Hz, 3 H), 2.60 (s, 3 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 7.22–7.26 (m, 2 H), 7.39 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.89–7.92 (m, 1 H).

Ethyl 2-chlorobenzoate (3c) (CAS No. 7335-25-3). Colorless oil, 33.2 mg, 60% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.40 (t, *J* = 7.0 Hz, 3 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 7.30 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.37-7.46 (m, 2 H), 7.80 (dd, J = 1.5, 8.0 Hz, 1 H).

Ethyl 3-methoxybenzoate (3d) (CAS No. 10259-22-0). Colorless oil, 23.2 mg, 43% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.39 (t, *J* = 7.0 Hz, 3 H), 3.85 (s, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 7.09 (ddd, J = 1.0, 2.5, 8.0 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 7.56 (dd, J = 1.5, 3.0 Hz, 1 H), 7.64 (td, 1.5, 7.5 Hz, 1 H).

Ethyl 3-methylbenzoate (3e) (CAS No. 120-33-2). Colorless oil, 39.9 mg, 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.39 (t, *J* = 7.0 Hz, 3 H), 2.40 (s, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 7.30-7.37 (m, 2 H), 7.83-7.87 (m, 2 H).

Ethyl 3-chlorobenzoate (3f) (CAS No. 1128-76-3). Colorless oil, 32.1 mg, 58% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.38 (t, *J* = 7.0 Hz, 3 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.46-7.51 (m, 1 H), 7.90 (d, *J* = 7.5 Hz, 1 H), 7.99 (t, *J* = 1.5 Hz, 1 H).

Ethyl 3-bromobenzoate (3g) (CAS No. 24398-88-7). Colorless oil, 43.3 mg, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.39 (t, *J* = 7.0 Hz, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 7.65–7.68 (m, 1 H), 7.96 (d, *J* = 8.0, 1 H), 8.16–8.18 (m, 1 H).

Ethyl 3-acetylbenzoate (3h) (CAS No. 37847-24-8). Colorless oil, 32.9 mg, 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.42 (t, *J* = 7.0 Hz, 3 H), 2.65 (s, 3 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 8.15 (td, *J* = 1.5, 7.5 Hz, 1 H), 8.24 (td, *J* = 1.5, 7.5 Hz, 1 H), 8.59 (t, *J* = 1.5 Hz, 1 H).

Ethyl 4-methoxybenzoate (3i) (CAS No. 94-30-4). Colorless oil, 23.8 mg, 44% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.38 (t, *J* = 7.0 Hz, 3 H), 3.86 (s, 3 H), 4.34 (q, *J* = 7.0 Hz, 2 H), 6.89-6.93 (m, 2 H), 7.98-8.02 (m, 2 H).

Ethyl 4-methylbenzoate (3j) (CAS No. 94-08-6). Colorless oil, 36.9 mg, 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.39 (t, *J* = 7.0 Hz, 3 H), 2.40 (s, 3 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 8.11-8.14 (m, 2 H).

Ethyl 4-fluorobenzoate (3k) (CAS No. 451-46-7). Colorless oil, 39.9 mg, 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.38 (t, *J* = 7.0

Hz, 3 H), 4.36 (q, *J* = 7.0 Hz, 2 H), 7.07-7.11 (m, 2 H), 8.03-8.07 (m, 2 H).

Ethyl 4-chlorobenzoate (3l) (CAS No. 7335-27-5). Colorless oil, 37.1 mg, 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, *J* = 7.0 Hz, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 7.39-7.42 (m, 2 H), 7.96-7.99 (m, 2 H).

Ethyl 4-bromobenzoate (3m) (CAS No. 5798-75-4). Colorless oil, 43.4 mg, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (t, *J* = 7.0 Hz, 3 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 7.56-7.58 (m, 2 H), 7.89-7.91 (m, 2 H).

Ethyl 4-acetylbenzoate (3n) (CAS No. 38430-55-6). Colorless oil, 20.2 mg, 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (t, *J* = 7.0 Hz, 3 H), 2.64 (s, 3 H), 4.40 (q, *J* = 7.0 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.92-7.95 (m, 2 H).

Ethyl 4-(trilfuoromethyl)benzoate (3o) (CAS No. 93-58-3). Colorless oil, 22.9 mg, 35% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.0 Hz, 3 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 8.16 (d, *J* = 8.0 Hz, 2 H).

Methyl benzoate (3p) (CAS No. 1696-17-9). Colorless oil, 31.0 mg, 76% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.92 (s, 3 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.53-7.58 (m, 1 H), 8.04 (dd, J = 1.5, 8.0 Hz, 2 H).

Time–Yield Curve in Formation of Benzophenone (Figure 1, red markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $ArBF_3K$ (**1a**, 0.3 mmol), 2-oxo-2-phenylacetic acid (**4**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.6 mmol, 2.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.0075 mmol/1.2 mL, 2.5 mol %, 1.2 mL) and DI water (1.8 mL, DMSO: DI water = 1/1.5, v/v, 3 ml in total). The vial was capped and then the reaction mixture was stirred at room temperature. At each interval, NaOH (1 N, 3 mL) was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of benzophenone were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time–Yield Curve in Formation of *N,N*-diethylbenzamide at room temperature (Figure 1, purple markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol), 2-(diethylamino)-2-oxoacetic acid (**5**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.015 mmol/2.4 mL, 5 mol %, 2.4 mL), CH_3CN and DI water (DMSO: CH_3CN: DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and then the reaction mixture was stirred at room temperature. At each interval, NaOH (1 N, 3 mL) was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of *N,N*-diethylbenzamide were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time–Yield Curve in Formation of *N,N*-diethylbenzamide, heated (Figure 1, orange and blue markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol), 2-(diethylamino)-2-oxoacetic acid (**5**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.9 mmol, 3.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.015 mmol/2.4 mL, 5 mol %, 2.4 mL), CH_3CN and DI water (DMSO: CH_3CN: DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and the reaction mixture was stirred at 70 °C for 10 min, and then stirred at room temperature. At each interval, the vial is cooled with water bath immediately, and then 3 mL water was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of *N,N*-diethylbenzamide were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Time–Yield Curve in Formation of Ethyl benzoate (Figure 1, pink and green markers)

Parallel experiments were carried out with the procedure described below. An 8 mL vial was charged with magnetic stir bar, $PhBF_3K$ (**1a**, 0.3 mmol potassium 2-ethoxy-2-oxoacetate (**2a**, 0.6 mmol, 2.0 equiv.), $K_2S_2O_8$ (0.6 mmol, 2.0 equiv.), followed by $Pd(OAc)_2$ (DMSO solution, 0.03mmol/2.4mL, 10 mol%, 2.4 mL), CH_3CN and DI water (DMSO: CH_3CN: DI water = 4/4/2, v/v/v, 6 ml in total). The vial was capped and the reaction mixture was stirred at 70 °C for 5 min, and then stirred at room temperature. At each interval, the vial is cooled with water bath immediately, and then 3mL of water was added and the reaction mixture was extracted with EtOAc (5 mL × 3). The combined organic phase was concentrated under vacuum. The yields of ethyl benzoate were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Control Experiments with TEMPO in the Coupling Reactions

The reactions were performed with standard procedures described above or in our previous reports[14] except that TEMPO was added into the vial before $Pd(OAc)_2$ and the solvents. Product yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Synthesis of 2,2,6,6-tetramethylpiperidin-1-yl benzoate (6) *(CAS No. 7031-95-0)*. An 8 mL vial was charge with 2-oxo-2-phenylacetic acid (**4**, 0.6 mmol), $K_2S_2O_8$ (0.6 mmol, 1.0 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (1.2 mL) and DI water (1.8 mL). The vial was capped and the reaction was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (s, 6 H), 1.44 (s, 6 H), 1.58–1.65 (m, 1 H), 1.70–1.78 (m, 2 H), 1.81–1.98 (m, 3 H), 7.58–7.65 (m, 2 H), 7.69–7.75 (m, 1 H), 8.24 (d, *J* =7.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.6, 18.4, 29.5, 36.6, 57.9, 126.1, 127.1, 127.3, 130.5, 163.9. IR (neat), v: 3062, 2974, 2934, 2871, 1749, 1600, 1451, 1254 cm^{-1}. Ms (ESI): m/z = 262.4 [M + H^+].

Synthesis of 2,2,6,6-tetramethylpiperidin-1-yl diethylcarbamate (7). An 8 mL vial was charge with 2-(diethylamino)-2-oxoacetic acid (**5**, 0.6 mmol), $K_2S_2O_8$ (0.9 mmol, 1.5 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction was stirred at 70 °C for 30 min, and then stirred at room temperature overnight. The reaction

mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07–1.21 (m, 18 H), 1.36–1.43 (m, 1 H), 1.47–1.53 (m, 2 H), 1.56–1.66 (m, 1 H), 1.67–1.74 (m, 2 H), 3.30 (q, J = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 14.8, 17.4, 21.4, 32.1, 39.4, 41.5, 42.5, 60.3, 157.1. IR (neat), v: 2973, 2933, 2873, 1729, 1472, 1456, 1412, 1265 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{29}N_2O_2$ 257.2224, found 257.2226.

Synthesis of ethyl (2,2,6,6-tetramethylpiperidin-1-yl) carbonate (8). An 8 mL vial was charge with potassium 2-ethoxy-2-oxoacetate (**2a**, 0.6 mmol), $K_2S_2O_8$ (0.6 mmol, 1.0 equiv.) and TEMPO (0.6 mmol, 1.0 equiv.), followed by DMSO (2.4 mL), CH_3CN (2.4 mL) and DI water (1.2 mL). The vial was capped and the reaction was stirred at 70 °C for 30 min, and then stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (5 mL × 3), and the combined organic phase was dried over Na_2SO_4, concentrated. Flash chromatography afforded the desired product as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (s, 6 H), 1.17 (s, 6 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.37–1.42 (m, 1 H), 1.49–1.55 (m, 2 H), 1.60–1.72 (m, 3 H), 4.22 (q, J = 7.1 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 17.3, 20.8, 31.9, 39.6, 60.8, 64.4, 157.1. IR (neat), v: 2979, 2935, 2873, 2860, 1775, 1747, 1465, 1365, 1220 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{24}NO_3$ 230.1751, found 230.1751.

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