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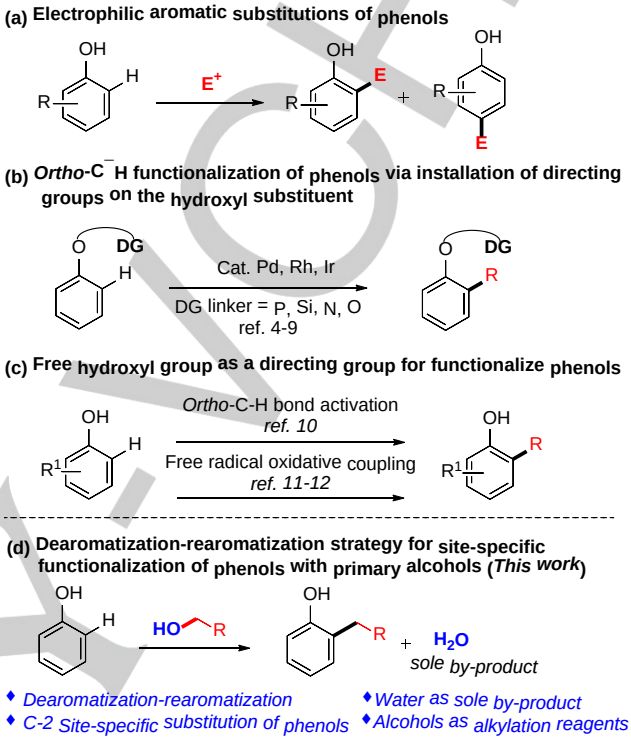
Dearomatization–Rearomatization Strategy for *ortho*-Selective Alkylation of Phenols with Primary Alcohols

Jianjin Yu,[a] Chao-Jun Li[b],* and Huiying Zeng[a],*

Abstract: Phenols are common precursors and core structures of a variety of industrial chemicals, ranging from pharmaceuticals to polymers. However, the synthesis of site-specifically substituted phenols is challenging, and thus the development of new methods for this purpose would be highly desirable. Herein, we report a protocol for palladium-catalyzed *ortho*-selective alkylation reactions of phenols with primary alcohols via a dearomatization–rearomatization strategy, with water as the sole by-product. Various substituted phenols and primary alcohols were compatible with the standard reaction conditions. The detailed mechanism of this transformation was also investigated.

Phenols are prevalent structural motifs in natural products, dyes, and biologically active compounds (including pharmaceuticals and agrochemicals), as well as other fine and bulk chemicals.[1] Therefore, the development of new methods for site-selectively functionalizing the aromatic ring of phenols would be highly attractive. The classical method for this purpose is the electrophilic aromatic substitution,[2] but it yields a mixture of *ortho*- and *para*-substituted phenol derivatives, owing to the strong electronic directing effects of the hydroxyl group (Scheme 1a). Alternatively, a two-step process involves allylation of the hydroxyl group and subsequent Claisen rearrangement, which also generates *ortho*- or *para*-allylated phenols.[3] Over the past several decades, many complementary methods for *ortho*-C–H functionalization of phenols have been developed. To achieve *ortho*-selectivity, researchers have developed methods that involve modifying the hydroxyl group with a directing group,[4] such as a silane or silanol,[5] an ester,[6] a carbamate,[7] an ether,[8] or a traceless phosphite group[9] (Scheme 1b). However because the directing group must be pre-synthesized and then removed afterwards, these methods are not atom or step economical. More recently, new methods that use the free hydroxyl group as a directing group to control the regioselectivity have been reported (Scheme 1c). For example, Yi and co-workers reported a protocol for *ortho*-vinylation of phenols with alcohols (or ketones) via hydroxyl-group-directed *ortho*-C–H bond activation reactions catalyzed by a cationic Ru–H complex.[10] In addition, oxidative cross-coupling reactions have been used to synthesize *ortho*-functionalized phenols via single electron transfer.



Scheme 1. Site-selective functionalization of phenols.

For example, iron-catalyzed oxidative coupling and annulation reactions of phenols and *β*-keto esters for the synthesis of benzofurans were reported by Li and Pappo groups;[11] while Wang and co-workers reported copper-catalyzed *ortho*-selective aminomethylation reactions of phenols via a single-electron-transfer radical-coupling process.[12]

However, because indigestible biomass is an abundant, sustainable source of primary alcohols,[13] the development of methods for direct reaction of such alcohols with phenols to generate *ortho*-substituted phenols would be highly desirable. The traditional protocol for such reactions involves the use of a strong Lewis or Brønsted acid to activate the primary alcohol to facilitate formation of a carbocationic alkylation reagent, which then undergoes nucleophilic attack by the phenol to form *ortho*- and *para*-substituted phenolic products. This chemistry poses two challenges: (1) primary carbocations readily rearrange to more-stable secondary carbocations, and thus secondary-alkyl-substituted phenols are obtained as the major products; and (2) both *ortho*- and *para*-substituted phenols are generated, which greatly reduces the yields of the desired *ortho*-substituted products and increases the difficulty of isolation.

Based on our previous work on cross-coupling of diaryl ethers or phenols via C(Ar)–O bond cleavage,[14] we recently developed a dearomatization–rearomatization strategy for reductive cross-coupling of indoles with ketones.[15] We hypothesized that a

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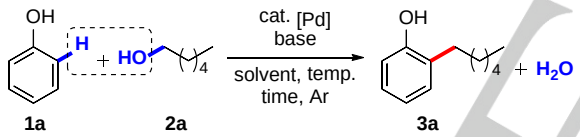
similar strategy could be used to synthesize *ortho*-substituted phenols. Specifically, if a primary alcohol could be converted to an aldehyde[16] and a phenol could simultaneously undergo reductive dearomatization to generate a small amount of the corresponding ketone, an aldol reaction between the aldehyde and ketone with subsequent dehydrogenative rearomatization would form an *ortho*-substituted phenol. Herein, we report that we have successfully developed a protocol for palladium-catalyzed *ortho*-selective alkylation of phenols with primary alcohols via a dearomatization–rearomatization strategy (Scheme 1d).

We began by elucidating the optimal conditions via the reaction of phenol (**1a**) and 1-hexanol (**2a**) (Table 1). To our delight, a Pd/C-catalyzed reaction of these two model compounds in the presence of NaOH as an additive in toluene at 160 °C under argon for 12 h afforded 12% yield of the desired *ortho*-substituted product **3a** (Table 1, entry 1). Exploration of various acidic and basic additives revealed that *t*-BuOLi improved the yield to 55% (entries 2–4). Other palladium catalysts were also tested, but Pd/C gave the best results (entries 5–7). A 1:2 phenol/1-hexanol ratio was found to be optimal (entry 8), and the amount of *t*-BuOLi could be decreased to 10 mol% (entry 9). Evaluation of different solvents revealed that toluene was the best one (entries 10–12). Prolonging the reaction time to 24 h improved the yield to 84% (entry 13). Increasing or decreasing the reaction temperature had a deleterious effect on the yield (entries 14 and 15), and so did reducing the catalyst loading (entry 16). In contrast, increasing the catalyst loading to 10 mol% had essentially no effect on the yield (entry 17). For details, please see Table S1 in Supporting Information.

Table 1. Optimization of reaction conditions.[a]



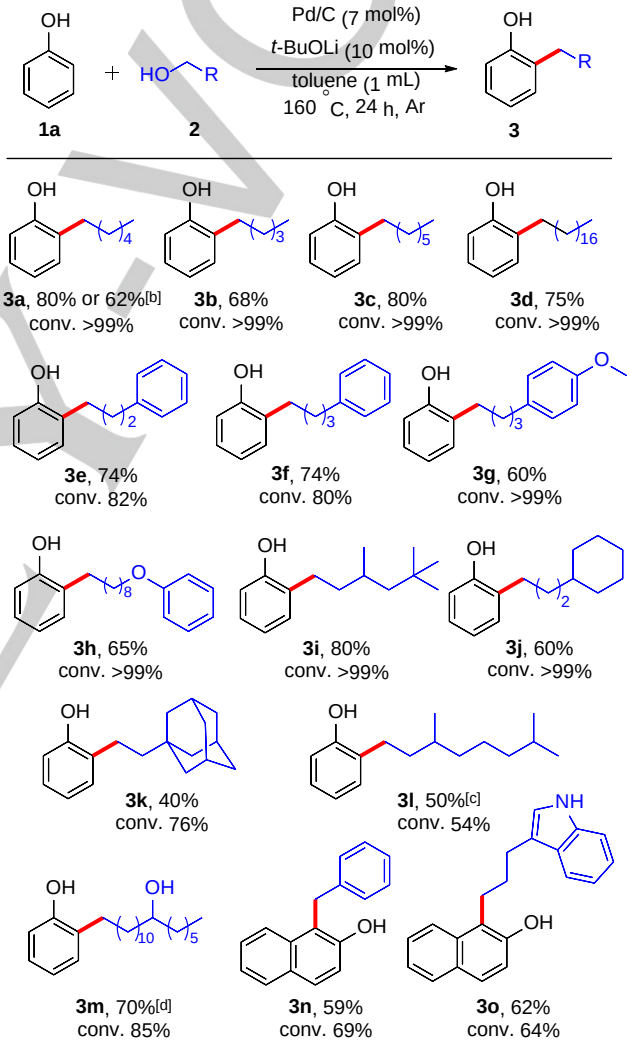
1a 2a 3a

Entry	Catalyst	Additive	Solvent	*T* (ºC)	Yield of 3a (%)[b]
1	Pd/C	NaOH	toluene	160	12
2	Pd/C	*t*-BuOLi	toluene	160	55
3	Pd/C	LiOH	toluene	160	43
4	Pd/C	TFA	toluene	160	n.p.
5	Pd/Al_2O_3	*t*-BuOLi	toluene	160	n.p.
6	$Pd(OH)_2/C$	*t*-BuOLi	toluene	160	5
7	$Pd(OAc)_2$	*t*-BuOLi	toluene	160	n.p.
8[c]	Pd/C	*t*-BuOLi	toluene	160	67
9[c,d]	Pd/C	*t*-BuOLi	toluene	160	67
10[c,d]	Pd/C	*t*-BuOLi	*m*-xylene	160	18
11[c,d]	Pd/C	*t*-BuOLi	heptane	160	50
12[c,d]	Pd/C	*t*-BuOLi	DMF	160	n.p.
13[c,d,e]	Pd/C	*t*-BuOLi	toluene	160	84 (80)
14[c,d,e]	Pd/C	*t*-BuOLi	toluene	150	70
15[c,d,e]	Pd/C	*t*-BuOLi	toluene	170	82
16[c,d,e,f]	Pd/C	*t*-BuOLi	toluene	160	77
17[c,d,e,g]	Pd/C	*t*-BuOLi	toluene	160	84

[a] General conditions: phenol (**1a**, 0.3 mmol), 1-hexanol (**2a**, 0.2 mmol), [Pd] (7 mol%), and additive (12.5 mol%) in solvent (1.0 mL) were heated at 160 °C for 12 h under argon. [b] Yields were determined by ^{1}H NMR with nitromethane as an internal standard; n.p. = no product. The yield in parentheses in entry 22 is an isolated yield. [c] Phenol (0.2 mmol), 1-hexanol (0.4 mmol). [d] *t*-BuOLi (10 mol%). [e] 24 h. [f] Pd/C (5 mol%). [g] Pd/C (10 mol%).

With the optimized conditions in hand (Table 1, entry 13), we set out to explore the scope of this *ortho*-selective alkylation reaction with respect to the primary alcohol (Table 2). All the tested linear aliphatic primary alcohols, regardless of their length, afforded the corresponding products in good to high yields (**3a–d**). When the scale of the reaction was enlarged to 3 mmol, the desired product **3a** was obtained in good yield (62%). Linear alcohols with a terminal phenyl group also afforded good yields of the desired products (**3e–f**), and so did alcohols with methoxy- and phenoxy-substituted phenyl groups (**3g** and **3h**). Terminal cyclohexyl and *tert*-butyl groups were also tolerated (**3i–j**). An alcohol with a sterically bulky *β*-adamantane group gave a moderate yield of **3k**. When citronellol was used as a substrate, we obtained product **3l**, resulting from reduction of the double bond in addition to alkylation. Notably, the reaction showed high chemoselectivity; a substrate with both a primary and a secondary

Table 2. Cross-coupling reactions of phenol with various primary alcohols.[a]



[a] Reaction conditions: phenol (**1a**, 0.2 mmol), alcohol **2** (0.4 mmol), Pd/C (7 mol%), and *t*-BuOLi (10 mol%) in toluene (1.0 mL) were heated at 160 °C for 24 h under argon. [b] 3 mmol scale reaction of **1a**. [c] Citronellol (0.4 mmol) was used as the starting material. [d] *t*-BuOLi (25 mol%).

hydroxyl group gave only the product of reaction with the primary hydroxy group (**3m**), in sharp contrast to the classical Friedel-Crafts reaction. Moreover, benzyl alcohol reacted well with 2-naphthol, affording **3n** in moderate yield. A heterocyclic alcohol was also tolerated: specifically, 3-(1*H*-indol-3-yl)propan-1-ol reacted smoothly with 2-naphthol to generate **3o** in good yield.

We also evaluated various substituted phenols (Table 3). When the phenol had a *para*- or *meta*-substituent, moderate yields of

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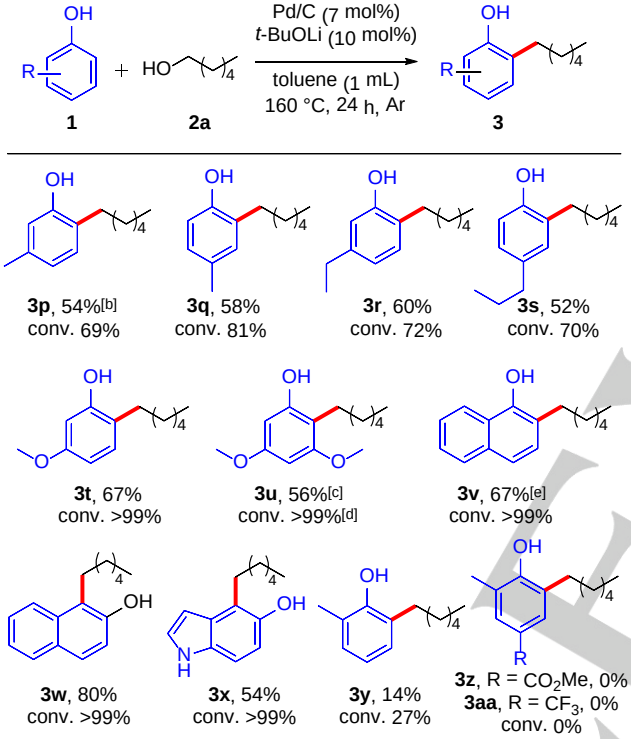
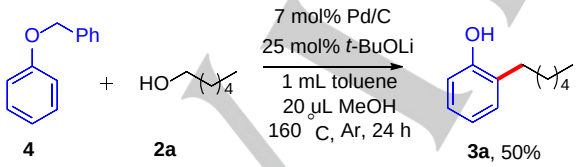
the desired products (**3p**–**3t**) were obtained. In addition, reactions of phenols bearing two substituents proceeded smoothly; for example, a phenol with methoxy groups at the *meta*-position gave the corresponding product (**3u**) in moderate yield. Furthermore, 2-naphthol and 1-naphthol were acceptable substrates, affording good yields of **3v** and **3w**, respectively. Finally, 5-hydroxyindole, a heterocyclic phenol, reacted with 1-hexanol to generate 4-substituted indole **3x** in moderate yield. Due to the low reactivity of reductive dearomatization, only 27% of the o-cresol was consumed and the desired product **3y** was obtained in 14% yield, which could explain the fact that *ortho*-dual alkylation is not preferable. For the phenol with electron-withdrawing group (R = CO_2CH_3, CF_3), only recovered the corresponding phenols (**3z** and **3aa**) were obtained.

Table 3. Cross-coupling reactions of 1-hexanol with various phenols.[a]



[a] Reaction conditions: phenol **1** (0.2 mmol), 1-hexanol (**2a**, 0.4 mmol), Pd/C (7 mol%), and *t*-BuOLi (10 mol%) in toluene (1.0 mL) were heated at 160 °C for 24 h under argon. [b] *t*-BuOLi (20 mol%). [c] 3,5-Dimethoxyphenol (0.3 mmol) and **2a** (0.2 mmol) were used as starting materials. [d] Conversion of 1-hexanol. [e] HCO_2Na (1 equiv), *t*-BuOLi (20 mol%).



Scheme 2. Cross-coupling of benzyl phenyl ether with 1-hexanol.

When benzyl phenyl ether (**4**) and 1-hexanol (**2a**) were subjected to the standard reaction conditions, *ortho*-substituted phenol **3a** was obtained by means of reduction of the C–O bond of the benzyl ether (Scheme 2).

To have a better understanding of the catalyst, we examined the structures of the Pd/C before (Figure 1a) and after (Figure 1b) the reaction by transmission electron microscopy (TEM), respectively. As shown in Figure 1, Pd nanoparticles were highly dispersed over the entire carbon support. The particles approximately 2-8 nm in size were visible on the surface of carbon, indicating little change in morphology after the reaction. As expected, this little change in Pd dispersion during the reaction led to little difference in catalytic activity, in which 70% yield was obtained when the recovered Pd/C catalyst was re-used in the next catalytic reaction (Scheme S1, SI). Considering that the nanoparticle size of Pd/C was sensitive to catalytic efficiency, four different commercially available Pd/C catalysts were investigated for this transformation, which were also examined by TEM, respectively. The results illustrated that small size (2-8 nm) nanoparticles of Pd/C were beneficial to this reaction, giving higher yield (please see the detail TEM pictures and yields in Figure S2, SI).

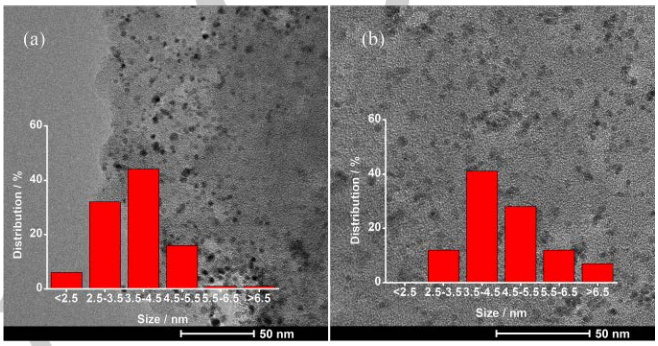


Figure 1. TEM images of Pd/C catalysts and size distribution of the Pd particle, (a) before the reaction and (b) after the reaction.

To investigate the reaction mechanism, we monitored distributions of all substances versus time for the reaction of phenol with 1-hexanol under standard reaction conditions by GC (please see Figure S3 in SI). The phenol and 1-hexanol were steadily consumed with time and the desired product was increased in tune. The by-product 2-hexylcyclohexan-1-one (**11**) increased slowly without decreasing over time. This information indicated that this by-product may not be an intermediate for the *ortho*-alkylation product. Several control experiments were also carried out (Scheme 3). Because direct cleavage of the C–O bond of the alcohol under our catalytic conditions would be difficult, it is likely that the first step was dehydrogenation of the alcohol to an aldehyde. Therefore, we carried out a reaction of hexanal (**5**) with phenol (**1a**) under the standard conditions and were surprised to find that the yield of desired product **3a** was poor, even when 1 equiv of sodium formate was added as a hydride source (Scheme 3a). The major by-product was undec-5-ene (**6**), which was generated by homocoupling of hexanal via an aldol/dehydration/decarbonylation process.[17] This result indicates that our catalytic conditions produced the aldehyde only transiently, in small amounts, which would be beneficial to achieve the desired reaction. Any aldehyde that was produced would react with the cyclohexanone produced by reduction of phenol, effectively preventing homocoupling of the aldehyde. We verified this possibility by carrying out a reaction of cyclohexanone (**7**) with hexanal (**5**),

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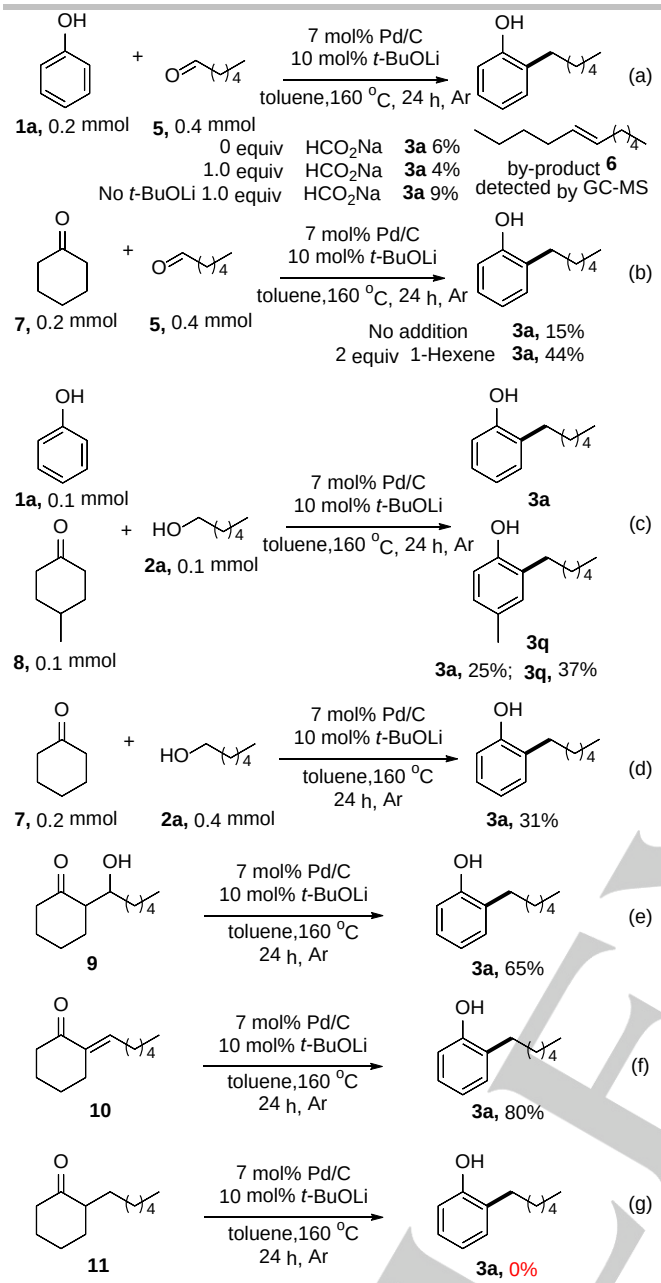
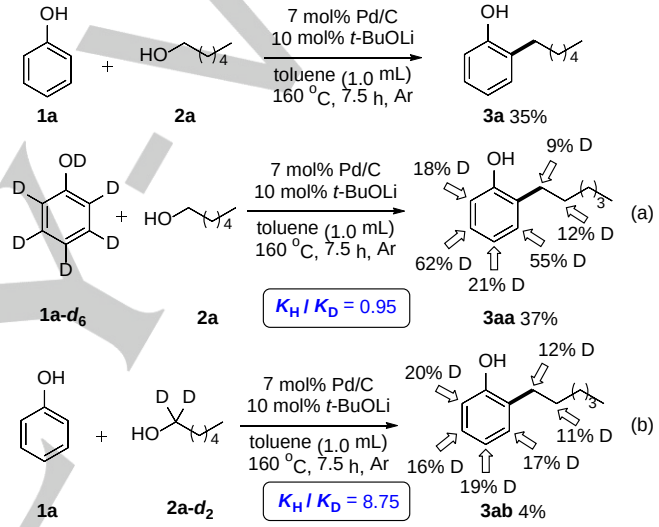


Scheme 3. Control experiments.

which afforded a 15% yield of **3a** even in the absence of an extra oxidant. When 2 equiv of 1-hexene was added to react with the hydrogen gas (please see Figure S7 in SI), the yield of **3a** increased to 44% (Scheme 3b). If both phenol (**1a**) and cycloketone **8** were present in the reaction system, two *ortho*-substituted phenols, **3a** and **3q**, were generated (Scheme 3c). In addition, reaction of cyclohexanone (**7**) with alcohol **2a** under the standard reaction conditions gave **3a** (Scheme 3d). These results show that phenol was first reduced to cyclohexanone, which then underwent further reaction. Specifically, either **9** or **10** was successfully converted to **3a** with good yield when either of these compounds was exposed to the standard reaction conditions (Scheme 3e and 3f). Those results illustrated that both **9** and **10** might be reaction intermediates for this transformation; however, none of the desired product was detected when by-product **11** was used (Scheme 3g). Taken together (Schemes 3f and 3g), these results illustrated the importance of the double bond, suggesting that it was not easily reduced under the conditions of our protocol.

In order to further explore the mechanism, kinetic isotope effect (KIE) experiments were also carried out (Scheme 4). Considering the possibility of *ortho*-C–H activation of phenol, phenol-d_6 and phenol were reacted under standard conditions for 7.5 h, respectively (Scheme 4a). The value of k_H/k_D was 0.95, demonstrated that there was no obvious KIE in this reaction (Please see detail in SI). In contrast, when C-1 positions deuterated alcohol **2a-*d*$_2$** and alcohol **2a** were explored under standard reaction conditions, respectively (Scheme 4b), the k_H/k_D = 8.75 of deuterated alcohol and alcohols indicated the dehydrogenation of the alcohol to aldehyde being the rate-limiting step for this transformation. At the same time, the C–H at all positions of phenol (**3ab**) was partially exchanged to deuterium (please see the detailed NMR spectrum,



Scheme 4. KIE experiments of phenol and alcohol.

Figure S5 in SI). This information suggested that the deuterium comes from the dehydrogenation of deuterated alcohol and further supported the process of dearomatization-rearomatization. It was interesting to note that the *C2*-position of the chain was also deuterated. This result further indicated the existence of the aldehyde intermediate, which underwent H–D exchange at the *alpha*-position of this aldehyde. These results also excluded the possibility of Pd-assisted dehydrogenative electrophilic aromatic substitution of alcohols. Furthermore, to exclude the possibility of the alcohol dehydration in this reaction, 1-octanene was used instead of 1-octanol under the standard conditions with or without adding water; no desired product was detected (please see Scheme S4 in SI).

On the basis of our experimental results, we propose the mechanism outlined in Figure 2. First, alcohol **A** is oxidized by the palladium catalyst to form aldehyde **B** and [HPd^{II}H]. Phenol **C** is reduced by [HPd^{II}H] to form cyclohexanone **D**, which undergoes a *t*-BuOLi-catalyzed aldol-type reaction with aldehyde **B** to generate alcohol **E**. Dehydration of **E** produces α,β-unsaturated ketone **F**, and then the exocyclic double bond of **F** isomerizes to an endocyclic double bond to generate ketone **G**. Finally, **G** undergoes oxidative aromatization to produce phenol **H** and regenerate [HPd^{II}H].

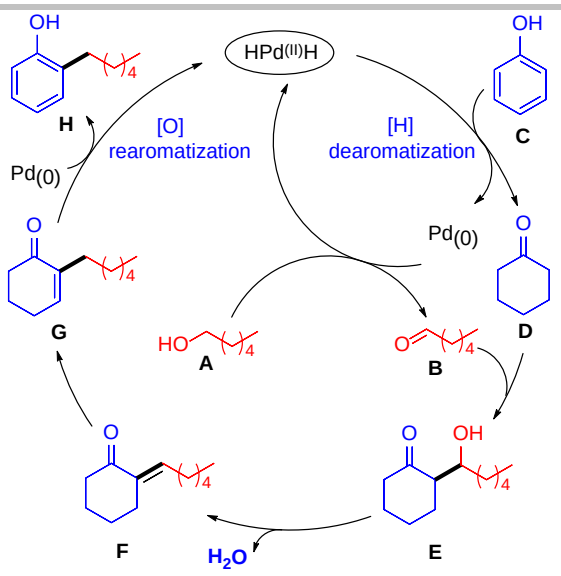


Figure 2. Plausible mechanism.

In conclusion, we have developed a protocol for palladium-catalyzed synthesis of *ortho*-alkyl-substituted phenols from phenols and primary alcohols via a dearomatization–rearomatization strategy. Water was the sole by-product of the reaction, making it a sustainable method for site-specific synthesis of these phenols.

Acknowledgements

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Keywords: dearomatization–rearomatization • *ortho*-substituted phenol • primary alcohol • palladium-catalysis

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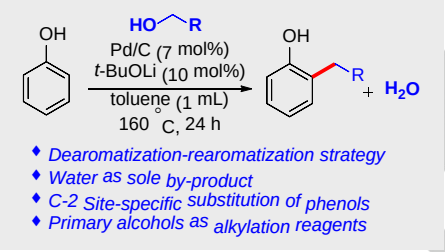
Layout 1:

COMMUNICATION

A dearomatization–rearomatization strategy was developed for palladium-catalyzed cross-coupling reactions of phenols and inexpensive primary alcohols to site-specifically generate *ortho*-alkyl-substituted phenols. Water was the sole by-product of the reaction, making it a green method for site-specific synthesis of these phenols.



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Dearomatization–Rearomatization Strategy for *ortho*-Selective Alkylation of Phenols with Primary Alcohols