

Ortho-C–H methoxylation of aryl halides enabled by a polarity reversed N–O reagent

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Oxygen-substituted arenes widely exist in biologically important molecules and can serve as versatile handles to install other functional groups. However, direct and site-selective installation of oxygen groups to common aromatic compounds remains challenging, especially when additional arene functionalization is simultaneously required. Current arene C–H oxidation strategies generally require directing groups or precisely pre-functionalized substrates to control site-selectivity. While palladium/norbornene (Pd/NBE) cooperative catalysis is promising for site-specific arene vicinal difunctionalization through simultaneous reactions with an electrophile and a nucleophile, the electrophile scope has been limited to species based on relatively “soft” elements, such as carbon, nitrogen, and sulfur. Here we report the development of an ortho oxygenation reaction with common aryl halides to rapidly deliver diverse 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.

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 Njardarson¹, 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 partner² 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 approach³; 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 tolerance⁴. 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 (Fig. 1c).

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. 1d), 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., carbon¹⁵⁻²³, nitrogen²⁴, 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.

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 electrophile¹². 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 mechanism²⁷, 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 catalysis²⁴ and other amination reactions²⁸⁻³⁴, in which the amine part is the electrophilic site with the more electronegative oxygen as the leaving group (Fig. 1e). 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 swapped. 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 elimination³⁵; 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 elimination³⁶.

Results 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. PdCl₂ and bis(2-pyridyl)phenylphosphine [PPh(2-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 PPh₃ only slightly reduced the yield, the more electron-deficient P(2-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 only gave a trace amount of the desired product (Supplementary Table 1). This observation is consistent with the previously established feature of **N1** in minimizing side reactions in the Pd/NBE catalysis³⁶. While 1.5 equivalent of **N1** was employed to suppress the undesired direct ipso Heck reaction, most **N1** (81%, Supplementary Table 3) 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, Cs₂CO₃ and 1,4-dioxane were the best base/solvent combination (for more details, see Supplementary Table 1).

Reaction scope

The aryl iodide scope was then studied for this ortho methoxylation reaction (Table 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 Figure 1). 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 Figure 1).

Compared to aryl iodides, aryl bromides are known to be more challenging substrates for the Catellani reactions³⁹ despite their greater accessibility and lower cost. To our delight, the use of DPEPhos (bis[(2-diphenylphosphino)phenyl] ether) as the ligand and KI as an additive (Supplementary Table 2) allowed various aryl bromides to be competent substrates for the ortho methoxylation (Table. 2). 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**).

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. 2). After the formation of ANP intermediate **6a** via oxidative addition (OA) of aryl iodide (ArI) **1a**, NBE migratory insertion, and C–H palladation²⁷, several OA pathways with electrophile **2a** were considered (Fig. 2a), 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 substrates³⁹.

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** ($\Delta G = 10.0$ 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 Figure 7). After the S_N2-type OA via **TS1b** and pseudorotation/reassociation of the bis(sulfonyl)amide anion leaving group (see Supplementary Information Section VIII 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 Figure 4).

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. 2b), 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 ($\Delta E^\ddagger_{\text{dist}} = 50.9$ 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 Figure 5), 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 ($\Delta E^\ddagger_{\text{int}}$) 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.

The utility of this method can first be seen in the streamlined preparation of bioactive compounds that contain methyl aryl ethers (Fig. 3). 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 materials⁴¹. In the second case, ester **13** exhibits promising anticonvulsant activity for treating epilepsy⁴², 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-trimethoxybenzene⁴³, the ortho oxygenation/ipso Heck reaction (with methyl acrylate) followed by ester hydrolysis rapidly delivered carboxylic acid **12** in good overall yield.

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 cause⁴⁴. 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. 4a). 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. 4b). 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. 4c). 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-tetrasubstituted benzene (**18**) with excellent para selectivity. Next, treatment of intermediate **18** under the ortho alkylation/ipso arylation condition⁴⁵ gave penta-substituted benzene (**19**). Then, a gold-catalyzed bromination⁴⁶ 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 reaction⁴⁷ 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**).

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

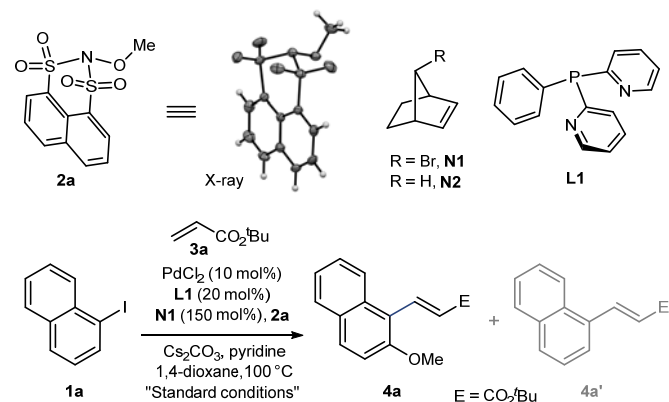
X.L. and G.D. conceived and designed the experiments. X.L. and Z.C. performed experiments. Y.F. and P.L. designed and conducted the DFT calculations. X.L., Y.F., P.L. and G.D. wrote the manuscript. P.L. and G.D. directed the research.

Competing interests

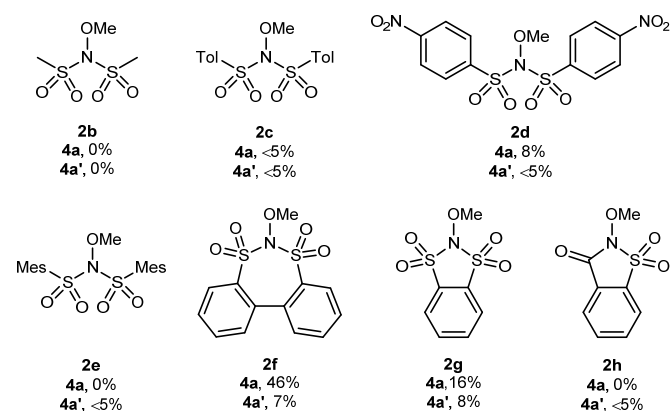
The authors declare no competing interests.

Tables and figures

Table 1 | Reaction discovery and optimization.

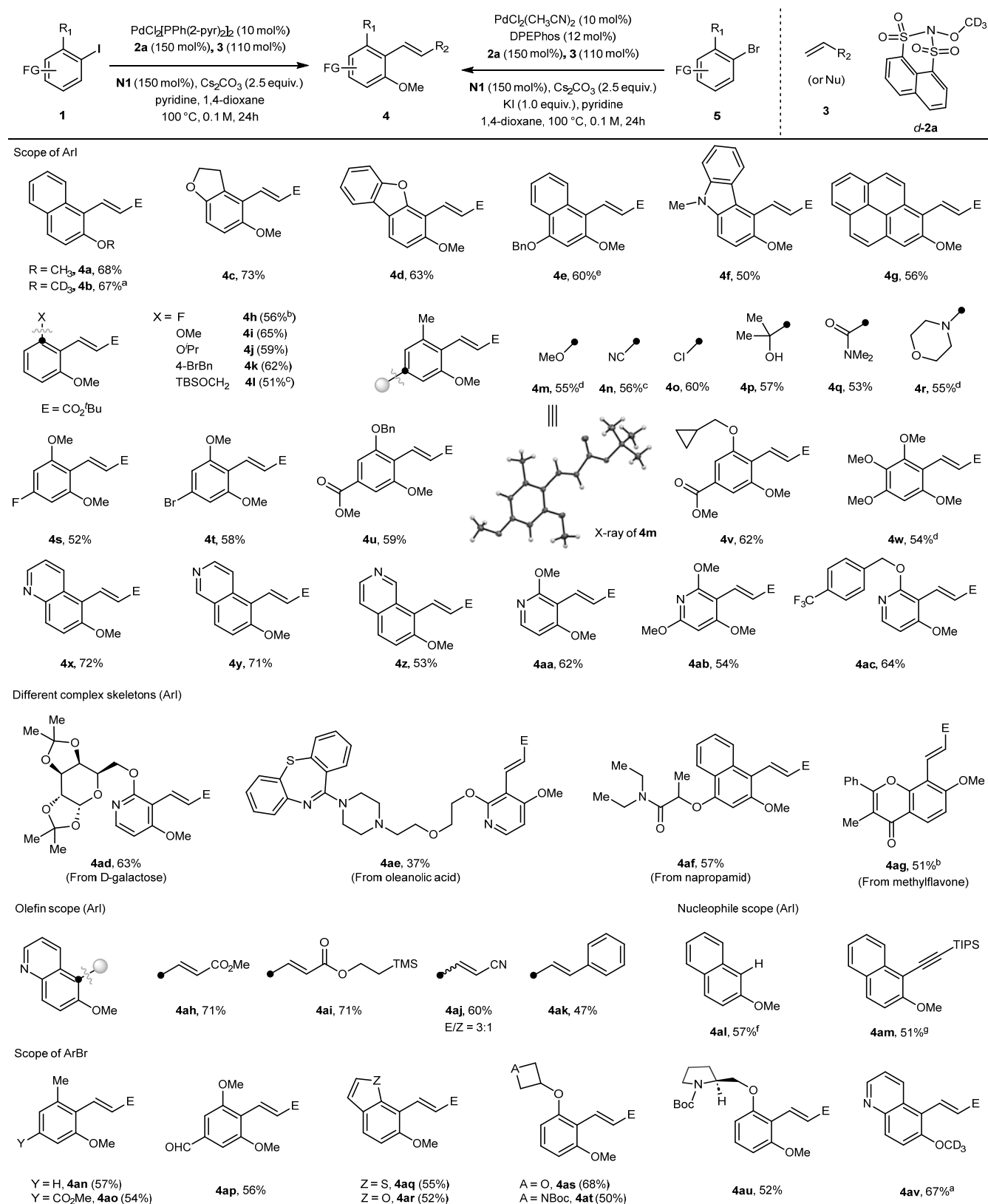


Entry	Variations from the "standard conditions"	Yield of 4a (%) ^a	Yield of 4a' (%) ^a
1	None	74 (68 ^b)	15
2	Other electrophile instead of 2a	Listed below	Listed below
3	No Pd	0	0
4	$\text{Pd}(\text{OAc})_2$ instead of PdCl_2	45	11
5	No L1	14	<5
6	PPh_3 instead of L1	65	16
7	$\text{P}(\text{2-pyr})_3$ 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



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. ^aYield was determined by ^1H NMR using dibromomethane as the internal standard. ^bIsolated yield. Pyr, pyridyl.

Table 2 | Reaction scope.



dioxane (1.0 mL), 100 °C, 24 h. TBS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl; TIPS, triisopropylsilyl; Bn, benzyl; *t*Bu, *tert*butyl; *i*Pr, isopropyl. All yields are isolated yields of the products. ^aReagent *d*-**2a** was used instead of **2a**. ^b110 °C, 48 h. ^cPdCl₂[PPh(2-pyr)₂]₂ (0.015 mmol) was used. ^dPdCl₂ (0.01 mmol) and AsPh₃ (0.02 mmol) was used instead of PdCl₂[PPh(2-pyr)₂]₂ (0.01 mmol). ^ePdCl₂ (0.01 mmol) and P(C₆F₅)₃ (0.02 mmol) was used instead of PdCl₂[PPh(2-pyr)₂]₂ (0.01 mmol). ^f2-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.

Figure 1 | Alkyl aryl ethers and their preparations. **a**, Selected approved small-molecule drugs containing alkyl aryl ethers. **b**, Directing groups (DGs) can be used to control site-selectivity of C–H oxygenation of arenes. **c**, Precisely pre-functionalized substrates are often employed for nucleophilic aromatic substitution (S_NAr) or cross couplings when installing methoxy groups. **d**, 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. **e**, 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.

Figure 2 | Computational study of the Pd/NBE-catalyzed ortho-C–H oxygenation reaction. **a**, Free energy profile of the reaction indicates involvement of a S_N2-type oxidative addition of electrophile **2a** with square-planar anionic ANP **6b**. **b**, Due to its pre-distorted and planar geometry, electrophile **2a** is more favored 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.

Figure 3 | Synthetic applications. **a**, Synthesis of a potent 5-HT_{2C} receptor agonist (**10**) can be streamlined by this method. **b**, Preparation of a known carboxylic acid intermediate (**12**) can be simplified by this method.

Figure 4 | 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), PdCl₂[PPh(2-pyr)₂]₂ (0.2 mmol), **N1** (3.0 mmol), pyridine (20.0 mmol), and Cs₂CO₃ (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), PdCl₂[PPh(2-pyr)₂]₂ (0.05 mmol), **N1** (0.75 mmol), pyridine (5.0 mmol), and Cs₂CO₃ (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.

References:

1. Scott, K. A., Cox, P. B. & Njardarson, J. T. Phenols in pharmaceuticals: analysis of a recurring motif. *J. Med. Chem.* **65**, 7044–7072 (2022).

2. Qiu, Z. H. & Li, C. J. Transformations of less-activated phenols and phenol derivatives via C-O cleavage. *Chem. Rev.* **120**, 10454-10515 (2020).
3. Liu, B. & Shi, B. F. Transition-metal-catalyzed etherification of unactivated C-H bonds. *Tetrahedron Lett.* **56**, 15-22 (2015).
4. Yang, F. Z., Zhang, H., Liu, X. R., Wang, B. & Lutz, A. Transition metal-catalyzed regio-selective aromatic C-H bond oxidation for C-O bond formation. *Chin. J. Org. Chem.* **39**, 59-73 (2019).
5. Mann, G., Incarvito, C., Rheingold, A. L. & Hartwig, J. F. Palladium-catalyzed C-O coupling involving unactivated aryl halides. Sterically induced reductive elimination to form the C-O bond in diaryl ethers. *J. Am. Chem. Soc.* **121**, 3224-3225 (1999).
6. Torraca, K. E., Huang, X. H., Parrish, C. A. & Buchwald, S. L. An efficient intermolecular palladium-catalyzed synthesis of aryl ethers. *J. Am. Chem. Soc.* **123**, 10770-10771 (2001).
7. Qiao, J. X. & Lam, P. Y. *Recent advances in Chan-Lam coupling reaction: copper-promoted C-heteroatom bond cross-coupling reactions with boronic acids and derivatives*. Vol. 1 (Wiley-VCH Weinheim, Germany, 2011).
8. Terrett, J. A., Cuthbertson, J. D., Shurtleff, V. W. & MacMillan, D. W. C. Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **524**, 330-334 (2015).
9. Yang, Q., Zhao, Y. S. & Ma, D. W. Cu-mediated Ullmann-type cross-coupling and industrial applications in route design, process development, and scale-up of pharmaceutical and agrochemical processes. *Org. Process Res. Dev.* **26**, 1690-1750 (2022).
10. Ye, J. T. & Lautens, M. Palladium-catalysed norbornene-mediated C-H functionalization of arenes. *Nat. Chem.* **7**, 863-870 (2015).
11. Della Ca, N., Fontana, M., Motti, E. & Catellani, M. Pd/norbornene: A winning combination for selective aromatic functionalization via C-H bond activation. *Acc. Chem. Res.* **49**, 1389-1400 (2016).
12. Wang, J. C. & Dong, G. Palladium/norbornene cooperative catalysis. *Chem. Rev.* **119**, 7478-7528 (2019).
13. Dong, S. C. & Luan, X. J. Catellani reaction: An enabling technology for vicinal functionalization of aryl halides by palladium(0)/norbornene cooperative catalysis. *Chin. J. Chem.* **39**, 1690-1705 (2021).
14. Zhao, K., Ding, L. L. & Gu, Z. H. Development of new electrophiles in palladium/norbornene-catalyzed ortho-functionalization of aryl halides. *Synlett* **30**, 129-140 (2019).
15. Catellani, M., Frignani, F. & Rangoni, A. A complex catalytic cycle leading to a regioselective synthesis of o,o'-disubstituted vinylarenes. *Angew. Chem., Int. Ed. Engl.* **36**, 119-122 (1997).
16. Catellani, M., Motti, E. & Baratta, S. A novel palladium-catalyzed synthesis of phenanthrenes from ortho-substituted aryl iodides and diphenyl- or alkylphenylacetylenes. *Org. Lett.* **3**, 3611-3614 (2001).
17. Lautens, M. & Piguel, S. A new route to fused aromatic compounds by using a palladium-catalyzed alkylation - Alkenylation sequence. *Angew. Chem., Int. Ed.* **39**, 1045-1056 (2000).
18. Dong, Z., Wang, J. C., Ren, Z. & Dong, G. Ortho C-H acylation of aryl iodides by palladium/norbornene catalysis. *Angew. Chem., Int. Ed.* **54**, 12664-12668 (2015).
19. Huang, Y. Z., Zhu, R., Zhao, K. & Gu, Z. H. Palladium-catalyzed Catellani ortho-acylation reaction: An efficient and regiospecific synthesis of diaryl ketones. *Angew. Chem., Int. Ed.* **54**, 12669-12672 (2015).
20. Zhou, P. X. *et al.* Palladium-catalyzed acylation/alkenylation of aryl iodide: A domino approach based on the Catellani-Lautens reaction. *ACS Catal.* **5**, 4927-4931 (2015).
21. Liu, C. *et al.* Synthesis of indolines via a palladium/norbornene-catalyzed reaction of aziridines with aryl iodides. *Chem. Commun.* **54**, 3407-3410 (2018).
22. Ding, Y. N. *et al.* Palladium-Catalyzed ortho-C-H Glycosylation/ipso-Alkenylation of Aryl Iodides. *J. Org. Chem.* **85**, 11280-11296 (2020).
23. Lv, W. W., Chen, Y. H., Wen, S., Ba, D. & Cheng, G. L. Modular and Stereoselective Synthesis of C-Aryl Glycosides via Catellani Reaction. *J. Am. Chem. Soc.* **142**, 14864-14870 (2020).
24. Dong, Z. & Dong, G. Ortho vs ipso: site-selective Pd and norbornene-catalyzed arene C-H amination using aryl halides. *J. Am. Chem. Soc.* **135**, 18350-18353 (2013).
25. Cai, W. Q. & Gu, Z. H. Selective ortho thiolation enabled by tuning the ancillary ligand in palladium/norbornene catalysis. *Org. Lett.* **21**, 3204-3209 (2019).
26. Li, R. H., Zhou, Y., Yoon, K. Y., Dong, Z. & Dong, G. Sulfenamide-enabled ortho thiolation of aryl iodides via palladium/norbornene cooperative catalysis. *Nat. Commun.* **10**, 3555 (2019).
27. Qi, X. T., Wang, J. C., Dong, Z., Dong, G. & Liu, P. Compatibility score for rational electrophile selection in Pd/NBE cooperative catalysis. *Chem* **6**, 2810-2825 (2020).
28. Dong, X., Liu, Q., Dong, Y. H. & Liu, H. Transition-metal-catalyzed electrophilic amination: Application of O-benzoylhydroxylamines in the construction of the C-N bond. *Chem. - Eur. J.* **23**, 2481-2511 (2017).
29. Korch, K. M. & Watson, D. A. Cross-coupling of heteroatomic electrophiles. *Chem. Rev.* **119**, 8192-8228 (2019).
30. Berman, A. M. & Johnson, J. S. Copper-catalyzed electrophilic amination of diorganozinc reagents. *J. Am. Chem. Soc.* **126**, 5680-5681 (2004).
31. Yoo, E. J., Ma, S., Mei, T. S., Chan, K. S. L. & Yu, J. Q. Pd-catalyzed intermolecular C-H amination with alkylamines. *J. Am. Chem. Soc.* **133**, 7652-7655 (2011).

32. Rucker, R. P., Whittaker, A. M., Dang, H. & Lalic, G. Synthesis of hindered anilines: Copper-catalyzed electrophilic amination of aryl boronic esters. *Angew. Chem., Int. Ed.* **51**, 3953-3956 (2012).
33. Zhu, S. L., Niljianskul, N. & Buchwald, S. L. Enantio- and regioselective CuH-catalyzed hydroamination of alkenes. *J. Am. Chem. Soc.* **135**, 15746-15749 (2013).
34. McDonald, S. L. & Wang, Q. Copper-catalyzed α -amination of phosphonates and phosphine oxides: A direct approach to α -amino phosphonic acids and derivatives. *Angew. Chem., Int. Ed.* **53**, 1867-1871 (2014).
35. Canty, A. J., Denney, M. C., Skelton, B. W. & White, A. H. Carbon-oxygen bond formation at organopalladium centers: The reactions of $\text{PdMeR}(\text{L}_2)$ ($\text{R} = \text{Me}$, 4-tolyl; $\text{L}_2 = \text{tmeda}$, bpy) with diaroyl peroxides and the involvement of organopalladium(IV) species. *Organometallics* **23**, 1122-1131 (2004).
36. Liu, X., Wang, J. C. & Dong, G. Modular entry to functionalized tetrahydrobenzo[*b*]azepines via the palladium/norbornene cooperative catalysis enabled by a C7-modified norbornene. *J. Am. Chem. Soc.* **143**, 9991-10004 (2021).
37. Patel, B. *et al.* In search of a new class of stable nitroxide: Synthesis and reactivity of a peri-substituted *N,N*-bissulfonylhydroxylamine. *Org. Biomol. Chem.* **9**, 2336-2344 (2011).
38. Xie, Y., Lee, C. L., Yang, Y. P., Rettig, S. J. & James, B. R. Mononuclear and dinuclear palladium complexes containing 2-pyridylphosphine ligands, including X-ray characterization of $\text{Pd}_2\text{I}_2(\mu\text{-PPh}_2\text{py})_2$ and a dimethylacetylenedicarboxylate A-frame complex $\text{Pd}_2\text{Cl}_2(\mu\text{-Ppy}_3)_2(\mu\text{-MeO}_2\text{C}\cdot\text{C}\equiv\text{C}\cdot\text{CO}_2\text{Me})$; $\text{py} = 2\text{-pyridyl}$. *Can. J. Chem.* **70**, 751-762 (1992).
39. Dong, Z., Lu, G., Wang, J. C., Liu, P. & Dong, G. Modular ipso/ortho difunctionalization of aryl bromides via palladium/norbornene cooperative catalysis. *J. Am. Chem. Soc.* **140**, 8551-8562 (2018).
40. Cheng, J. J. *et al.* Design and discovery of functionally selective serotonin 2C (5-HT_{2C}) receptor agonists. *J. Med. Chem.* **59**, 9866-9880 (2016).
41. Gao, S. J., Qian, G. Y., Tang, H., Yang, Z. & Zhou, Q. H. Three-step total synthesis of ramelteon via a Catellani strategy. *Chemcatchem* **11**, 5762-5765 (2019).
42. Bai, Y. J. *et al.* Polygala tenuifolia-Acori tatarinowii herbal pair as an inspiration for substituted cinnamic α -asaronol esters: Design, synthesis, anticonvulsant activity, and inhibition of lactate dehydrogenase study. *Eur. J. Med. Chem.* **183**, No. 111650 (2019).
43. Farina, A., Ferranti, C., Marra, C., Guiso, M. & Norcia, G. Synthesis of hydroxystilbenes and their derivatives via Heck reaction. *Nat. Prod. Res.* **21**, 564-573 (2007).
44. Nilova, A., Campeau, L. C., Sherer, E. C. & Stuart, D. R. Analysis of benzenoid substitution patterns in small molecule active pharmaceutical ingredients. *J. Med. Chem.* **63**, 13389-13396 (2020).
45. Catellani, M., Motti, E. & Minari, M. Symmetrical and unsymmetrical 2,6-dialkyl-1,1'-biaryls by combined catalysis of aromatic alkylation via palladacycles and Suzuki-type coupling. *Chem. Commun.*, 157-158 (2000).
46. Mo, F. Y. *et al.* Gold-catalyzed halogenation of aromatics by *N*-halosuccinimides. *Angew. Chem., Int. Ed.* **49**, 2028-2032 (2010).
47. Ye, C. Q., Zhu, H. & Chen, Z. Y. Synthesis of biaryl tertiary amines through Pd/norbornene joint catalysis in a remote C-H amination/Suzuki coupling reaction. *J. Org. Chem.* **79**, 8900-8905 (2014).

Methods

General procedure for methoxylation of aryl iodides

An oven-dried 4 mL vial equipped with a Teflon-coated magnetic stir bar was charged with aryl iodide **1** (0.1 mmol, 1.0 equiv.), *N*-alkoxybenzenesulfonimide **2a** (44.0 mg, 0.15 mmol, 1.5 equiv.), olefine **3** (0.11 mmol, 1.1 equiv.), $\text{PdCl}_2(\text{PPh}(2\text{-pyr})_2)_2$ (7.0 mg, 0.01 mmol, 10 mol%), **N1** (18.6 μL , 0.15 mmol, 1.5 equiv.), pyridine (79 mg, 1.0 mmol, 10.0 equiv.), Cs_2CO_3 (81 mg, 0.25 mmol, 2.5 equiv.), and 1,4-dioxane (1.0 mL) in a glovebox. The vial was tightly sealed and transferred out of the glovebox. The reaction mixture was first stirred at room temperature for 10 minutes and then stirred on a pie-block preheated to 100 °C for 24 h. Upon completion of the reaction, the mixture was filtered through a thin pad of silica gel (down) and Celite (up). The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield desired product **4**.

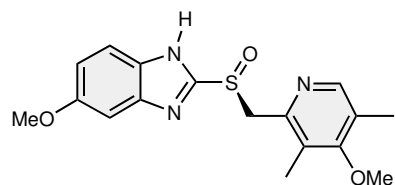
General procedure for methoxylation of aryl bromides

An oven-dried 4 mL vial equipped with a Teflon-coated magnetic stir bar was charged with aryl bromide **5** (0.1 mmol, 1.0 equiv.), *N*-alkoxybenzenesulfonimide **2a** (44.0 mg, 0.15 mmol, 1.5 equiv.), olefine **3** (0.11 mmol, 1.1 equiv.), $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (2.6 mg, 0.01 mmol, 10 mol%), DPEPhos (6.4 mg, 0.012 mmol, 12 mol%), **N1** (18.6 μL ,

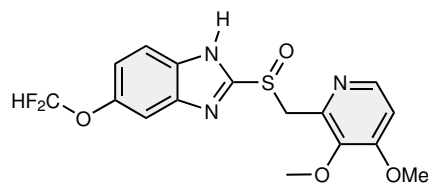
0.15 mmol, 1.5 equiv.), KI (16.6 mg, 0.1 mmol, 1.0 equiv.), pyridine (23.7 mg, 0.3 mmol, 3.0 equiv.), Cs₂CO₃ (81 mg, 0.25 mmol, 2.5 equiv.), and 1,4-dioxane (1.0 mL) in a glovebox. The vial was tightly sealed and transferred out of the glovebox. The reaction mixture was first stirred at room temperature for 10 minutes and then stirred on a pie-block preheated to 100 °C for 24 h. Upon completion of the reaction, the mixture was filtered through a thin pad of silica gel (down) and Celite (up). The filter cake was washed with ethyl acetate, and the combined filtrate was concentrated. The residue was directly purified by flash column chromatography on silica gel to yield the desired product **4**.

Data availability

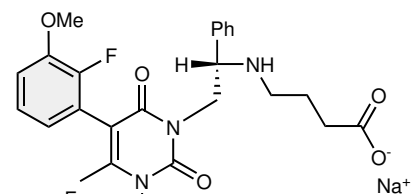
The data supporting the findings of this study are available within the Article and its Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2209874 (**4m**) and 2209875 (**2a**). Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>.

a

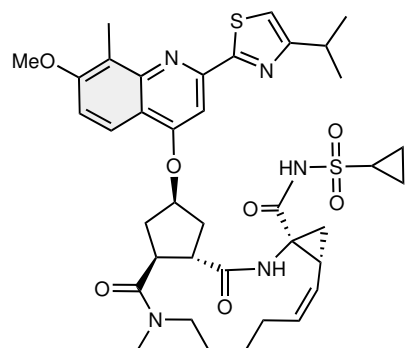
Esomeprazole
(Proton pump inhibitor)



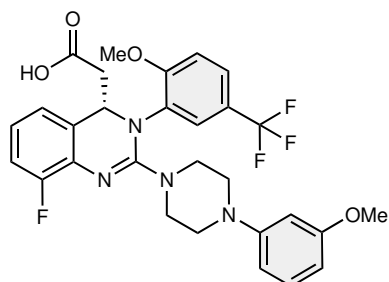
Pantoprazole
(Proton pump inhibitor)



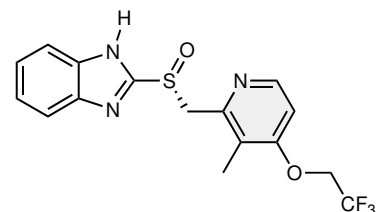
Elagolix sodium
(GnRH antagonist)



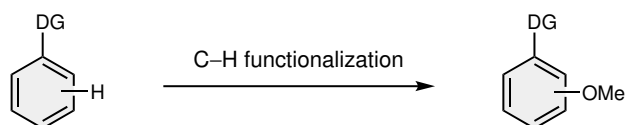
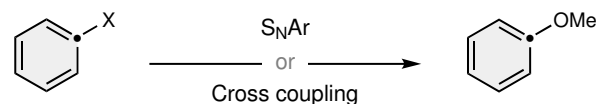
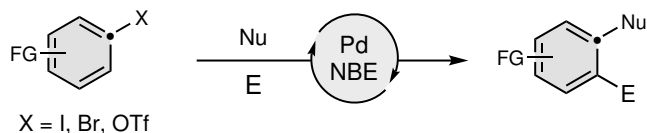
Simeprevir
(HCV protease inhibitor)



Letemovir
(Viral terminase inhibitor)

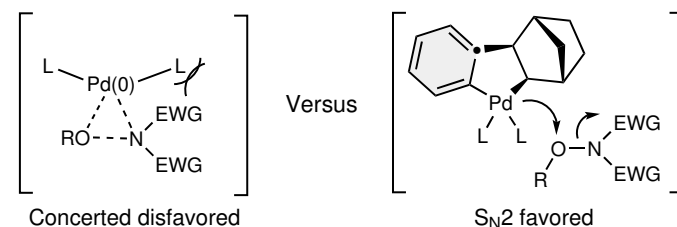
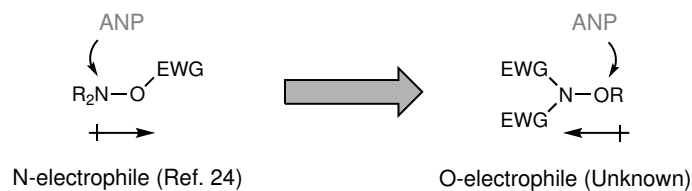
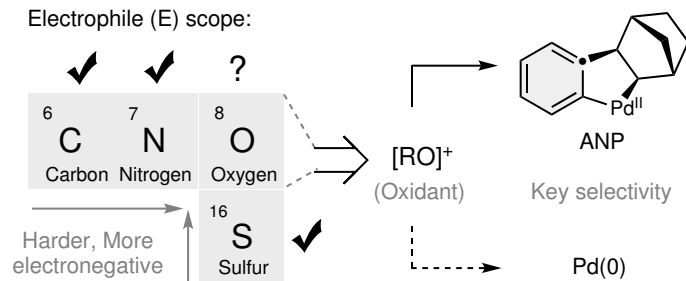
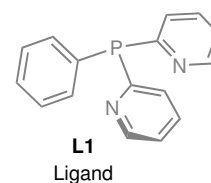
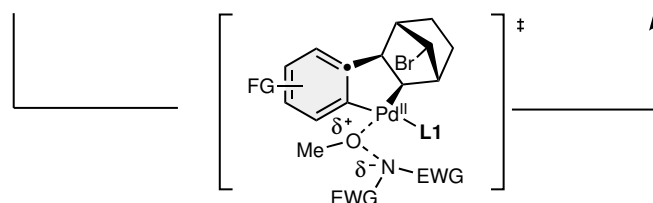
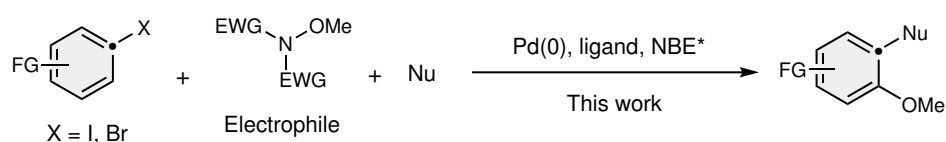


Dexlansoprazole
(Proton pump inhibitor)

b**c****d**

X = I, Br, OTf

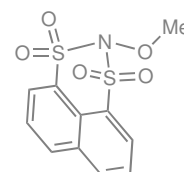
Electrophile (E) scope:

**e**

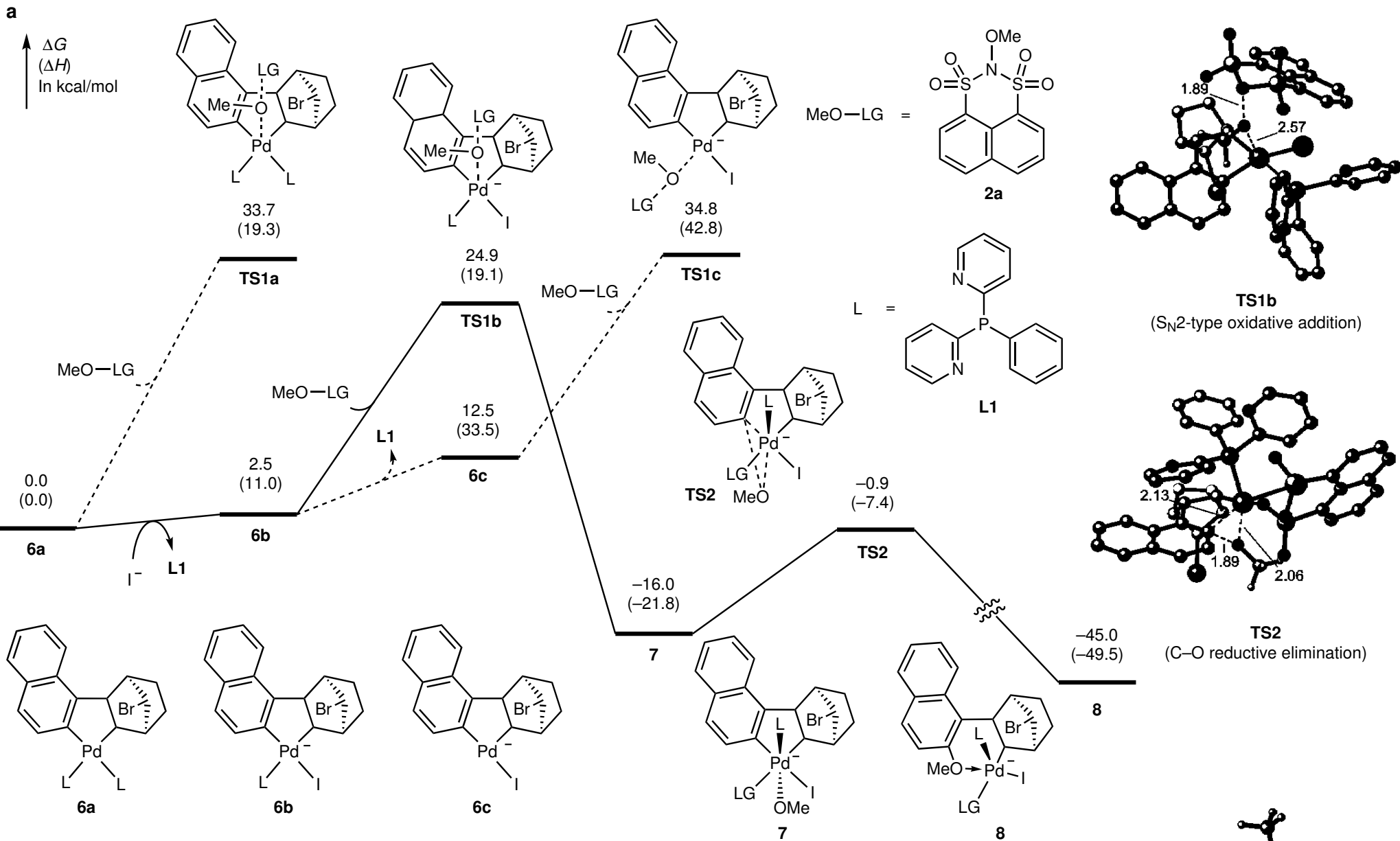
L1
Ligand



N1
NBE*

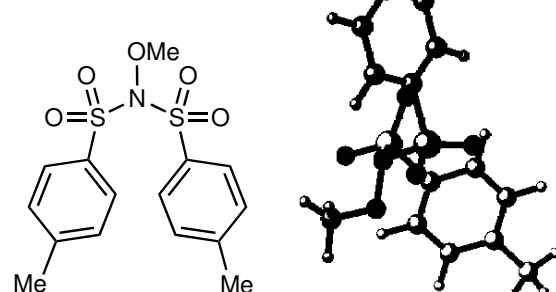
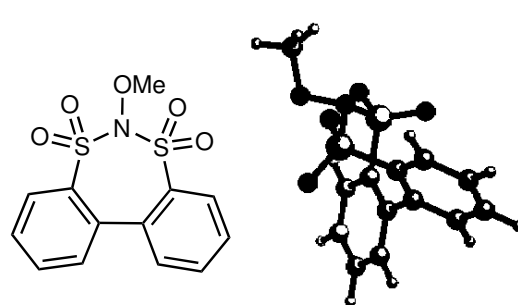
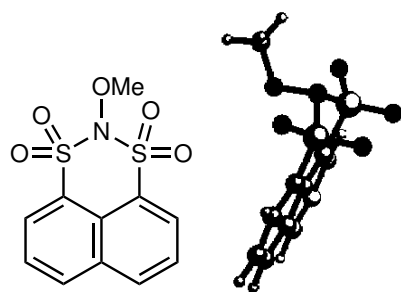


2a
Electrophile

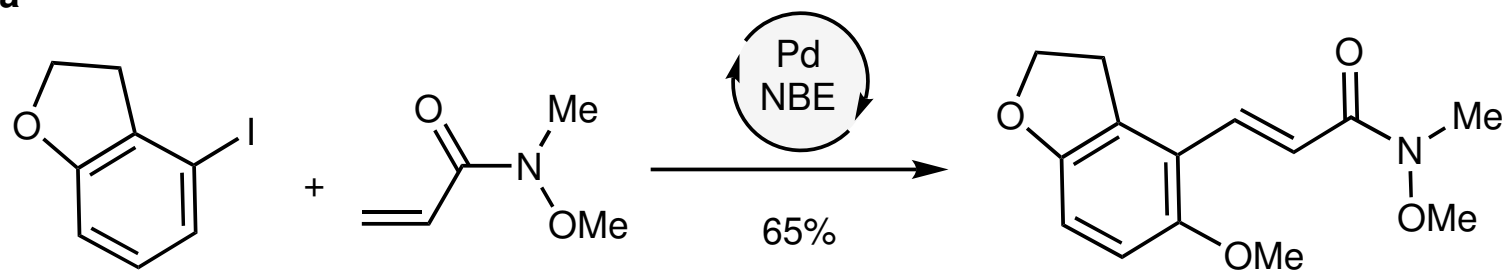


b

	$\Delta G^\ddagger$	$\Delta E_{\text{dist}}^\ddagger$	$\Delta E_{\text{int}}^\ddagger$
2a	22.4	45.1	-37.4
2f	27.3	37.8	-25.3
2c	32.7	50.9	-35.9



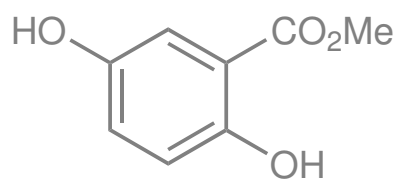
All energies are in kcal/mol with respect to **6b**.

a**1c****3f**

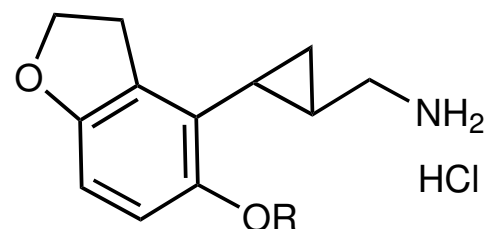
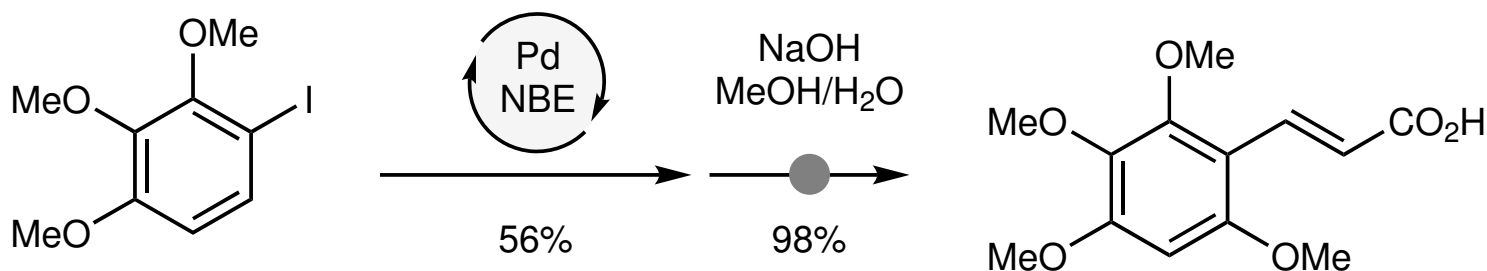
With this method: 2 total steps

9

Prepared in one step

**11**

Methyl 2,5-dihydroxybenzoate

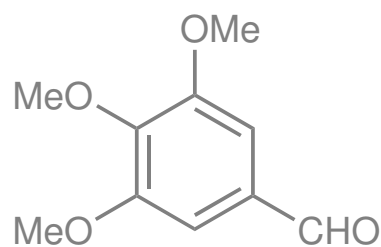
Prior approach
7 steps**10**R = Alkyl or Allyl
5-HT_{2C} Receptor agonist**b****1w**

With this method: 3 total steps

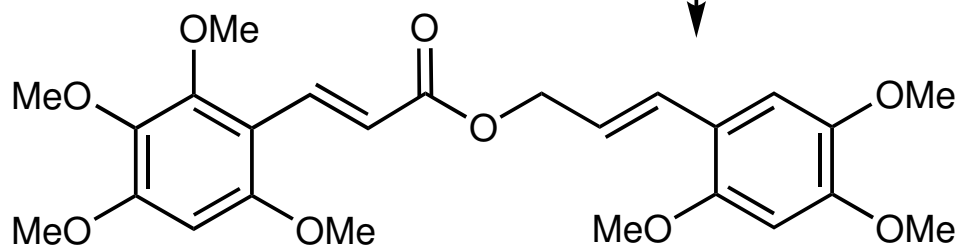
12

Prepared in one step

Prior approach 6 steps

**14**

3,4,5-Trimethoxybenzaldehyde

**13**Cinnamic α -asaronol esters
(Anticonvulsant activity)

Simple & Commerical

1,2,3,4,5,6-

1,2,3,4,5-

1,2,3,4-

1,3,5-


X = I, Br

Widely available

Methoxylation

Para-selective



15

Condition A
50%
2.0 mmol scale

16

72%

17

94%

1,2,3,4-

18

1,2,3,4,5,6-
21

 TIPS
 Pd(PPh₃)₄, CuI

 TEA, DMF, 110 °C
 70%



 1,2,3,4,5,6-
20

NBS, AuCl₃
DCE, r.t.
←
53%

1,2,3,4,5-
19

25

$\text{PdCl}_2, \text{PPh}_3$

 87%



24

PhNTf₂, TEA
←
DMAP, DCM
90%

23

$\xleftarrow[\text{-78 } ^\circ\text{C to 0 } ^\circ\text{C}]{\text{BBr}_3, \text{ DCM}}$
 81%

1,2,3,4,5-
22



 26

 Condition B

 52%

 (Borneol)

27

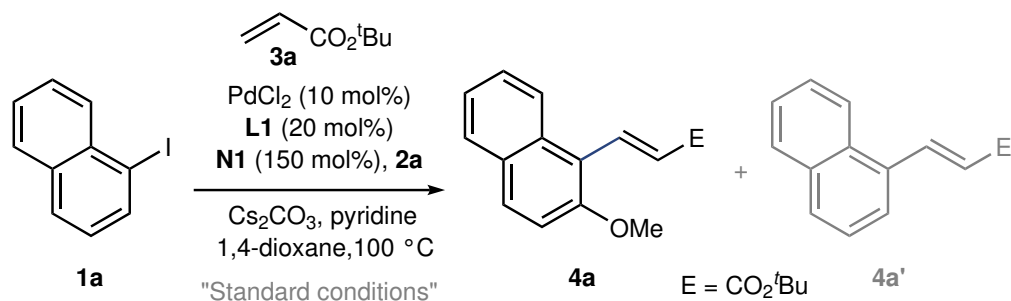
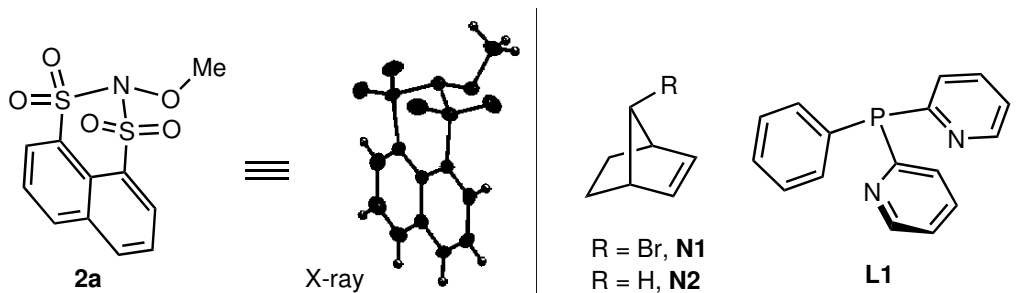
I₂, Ag₂SO₄
MeOH, r.t.

85%
p/o = 10:1

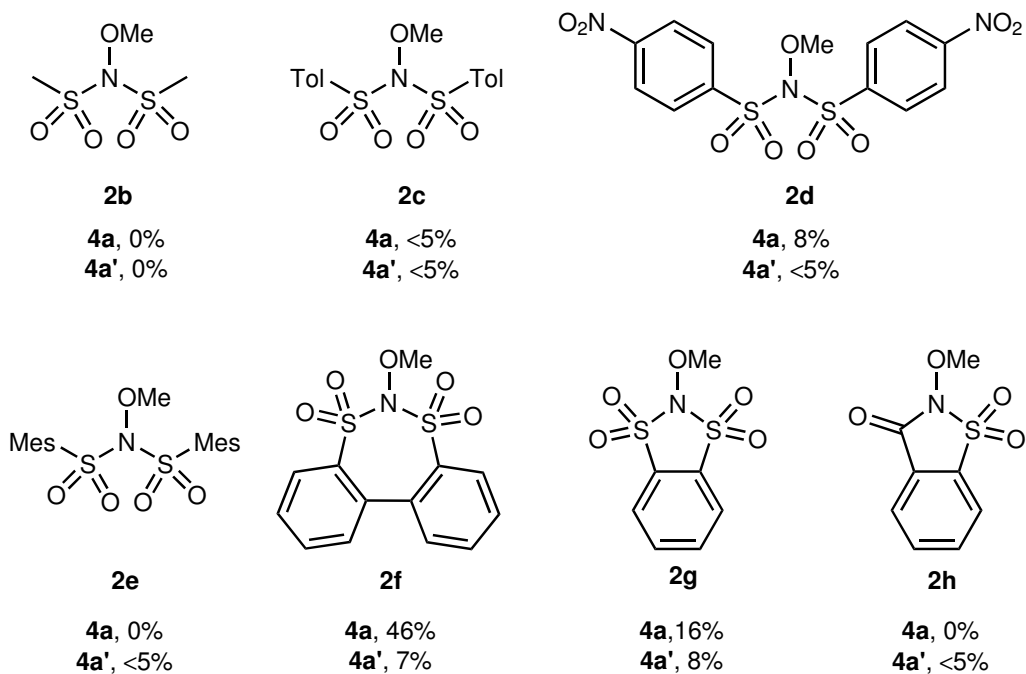


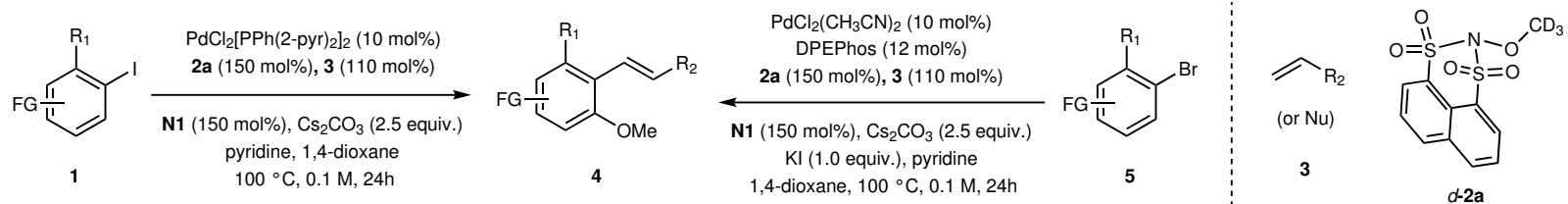


Chemical structure of compound **29**: 1,3,5-trimethyl-2-(benzyl(methyl)amino)-4-(trifluoromethoxy)benzene. The structure shows a benzene ring with a methyl group (Me) at position 1, a trifluoromethoxy group (OCD₃) at position 4, and a benzyl(methyl)amino group (N(Me)Bn) at position 2. The positions 1, 3, and 5 are labeled with 'Me'.

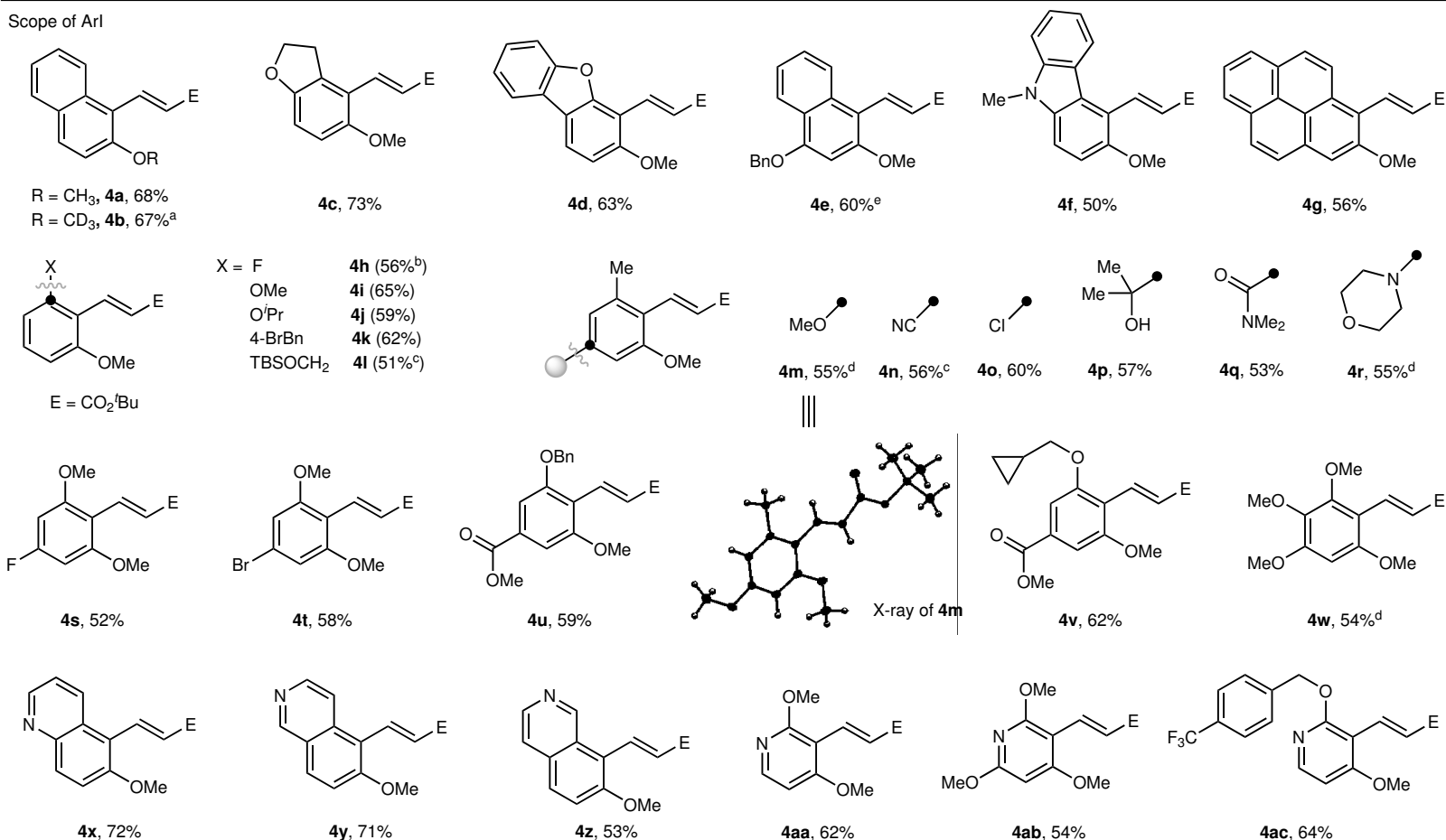


Entry	Variations from the "standard conditions"	Yield of 4a (%) ^a	Yield of 4a' (%) ^a
1	None	74 (68 ^b)	15
2	Other electrophile instead of 2a	Listed below	Listed below
3	No Pd	0	0
4	$\text{Pd}(\text{OAc})_2$ instead of PdCl_2	45	11
5	No L1	14	<5
6	PPh_3 instead of L1	65	16
7	$\text{P}(\text{2-pyr})_3$ 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

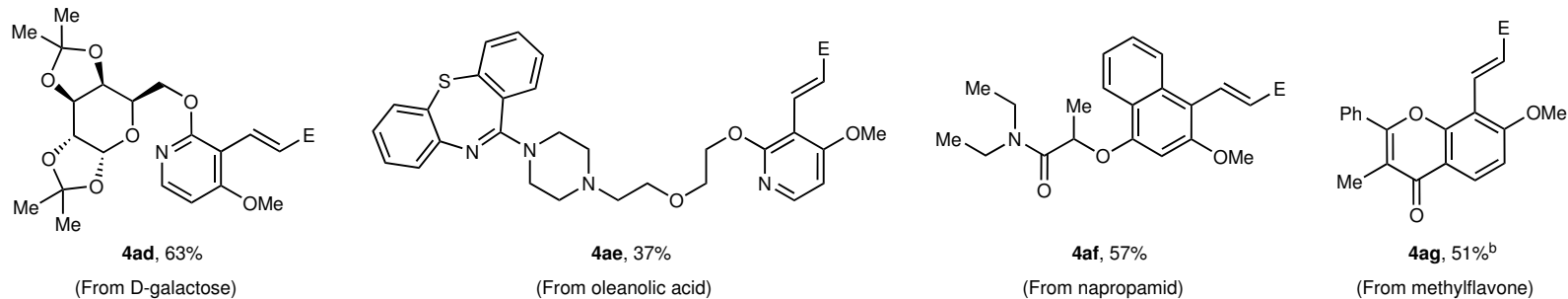




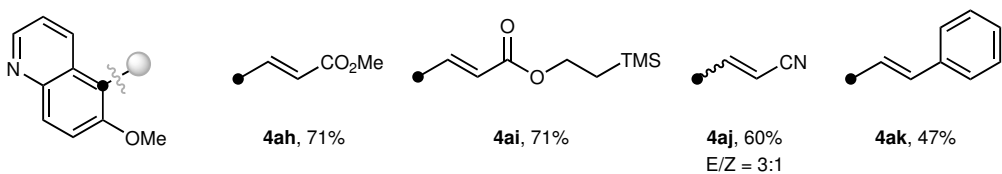
Scope of ArI



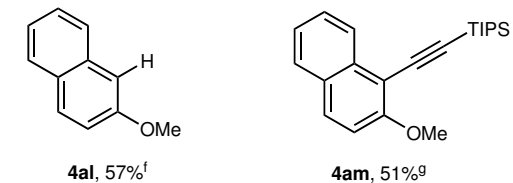
Different complex skeletons (ArI)



Olefin scope (ArI)



Nucleophile scope (ArI)



Scope of ArBr

