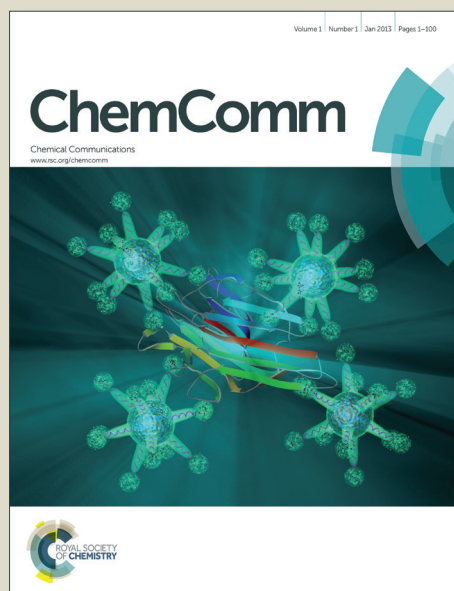


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Pd (II) Catalyzed *ortho* C-H Iodination of Phenylcarbamates at Room Temperature with Cyclic Hypervalent Iodine Reagents

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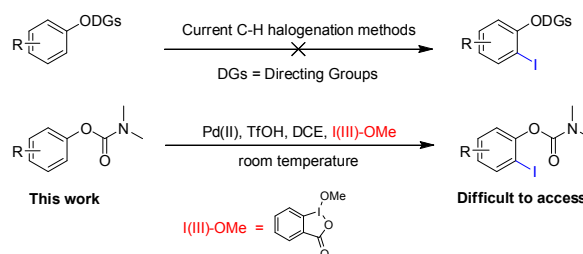
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A novel approach to access *ortho* iodinated phenols with cyclic hypervalent iodine agents through palladium (II) catalyzed C-H activation has been developed through weak coordination. The reaction showed excellent regioselectivity, reactivity and good functional group tolerance. A unique mechanism was proposed.

Aryl iodides are indispensably important chemicals both in natural product and pharmaceutical drug synthesis.¹ Traditional approaches to access aryl iodides involve *ortho*-deprotonative metalation,² electrophilic aromatic substitution³ or Sandmeyer reaction,⁴ which usually suffer from several disadvantages, such as harsh reaction conditions, dangerous operations and toxic reagents. In the last decade, transition metal catalyzed C-H halogenation of arenes had emerged as a powerful tool to prepare aryl halides.⁵ Among these significant progress, direct C-H iodination through palladium catalysis with IOAc or I₂ as iodine source has been well established by Yu's group.⁶ Meanwhile, Glorius and coworkers reported the first example of rhodium (III) catalyzed *ortho* iodination of ketones, benzoates and aromatic amides with NIS.⁷ Although the impressive advances had been made, there are important challenges remain for *ortho* C-H iodination in terms of substrate scope and efficiency of these protocols. For instance, there is no effective and mild method to obtain *ortho* iodinated phenols yet. Current C-H iodination methods will provide *para*-iodinated phenols by electrophilic iodination as the major products. Therefore, due to their extreme significance, developing new practical method to synthesize aryl iodides is still highly desired. Herein, we report the development of an *ortho*-iodinated phenol synthesis under palladium catalysis at room temperature with hypervalent iodine reagents as effective iodination agents.

Recently we reported a new method to construct C-Cl and C-Br bonds in arenes containing different weak coordinating groups.⁸ In our group continuous studies of preparation of aryl halides via transition-metal catalysis, we tried to access *ortho* C-I bond with phenol substrates by the same strategy. However, the attempt failed with different iodine (I) reagents and palladium catalysts. In those cases, electrophilic iodination always dominated the regioselectivity outcome of reactions to give *para*-iodinated

phenols. After many fruitless efforts, we turned our attentions to other type iodine sources



Scheme 1 A new approach to access *ortho*-iodinated phenols.

Hypervalent iodine reagents have been broadly utilized as oxidants in organic synthesis.⁹ In recent years, it has found further applications in transition metal-catalyzed C-H functionalizations. For example, PhI(OAc)₂ were employed to build C-C bonds or as powerful oxidants in C-H activation reactions.¹⁰ Two kinds of Togni's reagents (cyclic iodine(III)) were used for constructing C-trifluoromethyl bonds.¹¹ More recently, a new sp³ C-H alkoxylation method by palladium(II) with cyclic iodine (III) reagents were developed by our laboratory.¹² During our investigations of this sp³ C-H alkoxylation reaction, a trace amount of sp² C-H iodinated 4-aminoquinoline derivatives were observed, which aroused our curiosity. We proposed the cyclic iodine (III) reagents might promote a palladium-iodide complex intermediate formation through oxidative addition, then reductive elimination can form C-I bond under our reaction conditions. Inspired by this result, we envisioned that the cyclic iodine (III) reagents may serve not only as a critical oxidant but also a potential iodine source in sp² C-H iodination. Therefore, we describe the first example of employing hypervalent iodine reagents in palladium catalyzed *ortho* iodination of phenols at room temperature.

To test our hypothesis, a model investigation was initiated with a carbamate derivative **1**. At the beginning of our studies, a variety of hypervalent iodine oxidants including cyclic hypervalent iodine (III) oxidants (I-OAc, I-OMe, Togni's reagent) and acyclic hypervalent PhI(OAc)₂, etc, were examined in the presence of Pd(OAc)₂ in DCE

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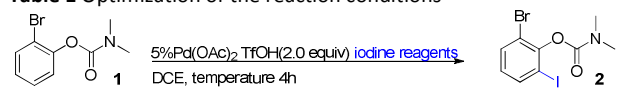
[†] These authors contributed equally to this work.

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(Table 1). To our delight, desired ortho-iodinated phenol **2** was formed smoothly with Togni's reagent at room temperature in a yield of 20% and no *para*-iodination isomer can be observed (entry 1). Among all surveyed cyclic iodine (III) reagents, 1-methoxy-1,2-benziodoxole-3(1H)-one (I(III)-OMe) was found to be superior over others.¹³ Further testing revealed that the combination of I(III)-OMe/DCE/TfOH gave the best results (entry 9) in a good yield of 70%. In contrast, no product was detected with acyclic iodine (III) reagents (entry 3-5). Remarkably, this reaction could be conducted at room temperature and finished within several hours without the need of air- and moisture-proof. It was found higher reaction temperature (entry 10-12) resulted in lower yields because of the potential decomposition of products. Additionally, conventional iodine (I) reagents such as NIS or I₂/PhI(OAc)₂ gave mainly electronic iodinated products (entry 13-14) under this reaction conditions. Further investigations confirmed that palladium catalyst was essential for the reaction (entry 16). Meanwhile, Other metal catalysts including Ru(II) and Rh(III), etc, cannot promote this transformation under the reaction conditions (entry 17).

Table 1 Optimization of the reaction conditions



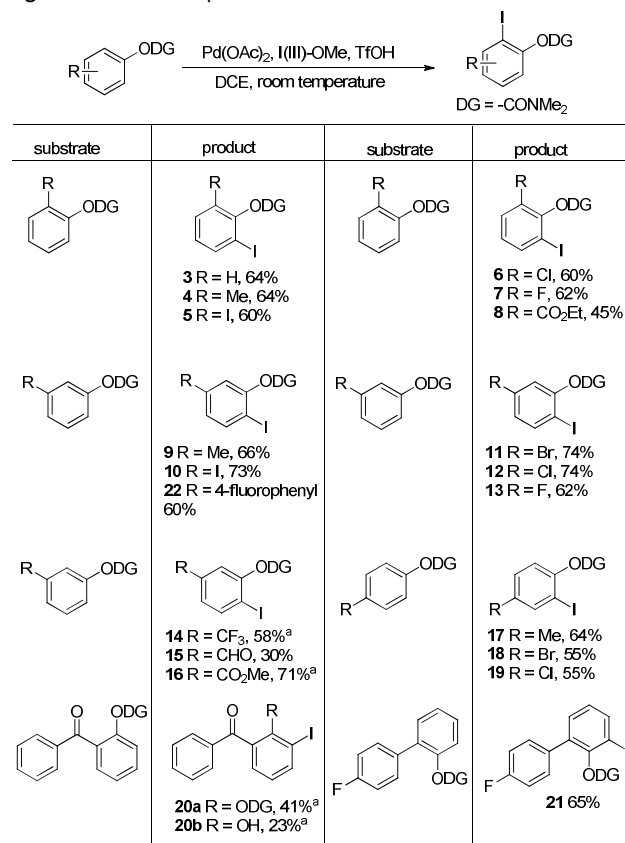
| entry | catalyst | iodine reagents | conditions | yield(%) ^a |
|-------|--|---------------------------------------|-----------------|-----------------------|
| 1 | Pd(OAc) ₂ | Togni's reagent II | TfOH, DCE, rt | 20 |
| 2 | Pd(OAc) ₂ | Togni's reagent | TfOH, DCE, rt | NR |
| 3 | Pd(OAc) ₂ | PhI(OAc) ₂ | TfOH, DCE, rt | NR |
| 4 | Pd(OAc) ₂ | [Hydroxy(tosyloxy)iodo]benzene | TfOH, DCE, rt | n.t. |
| 5 | Pd(OAc) ₂ | Diphenyliodonium iodide | TfOH, DCE, rt | NR |
| 6 | Pd(OAc) ₂ | I(III)-OTs | TfOH, DCE, rt | 37 |
| 7 | Pd(OAc) ₂ | I(III)-OAc | TfOH, DCE, rt | 32 |
| 8 | Pd(OAc) ₂ | I(III)-OH | TfOH, DCE, rt | 47 |
| 9 | Pd(OAc) ₂ | I(III)-OMe | TfOH, DCE, rt | 70 ^b |
| 10 | Pd(OAc) ₂ | I(III)-OMe | TfOH, DCE, 40°C | 68 |
| 11 | Pd(OAc) ₂ | I(III)-OMe | TfOH, DCE, 60°C | 45 |
| 12 | Pd(OAc) ₂ | I(III)-OMe | TfOH, DCE, 80°C | 30 |
| 13 | Pd(OAc) ₂ | NIS | TfOH, DCE, rt | 10%+62%SP |
| 14 | Pd(OAc) ₂ | I ₂ +PhI(OAc) ₂ | TfOH, DCE, rt | 78%SP |
| 15 | Pd(OAc) ₂ | I ₂ | TfOH, DCE, rt | NR |
| 16 | no Pd(OAc) ₂ | I(III)-OMe | TfOH, DCE, rt | NR |
| 17 | [Rh(Cp*)Cl ₂] ₂ or [Ru(p-cymene) ₂ Cl ₂] | I(III)-OMe | TfOH, DCE, rt | NR |

^aNMR yield using 4-nitrobenzaldehyde as internal standard. ^bIsolated yield. DCE(1,2-dichloroethane), TfOH(trifluoromethanesulfonic acid), SP(para-iodinated product of **1**).

With the optimized conditions in hand, we next set up to explore the reaction scope. As displayed in figure 1, a variety of phenol carbamates were efficiently converted into ortho-iodinated phenol derivatives in moderate to good yields.¹⁴ The scope of the reactions were found to be broad. Both electron-donating and electron-withdrawing substituents in ortho, meta and para positions (-Me, -CF₃, halides, ester and benzoyl group, etc.) were well tolerated, leading to the formation of the desired products (**3-22**). For instance, satisfactory yields were obtained with substrates which contained strong electron-withdrawing groups such as CF₃ and F (**13, 14**). It is notable that the aldehyde group was found to be compatible with the reaction conditions as well, albeit in a relatively low yield of **15**. To our delight, excellent ortho-selectivity was consistently observed and no corresponding para-isomers were formed in all ortho-substituted substrates (**4-8, 21**). Only one regioisomeric product was produced with meta-substituted substrates due to the steric discrimination (**9-16, 22**). As to para-

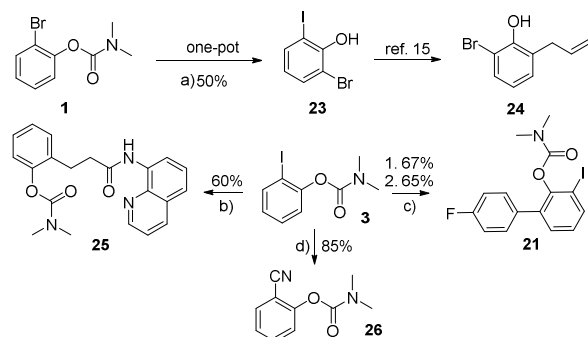
substituted substrates, C-H halogenation exclusively occurred at ortho-position of carbamate groups to give expected iodinated compounds (**17-19**). For substrate with a potential competing ketone directing group, corresponding products **20** can be obtained as well in a yield of 64%.

Figure 1 Reaction Scope



Reaction conditions: 5% Pd(OAc)₂, 1.1 equiv I(III)-OMe, 0.5-3.0 equiv TfOH, DCE, rt, 3-6h. ^a10% Pd(OAc)₂ and 1.5 equiv I(III)-OMe were used.

As illustrated in scheme 2, to prove the practicality of this method, 2-bromo-6-iodophenol **23** was readily synthesized from 2-bromophenyl dimethylcarbamate **1** through a one-pot procedure including C-H iodination and deprotection. **23** can be further transformed into compound **24** which serves as the synthetic building block of Honokiol derivatives for the treatment of proliferative disorders.¹⁵ To exemplify the synthetic utility of this iodination reaction, 2-iodophenol **3** was converted into diverse derivatives via different coupling reactions. For instance, biaryl compound **21** can be prepared from **3** via a sequential Suzuki coupling and C-H iodination reactions. With the newly installed iodine atom, **21** can undergo an iterative coupling reaction to provide various complex molecules. **3** was also successfully employed in the sp³ C-H arylation reaction¹⁶ to give corresponding compound **25**, which can be further transformed into chroman-2-one products. In addition, the cyanation reaction with **3** could afford useful chemical **26** respectively.

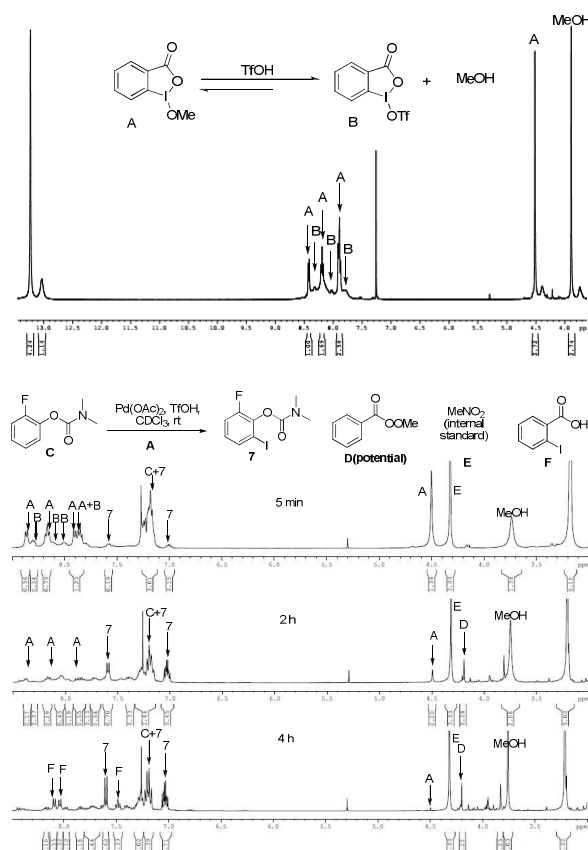


Reaction conditions: a) 1. Pd(OAc)₂, I(III)-OMe, TfOH, DCE, rt, 4h; 2. NH₂NH₂·H₂O, 80°C, 8h. b) Pd(OAc)₂, *N*-(quinolin-8-yl)propionamide, K₂CO₃, *t*-Amyl-OH/H₂O, 100°C, 36h. c) 1. Pd(OAc)₂, (4-fluorophenyl)boronic acid, PPh₃, K₃PO₄, Toluene, 100°C, 12h; 2) Pd(OAc)₂, I(III)-OMe, TfOH, DCE, rt, 4h. d) DDQ, Cu(OAc)₂, Ag₂O, NMP, 120°C, 22h.

Scheme 2 Semi one-pot synthesis and applications.



Scheme 3 KIE study.



Scheme 4 NMR studies of the mechanism.

As shown in scheme 3, an intra-molecular isotope effect study was conducted and no kinetic isotope effect was observed. In addition, parallel competition experiments had shown that the electron-poor

aromatic substrate reacted slower than its electron-rich counterparts to give iodinated products (please see SI for details). These results suggested that C-H activation may not be involved in the rate-limiting step of this transformation. Further NMR studies were performed to gain more insight into the reaction mechanism. As illustrated in scheme 4, some part of cyclic iodine (III) reagent A will be quickly converted to oxidant B in the presence of TfOH. After addition of substrate C and palladium catalysts, the amount of product 7 gradually increased with the consumption of C and oxidants A, B over 4 hrs at room temperature. During progress of reaction, the formation of the possible methyl benzoperoxoate D¹⁷ can be found from proton-NMR. Corresponding mass signal of D was observed by LC-MS analysis (please see SI for details). We also found a small amount of F (2-iodobenzoic acid) which should result from decomposition of oxidants.

Although mechanism details remain to be ascertained, on the basis of our experimental studies, a possible mechanism for this C-H iodination reaction can be proposed as followings. In the plausible catalytic cycle, step (i) would involve chelation of palladium(II) to carbonyl oxygen atom from the carbamate substrates and the formation of a six-membered cyclopalladium intermediate. In the second step (ii), Pd(II) can be oxidized into possible Pd(IV)¹⁸ intermediate by the cyclic hypervalent iodine(III) oxidant. During the process of oxidative addition, iodine was added to cyclopalladium intermediate. Finally, the third step (iii) involves carbon-iodine bond-forming reductive elimination to afford ortho-iodinated phenol product and turned Pd(IV) back into Pd(II).

In conclusion, we have established a unique Pd(II)-catalyzed ortho C-H iodination reaction. This method provides a novel and convenient access to a broad range of highly valuable 2-iodine phenols from readily accessible substrates. The cyclic hypervalent iodine(III) oxidant plays a critical role in this reaction. A possible Pd(II)/(IV) pathway might be involved. This reaction shows broad functional-group tolerance, excellent reactivity and good yields. Further studies into the mechanism and synthetic applications of this reaction are in progress in our laboratory.

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