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Communication

Pd-Catalyzed *ipso*,*meta*-Dimethylation of *ortho*-Substituted Iodoarenes via a Base-Controlled C−H Activation Cascade with Dimethyl Carbonate as the Methyl Source

Zhuo Wu, Feng Wei, Bin Wan, and Yanghui Zhang*

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ABSTRACT: A methyl group can have a profound impact on the pharmacological properties of organic molecules. Hence, developing methylation methods and methylating reagents is essential in medicinal chemistry. We report a palladium-catalyzed dimethylation reaction of *ortho*-substituted iodoarenes using dimethyl carbonate as a methyl source. In the presence of K_2CO_3 as a base, iodoarenes are dimethylated at the *ipso*- and *meta*-positions of the iodo group, which represents a novel strategy for *meta*-C−H methylation. With KOAc as the base, subsequent oxidative C(sp^3)−H/C(sp^3)−H coupling occurs; in this case, the overall transformation achieves triple C−H activation to form three new C−C bonds. These reactions allow expedient access to 2,6-dimethylated phenols, 2,3-dihydrobenzofurans, and indanes, which are ubiquitous structural motifs and essential synthetic intermediates of biologically and pharmacologically active compounds.

A methyl group can modulate the solubility, hydrophilicity, and conformation of drug molecules, which is termed the "magic methyl effect",[1,2] and a number of small-molecule drugs contain at least one methyl group.[3] In particular, 2,6-dimethylated arenes are essential motifs in many pharmaceutical and bioactive molecules. For example, among the top 200 small-molecule pharmaceuticals by retail sales in 2018, three drugs contain a 2,6-dimethylated arene moiety, and two drugs have a compound containing the moiety as the major ingredient (Figure 1).[4] Developing facile and efficient

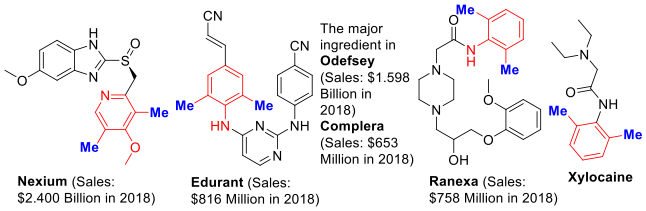

Figure 1. Drugs with an *ortho*,*ortho*-dimethylated arene moiety.

methylation methods is the long-term goal in organic synthesis. While the traditional methods are primarily based on nucleophilic substitution, transition-metal-catalyzed methylation reactions have made rapid progress.[5−9] Notably, direct C−H methylation is emerging as a highly desirable method.[10−32] C−H methylation not only provides an innovative strategy for introducing methyl groups but, more importantly, allows for the direct methylation of bioactive molecules at a late stage. The current transition-metal-catalyzed C−H methylation reactions primarily rely on the use of directing groups. For aryl C−H bond activation, C−H bonds *ortho* to the directing groups are methylated, which restricts the scope of accessible products. An exceptional example is the *meta*-C−H methylation reported by the Yu group.[33] Although non-chelate-assisted C−H methylation has been developed, the reactions were limited to heteroarenes containing reactive C−H bonds.[34−38]

On the other hand, although a variety of methylating reagents are available,[39] it is still desirable to develop low-cost and eco-friendly ones. Dimethyl carbonate (DMC) is undoubtedly an ideal methylating reagent, because it is inexpensive, easily handled, and eco-friendly.[40−42] However, as a methylating reagent, DMC has only been utilized in nucleophilic substitution reactions. To the best of our knowledge, it has not been applied in transition-metal-catalyzed cross-coupling reactions or C−H methylation reactions.

Herein, we report Pd-catalyzed *ipso*- and *meta*-dimethylation of *ortho*-functionalized iodoarenes through cascade C−H functionalization. In the presence of K_2CO_3, iodoarenes are dimethylated at the *ipso*- and *meta*-positions of the iodo group. By using KOAc, the third C−H activation and C(sp^3)−C(sp^3) coupling occurred (Figure 2). The *ortho*-functionalized iodoarene substrates are readily available. Notably, the reaction represents an innovative strategy for *meta*-C−H methylation.[43−48] The iodo group acted as a traceless directing group to enable the methylation of its *meta*-C−H bond with the *ortho*-substituents as the relaying directing group. It should be mentioned that the homocoupling of *ortho*-iodoanisoles has been reported.[49,50] The homocoupling has to be suppressed for

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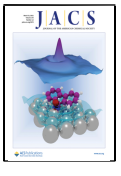

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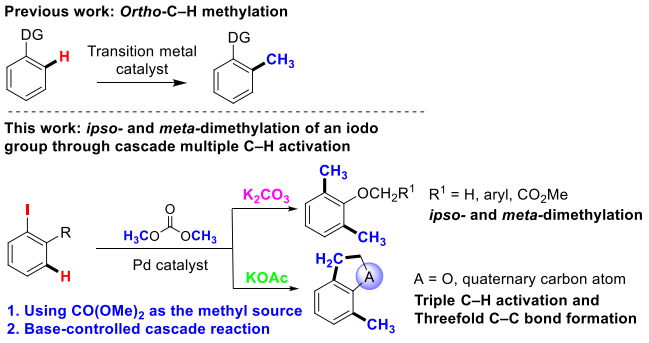
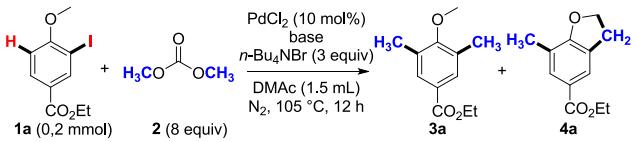


Figure 2. Transition-metal-catalyzed C−H methylation.

developing cross-coupling reactions with external reagents. DMC was used as the methyl source in the reactions. This is the first time DMC is used as a methyl source in transition-metal-catalyzed cross-coupling reactions and C−H methylation reactions.

We commenced research by using **1a** as the model substrate. After extensive studies, **3a** was formed in 80% yield under the conditions shown in Table 1 (entry 1). The yield remained

Table 1. Condition Survey



		yield (%)[a]	
entry	base (equiv)	3a	4a
1	***K_2CO_3 (2)***	***80 (75[b], 78[c])***	***trace***
2[d]	K_2CO_3 (4)	53	trace
3[e]	K_2CO_3 (2)	62	6
4[e]	KOAc (4)	5	58
5[e,f]	***KOAc (4)***	***3***	***80 (77[b])***
6[e,f,g]	KOAc (4)	7	48

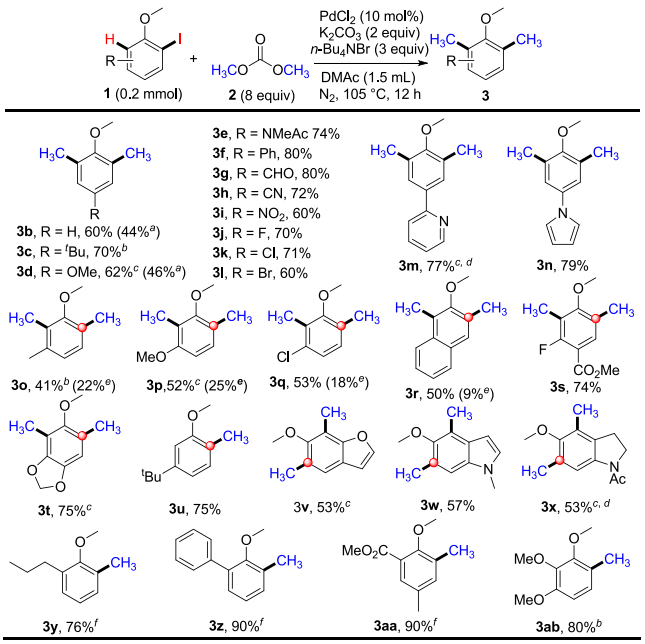
[a]The yields were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield. [c]1.22 g of **1a**. [d]Ethyl 3-bromo-4-methoxybenzoate, P(*o*-tol)$_3$ (20 mol%), *n*-Bu_4NBr (4 equiv), 140 °C. [e]$Pd(OAc)_2$. [f]$CO(OMe)_2$ (12 equiv), *n*-Bu_4NBr (5 equiv), NMP solvent, 100 °C. [g]Ethyl 3-bromo-4-methoxybenzoate, P(*o*-tol)$_3$ (20 mol%), 120 °C.

unaffected when the reaction was scaled up to 1.22 g scale (entry 1), and a 2-bromoanisole derivative was also suitable by using a P(*o*-tol)$_3$ ligand (entry 2).

It is noted that a side product, **4a**, was observed when $Pd(OAc)_2$ was used (entry 3). The 2,3-dihydrobenzofuran-forming reaction is very intriguing. It involves triple C−H activation and threefold C−C bond formation. The reaction also represents an innovative and facile method for the synthesis of 2,3-dihydrobenzofurans,[51−54] which are ubiquitous in naturally occurring compounds, pharmaceuticals, and agrochemicals.[55−57] Therefore, we set out to study the reaction. Remarkably, **4a** was formed as the major product when KOAc was used (entry 4), and the yield was enhanced to 80% by tuning the conditions (entry 5). By using P(*o*-tol)$_3$, 2-bromoanisole was also reactive (entry 6). (For a detailed conditions survey, see the Supporting Information.)

The substrate scope of the dimethylation reaction was investigated. A range of 2-iodoanisoles bearing various functionalities were dimethylated efficiently (Scheme 1, **3b**−**3l**). 2-Bromoanisoles were also reactive by using P(*o*-tol)$_3$ (**3b**,

Scheme 1. Mono- and Dimethylation of 2-Iodoanisoles



[a]The corresponding 2-bromoanisole was used, P(*o*-tol)$_3$ (20 mol%), K_2CO_3 (4 equiv), *n*-Bu_4NBr (4 equiv), 140 °C. [b]*n*-Bu_4NBr (4 equiv). [c]K_2CO_3(4 equiv). *n*-Bu_4NBr (4 equiv). [d]120 °C. [e]Monomethylated product. [f]**2** (5 equiv). [g]The red circles indicate the initial position of the iodides.

3d), and heteroaryl groups, including pyridyl and pyrrolyl, were compatible (**3m**, **3n**). For transition-metal-catalyzed C−H functionalization, it is often challenging to functionalize aryl C−H bonds if both of the positions *ortho* to the C−H bonds are substituted. Notably, 2-iodoanisoles bearing a substituent *meta* to the methoxy group could be dimethylated (**3o**−**3t**), except for **1u** (**3u**). The substrates derived from heterocycles benzofuran and indole were suitable (**3v**, **3w**). If the other ortho positions of anisoles were blocked with a substituent, monomethylated products were formed (**3y**−**3ab**). The reaction of **1a** with diethyl carbonate was also examined. The desired diethylated product was not observed.

The substrate scope of the 2,3-dihydrobenzofuran-forming reaction was also probed. As shown in Scheme 2, the reaction was compatible with a wide array of functional groups (**4b**−**4ae**). Pyridyl and pyrrolyl groups were compatible (**4m**, **4n**), and 2-bromoanisoles were also reactive (**4b**, **4d**). Two isomers were generated in the formation of **4o**. *ortho*-Substituted 2-iodoanisoles could also be transformed into the corresponding 2,3-dihydrobenzofurans (**4y**, **4aa**, **4ab**, **4af**−**4ai**, and **4ak**). The optimal yields could still be obtained when the amounts of KOAc, *n*-Bu_4NBr, and **2** were reduced. For substrates **1aj** and **1z**, products resulting from aryl C−H bond activation were obtained. Notably, the reaction could be scaled up (**4ah**).

Next, we turned to study the reactions of other *ortho*-substituted iodobenzenes. Benzylic C−H bonds could also be utilized to enable the dimethylation (Scheme 3, **6a**−**6d**). For halogen-directed C−H activation, most of the current reactions involve the activation of methyl C−H bonds, and the reactions of secondary C−H bonds are scarce and limited

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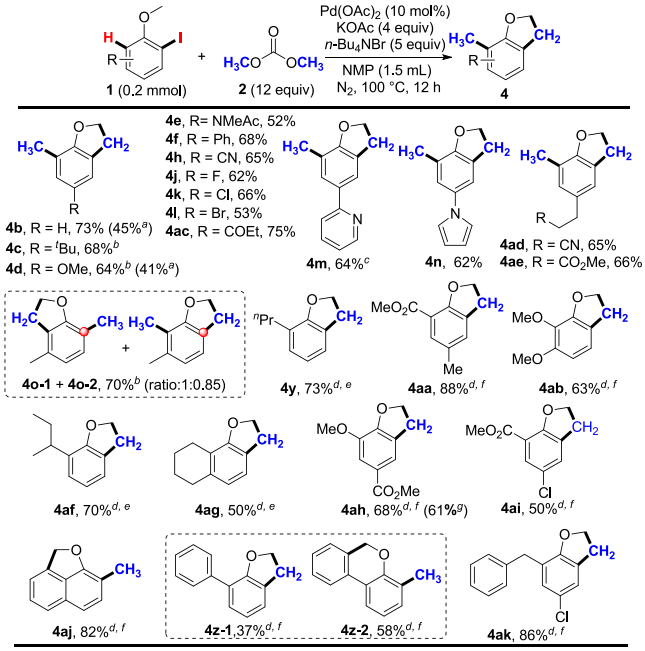
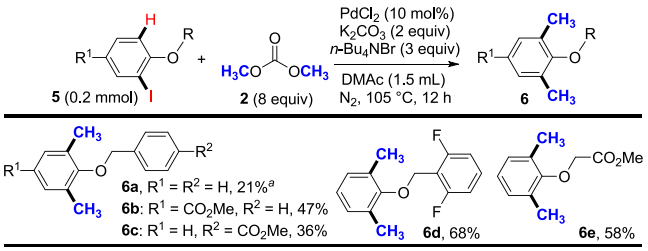
Scheme 2. 2,3-Dihydrobenzofuran-Forming Reactions



[a]The corresponding 2-bromoanisole was used, P(*o*-tol)$_3$ (20 mol%), 120 °C. [b]KOAc (6 equiv). [c]Pd(OAc)$_2$ (20 mol%), KOAc (6 equiv). [d]KOAc (2.5 equiv), *n*-Bu$_4$NBr (4 equiv). [e]**2** (5 equiv). [f]**2** (8 equiv). [g]1.29 g scale. [h]The red circles indicate the initial position of the iodides.

Scheme 3. Dimethylation of 2-Iodoanisole Derivatives



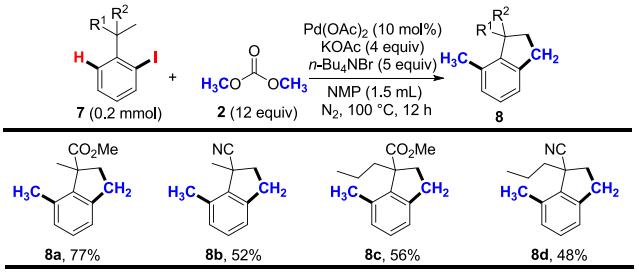
[a]K_2CO_3 (4 equiv), *n*-Bu$_4$NBr (4 equiv).

to intramolecular ones.[58−63] Halogen-directed benzylic secondary C−H activation under palladium catalysis has only been applied in intramolecular cyclization reactions.[61−63] Notably, a benzyl group is an ideal shuttle to activate remote C−H bonds in this reaction, because it is a common protecting group and can be removed easily. Furthermore, the α-C−H bond of an ester group also assisted the dimethylation reaction effectively (**6e**). However, 1-ethoxy-2-iodobenzene failed to form the dimethylated product.

Remarkably, *ortho*-alkyl-substituted iodobenzenes also underwent dimethylation and subsequent cyclization to form *ortho*-methylindanes (Scheme 4). The reaction provides an innovative synthetic method for substituted indanes,[64−68] which are widely found in drugs and natural products and find extensive applications in materials science.[69,70]

Trideuteriomethylation represents a valuable strategy for structural modification in drug discovery,[71,72] and trideuteriomethylated drugs have been developed.[73] Therefore, trideuteriomethylation was investigated. Both of the reactions proceeded smoothly when CO(OCD$_3$)$_2$ was used (Figure 3a).

Scheme 4. Dimethylation and Cyclization of 2-Alkyl-1-iodobenzenes



The deuteration of the methoxy group was also observed in the dimethylation reactions. (For the mechanism, see Figure 4.)

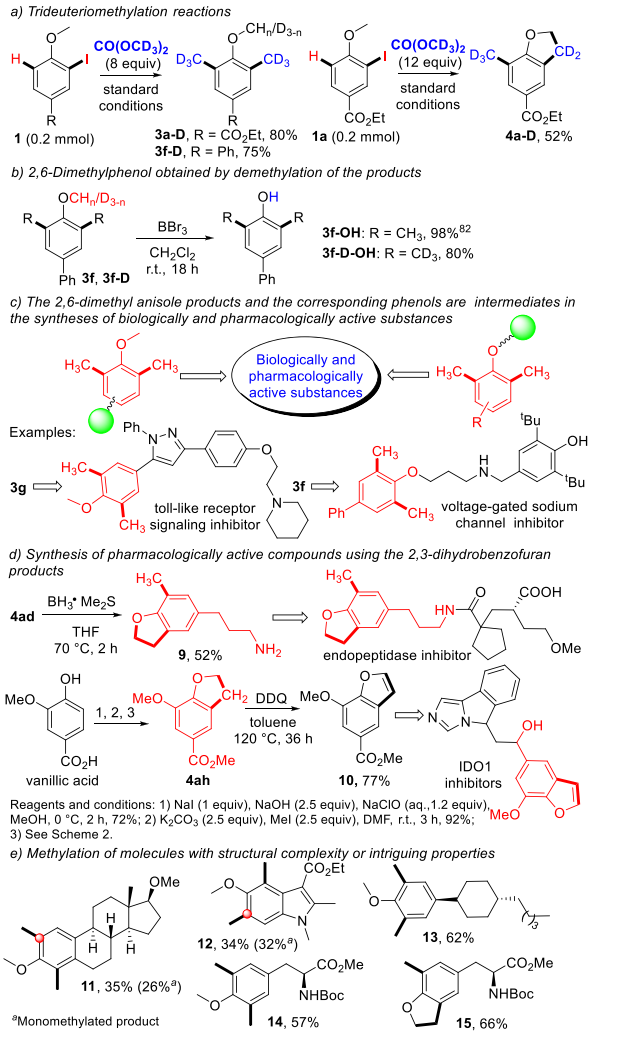


Figure 3. Practical applications.

Many of the 2,6-dimethylated anisole products, such as **3f**,[74] **3g**,[75] **3h**,[76] **3i**,[77] **3k**,[78] **3l**,[79] **3o**,[80] and **3p**,[81], and their demethylated analogues, the 2,6-dimethylphenols,[82−85] are essential intermediates in the syntheses of biologically and pharmacologically active compounds (Figure 3c). Demethylation of the 2,6-dimethylanisole products was exemplified by the reactions of **3f** and **3f-D** (Figure 3b). To demonstrate the synthetic utility of the 2,3-dihydrobenzofuran products, we synthesized compounds **9** and **10** by using products **4ad** and

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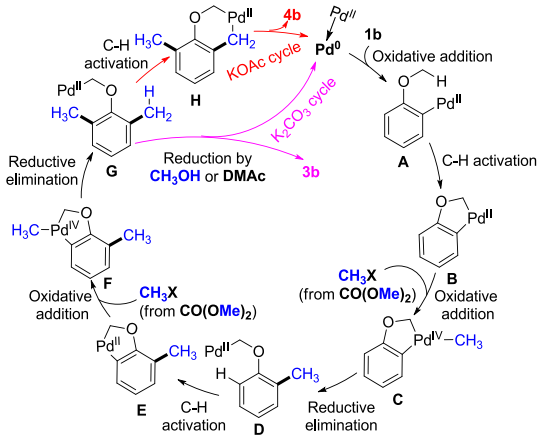

Figure 4. Plausible mechanism.

4ah, respectively (Figure 3d). **9** and **10** are the synthetic intermediates of an endopeptidase inhibitor[86] and an IDO1 inhibitor,[87] respectively. The 2-iodoanisole substrate in the synthesis of **4ah** was readily prepared from cheap vanillic acid. The reactions also allow for the methylation of molecules with structural complexity or intriguing properties (Figure 3e). For example, the estradiol-derived iodide and Mecarbinate[88] could be dimethylated (**11** and **12**). The dimethylation reaction also provides an easy access to a precursor for the synthesis of a liquid crystal with composition **13**[89,90] and bioactive compound **14**.[91−93] The tyrosine-derived iodide was also transformed to compound **15**. All the 2-iodoanisole substrates in the syntheses of **11**−**15** were readily prepared (see Supporting Information).

Preliminary mechanistic studies were conducted (see Supporting Information). Whereas the palladacycle derived from 2-iodoanisole did not react with DMC in the absence of a halide source, the dimethylated product was formed in the presence of *n*-Bu_4NBr, albeit in a low yield. On the other hand, when CH_3I was used instead of DMC in the reaction of **1a**, only a trace amount of the dimethylated product was observed. However, MeI could dimethylate the palladacycle in 10% yield. Therefore, MeBr could be the actual methylating reagent, and DMC may be a methyl source. However, MeI could not be ruled out as the methylating reagent. *n*-Bu_4NBr acted as the bromide source in the reaction. Furthermore, *n*-Bu_4NBr may also promote the reaction by stabilizing palladium catalyst.[94,95] It should be mentioned that the use of MeBr is not desirable due to its high toxicity and the difficult handling of a gas, which is evidenced by the fact that MeBr is much less frequently used as a methylating reagent than MeI. Therefore, DMC is still an ideal or even necessary methyl source. Furthermore, Me_2SO_4, $PO(OMe)_3$, and MeOTs were also competent methylating reagents in the dimethylation reaction, but the reactions were low-yielding. However, the 2,3-dihydrobenzofuran product was not observed using $PO(OMe)_3$ as the methylating reagent.

When the dimethylation reactions were carried out in the presence of deuterated reagents, the methoxy group was deuterated by CD_3OD and d_7-DMF, and the deuteration almost failed to occur in the presence of D_2O (see Supporting Information). These outcomes indicate that the alkylPd^{II} species were reduced primarily by CD_3OD or d_7-DMF instead of protonated by a free proton. It is noted that the two *ortho*-methyl groups were not deuterated, which implies that C−H bonds of the methyl groups were not activated. Therefore, it can be inferred that, although both KOAc and K_2CO_3 could promote the C−H activation of the methoxy groups and the arenes, only KOAc could enable the last $C(sp^3)$−H activation of the methyl group by the $C(sp^3)$−Pd^{II} species. As a consequence, the use of KOAc led to triple C−H activation and the formation of 2,3-dihydrobenzofuran, and K_2CO_3 only gave dimethylated products. The detailed mode of action of these two bases in the reactions remains to be investigated. Notably, the Baudoin group found very recently that pivalate could promote $C(sp^3)$−H activation by alkylpalladium species.[96] Furthermore, it has been reported that carboxylates could promote Pd-catalyzed C−H functionalization reactions of aryl halides more efficiently than carbonates.[97−101]

Based on the above results, a plausible mechanism is proposed in Figure 4. Palladacycle **B** is formed by $C(sp^3)$−H activation. **B** undergoes oxidative addition with methyl halides that are generated from DMC, affording **C**. The reductive elimination of **C** gives **D**, which then cleaves the aryl C−H bond to form a second palladacycle, **E**. **E** undergoes the same process as that for the formation of **D** to introduce a second methyl group and gives **G**. Using K_2CO_3, **G** is protonated by DMAc or CH_3OH that is generated from DMC, delivering dimethylated product **3b**. DMC not only should act as the methyl source but also could release CH_3OH to reduce Pd^{II} species. Using KOAc, the third activation of methyl C−H bonds occurs to form palladacycle **H**. The reductive elimination of **H** yields **4b** and releases Pd^0 species.

In summary, we have developed innovative Pd-catalyzed C−H methylation reactions of *ortho*-substituted iodoarenes by using dimethyl carbonate as a methyl source. It is the first time for DMC to be used as a methyl source in transition-metal-catalyzed cross-coupling reactions. By using K_2CO_3 as a base, iodoarenes are dimethylated at the *ipso*- and *meta*-positions of the iodo group, yielding 2,6-dimethylated arenes. The reaction represents a novel strategy for *meta*-C−H methylation. By using KOAc, dihydrobenzofurans or indanes are formed through cascade triple C−H activation. The methylation of complex molecules and trideuteriomethylation have been demonstrated. Further studies aimed at developing other DMC-based methylation reactions and elucidating the detailed mechanism, in particular the roles of inorganic bases, are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13057.

Experimental details, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yanghui Zhang − *School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, Shanghai 200092, China;* orcid.org/0000-0003-2189-3496; Email: zhangyanghui@tongji.edu.cn

Authors

Zhuo Wu − *School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, Shanghai 200092, China*

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Feng Wei − *School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, Shanghai 200092, China*
Bin Wan − *School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, Shanghai 200092, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c13057

Notes

The authors declare no competing financial interest.

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