Ortho-C–H Methoxylation of Aryl Halides Enabled by a Polarity Reversed N–O Reagent

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Oxygen-substituted arenes not only commonly exist in biologically important molecules, but also serve as a versatile handle to install other functional groups. However, to date it remains challenging to install oxygen groups directly and site-selectively to common aromatic compounds, especially when additional arene functionalization is simultaneously required. Current arene C−H oxidation strategies generally require directing groups to control site-selectivity and/or use strong oxidants, whereas other approaches need precisely pre-functionalized substrates. While the palladium/norbornene (Pd/NBE) cooperative catalysis is promising for site-specific arene vicinal difunctionalization through simultaneous reactions with an electrophile and a nucleophile, respectively, at the ortho and ipso positions, the electrophile scope has been limited to species based on relatively "soft" elements, such as carbon, nitrogen, and sulfur. To shift the Pd/NBE-catalysis paradigm, here we report the development of an ortho oxygenation reaction with readily available aryl halides to rapidly deliver diverse methyl aryl ethers. The coupling of the "hard" oxygen-electrophile is enabled by a stable, polarity reversed, conformationally pre-distorted N−O reagent and facilitated by a C7-bromo-substituted NBE mediator. Mechanistic studies reveal a unique S_N2-type pathway between the N−O reagent as the oxygen electrophile and an electron-rich Pd(II) nucleophile. This new C−H oxygenation reaction allows streamlined synthesis of complex bioactive compounds containing methyl aryl ethers and provides an efficient modular approach to access underrepresented benzenoid substitution patterns that are challenging to prepare otherwise.

Aryl ethers, especially methyl aryl ethers, have been an important class of compounds in organic chemistry. Notably, methoxy-substituted arenes commonly exist in approved small-molecule drugs (Fig. 1a). Through straightforward demethylation, they can serve as a surrogate for phenols, which are also prevalent in diverse biologically relevant compounds. According to a recent report by Njardarson[1], 62% of small-molecule drugs approved in 2020 contain at least one phenol ether or phenol moiety. In addition, as a strong electron-donating group, methoxy groups can promote further arene functionalization via electrophilic aromatic substitution. Moreover, they can be directly employed as a coupling partner[2] or converted to the corresponding triflates for installing new functional groups (FGs) through cross-coupling reactions. Considering the versatile roles of methyl aryl ethers, efficient arene oxygenation methods could represent a strategically valuable tactic for streamlined arene functionalization.

Undoubtedly, direct conversion of a ubiquitous arene C–H bond to a C–O bond would provide a straightforward methoxylation approach[3]; however, it has been difficult to control site-selectivity without employing auxiliary directing groups (Fig. 1b). In addition, the involvement of strong oxidants in most existing C–H oxygenation approaches could raise a concern for FG tolerance[4]. While the current paradigm, which is to use nucleophilic aromatic substitutions or cross couplings for ipso methoxylation, has been successful, the position to be functionalized is constrained by where the leaving (or activating) group locates in the arene substrates[5-9]. This would require precisely pre-functionalized substrates, and sometimes they are nontrivial to access.

On the other hand, the Pd/NBE cooperative catalysis, namely the Catellani-type reactions, provides a complementary means for arene functionalization, which exhibits merged features of C–H functionalization and cross couplings[10-12]. Through forming a key aryl-norbornyl-palladacycle (ANP) intermediate (Fig. 1c), this reaction functionalizes ortho C–H bonds by reacting with an electrophile and meanwhile, couples with a nucleophile (or an alkene) at the ipso position. Thus, this type of catalysis can result in unconventional site-selectivity (when hydride is employed for ipso hydrogenation) or vicinal difunctionalization of arenes. While enormous advance has been made, the current scope of ortho-C–H functionalization has been limited to introducing relatively "soft" elements[13,14], i.e., carbon[15-23], nitrogen[24], and sulfur[25,26]. In contrast, the coupling of "hard" electrophiles, such as oxygen-derived ones, has been an unmet challenge in the Catellani-type reactions. In this article, we describe the development of the Pd/NBE-catalyzed ortho-C–H methoxylation of aryl iodides and bromides, enabled by a unique *N*,*N*-bissulfonylmethoxyamine electrophile and C7-bromo-substituted NBE. This method allows streamlined synthesis of complex bioactive compounds containing methyl aryl ethers and offers new efficient strategies to access underrepresented arene substitution patterns.

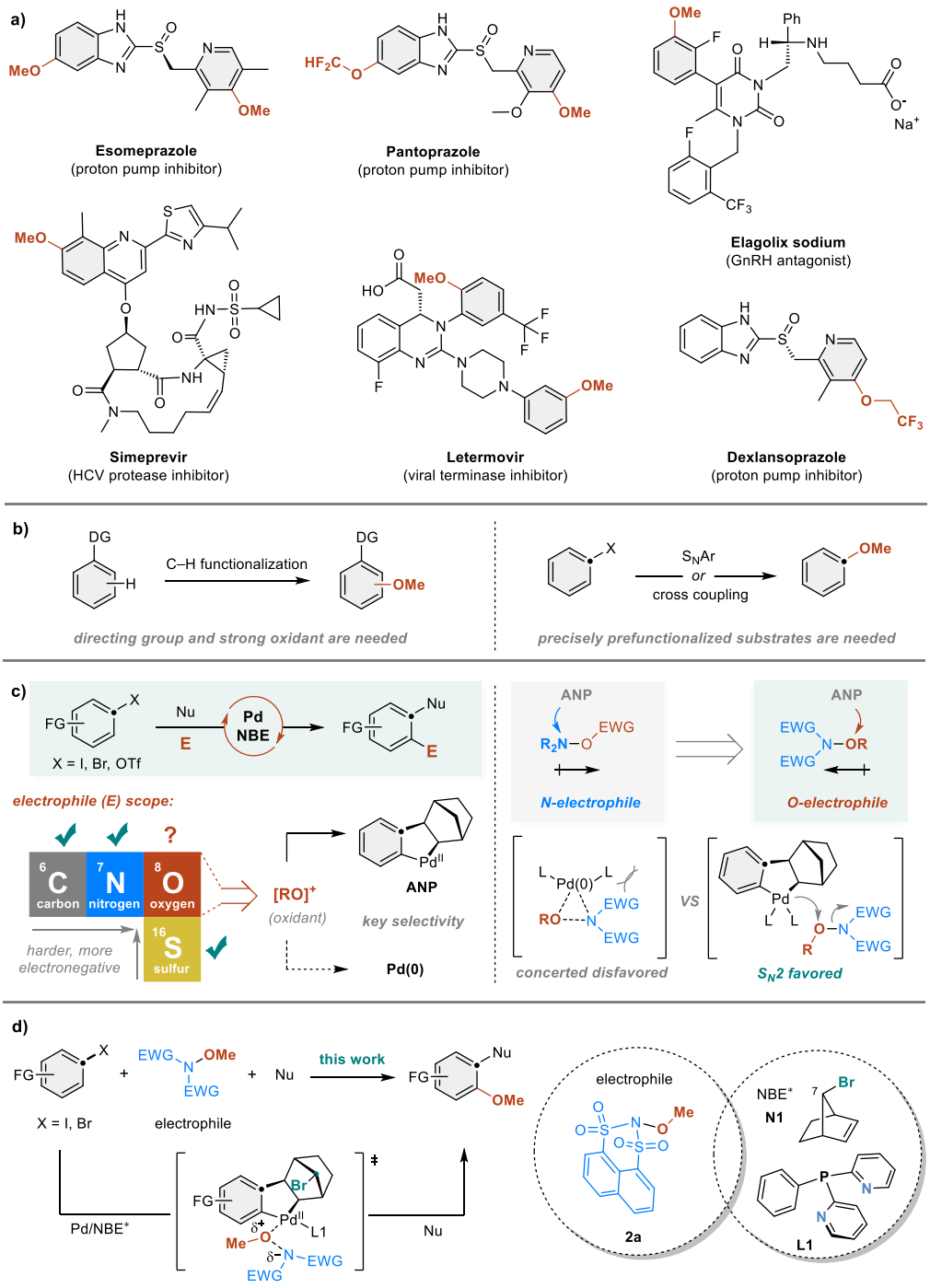


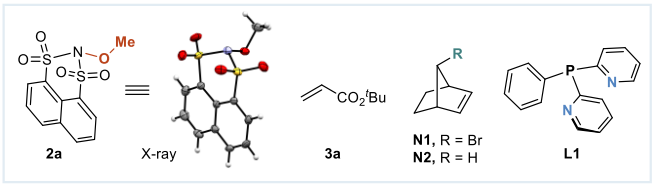
Figure 1 | Alkyl aryl ethers and their preparations. **a**, Selected approved small-molecule drugs containing alkyl aryl ethers. **b**, Current approaches for methoxylation of arenes. DG, directing group. **c**, Design of the Pd/NBE-catalyzed ortho C–H methoxylation with a polarity reversed N–O reagent. Nu, nucleophile; E, electrophile; ANP, aryl-norbornyl-palladacycle; EWG, electron-withdrawing group. **d**, The Pd/NBE-catalyzed ortho-C–H methoxylation of aryl iodides and bromides is enabled by a *N*,*N*-bissulfonylmethoxyamine electrophile and C7-bromo-substituted NBE mediator.

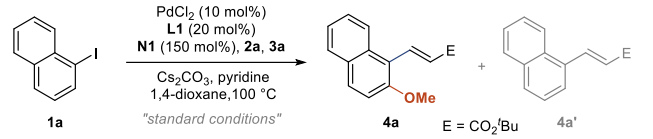
The success of the Pd/NBE catalysis relies on selective reactions between Pd(0) and the aryl halide substrate, as well as between ANP and the electrophile[12]. The main challenge of the ortho oxygenation is that, as a highly electronegative element, oxygen-based electrophiles (O-electrophile) are often strong oxidants, which can easily oxidize Pd(0) via single-electron transfer (SET), thus shutting down the catalysis. Considering that ANP can generally serve as a nucleophile to react with carbon and nitrogen-based electrophiles via a S_N2 mechanism[27], it could be reasonable to envision that, if the O-electrophile is made less prone to SET but more electrophilic, its selective reaction with ANP (instead of Pd(0)) should be possible. Previously, N–O type reagents have found great success in the Pd/NBE catalysis[24] and other amination reactions[28-34], in which the amine part is the electrophilic site with the more electronegative oxygen as the leaving group (Fig. 1d). To realize the ortho oxygenation, we hypothesize that, if the amine part is made bulkier and more electron-deficient whereas having the oxygen part less bulky and more electron-rich, *the roles of these parts could be swamped*. Such a "polarity reversed" N–O reagent could become a suitable electrophile for ortho oxygenation. Another challenge of the proposed ortho oxygenation could be the C–O bond forming process. It is known that C–O reductive elimination from a Pd(IV) species is more difficult than the C–C reductive elimination[35]; thus, the competing pathway to form the benzocyclobutene side-product via C–C reductive elimination could be more favorable. To circumvent this issue, we further hypothesized that, using the C7-bromo-substituted NBE as a mediator, the undesired benzocyclobutene formation could be inhibited due to the established electronic repulsive effect of the bromo substituent during the C–C reductive elimination[36].

Result and discussion

Reaction development

To test these hypotheses, a number of *N*,*N*-bissulfonylmethoxyamines (**2a**-**2g**) were prepared and examined in the ortho methoxylation/ipso Heck reaction with 1-iodonaphthalene (**1a**) as the model substrate (Table 1). While the acyclic reagents (**2b**-**2e**) were found unstable under the reaction conditions, the cyclic ones (**2a**, **2f** and **2g**) proved to be much more stable (entry 2). After careful optimization of various reaction parameters, to our delight, the use of the naphthalene-derived reagent (**2a**)[37] effectively delivered the desired ortho methoxylation product (**4a**) in 74% yield (entry 1). The X-ray structure of **2a** shows an interesting twisted pseudo-axial orientation of the OMe group, implying that the electronegative OMe group prefers to avoid double gauche-like interactions with four highly polarized sulfonyl oxygens. Note that compound **2a** has not been used in any chemical reaction previously. Other O-electrophiles including the saccharin-derived one (**2h**) proved to be ineffective. $PdCl_2$ and bis(2-pyridyl)phenylphosphine [$PPh(2\text{-}pyr)_2$, **L1**][38] were found to be the optimal catalyst/ligand combination. As expected, no product was formed without Pd (entry 3) and the use of other Pd complexes, such as $Pd(OAc)_2$, led to lower efficiency (entry 4). The reaction showed a low conversion without the phosphine ligand, suggesting its important role in stabilizing Pd(0); while PPh_3 only slightly reduced the yield, the more electron-deficient $P(2\text{-}pyr)_3$ ligand gave much lower yield (entries 5-7). The use of the C7-bromo-substituted NBE (**N1**) proved to be essential because, except that simple NBE (**N2**) afforded 5% yield (entries 8 and 9), other NBEs with various substitutions all gave only a trace amount of the desired product (Supplementary Information Table S1). This observation is consistent with the previously established feature of **N1** in minimizing side reactions in the Pd/NBE catalysis[36]. While 1.5 equivalent of **N1** was employed to suppress the undesired direct ipso Heck reaction, most **N1** (81%, Supplementary Information Table S3) can be recovered after the reaction. In addition, reduction of the **N1** loading to 100 and 50 mol % still afforded 61% and 46% yield, respectively (entries 10 and 11). Moreover, addition of pyridine to this reaction can greatly benefit the selectivity, as more side reactions, such as direct Heck or ortho arylation, dominated without this additive (entry 12), though the exact reason remains unclear. Finally, Cs_2CO_3 and 1,4-dioxane were the best base/solvent combination (for more details, see Supplementary Information Table S1)





Entry	Variations from the "standard conditions"	Yield of **4a** (%)[a]	Yield of **4a'** (%)[a]
1	none	**74** (68[b])	15
2	other electrophile instead of **2a**	listed below	listed below
3	No Pd	0	0
4	$Pd(OAc)_2$ instead of $PdCl_2$	45	11
5	No **L1**	14	<5
6	PPh_3 instead of **L1**	65	16
7	$P(2\text{-pyr})_3$ instead of **L1**	26	8
8	No **N1**	0	77
9	simple NBE (**N2**) instead of **N1**	5	6
10	**N1** (100 mol%)	61	17
11	**N1** (50 mol%)	46	23
12	No pyridine	28	24

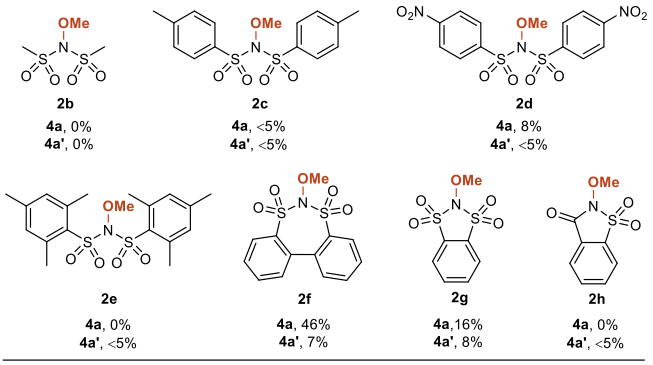


Table 1 | Reaction discovery and optimization. Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.11 mmol), $PdCl_2$ (0.01 mmol), ligand (0.02 mmol), NBE (0.15 mmol), pyridine (1.0 mmol), Cs_2CO_3 (0.25 mmol), 1,4-dioxane (1.0 mL), 100 °C, 24 h. [a]Yield was determined by ^1H NMR using dibromomethane as the internal standard. [b]Isolated yield.

Reaction scope

The aryl iodide scope was then studied for this ortho methoxylation reaction (Fig. 2). Beside the simple naphthalene substrate, aryl iodides in various fused structures, such as 2,3-dihydrobenzofuran (**4c**), dibenzofuran (**4d**), carbazole (**4f**), and pyrene (**4g**), could all give the desired products in good yield. In addition, monocyclic aryl iodides of different electronic properties, e.g., those with electron-donating and -withdrawing groups, also worked well (**4h**–**4w**). A wide range of FGs, including fluoro (**4h**), bromo (**4k** and **4t**), chloro (**4o**), silyl ether (**4l**), nitrile (**4n**), free alcohol (**4p**), amide (**4q**), amine (**4r**), ester (**4u**) and cyclopropane (**4v**), were tolerated. Moreover, *N*-heteroarene-based substrates, such as quinoline (**4x**), isoquinoline (**4y** and **4z**), and pyridine (**4aa**–**4ac**), can smoothly deliver the functionalized methyl ethers. Furthermore, late-stage modification of complex natural products and drugs (**4ad**–**4ag**) could be achieved with reasonably good efficiency indicating the generality of this method. Apart from ortho-substituted aryl iodides, para- and meta-substituted ones also reacted, albeit in moderate to low yield (Supplementary Information, Fig. S1). The scope of the reagents for functionalizing the ipso position was examined next. Beside *tert*-butyl acrylate, different Michael acceptors, including methyl acrylate, 2-(trimethylsilyl)ethyl acrylate, and acrylonitrile (**4ah**–**4aj**), and styrene (**4ak**) can be coupled to install diverse alkenyl groups. In addition

to the Heck quench, alkynylation and hydrogenation (**4al**, **4am**) are also feasible for the ipso functionalization. Lastly, the deuterated methoxy group (**4b**) can be introduced in a similar manner with the deuterated electrophile (*d*-**2a**). Beyond methoxylation, the coupling with a bulkier alkoxy group appears to be more challenging at this stage due to the increased steric hindrance, though a promising preliminary result has been obtained for the ortho ethoxylation reaction (Supplementary Information, Fig. S1).

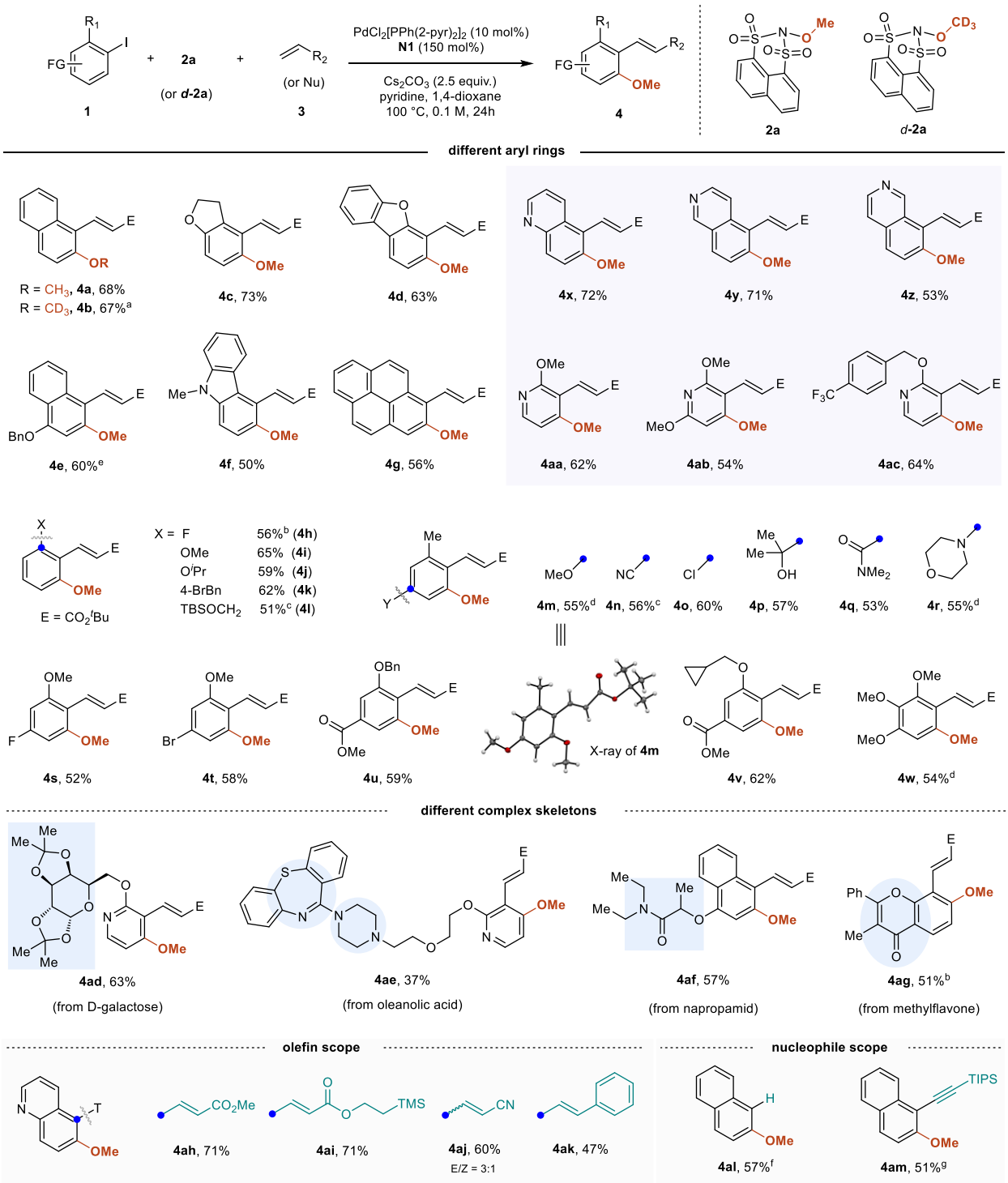


Figure 2 | Reaction scope with aryl iodides. Reaction conditions: **1** (0.1 mmol), **2a** (0.15 mmol), **3** (0.11 mmol), $PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.01 mmol), **N1** (0.15 mmol), pyridine (1.0 mmol), and Cs_2CO_3 (0.25 mmol) in 1,4-dioxane (1.0 mL), 100 °C, 24 h. TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl; TIPS, triisopropylsilyl; Bn, benzyl; ^{t}Bu, tertbutyl; ^{i}Pr, isopropyl. All yields are isolated yields of the products. [a]Reagent *d*-**2a** was used instead of **2a**. [b]110 °C, 48 h. [c]$PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.015 mmol) was used. [d]$PdCl_2$ (0.01 mmol) and $AsPh_3$ (0.02 mmol) was

used instead of $PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.01 mmol). [e]$PdCl_2$ (0.01 mmol) and $P(C_6F_5)_3$ (0.02 mmol) was used instead of $PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.01 mmol). [f]2-Borneol (0.11 mmol) was used instead of **3**. [g](Triisopropylsilyl)acetylene (0.15 mmol) was used instead of **3**, and 2.0 equivalent of **N1** (0.2 mmol) was used.

Compared to aryl iodides, aryl bromides are known to be more challenging substrates for the Catellani reactions[39] despite their greater accessibility and lower cost. To our delight, the use of DPEphos as the ligand and KI as an additive (Supplementary Information Table S2) allowed various aryl bromides to be competent substrates for the ortho methoxylation (Fig. 3). Sensitive FGs, such as aldehyde (**4ap**), benzothiophene (**4aq**), benzofuran (**4ar**), highly strained ether (**4as**) and amine (**4at**), were tolerated. Deuterated methoxy group can also be introduced with 5-bromoquinoline (**4av**).

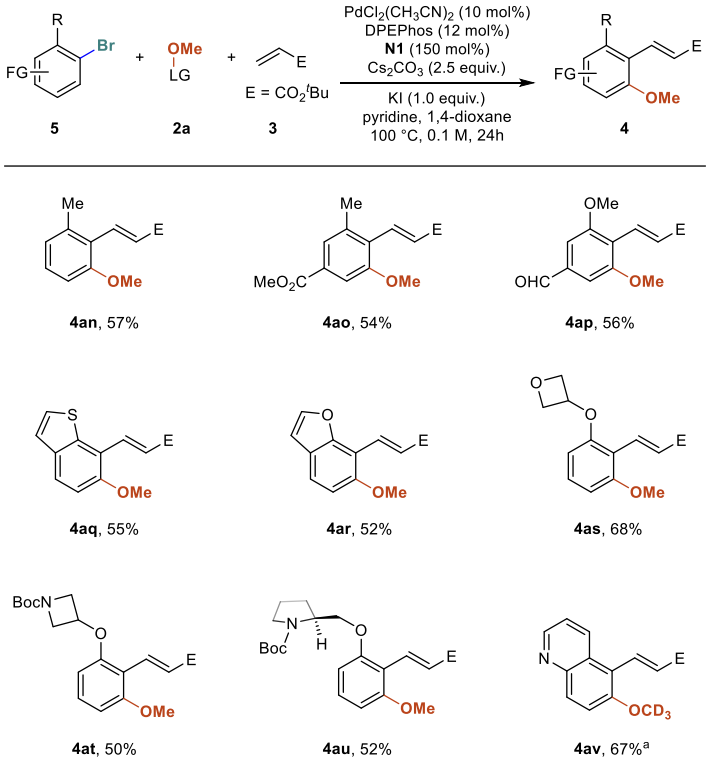


Figure 3 | Reaction scope with aryl bromides. Reaction conditions: **5** (0.1 mmol), **2a** (0.15 mmol), **3** (0.11 mmol), $PdCl_2(CH_3CN)_2$ (0.01 mmol), DPEPhos (0.012 mmol), **N1** (0.15 mmol), pyridine (0.3 mmol), KI (0.1 mmol), and Cs_2CO_3 (0.25 mmol) in 1,4-dioxane (1.0 mL), 100 °C, 24 h. All yields are isolated yields. DPEPhos, bis[(2-diphenylphosphino)phenyl] ether. [a]Reagent *d*-**2a** was used instead of **2a**.

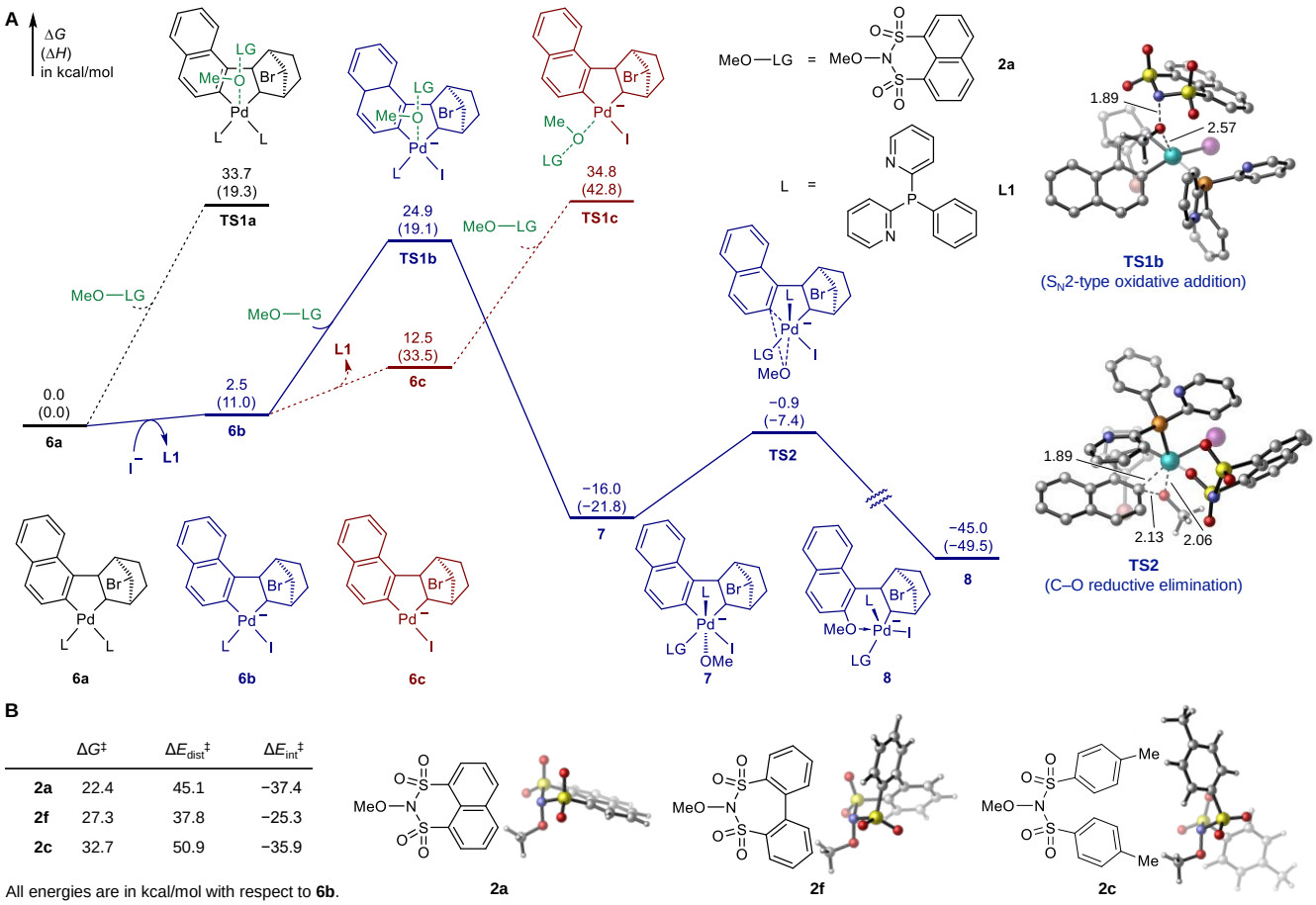
Reaction mechanism and synthetic applications

Density functional theory (DFT) calculations were next conducted to explore the mechanism of the ortho-C–H oxygenation and the origin of the unique reactivity of electrophile **2a** (Fig. 4). After the formation of ANP intermediate **6a** via oxidative addition (OA) of aryl iodide (ArI) **1a**, NBE migratory insertion, and C–H palladation[27], several OA pathways with electrophile **2a** were considered (Fig. 4a), including the S_N2-type OA with several ANP species **6a-c** that may exist in equilibrium. From the most stable neutral bis(2-pyridyl)phenylphosphine-supported ANP **6a**, the S_N2-type OA requires a relatively high barrier of 33.7 kcal/mol (**TS1a**). By contrast, anionic ANP **6b** bearing an iodide ligand and a bis(2-pyridyl)phenylphosphine (**L1**) ligand is much more nucleophilic. This is consistent with the "iodide additive" effect when using aryl bromide substrates[39]. Although the ligand exchange from **6a** to form **6b** is endergonic by 2.5 kcal/mol, the overall barrier to OA via the square-planar anionic ANP **6b** is only 24.9 kcal/mol (**TS1b**) with respect to **6a**, which is 8.8 kcal/mol lower than **TS1a**. The S_N2-type OA with three-coordinated anionic ANP **6c** has a relatively high overall barrier ($\Delta G^{\ddagger}$ = 34.8 kcal/mol with respect to **6a**), in part due to the unfavorable dissociation of **L1** from **6b** (ΔG = 10.0 kcal/mol). Our

previous computational study indicated ANP reacts with most "soft" electrophiles via the three-coordinated anionic complexes in analogy to **6c**[27]; however, here the reaction with the "hard" oxygen electrophile **2a** occurs via a distinct mechanism involving the more electron-rich four-coordinated anionic ANP **6b**. The square-planar geometry of the active ANP species **6b** is critical to achieve the desired electrophile selectivity by suppressing its reaction with ArI—because the OA with ArI would require two *cis* coordination sites for the three-centered transition state (TS); thus, **6b** cannot react with ArI without dissociating either the phosphine or the iodide ligand. Additionally, the use of 7-bromo-NBE (**N1**) suppresses the undesired C–C reductive elimination from ANP, whereas in reactions with simple NBE the C–C reductive elimination and S_N2-type OA have comparable activation barriers (Supplementary Information Fig. S7). After the S_N2-type OA via **TS1b** and pseudorotation/reassociation of the bis(sulfonyl)amide anion leaving group (see Supplementary Information for detailed discussion), a Pd(IV) intermediate (**7**) is formed, which undergoes facile and highly exergonic C–O reductive elimination (**TS2**) to form alkyl Pd(II) complex **8** ($\Delta G^{\ddagger}$ = 15.1 kcal/mol with respect to **7**).

The relatively high reactivity of electrophile **2a** with ANP **6b** is essential for the ortho C–H oxygenation reaction, as it must outcompete the aforementioned undesired reactions, including OA with ArI and C–C reductive elimination. In addition, OA of **2a** to Pd(0) needs to be much less favorable. Compared to the OA of ArI, the barrier is much higher for **2a** to react with Pd(0) through either a three-centered TS or an S_N2 pathway (Supplementary Information Fig. S4).

The S_N2-type OA of electrophiles **2f** and **2c** with ANP **6b** requires 4.9 and 10.3 kcal/mol, respectively, higher activation free energies than the reaction with **2a** (Fig. 4b), consistent with their incompetence as the electrophile (Table 1). Distortion/interaction model analysis indicates that the reaction with the acyclic electrophile **2c** suffers from a high distortion energy ($\Delta E^{\ddagger}_{dist}$ = 50.9 kcal/mol), whereas the distortion energies in the reactions with cyclic electrophiles **2a** and **2f** are smaller. The rigid six- and seven-membered rings in **2a** and **2f** pre-distort the electrophiles to the same conformation as in the S_N2-type OA TS (see Supplementary Information Fig. S5 for 3D structures), which decreases the distortion energies in the TS. The lower reactivity of the seven-membered-ring electrophile **2f** compared to **2a** is attributed to the non-planar geometry of the diphenyl moiety, which leads to greater steric repulsions with ANP in the S_N2-type OA TS. The six-membered ring in **2a** is mostly flat, making **2a** less sterically hindered than **2f**, allowing for more favorable interaction energy ($\Delta E^{\ddagger}_{int}$) in the TS. Collectively, the computational study suggests that **2a** is an excellent electrophile when reacting with ANP because of its steric accessibility and rigid, pre-distorted geometry.



	ΔG‡	ΔE$_{dist}$‡	ΔE$_{int}$‡
2a	22.4	45.1	−37.4
2f	27.3	37.8	−25.3
2c	32.7	50.9	−35.9

Figure 4 | Computational study of the Pd/NBE-catalyzed ortho-C–H oxygenation reaction. **a**, Free energy profile of the reaction of electrophile **2a** with ANP. **b**, Electrophile reactivity in the S_N2-type oxidative addition with **6b**. DFT calculations were performed at the M06/SDD–6-311+G(d,p), SMD(1,4-dioxane)//B3LYP-D3/LANL2DZ–6-31G(d) level of theory.

The utility of this method can first be seen in the streamlined preparation of bioactive compounds that contain methyl aryl ethers (Fig. 5). For example, 2,3-dihydrobenzofuran **9** is a known intermediate to access a potent 5-HT_{2C} receptor agonist (**10**)[40]; however, the previous route required seven steps to synthesize **9** from methyl 2,5-dihydroxybenzoate **11**. Using this ortho oxygenation/ipso Heck reaction, compound **9** can be directly prepared from 4-iodo-2,3-dihydrobenzofuran **1c** that was synthesized in one step from commercially available materials[41]. In the second case, ester **13** exhibits promising anticonvulsant activity for treating epilepsy[42], and the key carboxylic acid intermediate (**12**) was prepared in six steps from 3,4,5-trimethoxybenzaldehyde **14** in the reported synthesis. Now, starting with aryl iodide **1w**, made in one step from inexpensive 1,2,3-trimethoxylbenzene[43], the ortho oxygenation/ipso Heck reaction (with methyl acrylate) followed by ester hydrolysis rapidly delivered carboxylic acid **12** in good overall yield.

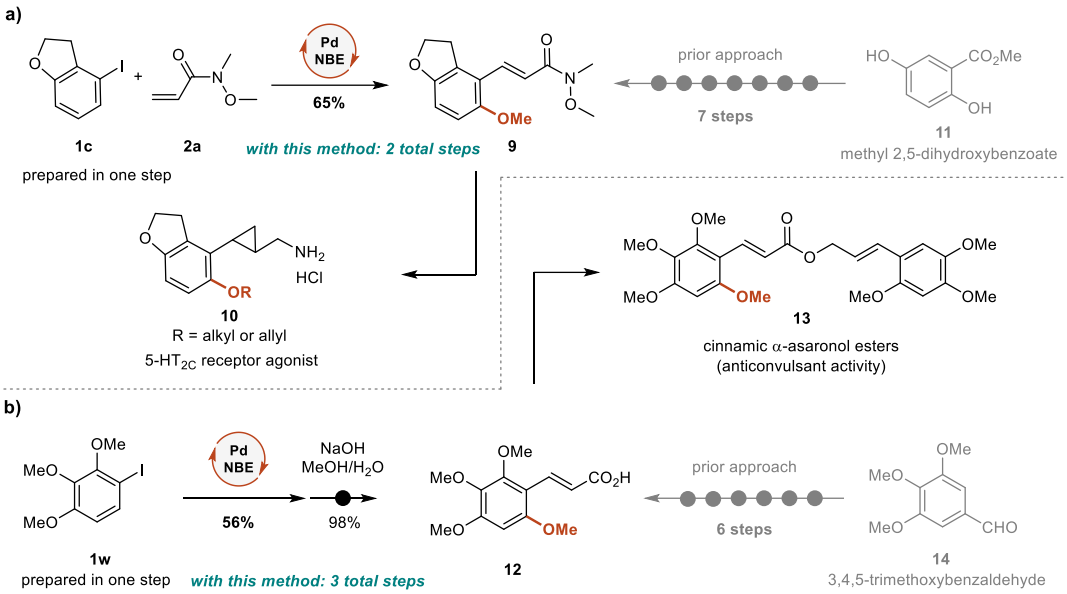


Figure 5 | Synthetic applications. Streamlined syntheses of compounds **9** and **12** are illustrated using this method.

On the other hand, according to a recent analysis by Merck & Co., Inc., certain substitution patterns in benzenoid are highly underrepresented in approved small-molecule drugs, and the lack of effective approaches to access such patterns was postulated to be the main cause[44]. In particular, 1,3,5-; 1,2,3,4-; 1,2,3,4,5-; 1,2,3,4,5,6-substituted benzene rings are among the four classes that are most difficult to target (Fig. 6a). Considering the versatile roles of the methoxy moiety, we proposed that *all these substitution patterns could be accessed from readily available ortho-substituted aryl halides via a relay C–H functionalization strategy*, which merges the ortho methoxylation reaction with other reactivities of the methyl aryl ether intermediate (Fig. 6b). Given the wide availability of ortho-substituted aryl halides, it could be envisaged that upon ortho methoxylation the C3-OMe substituted arene could undergo a para-selective halogenation to install an iodo or bromo group to the C6 position. The resulting tetra-substituted benzene can serve as the building block to access various 1,2,3,4-substituted benzenes because both the C6-halogen and the C3-OMe group can be independently converted to diverse other FGs. In addition, a second Catellani-type reaction with the C6-halogen could take place to functionalize both the C5 and C6 positions, leading to penta-substituted benzenes. Moreover, due to the strong electron-donating property of the C3-OMe group, another C−H halogenation could take place at the remaining C4 position, which should afford fully substituted benzenes. Note that during the synthesis of penta-substituted benzenes, if hydride sources are used as nucleophiles in these two Pd/NBE-catalysis steps, in which hydrogen would be installed at the C2 and C6 positions, 1,3,5-trisubstituted benzenes would then be obtained.

To test this proposal, 2-iodobenzyl acetate (**15**) was employed as a model substrate (Fig. 6c). The following ortho-C–H methoxylation reaction afforded the desired 1,2,3-trisubstituted benzene **16**. After transforming the vinyl group to a more versatile aldehyde moiety via ozonolysis, the subsequent electrophilic iodination gave the 1,2,3,4-tetrasubstitued benzene (**18**) with excellent para selectivity. Next, treatment of intermediate **18** under the ortho alkylation/ipso arylation condition[45] gave a new penta-substituted benzene (**19**). Then, a gold-catalyzed bromination[46] functionalized the last C−H bond on the benzene core, and the fully substituted benzene (**21**) was furnished through a Sonogashira coupling. It is noteworthy that there is *no same substituent* on the benzene core in all the intermediates from this synthesis, and these compounds would be difficult to access selectively via conventional approaches. On the other hand, an ortho amination/ipso arylation reaction[47] was chosen to further functionalize **18**, which gave the penta-substituted benzene (**22**). The methoxy group was smoothly converted to a

more reactive triflate group (**24**), which eventually delivered vinyl benzene **25** after the Suzuki coupling. Given the versatility of the Catellani, Suzuki, and Sonogashira couplings employed here, the tetra, penta- and hexa-substituted products obtained from this synthetic strategy should not be limited to the examples shown in this figure. Finally, to illustrate the synthesis of 1,3,5-substituted benzenes, the ortho oxygenation/ipso hydrogenation of 2-iodotoluene (**26**) with the deuterated electrophile, followed by the electrophilic iodination and ortho amination/ipso hydrogenation, rapidly generated the desired product (**29**).

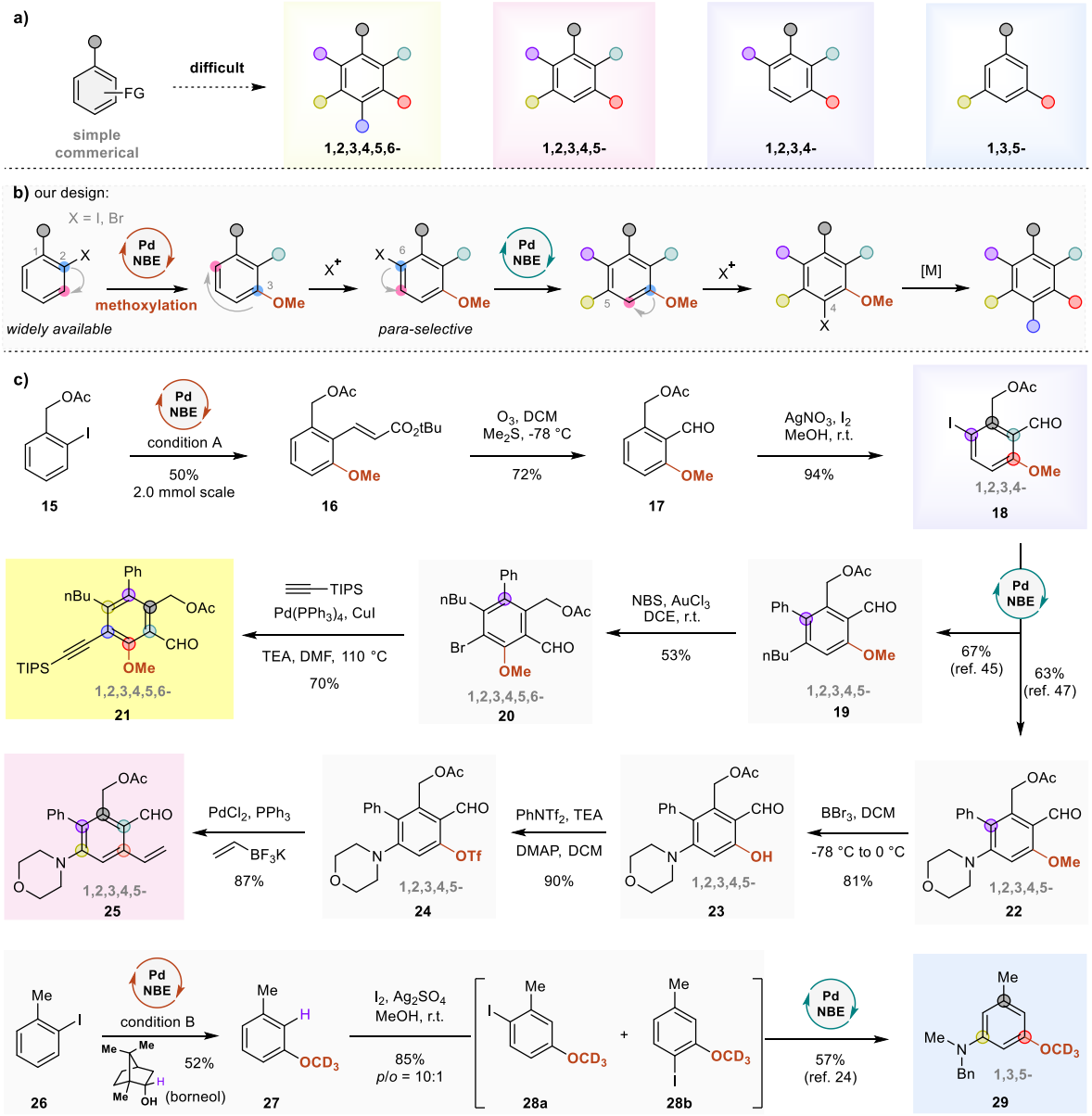


Figure 6 | Rapid access to challenging substitution patterns of benzenoids via a relay C–H functionalization strategy. **a**, The 1,3,5-; 1,2,3,4-; 1,2,3,4,5-; 1,2,3,4,5,6-substituted benzene rings are difficult to be efficiently prepared from simple commercially available materials. **b**, Our design is based on a relay C–H functionalization strategy by taking advantage of the ortho methoxylation and the versatile roles of the methoxy substituents. **c**, Representative examples are shown to access challenging substitution patterns of benzenoids, in which all the substituents are different. Condition A: **15** (2.0 mmol), **2a** (3.0 mmol), **3** (2.2 mmol), $PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.2 mmol), **N1** (3.0 mmol), pyridine (20.0 mmol), and Cs_2CO_3 (5.0 mmol) in 1,4-dioxane (20.0 mL), 100 °C, 24 h; Condition B: **26** (0.5 mmol), *d*-**2a** (0.55 mmol), 2-borneol (0.55 mmol), $PdCl_2[PPh(2\text{-}pyr)_2]_2$ (0.05 mmol), **N1** (0.75 mmol), pyridine (5.0 mmol), and Cs_2CO_3 (1.25 mmol) in 1,4-dioxane (5.0 mL), 100 °C, 24 h. NBS, *N*-bromosuccinimide; DCE, 1,2-dichloroethane; TEA, triethylamine; DMF, *N*,*N*-dimethylformamide; DCM, dichloromethane; DMAP, 4-dimethylaminopyridine.

Conclusions

In summary, a Pd/NBE-catalyzed ortho-C–H methoxylation of common aryl halides has been realized, which is enabled by a polarity reversed N–O reagent. The reaction shows a broad substrate scope and high FG tolerance, rendering it suitable for late-stage functionalization of complex bioactive molecules. In addition, synthesis of polysubstituted methyl aryl ethers can be streamlined by this method. Owing to the versatile reactivity of methoxy group, access to challenging benzenoid substitution patterns can be accelerated by strategically merging this method with other C–H functionalization tactics, which is expected to offer a useful tool for medicinal chemistry research. Finally, the mechanistic insights gained on the coupling of harder electrophiles in the Pd/NBE catalysis could have broad implications on developing other oxygen-based coupling reactions and other ortho-C–H functionalization reactions.

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Author contributions

X.L. and G.D. conceived and designed the experiments. X.L. and Z.C. performed experiments. Y.F. and P.L. designed and conducted the DFT calculations. X.L., Y.F., P.L. and G.D. wrote the manuscript. P.L. and G.D. directed the research.

Competing interests

The authors declare no competing interests.

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Data availability

All data are available in the main text or the supplementary materials. Additional data are available from the corresponding authors upon request. Metrical parameters for the structure of **4m** and **2a** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference number CCDC 2209874 and 2209875, respectively.

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