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

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Transition-metal-catalyzed cross-electrophile C(sp<sup>2</sup>)–C(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-iodoalkoxylarenes 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.

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. 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>3</sup>)–C(sp<sup>3</sup>) bond formation. 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 β-H elimination of alkyl-metal species. Despite these difficulties, in the past few decades, the cross-electrophile C(sp<sup>3</sup>)–C(sp<sup>3</sup>) coupling reactions have been successfully developed with Ni<sup>2+</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. 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.

The alkylation of arenes via C–H bond activation represents an even more efficient strategy for the incorporation of an aliphatic moieties. In recent years, great progress has been made in transition-metal-catalyzed alkylation reactions of arenes with alkyl halides, alkenes, or alkylmetal reagents. In most cases, an ortho-directing group was required, and the majority of the directing groups were derived from carbonyl, carboxyl, amido, or N-heteroaryl groups. By contrast, the hydroxyl
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). 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(sp2)–H alkylation reactions. Pd catalysts are more selective than Ni catalysts,13 because they tend not to undergo a radical mechanism,13 which sets the cross-selectivity difficult to achieve. In this reaction, C(sp2)–H bond activation of the ortho-methoxy and benzyloxy groups plays a crucial role for the cross-selectivity.14 For substrates with the positions ortho to the alkoxyl group unsubstituted, C–H alkylation was initiated. The methoxy and benzyloxy groups served as directing groups and represent a new class of directing groups for transition-metal-catalyzed C–H functionalization.

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 iodonation of anisoles or phenols. Cheap and low-toxicity alkyl chlorides are also ideal alkylation reagents. It should be mentioned that 2-iodoanisoles could undergo homocoupling using a methoxy group as the directing group.15 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 K3PO4 (Table 1, entry 1).16 When K2CO3 was used as a base, the homocoupling product was suppressed (entry 2). The addition of n-Bu4NBr 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.17 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-Bu4NCl was used instead of n-Bu4NBr, the yield decreased to 27% (entry 8). 1-Bromo or 1-iodobutane was also a suitable alkylation 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 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,
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 dialkylated 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 alkylation 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. The reactivity of secondary alkyl halides in the coupling reaction was 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). Substituted benzyl groups also 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; (2) Coupling of 2,6-dihalophenol derivatives with alkyl organometallic reagents. The first method requires multistep synthesis, and the Claisen rearrangement was usually
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. 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. 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. 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. Furthermore, monoalkylated product 5di could afford 5di-A, which was used to synthesize an anti-cancer agent. 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 alkylation 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. Deuteration-labeling experiments were also carried out (Fig. 3b). When the deuterated analogue 1a-D3 was subjected to the standard conditions, 3aa-D2 was obtained as the major product. The proportion of 3aa-D2 was further enhanced to 95% when 20 equivalents of water was added. Moreover, when the alkylation reaction of 1a was carried out using CD3OD as the reductant, deuteration occurred at the methoxy group in 40% yield. These experiments implied that the activation of the methoxyl C(sp3)–H bond occurred and the alcohol was one of the major reductants. Intermolecular competition experiments between 1a and 1a-D3 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)2, 5 equiv. of K2CO3, 3 equiv. of n-Bu4NBr, 1 equiv. of A2, NMP, 85 °C, 12 h; standard condition B: 10 mol% of Pd(OAc)2, 4 equiv. of K2CO3, 2 equiv. of n-Bu4NBr, 1 equiv. of A2, NMP, 85 °C, 12 h. Other conditions: (1) NaOH, MeOH/H2O, 60 °C; (2) BnCl, K2CO3, DMF, rt; (3) a. NaI, NaOH, NaClO aq., MeOH, 0 °C; b. MeI, K2CO3, DMF, rt; (4) CF3CO2H, NIS, MeCN, rt.

Fig. 3 Preliminary mechanistic studies.
On the basis of the mechanistic studies and the previous reports, a possible mechanism was proposed in Fig. 4 for the dialkylation reaction. The substrate undergoes oxidative addition and C(sp^3)-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. 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^0.

Conclusions

In conclusion, we have developed cascade Pd-catalyzed cross-electrophile coupling and C-H alkylation reaction of 2-iodoalkylarenes with alkyl chlorides. The ortho-methoxy or benzyloxy group also served as non-heteroatom-chelating directing groups for C-H alkylation groups, 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.

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