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Communication

Meta Alkylation

A Mild *meta*-Selective C–H Alkylation of Catechol Mono-Ethers

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Abstract: Catechol mono-ethers are an important class of phenols. They are found in a number of pharmaceuticals, flavoring agents, perfumes, and are used for the preparation of numerous drugs. Herein, we report a mild *meta*-selective C–H alkylation of these phenols, which is enabled by a cascade of oxidative dearomatization – radical addition – rearomatization process. The method is compatible with reactive functional groups on the parent arenol, such as olefins and halides. Primary, secondary, and teriary alkyl groups can be used, the source of which is most commonly an alkylborane. This process is operationally simple, does not require heating and generally proceeds in good yields.

Introduction

C–H functionalizations of aromatic compounds have relied on their electronic nature for over a century, in which electron-rich substrates have high selectivity for electrophilic attack at the *ortho*/*para* positions, while electron-deficient substrates undergo electrophilic attack at the *meta* position. Nevertheless, site-selective C–H functionalization of arenes, in which only one C–H bond is differentiated from the rest of the C–H bonds to give a single regioisomer, remains of particular interest. This is especially the case when the desired position of functionalization is contrary to the electronic bias of the arene. Of the selective C–H functionalizations of arenes, *meta*-selective C–H functionalization remains the most significant challenge, for which a number of state-of-the-art solutions have recently been reported.[1] Interestingly, phenol and its derivatives appear to be the most difficult arenes to undergo selective *meta*-functionalization. This is not entirely surprising as their electron-donating hydroxyl group directs the functionalization to *ortho* and *para* positions, for which a number of methods have been reported.[2]

One of the important classes of phenols are catechol mono-ethers, which include guaiacol, eugenol, vanillin, capsaicin, etoposide, and morphine and its analogues, among other compounds (Figure 1). Guaiacol is the most abundant catechol mono-ether, commonly obtained from the pyrolysis of lignin, and is used as a precursor to various other catechol mono-ethers. Due to the high demand and various uses of these phenol derivatives,[3] such as in pharmaceuticals, drug preparations, and flavor and fragrance industries, methods for selective functionalization of this class of phenols are of high value.

Recently, inspired by their work on *meta*-functionalization of arenes, Yu and co-workers[4] described a *meta*-functionalization

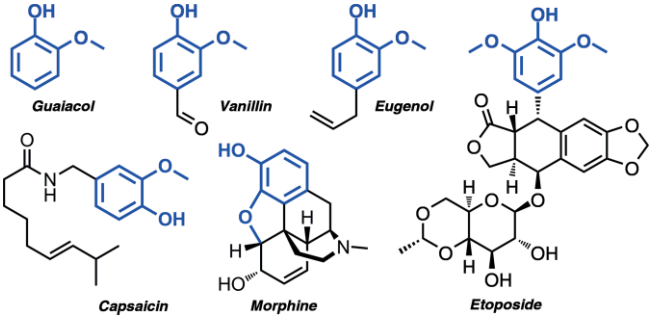

Figure 1. Examples of important catechol mono-ethers.

of phenols using an "end-on template." Here, an α-phenoxy acetamide bearing two nitrile-chelating groups is used to direct C–H palladation in the *meta*-position, upon which a 13-membered cyclopalladated intermediate forms and directs the addition of olefins (Scheme 1). Thereafter, Larossa and co-workers[5] reported a one-pot *meta*-arylation of phenols using a traceless directing group relay strategy. This method uses the well-established *ortho*/*para*-directing effect of a phenol to install a transient carboxyl group, allowing palladium-enabled cross-coupling arylation *ortho* to the carboxyl group, and thus *meta* to the hydroxyl group, which is then followed by a decarboxylation. Most recently, Wang and co-workers[6] have reported a *meta*-functionalization of naphthols using a carbamate-directing group, which allows *ortho*-palladation, and a sequential transmetallation to yield *meta*-arylated naphthols.

We hypothesized that the selective *meta*-functionalization of catechol mono-ethers (**1**) could be possible by means of polarity inversion, or an *umpolung* strategy (Scheme 2). By oxidative dearomatization,[7] the inherent *ortho*/*para*-directing "donor" nucleophilic catechol mono-ethers, could be changed into electrophilic *meta* "acceptors" (**2**). Our goal was to use a mild tin-free, radical addition – rearomatization cascade to furnish net *meta*-alkylation products (**3**). This $C(sp^3)$–$C(sp^2)$ bond forming process is not feasible by the currently reported methods shown in Scheme 1, thus it presents a new strategy for *meta*-functionalization of this class of phenol derivatives.

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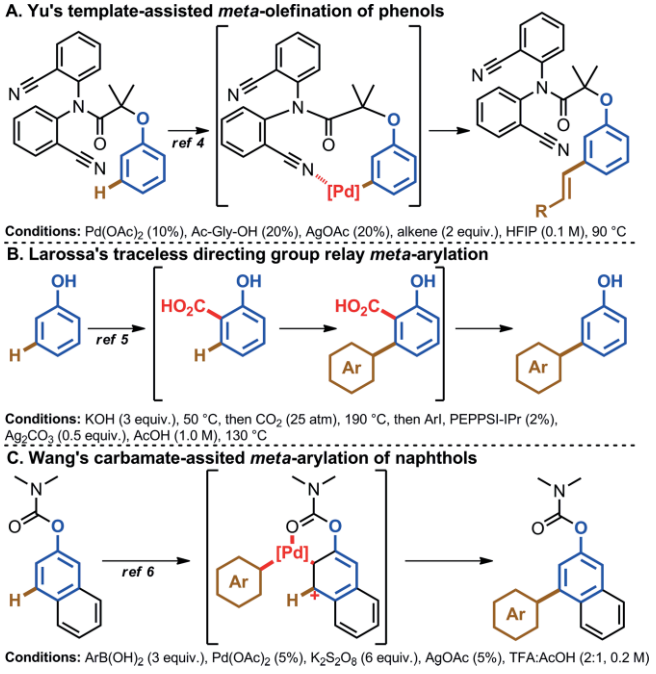
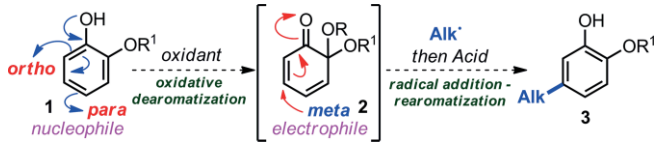


Scheme 1. *meta*-Selective C–H functionalization of phenols.

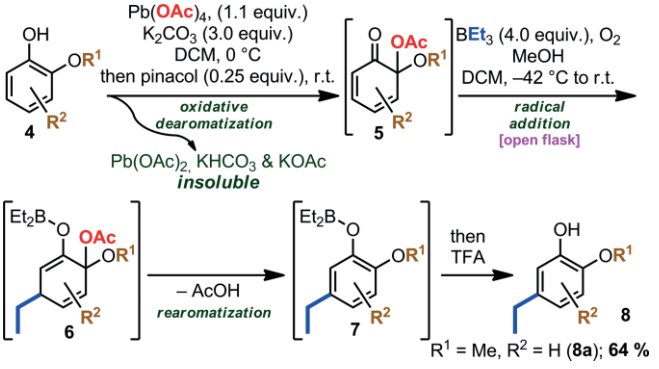


Scheme 2. *meta*-Selective alkylation via oxidative dearomatization – radical addition – rearomatization of catechol mono-ethers.

Results and Discussion

Based on our previous dearomatization – rearomatization investigations,[8] we decided to use the more stable *ortho*-quinone acetates[9] (**5**) as the radical acceptors (Scheme 3). They are readily generated using lead(IV) acetate[10] as the oxidant, which is our preferred method, and as shown by Quideau and co-workers, they can also be generated using phenyliodine diacetate (PIDA) in presence of acetic acid for a subset of substrates due to PIDA's lower reactivity compared to lead(IV) acetate.[11] Accordingly, we optimized the oxidative dearomatization reaction to telescope the isolation of the *ortho*-quinone acetates. This was accomplished by the addition of potassium carbonate and pinacol, which were used to quench the in-situ-formed acetic acid, and consume the leftover lead(IV) acetate, respectively. This protocol then allows filtration of the resulting insoluble potassium and lead(II) salts, providing an opportunity to *recycle* the oxidant by converting lead(II) acetate back into lead(IV) acetate.[12] The resulting filtrate now contains the desired *ortho*-quinone acetate, along with acetone, and traces of unreacted pinacol, neither of which interfere with the radical addition – rearomatization steps.

For our radical addition step, we chose trialkylboranes[13] because they can easily be converted to alkyl radicals under mild conditions upon treatment with molecular oxygen (O_2).[14] The radical formation is very facile, commonly taking place at low



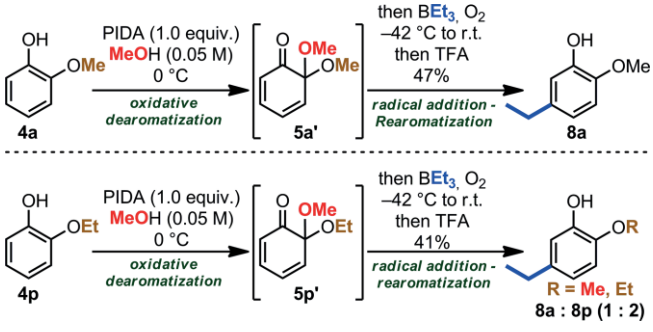
Scheme 3. Stepwise *meta*-alkylation of catechol mono-ethers.

temperatures, and the resulting radicals are more compatible with a broad range of functional groups than typically employed anion or organometallic-based nucleophiles. For our initial studies, we employed triethylborane as a source of an ethyl radical due to its commercial availability. We found that the radical addition step is compatible in various solvents with non-radical abstractable protons, such as dichloromethane (DCM), ethyl acetate, and trifluorotoluene, whereas solvents such as tetrahydrofuran (THF) and toluene proved to undergo competitive radical addition reactions.[14a] Therefore, our solvent of choice was DCM so both oxidative dearomatization and radical addition steps could be performed in the same solvent. We discovered that four equivalents of triethylborane ensured full consumption of *ortho*-quinone acetates, and that allowing the reaction to stir under open atmosphere proved most optimal. Addition of methanol demonstrated to reduce formation of polymers and other undesired products. Using these conditions, the reaction works at ambient conditions, but we chose to run the reaction at –42 °C to room temperature since it showed to be most reproducible. Trifluoroacetic acid (TFA) then helped protonate any remaining boron phenolate (**7**) to give the *meta*-alkylated phenol (**8a**) in a good yield upon isolation.[15]

For our reaction scope, we chose substrates containing halides (F, Cl, Br and I), and alkyl (methyl) groups in all three remaining available positions, as well as different mono-ether alkyl substituents (methyl, ethyl, allyl). These studies reveal that the method is compatible with halide substituents in all three positions, methyl substituents in two positions, and all mono-ether alkyl substituents. When R^4 is a methyl substituent, a mixture of the desired product **8k** along with other products formed, from which **8k** proved difficult to isolate. Additionally, substituents on the R^4 position make the resulting *ortho*-quinone acetates less reactive towards ethyl radicals, thus for substrates **4k**–**4o** the radical addition step was performed at room temperature. On the other hand, substrates with strong electron-donation or -withdrawing groups proved difficult to undergo complete dearomatization, or the resulting *ortho*-quinone acetates were too labile under our reaction conditions.

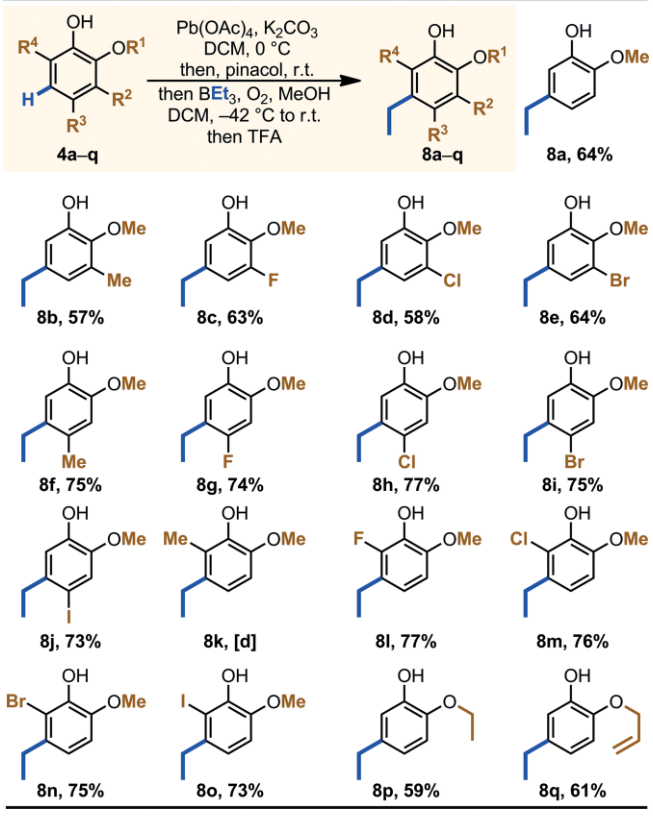
We also investigated whether *ortho*-quinone ketals, which are typically generated using PIDA in presence of an alcohol, were compatible with the radical addition step. When the dimethoxy *ortho*-quinone ketal (**5a′**) of guaiacol (**4a**) was treated with triethylborane in the same pot, **8a** was obtained in 47 %

yield. Although this makes the method more attractive, this results in a lower yield due to the inherent reactivity difference of the *ortho*-quinone ketal **5a′** compared to the *ortho*-quinone acetate **5a**. Additionally, as expected, this protocol cannot be used for *ortho*-quinone *mixed* ketals, as exposing **4p** to the same conditions gives a 2:1 mixture of **8p** and **8a**, due to the similar leaving group ability of methoxy and ethoxy groups. While this work was underway, Chittimalla reported that *stabilized ortho*-quinone ketals could be reacted with aryl and enolate nucleophiles to furnish *meta*-functionalized catechol mono-ethers.[16] Here, the use of *stabilized ortho*-quinone ketals, such as 3- and 4-substituted alkyl or ketal *ortho*-quinone ketals, is necessary to avoid the competing Diels–Alder self-dimerization (Scheme 4).



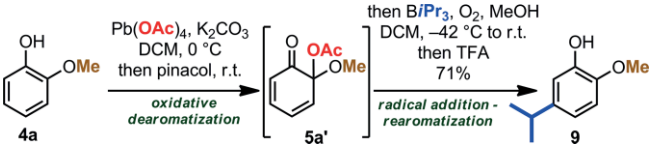
Scheme 4. PIDA-mediated *meta*-alkylation of catechol mono-ethers.

Table 1. Substrate scope.[a–c]



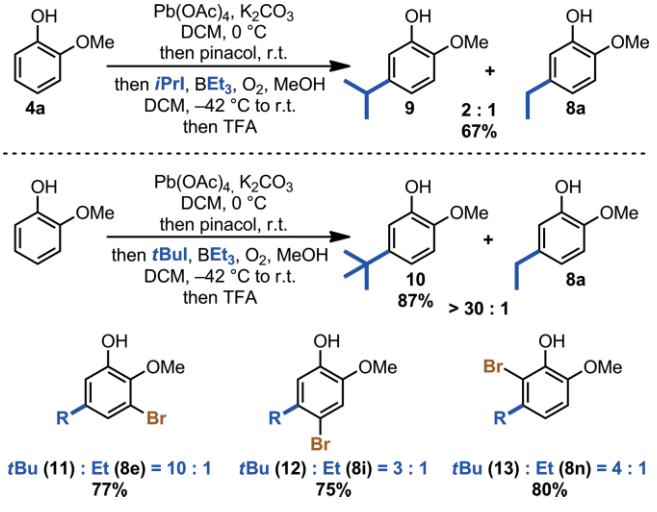
[a] Reaction conditions: substrate (1.0 mmol, 1.0 equiv.), lead(IV) acetate (1.1 mmol, 1.1 equiv.), potassium carbonate (3.0 mmol, 3.0 equiv.), DCM (10.0 mL), 0 °C, 30 min, then pinacol (0.25 mmol, 0.25 equiv.), r.t., 1 h, then filter through alumina plug (1.0 × 1.0 cm; basic, activity III), DCM (10.0 mL), methanol (1.0 mL), triethylborane (4.0 mmol, 4.0 equiv.), - 42 °C to r.t., overnight, then TFA (10.0 mmol, 10.0 equiv.), r.t., 1 h. [b] Radical addition step is run at room temp. instead of –42 °C to r.t. for substrates **4k**–**4o**. [c] Yield of isolated product is given. [d] Mixture of desired product and other products from which **8k** proved hard to be isolated.

Having chosen triethylborane as a source of an ethyl radical due to its commercial availability, we next explored triisopropylborane as a source of an isopropyl radical,[17] to showcase a difference between primary and secondary alkyl radical addition. When **4a** was exposed to the same conditions as those in Table 1, 5-isopropylguaiacol (**9**) was isolated in a 71 % yield (Scheme 5). Yet, it is our belief that this method should not be limited to trialkylboranes as evidence shows that under similar mild conditions, other *B*-alkylborane derivatives could also be used to generate alkyl radicals, including *B*-alkylcatecholboranes,[18] *B*-alkylboracyclanes,[19] and *B*-alkyldiphenylboranes.[20]



Scheme 5. *meta*-Isopropylation of guaiacol with triisopropylborane.

We also explored whether selective alkyl radical addition is possible when alkyl halides are used in presence of triethylborane.[21] When isopropyl iodide (15.0 equiv.) was used in presence of triethylborane, **4a** gave a 2:1 mixture of **9**:**8a** (Scheme 6). Attempts to optimize this reaction, such as by increasing the equivalents of isopropyl iodide, increasing the temperature of the reaction, slow addition of triethylborane, as well as running the reaction in neat isopropyl iodide, yielded no significant improvement. When *tert*-butyl iodide was used in presence of triethylborane, 5-*tert*-butylguaiacol (**10**) was formed almost selectively (> 30:1), and isolated in a great yield. However, when other catechol mono-ethers were used (brominated guaiacols) under the same conditions, the ratio of *tert*-butylated to ethylated products ranged from 3:1 to 10:1. These results



Scheme 6. Alkyl iodides as source of alkyl radicals.

reveal that the selectivity of alkyl radical addition is controlled by the difference between the rates of ethyl radical addition vs. iodine atom abstraction. Therefore, to selectively deliver an alkyl group of choice, it is best if a *B*-alkylborane derivative, such as a trialkylborane, is used as the alkyl radical source.

Conclusions

In summary, we have developed a mild, transition metal-free, and directing-group-free strategy for C–H *meta*-alkylation of catechol mono-ethers. This method utilizes a tandem oxidative dearomatization – radical addition – rearomatization protocol to form an otherwise challenging $C(sp^2)$–$C(sp^3)$ bond. Alkyl groups can be primary, secondary, or tertiary, and their source is commonly a trialkylborane, though in rare cases, it can also be an alkyl iodide in presence of triethylborane. The method is regioselective and orthogonal to traditional electrophilic substitution, and is compatible with various radical labile groups on the parent arene, such as halides and olefins.

Experimental Section

General Procedure for *meta*-Ethylation of Catechol Mono-Ethers with Triethylborane: To a flame-dried 50 mL round-bottom flask equipped with a stir bar, anhydrous potassium carbonate (414 mg, 3.0 mmol, 3.0 equiv) and lead(IV) acetate [95 %] (513 mg, 1.1 mmol, 1.1 equiv.) were added, the flask capped with a septum, cooled to 0 °C and purged with N_2. DCM (8 mL) was syringed in, and the slurry was vigorously stirred. To this slurry, a catechol mono-ether derivative (1.0 mmol, 1.0 equiv) in DCM (2 mL) was syringed in over 30 sec and the reaction was vigorously stirred at 0 °C until TLC showed complete consumption of the starting material (typically less than 30 min). The ice bath was removed, and pinacol (30 mg, 0.25 mmol, 0.25 equiv) in DCM (0.5 mL) was syringed in to consume left-over lead(IV) acetate and the reaction was stirred at room temperature for 1 h. To remove the insoluble solids, the slurry was then filtered through an alumina plug [1.0 × 1.0 cm] (Basic Alumina, Activity III) into a flame dried 100 mL round-bottom flask equipped with a stir bar, and the solids were thoroughly washed with DCM (10 mL). The filtrate was then equipped with an air condenser, and the flask cooled to –42 °C (dry ice/acetonitrile bath). Methanol (1.0 mL) was added, and the reaction mixture was stirred at –42 °C under open atmosphere (substrates **4k**–**4o** were ran at room temperature in absence of an air condenser and methanol). Triethylborane [1.0 M in hexanes] (4.0 mL, 4.0 mmol, 4.0 equiv) was syringed in and the reaction mixture was stirred at –42 °C to room temperature by allowing the cold bath to gradually warm to room temperature, and stirred overnight. Trifluoroacetic acid (0.8 mL, 10.0 mmol, 10.0 equiv) was syringed in to hydrolyze any remaining catechol mono-ether derivative O–B bonds, and the reaction was stirred for 1 h, following which methanol (5.0 mL) was added and the reaction mixture was concentrated in vacuo, and the remaining boron-containing species were co-evaporated with methanol (3 × 5 mL) to give the product as a residue, which was purified using acetic acid pre-treated silica gel flash column chromatography.

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Keywords: C–H substitution · Alkylation · Oxidative dearomatization · Radicals · Regioselectivity

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[15] Addition of silica gel (ca. 2 g/mmol substrate) to the reaction mixture also protonates the boron phenolate. This slurry is stirred for an hour, then filtered and flushed with diethyl ether.

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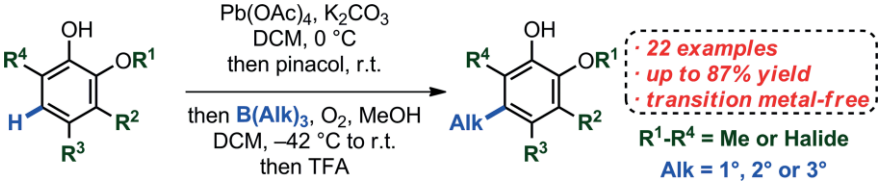

Catechol mono-ethers are dearomatized via lead(IV) acetate then reacted with trialkylboranes to give net *meta*-alkylated products. Primary, secondary and tertiary radicals can be added, and the method is compatible with reactive groups on the parent arene.

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