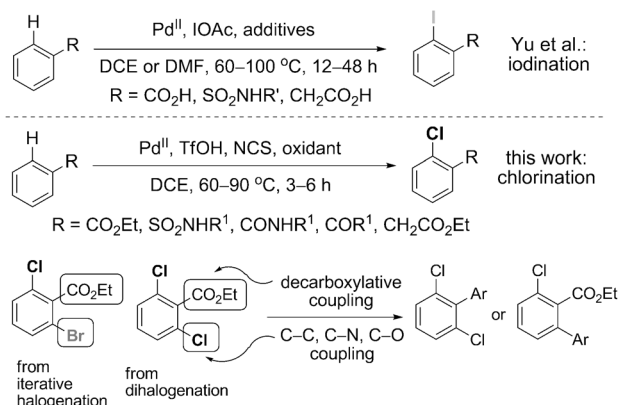**C−H Activation**

Regio- and Chemoselective C−H Chlorination/Bromination of Electron-Deficient Arenes by Weak Coordination and Study of Relative Directing-Group Abilities**

Xiuyun Sun, Gang Shan, Yonghui Sun, and Yu Rao

Dedicated to Professor Samuel J. Danishefsky

Aromatic chlorides are an important class of compounds utilized in drug and natural product syntheses.[1] Today, about 85 % of all pharmaceuticals contain or are manufactured using chlorine. By far the most prevalent strategies for preparing aromatic chlorides are still the classic directed *ortho* lithiation, eletrophilic aromatic substitution, and Sandmeyer reaction. However, these methods usually suffer from one or more limitations including poor regioselectivity, low yield, harsh reaction conditions, long reaction time, and tedious reaction procedures. Therefore, the development of a general, mild, and practical approach to aromatic chlorides is still highly desired because of their significance.

Over the past decade, transition-metal-catalyzed C−H activation methods for the synthesis of aromatic compounds[2,3] has emerged as a powerful tool for C_{Ar}−C and C_{Ar}−heteroatom[4] bond formation. Among these significant advances direct C−H cleavage, through weak coordination[5] to commonly occurring functional groups on the ring has been well established by Yu and co-workers for various C−H functionalization reactions. For instance, this approach has been successfully employed to make aromatic iodides with benzoic acids, phenyl acetic acids, and sulfonamides[5d,e] (Scheme 1). However, application of this strategy to create a C_{Ar}−Cl bond is still surprisingly underdeveloped. Although impressive progress[6] had been made with palladium catalysts, important challenges remain for directed C−H chlorination in terms of scope, efficiency, and practicality of these protocols. Currently the reaction scope of C−H chlorination is generally limited to substrates having heteroaromatics or electron-donating directing groups (DGs), such as anilide. In contrast, electron-poor arenes such as benzoic esters, sulfonamides, benzamides, and aromatic ketones have not yet been reported as substrates for directed C−H chlorination. Regio- and chemoslective transformation of these substrates into the

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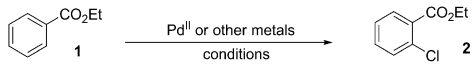
[+] These authors contributed equally to this work.

Scheme 1. A general approach to regio- and chemoselective C−H chlorination of unprecedented arenes through weak coordination. DCE = 1,2-dichloroethane, DMF = *N,N*-dimethylformamide, NCS = *N*-chlorosuccinimide, Tf = trifluoromethanesulfonyl.

corresponding chlorinated products through a weak-coordination approach is arguably a highly efficient, atom-economic, and desirable method. Herein, we report the first example of a palladium(II)-catalyzed regio- and chemoselective chlorination of a variety of challenging substrates including benzoates, benzamides, sulfonamides, aromatic ketones, and 2-phenylacetates, and its broad utility in organic synthesis. The *ortho*-bromination products of those substrates can also be readily prepared by the simple replacement of NCS with NBS as the bromine source under the same reaction conditions. Furthermore, a preliminary study of relative DG abilities was conducted to help provide some guidance for designing synthesis strategies using this chemistry.

We proposed that under proper acidic conditions, palladium(II) catalysts can promote C−H bond cleavage by an orthometalation process through weak coordination[5] with the carbonyl oxygen atom of a benzoate, benzamide, sulfonamide, benzoic acid, or aromatic ketone. Consequently, with suitable chlorine sources and co-oxidants, a C−Cl bond formation is possible through the reductive elimination from Pd^{IV} [7] to afford the corresponding chlorinated arenes. To test our hypothesis, benzoates were selected as the initial substrates for the following reasons: 1) benzoates are rather electron poor, 2) the utility of an ester functionality as a feasible DG in C−H activation has been rarely reported,[4,8] 3) benzoic esters are not only readily available but also easily converted into alcohols, amides, and other carbonyl com-

pounds, 4) the ester group itself can be further utilized in decarboxylative coupling and decarboxylation reactions to provide convenient access to various biaryl and aromatic compounds (Scheme 1).

Firstly, a model study with ethyl benzoate (**1**) was conducted in the presence of Pd(OAc)$_2$ in AcOH with commercially available NCS as the chlorinating reagent and Na$_2$S$_2$O$_8$[9] as the co-oxidant (Table 1). However, no desired

Table 1: Optimization of the reaction conditions.[a]

Entry	Conditions	Yield [%][a]
1	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, HOAc	n.r.
2	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, TFA	21
3	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, TFA/TFAA (9:1)	26
4	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, TFA, DCE	n.r.
5	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, TfOH, DCE	74(69)[b]
6	**1**, Na$_2$S$_2$O$_8$, NCS, TfOH, DCE	n.r.
7	**1**, Pd(OAc)$_2$, NCS, TfOH/Tf$_2$O (1:1), DCE	n.r.
8	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, CuCl$_2$, TfOH, DCE	n.r.
9	**1**, Pd(OAc)$_2$, K$_2$S$_2$O$_8$, CuCl$_2$, TfOH, DCE	n.r.
10	**1**, PdCl$_2$, Na$_2$S$_2$O$_8$, NCS, TfOH, DCE	n.r.
11	**1**, Pd(OAc)$_2$, K$_2$S$_2$O$_8$, NCS, TfOH, DCE	38
12	**1**, Pd(OAc)$_2$, (NH$_4$)$_2$S$_2$O$_8$, NCS, TfOH, DCE	44
13	**1**, Pd(OAc)$_2$, Selectfluor, NCS, TfOH, DCE	60
14	**1**, Pd(OAc)$_2$, PhI(OAc)$_2$, NCS, TfOH, DCE	10
15	**1**, Pd(OAc)$_2$, NFPy·BF$_4$, NCS, TfOH, DCE	59
16	**1**, Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NCS, TfOH (3 equiv), DCE	45[c]
17	Pd(OAc)$_2$, Na$_2$S$_2$O$_8$, NBS, TfOH (3 equiv), DCE	72

[a] Conversion ratio. [b] Yield of isolated product. [c] Yield for dihalogenated product. n.r. = no reaction. TFA = trifluoroacetic acid.
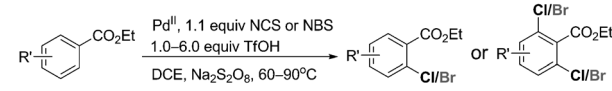
product was detected even when the reaction was run at high temperature for a prolonged time. After screening many additives, co-oxidants, solvents, and temperatures, we turned our attention to TFA.[10] To our delight, the chlorinated product **2** was observed in 21% yield after stirring for 10 hours at 90°C with TFA as the solvent (entry 2). Further investigation revealed that TFA is not a prerequisite for this reaction and it can be replaced by DCE with a small amount of TfOH (1.0 equiv). A control reaction showed that omission of the palladium catalyst resulted in complete inactivity of this catalytic system. Remarkably, in the absence of strong oxidants, the regioselectivity of the reaction was very poor with the major product being that of an eletrophilic aromatic substitution (*meta*-chlorination). Encouraged by the preliminary results, we optimized the reaction conditions. We found that Na$_2$S$_2$O$_8$ and Selectfluor were generally superior over other co-oxidants with a remarkably high level of efficiency (for details, see the Supporting Information). Using oxidants[11] such as persulfate and F$^+$ has been well developed by Yu and co-workers as an efficient strategy to achieve selective reductive elimination in Pd^{II}/Pd^{IV} catalysis. Our results indicate that the use of proper oxidant is an essential factor for the *ortho* selectivity of this reaction. Notably, it was found the amount of TfOH significantly affects both the rate and outcome of the reaction. For example, 1–2 equivalents of

TfOH is most suitable for furnishing monochlorinated products. In contrast, a larger amount of TfOH (>3.0 equiv) and a co-oxidant (>2.0 equiv) will lead to significant formation of the dichlorinated benzoate as the major product (entry 16). In general, 0.05 equivalents of Pd(OAc)$_2$[12] was enough to effectively promote the reaction. Typically the reaction will proceed to completion within 6 hours at 60–90°C. Delightfully, we found that the *ortho*-bromination product of **1** can also be readily prepared with NBS as the bromine source under the same reaction conditions (entry 17).
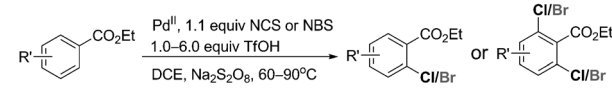
With the optimal reaction conditions in hand, we explored the scope for this new halogenation reaction. As displayed in Table 2, a variety of benzoates were smoothly transformed into the corresponding *ortho*-chlorinated and *ortho*-brominated products in moderate to excellent yields. The scope of the substituents was found to be very broad. The *ortho*-, *meta*-, and *para*-substituted aryl groups, as well as electron-withdrawing and electron-donating groups were well tolerated. When using Selectfluor as the oxidant, satisfactory yields were observed with substrates containing strong electron-withdrawing groups (**5**, **7**, **8**). All *meta*-substituted substrates
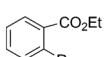
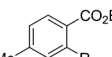***Table 2:*** Mono- and dihalogenation of benzoates.[a]
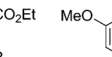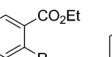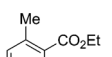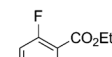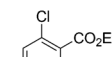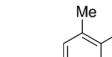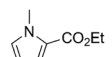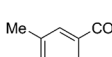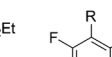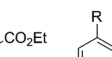
[a] Yield is that of the isolated product. NBS = *N*-bromosuccinimide.

gave only one regioisomeric product (**9–12**) because of sterics. Notably, heteroaromatic ethyl esters were also successfully employed to provide *ortho*-halogenated products (**18**, **22**, **23**). In addition to ethyl benzoates, methyl benzoates were found to have similar reactivity and furnished chlorinated products in good yields (**4**, **8**). Additionally, the feasibility of a double C–H halogenation using this transformation was tested, and we were pleased to find that the desired dichlorination and dibromination compounds (**13b**, **16a**, **24**, **25**) can be smoothly prepared in satisfactory yields by using 5.0 equivalents of TfOH.

The efficiency and usefulness of this reaction was further demonstrated in an iterative *ortho* halogenation of two *meta*-substituted substrates. As shown in Scheme 2, the optimum
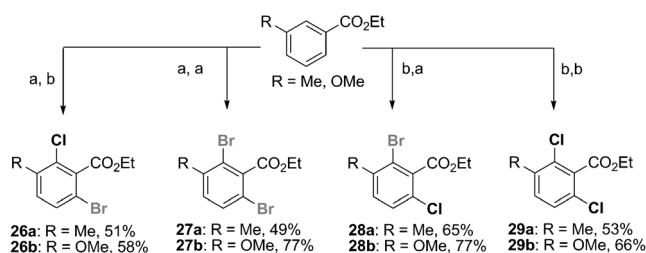
Scheme 2. Highly diversified iterative C–H halogenation of benzoates. Reaction conditions: a) 5 mol% Pd(OAc)$_2$, NBS, TfOH, DCE, Na$_2$S$_2$O$_8$, 60°C, 6h. b) 5 mol% Pd(OAc)$_2$, NCS, TfOH, DCE, Na$_2$S$_2$O$_8$, 60°C, 6h.

reaction conditions proved to be successful to provide eight different dihalogenated benzoates[13] (**26–29**) in two steps from two simple benzoates. Notably, the second halogenation step is very challenging because of the steric bulk and electron-poor nature of the intermediates from the first halogenation step. Moreover, all these dihalogenated products are either difficult to prepare or require extra and tedious steps when using traditional methods.

To prove both practicality and effectiveness of this method for large-scale synthesis, we prepared **3a** and **14a** on a gram scale under the optimized reaction conditions with only a 2 mol% Pd(OAc)$_2$ catalyst loading (Scheme 3). Notably, this protocol was conducted without the need for air- or moisture-free reaction conditions. In comparison to conventional approaches requiring air- or moisture-free conditions, our method is advantageous for rapid access to these molecules because of its operational simplicity and ready availability of starting materials.

The synthetic utility of *ortho*-chlorinated benzoates is shown in Scheme 4. The dichlorinated benzoate **24** was efficiently transformed into the synthetically challenging 1,3-dichlorinated biaryl compound **30** and 1,3-dichlorinated toluene **31** by decarboxylative C–C coupling and decarboxylation, respectively. Notably, both **30** and **31**, as well as **24** can be further used to prepare a variety of C–C, C–N, and C–O coupling products via the installed chlorine atom.

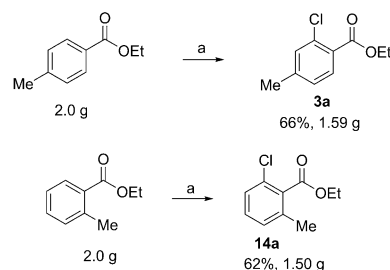The reaction conditions were next applied to substrates including 2-phenylacetates, aromatic ketones, benzamides, and sulfonamides (Table 3). These molecule types were all successfully transformed into the corresponding chlorinated

Scheme 3. Gram-scale synthesis of *ortho*-chlorinated benzoates. Reaction conditions: a) 2 mol% Pd(OAc)$_2$, 1.1 equiv NCS, 1.1–1.2 equiv TfOH, DCE, Na$_2$S$_2$O$_8$, 60°C, 6h.
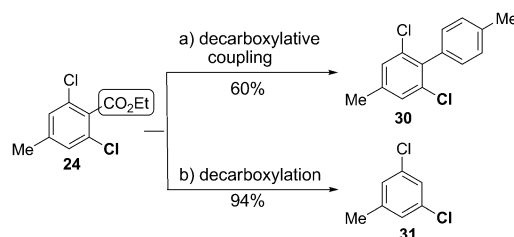
Scheme 4. Synthetic utility of *ortho*-chlorinated benzoates. Reaction conditions: a) 1. KOH, MeOH; 2. Ag$_2$CO$_3$, DMSO, 100°C. b) 1. KOH, MeOH; 2. PdCl$_2$, 4-iodotoluene, Ag$_2$CO$_3$, DMA, 150°C. All three molecules can be used for C–C, C–N, and C–O bond formations. DMSO = dimethylsulfoxide.

arenes (**32–52**) in modest to good yields. To the best of our knowledge, this represents the first example of palladium(II)-catalyzed *ortho* chlorination of such a diverse array of arenes. Especially for sulfonamides, it is important to note that *ortho*-chlorinated sulfonamides serve as highly valuable synthetic intermediates for making antibacterial agents and analogues such as Furosemide, Clopamide, and Hydrochlorothiazide.

To further exemplify the synthetic utility of this chlorination reaction, two important pharmaceutical intermediates were selected as synthetic targets (Scheme 5). The compound **54** was readily prepared from the corresponding 2-phenylacetate **53** in a satisfactory yield by a convenient, sequential C–H chlorination and benzylic bromination. In parallel, **56** was prepared from the commercially available sulfonamide **55**. Using known transformations,[14] these two valuable compounds, **54** and **56**, can be transformed into the drugs Plavix and Clopamide, respectively, in a single step. Additionally, two anti-inflammatory drugs, Ibuprofen and Flurbiprofen, were also tested in this reaction and transformed into the corresponding analogues **57** and **58** in good yields. Importantly, all these reactions demonstrated excellent regio- and chemoselectivity, as well as reactivity.

To date, the vast majority of C–H activation research has been focused on the employment of relatively simple molecules which usually contain only one DG. However, in multistep synthesis, many compounds have multiple functional groups which could potentially direct C–H bond activation. As such, the question of DG ability arises if selective and iterative C–H chlorination were desired. A good understanding of various DG abilities would be highly valuable for practical applications of our reaction. Although

Table 3: Substrate scope.[a]

R'— (aryl)—DG, H → Pd(II), 1.1 equiv NCS or NBS, DCE; 1.0–6.0 equiv TfOH, Na$_2$S$_2$O$_8$; DG = CONHR, SO$_2$NHR, COR, CH$_2$CO$_2$R → R'—(aryl)—DG, Cl/Br

32a R = Cl 61%
32b R = Br 71%

33a R = Cl 66%
33b R = Br 84%

34 66%

35a R = Cl 80%
35b R = Br 75%

36a R = Cl 70%
36b R = Br 63%

37 41%

38 93%

39 74%

40 61%

41 R = Cl, 40%
43 R = Br, 41%

44 86%

44 83%

45 50%

46 52%

47 49%

48 59%

49 75%

50 71%

51 93%

52 70%

[a] Yield is that of the isolated product.

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53 → a 71% / b 76% → **54** → Ref. [18a] → Plavix

55 → a 54% → **56** → Ref. [18b] → *N*-methyl Clopamide

R^1 = F, R^2 = Ph: Flurbiprofen
R^1 = H, R^2 = *i*Bu: Ibuprofen
→ a 77% → **57**
→ a 53% → **58**

Scheme 5. Applications in drug and drug analogue synthesis. Reaction conditions: a) 5 mol% Pd(OAc)$_2$, 1.1 equiv NCS, 2.5–4.0 equiv TfOH, DCE, Na$_2$S$_2$O$_8$, 60°C, 6 h; b) 1.1 equiv NBS, benzyl peroxide, 80°C.

C=O > SO$_2$NHR > CO$_2$Et, CONR^{1}R^2, SO$_2$NR^{1}R^2. This preliminary knowledge of DG abilities should be generally useful for a systematic study of C–H activation involving DGs, especially for the design and synthesis of chlorine-containing molecules.

Investigations were performed to gain some insight into the reaction mechanism. Consistent and significant KIE

in recent years a considerable number of investigations have been carried out on C–H activation with various DGs, so far, the knowledge about the priority ordering of various DGs is still surprisingly limited.[15] With this in mind, a variety of molecules containing two different DGs were designed for our study (Table 4). The twelve substrates were readily chlorinated under the optimized reaction conditions in modest to good yields (**59–69**), and in all cases, only a single regioselective C–H chlorination product was observed. The results clearly show the priority ordering of the DGs in this chlorination reaction. For instance, **63** which contains both an amide and a sulfonamide DG, was chlorinated exclusively *ortho* to the amide, and none of the corresponding product of sulfonamide-directed C–H chlorination was found. Thus, the amide is has a higher priority than the sulfonamide as a DG in this reaction. Interestingly, the regioselectivity outcome of **64** showed a preference of a secondary amide over a ketone. In contrast, when both a tertiary amide and ketone were present in the molecule (**68**) the ketone had the higher priority, thus suggesting that the NH proton is essential for the DG ability of amides. Finally, based on these observations, an order of priority can be roughly summarized as: NHAc > CONHR >

Table 4: Evaluation of relative DG ability in chlorination.[a]

DG^1—(aryl)—DG^2, H, H → Pd(II), 1.1 equiv NCS, Na$_2$S$_2$O$_8$; 1.0–4.0 equiv TfOH, DCE, 70 °C → DG^1—(aryl)—DG^2, Cl, H or DG^1—(aryl)—DG^2, H, Cl

59 (40%)
(NHAc > CONHR)

60 (36%)
(NHR > SO$_2$NHR)

61 (51%)
(NHAc > CO$_2$Et)

62 (68%)
(NHAc > CONHR > C=O)

63 (69%)
(CONHR > SO$_2$NHR)

64 (72%)
(CONHR > C=O)

65 (62%)
(CONHR > CO$_2$Et)

66 (75%)
(C=O > SO$_2$NHR)

66' (65%)
(C=O > SO$_2$NRR')

67 (49%)
(SO$_2$NHR > CO$_2$Et)

68 (71%)
(C=O > CONRR')

69 (68%)
(C=O > CO$_2$Et)
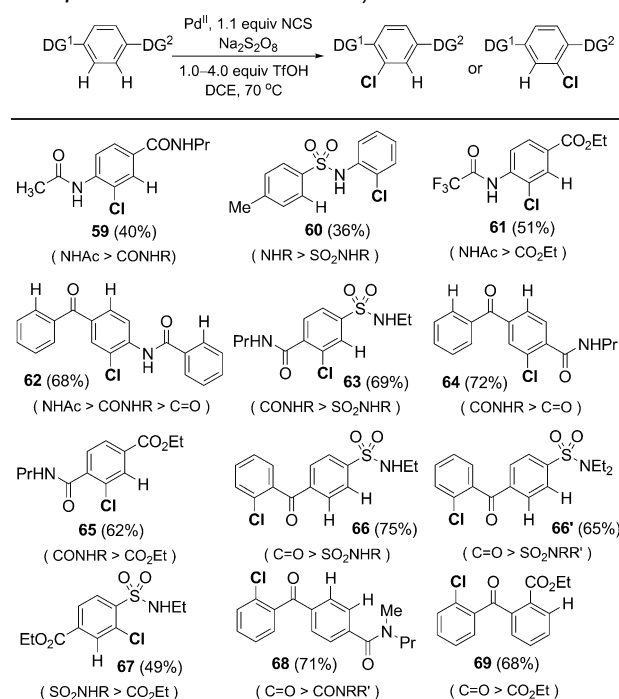
Order of DG priority:
NHAc > CONHR > C=O > SO$_2$NHR > CO$_2$Et, CONR^{1}R^2, SO$_2$NR^{1}R^2

[a] Yield is that of the isolated product.

values were observed from both intra- ($k_H/k_D = 4.9$) and intermolecular ($k_H/k_D = 2.6$) isotope effect studies of **1**, and thus indicated that the C−H bond cleavage step might be involved in the rate-limiting step of this transformation[16] (for details see the Supporting Information). Although details about the mechanism remain to be ascertained, on the basis of these observations, a plausible mechanism for this reaction is depicted as follows: 1) chelate-directed C−H activation of the substrate to afford a five-membered cyclopalladium(II) intermediate, 2) Pd[II] is oxidized to a possible Pd[IV] intermediate[14] by co-oxidants, 3) a C−Cl bond-forming reductive elimination affords the chlorinated product and regenerates Pd[II] from Pd[IV].

In summary, a novel palladium(II)-catalyzed *ortho*-chlorination/bromination reaction has been developed for the synthesis of a broad range of arene chlorides from easily accessible electron-deficient arenes. It was found that both the co-oxidant and TfOH[17] serve as critical factors for regio- and chemoselective C−H activation. A preliminary evaluation of relative DG abilities was conducted to provide some insight into the priority ordering of DG abilities. Further studies into the applications and mechanism of this new reaction are in progress in our laboratory.

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