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Remote *Para*-C−H Acetoxylation of Electron-Deficient Arenes

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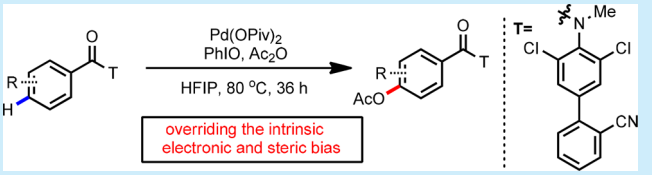
Supporting Information

ABSTRACT: One formidable challenge in sp^2 C−H activation is how to achieve high *para* selectivity on electron-deficient arenes because such site selectivity is disfavored by the electronic bias induced by the electron-withdrawing groups. The first highly selective *para*-C−H acetoxylation of various benzoic acids using a nitrile-based template was realized. Removal of the template leads to *para*-hydroxylated benzoic acids, which are versatile intermediates for a wide range of synthetically useful transformations.



Benzoic acid and its derivatives are ubiquitous in pharmaceutical compounds, agrochemicals, and materials.[1] Traditionally, derivatization and modification of benzoic acids highly depend on the electrophilic aromatic substitution, where the reaction usually takes place at the *meta* position with respect to the carboxylic acid functional group.[2] However, harsh conditions, such as high reaction temperature and/or strong acid additives, are often required for achieving reactivity because of the deactivating effect of the carboxylic acid. Recently, a transition-metal-based directing group assisted C−H activation reaction has emerged as a useful tool for rapid access to these types of molecules. A number of directing groups including native, free carboxylic acids were developed for the *ortho*-functionalization of benzoic acids under different metal catalysis through the formation of thermodynamically stable five-membered cyclometal intermediates (Scheme 1A).[3] *Meta*-selective C−H activation is another notable area.[4] Although sterics and electronics can be utilized to achieve *meta*-selectivity in the nondirected C−H activation, a series of drawbacks such as the excess amount of substrate and limited scope of transformation hampered its utility.[5] To address this issue, in 2012, our group developed an end-on template which typically contains a linear nitrile group for *meta*-selective C−H functionalization of toluene derivatives and hydrocinnamic acids.[6]

In this case, a large cyclophane-like transition state (>12 membered ring) was required for precisely dictating the *meta* selectivity. Since then, this template-directed strategy has proven to be applicable to a variety of arenes, such as phenyl acetic acids, benzyl alcohols/amines, and benzoic acids, by our group and others.[7] Despite the rapid growth in both *ortho*-selective C−H activation and *meta*-selective C−H activation reactions, remote *para*-selective C−H activation reactions still remain a formidable challenge for the following reasons: (a) the long distance between the target C−H bond and directing group; (b) the *ortho* directing effect arising from directing group; and (c) the high strain energy for the large cyclophane-like transition state. In 2015, the group of Maiti reported a *para*-C−H functionalization of toluene derivatives by using a nitrile-based D-shaped biphenyl template (Scheme 1A).[8] A specially designed two sterically incumbent isopropyl moiety at the tethered Si atom ensured the high *para*-selectivity through the Thorpe−Ingold effect. Following this work, a *para*-C−H functionalization of electron-rich phenols was accomplished by switching the connecting carbon and oxygen atom in the template.[9] However, to the best of our knowledge, there are still no precedents of remote *para*-selective C−H functionalization of electron-deficient arenes, possibly due to the low reactivity of electron-deficient arenes toward C−H palladation as well as the difficulty of overriding the innate *ortho* and *meta* selectivity.[10] Herein, we disclose the first remote *para*-selective C−H acetoxylation of electron-deficient benzoic acid derivatives (Scheme 1B). Simple hydrolysis of the products can deliver the *p*-hydroxybenzoic acids, which are a key structure moiety for many bioactive compounds including diploicin, platencin, and zeranol (Scheme 1C).

We commenced our study by designing a new template suited for *para*-C−H functionalization of benzoic acid (Scheme 2). Inspired by the previous work on the development of a nitrile-containing end-on template, we envisioned three basic rules for the template design as follows: (1) a simple amide or ester linkage is desirable in terms of practicality; (2) an appropriate conformational rigid biphenyl skeleton is considered to be able to fix the metal to the target *para*-C−H bond without interference with the *ortho*/*meta*-C−H bonds; and (3) easy preparation of the template is required

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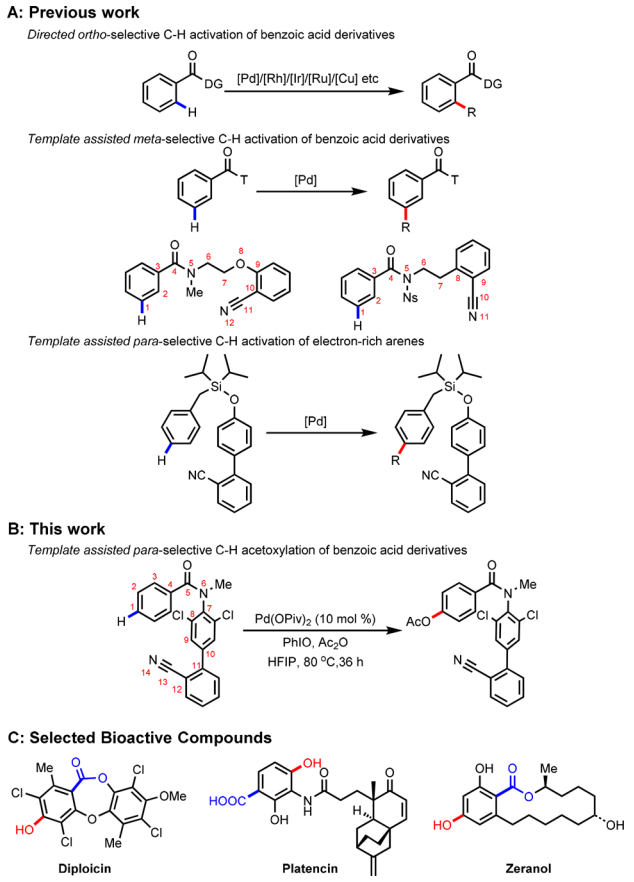
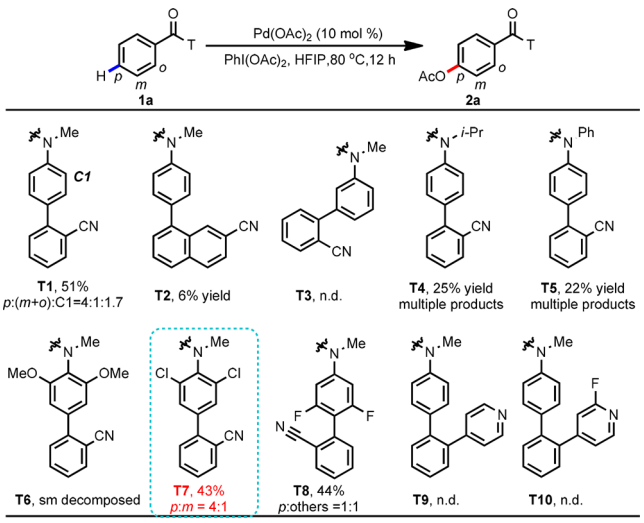
Scheme 1. Transition-Metal-Catalyzed C−H Functionalization of Arenes



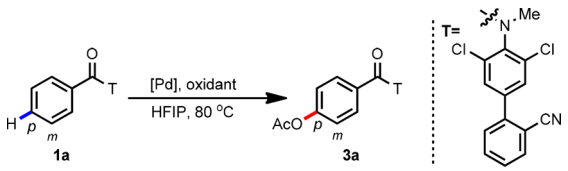
Scheme 2. Different Template for *Para*-Selective Acetoxylation



to avoid the pitfall of overengineering. With these in mind, we first attached a simple template **T1** bearing a methyl group on the nitrogen atom to benzoic acid and tested the Pd-catalyzed C−H acetoxylation reaction. The substrate was treated with 10 mol % of $Pd(OAc)_2$ and 2 equiv of $PhI(OAc)_2$ in HFIP at 80 °C for 12 h. To our delight, the acetoxylation products were obtained in 51% yield with the *para* position as the dominating product. However, product formation at the *ortho*/*meta* positions as well as the **C1** position of the template was also obtained in a considerable amount with a ratio of *p*/(*o* + *m*):**C1** = 4:1:1.7. Subsequently, regulating the distance and geometry between the coordinating CN group and the *para*-C−H bond leads to the templates **T2** and **T3**, but diminished yield (<10%) was observed for the desired product. Since the substituent on the nitrogen atom can change the conformation of the template due to steric repulsion, we explored the effect of different substituents such as isopropyl and phenyl. Poor yields and selectivities were obtained by using **T4** and **T5** as the templates, indicating that the small methyl group is better suited for delivering the Pd to the *para*-C−H bond. To suppress side reactions occurring on the template, we blocked the **C1** position with 2,6-dimethoxy and 2,6-dichloro substituents. While **T6** led to the decomposition of starting material, **T7** gave the desired product in 43% yield with two separate products and a better selectivity (*p*/*m* = 4:1). Notably, the *ortho*-C−H activation side reaction was also suppressed, possibly due to the steric hindrance cause by the dichloro substituents. 3,5-Difluoro-substituted **T8** gave a comparable yield (44%) but poor selectivity (*p*/others = 1:1). Although proven successful for *meta*-C−H activation, the pyridine-based templates (**T9**, **T10**) failed to give any products.

Having identified the optimal template (**T7**), we next evaluated the reaction parameters to further improve the yield (Table 1). First, after a careful analysis of the reaction mixture,

Table 1. Optimization of Reaction Parameters[a,c]



entry	oxidant	[Pd]	atmosphere	yield (*p*/*m*) (%)
1	$PhI(OAc)_2$ (3 equiv)	$Pd(OAc)_2$	air	43 (4:1)
2	PhIO (3 equiv) + Ac_2O (6 equiv)	$Pd(OAc)_2$	air	48 (4:1)
3	PhIO (3 equiv) + Ac_2O (6 equiv)	$Pd(OAc)_2$	N_2	34 (3.8:1)
4	PhIO (3 equiv) + Ac_2O (6 equiv)	$Pd(OAc)_2$	O_2	55 (4:1)
5	PhIO (3 equiv) + Ac_2O (14 equiv)	$Pd(OAc)_2$	O_2	66 (4.2:1)
6[b]	PhIO (3 equiv) + Ac_2O (14 equiv)	$Pd(OAc)_2$	O_2	73 (4.2:1)
7[b]	PhIO(3 equiv) + Ac_2O (20 equiv)	$Pd(OAc)_2$	O_2	73 (4.2:1)
8[b]	PhIO (3 equiv) + Ac_2O (0 equiv)	$Pd(OAc)_2$	O_2	nd
9[b]	PhIO (3 equiv) + Ac_2O (14 equiv)	$PdCl_2$	O_2	45 (4:1)
10[b]	PhIO (3 equiv) + Ac_2O (14 equiv)	$Pd(TFA)_2$	O_2	60 (4:1)
11[b]	PhIO (3 equiv) + Ac_2O (14 equiv)	$Pd(OPiv)_2$	O_2	78 (4:1)
12[b]	PhIO (3 equiv) + Ac_2O (14 equiv)		O_2	nd

[a]The reaction conditions: **1a** (0.05 mmol), $Pd(OAc)_2$(10 mol %), oxidant, HFIP(0.5 mL), 80 °C, 12 h. [b]36 h. [c]Yield was determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. The ratio of the product was determined by GC−MS analysis of the crude reaction mixture.

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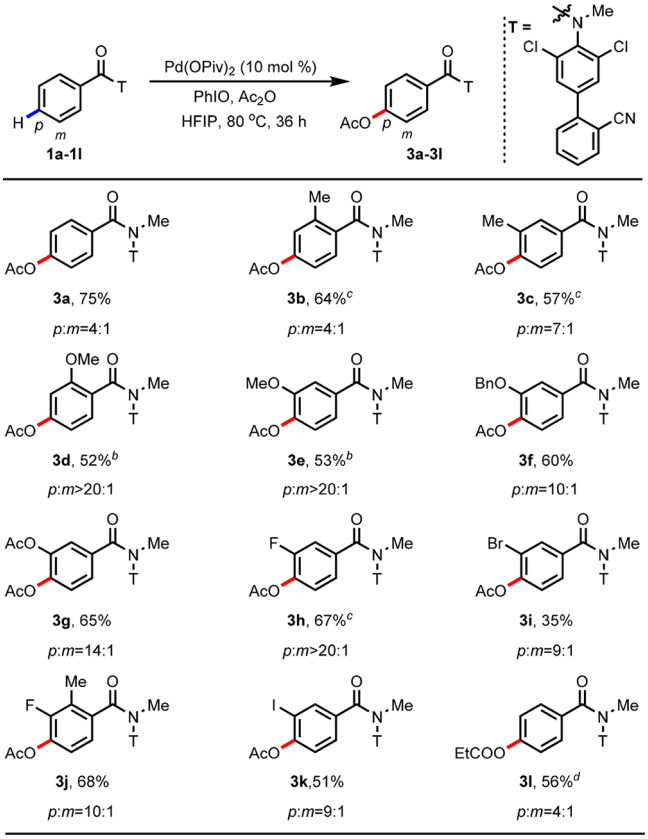
we found that a significant amount of $PhI(OAc)_2$ was reduced to PhI by HFIP (see the Supporting Information), which could be the reason for the low yield obtained in this transformation. We speculated that the yield may be able to be improved by generating the effective oxidant $PhI(OAc)_2$ in situ from PhIO and Ac_2O. Indeed, when we used 3 equiv of PhIO in combination with 6 equiv of Ac_2O as the oxidant, we obtained the desired product in 48% yield with the same selectivity (Table 1, entry 2). From the perspective of practicality, a series of acylation products could be accessed by using the combination of PhIO with the different anhydrides. Subsequently, we found that the yield could be improved to 55% when the reaction was performed under an atmosphere of O_2, while a diminished yield (34%) was obtained under the N_2 atmosphere, presumably because O_2 is capable of facilitating the oxidation of Pd^{II} to Pd^{IV} species (Table 1, entries 3 and 4). Higher loadings of Ac_2O (14 equiv) led to a dramatic increase in yield, delivering **3a** in 66% yield with a selectivity of p/m = 4.2:1 (Table 1, entry 5). Furthermore, we found that the yield was improved to 73% by prolonging the reaction time to 36 h (Table 1, entry 6). As expected, no product was observed in the absence of Ac_2O (Table 1, entry 8). Finally, among the various sources of Pd that we screened, $Pd(OPiv)_2$ proved to be optimal, giving the product **3a** in 78% yield (Table 1, entries 9−12).

With the optimal conditions in hand, we further explored the scope of this *para*-C−H acetoxylation reaction (Scheme 3). To our delight, both electron-donating groups and electron-withdrawing groups can be tolerated in this transformation. For example, substrates bearing a methyl group at the *ortho* and *meta* position underwent *para*-selective C−H acetoxylation smoothly, providing the corresponding products in 64% yield (p/m = 4:1) and 57% yield (p/m = 7:1), respectively. Notably, the template-directed C−H acetoxylation can override the *ortho*- and *para*-selective effect that originates from strong electron-donating substituents such as OMe and OBn, giving the products with excellent *para* selectivity (**3d**−**f**). These observations further suggest that a simple electrophilic aromatic substitution (S_EAr) process is not likely involved in this approach. Halogen atoms such as F, Br, and I are also compatible, giving the acetoxylation products in moderate to good yields and high *para* selectivity (**3h**, **3i**, **3k**), which provides products with further functional handles for other organic transformations. Moreover, a continuous tetrasubstituted benzoic acid derivative can also be obtained by using this strategy (**3j**, 68% yield, p/m = 10:1). In addition, using other anhydrides, such as propionic anhydride, consistently affords the corresponding carboxylates **3l** in 56% yield. This result further suggests that this oxidant system ($PhIO/Ac_2O$) is more versatile than $PhI(OAc)_2$, which only resulted in acetoxylation products.

Removal of the template proceeded smoothly under basic hydrolysis conditions, yielding the desired product *p*-hydroxybenzoic acid in 65% yield (Scheme 4). The *para*-acetoxylation product can be converted to the corresponding aryl triflate,[11] which is a valuable intermediate for a variety of transformations.[12−18]

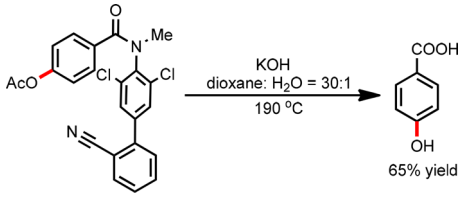
In summary, we have developed the first Pd-catalyzed *para*-C−H acetoxylation of electron-deficient benzoic acid derivatives. A variety of synthetically useful products were obtained with good to excellent *para* selectivity, demonstrating the ability of this template-directed strategy overriding steric and electron interference in catalysis.

Scheme 3. Substrate Scope of *Para*-Selective C−H Acetoxylation[a]



[a]Reaction conditions: **1a**−**l** (0.05 mmol), $Pd(OPiv)_2$ (10 mol %), Ac_2O (0.7 mmol), PhIO (0.15 mmol) in HFIP (0.5 mL), under O_2, 80 °C for 36 h; isolated yield; selectivity of the products were determined by GC−MS. [b]0.5 equiv of PhOMe was added. [c]$Pd(OAc)_2$ was the catalyst. [d]$(C_2H_5CO)_2O$ (0.7 mmol) was used instead of Ac_2O.

Scheme 4. Removal of Template



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03871.

Experimental procedures, characterizations of new compounds, NMR spectra, and X-ray data (PDF)

Accession Codes

CCDC 1874180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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