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Expedient Drug Synthesis and Diversification via ortho-C−H Iodination using Recyclable PdI_2 as the Precatalyst

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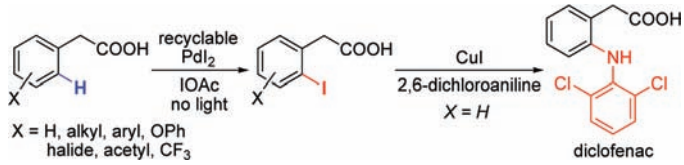
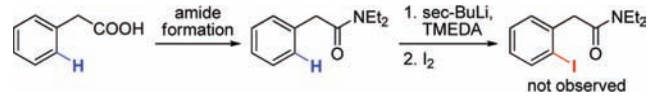
ABSTRACT



Pd(II)-catalyzed ortho-C−H iodination reactions of phenylacetic acid substrates have been achieved using recyclable PdI_2 as the precatalyst. This class of substrates is incompatible with the classic amide formation/ortho-lithiation/iodination sequence. The power of this new technology is demonstrated by facile drug functionalization and drastically shortened syntheses of the drugs diclofenac and lumiracoxib.

Palladium-catalyzed coupling reactions, such as Mizoroki−Heck olefination, Tsuji−Trost allylation, Suzuki−Miyaura coupling, Negishi coupling, Hiyama coupling, and Buchwald−Hartwig amination, are among the most useful tools for constructing carbon−carbon and carbon−heteroatom bonds.[1] The remarkable power of these reactions stems from the widespread availability and diverse reactivity of the aryl and alkyl halide starting materials and from advances made in ligand design. Nevertheless, a potential hurdle that remains in applying one of these methods as a step in a particular synthetic sequence is the position-selective installation of the halide onto the arene precursor. In this context, two classical approaches to prepare halogenated arenes are particularly useful: (i) eletrophilic aromatic substitution (EAS)[2] and (ii) directed ortho-lithation (DoL) with a subsequent halogen quench.[3] Following the early reports of both stoichiometric[4] and catalytic C−H halogenation, Pd(II)-catalyzed halogenation methods for both sp^2 and sp^3 C−H bonds have recently been developed, including a diastereoselective version.[5−11] However, the majority of these reactions compare unfavorably with conventional DoL methods in terms of practicality and versatility, particularly for applications in large-scale syntheses. With these considerations in mind, we set out to design a truly enabling C−H iodination reaction using phenyl acetic acid substrates that are incompatible with DoL methods (Scheme 1).[3a]

Scheme 1. Directed ortho-Lithation (DoL) Follwed by a Halogen Quench



Moreover, we endeavored to achieve a high level of operational simplicity and practicality by developing a recy-

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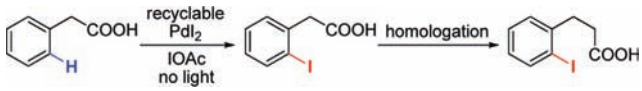
clable catalytic system. Herein, we report a Pd-catalyzed ortho-C−H iodination reaction of phenylacetic acid substrates, a class of substrates that is incompatible with classic DoL conditions because the chelating functional group is remote from the targeted C−H bond and also because these compounds contain acidic protons at the α-position. The iodinated phenylacetic acid products can easily be converted to 3-phenylpropionic acids through the Arndt−Eistert homologation, which allows for convenient access to another major class of ortho-iodinated carbon skeletons (Scheme 2).[12] In addition, the resulting

Scheme 2. Pd(II)-Catalyzed ortho-Iodination of Phenylacetic Acid

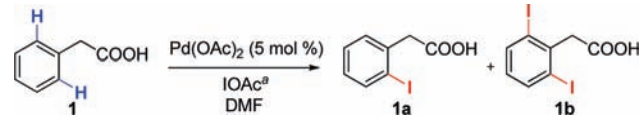


iodinated products can be readily converted to a wide range of highly valuable synthons through subsequent cross-coupling or Buchwald−Hartwig amination.[13] The potential power of this technology is demonstrated through remarkably short syntheses of two multibillion dollar drugs.

Recently, we discovered that the presence of a wide range of cations including organic cations in the reaction medium drastically promotes ortho-iodination of benzoic acid substrates.[10a] Although sodium and potassium countercations had been present in a number of earlier Pd- and Pt-catalyzed C−H activation reactions,[6,14] the significant effects of cations on carboxyl-directed C−H insertion had not been realized prior to the extensive development of various sodium- and potassium-promoted C−H activation reactions in conjunction with a mechanistic hypothesis and characterization of reaction intermediates.[10a,15] These findings have prompted us to focus on a new strategy of using chemical functional groups that exhibit weak coordination with Pd to direct C−H insertion (e.g., the carbonyl of a CO_2X moiety), including commonly encountered, synthetically useful compounds such as carboxylic acids[16] and alcohols.[17] Not only does this philosophy open up a convenient pool of starting materials but also we have found significantly broader scope in the types of carbon−carbon and carbon−heteroatom bond-forming reactions that can be performed due to the fact that the resulting palladated intermediates are highly reactive in the functionalization step. While some carboxyl-directed C−H activation reactions have been extended to phenylacetic and 3-phenylpropionic acids, our iodination reaction protocol has been limited to benzoic acids, a shortcoming that has hampered broad applications of the protocol when alternative carbon skeleton are desired. Considering the fact that the traditional amide formation/ortho-lithiation/iodination sequence (DoL) is unsuitable for phenylacetic acids, a Pd-catalyzed ortho-C−H iodination method for these substrates will be especially valuable.

We began our investigation by optimizing previously developed catalytic systems, but unfortunately, the iodination products were obtained in very low yields, despite extensive efforts (Table 1, entries 1−4). Upon further analysis, we found that substantial decarboxylation of the substrate was taking place, giving a mixture of benzaldehydes, toluenes,

Table 1. Iodination in the Absence of Light



			^{1}H NMR yield (%)		
entry	IOAc (equiv)	t (°C)	**1a**	**1b**	s.m. (%)
1	3	100	19	0	17
2	3	80	14	3	34
3	3	60	17	4	34
4	3	40	13	4	20
5[b]	3	60	26	41	0
6[b]	2	60	51	36	0
7[b]	1.5	60	74	12	12
8[b]	1.0	60	58	6	35

[a] IOAc was generated *in situ* from $PhI(OAc)_2$ and I_2. [b] The reaction was carried out in the dark.

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Table 2. Screening of Pd Catalysts and Oxidants

entry	Pd	oxidant	yield (%)	entry	Pd	oxidant	yield (%)
1	$Pd(CH_3CN)_2(OTs)_2$	IOAc	86	9	PdI_2	IOAc	90
2	$Pd(OTf)_2 \cdot 2H_2O$	IOAc	84	10	$Pd(OAc)_2$	IOAc	92
3	$[Pd(CH_3CN)_4](OTf)_2$	IOAc	86	11	$Pd(OTFA)_2$	IOAc	85
4	$Pd_2(dba)_3$	IOAc	30	12	$Pd(OAc)_2$	NIS	75
5	$Pd(PPh_3)_4$	IOAc	20	13[a]	$Pd(OAc)_2$	NIS	55
6	$Pd(PPh_3)_2Cl_2$	IOAc	30	14	$Pd(OAc)_2$	ICl	10
7	$Pd(PhCN)_2Cl_2$	IOAc	75	15	$Pd(OAc)_2$	NBS	20
8	$PdCl_2$	IOAc	88	16	$Pd(OAc)_2$	NCS	50

[a] The reaction was carried out in the presence of light.

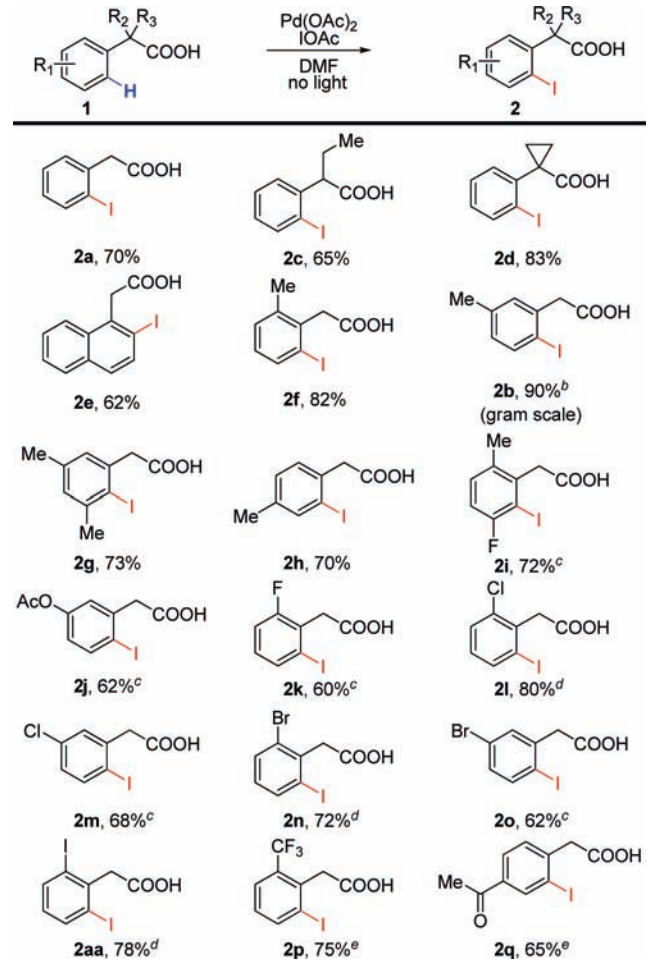
as well as other unknown compounds, presumably through the formation of $PhCH_2COOI$. Although decarboxylation of this type has previously been reported with alkyl carboxylic acids under irradiation with 100 W tungsten-filament lamps,[18] phenylacetic acid appears to be particularly prone to such a reaction because of the stability of the resulting benzylic radical. We were delighted to find that this decomposition pathway could be suppressed by performing the iodination in the dark. Under these new conditions, the efficiency of this catalytic system was also significantly improved; hence, the iodination reaction proceeded to give the product in 74% yield (entry 7). It is worth noting that **1a** and other α-hydrogen-containing substrates are substantially less reactive in C−H activation, in accordance with the Thorpe−Ingold effect.[19]

Next, various Pd(II) catalysts were screened (Table 2). In general, most Pd(II) sources were found to be effective, and commonly used ligands that stabilize Pd(0) (dba, PPh_3) were found to inhibit the reaction (entries 4−6). As anticipated, the anions of the Pd(II) precatalyst did not have a significant influence on the reaction because IOAc (generated instantly from $PhI(OAc)_2/I_2$) converts PdX_2 to $Pd(OAc)_2$ in a highly efficient manner (eq 1).[20] Other commonly used electrophilic halogenating reagents were not as effective (entries 12−16).[10] The use of $PhI(OAc)_2$ or I_2 alone results in recovery of starting material.

$$PdI_2 \xrightarrow{\text{IOAc}} Pd(OAc)_2 + I_2 \qquad (1)$$

To establish the scope of this newly developed iodination protocol, we subjected a wide range of commonly used phenylacetic acids to the standard conditions (Scheme 3). Simple arenes were iodinated smoothly with excellent monoselectivity (**2a**, **2c**, **2d**, and **2h**). With meta-substituted arenes, the less-hindered ortho position was iodinated exclusively (**2b**, **2j**, **2m**, and **2o**). This reaction was also found to tolerate an acetate group on the arene (**2j**). Arenes containing halides could also be iodinated in synthetically useful yields (**2i** and **2k**−**2o**). The different reactivity profiles between iodides and other halides offer convenient handles

Scheme 3. Pd-Catalyzed C−H Iodination of Phenylacetic Acids[a]



[a] General reaction conditions: 5 mol % of $Pd(OAc)_2$, 0.75 equiv of $PhI(OAc)_2$, 0.75 equiv of I_2, DMF, 60 °C, 12 h, no light. **2c**, **2h**, **2j**−**2k**, **2m**, **2o**, and **2q** were isolated as methyl esters following treatment of the crude reaction mixture with CH_2N_2. [b] 2 mol % of $Pd(OAc)_2$. [c] 10 mol % of $Pd(OAc)_2$, 24 h. [d] 2.0 equiv of $PhI(OAc)_2$, 2.0 equiv of I_2, 36 h. [e] 15 mol % of $Pd(OAc)_2$, 2.0 equiv of $PhI(OAc)_2$, 2.0 equiv of I_2, 36 h.

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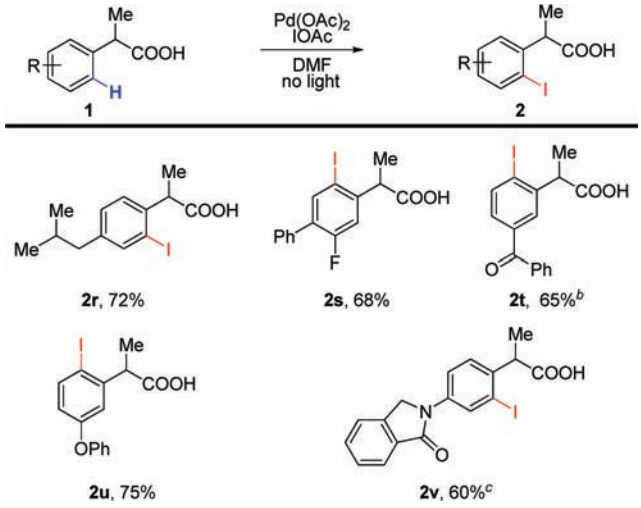
for subsequent differential functionalization. Strongly electron-withdrawing groups such as trifluoromethyl and acetyl groups were found to reduce the yield to 75% and 65%, respectively, even in the presence of 15 mol % of $Pd(OAc)_2$ (**2p** and **2q**). It should be noted that the MeO-substituted aryl ring reacts with IOAc nonselectively in the absence of Pd catalyst. The efficiency of this catalytic iodination transformation was also demonstrated by running the reaction on gram-scale using 2 mol % of $Pd(OAc)_2$ (**2b**).

Position-selective iodination of existing bioactive drug scaffolds is a potentially powerful tool for expedient drug diversification. Thus, we found that a series of nonsteroidal anti-inflammatory drugs (NSAIDs),[21] including ibuprofen, flurbiprofen, ketoprofen, fenoprofen, and indoprofen, could be smoothly converted into the corresponding *ortho*-iodinated products in good yields and with excellent positional selectivity (Scheme 4). It is worth noting that electrophilic

Scheme 4. Site-Selective Functionalization of Drug Scaffolds[a]



[a] General reaction conditions: 10 mol % of $Pd(OAc)_2$, 0.75 equiv of $PhI(OAc)_2$, 0.75 equiv of I_2, DMF, 60 °C, 24 h, no light. **2r** and **2t**−**2v** were isolated as methyl esters following treatment of the crude reaction mixture with CH_2N_2. [b] 15 mol % of $Pd(OAc)_2$, 2.0 equiv of $PhI(OAc)_2$, 2.0 equiv of I_2, 36 h. [c] The temperature was 40 °C.

iodination of relatively electron-rich **2u** did not occur in the absence of Pd catalyst. Interestingly, the amide group in **2v** is not effective in directing the iodination as shown by the lack of reactivity with the corresponding ester substrate.

Furthermore, we found that PdI_2 could conveniently be reused as a precatalyst at least five times without substantial erosion of the product yield. After completion of the reaction, the PdI_2 precipitate could be recycled from the solution by centrifugation.[8] With substrate **1b**, five reaction cycles starting with only 44.8 mg (0.2 mmol) of $Pd(OAc)_2$ produced 12.01 g (43.5 mmol) of the iodinated product (Table 3).

Finally, the broad synthetic utility of these ortho-iodinated products was demonstrated by carrying out subsequent amination, cyanation,[22] acetylenation,[23] and homologation following established procedures.[24] Notably, amination of

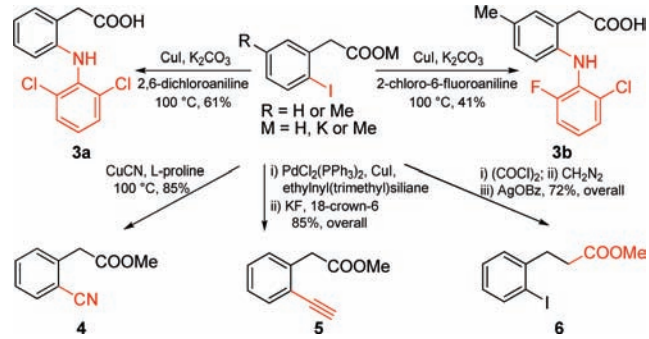
Table 3. Catalyst Recycling Experiment with Substrate **1b**[a]

run	1	2	3	4	5
yield (%)	92	90	88	85	80

[a] Reaction conditions: $Pd(OAc)_2$ (2 mol %), $PhI(OAc)_2$ (0.75 equiv), I_2 (0.75 equiv), DMF, 60 °C, 12 h.

the iodinated products **2a** and **2b** through a modified Ullmann coupling furnishes the commercial drugs diclofenac and lumiracoxib in a single step, which compares favorably with multistep procedures (Scheme 5).[25]

Scheme 5. Synthetic Applications and Drug Syntheses



In summary, we have developed a highly versatile C−H iodination reaction of phenylacetic acids. ortho-Iodinated 3-phenylpropionic acids could also be accessed through subsequent homologation. Facile drug functionalization and concise drug syntheses showcase the synthetic utility of this iodination reaction.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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