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Room-temperature Pd-catalyzed C–H chlorination by weak coordination: one-pot synthesis of 2-chlorophenols with excellent regioselectivity†

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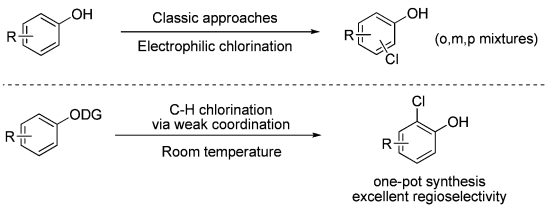
A room-temperature Pd(II)-catalyzed regioselective chlorination reaction has been developed for a facile one-pot synthesis of a broad range of 2-chlorophenols. The reaction demonstrates an excellent regioselectivity and reactivity for C–H chlorination. This reaction represents one of the rare examples of mild C–H functionalization at ambient temperature.

2-Chlorophenols serve as important structural motifs found in a diversity of bioactive molecules and valuable intermediates utilized in modern pharmaceutical industries.[1] Classic approaches to the synthesis of 2-chlorophenols generally involve electrophilic aromatic substitution. However, these reactions lack site-selectivity and always provide a mixture of *o*- and *p*-isomers[2] (in most cases, the undesired *p*-substituted isomers were major products). Palladium-catalyzed C–H functionalization/halogenation[3–5] has emerged as a particularly useful approach for producing halogenated aromatic products with selectivity that normally could not be obtained under simple electrophilic halogenation conditions. A significant advance in this area was reported by the Shi[6] and Bedford[7] groups who demonstrated that anilides could be *ortho* chlorinated in good to excellent yields using $Pd(OAc)_2$ as the catalyst. However, compared with anilines, palladium catalyzed *ortho*-functionalization of phenols is lagging far behind. A highly *ortho*-selective chlorination of phenols remains to be developed, which might be due to the following difficulties: (1) the coordinating ability of phenol derivatives is generally much weaker than aniline derivatives (oxygen *versus* nitrogen); (2) phenol derivatives are less stable than aniline derivatives under current C–H functionalization conditions (nearly all of them require high temperatures and/or powerful oxidants).

In our continuous studies of functionalized phenol synthesis through transition-metal catalysis by weak coordination,[8] we envisioned that palladium catalysts, under certain acidic conditions, could promote C–H bond activation *via* an orthometalation[9] process *even at room temperature* through weak coordination with the carbonyl oxygen of phenol esters, carbonates or carbamates.



Scheme 1 A general approach to 2-chlorophenols *via* weak coordination.

Following that step, a potential subsequent C–Cl bond formation *via* the reductive elimination could afford the corresponding 2-chlorophenol derivatives with suitable acids and chlorine containing oxidants[10] (Scheme 1). Herein we report the first example of a one-pot synthesis of valuable 2-chloro/bromophenols through a room-temperature, carbamate-directed, palladium-catalyzed halogenation reaction with excellent regioselectivity and reactivity (Table 1).

To test our hypothesis, different protected phenol esters,[11] carbonates[12] and carbamates[13] were explored under various acidic conditions at room temperature. After many attempts including use of various additives, co-oxidants and solvents, we were delighted to find that phenol carbamate substrate **1** could be transformed into the corresponding desired product **2** in the presence of a small amount of TfOH (0.5 equivalent) at ambient temperature in a yield of 26% (entry 1). It was observed that the addition of TfOH is critical for this reaction and other acids cannot promote it at all at room temperature. A control reaction showed that omission of the $Pd(OAc)_2$ catalyst resulted in complete inactivity of this catalytic system. Encouraged by the preliminary results, we next started the optimization of reaction conditions. It was found that co-oxidants, such as $Na_2S_2O_8$, selectfluor and $PhI(OAc)_2$, are not essential and DCE is superior to other solvents for this reaction. Remarkably, no *para*- or *meta*-chlorination occurred and only *ortho*-chlorinated products could be obtained under the conditions. In general, 0.05 equiv. amount of $Pd(OAc)_2$ was enough to effectively catalyze the reaction. $Pd(TFA)_2$ was found to have a similar catalytic efficiency to $Pd(OAc)_2$. Attempts to use other metal catalysts, such as Ru and Rh,[14] were not successful. Typically the reaction will proceed to completion within 5 hours at room temperature. Gratifyingly, it was found that the 2-bromophenol derivative of **1** could

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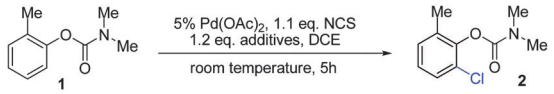
Table 1 Optimization of the reaction conditions



Entry	Catalyst	Conditions	Yield[a] (%)
1	$Pd(OAc)_2$	NCS, TfOH (0.5 equiv.), DCE	26
2	$Pd(OAc)_2$	NCS, CH_3SO_3H, DCE	NR
3	$Pd(OAc)_2$	NCS, TFA, DCE	NR
4	$Pd(OAc)_2$	NCS, HOAc, DCE	NR
5	$Pd(OAc)_2$	NCS, $TsOH{\cdot}H_2O$, DCE	NR
6	$Pd(OAc)_2$	NCS, TfOH, $Na_2S_2O_8$, DCE	61
7	$Pd(OAc)_2$	NCS, TfOH, $K_2S_2O_8$, DCE	61
8	$Pd(OAc)_2$	NCS, TfOH, $PhI(OAc)_2$, DCE	Side product
9	$Pd(OAc)_2$	NCS, TfOH, DMSO	NR
10	$Pd(OAc)_2$	NCS, TfOH, Toluene	Side product
11	$Pd(OAc)_2$	NCS, TfOH, MeCN	NR
12	No	NCS, TfOH, DCE	NR
13	$PdCl_2$	NCS, TfOH, DCE	NR
14	$Pd(TFA)_2$	NCS, TfOH, DCE	66
15	$Rh(OAc)_2$	NCS, TfOH, DCE	NR
16	$Ru(p\text{-cymene})Cl_2$	NCS, TfOH, DCE	NR
17	$Pd(OAc)_2$	NCS, TfOH, DCE	60
18	$Pd(OAc)_2$	NCS, TfOH (1.0 equiv.), DCE	55
19	$Pd(OAc)_2$	NCS, TfOH (1.5 equiv.), DCE	83 (75)[b]
20	$Pd(OAc)_2$	NCS, TfOH (2.0 equiv.), DCE	85
21	$Pd(OAc)_2$	NCS, TfOH, DCE, 8 h	69
22	$Pd(OAc)_2$	NBS, TfOH, DCE	89 (80)[b]

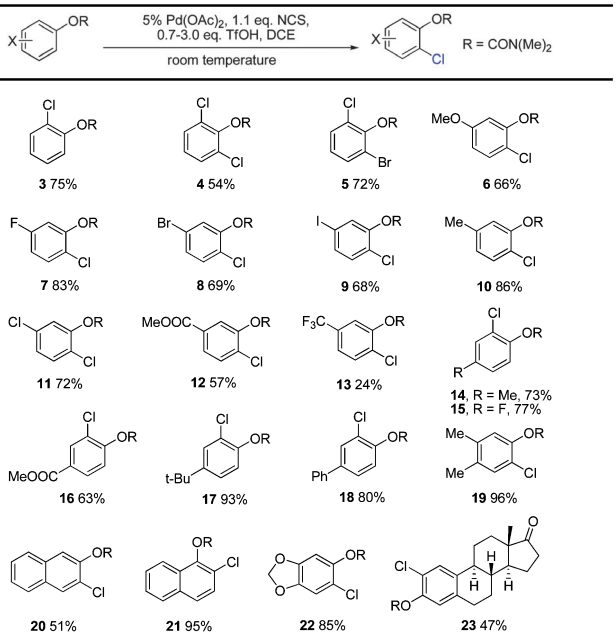
[a] Conversion ratio. [b] Isolated yield; NBS (*N*-bromosuccinimide); NCS (*N*-chlorosuccinimide); DCE (1,2-dichloroethane); TfOH (trifluoromethanesulfonic acid).

be readily prepared with NBS as the bromine source under the same conditions as well (entry 22). *It is noteworthy to mention that this protocol was conducted without the need for air- or moisture-proof conditions.*

With the optimal conditions in hand, we next set out to survey this new reaction scope. As shown in Table 2, a variety of phenol derivatives were efficiently converted into desired *ortho*-chlorinated products in moderate to excellent yields. We found that the scope of the substituents was very broad. The electron donating and electron withdrawing functional groups (methyl, methoxyl, halides and CF_3, *etc.*) as well as the *ortho*-, *meta*- and *para*-substituted aryl groups were well tolerated. For instance, satisfactory yields were observed with substrates which contained strong electron-withdrawing groups, such as F and CO_2Me (**7**, **12**, **15**). Only one regioisomeric product (compounds **6–13**) was formed with all *meta*-substituted substrates due to the steric discrimination. We were pleased to find the *ortho*-chlorination exclusively occurred at the directing group side for all *para*-substituted substrates. It is notable that the excellent regioselectivities were consistently observed in all examples. Additionally, only mono-chlorination products, no di-chlorination products were found. To the best of our knowledge, this represents the first example of Pd(II) catalyzed *ortho*-chlorination of phenol derivatives at ambient temperature. The efficiency and usefulness of this reaction was also demonstrated in the *ortho*-bromination at room temperature. As displayed in Table 3, the optimum reaction conditions proved to be successful in providing 2-bromophenols with excellent regioselectivity at room temperature (**24–30**).

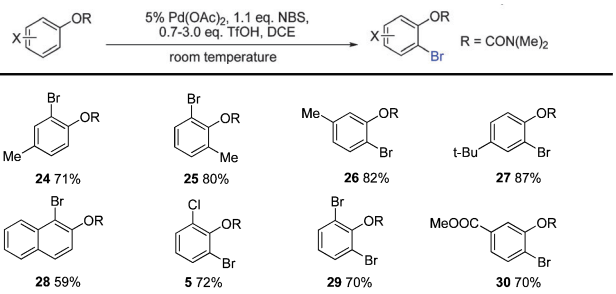
To further prove the practicality of this new approach, compounds **2** and **10** were prepared on a gram scale (yields of 84% and 75% respectively) under the optimized reaction conditions with only 1 mol% $Pd(OAc)_2$ catalyst loading (Scheme 2). In addition, as

Table 2 *Ortho* chlorination of carbamates at room temperature[a]



[a] Isolated yield.

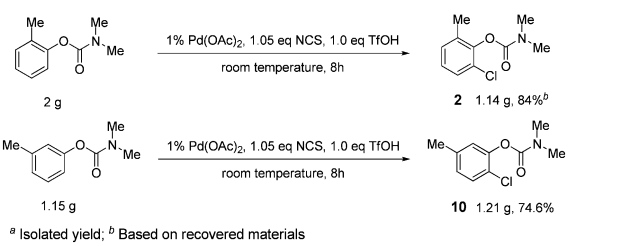
Table 3 *Ortho* bromination of carbamates at room temperature[a]



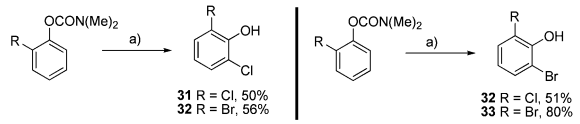
[a] Isolated yield.

shown in Scheme 3, the applicability and effectiveness of this reaction were further demonstrated in a sequential one-pot halogenation/deprotection procedure which could directly transform phenol carbamates to unprotected 2-chloro/bromophenols (**31–33**) in good yields.

Further investigations were performed to gain some insight into the reaction mechanism. As shown in Scheme 4, parallel competition experiments clearly show that the electron-rich aromatic ring reacts faster than its eletron-poor counterpart to furnish the 2-chlorophenol derivative **3**. In addition, an intramolecular isotope effect study was conducted and a significant KIE value of 3.0 was obtained. These

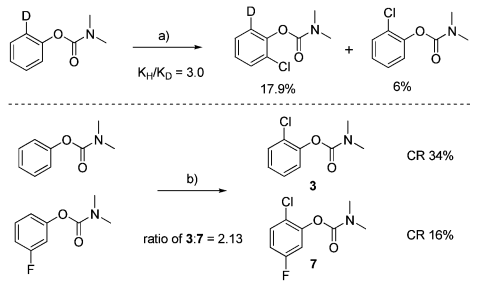


Scheme 2 Gram-scale synthesis of *ortho*-chlorinated phenols.[a]



Conditons: a) 1. $Pd(OAc)_2$, NXS, TfOH, DCE, rt, 4-6h; 2. $NH_2NH_2.H_2O$, 60°C, 2h or r.t. 12h;

Scheme 3 One-pot synthesis of 2-chloro/bromophenols.



Condtions: a) $Pd(OAc)_2$ (0.05 eq) NCS (1.1eq) TfOH (1.5 eq) rt 10min; b) $Pd(OAc)_2$ (0.05 eq) NCS (1.1eq) TfOH (1.8 eq) rt 10min

Scheme 4 KIE and separate rate constant studies.

results indicate that C–H activation was involved in the rate-limiting step of this transformation. Although details about the mechanism remain to be ascertained, on the basis of these observations, a plausible mechanism for this reaction can be delineated as in the following. Step (i) involves chelate-directed C–H activation of the substrate which will afford a five-membered cyclopalladium (II) intermediate (TfOH might be involved in the *in situ* generation of an electron-deficient Pd complex, $Pd(OTf)_2$,[15] which can promote more challenging C–H activation through weak coordination, even at room temperature). In the second step (ii), Pd(II) was oxidized into a possible Pd(IV) intermediate[16] by NCS. The final step (iii) involved C–Cl bond-forming reductive elimination to afford the chlorinated product and turned Pd(IV) back into Pd(II).

In summary, a practical, room-temperature Pd(II) catalyzed *ortho*-chlorination/bromination reaction has been developed for the synthesis of 2-chloro/bromophenol derivatives from easily accessible phenols. This reaction represents one of the rare examples of mild C–H functionalization at ambient temperature. Moreover, it demonstrates an excellent regioselectivity and reactivity in comparison with literature conditions for C–H halogenation. The practicality and efficiency of this reaction was further exemplified by a gram-scale synthesis and one-pot protocol for the preparation of 2-chloro/bromophenols. Further studies on the application and mechanism of this new reaction are in progress in our laboratory.

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