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## Palladium-catalyzed aerobic synthesis of orthosubstituted phenols from cyclohexanones and primary alcohols<sup>†</sup>

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Due to the importance of phenols as structural cores and precursors of chemical products, synthesis of site-specific substituted phenols is highly desirable and a significant challenge. An aerobic palladium-catalyzed site-specific synthesis of *ortho*-substituted phenols from cyclohexanones and primary alcohols *via* an oxidation/aldol/dehydration/aromatization process has been developed. Various substituted cyclohexanones and primary alcohols are successfully transformed into *ortho*-substituted phenols. In addition, this catalytic reaction uses air as the terminal oxidant and generates water as the sole by-product. Furthermore, the method can also be extended to polyhydroxyl substituted substrates with high chemoselectivity between primary and secondary alcohols. This method provides a greener tool for synthesizing primary alkyl *ortho*-substituted phenols.

Phenols are common structural motifs and precursors of fine chemicals, such as pharmaceuticals and polymers. Functionalization of phenols at specific sites around the aromatic ring represents a key synthetic challenge.<sup>1</sup> The classical approaches to the synthesis of substituted phenols are via electrophilic aromatic substitutions of phenol.<sup>2</sup> However, strong electronically directing effects by the hydroxyl group of phenol associated with these reactions result in mixture of ortho- and para-substituted derivatives, which greatly affects the efficiency of synthesis and isolation.3 Therefore, extensive efforts were made to develop new methods to synthesize substituted phenols, e.g. via C-H oxidation to introduce a hydroxyl group into an aromatic ring<sup>4</sup> and transition-metal-catalyzed alkylation of phenols etc.<sup>5</sup> Recently, a new methodology of synthesizing substituted phenols via aerobic dehydrogenation of substituted cyclohexanones was pioneered by Stahl (Scheme 1a).<sup>6</sup> More recently, cyclohexanone or cyclohexenone were reacted with different nucleophilic reagents, such as alcohols,<sup>7</sup> amines,<sup>8</sup>

(a) Dehydrogenation synthesis of substituted phenols from substituted cyclohexanones



(b) Synthesis of 1-substituted arenes from cyclohexanone and nucleophiles



(c) Synthesis of 3-substituted phenols from cyclohexenone and boric acids



(d) Synthesis of 2-substituted phenols from cyclohexanone and primary alcohols (*This work*)



Scheme 1 Strategies for converting cyclohexanone and cyclohexenone into substituted arenes and phenols.

anilines,<sup>9</sup> indoles,<sup>10</sup> sulfonamides,<sup>11</sup> nitroarenes<sup>12</sup> and Grignard reagents,<sup>13</sup> followed by dehydrogenation aromatization to synthesize 1-substituted arenes (Scheme 1b). To synthesize 3-substituted phenols, a Heck reaction of cyclohexenone with boronic acid followed by oxidative dehydrogenation was also achieved by the Stahl group (Scheme 1c).<sup>14</sup>

As primary alcohols are usually very cheap and abundant commercially available organic chemicals. Thus, it is highly desirable to explore methods that can directly react primary

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alcohols with cyclohexanone to generate alpha-substituted phenols. Strong Lewis acids or Brønsted acids can active the C-OH bond of alcohols to form carbocation, which can undergo nucleophilic attack by phenols and serves as alkylation reagent.<sup>15</sup> However, there are still two problems for this reaction: (1) due to the easy rearrangement of primary carbocation to form the more stable secondary carbocation, secondary-alkyl substituted phenols are generally obtained; and (2) ortho- and para-substituted phenols are generated as a mixture with lower regioselectivity. We envisioned that primary alcohols can undergo oxidative dehydrogenation to form aldehydes, which can undergo an aldol-type reaction with cyclohexanone. Then facile dehydration generates  $\alpha,\beta$ -unsaturated ketone, which renders the C-OH bond much more easy to cleave than the C-OH bond of primary alcohols. Finally, oxidative aromatization forms the ortho-substituted phenols (Scheme 1d). This strategy can efficiently avoid the competing para-substituted phenol byproduct. Herein, we report the aerobic palladium-catalyzed site-specific synthesis of orthosubstituted phenols from cyclohexanones with primary alcohols via C-O cleavage and dehydrogenative aromatization.

We commenced our investigation by examining different bases to couple cyclohexanone with 1-hexanol (Table 1, entries 1-5). Fortunately, the highest yield (68%) of 2-hexylphenol was detected by <sup>1</sup>H NMR when Pd/C was used as catalyst in toluene at 150 °C under an air atmosphere for 12 h using lithium tert-butoxide (12.5 mol%) as base (Table 1, entry 1). Other inorganic bases were also examined with lower efficiency (Table 1, entries 2-4). When organic base (DBU) or acid (TFA) was used, no product was detected (Table 1, entries 5 and 6). Different palladium catalysts were then examined (Table 1, entries 7-10), and lower yields were obtained when palladium supported on Al<sub>2</sub>O<sub>3</sub> or Pd(OH)<sub>2</sub>/C was used (Table 1, entries 7 and 8). However, negative results were obtained when Pd(OAc)<sub>2</sub> or PdCl<sub>2</sub> was used as catalyst (Table 1, entries 9 and 10). Increasing or reducing the amount of lithium tert-butoxide led to lower yields (Table 1, entries 11 and 12). Less polar solvent (heptane) gave a lower yield (Table 1, entry 13). No product was detected when more polar solvent (DMSO or H<sub>2</sub>O) was used (Table 1, entries 14 and 15). When this reaction was performed under an argon atmosphere, the yield is lowered to 42% (Table 1, entry 16). However, a lower yield (50%) was also obtained when this reaction was performed under oxygen atmosphere (Table 1, entry 17). 1.5 equiv. of cyclohexanone appeared to be optimal for this reaction, as either higher or lower amount of cyclohexanone resulted in lower yields (Table 1, entries 18 and 19). Reducing the reaction temperature to 140 °C gave 55% yield of product (Table 1, entry 20). In contrast, increasing the temperature to 160 °C improved the yield to 75% (Table 1, entry 21). Further increasing the temperature to 170 °C almost gave the same yield (Table 1, entry 22). A similar yield was obtained when we reduced the catalyst loading to 7 mol% (Table 1, entry 23). On the other hand, increasing the catalyst loading to 15 mol% gave lowered yield (Table 1, entry 24). Reducing the reaction time to 5 h lowered the product yield (Table 1, entry 25). A 75% yield was obtained when prolonging the reaction time to 24 h (Table 1, entry 26).

With the optimized reaction conditions in hand, we next proceeded to explore cyclohexanone (1a) to react with different

 Table 1
 Evaluation of various conditions<sup>a</sup>

	о + но	[Pd] additiv solvent, T,	re time.	$\sim$	
	1a 2a			3a	
Entry	Catalyst	Additive	Solvent	$T/^{\circ}\mathbf{C}$	3a <sup>b</sup> /[%]
1	Pd/C	t-BuOLi	Toluene	150	68
2	Pd/C	NaOH	Toluene	150	35
3	Pd/C	NaH	Toluene	150	40
4	Pd/C	LiOH	Toluene	150	57
5	Pd/C	DBU	Toluene	150	n.p.
6	Pd/C	TFA	Toluene	150	n.p.
7	$Pd/Al_2O_3$	<i>t</i> -BuOLi	Toluene	150	26
8	$Pd(OH)_2/C$	<i>t</i> -BuOLi	Toluene	150	52
9	$Pd(OAc)_2$	t-BuOLi	Toluene	150	n.p.
10	$PdCl_2$	<i>t</i> -BuOLi	Toluene	150	n.p.
$11^c$	Pd/C	<i>t</i> -BuOLi	Toluene	150	25
$12^d$	Pd/C	<i>t</i> -BuOLi	Toluene	150	60
13	Pd/C	<i>t</i> -BuOLi	Heptane	150	61
14	Pd/C	<i>t</i> -BuOLi	DMSO	150	n.p.
15	Pd/C	<i>t</i> -BuOLi	$H_2O$	150	n.p.
$16^e$	Pd/C	<i>t</i> -BuOLi	Toluene	150	42
17 <sup>f</sup>	Pd/C	<i>t</i> -BuOLi	Toluene	150	50
$18^g$	Pd/C	<i>t</i> -BuOLi	Toluene	150	65
$19^h$	Pd/C	<i>t</i> -BuOLi	Toluene	150	65
20	Pd/C	<i>t</i> -BuOLi	Toluene	140	55
21	Pd/C	<i>t</i> -BuOLi	Toluene	160	75
22	Pd/C	<i>t</i> -BuOLi	Toluene	170	75
$23^{i}$	Pd/C	<i>t</i> -BuOLi	Toluene	160	75
$24^{j}$	Pd/C	t-BuOLi	Toluene	160	27
$25^{i,k}$	Pd/C	t-BuOLi	Toluene	160	60
$26^{i,l}$	Pd/C	t-BuOLi	Toluene	160	75(70)

<sup>*a*</sup> Reaction conditions: cyclohexanone **1a** (0.3 mmol), 1-hexanol **2a** (0.2 mmol), [Pd] (10 mol%), additive (12.5 mol%) and solvent (1.0 mL) at 150 °C for 12 h under an air atmosphere. <sup>*b*</sup> Yields were determined by <sup>1</sup>H NMR with nitromethane as internal standard; yields of isolated products were given in parentheses. <sup>*c*</sup> *t*-BuOLi (6.25 mol%). <sup>*d*</sup> *t*-BuOLi (25 mol%). <sup>*e*</sup> The reaction was performed under an argon atmosphere. <sup>*j*</sup> The reaction was performed under O<sub>2</sub> atmosphere. <sup>*s*</sup> Cyclohexanone (0.2 mol). <sup>*h*</sup> Cyclohexanone (0.4 mol). <sup>*i*</sup> Pd/C (7 mol%). <sup>*j*</sup> Pd/C (15 mol%). <sup>*k*</sup> For 5 h. <sup>*l*</sup> For 24 h.

primary alcohols at 160 °C under air atmosphere using 7 mol% of Pd/C as catalyst and 12.5 mol% of lithium tert-butoxide as base in toluene (1.0 mL) for 24 h. As shown in Table 2, various orthoalkylation of phenols were obtained with moderate to high yields (Table 2, 3a-p). Both cyclohexanone and cyclohexenone reacted very well with 1-hexanol, to give the same 2-hexylphenol product in high yields (Table 2, 3a). When alcohol was used as solvent, 2-ethylphenol was formed in moderate yield (Table 2, 3b). With the increasing in chain length, the yields of the corresponding ortho-alkylated phenols were formed with good yields (Table 2, 3c-d). Even though benzyl alcohol can be reduced to toluene readily with palladium catalysis under reductive conditions, 2-benzylphenol was also obtained in moderate yield under standard conditions (Table 2, 3e). 3-Phenylpropanol and 4-phenylbutanol were also successfully coupled with cyclohexanone in good yields (Table 2, 3f-g). Alcohol chain bearing terminal substituents, such as tert-butyl, cyclohexyl and adamantanyl, did not adversely affect this transformation and moderate to good yields were obtained (Table 2, 3h-j). The primary alcohol terminal substituted by a heterocycle, such as indole, benzofuran and thiophene, were also effective, giving moderate to



<sup>*a*</sup> Reaction conditions: cyclohexanone **1a** (0.3 mmol), alcohol **2** (0.2 mmol), Pd/C (7 mol%), *t*-BuOLi (12.5 mol%) in toluene (1.0 mL) at 160 °C for 24 h under an air atmosphere. <sup>*b*</sup> Cyclohexenone (0.2 mmol) and 1-hexanol (0.3 mmol) were used as starting materials. <sup>*c*</sup> Ethanol was used as solvent (1.0 mL). <sup>*d*</sup> Citronellol (0.2 mmol) was used as starting material.

good yields (Table 2, **3k–m**). Citronellol reacted smoothly in good yield; however, the double bond was also reduced under standard conditions (Table 2, **3n**). It is noteworthy that a free secondary alcohol group was also tolerated in this system, in which selective primary C–OH bond cleavage was achieved and the corresponding product **3o** was obtained in good yield (Table 2, **3o**). Interestingly, cholic acid derivative, polyhydroxyl steroid, was also successfully cross-coupled with cyclohexanone in good yield, in which three free secondary hydroxyl groups were not affected in this transformation (Table 2, **3p**).





<sup>*a*</sup> Reaction conditions: cyclohexanone **1** (0.3 mmol), 1-hexanol **2a** (0.2 mmol), Pd/C (7 mol%), *t*-BuOLi (12.5 mol%) in toluene (1.0 mL) at 160 °C for 24 h under an air atmosphere. <sup>*b*</sup> 3-methylcyclohexenone (0.3 mmol) was used as starting material. <sup>*c*</sup> 1-Tetralone (0.2 mmol) and 1-hexanol (0.3 mmol) were used as starting materials. <sup>*d*</sup> 1,2,3,4-tetrahydrocarbazol-4-one (0.2 mmol) and 1-hexanol (0.3 mmol) were used as starting materials.

We subsequently proceeded to investigate the generality of this system with different substituted cyclohexanones (Table 3). A methyl group substituted at different positions ( $\alpha$ -,  $\beta$ -,  $\gamma$ -) had no effect on this transformation, with moderate to good yields being obtained (Table 3, **3q**-**s**). When 3-methylcyclohexenone was used as a substrate, the corresponding product **3r** was obtained in moderate yield (Table 3, **3r**). With phenyl and *tert*-butyl groups substituted at the C-4 position, the corresponding phenol products were generated with moderate yields (Table 3, **3t** and **3u**). 1-Tetralone also successfully reacted with 1-hexanol, to give 80% yield of 2-hexylnaphthalen-1-ol (**3v**) (Table 3, **3v**). When 1,2,3,4-tetrahydrocarbazol-4-one bearing a free amine was used as substrates, the corresponding product **3w** was formed with good yield (Table 3, **3w**), and no competing *N*-alkylation byproduct was formed.<sup>16</sup>

To investigate the reaction mechanism, control experiments were carried out (Scheme 2). Considering the difficulty to cleave C–O bond of alcohol directly under our catalytic system, it is



Scheme 2 Control experiments.



more likely that the alcohol was oxidized to form aldehyde. With this conception in mind, hexanal (4) was reacted with cyclohexanone (1a) under standard reaction conditions, the desired product 3a was generated with 57% yield (Scheme 2a). This result was consistent with our proposal.  $\alpha$ , $\beta$ -Unsaturated ketone (5) was explored as a possible aldol-type reaction intermediate under our catalytic system, and the corresponding product was obtained in 64% yield (Scheme 2b).

According to these experimental results, a plausible mechanism for this transformation is proposed in Fig. 1. Alcohol **A** is oxidized by air catalyzed by palladium to form aldehyde **B**. Then, lithium *tert*-butoxide catalyzed aldol-type reaction with cyclohexanone **C** generates alcohol **D**, which readily dehydrates to form  $\alpha$ , $\beta$ -unsaturated ketone **E**. The exocyclic double bond of ketone **E** is isomerized to endocyclic double bond to generate ketone **F**, which tautomerizes to enol **G**. Finally, enol **G** undergoes oxidative aromatization to give the product phenol **H**.<sup>6d,8e,g</sup>

In conclusion, we have successfully developed an aerobic palladium-catalyzed synthesis of *ortho*-substituted phenols from cyclohexanones and primary alcohols *via* a tandem oxidation/ aldol/dehydration/dehydrogenation process. Various primary alkyl *ortho*-substituted phenols were generated by cross-coupling cyclohexanones with primary alcohols. In addition, this catalytic reaction uses air as the terminal oxidant and generates water as the sole by-product. Furthermore, the method can also be extended to polyhydroxyl substituted substrates with high chemoselectivity between primary and secondary alcohols. This method provides a greener pathway for site-specific synthesis of primary alkyl *ortho*-substituted phenols.

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#### Conflicts of interest

There are no conflicts to declare.

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