C–H Activation

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# $Pd^{II}$-Catalyzed Monoselective *ortho* Halogenation of C–H Bonds Assisted by Counter Cations: A Complementary Method to Directed *ortho* Lithiation**

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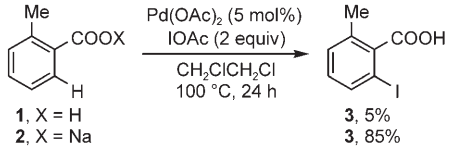
The transition-metal-catalyzed transformation of inactivated C–H bonds into C–heteroatom and C–C bonds has found synthetic utility in a number of total syntheses through the use of C–H activation as a strategic reaction.[1,2] Recently, progress has been made in Pd-catalyzed C–H activation reactions in terms of substrate scope and practicality.[3,4] However, two major obstacles prevent the broad synthetic application of C–H-functionalization reactions. First, the need for a nitrogen-containing directing group in the substrate imposes a fundamental limitation from the viewpoint of synthetic utility and atom economy. Second, external reagents capable of modulating the reactivity, especially the regio-, stereo-, and chemoselectivity, are lacking. Such reagents are key to the success of the widely used $Pd^0$-catalyzed coupling reactions. Herein, we report that tetraalkyl ammonium cations are effective in promoting C–H activation and enhancing the monoselectivity of the *ortho* iodination of aryl carboxylic acids.

A number of procedures for the *ortho* halogenation of C–H bonds have been reported previously.[5–7] A very interesting metal-free electrophilic iodination of arenes with $I(pyridine)_2BF_4$ was also developed recently.[8] As the selective *ortho* halogenation of aryl carboxylic acids is broadly useful in synthesis and medicinal chemistry, particularly for the preparation of a demanding class of 1,2,3-substituted arenes, we decided to test whether our previously reported $Pd^{II}$-catalyzed C–H activation/iodination[6b] could be extended to arene carboxylic acids. In this iodination reaction, IOAc oxidizes the aryl palladium(II) intermediate to a $Pd^{IV}$ species,[9] which undergoes reductive elimination to give the iodinated products. Another study by our research group showed that sodium and potassium carboxylates are reactive substrates for C–H activation.[10] Thus, we carried out iodination reactions of *o*-toluic acid (**1**) and sodium *o*-toluate (**2**) by using our recently developed protocol for C–H-bond iodination. The iodination of **2** proceeded to give the iodinated product **3** in 85% yield, whereas the reaction of **1** led mainly to the recovery of starting material (Scheme 1).



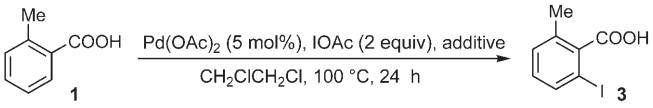

**1**, X = H
**2**, X = Na

**3**, 5%
**3**, 85%

***Scheme 1.*** Carboxylate-directed *ortho* iodination.

We then carried out the iodination of **1** in the presence of various amounts of inorganic bases (Table 1). A wide range of inorganic salts added to the reaction mixture were capable of promoting this C–H-activation reaction. Although the degree of impact of different anions on the reaction varied, the observed reactions with NaCl and NaI suggest strongly that counter cations are mainly responsible for the enhanced reactivity (Table 1, entries 5 and 6).

***Table 1:*** Effect of inorganic counter cations.[a]




**1** **3**

| Entry | Additive (equiv) | Yield[b] [%] | Entry | Additive (equiv) | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | none | 5 | 11 | KI (1) | 30 |
| 2 | LiI (1) | 36 | 12 | $K_2HPO_4$ (1) | 50 |
| 3 | $LiOAc·H_2O$ (1) | 20 | 13 | $K_2HPO_4$ (0.5) | 20 |
| 4 | NaF (1) | 40 | 14 | CsI (1) | 30 |
| 5 | NaCl (1) | 50 | 15 | CsOAc (1) | 33 |
| 6 | NaI (1) | 70 | 16 | $Cs_2CO_3$ (0.5) | 77 |
| 7 | NaOAc (1) | 85 | 17 | $Cs_2CO_3$ (1) | 50 |
| 8 | $Na_2CO_3$ (0.5) | 65 | 18 | $Mg(OAc)_2·4H_2O$ (1) | 10 |
| 9 | $Na_2CO_3$ (1) | 50 | 19 | $Ba(OAc)_2$ (1) | 18 |
| 10 | $Na_2CO_3$ (2) | 10 | 20 | $Mn(OAc)_2$ (1) | 41 |

[a] IOAc was generated in situ from $I_2$ (1 equiv) and $PhI(OAc)_2$ (1 equiv) by following a literature procedure.[11] [b] Yield of the isolated product.

Next, we investigated whether organic cationic counterions could also promote the C–H insertion. We found that the iodination reaction proceeds well with commonly used organic bases, such as DABCO and DBU (Table 2, entries 1

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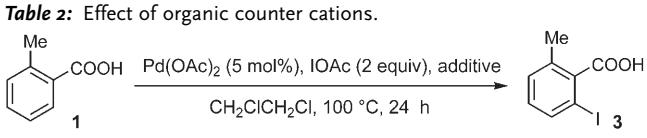
***Table 2:*** Effect of organic counter cations.

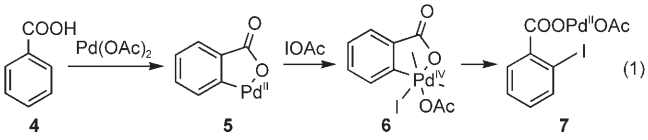



| Entry | Additive (equiv) | Yield[a] [%] | Entry | Additive | Yield[a] [%] |
|---|---|---|---|---|---|
| 1 | DABCO (0.5) | 70 | 7 | DMA[b] | 10 |
| 2 | DBU (0.5) | 40 | 8 | NMP (1) | 10 |
| 3 | DMF (1) | 77 | 9 | NMP[b] | 30 |
| 4 | DMF (5) | 88 | 10 | dimethylamine (0.2) | 2 |
| 5 | DMF[b] | 95 (90)[c] | 11 | dimethylamine (1) | 2 |
| 6 | DMA (1) | 14 | | | |

[a] The yield was determined by $^1$H NMR spectroscopy. [b] The additive was used as the solvent. [c] The yield of the isolated product is given in parentheses. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA = dimethylacetamide, DMF = *N*,*N*-dimethylformamide, NMP = 1-methyl-2-pyrrolidinone.

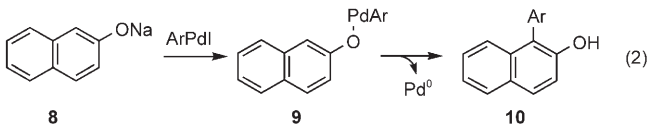
and 2). We also found that DMF is highly effective at promoting this reaction (Table 2, entries 3–5). It is known that DMF abstracts a proton from carboxylic acids to form $DMFH^+$ counteractions to a small extent in excess DMF.[12] The poor reactivity described in entries 10 and 11 of Table 2 suggests that the possible presence of a trace amount of dimethylamine from the decomposition of DMF is not responsible for the reaction. The solvents dimethylacetamide (DMA) and NMP, which have similar properties to those of DMF, were not as effective (Table 2, entries 6–9), possibly because of their stronger coordination to the $Pd^{II}$ catalyst.

Various approaches have been employed previously to activate C–H bonds in carboxylic acids.[13,14] However, the reactivity observed in the carboxylate-directed C–H iodination [Eq. (1)] appears to be related to that observed in the




(1)

$Pd^0/PPh_3$-catalyzed *ortho* arylation of phenols reported by Rawal and co-workers and Miura and co-workers [Eq. (2)],[15,16] although the redox chemistry of the latter

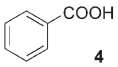
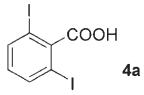
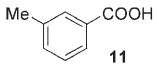
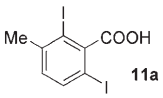
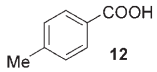
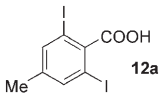
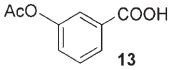
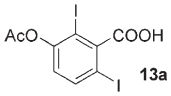
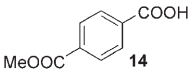
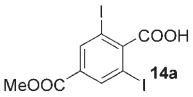
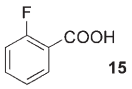
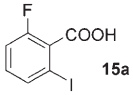
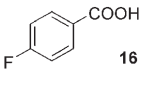
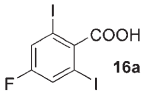
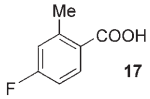
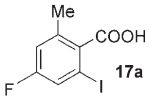
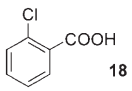
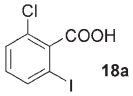
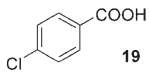
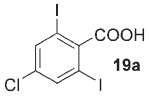
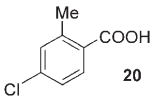
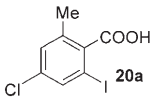
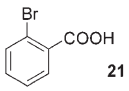
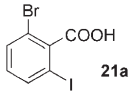



(2)

reaction involves $Pd^0/Pd^{II}$ catalysis. Rawal and co-workers observed a drastic acceleration of this reaction upon the formation of phenoxides. Miura et al. also observed *ortho* alkenylation reactions of benzoic acid in DMF in the absence of inorganic bases.[14a] However, whether similar counter cation effects were involved in these reactions remains to be ascertained.

To test the scope of this *ortho*-iodination reaction, we subjected variously substituted arene carboxylic acids to the reaction conditions (Table 3). As DMF is an effective additive, we simply carried out the reactions in DMF. The *ortho*-diiodinated products were obtained consistently in high yields. These reactions are complementary to directed *ortho* metalation (DoM) reactions[5] in terms of the observed

***Table 3:*** Palladium-catalyzed *ortho* iodination of arene carboxylic acids.[a]

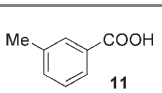
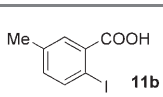
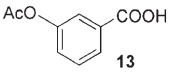
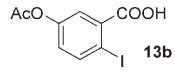
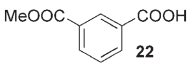
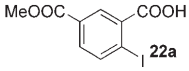
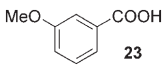
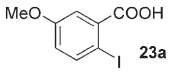
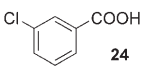
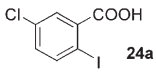
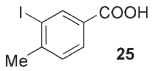
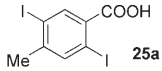
| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1[c] |  |  | 10 |
| 2[d] | | | 62 |
| 3 | **4** | **4a** | 85 |
| 4 |  **11** |  **11a** | 80 |
| 5 |  **12** |  **12a** | 87 |
| 6 |  **13** |  **13a** | 65 |
| 7 |  **14** |  **14a** | 74 |
| 8 |  **15** |  **15a** | 80 |
| 9 |  **16** |  **16a** | 72 |
| 10 |  **17** |  **17a** | 89 |
| 11 |  **18** |  **18a** | 87 |
| 12 |  **19** |  **19a** | 80 |
| 13 |  **20** |  **20a** | 88 |
| 14 |  **21** |  **21a** | 85 |

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), IOAc (3 equiv (entries 3–6, 9, and 12) or 2 equiv (entries 8, 10, 11, 13, 14)), DMF, 100°C, 36 h. [b] Yield of the isolated product. [c] IOAc was replaced by *N*-iodosuccinimide (3 equiv). [d] Reaction conditions: $Pd(OAc)_2$ (2 mol%), IOAc (3 equiv), DMF, 120°C, 36 h.

functional-group tolerance and site selectivity. They are therefore likely to find broad utility in synthesis. Ester and acetylated hydroxy groups are not usually tolerated by DoM methods (Table 3, entries 6 and 7). In DoM reactions, halides at *ortho* and *para* positions either affect the site selectivity (not the case in Table 3, entries 8–13) or react with the metalation reagent, which may be an alkyl lithium reagent (see, in contrast, Table 3, entry 14). The aryl halide products of the present *ortho*-iodination reaction, with F, Cl, Br, and I at various positions, can undergo further sequential coupling reactions owing to the different reactivities of the different halide substituents towards $Pd^0$.[17] The previously described use of NIS as the iodination reagent[6a,c] led to low conversion and a poor yield of the product (Table 3, entry 1).

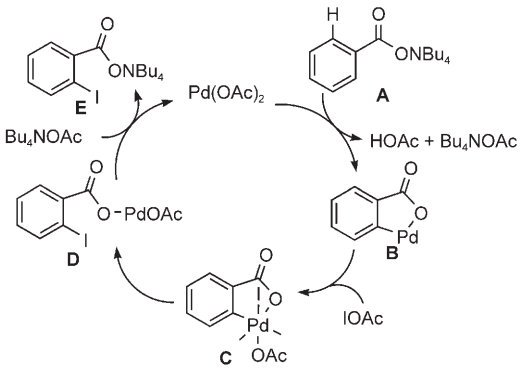
Unfortunately, monoselectivity was not observed, even if the reaction was stopped at an early stage (Table 4, entries 1–3). This problem is commonly encountered in $Pd^{II}/Pd^{IV}$ catalysis, as the product remains coordinated to $Pd^{II}$, and further reaction occurs before the products are exchanged for external substrates. Moderate monoselectivity was made possible previously through the use of biphenyl systems.[6c]

***Table 4:*** Monoselective iodination of *meta*-substituted benzoic acids.[a]

| Entry | Substrate | Product | Mono/Di[b] | Yield [%][c] |
|---|---|---|---|---|
| 1[d] |  **11** |  **11b** | 2:1 | 25 |
| 2[e] | | | 3:5 | 30 |
| 3[f] | | | 2:1 | 20 |
| 4[g] | | | 15:1 | 75 |
| 5[h] |  **13** |  **13b** | 5:1 | 63 |
| 6[h] |  **22** |  **22a** | 16:1 | 62 |
| 7[i] |  **23** |  **23a** | 5:1 | 65 |
| 8[h] |  **24** |  **24a** | 14:1 | 74 |
| 9[h] |  **25** |  **25a** | 16:1 | 72 |

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), IOAc (2 equiv), DCE, 80°C, 2 h. [b] Ratio of the monoiodinated to the diiodinated product. [c] Yield of the isolated product. [d] The reaction was carried out with 1 equivalent of IOAc in DMF. [e] DMF was used as the solvent. [f] The reaction was carried out with NaOAc (1 equiv). [g] The reaction was carried out with $Bu_4NI$ (1 equiv). [h] The reaction was carried out with IOAc (4 equiv) and $Bu_4NI$ (1.5 equiv) for 6 h. [i] The reaction was carried out with $Bu_4NI$ (1 equiv) at 60°C for 12 h. DCE = 1,2-dichloroethane.

In an attempt to make the current *ortho*-iodination reaction monoselective, we tested various $Pd^{II}$ sources, such as $Pd(tfa)_2$ (tfa = trifluoroacetate), $Pd(Piv)_2$ (Piv = pivolate), and $Pd(OTf)_2$ (OTf = *para*-toluenesulfonate), with the *meta*-substituted carboxylic acid **11** as the substrate. A number of sterically hindered and electron-deficient ligands were also screened as additives. (Strong donating ligands were not chosen, as they retard C–H insertion.) Despite the fact that the two *ortho* positions in **11** are sterically distinct, no significant improvement in monoselectivity was observed upon varying the catalyst in this way. However, we were pleased to find that tetraalkyl ammonium salts not only promote the C–H insertion in the absence of another base, but also drastically improve the monoselectivity (Table 4, entries 1–4).[18–20] A significant improvement in monoselectivity in favor of the less-hindered *ortho* position was also observed with substrates **22**, **24**, and **25**. The lower monoselectivity with substrates **13** and **23** is most likely a result of noncatalyzed electrophilic iodination of the electron-rich arenes. The proposed catalytic cycle in Scheme 2 shows the role of the tetraalkyl ammonium salt. The formation of an ion pair is crucial for the reaction,[18–20] although it is not clear at this stage whether the $Pd^{II}$ center initiates the C–H cleavage by coordinating with the lone pair of the carbonyl group or simply by displacing the ammonium cation to form a Pd carboxylate. Both pathways would lead to the formation of the same intermediate **B**.



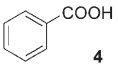
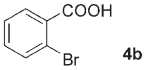
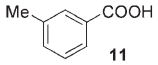
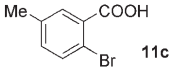
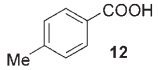
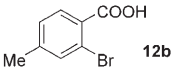
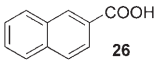
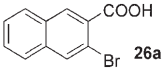
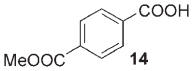
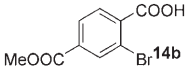
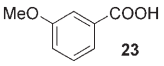
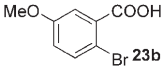
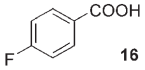
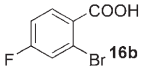

***Scheme 2.*** Monoselective *ortho* iodination assisted by tetraalkyl ammonium cations.

The next challenge was to develop the reaction further to proceed with monoselectivity in the absence of *meta* substitution. The difficulty of this problem is evident from the previously reported *ortho* C–H functionalization of benzoic acids.[10,14d] Poor monoselectivity was observed when substrate **4** was subjected to our newly developed iodination protocol (the ratio of diiodinated and monoiodinated products is typically 2:1) and the product was either not formed or obtained in low yield.

Extensive screening of tetraalkyl ammonium salts led us to find that the use of tetrabutylammonium bromide (1.5 equiv) gives the brominated product with greatly improved monoselectivity (Table 5, entry 3). The reaction of IOAc with $Bu_4NBr$ should form the known brominating reagent IBr,[21] which could brominate the aryl palladium intermediate to give the brominated product and $PdI_2$. We have shown previously that $PdI_2$ is converted into $Pd(OAc)_2$ by IOAc to regenerate the catalyst. The improved monoselectivity observed in the presence of ammonium cations can be attributed to the following factors: First, bromination deactivates the aryl ring. Second, $Pd^{II}$–I species are formed instead of $Pd^{II}$–OAc species (Scheme 2) following bromination with IBr. The $Pd^{II}$–I species are less reactive or

***Table 5:*** Monoselective bromination of benzoic acid and its derivatives.[a]

| Entry | Substrate | Product | Mono/Di | Yield [%][b] |
|---|---|---|---|---|
| 1[c] |  **4** |  **4b** | – | 18 |
| 2[d] | | | – | 0 |
| 3[e] | | | 10:1 | 60 |
| 4[e] |  **11** |  **11c** | 18:1 | 77 |
| 5[e] |  **12** |  **12b** | 8:1 | 70 |
| 6[f] |  **26** |  **26a** | 12:1 | 73 |
| 7[f] |  **14** |  **14b** | 9:1 | 42 |
| 8[f,g] |  **23** |  **23b** | 14:1 | 72 |
| 9[f] |  **16** |  **16b** | 12:1 | 49 |

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), IOAc (4 equiv), DCE, 100°C, 24 h. [b] Yield of the isolated product. [c] The reaction was carried out with NaBr (1.5 equiv). [d] IOAc was replaced by NBS (4 equiv), and DMF was used as the solvent. [e] The reaction was carried out with $Bu_4NBr$ (1.5 equiv). [f] The reaction was carried out with 2 equivalents of IOAc and $Me_4NBr$ (1.5 equiv). [g] The reaction was carried out at 60°C for 12 h.

unreactive for further C–H insertion steps. The results shown in Table 5 illustrate the scope of this reaction.

In summary, we have developed a monoselective *ortho* iodination and *ortho* bromination of arene carboxylic acids. The scope of the reaction with respect to the substrate and the site selectivity are complementary to those of the widely used directed *ortho* metalation. The enhanced reactivity observed in the presence of inorganic bases, organic bases, and tetraalkylammonium salts can be attributed to the presence of an appropriate counter cation. The large tetraalkyl ammonium cations had the biggest impact. The formation of an ion pair accelerates C–H cleavage, although the coordination mode of $Pd^{II}$ with this ion pair remains to be elucidated. Most importantly, the tetraalkyl ammonium cation appears to assist in the displacement of the monoiodinated (or monobrominated) product from the $Pd^{II}$ center, thereby preventing undesired dihalogenation.

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