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Communication

Palladium-catalyzed *meta*-C—H bond iodination of arenes with I_2

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ABSTRACT

Palladium-catalyzed highly *meta*-selective C—H iodination of phenylacetic acid, benzylphosphonate and benzylsulfonate scaffolds with molecular I_2 is developed using a pyridine-type template. The practical ester linkages enable the directing template easily installed and readily removed. The substrate scope is broad, and alkyl, methoxyl, trifluomethyl, and halo substituents are compatible with this reaction. Further transformations of ibuprofen iodide intermediates by Pd-catalyzed C—C and C–heteroatom bond formation illustrate the broad utility of this method.

Aryl iodides are widely utilized as important starting materials in organic chemistry and pharmaceutical drug syntheses [1]. Many synthetic methods have been developed for the construction of aryl iodide, and metal-catalyzed C—H iodination of arene is the most straightforward way [2]. Assisted by a directing group, Pd [3], Rh [4], Ru [5], Cu [6], Ni [7], and Co [8] have been adopted in the *ortho*-C—H iodination of arenes. Athough Pd-catalyzed *meta*-C—H chlorination using norbornene as the mediator and Ru-catalyzed *meta*-C—H bromination *via* electronic effects have been reported [9,10], *meta*-C—H iodination has been less explored. The rational design of a directing group with proper distance and geometry plays an important role to recognize the remote C—H bonds [11,12]. Recently, Yu elegantly designed pyridine-containing templates and realized the palladium-catalyzed *meta*-C—H iodination of benzyl and phenyl ethyl alcohols by using 1,3-diiodo-5,5-dimethylhydantoin (DIH) as the iodinating source [13] (Scheme 1a). Due to the high importance of the phenylacetic acid in organic synthesis and drug molecules, Yu subsequently applied this strategy to phenylacetic acid with the template anchoring into the substrates through an amide linkage [14] (Scheme 1b).

Using the inexpensive and milder molecular I_2 as iodinating reagent has become an attractable alternative in metal-catalyzed C—H iodination. In 2013, Yu reported the Pd-catalyzed *ortho*-C—H iodination of benzamides and phenylacetic amides using I_2 as the sole oxidant [3a]. Subsequently, Chatani and Koley realized the Ni-catalyzed *ortho*-C—H iodination of benzamides with molecular I_2 [7]. Very recently, Chatani reported Co-catalyzed chelation-assisted *ortho*-C—H iodination of benzamides with molecular I_2 as an iodinating reagent and Ag_2CO_3 as the oxidant [8]. Prompted by these reports and our recent achievement in *meta*-C—H deuteration of arenes [15], we questioned whether we could realize the *meta*-C—H iodination by using molecular I_2 as the iodinating source. Herein, we reported the template-directed *meta*-C—H iodination of phenylacetic acid, benzylphosphonate, and benzylsulfonate scaffolds by using molecular I_2 (Scheme 1c). Considering that the directing group should be easily installed and readily removed for bioactive molecules, we anchored the template into the substrates through a practical ester linkage.

We began our investigation by testing the *meta*-C—H iodination of phenylacetic acid containing a variety of 3-subsituted pyridine based templates (Table 1). When simple pyridyl moiety in substrate **1** is subjected to *meta*-C—H iodination, only <5% yields of iodination product could be formed (entry 1). It was possible that the coordination of pyridine with Pd(II) was too strong to form reactive complex. Introduce a methyl group at 6 position could improve the yields slightly to 25% (entry 2). Pyrimidine-based template has been recently explored by Maiti in Pd-catalyzed *meta*-C–H functionalizations [12]. When we change the heterocycle from pyridine to pyrimidine, the yields improve to 60% with 54% mono and 6% di (entry 3). Tuning the coordination ability by incorporation an electron-withdrawing fluoro group at the C-2 and C-6 position of

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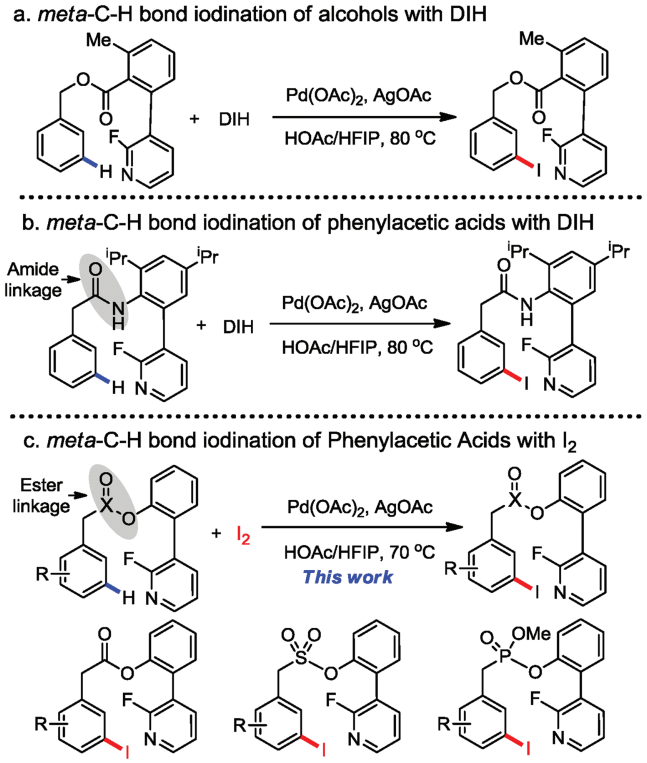
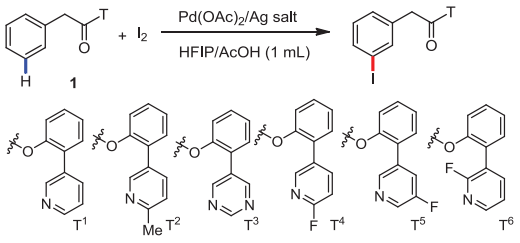


Scheme 1. Directed C—H iodinaion.

Table 1
Optimization of the reaction conditions for *meta*-C—H Iodination.

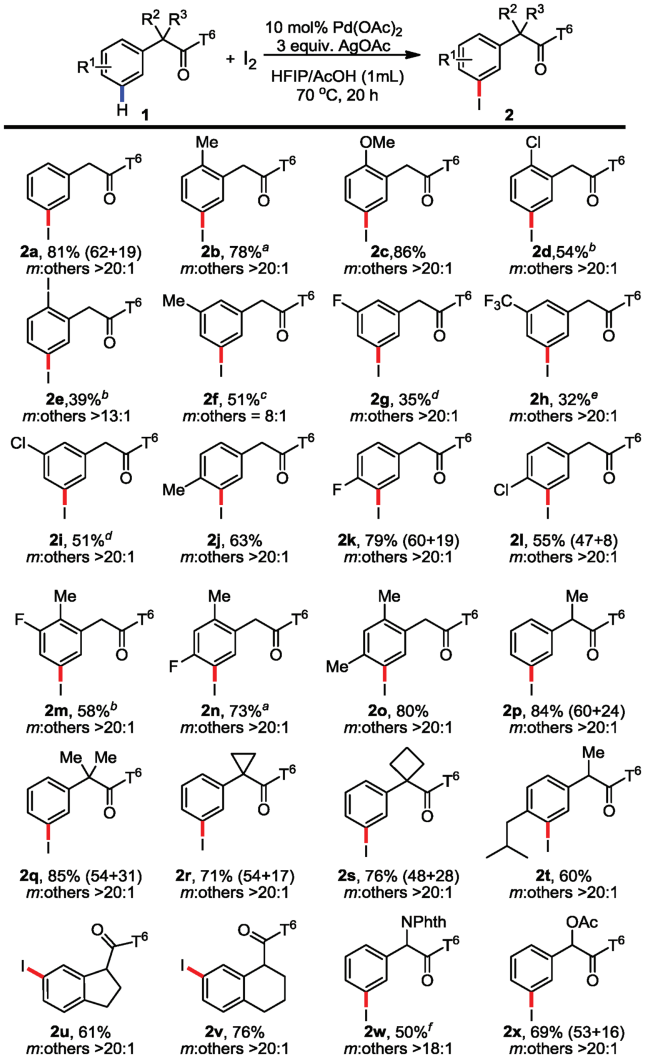


Entry	Template	Ag salt	Temp (°C)	Yield (mono + di)[a]	*meta*: others[b]
1	T^1	AgOAc	70	5%<	–
2	T^2	AgOAc	70	25% (24 + 1)	>20:1
3	T^3	AgOAc	70	60% (54 + 6)	12:1
4	T^4	AgOAc	70	61% (43 + 17)	>20:1
5	T^5	AgOAc	70	20% (19 + 1)	>20:1
6	T^6	AgOAc	70	85% (66 + 19)	>20:1
7	T^6	Ag_2O	70	82% (64 + 18)	>20:1
8	T^6	Ag_2CO_3	70	73% (41 + 32)	>20:1
9	T^6	Ag_2SO_4	70	31% (9 + 22)	3:1
10	T^6	AgOAc	40	27%	>20:1
11	T^6	AgOAc	50	40% (38 + 2)	>20:1
12	T^6	AgOAc	60	67% (61 + 7)	>20:1

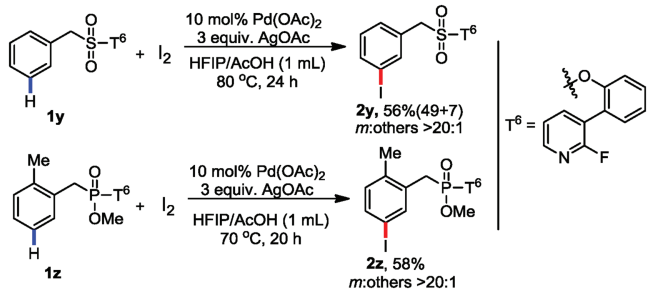
Reaction conditions: 0.1 mmol **1**, 0.4 mmol I_2, 10 mol% $Pd(OAc)_2$, 0.3 mmol Ag salt, HFIP/AcOH = 4/1 (1 mL), 20 h.
[a] Yields were determined by ^1H NMR using CH_2Br_2 as internal standard.
[b] Regioselectivity was determined by GC–MS.

the pyridine ring lead to improved yields, and 2-fluoro-3-pyridyl template T^6 showed the highest yield and *meta*-selectivity (entries 4–6). Among other silver salts, Ag_2O showed comparable results to AgOAc with 82% yields (entries 7–9). Lowering the reaction temperature lead to the decreased yield of iodinated product (entries 10–12).

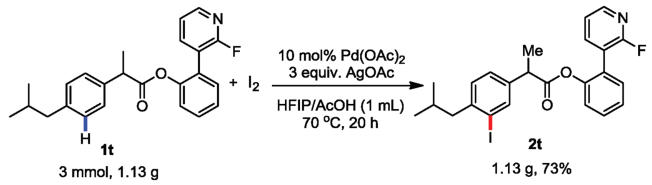
With the optimized reaction conditions in hand, we turned our attention to investigate the phenylacetic acid scope (Scheme 2). *meta*-C—H iodination of phenylacetic acid provided the desired products **2a** in 81% isolated yields (62% mono and 19% di) with high regioselectivity. Phenylacetic acid containing electron-donating methyl, methoxyl group at the 2-, 3- or 4-position position could be iodinated to give the corresponding products in moderate to good yields with excellect *meta* ratio (**2b**, **2c**, **2f**, **2j**). It is worth noting that substrates containing electron-withdrawing fluoro, chloro, iodo and even trifluoromethyl groups could react with I_2, giving the corresponding products with good to moderate yields (**2d**, **2e**, **2g**, **2i**, **2k**, **2l**). The halide groups in products are useful handle for further structural elaborations. For 2, 3- or 2, 4- disubstituted phenylacetic acids, C—H iodination occurred mainly at the less hindered positions with moderate to good yields (**2m**-**2o**). Furthermore, α-alkyl, cycloalkyl, heteroatom substituted phenylacetic acids were also compatible in this reaction (**2p**-**2s**, **2w**, **2x**). The versatility of this protocol was further validated by *meta*-C—H iodination of cyclic substrates (**2u**, **2v**). Ibuprofen derivative can also be *meta*-iodinated to give the corresponding mono iodinated



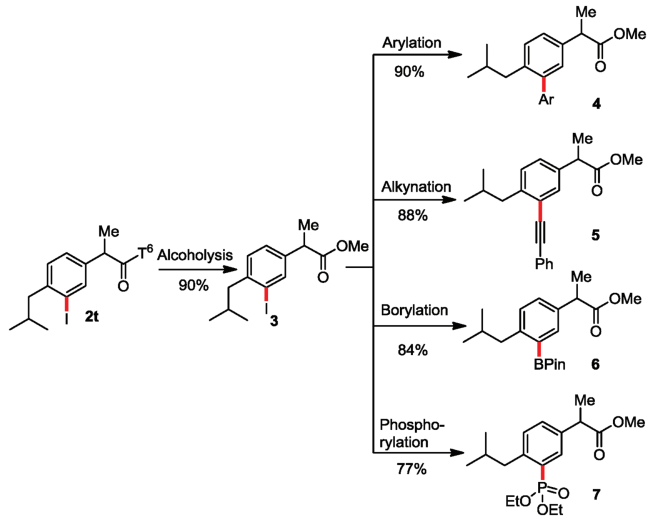
Scheme 2. Scope of phenylacetic acids for *meta*-C—H iodination. Reaction conditions: **1** (0.1 mmol), 0.4 mmol I_2, 10 mol% $Pd(OAc)_2$, 0.3 mmol AgOAc, HFIP/AcOH = 4/1 (1 mL), 70 °C, 20 h. Mono and di are showed in parenthesis. Regioselectivity was determined GC–MS. [a] 0.3 mmol I_2. [b] 80 °C. [c] 0.2 mmol I_2. [d] 20 mol% N-Ac-Gly-OH was added as ligands. [e] 100 °C. [f] Regioselectivity was determined LC–MS.



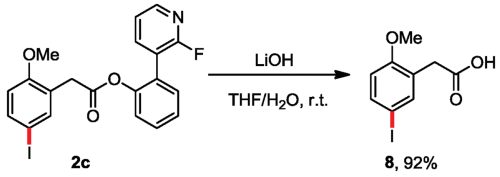
Scheme 3. *meta*-C—H iodination of benzylphosphonate and benzylsulfonate.



Scheme 4. Gram-scale reaction.



Scheme 5. Transformation of iodinated ibuprofen derivative **2t**.



Scheme 6. Removal of the directing template.

product in 60% yield with *meta*/others > 20/1 (**2t**). The regioselectivity of product **2t** was determined by NOE analysis.

Benzylphosphonate and benzylsulfonate substrates are common structural motifs and useful synthons in organic chemistry [16]. To demonstrate the broad utility of this methodology, we subjected the substrates **1y** and **1z** to the *meta*-C—H iodination conditions. The corresponding product **2y** and **2z** could be obtained in 56% and 58% yields respectively (Scheme 3).

We also applied this protocol for gram-scale reaction using ibuprofen derivative **1t** under the standard condition, giving the desired product **2t** in 73% isolated yields (Scheme 4).

meta-C—H iodinated products are versatile step stone for further functionalization at *meta* positions of arenes. For example, iodinated ibuprofen derivative **2t** could be converted to a diverse range of *meta*-substituted ibuprofen ester by alcoholysis and subsequently Pd-catalyzed cross-coupling reactions, illustrating the broad utility of this methodology (Scheme 5).

Finally, the template could be easily removed by hydrolysis of **2c** at room temperature by using LiOH in THF/H_2O, giving the *meta*-iodinated phenylacetic acids **8** in good yields (Scheme 6).

In summary, we developed Pd-catalyzed highly *meta*-selective C—H iodination of phenylacetic acid, benzylphosphonate, and benzylsulfonate scaffolds using a pyridine-type template. The directing template was anchored to the substrates *via* the practical ester linkage. A variety of phenylacetic acids containing electron-withdrawing and electron-donating substituents are compatible with these reactions. Further transformations of ibuprofen iodide intermediates by Pd-catalyzed C—C and C–heteroatom bond formation demonstrated the importance of this methodology in organic synthesis and drug discovery.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.057.

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