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Palladium (II)-Catalyzed Decarboxylative Cross-Dehydrogenative Coupling: Direct Synthesis of *meta*-Substituted Biaryls from Aromatic Acids

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Abstract: A palladium-catalyzed tandem process of simple aromatic acids has been achieved to afford *meta*-substituted biaryls in moderate to good yields. The reaction proceeds via carboxyl-directed intermolecular cross-dehydrogenative coupling and subsequent decarboxylation. The new C–C bonds in this transformation are formed in the *ortho* position of carboxyl and the reaction tolerates electron-rich acids. Both symmetrical and unsymmetrical *meta*-substituted biaryls can be directly synthesized via this method.

Keywords: biaryls; cross-dehydrogenative coupling; decarboxylation; palladium catalysis; aromatic acids

The biaryl motifs are vital intermediates for synthesizing many fine chemicals applied in various areas, such as natural products, pharmaceuticals, pesticides, dyes, and polymer materials.[1] Transition-metal-catalyzed cross coupling reactions such as Suzuki, Stille, Kumada-Corriu, Negishi, and Hiyama reactions, have become the most commonly used tools for the synthesis of biaryls.[2] However, these processes generally employ aryl halides as coupling partners. The requirements for pre-functionalized substances together with the generation of undesired byproducts arise as main limitations for these transformations. Therefore, the development of more efficient approaches for the synthesis of valuable biaryls from simple and readily available starting materials by concise steps continues to be an intense interest.[1]

In the last decade, the transition-metal-catalyzed decarboxylative coupling reactions have become an attractive approach for the regioselective formation of C–C bonds owing to that carboxylic acids are cheap synthons and can be easily prepared by a number of methods.[3] Various synthetic methodologies to generate biaryls have been developed based on this strategy. For example, decarboxylative cross-couplings of carboxylic acids with aryl halides,[4] aryl triflates[5] or phenylboronic acid[6] have been demonstrated to afford various biaryls, in which carboxyl served as a versatile arylating reagent via metal mediated decarboxylation to generate aryl-metal intermediates. A direct C–H bond functionalization combining the decarboxylation offers an alternative atom economical route delivering biaryls.[7-9] These decarboxylative cross couplings do not require any harmful halogenated benzene as starting materials. However, the arenes were restricted to a narrow range of substrates, such as benzene,[7] polyfluoroarenes,[8] or heteroaromatic compounds.[9]

In fact, biaryl compounds can also be formed via decarboxylative cross-coupling of aromatic acids (Scheme 1, a). Larrosa and Cai reported the decarboxylative homocoupling of (hetero)aromatic carboxylic acids to afford symmetrical biaryls catalyzed by $Pd(TFA)_2$ or CuI, respectively.[10] Unsymmetrical biaryls can also be synthesized through the palladium-catalyzed decarboxylative heterocoupling of substituted benzoic acids.[11] In these cases, *ortho*-substituted electron-deficient carboxylic acids or heteroaromatic acids are necessary to facilitate the coupling process, and the reaction takes place at the original position of the carboxyl. Thus, *ortho*-substituted biaryls could be generated via this decarboxylative coupling.

Employing traceless directing decarboxyltive coupling, Lorrosa, Su and You reported sequentially the *meta*-seletive arylation of aromatic acids with iodoarenes or heteroarenes as partners to produce *meta*-substituted biaryl compounds, which are difficult to access from inexpensive precursors by traditional methods.[12] In 2016, Li's group developed a regiospecific dimerization of simple aromatic acids to generate 2,2'-diaryl acids, which proceed through two rhodium-catalyzed C–H activation.[13] This result and our understanding on the decarboxylative reactions inspire us to conceive that *meta*-substituted biaryls can be generated through the cross-

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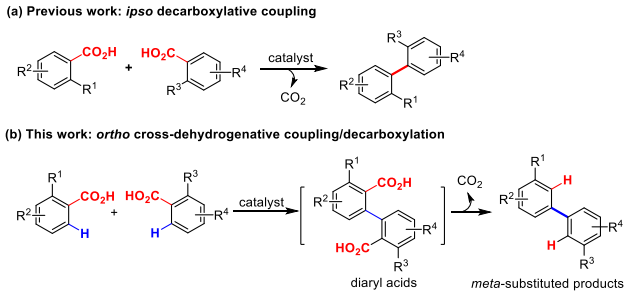
dehydrogenative coupling of *ortho*-substituted aromatic acids and the subsequent decarboxylation (Scheme 1, b). However, to realize this transformation, the challenges including protodecarboxylation and decarboxylative *ipso*-homocoupling of starting aromatic acids must be surmounted.[14] In this work, we describe an efficient and regioselective synthesis of symmetrical and unsymmetrical *meta*-substituted biaryls from simple aromatic acids (Scheme 1, b). The reaction proceeds through an intermolecular cross-dehydrogenative coupling directed by carboxyl and subsequent decarboxylation. This method is complementary to palladium-catalyzed cross-coupling between aryl halides and organometallic reagents.

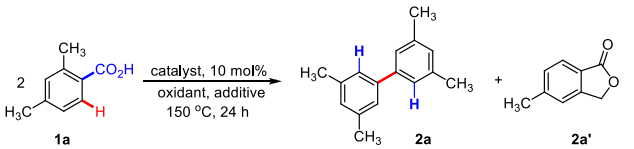


Scheme 1. Decarboxylative coupling of aromatic acids.

To validate our hypothesis, the reaction of 2,4-dimethylbenzoic acid (**1a**) was selected as a model substrate to optimize reaction conditions (Table 1). Gratifyingly, although the yield was rather low (9%), the desired homocoupling decarboxylative product was obtained when **1a** was treated with Ag_2CO_3 in DME employing $Pd(TFA)_2$ as a catalyst (Table 1, entry 1). 5-Methylisobenzofuran-1(3*H*)-one (**2a'**) was isolated as the main byproduct in this process (See Supporting Information, Table S1). Inspired by this result, different palladium catalysts were evaluated firstly (Table 1, entries 2-5), and $Pd(OAc)_2$ gave a slightly higher yield of **2a** (Table 1, entry 2). Considering the beneficial effect of K_2HPO_4 on the carboxyl-directed *ortho*-functionalization and subsequent decarboxylation,[12b-c,15] K_2HPO_4 (1.25 equiv) was introduced to the reaction system expecting to improve the selectivity of desired product. To our delight, a moderate yield of **2a** was achieved in the presence of K_2HPO_4 (Table 1, entry 6). Other alkali salts such as Na_2HPO_4, KH_2PO_4, NaOAc afforded lower yields of the product compared with K_2HPO_4 whereas NaH_2PO_4 or Na_2CO_3 only gave trace amounts of **2a**, K_2CO_3 failed to afford the product (Table 1, entries 7-12). Next, several commonly used solvents were screened. Unfortunately, no improvement in yield was observed and DME appeared to be the best solvent for this transformation (Table 1, entries 13-17). Among the oxidants investigated, Ag_2CO_3 was clearly the best choice. However, some oxidants such as AgOAc, $Cu(OAc)_2$, CuO, and $(NH_4)_2S_2O_8$ were found to be ineffective in this homocoupling reaction (Table 1, entries 18-21).

Subsequently, various conditions concerning the amount of catalyst, Ag_2CO_3 and K_2HPO_4, reaction time and reaction temperature were examined to further optimize the formation of this homocoupling product with DME as a solvent. When 1.25 equiv Ag_2CO_3 and 0.25 equiv K_2HPO_4 were utilized, 69% yield of **2a** could be obtained (Table 1, entry 22). Questions may be raised from the increased **2a** yield by decreasing the amount of K_2HPO_4 or increasing the amount of Ag_2CO_3 (Table 1, entries 6 and 22). To confirm this, the experiment employing 1.0 equiv Ag_2CO_3 and 0.25 equiv K_2HPO_4 was carried out (entry 23), the yield of **2a** was almost kept the same even if the K_2HPO_4 was decreased from 1.25 equiv to 0.25 equiv (entries 6 and 23). Thus, the enhancement of the yield lies in the increase of the oxidant. However, when the amount of $Pd(OAc)_2$ was reduced, unsatisfactory yield of **2a** was observed (see Supporting Information, Table S1, entries 24-26).

Table 1. Selected results for optimizing reaction conditions.[a]



Entry	Catalyst	Oxidant	Additive	Solvent	Yield (%)
1	$Pd(TFA)_2$	Ag_2CO_3	-	DME	9
2	$Pd(OAc)_2$	Ag_2CO_3	-	DME	14
3	$PdCl_2(PPh_3)_2$	Ag_2CO_3	-	DME	6
4	$PdCl_2(C_6H_5CN)_2$	Ag_2CO_3	-	DME	9
5	$Pd(PPh_3)_4$	Ag_2CO_3	-	DME	5
6	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	DME	45
7	$Pd(OAc)_2$	Ag_2CO_3	Na_2HPO_4	DME	24
8	$Pd(OAc)_2$	Ag_2CO_3	KH_2PO_4	DME	16
9	$Pd(OAc)_2$	Ag_2CO_3	NaOAc	DME	23
10	$Pd(OAc)_2$	Ag_2CO_3	NaH_2PO_4	DME	trace
11	$Pd(OAc)_2$	Ag_2CO_3	Na_2CO_3	DME	trace
12	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DME	ND
13	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	THF	ND
14	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	DMF	14
15	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	DMSO	5
16	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	dioxane	3
17	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	MePh	4
18	$Pd(OAc)_2$	AgOAc	K_2HPO_4	DME	ND
19	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2HPO_4	DME	trace
20	$Pd(OAc)_2$	CuO	K_2HPO_4	DME	ND
21	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	K_2HPO_4	DME	ND
22[b]	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	DME	69
23[c]	$Pd(OAc)_2$	Ag_2CO_3	K_2HPO_4	DME	46

[a] Reactions were carried out with **1a** (0.2 mmol), catalyst (10 mol%), Ag_2CO_3 (1 equiv), additive (1.25 equiv), solvent (0.6 mL) at 150 °C for 24 h, under Ar in pressure tubes. Yields were determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

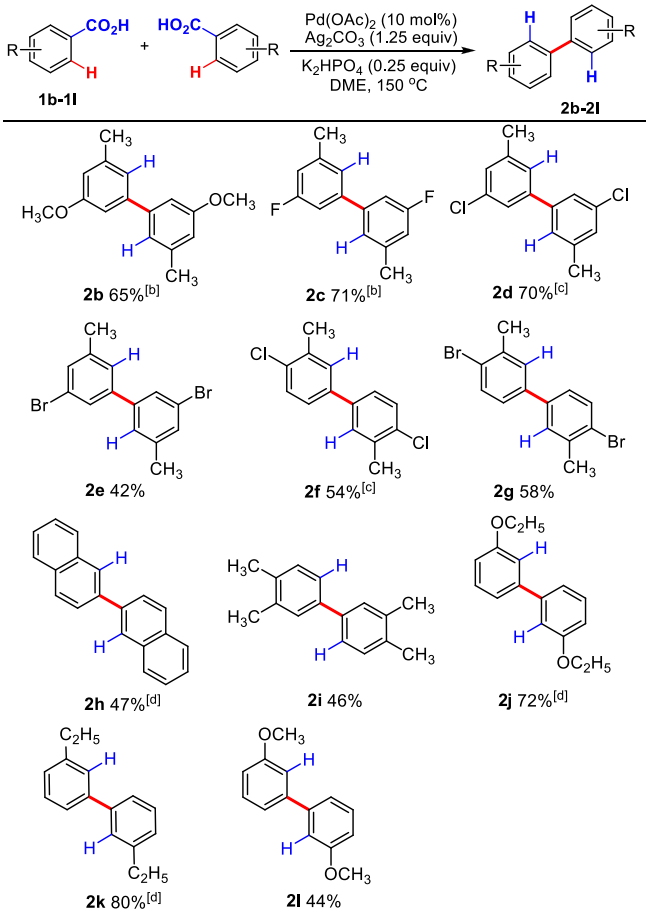
[b] With Ag_2CO_3 (1.25 equiv), K_2HPO_4 (0.25 equiv).

[c] With Ag_2CO_3 (1.0 equiv), K_2HPO_4 (0.25 equiv).

This can be explained as that $Pd(OAc)_2$ not only activates two C–H bonds but also catalyzes decarboxylation in this transformation (see Supporting Information, Table S2).

With the establishment of the optimal conditions, the scope and limitation of this homocoupling reaction were next explored and the results are presented in Table 2. As summarized in Table 2, the substituents' properties and their position had significant effect on the reactivity. For instance, the 2,3- or 2,4-di-substituted aromatic acids bearing a methyl at the *ortho* position of carboxyl all underwent this transformation smoothly to afford the corresponding biaryls in moderate to good yields (**2b-2g**, 42%-71%). This reaction was also found to be tolerant of 1-naphthoic acid (**2h**, 47%). It is worth to point out that the halogen at *meta* or *ortho*-position of the methyl were all compatible with the catalytic conditions and afforded 42-71% yields, which provides the possibility for further useful transformations through common cross-coupling method. 3,4-Disubstituted aromatic acids such as 3,4-dimethylbenzoic acid, gave the expected product **2i** in 46% yield. However, 2,5- or 3,5- di-substituted aromatic acids failed to afford the desired coupling products. The reason might lie in the steric effect, which hinders the formation of the *spiro* Pd intermediate. *Ortho* mono-substituted acids such as 2-ethoxybenzoic acid and 2-ethylbenzoic acid delivered the good yields of homocoupling products (**2j**, 72% and **2k**, 80%), whereas moderate yield was obtained employing 2-methoxybenzoic acid (**2l**, 44%). It's good to see that 2-methoxyl benzoic acid and 2-ethoxybenzoic acid were active in this transformation because 2-methoxyl benzoic acid retards the C–H functionalization in the previous carboxyl-directing reactions.[16] In the case of aromatic acids bearing a

Table 2. Substrate scope for the homocoupling reaction.[a]



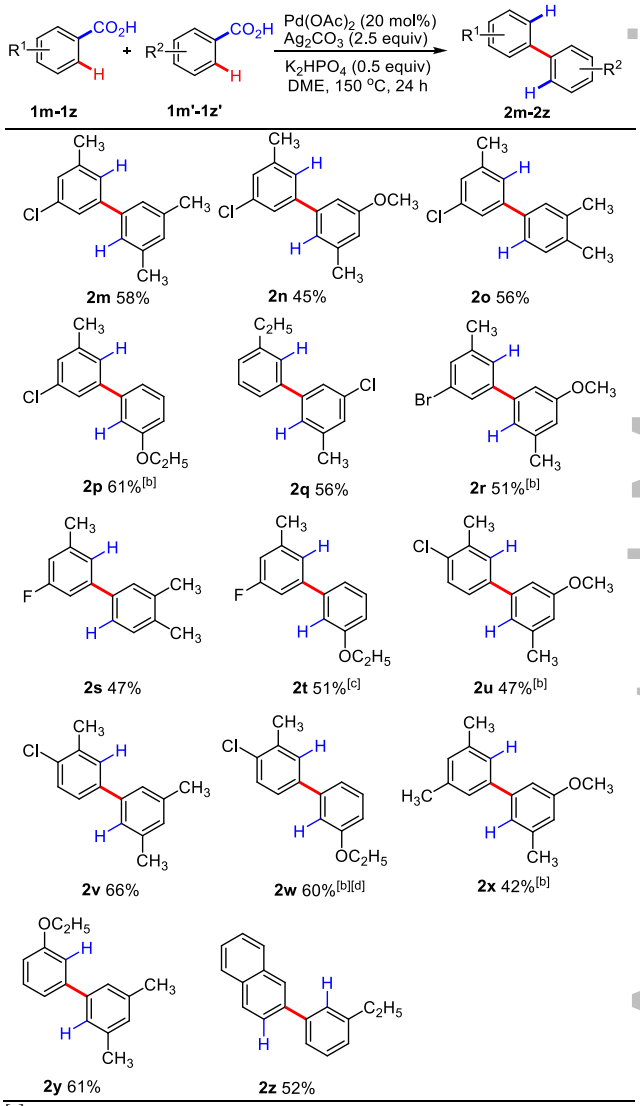
[a] Reactions were carried out with acids (0.2 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (1.25 equiv), K_2HPO_4 (0.25 equiv), DME (0.6 mL) at 150 °C for 24 h, under Ar in pressure tubes, isolated yields.

[b] K_2HPO_4 (1 equiv), $Ca(H_2PO_4)\cdot H_2O$ (0.5 equiv), 12 h.

[c] 12 h.

[d] Ag_2CO_3 (1.5 equiv), K_2HPO_4 (1.25 equiv), Cu_2O (0.25 equiv), 21 h.

Table 3. Substrate scope for the heterocoupling reaction.[a]



[a] Reactions were carried out with acids **1m-1z** (0.2 mmol), acids **1m'-1z'** (0.24 mmol), $Pd(OAc)_2$ (20 mol%), Ag_2CO_3 (2.5 equiv), K_2HPO_4 (0.5 equiv), DME (0.6 mL) at 150 °C for 24 h, under Ar in pressure tubes, isolated yields.

[b] 0.2 mmol acids (**1p'**, **1r'**, **1u'**, **1w'**, **1x'**) were used.

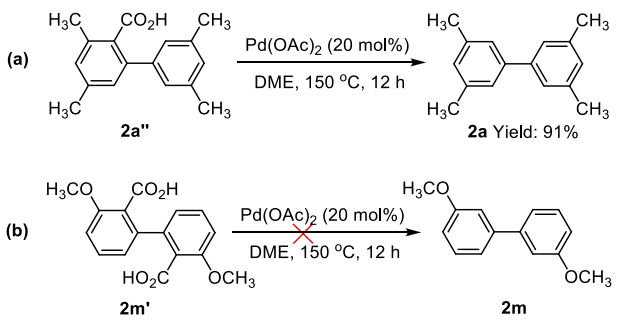
[c] 0.3 mmol **1t'** was used, 28 h.

[d] Ag_2CO_3 (3 equiv), K_2HPO_4 (2.5 equiv), Cu_2O (0.5 equiv), 21 h.

methyl at the *ortho* position of the carboxyl, substituted isobenzofuran-1(3*H*)-ones were formed as the main byproducts. In most cases, unreacted acids were observed after the reaction (See Supporting Information, Table S4). In contrast, self-decarboxylation of aromatic acids was not observed in this catalytic system.

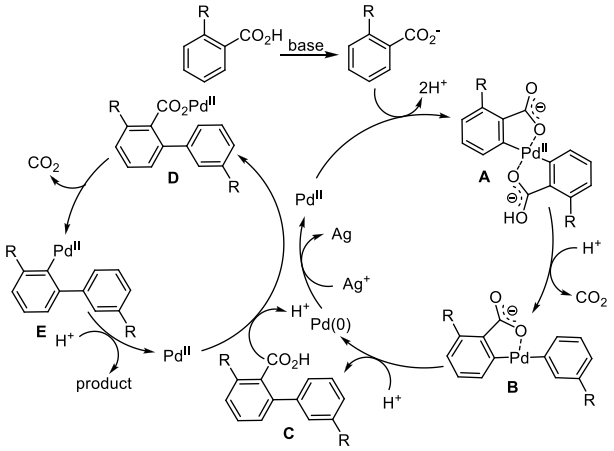
To our delight, the scope of this transformation could be further extended to the decarboxylative heterocoupling reaction between different aromatic acids delivering unsymmetrical biaryls (Table 3). However, the undesired byproducts via homo-coupling or intramolecular cyclization reactions were formed in this transformation (see Supporting Information, Table S5). It was found that utilizing equal or slightly excessive substrates, 4-chloro-2-methylbenzoic acid, 4-bromo-2-methylbenzoic acid, 4-fluoro-2-methylbenzoic acid and 3-chloro-2-methylbenzoic acid could be reacted with electron-rich disubstituted benzoic acids and furnished moderate yields of heterocoupling products (**2m**-**2w**, 45%-66%). Heterocoupling between two electron-rich benzoic acids were also compatible with this catalytic system. For instance, 4-methoxy-2-methylbenzoic acid, 2-ethoxybenzoic acid and 1-naphthoic acid underwent cross-dehydrogenative/decarboxylative reaction smoothly with 2,4-dimethylbenzoic acid and 2-ethylbenzoic acid, respectively, affording **2x** (42%), **2y** (61%) and **2z** (52%) in moderate yields.

Further experiments were performed to gain mechanism insight into this coupling system. When optimizing the reaction conditions, 33% yield of 3,3',5,5'-tetramethylbiphenyl-2-carboxylic acid (**2a''**) was observed in a shorter reaction time of 5 h. However, the yield of **2a''** decreased to trace with the extension of reaction time to 12 h. To test whether **2a''** was an intermediate to form **2a** via decarboxylation, we prepared **2a''** and treated it under different conditions. The results are given in Table S2 (see Supporting Information). As illustrated in Scheme 2a, a high yield of the product **2a** was obtained in the presence of $Pd(OAc)_2$ (Scheme 2a), indicating that **2a''** is very probably the intermediate of the catalytic cycle. More importantly, $Pd(OAc)_2$ played a key catalytic role in the decarboxylation. However, 3,3'-dimethoxybiphenyl-2,2'-dicarboxylic acid (**2m'**) failed to generate the decarboxylative product, although the reaction conditions were changed in a broad range (Scheme 2b, see Supporting Information, Table S3).



Scheme 2. Mechanistic investigations.

On the basis of the above experiment results as well as previous reports about palladium-catalyzed cross-dehydrogenative coupling and decarboxylation reactions,[17,18] a plausible mechanism is proposed in Scheme 3. With the help of base, the formed carboxylate would undertake a regioselective electrophilic C–H substitution by Pd(II) via the C–H activation directed by carboxyl to generate a dual cyclometallation **A**. Then, the mono-cyclemetallation **B** formes in the presence of proton with a CO_2 released. The reductive elimination and protonation of **B** deliver the biphenyl-2-carboxylic acid **C** and Pd(0). The Pd(0) is oxidized by Ag_2CO_3 to regenerate the Pd species. The reaction of biphenyl-2-carboxylic acid **C** with Pd(II) affords the intermediate **D**. Finally, the carboxylate **D** undergo another decarboxylation and protonation to produce the desired product, and regenerates the active Pd species. In this cylce, the $Pd(OAc)_2$ serves as two functions, i.e., the activation of two C–H bonds and the promotion of decarboxylation.



Scheme 3. A plausible mechanism.

In Summary, a novel synthetic route to *meta*-substituted biaryls has been discovered and developed via the dimerization of simple aromatic acids catalyzed by palladium catalyst. The reaction proceeds via intermolecular cross-dehydrogenative coupling directed by a carboxyl, and subsequent decarboxylation. Both symmetrical and unsymmetrical *meta*-substituted biaryls can be efficiently synthesized in moderate to good yields. Unlike previous in-situ decarboxylative coupling protocols, the new C–C bonds are formed in the *ortho* position of carboxyl in this transformation, and the reaction tolerates electron-rich acids. Further studies on the detailed mechanistic investigations are currently in progress in our laboratory.

Experimental Section

A typical experimental procedure: An oven-dried reaction vessel was charged with $Pd(OAc)_2$ (4.5 mg, 10 mol%, 0.02 mmol), Ag_2CO_3 (68.9 mg, 0.25 mmol), aromatic acids (0.2

mmol), K_2HPO_4 (8.7 mg, 0.05 mmol), 1,2-dimethoxyethane (0.6 mL). The mixture was stirred at 150 °C for 24 h under Ar. When the reaction was complete, the resulting mixture was cooled to room temperature, and filtered through a short silica gel pad. Then, the mixture was concentrated in vacuo to give a residue, which was purified by preparative thin-layer chromatography (TLC) on silica gel to afford the corresponding product.

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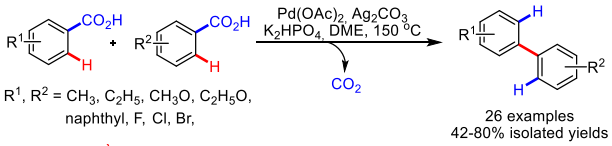
COMMUNICATION

Palladium(II)-Catalyzed Decarboxylative Cross-Dehydrogenative Coupling: Direct Synthesis of *meta*-Substituted Biaryls from Aromatic Acids



- *Decarboxylative cross-dehydrogenative coupling*
- *Carboxyl as a traceless directing group*

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