Isodesmic C–H Functionalization: Carboxyl-Assisted Remote *meta*- and *ortho*-C–H Iodination of Arenes *via* Shuttle Catalysis

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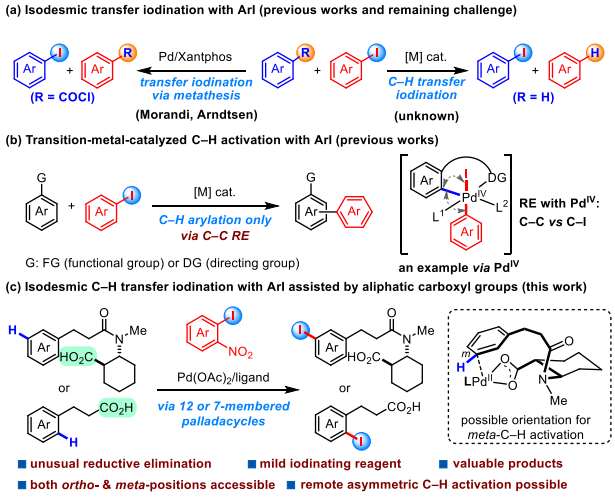
ABSTRACT: Isodesmic C–H functionalization reactions are extremely rare. Herein we report the first Pd(II)-catalyzed isodesmic C–H iodination of arenes using 2-nitrophenyl iodides as the mild iodinating reagents. Unusual C–I reductive elimination occurred in preference to competing C–C coupling in this reaction. Assisted by aliphatic carboxyl directing groups, a range of hydrocinnamic acids and related arenes could be selectively iodinated at either *meta*- or *ortho*-positions of the phenyl ring. Remote diastereoselective C–H activation was also promising. This method may open up a new way to iodinate challenging substrates.

The exploration of novel method to cleave and reorganize chemical bonds is the continuous pursuit of organic chemists.[1-6] In recent years, significant advances have been achieved in the study of isodesmic reactions, which often use user-friendly reagents and exhibit good functional group tolerance.[7-14] Of particular note, the groups of Morandi[7d] and Arndtsen[8] independently reported a functional group metathesis between aryl iodides and aroyl chlorides *via* a Pd(0)/Pd(II) catalysis (Scheme 1a),[15,16] enabling a mild transfer iodination of aroyl chlorides. However, catalytic C–H transfer iodination between two arenes is unknown.[1] Importantly, isodesmic C–H functionalization reactions are extremely rare.[10-14] Thus, the development of an isodesmic C–H transfer iodination using aryl iodides is highly attractive, since it may utilize readily available iodinating reagents and offer a novel strategy to generate sophisticated aryl iodides that are not easy to obtain *via* conventional methods.

Aryl iodides are extensively used as arylating reagents through exclusive C–C reductive elimination (RE) that is favored over C–I RE at the metal-center in transition-metal-catalyzed C–H activation reactions (Scheme 1b).[17] Notably, Sanford and co-workers reported the first carbon–halogen bond-forming reductive elimination that occurred in preference to aryl C–C coupling with a Pd(IV) complex to give aryl chloride in 2007.[18] However, such preference has not been reported in a catalytic reaction.[19,20] During our previous study of Pd-catalyzed remote *meta*-C–H arylation using 2-nitrophenyl iodide, we detected about 10% of *meta*-C–H iodination side product.[21] Inspired by this unexpected discovery, we envisioned that the successful development of C–H iodination reactions using aryl iodides[16,22] would introduce a mechanistically distinct pathway for catalytic halogenation reactions.

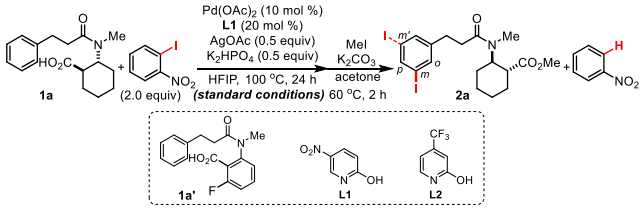
Scheme 1. Isodesmic Aryl C–H Transfer Iodination



In the past decade, site-selective C–H iodination reactions have become an important strategy for the synthesis of aryl iodides, which are versatile valuable chemicalssuch as being used in cross-coupling reactions.[23,24] Nonetheless, the classes of iodinating reagents for such reactions are still limited, and some of them are highly reactive such as IOAc generated from I_2 with $PhI(OAc)_2$ or AgOAc, which may lead to unwanted electrophilic iodination that reduces the site-selectivity of the overall reaction. Therefore, the exploration of a complementary mild iodinating reagent that is able to eliminate unwanted side reaction is desirable.

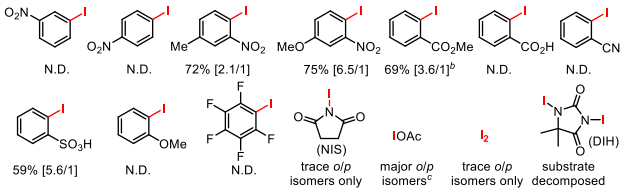
Herein, we report an unprecedented Pd(II)-catalyzed C–H transfer iodination reaction of arenes using aryl iodides as mild iodinating reagents (Scheme 1c). Assisted by the aliphatic carboxyl groups, site-selective *ortho*- and *meta*-C–H iodination of hydrocinnamic acids and related arenes have been achieved using commercially available 2-nitrophenyl iodides. Notably, challenging remote diastereoselective C–H activation was also possible.

Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield (%) [mono/di]
1	none	85 [3.3/1]
2	without **L1**	16 [1/0]
3	**L2** instead of **L1**	83 [1.9/1]
4	pyridin-2-ol instead of **L1**	70 [2.7/1]
5	*N*-Ac-L-Phe-OH instead of **L1**	78 [2.9/1]
6	without AgOAc	45 [1/0]
7	0.25 equiv of AgOAc	80 [3/1]
8	1.0 equiv of AgOAc	75 [2.9/1]
9	2.0 equiv of AgOAc	74 [3.6/1]
10	Ag_2CO_3 instead of AgOAc	82 [3.1/1]
11	without K_2HPO_4	39 [1/0]
12	K_2CO_3 instead of K_2HPO_4	81 [2.9/1]
13	Na_2HPO_4 instead of K_2HPO_4	76 [2.8/1]
14	*t*-Amyl-OH instead of HFIP	N.D.
15	TFE instead of HFIP	43 [1/0]
16	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	73 [4.2/1]
17	$PdCl_2(MeCN)_2$ instead of $Pd(OAc)_2$	61 [5.8/1]
18	90 °C instead of 100 °C	57 [1/0]
19	1.5 equiv of 2-nitrophenyl iodide	66 [5.6/1]

results by using other iodinating reagents (2 equiv) under standard conditions:



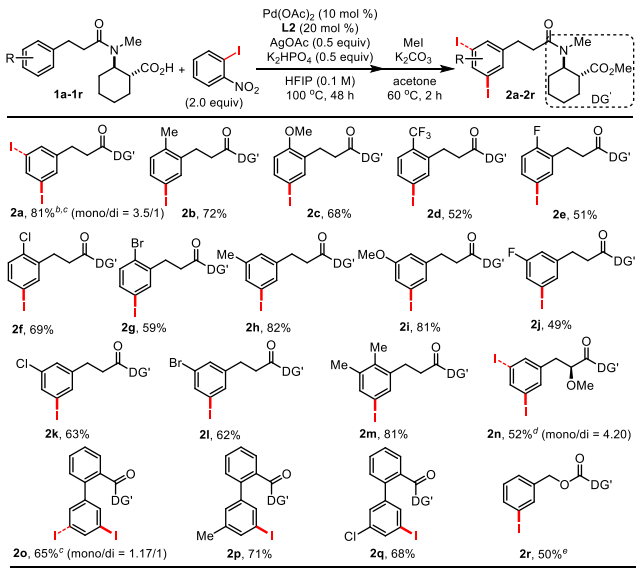
[a]Reaction conditions: 1) 0.1 mmol scale, HFIP (1 mL), under air; 2) MeI (0.2 mmol), K_2CO_3 (0.3 mmol). Yield of **2a** was determined by ^{1}H NMR with CH_2Br_2 as internal standard. Nitrobenzene product found in ^{1}H NMR. Unless otherwise noted, both C–H arylation side product and regioisomers were trace determined by GC-MS with an FID detector. [b]A little arylation and regioisomers detected. [c]Detected with GC-MS, IOAc (from I_2/PhIOAc). N.D.: no product detected.

Initially, we used the hydrocinnamic amide **1a'** (Table 1) bearing an aryl carboxyl *meta*-directing group as the substrate to investigate isodesmic C–H activation, since desired *meta*-C–H iodinated product had been obtained as a side product with **1a'** in our previous study.[21] Moreover, *meta*-C–H[17k,25,26] halogenation of arenes is still very limited to narrow substrate scope,[27-28] and hydrocinnamic acids are a class of important core structure of biologically active molecules such as drug Baclofen. However, we encountered difficulties especially in completely eliminating the undesired *meta*-C–H arylation product using **1a'**. Therefore, substrate **1a** was designed as the new substrate, the directing group of which could be prepared on a large scale from known *β*-amino acid [see supporting information (SI)]. Pleasingly, C–H arylation side product was almost eliminated while using **1a** to optimize the reaction possibly due to better chelating ability of the aliphatic carboxyl. After extensive tuning of the reaction conditions (see SI), the desired *meta*-C–H iodination products **2a**, which was methylated from the acid product for easier isolation, could be obtained in the 85% combined yield with 2-nitrophenyl iodide using $Pd(OAc)_2$ and pyridine-type **L1** as the ligand, in the presence of AgOAc (0.5 equiv) and K_2HPO_4 (0.5 equiv) in HFIP (hexafluoroisopropanol) at 100 °C for 24 h (entry 1). This represents the first example that suggests carbon–halogen RE is favored over competing C–C RE at the Pd center in a catalytic reaction. The yield decreased dramatically without **L1**, indicating ligand **L1** played a crucial role for the reaction (entry 2). Other ligands were also evaluated such as electron-deficient ligand **L2** that led to comparable overall yield with a little higher turnover number than **L1** (entry 3), but lower yield was obtained with pyridin-2-ol (entry 4). *N*-mono-protected amino acid ligands such as *N*-Ac-L-Phe-OH could also promote the reaction but was less effective (entries 5). The addition of silver salt was important but catalytic amount was feasible (entries 6-10). Surprisingly, although it was believed that silver salt was important to promote C–H arylation for iodide removal,[19a,b] C–H arylation was not detectable with one equivalent of AgOAc (entry 8) though trace C–H arylation product could be detected using two equivalents (entry 9). Base was beneficial, but other bases such as K_2CO_3 could also give comparable good yields (entries 11-13). Solvents were also evaluated, and HFIP proved to be the best. Subsequently, $Pd(OAc)_2$ was found to be superior to other Pd catalysts tested (entries 16 and 17). The reaction was also sensitive to temperature, as the yield decreased greatly at 90 °C. In addition, reducing the loading of 2-nitrophenyl iodide would decrease the yield (entry 19). Notably, *meta*-selectivity of the reaction was generally excellent while optimizing the reaction conditions, and only very trace regioisomers were detected. Evaluation of other iodinating reagents indicated electron-withdrawing *ortho*-substitution of the phenyl iodide was critical, but no better one was identified than 2-nitrophenyl iodide (bottom). In contrast, mainly *ortho*- and *para*-iodination products together with trace *meta*-isomer were observed with IOAc that might lead to direct electrophilic iodination, and only trace *ortho*- and *para*-isomers were detected with NIS and I_2 while DIH decomposed the substrate.

With the optimized conditions in hand, we tested this protocol with a series of hydrocinnamic acids and related arenes (Table 2). The combined yield of isolated $\mathbf{1a}_{\mathbf{mono}}$

and **1a**$_{di}$ is high, and ligand **L2** that led to higher turnover was employed for other substrates. To our delight, generally good yields of desired products were received with a range of mono-substituted substrates bearing either electron withdrawing or donating groups (**2b**-**2l**). Importantly, halides such as chloride (**2f** and **2k**) and bromide (**2g** and **2l**) could be tolerated, providing the opportunity for synthesis of diversely substituted arenes. However, *para*-substituted substrates only gave low yields of desired products. Furthermore, di-substitution (**2m**) and substitution on the alkyl chain such as 3-phenyllactic acid derivative (**2n**) were allowed. Finally, structurally related biphenylcarboxylic acids (**2o**-**2q**) and benzyl alcohol (**2r**) derivatives could also be iodinated at the desired *meta*-positions. The selectivity of the reactions was excellent with trace amount of regioisomers, and arylation side product was generally not observed.

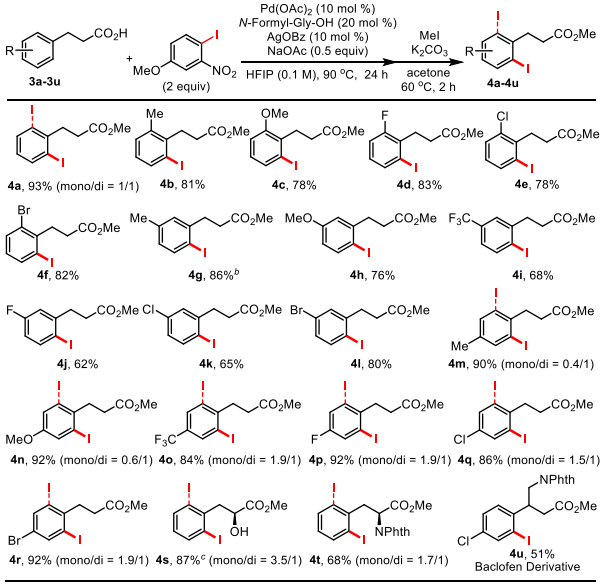
Table 2. Scope of *meta*-C–H Iodination[a]



[a]Reaction conditions: standard conditions, deviation: **L2** as the ligand, 48 h. Isolated yields. [b]**L1** used. [c]24 h. [d]Optical pure (>99% ee) directing group was used for **1n**; the yield of **2n**$_{mono}$ was calculated after hydrolysis. [e]About 10% di-product, but it could not be isolated.

Since *ortho*-iodinated hydrocinnamic acids are also valuable compounds, we moved on to test this method for *ortho*-C–H iodination of hydrocinnamic acids. Importantly, *ortho*-C–H functionalization of hydrocinnamic acids using their native free carboxyl as chelating group is extremely scarce,[29] possible due to the requirement of forming challenging 7-membered metallacycle. Based on the above reaction conditions and after careful investigation (see SI for details), we obtained the desired *ortho*-C–H iodination products after methylation (Table 3, **4a**) in excellent combined yield (93%) with 1-iodo-4-methoxy-2-nitrobenzene, which is commercially available and can be readily prepared,[30] using *N*-Formyl-Gly-OH as the ligand in the presence of AgOBz (0.1 equiv) and NaOAc (0.5 equiv). This protocol proved to be robust, leading to generally high yields of desired products with a broad range of hydrocinnamic acids (**4a**-**4r**). More complicated 3-phenyllactic acid (**4s**), phenylalanine (**4t**), and drug Baclofen (**4u**) derivatives could also be iodinated to give valuable products.

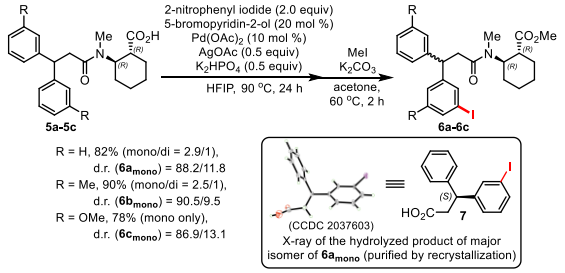
Table 3. Scope of *ortho*-C–H Iodination[a]



[a]Reaction conditions: **3** (0.2 mmol), 1-iodo-4-methoxy-2-nitrobenzene (0.4 mmol), Pd(OAc)$_2$ (0.02 mmol), *N*-Formyl-Gly-OH (0.04 mmol), AgOBz (0.02 mmol), NaOAc (0.1 mmol), HFIP (2 mL), 80 °C, 24 h. Isolated yields. [b]10% (*o*,*m*)-di-product was isolated, see SI. [c]$SOCl_2$/MeOH was used for methylation, see SI.

As remote asymmetric *meta*-C–H functionalization is still extremely rare and challenging,[31] we were curious to use optical pure directing group to induce diastereoselective remote *meta*-C–H iodination *via* desymmetrization. In our preliminary study (Scheme 2), good diastereoselectivity (up to d.r. = 90.5/9.5, **6b**$_{mono}$) could be achieved with 5-bromopyridin-2-ol ligand. The absolute configuration of **6a**$_{mono}$ after removal of the directing group was determined by x-ray crystallography (**7**). However, higher diastereoselectivity could not be obtained at present even after extensive study and further investigation is required.

Scheme 2. Diastereoselective Remote *meta*-C–H Iodination

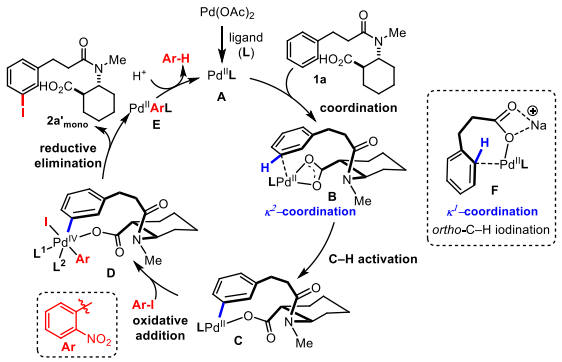


Finally, synthetic potential of the methods was briefly evaluated (see SI). Cross coupling reactions proceeded smoothly with product **2a**$_{mono}$ to afford *meta*-substituted derivatives (**8**-**10**). Moreover, unnatural chiral amino acid derivative (**11**) could also be efficiently produced with *ortho*-iodinated phenylalanine derivative. The *meta*-

directing group could be removed under acidic conditions to give high yield of iodide **12**. Moreover, large scale (7 mmol of **3a**) reaction could be performed to afford good combined yield of products using lower loading (3 mol %) of $Pd(OAc)_2$.

Based on previous works[19] and our recent work on carboxyl-assisted remote *meta*-C–H activation of arenes,[21] the catalytic cycle for above *meta*-C–H iodination is proposed as outlined in Scheme 4. First, active Pd catalyst **A** is generated through ligand exchange. Subsequently, the substrate **1a** may coordinate to Pd in a κ^1 or κ^2 coordination but the latter mode is believed to facilitate the approaching of the Pd center to the remote phenyl ring giving complex **B**. The C–H bond at the *meta*-position of the phenyl ring is then selectively cleaved via a potential concerted metalation deprotonation process, possible due to its best matched distance and geometry, affording palladacycle **C**. Oxidative addition of **C** with 2-nitrophenyl iodide gives a Pd(IV) intermediate **D**, which selectively undergoes C–I reductive elimination to afford product $\mathbf{2a'_{mono}}$ together with an arylated Pd(II) complex **E**. The rationale for the preference of this C–I reductive elimination is not clear at present, though our study in the optimization of reaction conditions (Table 1) suggested it might be related to the steric/electronic properties of the aryl iodide and the ligand, as well as those of the substrate.[18] Finally, protonolysis of complex **E** will regenerate active Pd(II) catalyst **A**. For *ortho*-C–H iodination, the catalytic cycle is similar except that κ^1 coordination of the substrate to Pd center is better to facilitate cyclopalladation at the *ortho*-position (**F**).

Scheme 4. Proposed Catalytic Cycle



In summary, we have developed the first Pd(II)-catalyzed isodesmic C–H iodination reaction of arenes using aryl iodides. Two 2-nitrophenyl iodides were identified as the mild iodinating reagents for *meta*- and *ortho*-C–H iodination of a range of hydrocinnamic acids and related arenes assisted by the carboxyl directing groups. In addition, remote diastereoselective C–H activation was also proved to be possible. This method may stimulate the study on developing isodesmic C–H activation reactions and open up a mild way to iodinate challenging substrates. Mechanistic study and further application of this method are currently underway in our laboratory.

Author Contributions

[†]Shangda Li and Chunhui Zhang contributed to the manuscript equally.

Notes

The authors declare no competing financial interest.

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