

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*

Cite This: *J. Am. Chem. Soc.* 2021, 143, 4524–4530

Read Online

ACCESS |



Metrics & More



Article Recommendations



Supporting Information

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

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

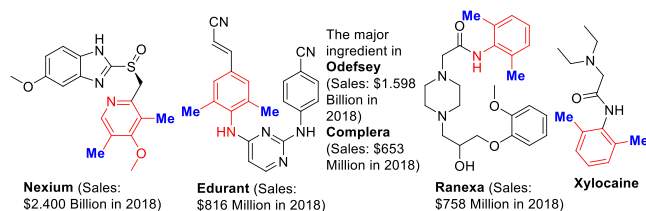
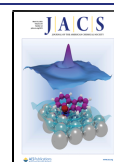


Figure 1. Drugs with an *ortho,ortho*-dimethylated arene moiety.

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

Received: December 17, 2020

Published: March 22, 2021



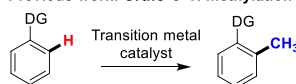
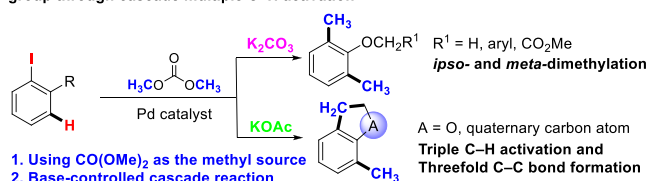
Previous work: *Ortho*-C–H methylationThis work: *ipso*- and *meta*-dimethylation of an iodo group through cascade multiple C–H activation

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

entry	base (equiv)	yield (%) ^{a,d}	
		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

^aThe yields were determined by ^1H NMR analysis of the crude reaction mixture. ^bIsolated yield. ^c1.22 g of **1a**. ^dEthyl 3-bromo-4-methoxybenzoate, $\text{P}(\text{o-tol})_3$ (20 mol%), $n\text{-Bu}_4\text{NBr}$ (4 equiv), 140 °C. ^e $\text{Pd}(\text{OAc})_2$. ^f $\text{CO}(\text{OMe})_2$ (12 equiv), $n\text{-Bu}_4\text{NBr}$ (5 equiv), NMP solvent, 100 °C. ^gEthyl 3-bromo-4-methoxybenzoate, $\text{P}(\text{o-tol})_3$ (20 mol%), 120 °C.

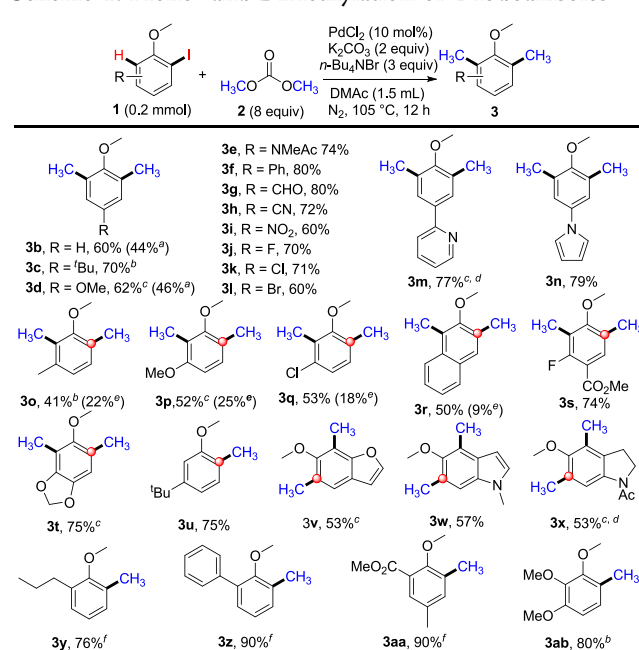
unaffected when the reaction was scaled up to 1.22 g scale (entry 1), and a 2-bromoanisole derivative was also suitable by using a $\text{P}(\text{o-tol})_3$ ligand (entry 2).

It is noted that a side product, **4a**, was observed when $\text{Pd}(\text{OAc})_2$ 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 $\text{P}(\text{o-tol})_3$, 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 $\text{P}(\text{o-tol})_3$ (**3b**,

Scheme 1. Mono- and Dimethylation of 2-Iodoanisoles



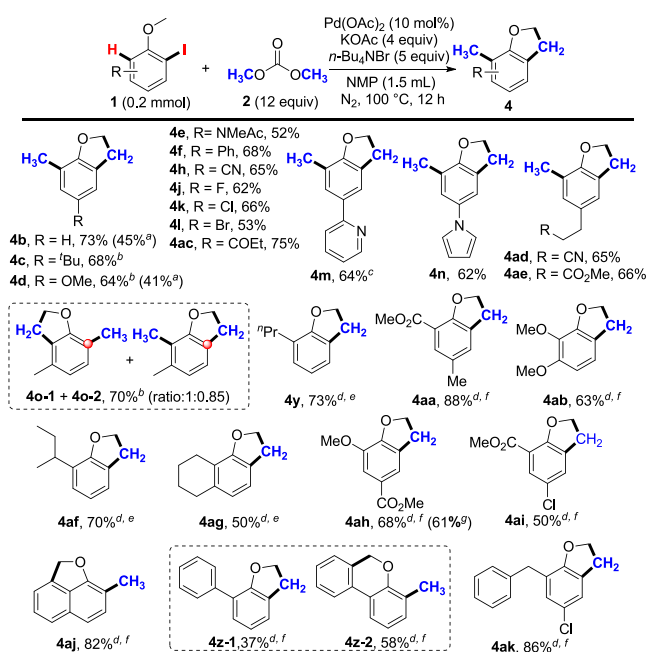
^aThe corresponding 2-bromoanisole was used, $\text{P}(\text{o-tol})_3$ (20 mol%), K_2CO_3 (4 equiv), $n\text{-Bu}_4\text{NBr}$ (4 equiv), 140 °C. ^b $n\text{-Bu}_4\text{NBr}$ (4 equiv). ^c K_2CO_3 (4 equiv). $n\text{-Bu}_4\text{NBr}$ (4 equiv). ^d120 °C. ^eMonomethylated product. ^f2 (5 equiv). ^gThe 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, $n\text{-Bu}_4\text{NBr}$, 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**).

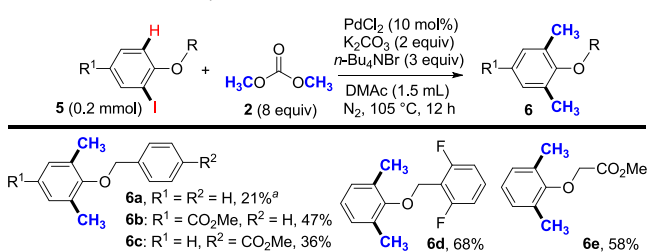
Next, we turned to study the reactions of other *ortho*-substituted iodobenzenes. Benzylic C–H bonds could also be utilized to enable the dimethylation (Scheme 3, **6a**–**6d**). For halogen-directed C–H activation, most of the current reactions involve the activation of methyl C–H bonds, and the reactions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

Scheme 2. 2,3-Dihydrobenzofuran-Forming Reactions



^aThe corresponding 2-bromoanisole was used, P(*o*-tol)₃ (20 mol%), 120 °C. ^bKOAc (6 equiv). ^cPd(OAc)₂ (20 mol%), KOAc (6 equiv). ^dKOAc (2.5 equiv), *n*-Bu₄NBr (4 equiv). ^e2 (5 equiv). ^f2 (8 equiv). ^g1.29 g scale. ^hThe red circles indicate the initial position of the iodides.

Scheme 3. Dimethylation of 2-Iodoanisole Derivatives



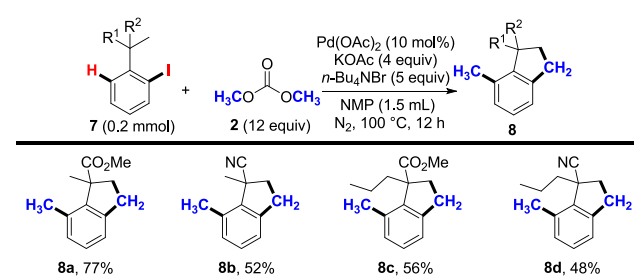
^aK₂CO₃ (4 equiv), *n*-Bu₄NBr (4 equiv).

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}

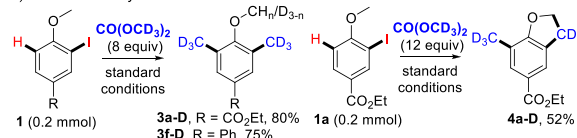
Trideuteriomethylation represents a valuable strategy for structural modification in drug discovery,^{71,72} and trideuteriomethylated drugs have been developed.⁷³ Therefore, trideuteriomethylation was investigated. Both of the reactions proceeded smoothly when CO(OCD₃)₂ was used (Figure 3a).

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

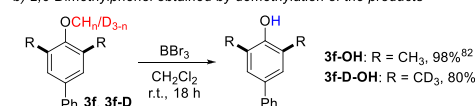


The deuteration of the methoxy group was also observed in the dimethylation reactions. (For the mechanism, see Figure 4.)

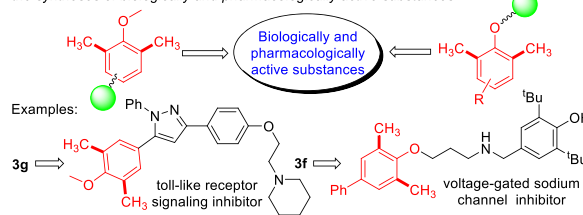
a) Trideuteriomethylation reactions



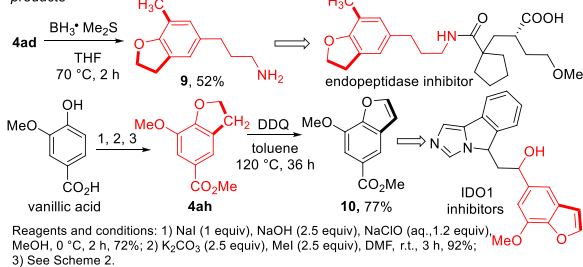
b) 2,6-Dimethylphenol obtained by demethylation of the products



c) The 2,6-dimethyl anisole products and the corresponding phenols are intermediates in the syntheses of biologically and pharmacologically active substances



d) Synthesis of pharmacologically active compounds using the 2,3-dihydrobenzofuran products



e) Methylation of molecules with structural complexity or intriguing properties

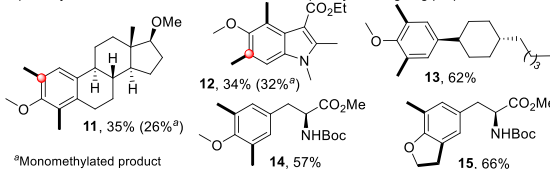


Figure 3. Practical applications.

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

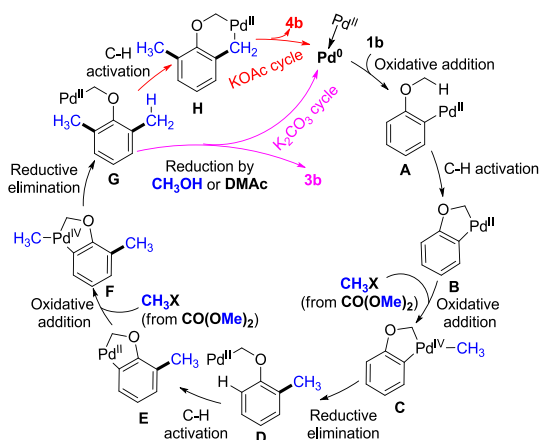


Figure 4. Plausible mechanism.

4ah, respectively (Figure 3d). **9** and **10** are the synthetic intermediates of an endopeptidase inhibitor⁸⁶ 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 Mecarbinat⁸⁸ 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*-Bu₄NBr, albeit in a low yield. On the other hand, when CH₃I 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*-Bu₄NBr acted as the bromide source in the reaction. Furthermore, *n*-Bu₄NBr 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, Me₂SO₄, PO(OMe)₃, and MeOTf 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 CD₃OD and *d*₇-DMF, and the deuteration almost failed to occur in the presence of D₂O (see Supporting Information). These outcomes indicate that the alkylPd^{II} species were reduced primarily by CD₃OD 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 K₂CO₃ could promote the C–H activation of the methoxy groups and the arenes, only KOAc could enable the last C(sp³)–H activation of the methyl group by the C(sp³)–Pd^{II} species. As a consequence, the use of KOAc led to triple C–H activation and the formation of 2,3-dihydrobenzofuran, and K₂CO₃ 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(sp³)–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(sp³)–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 K₂CO₃, **G** is protonated by DMAc or CH₃OH that is generated from DMC, delivering dimethylated product **3b**. DMC not only should act as the methyl source but also could release CH₃OH 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 Pd⁰ 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 K₂CO₃ 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

Yanghai 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

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.

ACKNOWLEDGMENTS

The work was supported by the National Natural Science Foundation of China (nos. 21971196 and 21672162)

REFERENCES

- (1) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C-H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256–12267.
- (2) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215–5246.
- (3) Smith, D. T.; Delost, M. D.; Qureshi, H.; Njardarson, J. T. Top 200 Pharmaceutical Products by Retail Sales in 2016, https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/2016Top200PharmaceuticalRetailSalesPosterLowResV3_0.pdf (accessed March 17, 2021).
- (4) Vitaku, E.; Ildardi, E. A.; Njardarson, J. T. Top 200 Pharmaceutical Products by Retail Sales in 2018, https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Small%20Molecule%20Pharmaceuticals%202018_0.pdf (accessed March 17, 2021).
- (5) Yan, G.; Borah, A. J.; Wang, L.; Yang, M. Recent Advances in Transition Metal-Catalyzed Methylation Reactions. *Adv. Synth. Catal.* **2015**, *357*, 1333–1350.
- (6) Hu, L.; Liu, Y. A.; Liao, X. Recent Progress in Methylation of (Hetero)Arenes by Cross-Coupling or C-H Activation. *Synlett* **2018**, *29*, 375–382.
- (7) Kariofillis, S. K.; Shields, B. J.; Tekle-Smith, M. A.; Zacuto, M. J.; Doyle, A. G. Nickel/Photoredox-Catalyzed Methylation of (Hetero)aryl Chlorides Using Trimethyl Orthoformate as a Methyl Radical Source. *J. Am. Chem. Soc.* **2020**, *142*, 7683–7689.
- (8) He, Z.-T.; Li, H.; Haydl, A. M.; Whiteker, G. T.; Hartwig, J. F. Trimethylphosphate as a Methylating Agent for Cross Coupling: A Slow-Release Mechanism for the Methylation of Arylboronic Esters. *J. Am. Chem. Soc.* **2018**, *140*, 17197–17202.
- (9) Wang, J.; Zhao, J.; Gong, H. Nickel-Catalyzed Methylation of Aryl Halides/Tosylates with Methyl Tosylate. *Chem. Commun.* **2017**, *53*, 10180–10183.
- (10) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C-H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452.
- (11) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C-H Bond Functionalization Chemistry for the Expedient Construction of C-C Bonds. *Chem. Rev.* **2020**, *120*, 1788–1887.
- (12) Meng, G.; Lam, N. Y. S.; Lucas, E. L.; Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. Achieving Site-Selectivity for C-H Activation Processes Based on Distance and Geometry: A Carpenter's Approach. *J. Am. Chem. Soc.* **2020**, *142*, 10571–10591.
- (13) Li, B.; Ali, A. I. M.; Ge, H. Recent Advances in Using Transition-Metal-Catalyzed C-H Functionalization to Build Fluorescent Materials. *Chem.* **2020**, *6*, 2591–2657.
- (14) Baudoin, O. Multiple Catalytic C-H Bond Functionalization for Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 17798–17809.
- (15) Liao, G.; Zhang, T.; Lin, Z.-K.; Shi, B.-F. Transition Metal-Catalyzed Enantioselective C-H Functionalization via Chiral Transient Directing Group Strategies. *Angew. Chem., Int. Ed.* **2020**, *59*, 19773–19786.
- (16) Ackermann, L. Metalla-electrocatalyzed C-H Activation by Earth-Abundant 3d Metals and Beyond. *Acc. Chem. Res.* **2020**, *53*, 84–104.
- (17) Tremont, S. J.; Rahman, H. U. Ortho-Alkylation of Acetanilides Using Alkyl Halides and Palladium Acetate. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760.
- (18) Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. Palladium-Catalyzed Picolinamide-Directed Alkylation of Unactivated C(sp³)-H Bonds with Alkyl Iodides. *J. Am. Chem. Soc.* **2013**, *135*, 2124–2127.
- (19) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. Palladium-Catalyzed Alkylation of Aryl C-H Bonds with sp³ Organotin Reagents Using Benzoquinone as a Crucial Promoter. *J. Am. Chem. Soc.* **2006**, *128*, 78–79.
- (20) Chen, X.; Goodhue, C. E.; Yu, J.-Q. Palladium-Catalyzed Alkylation of sp² and sp³ C-H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C-H Activation Pathways. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.
- (21) Giri, R.; Mangel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. Palladium-Catalyzed Methylation and Arylation of sp² and sp³ C-H Bonds in Simple Carboxylic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511.
- (22) Romero-Revilla, J. A.; Garcia-Rubia, A.; Gomez Arrayas, R.; Fernandez-Ibanez, M. A.; Carretero, J. C. Palladium-Catalyzed Coupling of Arene C-H Bonds with Methyl and Arylboron Reagents Assisted by the Removable 2-Pyridylsulfinyl Group. *J. Org. Chem.* **2011**, *76*, 9525–9530.
- (23) Neufeldt, S. R.; Seigerman, C. K.; Sanford, M. S. Mild Palladium-Catalyzed C-H Alkylation Using Potassium Alkyltrifluoroborates in Combination with MnF₃. *Org. Lett.* **2013**, *15*, 2302–2305.
- (24) Chen, X.-Y.; Sorensen, E. J. Pd-Catalyzed ortho-C-H Methylation and Fluorination of Benzaldehydes Using Orthoanilic Acids as Transient Directing Groups. *J. Am. Chem. Soc.* **2018**, *140*, 2789–2792.
- (25) Gao, Q.; Shang, Y.; Song, F.; Ye, J.; Liu, Z.-S.; Li, L.; Cheng, H.-G.; Zhou, Q. Modular Dual-Tasked C-H Methylation via the Catellani Strategy. *J. Am. Chem. Soc.* **2019**, *141*, 15986–15993.
- (26) Zhang, Y.; Feng, J.; Li, C.-J. Palladium-Catalyzed Methylation of Aryl C-H Bond by Using Peroxides. *J. Am. Chem. Soc.* **2008**, *130*, 2900–2901.
- (27) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. Cobalt-Catalyzed Coupling of Alkyl Grignard Reagent with Benzamide and 2-Phenylpyridine Derivatives through Directed C-H Bond Activation under Air. *Org. Lett.* **2011**, *13*, 3232–3234.
- (28) Friis, S. D.; Johansson, M. J.; Ackermann, L. Cobalt-Catalyzed C-H Methylation for Late-Stage Drug Diversification. *Nat. Chem.* **2020**, *12*, 511–519.
- (29) Pan, F.; Lei, Z.-Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z.-J. Rhodium(I)-Catalyzed Redox-Economic Cross-Coupling of Carboxylic Acids with Arenes Directed by N-Containing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 2063–2067.
- (30) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed Directed C(sp²)-H and C(sp³)-H Functionalization with Trimethylaluminum. *J. Am. Chem. Soc.* **2015**, *137*, 7660–7663.
- (31) Graczyk, K.; Haven, T.; Ackermann, L. Iron-Catalyzed C(sp²)-H and C(sp³)-H Methylations of Amides and Anilides. *Chem. - Eur. J.* **2015**, *21*, 8812–8815.
- (32) Uemura, T.; Yamaguchi, M.; Chatani, N. Phenyltrimethylammonium Salts as Methylation Reagents in the Nickel-Catalyzed Methylation of C-H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 3162–3165.
- (33) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-Enabled meta-C-H Activation Using a Transient Mediator. *Nature* **2015**, *519*, 334–338.

- (34) Gui, J.; Zhou, Q.; Pan, C. M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. C-H Methylation of Heteroarenes Inspired by Radical SAM Methyl Transferase. *J. Am. Chem. Soc.* **2014**, *136*, 4853–4856.
- (35) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. Late-Stage Functionalization of Biologically Active Heterocycles through Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802–4806.
- (36) Jin, J.; MacMillan, D. W. C. Alcohols as Alkylating Agents in Heteroarene C-H Functionalization. *Nature* **2015**, *525*, 87–90.
- (37) Li, Y.; Yan, T.; Junge, K.; Beller, M. Catalytic Methylation of C-H Bonds Using CO₂ and H₂. *Angew. Chem., Int. Ed.* **2014**, *53*, 10476–10480.
- (38) Liu, W.; Yang, X.; Zhou, Z.-Z.; Li, C.-J. Simple and Clean Photo-Induced Methylation of Heteroarenes with MeOH. *Chem.* **2017**, *2*, 688–702.
- (39) Chen, Y. Recent Advances in Methylation: A Guide for Selecting Methylation Reagents. *Chem. - Eur. J.* **2019**, *25*, 3405–3439.
- (40) Tundo, P.; Selva, M. The Chemistry of Dimethyl Carbonate. *Acc. Chem. Res.* **2002**, *35*, 706–716.
- (41) Tundo, P.; Musolino, M.; Arico, F. The Reactions of Dimethyl Carbonate and Its Derivatives. *Green Chem.* **2018**, *20*, 28–85.
- (42) Fiorani, G.; Perosa, A.; Selva, M. Dimethyl Carbonate: A Versatile Reagent for a Sustainable Valorization of Renewables. *Green Chem.* **2018**, *20*, 288–322.
- (43) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. Activation of Remote meta-C-H Bonds Assisted by an End-on Template. *Nature* **2012**, *486*, 518–522.
- (44) Bag, S.; K, S.; Mondal, A.; Jayarajan, R.; Dutta, U.; Porey, S.; Sunoj, R. B.; Maiti, D. Palladium-Catalyzed meta-C-H Allylation of Arenes: A Unique Combination of a Pyrimidine-Based Template and Hexafluoroisopropanol. *J. Am. Chem. Soc.* **2020**, *142*, 12453–12466.
- (45) Dong, Z.; Wang, J.; Dong, G. Simple Amine-Directed meta-Selective C-H Arylation via Pd/Norbornene Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5887–5890.
- (46) Phipps, R. J.; Gaunt, M. J. A meta-Selective Copper-Catalyzed C-H Bond Arylation. *Science* **2009**, *323*, 1593–1597.
- (47) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Kohn, G.; Whittlesey, M. K.; Frost, C. G. Ruthenium-Catalyzed meta Sulfonation of 2-Phenylpyridines. *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301.
- (48) Hofmann, N.; Ackermann, L. Meta-Selective C-H Bond Alkylation with Secondary Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884.
- (49) Dyker, G. Palladium-Catalyzed C-H Activation of Methoxy Groups: A Facile Synthesis of Substituted 6H-Dibenzo[b, d]pyrans. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023–1025.
- (50) Dyker, G. Palladium-Catalyzed C-H Activation at Methoxy Groups: Regiochemistry of the Domino Coupling Process. *Chem. Ber.* **1994**, *127*, 739–742.
- (51) Bertolini, F.; Pineschi, M. Recent Progress in the Synthesis of 2, 3-Dihydrobenzofurans. *Org. Prep. Proced. Int.* **2009**, *41*, 385–418.
- (52) Sheppard, T. D. Strategies for the Synthesis of 2, 3-Dihydrobenzofurans. *J. Chem. Res.* **2011**, *35*, 377–385.
- (53) Rocaboy, R.; Anastasiou, I.; Baudoin, O. Redox-Neutral Coupling between Two C(sp³)-H Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 14625–14628.
- (54) Shi, J.-L.; Wang, D.; Zhang, X.-S.; Li, X.-L.; Chen, Y.-Q.; Li, Y.-X.; Shi, Z.-J. Oxidative Coupling of sp² and sp³ Carbon-Hydrogen Bonds to Construct Dihydrobenzofurans. *Nat. Commun.* **2017**, *8*, 238–244.
- (55) Monte, A. P.; Marona-Lewicka, D.; Cozzi, N. V.; Nichols, D. E. Synthesis and Pharmacological Examination of Benzofuran, Indan, and Tetralin Analogs of 3, 4-(Methylenedioxy) amphetamine. *J. Med. Chem.* **1993**, *36*, 3700–3706.
- (56) Huang, Z.; Cui, Q.; Xiong, L.; Wang, Z.; Wang, K.; Zhao, Q.; Bi, F.; Wang, Q. Synthesis and Insecticidal Activities and SAR Studies of Novel Benzoheterocyclic Diacylhydrazine Derivatives. *J. Agric. Food Chem.* **2009**, *57*, 2447–2456.
- (57) Radadiya, A.; Shah, A. Bioactive Benzofuran Derivatives: An Insight on Lead Developments, Radioligands and Advances of the Last Decade. *Eur. J. Med. Chem.* **2015**, *97*, 356–376.
- (58) Melot, R.; Zuccarello, M.; Cavalli, D.; Niggli, N.; Devereux, M.; Burgi, T.; Baudoin, O. Pd⁰-catalyzed Enantioselective Intramolecular Arylation of Enantiotopic Secondary C-H Bonds. *Angew. Chem., Int. Ed.* **2021**, *60*, 7245–7250.
- (59) Holstein, P. M.; Vogler, M.; Larini, P.; Pilet, G.; Clot, E.; Baudoin, O. Efficient Pd⁰-Catalyzed Asymmetric Activation of Primary and Secondary C-H Bonds Enabled by Modular Binapine Ligands and Carbonate Bases. *ACS Catal.* **2015**, *5*, 4300–4308.
- (60) Saget, T.; Cramer, N. Palladium(0)-Catalyzed Enantioselective C-H Arylation of Cyclopropanes: Efficient Access to Functionalized Tetrahydroquinolines. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842–12845.
- (61) Pedroni, J.; Boghi, M.; Saget, T.; Cramer, N. Access to b-Lactams by Enantioselective Palladium(0)-Catalyzed C(sp³)-H Alkylation. *Angew. Chem., Int. Ed.* **2014**, *53*, 9064–9067.
- (62) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, E. P. Asymmetric C(sp³)-H/C(Ar) coupling reactions. Highly enantio-enriched indolines via regiodivergent reaction of a racemic mixture. *Chem. Sci.* **2012**, *3*, 1422–1425.
- (63) Dailier, D.; Rocaboy, R.; Baudoin, O. Synthesis of β-Lactams by Palladium(0)-Catalyzed C(sp³)-H Carbamoylation. *Angew. Chem., Int. Ed.* **2017**, *56*, 7218–7222.
- (64) Wu, Z.; Ma, D.; Zhou, B.; Ji, X.; Ma, X.; Wang, X.; Zhang, Y. Palladium-Catalyzed Alkylation with Alkyl Halides by C(sp³)-H Activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12288–12291.
- (65) Hitce, J.; Retailliau, P.; Baudoin, O. Palladium-Catalyzed Intramolecular C(sp³)-H Functionalization: Catalyst Development and Synthetic Applications. *Chem. - Eur. J.* **2007**, *13*, 792–799.
- (66) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. Intramolecular Palladium-Catalyzed Alkane C-H Arylation from Aryl Chlorides. *J. Am. Chem. Soc.* **2010**, *132*, 10706–10716.
- (67) Holstein, P. M.; Vogler, M.; Larini, P.; Pilet, G.; Clot, E.; Baudoin, O. Efficient Pd⁰-Catalyzed Asymmetric Activation of Primary and Secondary C-H Bonds Enabled by Modular Binapine Ligands and Carbonate Bases. *ACS Catal.* **2015**, *5*, 4300–4308.
- (68) Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; de Luis, B.; Martín, R. Pd-Catalyzed C(sp³)-H Functionalization/Carbenoid Insertion: All-Carbon Quaternary Centers via Multiple C-C Bond Formation. *J. Am. Chem. Soc.* **2016**, *138*, 6384–6387.
- (69) Gabriele, B.; Mancuso, R.; Veltri, L. Recent Advances in the Synthesis of Indanes and Indenes. *Chem. - Eur. J.* **2016**, *22*, 5056–5094.
- (70) Borie, C.; Ackermann, L.; Nechab, M. Enantioselective syntheses of indanes: From organocatalysis to C-H functionalization. *Chem. Soc. Rev.* **2016**, *45*, 1368–1386.
- (71) Gant, T. G. Using Deuterium in Drug Discovery: Leaving the Label in the Drug. *J. Med. Chem.* **2014**, *57*, 3595–3611.
- (72) Tung, R. D. Deuterium Medicinal Chemistry Comes of Age. *Future Med. Chem.* **2016**, *8*, 491–494.
- (73) Russak, E. M.; Bednarczyk, E. M. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. *Ann. Pharmacother.* **2019**, *53*, 211–216.
- (74) Krippner, G.; Reece, P. A.; Watson, K. G.; Wu, W.-Y.; Jin, B.; Tucker, S. P. Patent WO 2001019822 A1, 2001.
- (75) Pollock, J. A.; Sharma, N.; Ippagunta, S. K.; Redecke, V.; Haecker, H.; Katzenellenbogen, J. A. Triaryl Pyrazole Toll-Like Receptor Signaling Inhibitors: Structure-Activity Relationships Governing Pan- and Selective Signaling Inhibitors. *ChemMedChem* **2018**, *13*, 2208–2216.
- (76) Diana, G. D.; Cutcliffe, D.; Volkots, D. L.; Mallamo, J. P.; Bailey, T. R.; Vescio, N.; Oglesby, R. C.; Nitz, T. J.; Wetzel, J.; Giranda, V.; Pevear, D. C.; Dutko, F. J. Antipicornavirus Activity of Tetrazole Analogs Related to Disoxaril. *J. Med. Chem.* **1993**, *36*, 3240–3250.

- (77) Knight, D. W.; Xu, Q. A New Tactic for Tocopherol Synthesis Using Intramolecular Benzyne Trapping by an Alcohol. *Heterocycles* **2016**, *93*, 647–672.
- (78) Lenz, C. A.; Rychlik, M. Efficient Synthesis of (R)-Ochratoxin Alpha, the Key Precursor to the Mycotoxin Ochratoxin A. *Tetrahedron Lett.* **2013**, *54*, 883–886.
- (79) Ishiyama, H.; Ohshita, K.; Abe, T.; Nakata, H.; Kobayashi, J.. Synthesis of Eudistomin D Analogues and Its Effects on Adenosine Receptors. *Bioorg. Med. Chem.* **2008**, *16*, 3825–3830.
- (80) Tsubogo, T.; Aoyama, S.; Takeda, R.; Uchiro, H. Synthesis of 2, 2-Dialkyl Chromanes by Intramolecular Ullmann C-O Coupling Reactions toward the Total Synthesis of D- α -Tocopherol. *Chem. Pharm. Bull.* **2018**, *66*, 843–846.
- (81) Qi, C.; Qin, T.; Suzuki, D.; Porco Jr, J. A. Total Synthesis and Stereochemical Assignment of (\pm)-Sorbiterin A. *J. Am. Chem. Soc.* **2014**, *136*, 3374–3377.
- (82) Johnson, S. M.; Connelly, S.; Wilson, I. A.; Kelly, J. W. Toward Optimization of the Linker Substructure Common to Transthyretin Amyloidogenesis Inhibitors Using Biochemical and Structural Studies. *J. Med. Chem.* **2008**, *51*, 6348–6358.
- (83) Hidaka, K.; Kimura, T.; Ruben, A. J.; Uemura, T.; Kamiya, M.; Kiso, A.; Okamoto, T.; Tsuchiya, Y.; Hayashi, Y.; Freire, E.; Kiso, Y. Antimalarial Activity Enhancement in Hydroxymethylcarbonyl (HMC) Isostere-Based Dipeptidomimetics Targeting Malarial Aspartic Protease Plasmeprin. *Bioorg. Med. Chem.* **2008**, *16*, 10049–10060.
- (84) Bolli, M. H.; Velker, J.; Muller, C.; Mathys, B.; Birker, M.; Bravo, R.; Bur, D.; de Kanter, R.; Hess, P.; Kohl, C.; Lehmann, D.; Meyer, S.; Nayler, O.; Rey, M.; Scherz, M.; Steiner, B. Novel S1P1 Receptor Agonists Part 2: From Bicyclo[3.1.0]hexane-Fused Thiophenes to Isobutyl Substituted Thiophenes. *J. Med. Chem.* **2014**, *57*, 78–97.
- (85) van der Peet, P. L.; Sandanayake, S.; Jarrott, B.; Williams, S. J. Discovery of N-Aryloxypropylbenzylamines as Voltage-Gated Sodium Channel Na_v1.2-Subtype-Selective Inhibitors. *ChemMedChem* **2019**, *14*, 570–582.
- (86) Challenger, S.; Cook, A. S.; Gillmore, A. T.; Middleton, D. S.; Pryde, D. C.; Stobie, A. Patent WO 2002079143 A1, 2002.
- (87) Cai, X.; Qian, C.; Weng, Y.; Qing, Y.; Liu, B.; Lin, M.; Wang, Y. Patent CN 107383024 A, 2017.
- (88) Luo, D.; Ma, L.; Zhou, Z.; Huang, Z. Synthesis, single crystal X-ray analysis, and vibrational spectral studies of ethyl 6-bromo-5-((5-bromopyrimidin-2-yl)oxy)-2-((2,6-dimethylmorpholino)methyl)-1-methyl-1H-indole-3-carboxylate. *J. Mol. Struct.* **2019**, *1198*, 126857.
- (89) Suwa Seikosha Co. Ltd. Patent JP 60078931 A, 1985.
- (90) Gotoh, Y.; Satou, T.; Matsukuma, M.; Kanadani, C.; Furusato, Y. Patent US 20140027671 A1, 2014.
- (91) Nara, S. J.; Valgimigli, L.; Pedulli, G. F.; Pratt, D. A. Tyrosine Analogs for Probing Proton-Coupled Electron Transfer Processes in Peptides and Proteins. *J. Am. Chem. Soc.* **2010**, *132*, 863–872.
- (92) Leeson, P. D.; Emmett, J. C.; Shah, V. P.; Showell, G. A.; Novelli, R.; Prain, H. D.; Benson, M. G.; Ellis, D.; Pearce, N. J.; Underwood, A. H. Selective Thyromimetics Cardiac-Sparing Thyroid Hormone Analogs Containing 3'-Arylmethyl Substituents. *J. Med. Chem.* **1989**, *32*, 320–336.
- (93) Arnould, J.-C.; Delouvrie, B.; Ducray, R.; Lambert-Van Der Brempt, C. M. P. Patent WO 2007141473 A1, 2007.
- (94) Reetz, M. T.; de Vries, J. G. Ligand-Free Heck Reactions Using Low Pd-Loading. *Chem. Commun.* **2004**, 1559–1563.
- (95) Piber, M.; Jensen, A. E.; Rottlaender, M.; Knochel, P. New Efficient Nickel- and Palladium-Catalyzed Cross-Coupling Reactions Mediated by Tetrabutylammonium Iodide. *Org. Lett.* **1999**, *1*, 1323–1326.
- (96) Clemenceau, A.; Thesmar, P.; Gicquel, M.; Le Flohic, A.; Baudoin, O. Direct Synthesis of Cyclopropanes from gem-Dialkyl Groups through Double C-H Activation. *J. Am. Chem. Soc.* **2020**, *142*, 15355–15361.
- (97) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345.
- (98) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. Mechanistic Analysis of Azine N-Oxide Direct Arylation: Evidence for a Critical Role of Acetate in the Pd(OAc)₂ Precatalyst. *J. Org. Chem.* **2010**, *75*, 8180–8189.
- (99) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. High-Yielding Palladium-Catalyzed Intramolecular Alkane Arylation: Reaction Development and Mechanistic Studies. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571.
- (100) Kefalidis, C. E.; Baudoin, O.; Clot, E. DFT study of the mechanism of benzocyclobutene formation by palladium-catalysed C(sp³)-H activation: role of the nature of the base and the phosphine. *Dalton Trans.* **2010**, *39*, 10528–10535.
- (101) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. Synthesis of Benzocyclobutenes by Palladium-Catalyzed C-H Activation of Methyl Groups: Method and Mechanistic Study. *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166.