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Pd(II)-Catalyzed C−H Iodination Using Molecular I_2 as the Sole Oxidant

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Supporting Information

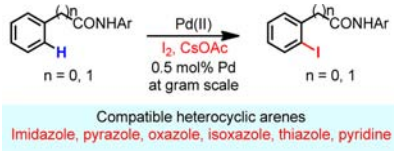
ABSTRACT: Pd-catalyzed *ortho*-C−H iodination directed by a weakly coordinating amide auxiliary using I_2 as the sole oxidant was developed. This reaction is compatible with a wide range of heterocycles including pyridines, imidazoles, oxazoles, thiazoles, isoxazoles, and pyrazoles.

Aryl halides (Ar-X, X = Cl, Br, and I) are extensively used in Grignard[1] and cross-coupling[2] reactions. Directed lithiation followed by reaction with a halogen-containing electrophile has been a major method for the regioselective preparation of aryl halides.[3] In the past decade, Pd(II)-catalyzed C−H halogenation utilizing electrophilic halogenating reagents has been extensively studied,[4−10] and these collective efforts have significantly improved the synthetic utility of this potentially powerful transformation. Notably, the diastereoselective iodination of both prochiral sp^3 and sp^2 C−H bonds was demonstrated.[8] Protocols to iodinate broadly useful substrates such as carboxylic acids and protected amines have also been developed.[10] Unfortunately, the use of the Suárez reagent IOAc[11] generated by reacting I_2 with AgOAc or $PhI(OAc)_2$ is not practical. Furthermore, noncatalyzed electrophilic iodination of electron-rich arenes can occur with this highly reactive iodinating reagent, leading to a scrambling of regioselectivity.[12] Recently, Kakiuchi[9d] has demonstrated the C−H chlorination of 2-phenylpyridine using a chloronium species generated *in situ via* electro-oxidation of HCl. Alternatively, the use of a combination of metal chlorides,[9b,e] NCS[10d] or NIS,[9f] and strong co-oxidants to achieve halogenation is also an improvement in terms of catalysis. A rare example of Rh(III)-catalyzed iodination of benzamides using NIS reported by Glorius is also an important advance.[13] We envision that development of a simple catalytic system, using cheaper and milder molecular I_2 as the sole oxidant, will greatly improve the practicality of Pd-catalyzed C−H iodination reactions.

Herein we report an efficient and operationally simple Pd-catalyzed C−H iodination reaction that uses I_2 as the sole oxidant (Scheme 1). For the first time, directed C−H iodination was successfully applied to a wide range of heterocycles, which typically inhibit directed C−H activation. The success of this development hinges upon the combination of an amide auxiliary for promoting C−H activation and CsOAc as iodide scavenger to close the catalytic cycle.

We commenced our study by revisiting our earlier diastereoselective C−H iodination chemistry using a chiral auxiliary.[8] Therein we observed two turnovers in iodination with I_2 which can be explained by the extensively studied Pd(II)/Pd(IV) or Pt(II)/Pt(IV) redox chemistry with IX reagents including I_2 (Figure 1).[14] As expected from the redox chemistry shown in Figure 1, unreactive crystalline PdI_2 was formed following two turnovers of iodination when I_2 is used.[8] We have previously used IOAc to regenerate $Pd(OAc)_2$ and close the catalytic cycle.[8,10]

Scheme 1. A Practical C−H Iodination Reaction



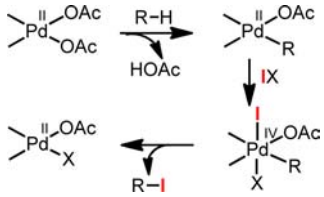


Figure 1. Redox chemistry of C−H iodination with IX.

A single example of Pd-catalyzed iodination of azobenzene using I_2 as the halogen source and $CuCl_2$ as a co-oxidant indicated the possibility of using molecular I_2 as the halogenation reagent for C−H iodination.[5b] We envision that an efficient anionic ligand exchange of $PdI(OAc)$ or PdI_2 with other added metal salts MXn could provide a practical solution to regenerate PdXn as reactive catalysts. To ensure that the C−H activation step can proceed under various conditions and with additives that may be beneficial for the anionic ligand exchange, we attached one of the most efficient auxiliaries to phenylacetic acid to give amide **1a** (Table 1) as the substrate,[15] and began to test conditions for catalytic C−H iodination with I_2.

Considering the poor solubility of PdI_2 in organic solvents, we anticipated that the use of a coordinative solvent could help solubilize PdI_2 and facilitate subsequent anionic exchange. After a short screening of inorganic salts (see the Supporting

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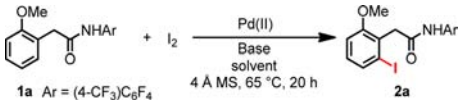
Table 1. Screening of Iodination Conditions[a]



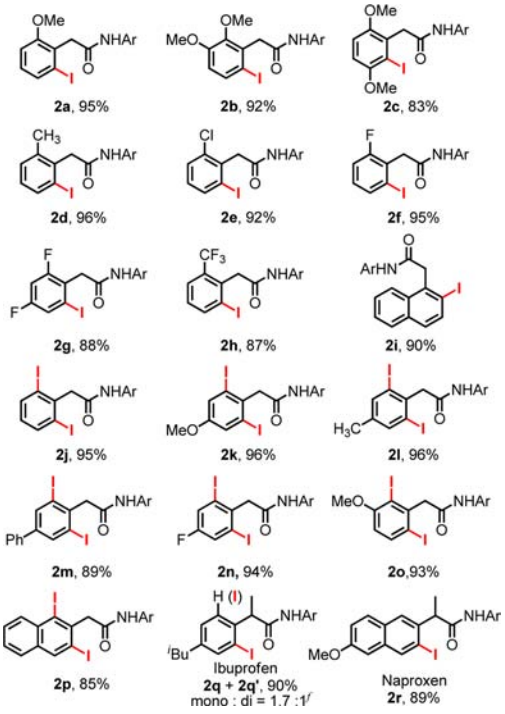
entry	Pd (II)[b]	base[c]	solvent[d]	yield (%)[e]
1	$Pd(OAc)_2$	none	DMF	15
2	$Pd(OAc)_2$	CsOAc	DMF	62
3	$Pd(OAc)_2$	CsOAc	*t*-AmylOH	<5
4	$Pd(OAc)_2$	CsOAc	DMF/t-AmylOH	80
5	$Pd(OAc)_2$	CsOAc/$NaHCO_3$[f]	DMF/*t*-AmylOH	99
6	$Pd(OAc)_2$	$NaHCO_3$[f]	DMF/*t*-AmylOH	35
7[g]	$Pd(OAc)_2$	CsOAc/$NaHCO_3$[f]	DMF/*t*-AmylOH	98 (95%[h])
8	none	CsOAc/$NaHCO_3$[f]	DMF/*t*-AmylOH	0
9	$PdCl_2$	CsOAc/$NaHCO_3$[f]	DMF/*t*-AmylOH	83
10	PdI_2	CsOAc/$NaHCO_3$[f]	DMF/*t*-AmylOH	75
11	PdI_2	none	DMF/*t*-AmylOH	<5

[a]The reactions were run on 0.10 mmol scale in a 25 mL-sealed tube under air. [b]5 mol % of the Pd(II) catalyst was used unless otherwise stated. [c]1.2 eq of CsOAc was used. [d]Solvent volume = 2.0 mL; DMF/*t*-AmylOH = 1:1. [e]% yield was determined by the ^{1}H NMR spectroscopy using CH_2Br_2 as the internal standard. [f]1.0 eq of $NaHCO_3$ was added. [g]The reaction was run on 0.30 mmol scale with 2 mol % $Pd(OAc)_2$ in 5.0 mL of solvent. [h]Yield of the isolated product.

Information), we found that addition of cesium acetate (CsOAc) effectively improved catalytic turnovers (Table 1, entries 1, 2). Treatment of **1a** with 2.5 equiv of I_2 at 65 °C in the presence of 5 mol % of $Pd(OAc)_2$ and 1.2 equiv of CsOAc in DMF produced the *ortho*-iodinated product **2a** in 62% yield after 20 h (entry 2). Four Å molecular sieves were added to prevent the hydrolysis of the amide. While *t*-amyl alcohol alone is a poor solvent for this reaction (entry 3), a mixture of DMF and *t*-amyl alcohol in a 1:1 ratio was found to improve the yield to 80% (entry 4). The use of $NaHCO_3$ as a coadditive improved yield to 99% (entry 5). The enhanced reactivity can be attributed to the N−H deprotonation of the amide to form the imidate structure by using $NaHCO_3$ as a coadditive as established previously.[15g] We were pleased to find that these conditions allowed us to reduce the Pd loading to 2 mol % while maintaining the yield as high as 98% (entry 7). Both $PdCl_2$ and PdI_2 are effective catalysts in the presence of CsOAc, albeit less effective than $Pd(OAc)_2$ (entries 9, 10). The loss of reactivity of PdI_2 in the absence of CsOAc suggests that the formation of $Pd(OAc)_2$ or PdI(OAc) via anionic ligand exchange is essential for catalysis (entry 11). Notably, treatment of **1a** with NIS under these conditions led to full recovery of the starting material.

With our newly developed iodination method in hand, the substrate scope of this reaction was investigated. As shown in Table 2, both electron-donating methyl and methoxy groups (**2a**−**d**) and electron-withdrawing chloro, fluoro, and trifluoromethyl groups (**2e**−**h**) were well tolerated as demonstrated by the excellent yields of the iodinated products. Naphthalene was iodinated at the *β*-position selectively (**2i**). Typically only 2 mol % $Pd(OAc)_2$ was used except for substrates bearing strong electron-withdrawing groups which required 5 mol % Pd for obtaining high yields (**2g** and **2h**). When the *ortho*-positions of substrates were unsubstituted, di-iodinated products were formed exclusively (product **2j**−**n**). With substrates bearing *meta*-substituents, the hindered *ortho*-position can still be iodinated to give the di-iodinated products (**2o**, **2p**) in very high yields. To secure high conversions of these di-iodinations, 5 mol % of $Pd(OAc)_2$ was used. Interestingly, the *α*-methyl group

Table 2. Ortho-iodination of Phenylacetic Amides[a,b,c,d,e]



[a]Ar = $(4\text{-}CF_3)C_6F_4$. [b]Reaction conditions for monoiodination: 0.30 mmol of phenylacetic amide, 2 mol % $Pd(OAc)_2$, 0.75 mmol I_2, 0.36 mmol CsOAc, 0.30 mmol $NaHCO_3$, 150 mg of 4 Å molecular sieves, and 5.0 mL of *t*-AmylOH/DMF (1:1) in a sealed tube, 65 °C, 20 h. [c]For products **2g**, **2h**, and **2r**, 5 mol % $Pd(OAc)_2$ was used. [d]Reaction conditions for di-iodination: 0.10 mmol of phenylacetic amide, 5 mol % $Pd(OAc)_2$, 0.50 mmol I_2, 0.24 mmol CsOAc, 0.20 mmol $NaHCO_3$, 50 mg 4 Å molecular sieves, and 2.0 mL of *t*-AmylOH/DMF (1:1) in a sealed tube, 65 °C, 20 h. [e]Yields of the isolated product. [f]Ratio was determined by the ^{1}H NMR spectroscopy.

in the arene substrates derived from ibuprofen and naproxen hampered the di-iodination (**2q**, **2r**), presumably due to the steric buttress. The iodination of the latter substrate afforded the monoiodinated product exclusively in 89% yield. This result suggests that monoselective iodination of *α*-substituted phenylacetic amides is possible.

To further demonstrate the advantage of this method, we carried out gram-scale reactions using *o*-MeO, CH_3, and CF_3-substituted phenylacetic amide substrates in the presence of only 0.5 mol % of $Pd(OAc)_2$ (Scheme 2). The *o*-Me-substituted amide was iodinated to give the desired product in 75% yield (150 turnovers) while the iodination of *o*-CF_3-substituted substrate afforded a lower yield.

Next, we subjected benzamide **3a** to the optimized iodination conditions (Table 3). Unfortunately, severe decomposition occurred to give an unidentified mixture. In the absence of $NaHCO_3$, reaction proceeded to give small amount of the iodination product **4a** (15%) and the dimer **4a′** as the main

Scheme 2. Gram-Scale Iodination with 0.5 mol % $Pd(OAc)_2$

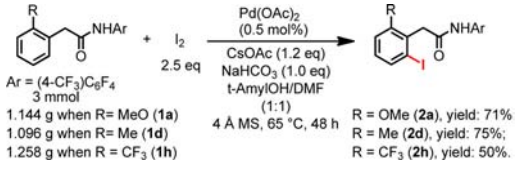


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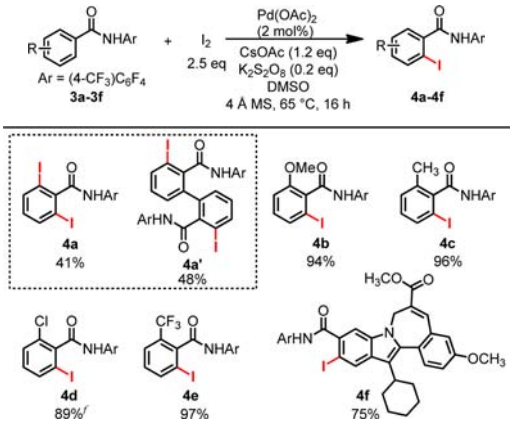
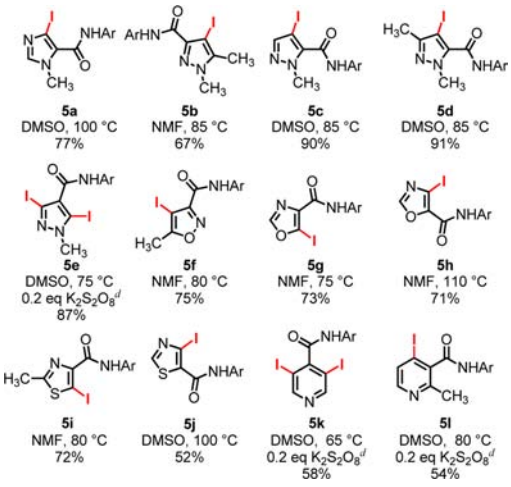
Table 3. Ortho-iodination of Benzamides[a,b,c,d,e]



[a]Reaction conditions: 0.30 mmol of benzamide, 2 mol % $Pd(OAc)_2$, 0.75 mmol I_2, 0.36 mmol CsOAc, 0.06 mmol $K_2S_2O_8$, 150 mg of 4 Å molecular sieves, and 4.0 mL DMSO in a sealed tube, 65 °C, 16 h. [b]For **4a**, 5 mol % $Pd(OAc)_2$ was used, the loadings of I_2 and CsOAc were doubled, and the reaction time was shortened to 5 h. [c]For **4e**, 5 mol % $Pd(OAc)_2$ was used. [d]For **4f**, 10 mol % $Pd(OAc)_2$ was used and the reaction solvent was changed to DMF. [e]Yields of the isolated product. [f]Trace dimer was formed.

Table 4. Ortho-iodination of Heterocyclic Compounds[a,b,c]



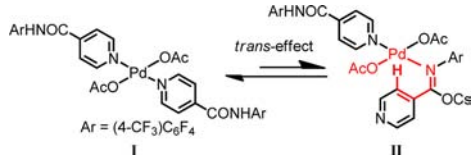
[a]Ar = $(4\text{-}CF_3)C_6F_4$. [b]Reaction conditions: 0.10 mmol substrate, 10 mol % $Pd(OAc)_2$, 0.40 mmol I_2, 0.24 mmol CsOAc, 0.10 mmol $NaHCO_3$, 50 mg of 4 Å molecular sieves, and 2.0 mL of solvent in a sealed tube, 16–48 h. [c]Yields of the isolated product. [d]0.2 eq $K_2S_2O_8$ was used in place of $NaHCO_3$.

product (58%). The dimer is likely formed via the C–H arylation of the monoiodinated product with **4a** which could be catalyzed by the traces of Pd(0) species present in the reaction. Switching the solvent to DMSO and use of $K_2S_2O_8$ (0.2 equiv) as an additive to remove Pd(0) from the system increased the yield of **4a** (41%), with only a slight decrease of the formation of **4a′** (48% yield). Nonetheless, monoiodination of *ortho*-substituted benzamide substrates under these conditions proceeded to give the desired products in excellent yields without forming the dimers (**4b–e**). To probe the potential of developing a late-stage iodination method we subjected the complex drug candidate **3f**[16] to our iodination procedure and obtained the desired iodinated product **4f** in 75% yield. Aryl iodide **4f** can potentially react with a wide range of coupling partners using metal catalysts to provide a series of analogues for drug discovery. In particular, iodoarenes are superior substrates over bromo or chloro analogues for the preparation of tritium labeled compounds in high yield and radiospecific activity which are of great importance to late-stage tritio-dehalogenation of drug molecules to facilitate *in vivo* study of metabolic processes.[17]

Considering the lack of success of directed C–H activation reactions of heterocycles[18,19] and the prevalence of heteroarenes in drug molecules,[20] we were eager to test whether this iodination protocol is compatible with heterocyclic substrates. Remarkably, directed *ortho*-iodination readily occurred with a wide range of heterocycles under the standard conditions (Table 4). Minor adjustment of the reaction solvent and the temperature were needed for obtaining the optimum yields with each substrate. In general, either *N*-methylformamide (NMF) or DMSO is the most effective solvent. Unlike the iodination of benzamides (Table 3), dimerization did not occur with most of the heterocyclic substrates. However, additive $K_2S_2O_8$ (0.2 equiv) was needed to minimize dimerization with pyrazole **5e** and pyridines **5k** and **5l**.

Notably, various regioisomers of iodinated pyrazoles (**5b–e**), oxazoles (**5g**, **5h**) and thiazoles (**5i**, **5j**) can be prepared using these heterocycles containing the amide directing group at different positions. Although electrophilic iodination of electron-rich pyrazoles can occur at C-4 positions,[21] the presence of other electron-rich arenes within a complex molecule could scramble the site selectivity under such conditions. We were pleased to find that pyridine-containing isonicotinic amide and methylnicotinic amide were also suitable substrates for this iodination reaction (**5k**, **5l**). Although a single example of Pd(0)/PR_3-catalyzed arylation of these pyridine substrates has been reported,[19a] this iodination represents the first example of Pd(II)-catalyzed C–H activation reactions for a broad range of heterocycles using a directing group. The observed reactivity of these strongly coordinative heterocycles, especially the thiazole and pyridine substrates, can be attributed to the following two factors. First, a strong trans-effect and sterics between the pyridyl groups in complex I (Scheme 3) can promote formation of a small amount complex II,[22] in which the moderately coordinating amide is bound to the Pd center. Second, this amide directing group is highly effective in promoting C–H activation: the coordinated amide contains a strongly electron-withdrawing aryl group [Ar = $(4\text{-}CF_3)C_6F_4$], rendering the Pd(II) center sufficiently electrophilic for C–H bond cleavage and the imidate structure enables the assembly of an approximately coplanar pretransition state with minimum entropic cost.

Scheme 3. Assembly of the Reactive Precursor



In summary, we have developed the first Pd-catalyzed C–H iodination reaction using molecular iodine as the sole oxidant. The Pd catalyst loading can be reduced to 0.5 mol % in gram scale reaction. This reaction also demonstrates broad substrate scope with respect to a wide range of heterocycles that were previously incompatible with directed C–H activation. Our collaborators in Bristol-Myers Squibb Co. are currently applying this reaction for

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late-stage tritio-deiodination of drug molecules to facilitate *in vivo* study of metabolic processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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