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A New Route to Phenols: Palladium-Catalyzed Cyclization and Oxidation of γ,δ-Unsaturated Ketones

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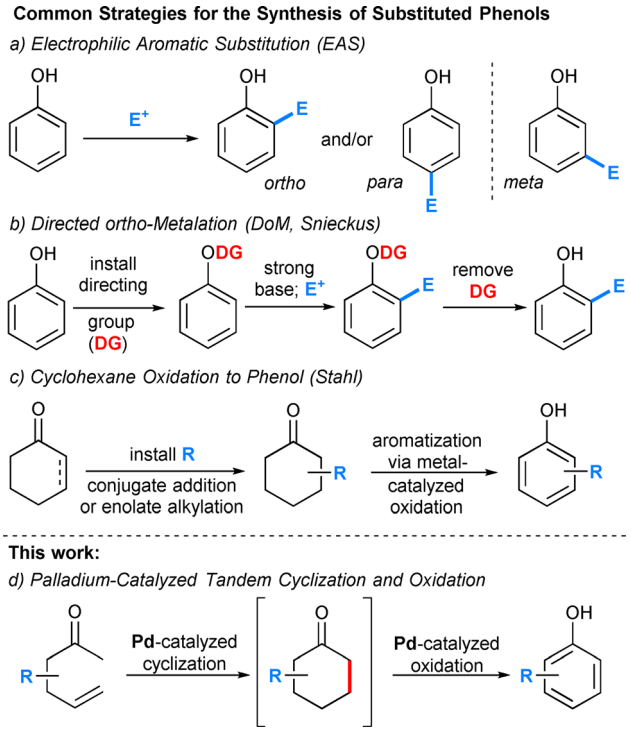
We report a new strategy for the synthesis of phenols from acyclic unsaturated ketones in one pot. The reaction proceeds by palladium-catalyzed carbopalladation of an alkene with the enol form of the tethered ketone, generating a substituted cyclohexanone. Upon introduction of a terminal oxidant a palladium-catalyzed oxidation ensues to give the desired phenol. This approach allows the programming of phenol substituents on the acyclic substrate and therefore circumvents the limitations inherent in traditional syntheses of phenols.

Polysubstituted phenols feature prominently as final products or intermediates in the synthesis of pharmaceuticals, complex natural products or functional materials.[1] The development of efficient strategies for their preparation is therefore an enduring challenge.[2] Depending on the substitution pattern present, their synthesis can be straightforward or may involve a considerable number of steps. Electrophilic aromatic substitution of phenols exploits the inherent nucleophilicity of the *ortho*- and *para*-positions (Scheme 1, a), and is therefore not suitable for the installation of substituents at the *meta*-position. Furthermore, it is possible to generate mixtures of compounds through double substitution. Perhaps the most common alternative to this approach is the directed *ortho*-metalation (DoM) strategy (Scheme 1 b).[3] This is an effective method for introducing substituents *ortho* to the hydroxyl group of the phenol, but requires the introduction and removal of directing groups, and is not suitable for the installation of groups at the *meta*- or *para*-position. Methods that selectively install *meta*-substituents on a phenol while leaving the *ortho*-position intact are rare and require the introduction and removal of cumbersome directing groups[4] or special reaction conditions.[5,6] The oxidation of substituted cyclohexanones with palladium has long been recognized as a method for the preparation of phenols (Scheme 1 c).[7] The need for environmentally responsible synthesis, combined with more sophisticated mechanistic understanding of palladium catalysis have renewed interest in this reaction.[8,9] This approach to substituted phenols circumvents the selectivity and reactivity constraints imposed by the hydroxyl group because substituents can be introduced at the cyclohexanone stage by conjugate addition or enolate alkylation reactions.



Scheme 1. Strategies for the synthesis of functionalized phenols: a) electrophilic aromatic substitution, b) directed *ortho*-metalation, c) oxidation of cyclohexanone to phenols, and d) palladium-catalyzed tandem cyclization and oxidation.

We envisioned a conceptually different method for the preparation of polysubstituted phenols. Specifically, we reasoned that a single palladium catalyst could promote the redox-neutral cyclization of γ,δ-unsaturated ketones and also catalyze the oxidation of the resulting cyclohexanones to substituted phenols upon the introduction of an oxidative switch (Scheme 1 d).[10,11] In this approach, the desired substituents on the phenol can be preprogrammed into the acyclic γ,δ-unsaturated ketones, which can be readily prepared using a variety of methods, thereby circumventing some of the limitations inherent in other approaches to phenols.

Our strategy for developing this reaction was to first identify practical conditions for the cyclization and aromatization reactions independently, and then combine them in a one-pot process. In a series of reports, Widenhoefer[12] and coworkers showed that γ,δ-unsaturated ketones could be converted to cyclohexanones using a Pd^{II} catalyst.[13] The proposed mechanism involves carbopalladation[14] of the alkene with the enol form of the ketone, a series of β-hydride elimination and insertion steps, and protonation of a palladium enolate (Scheme 2). These reactions required a high loading (10%) of palladium

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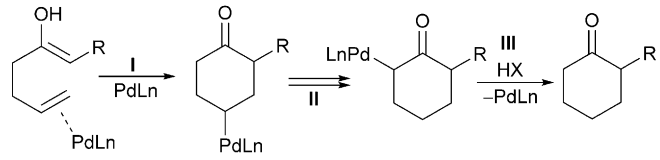
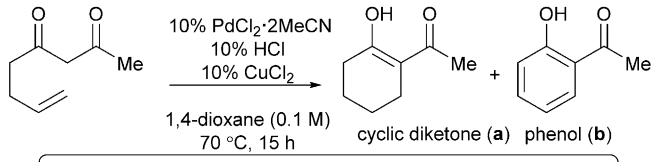
Key steps in palladium-catalyzed cyclization of unsaturated ketones



I carbopalladation, **II** sequential β-hydride eliminations and insertions. **III** protonolysis

Optimized conditions for palladium-catalyzed cyclization

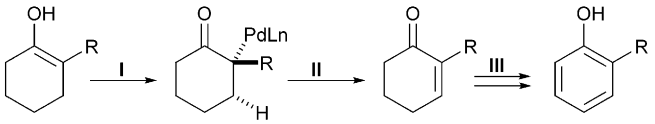


cyclic diketone (**a**) phenol (**b**)

	variation from optimized conditions	yield **a**	yield **b**
1	none	52%	15%
2	1% instead of 10% $PdCl_2$·2MeCN	53%	16%
3	no $CuCl_2$	48%	15%
4	toluene instead of 1,4-dioxane	60%	5%
5	DMF or DMSO instead of 1,4-dioxane	0%	0%

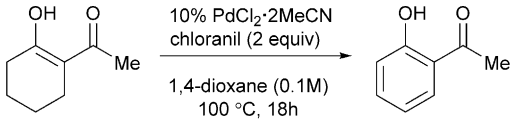
Scheme 2. a) Key steps in the palladium-catalyzed cyclization of γ,δ-unsaturated ketones, and b) summary of optimized conditions.

Key steps in palladium-catalyzed oxidation of cyclohexanones

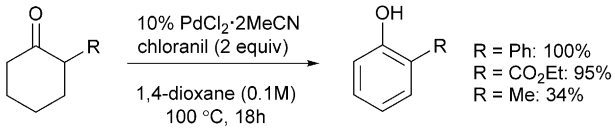


I Palladium enolate formation, **II** β-hydride elimination, **III** second oxidation and tautomerization

Optimized conditions



	variation from optimized conditions	yield
1	none	68%
2	5% instead of 10% $PdCl_2$·2MeCN	40%
3	1 instead of 2 equiv of chloranil	30%
4	toluene instead of 1,4-dioxane	<15%
5	no $PdCl_2$·2MeCN	0%



Scheme 3. a) Key steps in the palladium-catalyzed oxidation of cyclohexanones to phenols, and b) summary of optimized conditions.

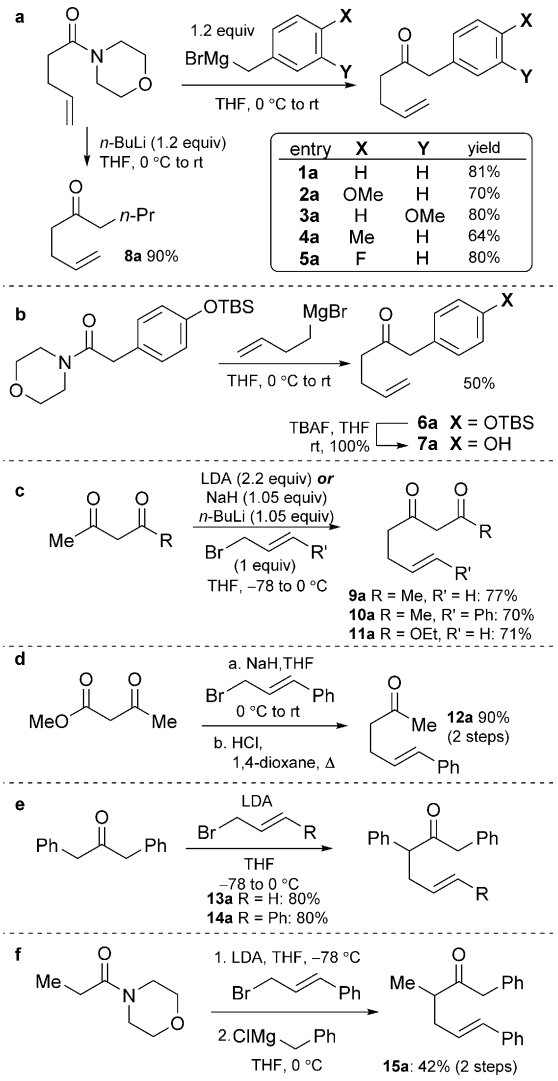
catalyst, and very low substrate concentrations owing to the formation of off-cycle substrate-bound polymeric palladium complexes at high concentration.[12] Furthermore, the addition of an acid was required to promote the formation of the enol tautomer of the ketone.

At the outset of our studies we aimed to identify a robust catalytic system that would allow us to run reactions at higher concentration and avoid the formation of unproductive palladium complexes. We thus evaluated a number of palladium(II) salts in combination with bidentate pyridine-like ligands. Despite extensive exploration, however, we were unable to identify a better catalyst than the $PdCl_2$·2 CH_3CN complex previously employed (see ESI). Nevertheless, we established that the reaction could be conducted with a lower catalyst loading (Scheme 2, entry 2). Using a combination $CuCl_2$ and HCl appeared to have a subtle but beneficial effect on the reaction (entry 3).[15] Furthermore, the reaction could be conducted in both dioxane and toluene as solvents (entry 4), but more polar solvents, such as DMF and DMSO, were not suitable (entry 5). We also observed that the desired phenol was formed along with the expected cyclohexanone.

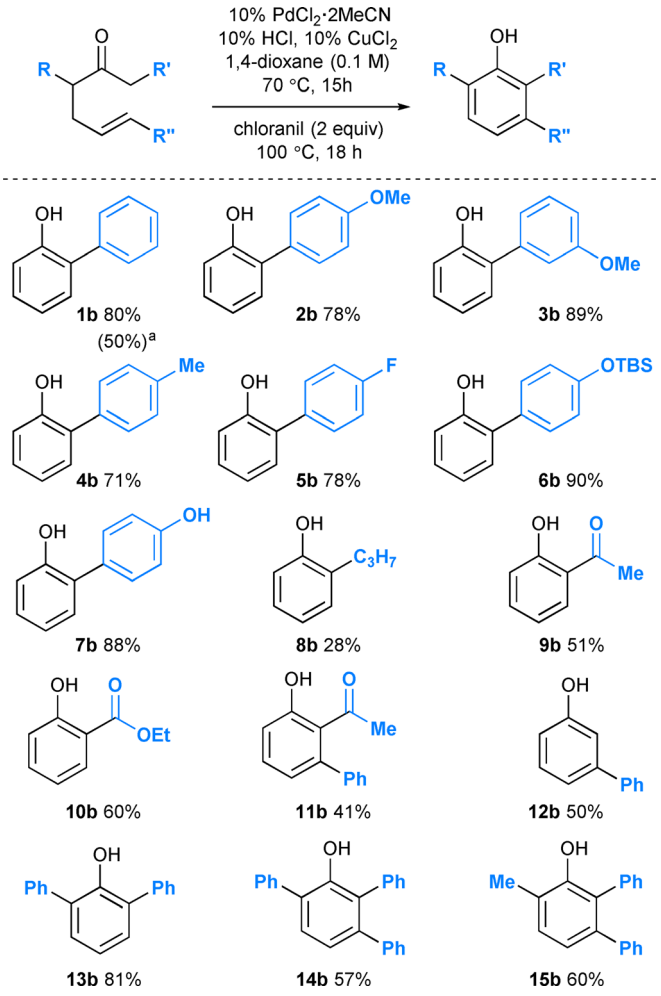
We then explored a variety of oxidants and reaction conditions for the oxidation step. We initially employed an atmosphere of oxygen as the terminal oxidant, but this proved ineffective. Similarly, the use of additives such as H_2O, which is required for oxidation of Cu in the Wacker process, and a range of electron transfer mediators (ETMs)[16] provided unsatisfactory results (see ESI for details). On the other hand, the use of stoichiometric amounts of quinone oxidants led to the expected product in good yield (Scheme 3). Reducing the catalyst loading from 10% to 5% (entry 2), or the amount of quinone oxidant from two to one equivalent (entry 3) led to a reduced yield. Although toluene was shown to be effective for the initial cyclization step (Scheme 2) it was not suitable for the oxidation step (Scheme 3, entry 4). Finally, removal of the palladium catalyst from the mixture does not lead to phenol, demonstrating that it is required for the aromatization step (entry 5). We wondered if the chelating ability of the product could interfere with the oxidation reaction, and therefore tested other substrates. If α-phenyl cyclohexanone is subjected to the same reaction conditions for oxidation, the corresponding phenol is obtained in high yield. A similar result is obtained if a cyclic ketoester is used, however the yield is diminished significantly if 2-methylcyclohexanone is used. This last observation may reflect the low enol concentration for this substrate.

Having identified suitable conditions for the cyclization and oxidation steps, we prepared a number of substrates that would lead to substituted phenols (Scheme 4). To demonstrate the flexibility of this strategy towards phenol synthesis, we employed a variety of routes to γ,δ-unsaturated ketones, including addition of Grignard reagents to morpholine amides (**a** and **b**, substrates **1a**–**8a**), Weiler alkylation of dienolates (**c**, substrates **9a**–**11a**), alkylation and decarboxylation of β-ketoesters (**d**, substrate **12a**), alkylation of ketone enolates (**e**, substrates **13a** and **14a**), or a combination of these steps (**f**, substrate **15a**).

Finally, we subjected these substrates to optimized conditions for the palladium-catalyzed cyclization and oxidation steps (Scheme 5). Substrates bearing a methylene flanked by a carbonyl group and an aryl group generated the desired phenols in uniformly good yields (**1b**–**7b**, 71–90%). If the reaction is conducted without $CuCl_2$ the yield of phenol **1b** was reduced from 80 to 50%, and therefore all other reactions were conducted using $CuCl_2$. The uniformly high yields for this substrate class may reflect the fact that a conjugated nucleophilic



Scheme 4. Strategies for the preparation of substituted γ-unsaturated acyclic ketones.



Scheme 5. One-pot palladium-catalyzed cyclization and oxidation of γ,δ-unsaturated ketones to phenols. [a] Reaction conducted without $CuCl_2$.

enol is readily formed prior to cyclization, and similarly during the first oxidation step. In contrast, substrate **8a** provides a poor yield of phenol **8b**, which may reflect the diminished acidity of the ketones, resulting in low concentration of the enols required for cyclization and oxidation. This result is consistent with the previous observations during our optimization studies (Scheme 3). Substrates bearing a 1,3-dicarbonyl group provided the desired phenols (**9b**–**11b**) in modest yields, which are also consistent with those observed in our optimization experiments. The reasons for these diminished yields are unclear, however, we note that *ortho*-acyl phenols are often used as chelating ligands on transition metal complexes, and may indeed remain bound to the catalysts (Pd or Cu) in this reaction. Substrate **12a**, bearing a methyl ketone group (see Scheme 4), allows the direct formation of a *meta*-substituted phenol, which can be hard to access. Under optimized reaction conditions this substrate yields the expected *meta*-phenol in modest yield, which again may reflect the low concentration of the enol tautomer required for both steps. Finally, substrates **13a**–**15a** provide trisubstituted products in good yields.

We have developed the first method for the direct conversion of acyclic, γ,δ-unsaturated ketones to phenols. In this method, the palladium catalyst serves to first cyclize the γ,δ-unsaturated ketone and then to oxidize the resulting cyclohexanone to the corresponding phenol upon the addition of a terminal oxidant. This strategy allows the pre-installation of multiple phenol substituents on the acyclic substrate and therefore circumvents the limitations inherent in other strategies. One current limitation of this method is the need for stoichiometric amounts of quinone oxidants for the aromatization step, and therefore further work will focus on identifying better catalyst systems and atom economical oxidants. Nevertheless, this strategy should streamline the preparation of phenols bearing difficult to access substitution patterns.

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Keywords: oxidation · palladium · phenol

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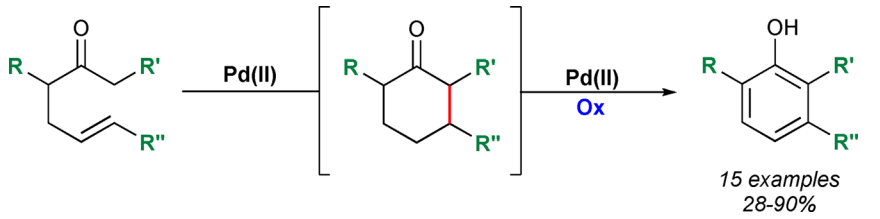

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A New Route to Phenols: Palladium-Catalyzed Cyclization and Oxidation of γ,δ-Unsaturated Ketones

2-in-1: A new strategy for the synthesis of substituted phenols from acyclic unsaturated ketones is described. The reaction features sequential redox-neutral palladium-catalyzed cyclization and palladium-catalyzed oxidation steps. This approach to phenols enables pre-programming of substituents on the acyclic system, and circumvents selectivity issues frequently encountered in the functionalization of phenols.