

Cite this: *Chem. Sci.*, 2021, 12, 8531

All publication charges for this article have been paid for by the Royal Society of Chemistry

# Pd-catalyzed cross-electrophile Coupling/C–H alkylation reaction enabled by a mediator generated *via* C(sp<sup>3</sup>)–H activation†

Zhuo Wu, Hang Jiang and Yanghui Zhang \*

Transition-metal-catalyzed cross-electrophile C(sp<sup>2</sup>)–(sp<sup>3</sup>) coupling and C–H alkylation reactions represent two efficient methods for the incorporation of an alkyl group into aromatic rings. Herein, we report a Pd-catalyzed cascade cross-electrophile coupling and C–H alkylation reaction of 2-iodo-alkoxyarenes with alkyl chlorides. Methoxy and benzyloxy groups, which are ubiquitous functional groups and common protecting groups, were utilized as crucial mediators *via* primary or secondary C(sp<sup>3</sup>)–H activation. The reaction provides an innovative and convenient access for the synthesis of alkylated phenol derivatives, which are widely found in bioactive compounds and organic functional materials.

Received 26th March 2021

Accepted 19th May 2021

DOI: 10.1039/d1sc01731d

rsc.li/chemical-science

## Introduction

The introduction of alkyl moieties into aromatic rings is an essential transformation in organic synthesis. Nowadays, transition-metal-catalyzed cross-coupling reactions between an electrophile and a nucleophile, generally an organic (pseudo) halide and an organometallic reagent, have been a powerful tool for this transformation.<sup>1</sup> However, organometallic reagents used in these reactions need presynthesis and careful handling, which limits their applications.

The coupling between two electrophiles avoids the use of organometallic reagents and thus becomes a promising alternative strategy for C(sp<sup>2</sup>)–C(sp<sup>3</sup>) bond formation.<sup>2</sup> However, there are several obstacles for developing cross-electrophile coupling reactions. Firstly, because of electrophilic properties of both halides, achieving the selective formation of cross-products over two potential symmetric dimers is challenging. Secondly, unlike the traditional coupling between an electrophile and a nucleophile, the catalyst loses electrons in total after coupling two electrophiles, and thus appropriate reductants are required to regenerate the catalyst. Moreover, the coupling becomes even more challenging, considering the great tendency of  $\beta$ -H elimination of alkyl-metal species. Despite these difficulties, in the past few decades, the cross-electrophile C(sp<sup>2</sup>)–C(sp<sup>3</sup>) coupling reactions have been successfully developed with Ni<sup>3</sup> or Co<sup>4</sup> catalysts (Fig. 1a). These reactions proceeded through an alkyl radical mechanism. Typically, alkyl iodides or bromides

were reactive agents, whereas alkyl chlorides, which are more inexpensive and less toxic, were usually unreactive.<sup>3f</sup> A stoichiometric amount of metals, such as Zn or Mn, were frequently employed as reductants in these reactions, which produced a large amount of metal waste.<sup>5</sup>

The alkylation of arenes *via* C–H bond activation represents an even more efficient strategy for the incorporation of an aliphatic moiety. In recent years, great progress has been made in transition-metal-catalyzed alkylation reactions of arenes with alkyl halides, alkenes, or alkylmetal reagents.<sup>6</sup> In most cases, an *ortho*-directing group was required, and the majority of the directing groups were derived from carbonyl,<sup>7</sup> carboxyl,<sup>8</sup> amido,<sup>9</sup> or *N*-heteroaryl<sup>10</sup> groups. By contrast, the hydroxyl

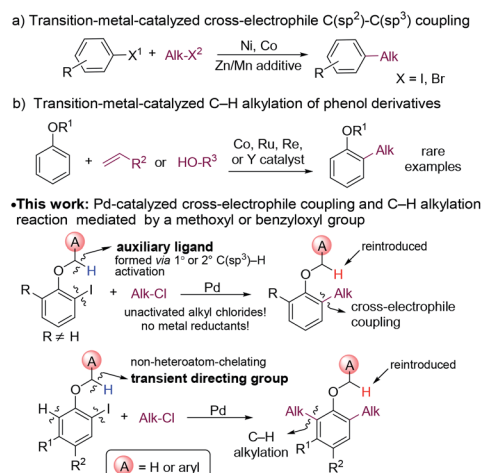


Fig. 1 Cross-electrophile C(sp<sup>2</sup>)–C(sp<sup>3</sup>) coupling and C–H alkylation of phenol derivatives.

School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, 1239 Siping Road, Shanghai 200092, China. E-mail: zhangyanghui@tongji.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc01731d

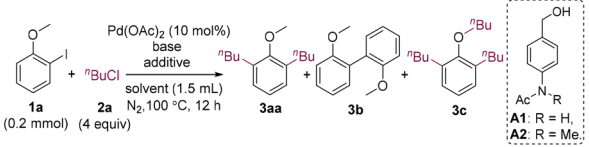
group of phenols and their derivatives was much less frequently utilized as a directing group for C–H alkylation. In the current C–H alkylation reactions of phenol derivatives, transition metal catalysts are primarily limited to Co, Ru, Re and Y (Fig. 1b).<sup>11</sup> Furthermore, for directing groups in transition metal-catalyzed C–H activation, almost all of them rely on the coordination of catalysts to heteroatoms they contain to assist C–H cleavage. It is desirable to develop new directing strategies for C–H functionalization.

Herein, we report an unusual Pd-catalyzed cascade cross-electrophile coupling and C–H alkylation reaction between *ortho*-iodophenol derivatives and alkyl chlorides by utilizing a methoxy or benzyloxy group as a mediator. Pd catalysts are much less frequently applied in cross-electrophile C(sp<sup>2</sup>)–C(sp<sup>3</sup>) coupling than Ni catalysts,<sup>12</sup> because they tend not to undergo a radical mechanism,<sup>13</sup> which sets the cross-selectivity difficult to achieve. In this reaction, C(sp<sup>3</sup>)–H bond activation of the *ortho*-methoxy and benzyloxy groups plays a crucial role for the cross-selectivity.<sup>14</sup> For substrates with the positions *ortho* to the alkoxy group unsubstituted, C–H alkylation was initiated. The methoxy and benzyloxy groups served as directing groups herein. The methoxy and benzyloxy groups are different from traditional directing groups relying on the coordination of heteroatoms and represent a new class of directing groups for transition-metal-catalyzed C–H activation.

## Results and discussion

We commenced our research by investigating the reaction of 2-iodoanisole (**1a**) with 1-chlorobutane (**2a**). The 2-iodoanisole substrates can be readily synthesized *via* iodination of anisoles or phenols. Cheap and low-toxicity alkyl chlorides are also ideal alkylating reagents. It should be mentioned that 2-iodoanisoles could undergo homocoupling using a methoxy group as the directing group.<sup>15</sup> The homocoupling should be overcome to develop reactions with external reagents. Surprisingly, the expected monoalkylated product was not formed, whereas dialkylated product **3aa** and homocoupling product **3b** were obtained in low yields in the presence of K<sub>3</sub>PO<sub>4</sub> (Table 1, entry 1).<sup>16</sup> When K<sub>2</sub>CO<sub>3</sub> was used as a base, the homocoupling product was suppressed (entry 2). The addition of *n*-Bu<sub>4</sub>NBr and benzyl alcohol improved the yield of **3aa** greatly, and the yield was further increased to 73% when NMP was used as the solvent (entries 3 and 4). Tetraalkylammonium halides can promote the coupling reactions of aryl halides by stabilizing nano-sized palladium colloids.<sup>17</sup> The reaction remained almost unaffected when carried out at 85 °C (entry 5). Although benzyl alcohol was beneficial to the reaction, its oxidized and *O*-alkylated products caused difficulty for the isolation of the desired product. Thus, a range of alcohols with high polarity were surveyed, and **A2** was found to be an effective reductant (entries 6 and 7). When *n*-Bu<sub>4</sub>NCl was used instead of *n*-Bu<sub>4</sub>NBr, the yield decreased to 27% (entry 8). 1-Bromo or 1-iodobutane was also a suitable alkylating agent (entries 9 and 10). However, the yields were much lower. It should be mentioned that the addition of an alcohol is necessary for the reaction. In the absence of

Table 1 Survey of reaction conditions for coupling of **1a** with 1-chlorobutane



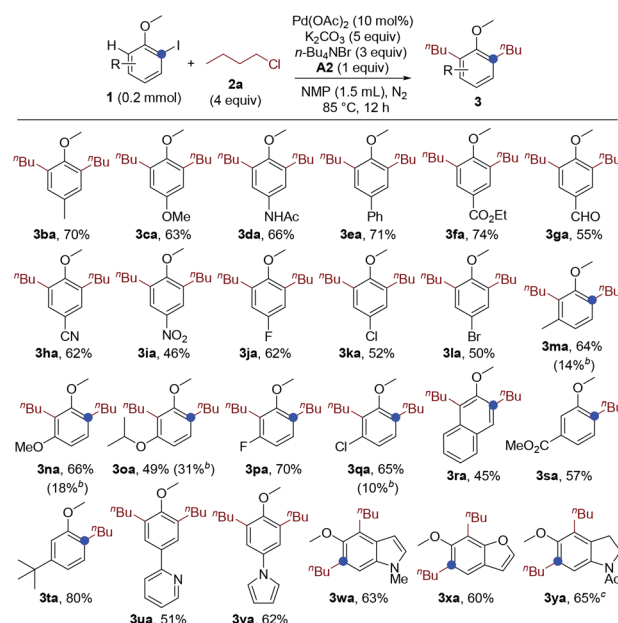
Entry	Base (equiv.)	Additive (equiv.)	Solvent	<b>3aa</b> <sup>a</sup> (%)	<b>3b</b> <sup>a</sup> (%)
1	K <sub>3</sub> PO <sub>4</sub> (3)	—	DMF	9	10
2	K <sub>2</sub> CO <sub>3</sub> (3)	—	DMF	7	0
3	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), BnOH (1)	DMF	64	0
4	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), BnOH (1)	NMP	73	0
5 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), BnOH (1)	NMP	71	0
6 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), <b>A1</b> (1)	NMP	66	0
7 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), <b>A2</b> (1)	NMP	72 (68 <sup>b</sup> )	0
8 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NCl (3), <b>A2</b> (1)	NMP	27	0
9 <sup>c,d</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), <b>A2</b> (1)	NMP	45	0
10 <sup>c,e</sup>	K <sub>2</sub> CO <sub>3</sub> (5)	<i>n</i> -Bu <sub>4</sub> NBr (3), <b>A2</b> (1)	NMP	14	0

<sup>a</sup> The yields were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using CHCl<sub>2</sub>CHCl<sub>2</sub> as the internal standard. <sup>b</sup> Isolated yield.

<sup>c</sup> 85 °C. <sup>d</sup> *n*-BuBr. <sup>e</sup> *n*-BuI.

an alcohol, the repeatability of the reaction became low, and an undesired trialkylated product **3c** was formed in 5–10% yield.

Next, we studied the substrate scope of the dialkylation reaction. The *ortho*-iodoanisole scope was first probed. The functional group compatibility was investigated by examining the reactions of *ortho*-iodoanisoles bearing various substituents *para* to the methoxy group. The reaction has very high functional group compatibility. A wide range of functionalities,



Scheme 1 *Ortho*-iodoanisole scope. <sup>a</sup>Isolated yields. <sup>b</sup>Monoalkylated product. <sup>c</sup>100 °C.



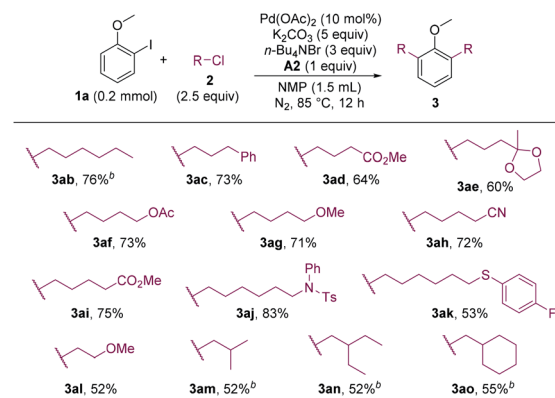
including electron-donating and -withdrawing ones, were compatible (Scheme 1, **3ba–3ia**), and halo groups were well-tolerated (**3ja–3la**). The performance of *meta*-substituted *ortho*-iodoanisoles was also investigated. Notably, even in the presence of a *meta*-substituent, *ortho*-iodoanisoles were dialkylated by overcoming the steric hindrance imposed by the *meta*-substituents, forming tetrasubstituted arenes (**3ma–3ra**). However, for the substrates bearing a *meta*-ester or *-tert*-butyl group, only monoalkylated products were formed due to the steric hindrance (**3sa** and **3ta**). Heteroaryl groups including pyridyl and pyrrolyl groups were compatible (**3ua** and **3va**), and heteroarenes and its derivative could also undergo the dialkylation reaction (**3wa–3ya**).

The first step of the dialkylation reaction should be the alkylation of aryl iodides, which represents a new Pd-catalyzed cross-electrophile coupling. Therefore, we sought to study the reactions by using *ortho*-iodoanisoles without an *ortho*-hydrogen. As shown in Scheme 2, a range of *ortho*-substituted *ortho*-iodoanisoles cross-coupled with *n*-butyl chloride to form alkylated anisole products (**5aa–5ia**). Intriguingly, for 2-iodo-1-methoxynaphthalene, the dehydrogenative coupling reaction occurred after the alkylation to form cyclized product **5ja**.

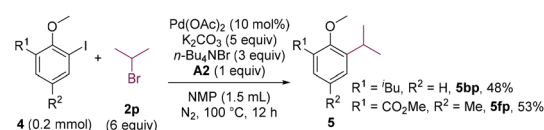
The alkyl chloride scope was then probed. A wide array of alkyl chlorides containing various functionalities and with different alkyl-chain lengths were effective alkylating reagents, and a range of dialkylated anisoles were formed (Scheme 3, **3ab–3al**). Sterically hindered alkyl chlorides could also couple with **1a**, albeit in lower yields (**3am–3ao**).

The cross-coupling involving secondary alkyl halides is usually challenging.<sup>18</sup> The reactivity of secondary alkyl halides in the coupling reaction were examined. Whereas 2-chloropropane failed to alkylate **4b**, 2-bromopropane could couple with **4b** in a moderate yield (Scheme 4, **5bp**). The substrate bearing an *ortho*-ester group (**4f**) was also compatible.

The methoxy group of *ortho*-iodoanisoles acts as a mediator to enable the cross-electrophile coupling and C–H alkylation reaction. We envisioned that other alkoxy groups could also facilitate such a cascade reaction. Gratefully, the benzyloxy group was found to be an effective mediator for the dialkylation reaction (Scheme 5, **7aa**).<sup>19</sup> Substituted benzyloxy groups also



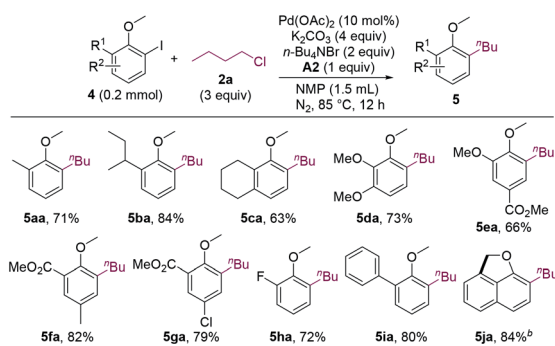
Scheme 3 Alkyl chlorides scope. <sup>a</sup>Isolated yields. <sup>b</sup>4 equiv. of alkyl chloride.



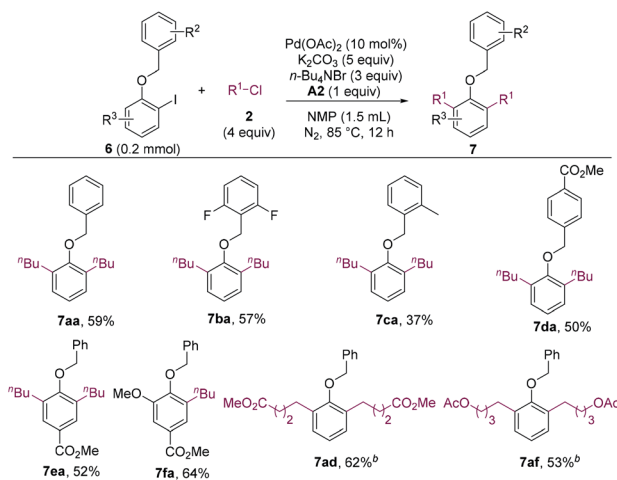
Scheme 4 Coupling of 2-iodoanisoles with 2-bromopropane.

enabled the alkylation (**7ba–7da**), and functionalized iodo-benzenes and alkyl chlorides could undergo the cascade reaction smoothly (**7ea**, **7fa**, **7ad**, and **7af**). It should be noted that benzyl groups could be cleaved readily, which allows for the further manipulation of the resulted phenol products.

The dialkylation reaction provides a straightforward method for the synthesis of *ortho*-dialkylated phenol derivatives. The current synthetic methods for *ortho*-dialkylated phenols primarily include: (1) Claisen rearrangement of phenoxy allyl ether;<sup>20</sup> (2) Coupling of 2,6-dihalophenol derivatives with alkyl organometallic reagents.<sup>21</sup> The first method requires multiple-step synthesis, and the Claisen rearrangement was usually



Scheme 2 *Ortho*-Substituted 2-iodoanisoles scope. <sup>a</sup>Isolated yields. <sup>b</sup>10 mol% of Pd(OAc)<sub>2</sub>, 5 equiv. of K<sub>2</sub>CO<sub>3</sub>, 3 equiv. of KOAc, 2 equiv. of *n*-Bu<sub>4</sub>NBr, and 4 equiv. of *n*-BuCl were used. A2 was not added.



Scheme 5 Coupling reaction utilizing a benzyloxy group as a mediator. <sup>a</sup> Isolated yields. <sup>b</sup> 2.5 equiv. of alkyl chloride.

carried out under harsh conditions. The second method employs alkylmetallic reagents, and the use of dihalogenated substrates is not atom-economic. Our dialkylation reaction features readily available reagents, comparatively mild conditions, and high atom-economy.

It should be noted that dialkylated phenol derivatives are essential structural motifs widely found in bioactive molecules.<sup>22</sup> Furthermore, they are also key intermediates in the synthesis of biologically active compounds and organic functional materials. For example, compound **3aq**, which was synthesized by the dialkylation of **1a** with **2q** under the standard conditions, could be hydrolyzed to **3aq-A** (Fig. 2a). **3aq-A** was the synthetic intermediate for a novel H-shaped chromophore.<sup>20a</sup> And **7er-A**, which could be readily obtained from compound **7er**, was the intermediate in the synthesis of a liver X receptor b-selective agonist.<sup>20b</sup> For the original method, **7er-A** was synthesized in eight steps under harsh conditions. The monoalkylated anisoles were also intermediates in the synthesis of bioactive compounds. For instance, compound **5ea** was the synthetic intermediate for an antibacterial agent.<sup>23</sup> Furthermore, monoalkylated product **5di** could afford **5di-A**, which was used to synthesize an anti-cancer

agent.<sup>24</sup> It should be noted that all the 2-iodoanisole substrates in our alkylation reactions were prepared in one or two steps by using low-cost reagents.

The dialkylation reaction is also applicable to the dialkylation of complex molecules. For example, the estradiol- and tyrosine-derived iodides could be dialkylated under the standard conditions (Fig. 2b). It should be mentioned that the product **9aa** was slightly racemized, which could be caused by the base and the high temperature. Furthermore, the dialkylation reaction was scalable, and the methyl group of dialkylated anisoles could be removed (Fig. 2c). The resulting hydroxy group allows for further functionalization.

Preliminary mechanistic studies were conducted (Fig. 3). When 3-iodoanisole **10a** (or 4-iodoanisole **10b**) and 1-chlorobutane were subjected to the standard conditions, the alkylated products were not detected, and only the homocoupling product **11a** (or **11b**) was obtained (Fig. 3a). The outcomes indicated that the presence of the *ortho*-methoxy group is crucial for the alkylation reaction. Deuterium-labeling experiments were also carried out (Fig. 3b). When the deuterated analogue **1a-D<sub>3</sub>** was subjected to the standard conditions, **3aa-D<sub>2</sub>** was obtained as the major product. The proportion of **3aa-D<sub>2</sub>** was further enhanced to 95% when 20 equivalents of water was added. Moreover, when the alkylation reaction of **1a** was carried out using CD<sub>3</sub>OD as the reductant, deuteration occurred at the methoxy group in 40% yield. These experiments implied that the activation of the methoxyl C(sp<sup>3</sup>)-H bond occurred and the alcohol was one of the major reductants.<sup>25</sup> Intermolecular competition experiments between **1a** and **1a-D<sub>3</sub>** were conducted, and the KIE value was 1.4 : 1 (Fig. 3c). The kinetic isotope effect supported the involvement of the methoxy group in the reaction *via* C-H bond activation, which might be involved in the rate-determining step.

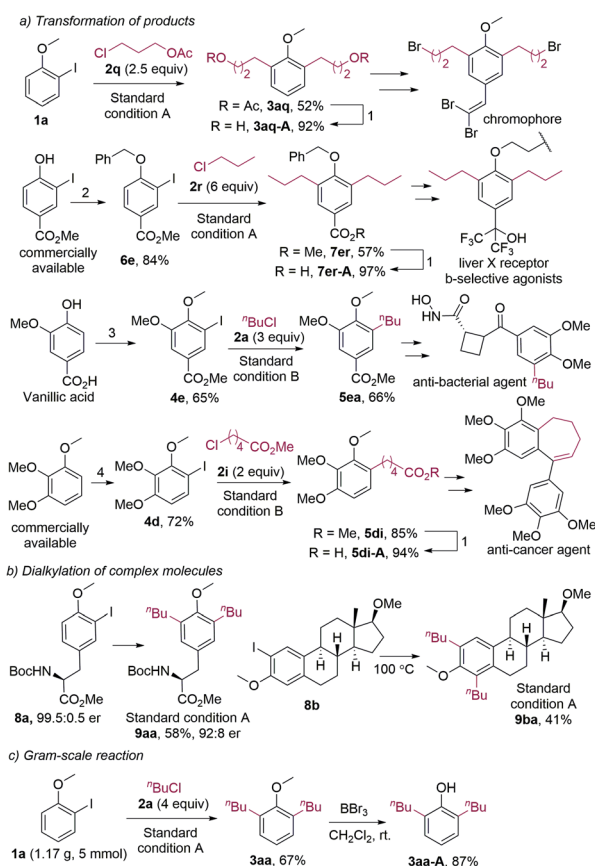


Fig. 2 Practical applications. Standard condition A: 10 mol% of Pd(OAc)<sub>2</sub>, 5 equiv. of K<sub>2</sub>CO<sub>3</sub>, 3 equiv. of *n*-Bu<sub>4</sub>NBr, 1 equiv. of A2, NMP, 85 °C, 12 h; standard condition B: 10 mol% of Pd(OAc)<sub>2</sub>, 4 equiv. of K<sub>2</sub>CO<sub>3</sub>, 2 equiv. of *n*-Bu<sub>4</sub>NBr, 1 equiv. of A2, NMP, 85 °C, 12 h. Other conditions: (1) NaOH, MeOH/H<sub>2</sub>O, 60 °C; (2) BnCl, K<sub>2</sub>CO<sub>3</sub>, DMF, rt; (3) a. NaI, NaOH, NaClO aq., MeOH, 0 °C; b. MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, rt; (4) CF<sub>3</sub>CO<sub>2</sub>H, NIS, MeCN, rt.

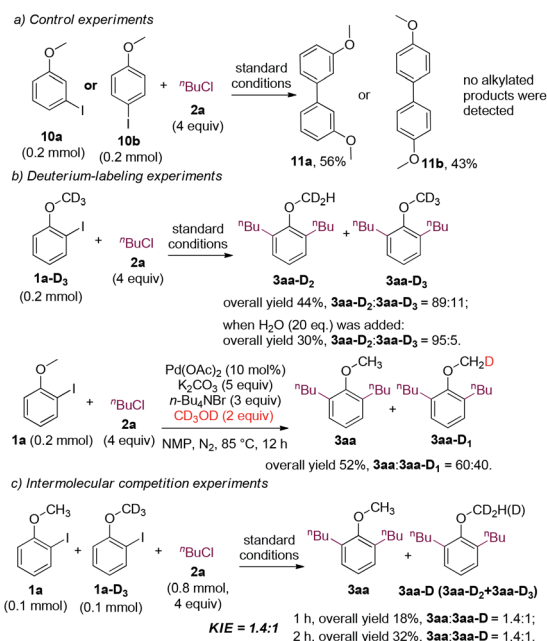


Fig. 3 Preliminary mechanistic studies.



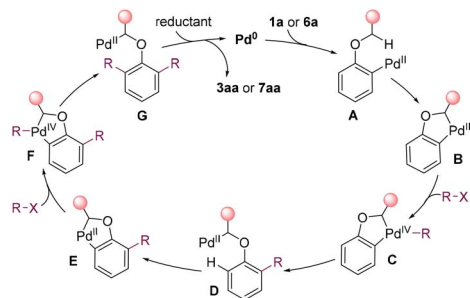


Fig. 4 Plausible mechanism.

On the basis of the mechanistic studies and the previous reports,<sup>14,15,26</sup> a possible mechanism was proposed in Fig. 4 for the dialkylation reaction. The substrate undergoes oxidative addition and C(sp<sup>3</sup>)-H activation to afford palladacycle **B**. Palladacycle **B** has high reactivity towards alkyl halides, and undergoes the oxidative addition to generate Pd(IV) species **C**.<sup>27</sup> The reductive elimination of **C** gives **D**. Then, the aryl C-H is cleaved, affording a second palladacycle **E**. **E** undergoes the same process as that for the formation of **D** to introduce a second alkyl group. Eventually, alkylpalladium **G** is reduced, yielding the product and releasing Pd<sup>0</sup>.

## Conclusions

In conclusion, we have developed cascade Pd-catalyzed cross-electrophile coupling and C-H alkylation reaction of 2-iodo-alkoxylarenes with alkyl chlorides. The *ortho*-methoxy or benzyloxy group acted as a mediator *via* primary or secondary C(sp<sup>3</sup>)-H activation. It is very rare and intriguing that the cross-electrophile coupling is achieved by the assistance of an alkoxy group, which can be readily removed. The methoxy and benzyloxy groups also served as non-heteroatom-chelating directing groups for C-H alkylation reaction. The reaction provides an efficient and innovative method for the synthesis of alkylated, especially 2,6-dialkylated, phenol derivatives, which are ubiquitous in bioactive compounds and organic functional materials.

## Author contributions

Z. Wu and H. Jiang performed the experiments and analysed the data. Y. Zhang conceived the project and analysed experimental data. The manuscript was written by Y. Zhang and Z. Wu.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The work was supported by the National Natural Science Foundation of China (No. 21971196).

## Notes and references

- (a) G. Manolikakes, Coupling Reactions Between sp<sup>3</sup> and sp<sup>2</sup> Carbon Centers, in *Comprehensive Organic Synthesis*, ed. P. Knochel and G. Molander, Elsevier, Oxford, 2nd edn, vol. 3, 2014, pp. 392–464; (b) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417–1492; (c) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *Chem. Rev.*, 2015, **115**, 9587–9652.
- (a) J. Liu, Y. Ye, J. L. Sessler and H. Gong, *Acc. Chem. Res.*, 2020, **53**, 1833–1845; (b) D. J. Weix, *Acc. Chem. Res.*, 2015, **48**, 1767–1775; (c) C. E. I. Knappke, S. Grupe, D. Gaertner, M. Corpet, C. Gosmini and A. Jacobi von Wangelin, *Chem.-Eur. J.*, 2014, **20**, 6828–6842; (d) W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin and H. Gong, *Chem. Soc. Rev.*, 2021, **50**, 4162–4184.
- (a) M. Durandetti, C. Gosmini and J. Perichon, *Tetrahedron*, 2007, **63**, 1146–1153; (b) D. A. Everson, R. Shrestha and D. J. Weix, *J. Am. Chem. Soc.*, 2010, **132**, 920–921; (c) S. Wang, Q. Qian and H. Gong, *Org. Lett.*, 2012, **14**, 3352–3355; (d) X. Wang, S. Wang, W. Xue and H. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 11562–11565; (e) J. Sheng, H.-Q. Ni, H.-R. Zhang, K.-F. Zhang, Y.-N. Wang and X.-S. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 7634–7639; (f) S. Kim, M. J. Goldfogel, M. M. Gilbert and D. J. Weix, *J. Am. Chem. Soc.*, 2020, **142**, 9902–9907.
- (a) P. Gomes, C. Gosmini and J. Perichon, *Org. Lett.*, 2003, **5**, 1043–1045; (b) M. Amatore and C. Gosmini, *Chem.-Eur. J.*, 2010, **16**, 5848–5852; (c) S. Pal, S. Chowdhury, E. Rozwadowski, A. Auffrant and C. Gosmini, *Adv. Synth. Catal.*, 2016, **358**, 2431–2435.
- The use of organic reductants, photoredox catalysts, and electrochemical methods have been alternative strategies to avoid the usage of metallic reductants: (a) L. L. Anka-Lufford, K. M. M. Huihui, N. J. Gower, L. K. G. Ackerman and D. J. Weix, *Chem.-Eur. J.*, 2016, **22**, 11564–11567; (b) A. Garcia-Dominguez, Z. Li and C. Nevado, *J. Am. Chem. Soc.*, 2017, **139**, 6835–6838; (c) Z. Duan, W. Li and A. Lei, *Org. Lett.*, 2016, **18**, 4012–4015; (d) P. Zhang, C. Le and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2016, **138**, 8084–8087; (e) K.-J. Jiao, D. Liu, H.-X. Ma, H. Qiu, P. Fang and T.-S. Mei, *Angew. Chem., Int. Ed.*, 2020, **59**, 6520–6524.
- For reviews, see: (a) G. Evans and C. Theunissen, *Angew. Chem., Int. Ed.*, 2019, **58**, 7202–7236; (b) G. Evans and C. Theunissen, *Angew. Chem., Int. Ed.*, 2019, **58**, 7558–7598; (c) L. Ackermann, *Chem. Commun.*, 2010, **46**, 4866–4877; (d) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi and J.-A. Ma, *Chem. Soc. Rev.*, 2019, **48**, 4921–4942.
- For selected examples, see: (a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529–531; (b) L. Ackermann, N. Hofmann and R. Vicente, *Org. Lett.*, 2011, **13**, 1875–1877; (c) K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, 2013, **135**, 9279–9282; (d) N. Kimura, T. Kochi and F. Kakiuchi, *J. Am. Chem. Soc.*, 2017, **139**, 14849–14852.
- For selected examples, see: (a) P. S. Thuy-Boun, G. Villa, D. Dang, P. Richardson, S. Su and J.-Q. Yu, *J. Am. Chem.*



- Soc.*, 2013, **135**, 17508–17513; (b) H. Wang, N. Schröder and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5386–5389; (c) R.-Y. Zhu, J. He, X.-C. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 13194–13197; (d) B. M. Monks, E. R. Fruchey and S. P. Cook, *Angew. Chem., Int. Ed.*, 2014, **53**, 11065–11069.
- 9 For selected examples, see: (a) S. J. Tremont and H. U. Rahman, *J. Am. Chem. Soc.*, 1984, **106**, 5759–5760; (b) S. R. Neufeldt, C. K. Seigerman and M. S. Sanford, *Org. Lett.*, 2013, **15**, 2302–2305; (c) Z. Ruan, S. Lackner and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 3153–3157; (d) X. Zhou, J. Xia, G. Zheng, L. Kong and X. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 6681–6685; (e) Z. Shen, H. Huang, C. Zhu, S. Warratz and L. Ackermann, *Org. Lett.*, 2019, **21**, 571–574; (f) X. Wu, Y. Zhao and H. Ge, *J. Am. Chem. Soc.*, 2014, **136**, 1789–1792.
- 10 For selected examples, see: (a) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109–1113; (b) J. M. Wiest, A. Pothig and T. Bach, *Org. Lett.*, 2016, **18**, 852–855; (c) X. Wang, X. Ji, C. Shao, Y. Zhang and Y. Zhang, *Org. Biomol. Chem.*, 2017, **15**, 5616–5624; (d) K. Korvorapun, M. Moselage, J. Struwe, T. Rogge, A. M. Messinis and L. Ackermann, *Angew. Chem., Int. Ed.*, 2020, **59**, 18795–18803.
- 11 For a review on phenol and its derivative-directed C–H functionalization, see: (a) Z. Huang and J.-P. Lumb, *ACS Catal.*, 2019, **9**, 521–555; For phenol and derivative-directed C–H alkylation, see: (b) R. Dorta and A. Togni, *Chem. Commun.*, 2003, 760–761; (c) Y. Kuninobu, T. Matsuki and K. Takai, *J. Am. Chem. Soc.*, 2009, **131**, 9914–9915; (d) J. Oyamada and Z. Hou, *Angew. Chem., Int. Ed.*, 2012, **51**, 12828–12832; (e) D.-H. Lee, K.-H. Kwon and C. S. Yi, *J. Am. Chem. Soc.*, 2012, **134**, 7325–7328; (f) S. S. Bera and M. S. Maji, *Org. Lett.*, 2020, **22**, 2615–2620.
- 12 Although Pd-catalyzed cross-coupling between aryl and alkyl halides has been reported, the actual reactive species were *in situ* formed alkylzincs. (a) A. Krasovskiy, C. Duplais and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2009, **131**, 15592–15593; (b) C. Duplais, A. Krasovskiy and B. H. Lipshutz, *Organometallics*, 2011, **30**, 6090–6097.
- 13 Single electron transfer (SET) processes involving Pd(I) and Pd(III) intermediates are not common. For reviews, see: (a) Q. Liu, X. Dong, J. Li, J. Xiao, Y. Dong and H. Liu, *ACS Catal.*, 2015, **5**, 6111–6137; (b) P. Chuentragool, D. Kurandina and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2019, **58**, 11586–11598.
- 14 Although the alkylation of palladacycles formed *via* C–H activation with alkyl halides has been reported, the works involve C(sp<sup>2</sup>), C(sp<sup>2</sup>)- and *tert*-butyl-derived C(sp<sup>3</sup>), C(sp<sup>2</sup>)-palladacycles: (a) D. Chen, G. Shi, H. Jiang, Y. Zhang and Y. Zhang, *Org. Lett.*, 2016, **18**, 2130–2133; (b) Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 12288–12291.
- 15 G. Dyker, *Angew. Chem., Int. Ed.*, 1992, **31**, 1023–1025.
- 16 For the dimethylation of 2-iodoanisoles reported very recently, see: Z. Wu, F. Wei, B. Wan and Y. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 4524–4530.
- 17 M. T. Reetz and J. G. de Vries, *Chem. Commun.*, 2004, 1559–1563.
- 18 For a review, see: (a) Z. Qureshi, C. Toker and M. Lautens, *Synthesis*, 2017, **49**, 1–16. For selected Pd-catalyzed C–H alkylation with secondary alkyl halides, see: (b) Q. Wang, S. An, Z. Deng, W. Zhu, Z. Huang, G. He and G. Chen, *Nat. Catal.*, 2019, **2**, 793–800; (c) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.*, 2015, **137**, 531–539; (d) Y.-C. Luo, C. Yang, S.-Q. Qiu, Q.-J. Liang, Y.-H. Xu and T.-P. Loh, *ACS Catal.*, 2019, **9**, 4271–4276.
- 19 (a) D. Dailler, R. Rocaboy and O. Baudoin, *Angew. Chem., Int. Ed.*, 2017, **56**, 7218–7222; (b) J. Pedroni, M. Boghi, T. Saget and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 9064–9067; (c) D. Katayev, M. Nakanishi, T. Bürgi and E. P. Kündig, *Chem. Sci.*, 2012, **3**, 1422–1425.
- 20 (a) J.-P. Shi, D.-L. Wu, Y. Ding, D.-H. Wu, H.-W. Hu and G.-Y. Lu, *Tetrahedron*, 2012, **68**, 2770–2777; (b) M. Koura, T. Matsuda, A. Okuda, Y. Watanabe, Y. Yamaguchi, S. Kurobuchi, Y. Matsumoto and K. Shibuya, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2668–2674.
- 21 A. V. Predeus, V. Gopalsamuthiram, R. J. Staples and W. D. Wulff, *Angew. Chem., Int. Ed.*, 2013, **52**, 911–915.
- 22 (a) K. J. Lafferty and J. A. Panetta, EP 500337 A1, 1992; (b) D. S. Dhanoa, K. J. Fitch, D. F. Veber, T. F. Walsh and D. L. Williams Jr, GB 2276383 A, 1994; (c) M. M. Butler, WO 2004094370 A2, 2004; (d) G. Q. Shi, J. F. Dropinski, B. M. McKeever, S. Xu, J. W. Becker, J. P. Berger, K. L. MacNaul, A. Elbrecht, G. Zhou, T. W. Doebber, P. Wang, Y.-S. Chao, M. Forrest, J. V. Heck, D. E. Moller and A. B. Jones, *J. Med. Chem.*, 2005, **48**, 4457–4468.
- 23 B. G. Raju, H. Odowd, H. Gao, D. V. Patel and J. Trias, WO 2004007444 A2, 2004.
- 24 R. P. Tanpure, C. S. George, T. E. Strecker, L. Devkota, J. K. Tidmore, C.-M. Lin, C. A. Herdman, M. T. MacDonough, M. Sriram, D. J. Chaplin, M. L. Trawick and K. G. Pinney, *Bioorg. Med. Chem.*, 2013, **21**, 8019–8032.
- 25 An example where alkyl halide was used as a source of reductant or hydrogen transfer reagent has been reported: A. Martins and M. Lautens, *Org. Lett.*, 2008, **10**, 5095–5097.
- 26 D. J. Cárdenas, C. Mateo and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 1995, **33**, 2445–2447.
- 27 The palladacycle intermediates in Catellani reaction also show great reactivity towards alkyl halides. For a review, see: N. D. Ca', M. Fontana, E. Motti and M. Catellani, *Acc. Chem. Res.*, 2016, **49**, 1389–1400.

