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Palladium-Catalyzed Intramolecular Decarboxylative Coupling of Arene Carboxylic Acids/Esters with Aryl Bromides

Zengming Shen,*[a] Zhenjie Ni,[b] Song Mo,[b] Jing Wang,[b] and Yamin Zhu[a]

The transition-metal-catalyzed decarboxylation of aromatic carboxylic acids has emerged as an exciting strategy in organic synthesis because it enables the formation of aryl–metal intermediates by loss of CO_2. This process can provide unconventional alternatives to perform various types of C–C and C–heteroatom bond-forming reactions relative to typical organometallic reagents.[1]

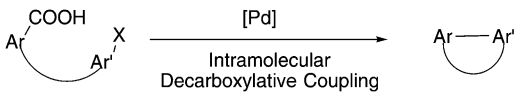
It is known that transition-metal-catalyzed cross-coupling reactions with organometallic reagents as coupling partners for the formation of unsymmetrical biaryl compounds, such as the Suzuki–Miyaura coupling reaction [Eq. (1)], have proven to be versatile and powerful methods.[2] However, drawbacks to this reaction still exist, including the limited commercial availability of some coupling partners or their tedious preparation and the sensitivity of some organometallic reagents. As an alternative approach, considerable attention has been paid to the investigation of transition-metal-catalyzed decarboxylative cross-coupling of arene carboxylic acids with aryl halides for the synthesis of biaryl motifs [Eq. (2)].[1]

$$Ar{-}B(OH)_2 + Ar'{-}X \xrightarrow{[Pd]} Ar{-}Ar' \quad (1)$$

$$Ar{-}COOH + Ar'{-}X \xrightarrow[\text{Intermolecular Decarboxylation Coupling}]{[Pd]/[Cu] \text{ or } [Pd]/[Ag] \text{ or } [Pd]} Ar{-}Ar' \quad (2)$$

Carboxylic acids are desirable cross-coupling partners owing to their prevalence in nature, ease of handling relative to organometallic reagents, high regioselectivity at the carboxylic acid position relative to that of C–H functionalization,[3,10c,11] and the generation of CO_2 as the waste product. Since Nilsson reported the first example of transition-metal-mediated decarboxylative biaryl coupling,[4] breakthroughs have been achieved by the groups of Goossen,[5] Myers,[6] and others[7–11] in the development of decarboxylative cross-coupling reactions. Prominent examples include the bimetallic Pd/Cu-catalyzed intermolecular decarboxylative coupling of benzoic acids with aryl halides, tosylates or triflates by Goossen et al.,[5] the palladium-catalyzed decarboxylative Heck-type coupling of olefin and arene carboxylic acids by Myers et al. (for which stoichiometric quantities of a Ag salt is often required),[6] and the Cu-catalyzed decarboxylative coupling of polyfluorobenzoates with aryl halides by Liu et al.[7a]

To the best of our knowledge, however, the Pd-catalyzed intramolecular decarboxylative arylation of benzoic acids with aryl halides has not been well explored. Steglich and co-workers have reported an intramolecular Heck-type coupling between a tetrasubstituted pyrrole carboxylic acid and a tethered aryl bromide in the synthesis of lamellarin L/G, employing a stoichiometric amount of palladium.[12] Recently, Forgione et al. improved this stoichiometric palladium-promoted intramolecular reaction to a catalytic system under microwave irradiation at 170 °C, but this reaction was demonstrated for only two heteroaromatic acids.[9] As a consequence, the development of a general intramolecular decarboxylative cross-coupling of benzoic acid with haloarenes is still a target in organic synthesis. Herein, we wish to report a concise and efficient protocol for the palladium-catalyzed intramolecular arylation of arene carboxylic acids with aryl halides through a decarboxylative cross-coupling pathway under mild conditions [Eq. (3)].



(3)

For our initial investigation of the intramolecular decarboxylative coupling, we chose the readily available 2-[(2-bromobenzyl)oxy]benzoic acid **1a** as a test substrate (Table 1). Inspired by the Goossen Pd/Cu catalyst system, we first attempted a combination of $Pd(OAc)_2$ (1 mol%) and CuI (3 mol%) as the catalyst with 1,10-phenanthroline as the ligand and K_2CO_3 as the base in *N*-methylpyrrolidone (NMP) at 170 °C for 24 h. Pleasingly, a 36% yield of the de-

[a] Prof. Dr. Z. Shen, Y. Zhu
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 DongChuan Road, Shanghai, 200240 (P.R. China)
Fax: (+86) 21-54741297
E-mail: shenzengming@sjtu.edu.cn

[b] M. Sc. Z. Ni, S. Mo, J. Wang
Department of Chemistry, College of Life and Environment Sciences
Shanghai Normal University
100 Guilin Road, Shanghai, 200234 (P.R. China)

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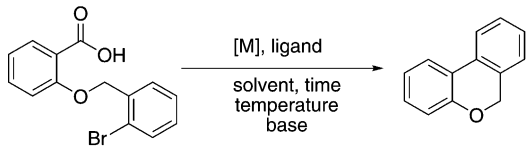
Table 1. Screening of reaction conditions.[a]



1a **2a**

	Catalyst ([mol%])	Ligand ([mol%])	T [°C]	Yield [%][b]
1	CuI (3), $Pd(OAc)_2$ (1)	1,10-Phen (5)	170	36
2	CuI (10)	1,10-Phen (11)	150	trace
3	$Cu(OTf)_2$ (10)	1,10-Phen (11)	150	trace
4	$Pd(OAc)_2$ (10)	1,10-Phen (11)	150	87
5	$[Pd_2(dba)_3]$ (10)	–	150	22
6	$[Pd(PPh_3)_4]$ (10)	–	150	62
7[c]	$Pd(OAc)_2$ (10)	PPh_3 (20)	120	96
8[c]	$Pd(OAc)_2$ (4)	PPh_3 (8)	120	97
9[c]	$Pd(OAc)_2$ (4)	PCy_3 (8)	120	96
10[c]	$Pd(OAc)_2$ (4)	PCy_3 (8)	75	trace
11[c]	$Pd(OAc)_2$ (4)	PPh_3 (8)	75	96[d]
12[c]	$Pd(OAc)_2$ (4)	PPh_3 (8)	60	0

[a] Reaction conditions: substrate **1a** (1 equiv), catalyst, ligand, K_2CO_3 (1.2 equiv), NMP (0.2 M), under a nitrogen atmosphere for 24 h (dba = dibenzylideneacetone; 1,10-Phen = 1,10-phenanthroline). [b] Yield determined by GC with *n*-dodecane as the internal standard. [c] Reaction time: 12 h. [d] Isolated yield.

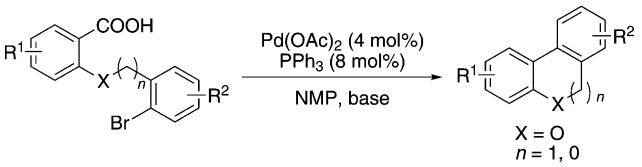
sired compound 6*H*-benzo[*c*]chromene (**2a**) was obtained under these conditions together with the competing protodecarboxylation product (Table 1, entry 1). This observation indicated that a good yield of **2a** could potentially be achieved by suppressing the formation of the decarboxylative protonolysis product in an optimized system.

Further investigations showed that catalytic copper alone, such as CuI or $Cu(OTf)_2$ (OTf = triflate), could not promote this reaction (Table 1, entries 2 and 3). Surprisingly, $Pd(OAc)_2$ (10 mol%) with 1,10-phenanthroline (11 mol%) at 150 °C in the absence of a copper catalyst smoothly provided product **2a** in an 87% yield (Table 1, entry 4). Other palladium complexes, such as $[Pd_2(dba)_3]$ and $[Pd(PPh_3)_4]$, were found to be inferior to $Pd(OAc)_2$ (Table 1, entries 5 and 6). If 1,10-phenanthroline was replaced with PPh_3, an excellent yield (96%) of **2a** was obtained at 120 °C (Table 1, entry 7). Decreasing the loading of $Pd(OAc)_2$ from 10 mol% to 4 mol% resulted in full conversion within 12 h (Table 1, entry 8). Finally, we were pleased to discover that the intramolecular decarboxylative coupling reaction could be conducted at a lower temperature (75 °C). It is interesting that, at 75 °C, $Pd(OAc)_2/PPh_3$ smoothly catalyzed this decarboxylative coupling process, whereas $Pd(OAc)_2/PCy_3$ (Cy = cyclohexyl) shut down the reaction at this temperature (Table 1, entries 10 and 11). Accordingly, the Pd-catalyzed decarboxyaltive coupling performed in the presence of $Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), and K_2CO_3 (1.2 equiv) in NMP at 75 °C for 12 h provided the desired coupling product **2a** exclusively (Table 1, entry 11).

With the optimized reaction conditions in hand, we attempted to extend the scope and generality of this intramolecular decarboxylative coupling reaction, as shown in Tables 2 and 3. We found that ether- and amine-containing arene carboxylic acids **1** were highly reactive and efficiently provided the intramolecular decarboxylative coupling products.

For the ether-containing substrates (Table 2), electron-rich groups (e.g., CH_3 and OMe) either on the benzoic acid or on the haloarene portion of the reagent could smoothly undergo the decarboxylation/coupling process at 75 °C to exclusively provide the desired products in 88–99% yields (Table 2, entries 2–4 and 8). However, for the naphthyl-based acid **1e** and electron-deficient substituents (for exam-

Table 2. Scope of the biaryl formation.[a]



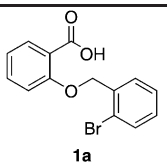
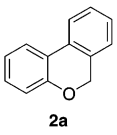
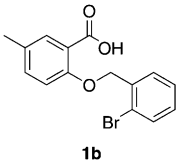
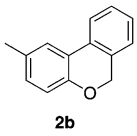
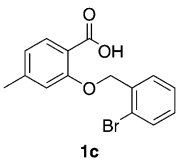
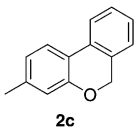
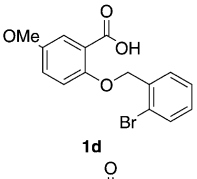
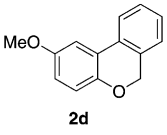
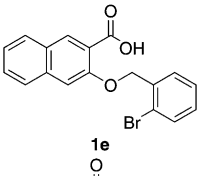
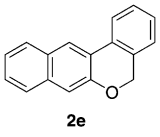
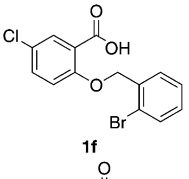
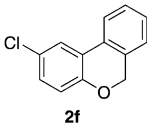
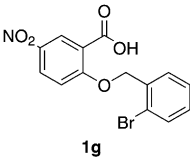
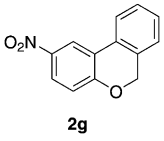
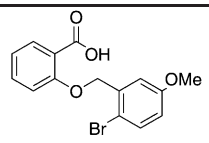
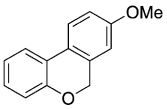
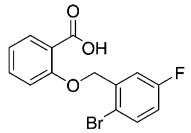
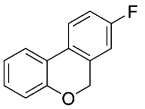
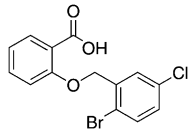
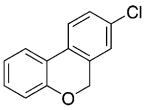
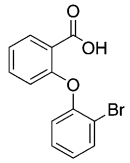
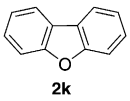
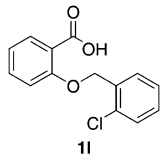
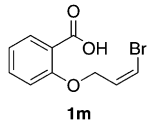
	Substrate	Product	T [°C]	t [h]	Yield [%][b]
1	 **1a**	 **2a**	75	12	96
2	 **1b**	 **2b**	75	12	>99
3	 **1c**	 **2c**	75	12	92
4	 **1d**	 **2d**	75	12	88
5	 **1e**	 **2e**	120	7	98
6	 **1f**	 **2f**	120	7	92
7	 **1g**	 **2g**	150	24	–

Table 2. (Continued)

	Substrate	Product	*T* [°C]	*t* [h]	Yield [%][b]
8	 **1h**	 **2h**	75	21	96
9	 **1i**	 **2i**	75	12	85
10	 **1j**	 **2j**	120	7	74
11	 **1k**	 **2k**	120	24	83
12	 **1l**	**2a**	150	72	25
13	 **1m**		120	24	–

[a] Reaction conditions: under a nitrogen atmosphere, substrate (1 equiv), $Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), K_2CO_3 (1.2 equiv), NMP (0.2 M). [b] Isolated yield.

ple, Cl (**1f**) and NO_2 (**1g**)), no reaction was observed at 75 °C. However, upon heating to 120 °C, **1e**, **1f**, and **1j** smoothly produced the coupling products in high yields (74–98%; Table 2, entries 5, 6, and 10). Notably, naphthyl-based acid **1e** gave a single coupling product **2e** (Table 2, entry 5). In the report by Fagnou et al., on the other hand, the naphthyl substrate with a tethered aryl bromide gave two regioisomeric products through C–H bond activation at the α and β positions on the naphthyl ring.[3d] This case shows that the decarboxylative coupling has higher regioselectivity for the carboxylic acid position than C–H activation. Disappointingly, the strongly electron-withdrawing NO_2 group (**1g**) did not provide the corresponding product even at 150 °C (Table 2, entry 7). Cl and F atoms were tolerated in biaryl products **2f**, **2i**, and **2j**, which provides possible pathways for further functionalization and applications in organic synthesis (Table 2, entries 6, 9, and 10).

In addition to six-membered-ring products, dibenzo[*b*,*d*]furan (**2k**) was formed under the standard conditions in 83% yield (Table 2, entry 11). Furthermore, we observed that aryl chloride substrate **1l** could also be utilized in the decarboxylative coupling at 150 °C over 3 days to provide the corresponding product **2a**, albeit in a moderate 25% yield (Table 2, entry 12). This result indicates that the reactivity of the aryl chloride is substantially lower than that of the corresponding aryl bromide substrate. Unfortunately, alkenyl bromide **1m** did not lead to the desired coupling product, due to the formation of 2-(prop-2-yn-1-yloxy)benzoic acid through dehydrobromidation under the reaction conditions (Table 2, entry 13).

The reaction scope is not limited to ether substrates, amine-containing substrates and heteroaromatic acids are also tolerated (Table 3). During these studies, a strong dependence on the nitrogen substitution pattern was ob-

Table 3. Scope of the biaryl formation.[a]

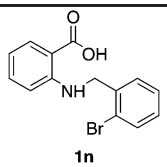
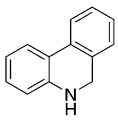
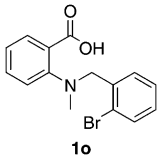
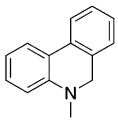
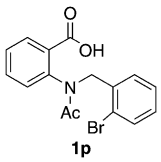
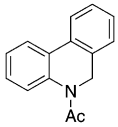
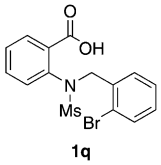
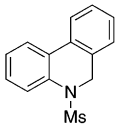
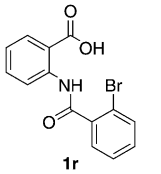
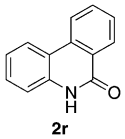
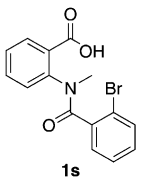
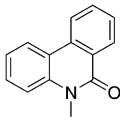
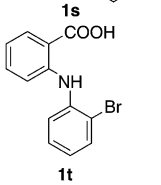
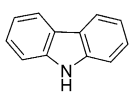
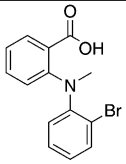
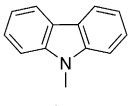
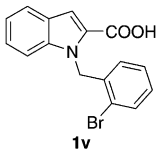
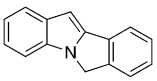
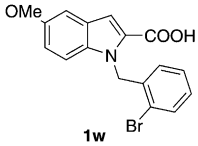
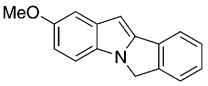
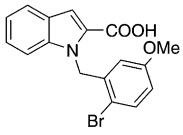
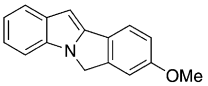
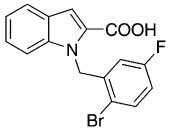
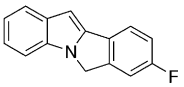
	Substrate	Product	*T* [°C]	*t* [h]	Yield [%][b]
1	 **1n**	 **2n**	120	24	–
2	 **1o**	 **2o**	120	48	72
3	 **1p**	 **2p**	120	72	58
4	 **1q**	 **2q**	120	24	–
5	 **1r**	 **2r**	120	24	–
6	 **1s**	 **2s**	120	24	60
7	 **1t**	 **2t**	120	24	–

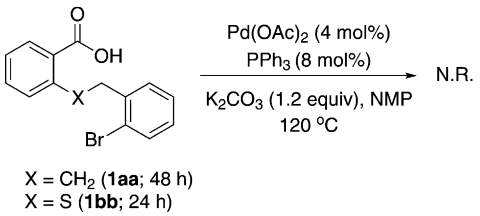
Table 3. (Continued)

	Substrate	Product	*T* [°C]	*t* [h]	Yield [%][b]
8	 **1u**	 **2u**	75	28	86
9	 **1v**	 **2v**	75	24	93
10	 **1w**	 **2w**	120	60	79
11	 **1x**	 **2x**	120	48	85
12	 **1y**	 **2y**	75	48	74

[a] Reaction conditions: under a nitrogen atmosphere, substrate (1 equiv), $Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), K_2CO_3 (1.2 equiv), NMP (0.2 M). [b] Isolated yield.

served.[13] Surprisingly, when the ether oxygen was switched for an N–H group, substrate **1n** did not form the desired product under the standard conditions, even at 120 °C (Table 3, entry 1). We believe that the electronic and steric properties of the nitrogen atom may play a pivotal role in coordinating to the palladium catalyst and controlling the reaction efficiency. Keeping this hypothesis in mind, we adjusted the substituent on the nitrogen atom and discovered that a methyl (**1o**) or acetyl group (**1p**) on the nitrogen atom efficiently promoted the intramolecular decarboxylative coupling process (72 and 58% yields, respectively, Table 3, entries 2 and 3). Interestingly, when the nitrogen atom has a mesyl group attached to it, none of the corresponding product was observed (Table 3, entry 4). Analogous trends were discovered for substrates **1r–u** (Table 3, entries 5–8).

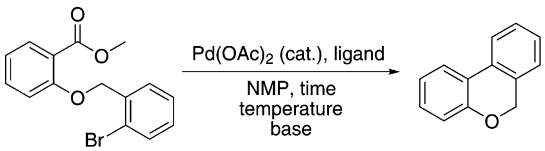
To further understand the effect of neighboring-group coordination, we subjected compound **1aa**, bearing a carbon atom in place of the oxygen atom, to our standard conditions, which resulted in no observable coupling product [Eq. (4)]. In addition, we synthesized thioether substrate **1bb**, which is considered to have strong coordination ability with transition metals, and found that no reaction occurred with this substrate either [Eq. (4)]. Thus, in agreement with our proposal, a suitable coordinating ability of the neighboring heteroatom appears to be critical for this reaction. Moreover, we were pleased to find that indole acids **1v–1y** could smoothly undergo the decarboxylative coupling reaction to form the corresponding products **2v–2y** in high yields (Table 3, entries 9–12). The reaction provides a simple and efficient method to synthesize potentially bioactive compounds containing an indole framework.[14]



(4)

Next, we envisaged that the direct use of esters instead of carboxylic acids could shorten synthetic sequences if the ester hydrolysis and cross-coupling could be conducted in one pot. One challenge in the design of such a process is the rate match between the hydrolysis/decaryboxylation of the ester and the oxidative addition of the aryl bromide. Pleasingly, our initial efforts to apply the optimized conditions for carboxylic acid substrates to ester substrates were successful, as summarized in Table 4. A 35% yield of **2a** formed from ester **3a** was obtained under the standard conditions ($Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (11 mol%), and K_2CO_3 (1.2 equiv) in NMP at 150 °C; Table 4, entry 1). With this promising preliminary result in hand, different bases

Table 4. Optimization of conditions for the intramolecular decarboxylative coupling of esters with aryl bromides.[a]



3a **2a**

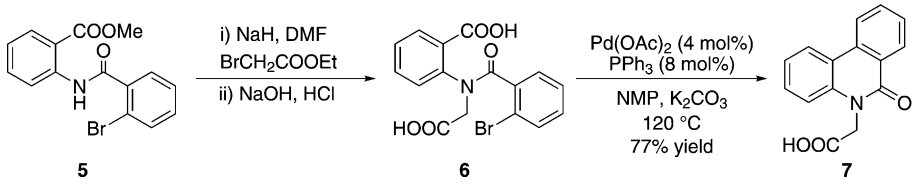
	Pd Loading [mol%]	Ligand ([mol%])	Base ([equiv])	Yield [%][b]
1	10	1,10-Phen (11)	K_2CO_3 (1.2)	35
2	10	1,10-Phen (11)	Na_2CO_3 (1.2)	7
3	10	1,10-Phen (11)	NaOH (1.2)	17
5	10	1,10-Phen (11)	KOH(1.2)	12
6	10	1,10-Phen (11)	Cs_2CO_3 (1.2)	9
7	10	1,10-Phen (11)	*t*BuOLi (1.2)	15
8	10	1,10-Phen (11)	*t*BuOK (1.2)	21
9	10	1,10-Phen (11)	*t*BuONa (1.2)	43
10	10	1,10-Phen (11)	*t*BuONa (1.2), H_2O (5)	24
11	10	1,10-Phen (11)	*t*BuONa (1.2), H_2O (2)	45
12	4	PPh_3 (8)	*t*BuONa (1.2), H_2O (2)	67
13[c]	4	PPh_3 (8)	*t*BuONa (1.2), H_2O (2)	85[d]

[a] Reaction conditions: under a nitrogen atmosphere, substrate (1 equiv), catalyst, ligand, base, NMP (0.2 M), 150 °C, 24 h. [b] Yield determined by GC with *n*-dodecane as the internal standard. [c] At 100 °C for 15 h. [d] Isolated yield.

were screened in the reaction and gave low to moderate yields (Table 4, entries 2–9). It is likely that some moisture in these systems promoted the reaction, allowing it to occur. We found that *t*BuONa with 2 equivalents of H_2O and by using PPh_3 as the ligand at 100 °C led to the best result and increased the yield to 85 % (Table 4, entry 13). The two equivalents of H_2O were required to promote the in situ hydrolysis of the ester.

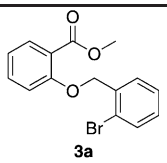
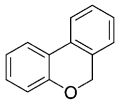
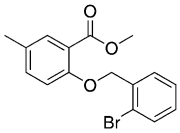
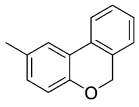
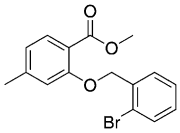
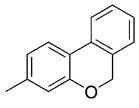
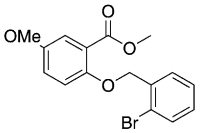
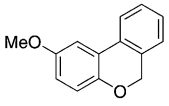
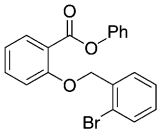
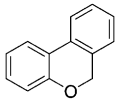
Next, we subjected substituted aryl bromide–esters to these optimized conditions to test this sequential hydrolysis/decarboxylative coupling reaction. As shown in Table 5, aromatic methyl esters containing electron-donating groups, such as Me and OMe **3b**–**3d**, on the aromatic ring could provide the desired products **2b**–**2d** in 71–90 % yields (Table 5, entries 2–4). Notably, phenyl ester **4a** was also tolerated in the sequential transformations to provide biaryl compound **2a** in a 71 % yield (Table 5, entry 5).

The intramolecular decarboxylative coupling reaction is highly attractive from a synthetic point of view in that the catalyst loading is low, the optimal reaction conditions are mild, and the substrate scope is broad. This method could be used in the synthesis of some biologically active compounds. A representative example is the synthesis of 2-[6-oxophenanthridin-5(6*H*)-yl]acetic acid **7**, which has been shown to have some activity in inhibiting aldose reductase.[15] As shown in Scheme 1, compound **5**, prepared by the condensation of methyl 2-aminobenzoate and 2-bromobenzoic acid, reacted with ethyl 2-bromoacetate and then hydrolyzed under basic conditions to yield compound **6**, containing an aromatic and an aliphatic carboxylic acid in one molecule. Notably, the aryl bromide preferentially reacted with the benzoic acid and not the aliphatic carboxylic acid to give the desired compound **7** under the standard decarboxylative coupling conditions. This selectivity indicates that an aromatic carboxylic acid is easier to decarboxylate and has higher reactivity than an aliphatic carboxylic acid. This conclusion is consistent with the observation that aliphatic carboxylic acid **1cc** did not react under the Pd-catalyzed coupling conditions.[16]



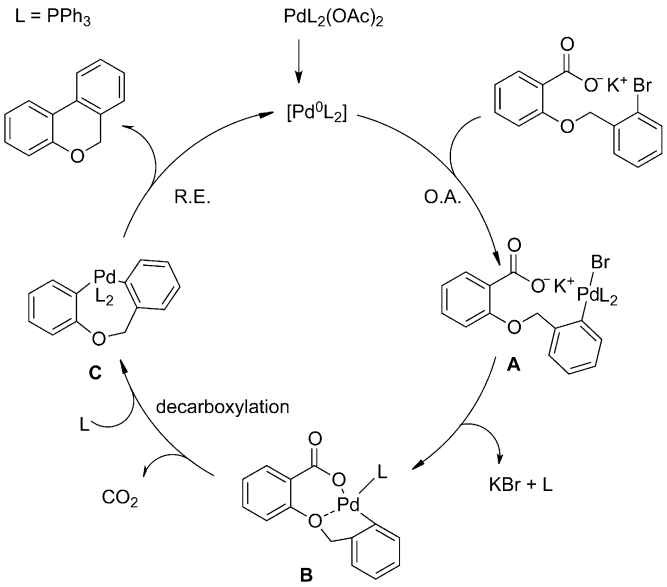
Scheme 1. Synthesis of biologically active compound **7**.

Table 5. Scope of the biaryl formation from esters.[a]

	Substrate	Product	Yield [%][b]
1	 **3a**	 **2a**	85
2	 **3b**	 **2b**	90
3	 **3c**	 **2c**	77
4	 **3d**	 **2d**	71
5	 **4a**	 **2a**	71

[a] Reaction conditions: under a nitrogen atmosphere, substrate (1 equiv), $Pd(OAc)_2$ (4 mol %), PPh_3 (8 mol %), *t*BuONa (1.2 equiv), H_2O (2 equiv), NMP (0.2 M), 100 °C. [b] Isolated yield.

On the basis of the previous investigations into decarboxylative coupling,[5a–b,6,7b–d,9,11c] a possible mechanism is outlined in Scheme 2. The highly active Pd^0 was generated in situ from Pd^{II}, followed by oxidative addition of the aryl bromide to the Pd^0 catalyst to form arylpalladium interme-



Scheme 2. Proposed mechanism for the decarboxylative biaryl synthesis.

diate **A**, which likely coordinates to Pd through both the carboxylate and ether oxygen atoms, forming intermediate **B**. Decarboxylation then occurs with extrusion of CO_2 to give cyclobiarylpalladium intermediate **C**. It is worth noting that the coordinating ability of the ether oxygen atom in the substrate may help stabilize intermediate **B** and facilitate the decarboxylation reaction.[13] Reductive elimination of intermediate **C** provides the desired product and regenerates the Pd^0 catalyst. A detailed mechanistic investigation is currently underway in our laboratory.

In summary, we have achieved an efficient protocol for forming biaryl compounds through palladium-catalyzed intramolecular decarboxylative coupling of arene carboxylic acids with aryl bromides. In contrast to the system reported by Goossen et al., only a single catalytic metal is required. This practical and convenient method has broad substrate scope, produces high yields under mild conditions, and is complementary to that of the intermolecular decarboxylative coupling reaction under Pd/Cu-cocatalyzed conditions. Furthermore, decarboxylative coupling from the ester instead of the carboxylic acid has also been shown to smoothly yield intramolecular biaryl coupling products.

Experimental Section

General procedure for intramolecular decarboxylative arylation: Synthesis of 6*H*-benzo[*c*]chromene (2a): Under a nitrogen atmosphere, a mixture of $Pd(OAc)_2$ (4 mol%, 0.9 mg), PPh_3 (8 mol%, 2.1 mg), **1a** (0.1 mmol, 30 mg), and K_2CO_3 (0.12 mmol, 17 mg) was dissolved in NMP (0.5 mL). The reaction system was stirred at 75 °C and monitored by TLC. Upon completion, the mixture was poured into aqueous HCl (1 N, 5 mL), and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (ethyl acetate/petroleum ether), yielding **2a** (96%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ=5.02 (s, 2H), 6.91 (dd, J=8.1, 1.2 Hz, 1H), 6.96 (dt, J=7.5, 1.2 Hz, 1H), 7.05 (d, J=7.4 Hz, 1H), 7.12–7.20 (m, 2H), 7.28 (t, J=7.6 Hz, 1H), 7.60 (d, J=7.7 Hz, 1H), 7.64 ppm (dd, J=7.7, 1.6 Hz, 1H); IR (KBr): $\tilde{\nu}$=3179, 1484, 1400, 1244, 1120, 1017, 755, 688 cm^{-1}; MS (EI): m/z: 182 $[M]^+$, 181, 152, 127, 115, 91, 76.

Acknowledgements

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Keywords: arenes · aryl halides · arylation · carboxylic acid · cross-coupling · decarboxylation · intramolecular reactions

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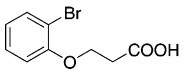

1cc

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