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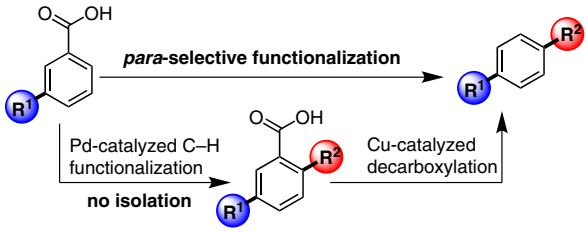
A Versatile Approach for the Synthesis of *para*-Substituted Arenes via Palladium-Catalyzed C–H Functionalization and Protodecarboxylation of Benzoic Acids

Shulei Pan
Bo Zhou
Yanghui Zhang*
Changdong Shao
Guangfa Shi

Shanghai Key Laboratory of Chemical Assessment and Sustainability, Department of Chemical, and UNEP-Tongji Institute of Environment for Sustainable Development, Tongji University, 1239 Siping Road, Shanghai 200092, P. R. of China
zhangyanghui@tongji.edu.cn



R^1 = Me, Ph, CF_3, COMe, CO_2Me, F, Cl, Br, OMe, OH, NO_2, NHAc
R^2 = Ar (16 examples, yield 25%–85%)
ArCO (13 examples, yield 45%–80%)
OH (9 examples, yield 40%–88%)

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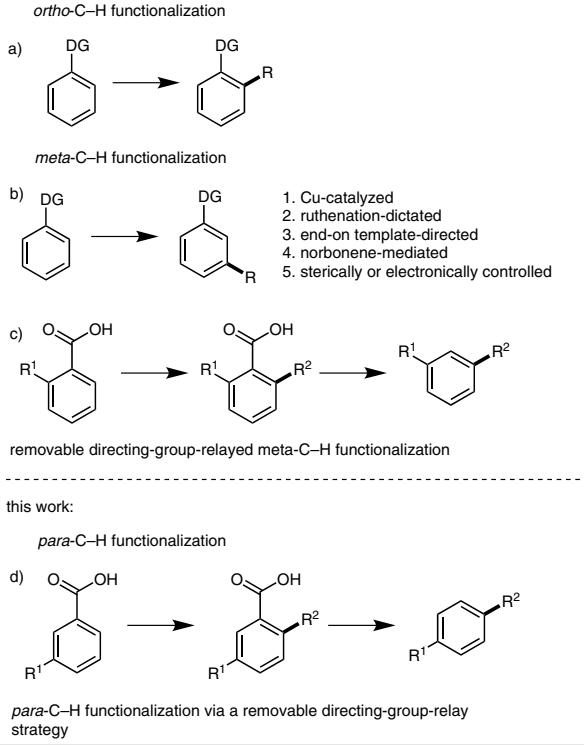
Abstract While a great number of *ortho* C–H functionalization reactions have been developed and several breakthroughs have been achieved in *meta* C–H activation, *para* C–H functionalization is still in its infancy stage. In this article, a versatile strategy for the synthesis of *para*-substituted arenes has been developed via a tandem process consisting of palladium-catalyzed C–H functionalization and subsequent copper-catalyzed protodecarboxylation of benzoic acids. Both electron-withdrawing and electron-donating functionalities can be introduced into the *para* positions of arenes bearing a variety of substituents.

Key words C–H activation, palladium, decarboxylation, arenes, regioselectivity

In the past few decades, transition-metal-catalyzed C–H functionalization has attracted great attention and is emerging as a powerful methodology in organic synthesis.[1] As C–H bonds are ubiquitous in organic molecules, it is crucial to activate desirable C–H bonds selectively for developing synthetically applicable C–H functionalization reactions. However, controlling site selectivity is a great challenge because the C–H bonds often have very subtle difference in intrinsic reactivity. At present, the most common strategy to achieve site selectivity is to use directing groups.[2] The directing groups chelate with transition-metal catalysts, and as a consequence, only C–H bonds at the appropriate positions can be cleaved through the formation of a cyclic pretransition state, which is normally a five- or six-membered ring. This strategy usually leads to *ortho* selectivity for the C–H functionalization of arenes. Currently, the vast majority of work in the literature has focused on *ortho* C–H functionalization via the directing-group strategy (Scheme 1, a), and the activation of *meta* and *para* C–H bonds remain comparatively underdeveloped. However, several breakthroughs were recently achieved in *meta* C–H activation,[3] primarily including selective *meta* C–H activation controlled by electronic or steric effects,[4] copper-catalyzed *meta*-selective arylation of anilides and β-aryl carbonyl compounds,[5] ruthenation-dictated functionalization of *meta* C–H bonds,[6] remote *meta* C–H activation directed by a U-shaped nitrile-containing template,[7] and norbonene-mediated *meta* C–H functionalization (Scheme 1, b).[8] *para*-C–H Functionalization still remains to be investigated. Very few examples of *para*-selective C–H functionalization reactions have been reported.[9] In the reported reactions, the site selectivity resulted primarily from steric or electronic factors, and the reactions were applicable to a limited substrate scope.

Recently, an intriguing traceless directing-group strategy for achieving *meta* C–H functionalization of arenes is arousing attention of organic chemists (Scheme 1, c).[10] For this strategy, *ortho*-substituted benzoic acids are functionalized at the other *ortho* positions via carboxylate-directed C–H activation in the first step. Subsequently, the carboxyl group is removed to give *meta*-substituted arenes. When we surveyed carboxylate-directed C–H functionalization reactions, we found that C–H activation took place at the less-hindered *ortho* positions for the majority of *meta*-substituted benzoic acids.[11] Therefore, we envisioned that *para*-functionalized products could be formed after the carboxyl groups are removed (Scheme 1, d). It should be mentioned that this type of reactions were observed in carboxylate-directed C–H alkoxylation with concomitant protodecarboxylation, which was reported by the Gooßen group.[10e]

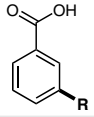
During the preparation of this manuscript, the Chang group reported the synthesis of *para*-substituted (*N*-sulfonyl)aniline derivatives via the traceless directing-group strategy.[10h]



Scheme 1 Strategies for regioselective C–H functionalization of arenes

We aimed to develop a versatile approach for the synthesis of *para*-substituted arenes. This approach should have broad substrate scopes and its *para* selectivity should be independent of the nature of the substituents. Benzoic acids are a very common class of organic molecules and widely exist in nature.[12] Carboxylate-directed C–H functionalization and decarboxylation reactions have been extensively investigated.[12,13] As *para*-functionalized products are expected to be obtained via carboxylate-directed *ortho* C–H functionalization and protodecarboxylation of *meta*-substituted benzoic acids, this traceless directing-group strategy is ideal for developing a versatile approach for the synthesis of *para*-substituted arenes.

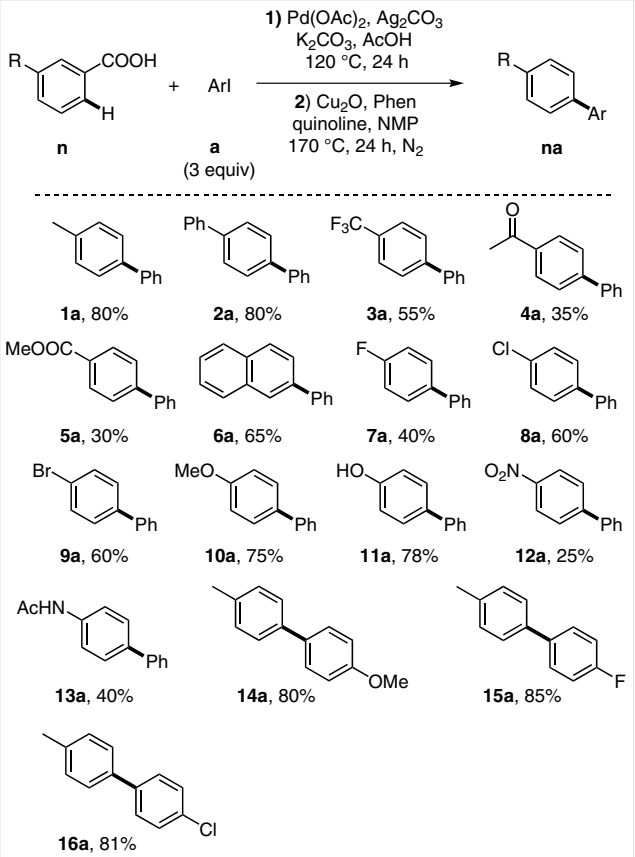
To develop a general method, we selected a range of *meta*-substituted benzoic acids, including those bearing C-, O-, and N-linked substituents and halides (Figure 1). The substituents also cover the majority of common electron-donating and electron-withdrawing functionalities.



1 R = Me
2 R = Ph
3 R = CF_3
4 R = COMe
5 R = COOMe
6 2-naphthoic acid
7 R = F
8 R = Cl
9 R = Br
10 R = OMe
11 R = OH
12 R = NO_2
13 R = NHAc

Figure 1 *meta*-Substituted benzoic acid substrates

The Daugulis and Larrosa group reported palladium-catalyzed *ortho* C–H arylation of benzoic acids independently.[14] Based on these excellent works, we first investigated the synthesis of *para*-arylated arene derivatives. Therefore, the benzoic acids in Figure 1 were subjected to the Larrosa conditions as shown in Scheme 2, yielding the corresponding 2-phenylbenzoic acid derivatives. We aimed to develop a tandem approach, so the subsequent protodecarboxylation was examined with the crude products without purification. After screening several current protodecarboxylation conditions,[15] we found that the *ortho*-phenylated benzoic acid crude products underwent protocarboxylation smoothly under the catalytic system discovered by the Gooßen group which comprises catalyst Cu_2O and ligand Phen.[16] All of the intermediates from benzoic acids in Figure 1 were converted into the corresponding *para*-arylated arene products. While the reactions of the benzoic acids bearing *meta*-electron-donating groups occurred efficiently, the overall yields for the benzoic acids with electron-withdrawing groups were much lower. The poor overall yields resulted primarily from the low efficiency of

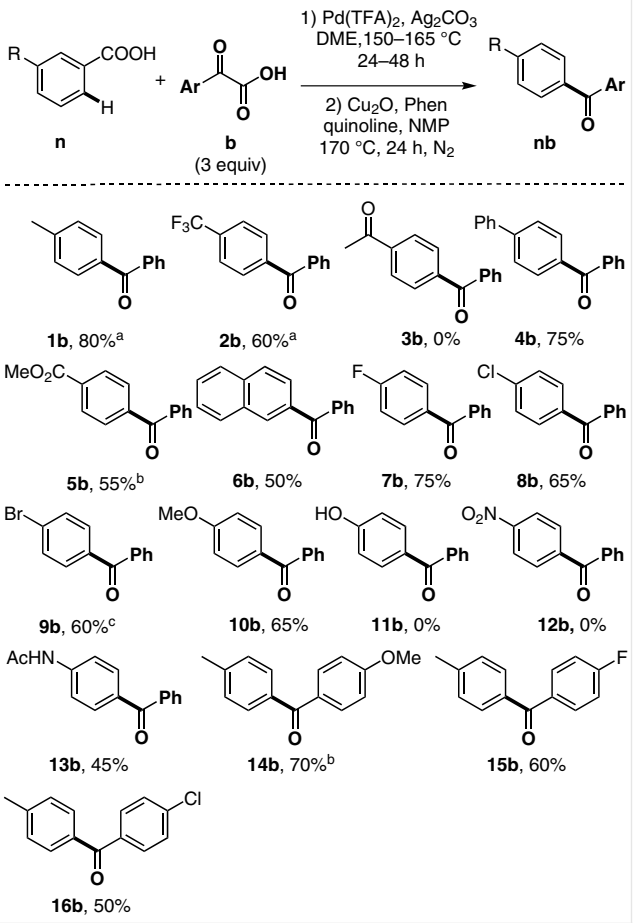


[a] Yields based on isolated produts on a 0.5 mmol scale.

Scheme 2 Formal *para*-C–H arylation of arenes; yields based on isolated products on a 0.5 mmol scale.

the first C–H arylation steps. Substituted phenyl iodides were also examined. Therefore, *m*-toluic acid was allowed to react with 4-methoxy, 4-fluoro-, or 4-chlorophenyl iodide under the standard conditions. The reactions formed the corresponding *para*-functionalized toluenes in high yields.

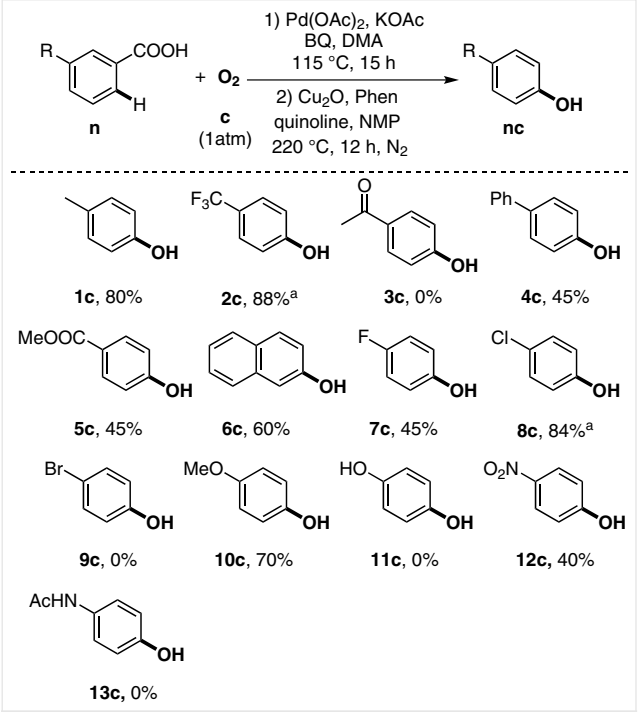
Next, we sought to develop a general protocol for the synthesis of *para*-substituted arenes bearing an electron-withdrawing group. The carbonyl group is a typical electron-withdrawing group and can be transformed into a variety of other functionalities, so it is a desirable example to be studied. Gratefully, the Ge and Gooßen group disclosed carboxylate-directed carbonylation reaction with α-oxocarboxylic acids and acetic anhydrides, respectively.[17] Thus, the benzoic acids were benzoylated following the Ge's conditions, and the resulting crude products were subjected to the same protodecarboxylation conditions as that employed for the decarboxylation of 2-phenylbenzoic acids (Scheme 3). As shown in Scheme 3 most of the benzoic acids were converted into *para*-substituted benzophenones.



Scheme 3 Formal *para* C–H benzoylation of arenes; yields based on isolated products on a 0.5 mmol scale. [a] Conditions: 165 °C, 24 h. [b] Conditions: 165 °C, 48 h. [c] Conditions: 130 °C, 24.

The substrates bearing MeCO, OH, or NO_2 were not reactive, also because the first step failed to form carbonylated products. Substituted 2-oxo-2-phenylacetic acids were also reactive. Therefore, 2-oxo-2-phenylacetic acids bearing a methoxy, fluoro, or chloro group reacted with *m*-toluic acid, affording the corresponding benzophenones in medium yields.

Having successfully developed methods for the synthesis of *para*-substituted arenes with a phenyl (almost neutral and weakly electron donating) or carbonyl group (electron withdrawing), we turned to investigate the synthetic means for *para*-substituted electron-rich arenes. The hydroxyl group, a strong electron-donating group, is an ideal target because phenols are a type of important organic molecules and versatile synthetic intermediate. The Yu group disclosed an intriguing C–H hydroxylation reaction of benzoic acids with O_2.[18] Therefore, following the Yu's conditions and the previous protodecarboxylation protocol, the benzoic acids underwent a tandem procedure of C–H hydroxylation and subsequent protodecarboxylation, affording a range of *para*-substituted phenols (Scheme 4). Benzoic acids with *meta*-MeCO, NHAc, Br, or OH failed to form the corresponding products, because the hydroxylation in the first step did not occur. As the former two reactions, the decarboxylation steps were high-yielding, and the overall yields depended on the efficiency of the hydroxylation step. Based on the Yu's work, the yield of the hydroxylation reaction increased



Scheme 4 Formal *para* C–H hydroxylation of arenes; yields based on isolated products on a 0.5 mmol scale. [a] Conditions: 5 atm O_2.

when O_2 (5.065 bar) was employed, so the overall yields of this protocol should be able to be improved by using O_2 (5.065 bar).

In summary, we have developed a versatile approach for the synthesis of *para*-substituted arenes.[19–21] In this approach, *meta*-substituted benzoic acids were first functionalized at the less hindered *ortho* positions via palladium-catalyzed C–H activation. The resulting intermediates underwent copper-catalyzed protodecarboxylation to give *para*-substituted arenes. Three classes of substituents, including phenyl group, electron-withdrawing benzoyl, and electron-donating hydroxyl, were introduced via palladium-catalyzed C–H functionalization reaction. A variety of functionalities were compatible with the protocols. Other removable directing group may also be utilized to develop synthetic approaches for *para*-substituted arenes.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560579.

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(19) **Synthesis of *para*-Arylated Arenes**
A mixture of *m*-toluic acid (68.0 mg, 0.50 mmol), iodobenzene (167.2 μL, 1.50 mmol), Ag_2CO_3 (76.0 mg, 0.28 mmol), K_2CO_3 (35.0 mg, 0.25 mmol), and $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) in AcOH (130.0 μL) was heated under an atmosphere of N_2 at 120 °C for 24 h. After cooling down to r.t., the reaction mixture was quenched by addition of 2.0 M aq HCl (10 mL), diluted with EtOAc (10 mL), and then filtered through a pad of Celite. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, yielding crude 2-phenylbenzoic acid derivatives. A mixture of the crude product, Cu_2O (3.6 mg, 0.025 mmol), and 1,10-phenanthroline (9.0 mg, 0.050 mmol) in a solution of NMP (1.5 mL) and quinoline (0.5 mL) was heated under an atmosphere of N_2 at 170 °C for 24 h. The reaction mixture was quenched by addition of 0.2 M aq HCl (10 mL), diluted with EtOAc (10 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give 4-methylbiphenyl. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H), 7.51–7.49 (m, 2 H), 7.45–7.41 (m, 2 H), 7.34–7.31 (m, 1 H), 7.26–7.24 (m, 2 H), 2.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.14, 138.34, 136.99, 129.45, 128.68, 126.97, 126.95, 21.08. HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{13}^+$: 169.1012 $[M + H]^+$; found: 169.0938.
(20) **Synthesis of *para*-Benzoylated Arenes**
A mixture of *m*-toluic acid (27.2 mg, 0.20 mmol), benzoylformic acid (90.1 mg, 0.60 mmol), $Pd(TFA)_2$ (6.6 mg, 0.020 mmol), and Ag_2CO_3 (165.5 mg, 0.60 mmol) in DME (2 mL) was heated at 150–165 °C for 24–48 h. After cooling down to r.t., the reaction mixture was diluted by addition of EtOAc (10 mL) and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford 2-benzoylbenzoic acid derivatives. A mixture of the crude product, Cu_2O (1.4 mg, 0.010 mmol), and 1,10-phenanthroline (3.6 mg, 0.020 mmol) in a solution of NMP (1.5 mL) and quinoline (0.5 mL) was heated under an atmosphere of N_2 at 170 °C for 24 h. The reaction mixture was quenched by addition of 0.2 M aq HCl (10 mL), diluted with EtOAc (10 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give phenyl(*p*-tolyl)methanone. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.1 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 7.9 Hz, 2 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.50, 143.22, 137.95, 134.87, 132.13, 130.29, 129.91, 128.95, 128.18, 21.64. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{12}NaO^+$: 219.0780 $[M + Na]^+$; found: 219.0774.
(21) **Synthesis of *para*-Hydroxylated Arenes**
A 50 mL Schlenk-type tube (with a Teflon high-pressure valve and side arm) was charged with *m*-toluic acid (68.0 mg, 0.50 mmol), benzoquinone (54.0 mg, 0.50 mmol), KOAc (98.0 mg, 1.00 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), and *N*,*N*-dimethylacetamide (1.5 mL). The reaction tube was evacuated and backfilled with O_2 (3×, ballon). After the reaction mixture was stirred at 115 °C for 15 h, it was allowed to cool down to r.t. The reaction mixture was diluted with EtOAc (10 mL) and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to yield crude 2-hydroxylbenzoic acid. A mixture of the crude product, Cu_2O (3.6 mg, 0.025 mmol), and 1,10-phenanthroline (9.0 mg, 0.050 mmol) in a solution of NMP (1.5 mL) and quinoline (0.5 mL) was heated under an atmosphere of N_2 at 220 °C for 12 h. The reaction mixture was quenched by addition of 0.2 M aq HCl (10 mL), diluted with EtOAc (10 mL), and then filtered through a pad of Celite. The filtrate was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel preparative TLC to give *p*-cresol. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.3 Hz, 2 H), 6.75 (d, *J* = 8.3 Hz, 2 H), 4.95 (br, 1 H), 2.29 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.18, 130.03, 129.92, 115.06, 20.43. HRMS (ESI-TOF): *m/z* calcd for $C_7H_9O^+$: 109.0648 $[M + H]^+$; found: 109.0657.