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An Unexpected α-Oxidation of Cyclic Ketones with 1,4-Benzoquinone by Enol Catalysis

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Abstract: *The first direct and asymmetric α-aryloxylation of cyclic ketones via enol catalysis has been achieved using quinones as the reaction partners. Catalytic amounts of a phosphoric acid promote the exclusive formation of α,α-disubstituted ketones from the corresponding α-substituted ketones in good yields and enantioselectivities (up to 96.5:3.5 er). Preliminary mechanistic experiments suggest that this reaction proceeds via a proton-coupled electron transfer (PCET) followed by radical recombination.*

Single-electron oxidation of enamines is a well-established activation mode for organocatalytic enantioselective α-functionalizations of simple aldehydes and ketones.[1] The oxidation of the corresponding α-branched ketones has so far not been reported because of the intrinsic limitations of enamine catalysis. Our group recently introduced enol catalysis as a versatile concept for the direct and selective α-functionalization of carbonyl compounds by in situ generated enols.[2] Accordingly, in the presence of a chiral phosphoric acid, α-branched ketones form the higher substituted enol, thereby enabling enantioselective access to the corresponding α,α-disubstituted ketones. A variety of catalytic asymmetric C–C and C–N bond-forming reactions utilizing this approach have been reported.[3] To further expand the scope of this activation mode, we envisioned a reaction of α-branched ketones with 1,4-benzoquinone, anticipating a 1,4-addition to the corresponding α-arylated product. Similar addition reactions have been reported with aldehydes, β-keto esters, substituted indoles, and 2-naphthol derivatives by using chiral secondary amines, cinchona alkaloids, or phosphoric acids as the catalysts.[4] However, to our surprise, the reaction of 2-phenylcyclohexanone (**1a**) and 1,4-benzoquinone (**2a**) in the presence of diphenyl phosphate (DPP) as catalyst did not provide products **3** or **4** but instead gave the α-aryloxylated product (**5a**, Figure 1).

Related products have previously only been observed as intermediates or side products in the oxidation of silyl vinyl ethers to enones using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant.[5] However, these reactions require preformed enol equivalents, strong oxidants, and have not been approached in a catalytic or an enantioselective fashion.

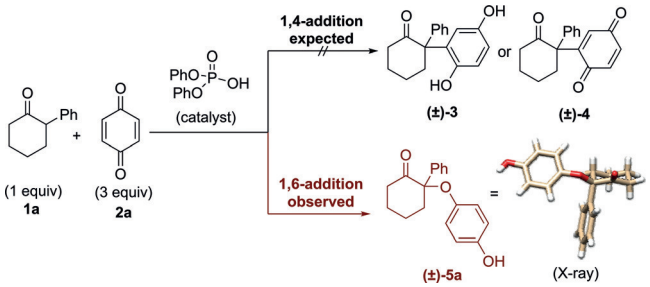

Figure 1. Initial discovery of a phosphoric acid catalyzed α-aryloxylation of α-branched ketones.

We also evaluated the catalytic potential of some other commonly used organic acids with 2-phenylcyclohexanone (**1a**) and 1,4-benzoquinone (**2a**) as the starting materials.[6] Interestingly, whereas catalytic amounts of DPP delivered exclusively the desired product, all other tested acids resulted in lower yields and selectivity towards aryloxylation, even at higher catalyst loadings. Notably, excess amounts of the quinone can be reduced with only a minor loss in yield; however, kinetic experiments suggest that it is involved in the rate-determining step (see below).[6]

We next turned our attention towards the generality of this transformation by testing various branched ketones under our reaction conditions (Scheme 1). Whereas α-aryl ketones readily reacted (**5a**–**5d**), α-alkyl ketones resulted in only trace amounts of the desired product, even after prolonged reaction times and elevated temperatures. In contrast to *ortho* substituents, *meta* and *para* substituents on the α-aryl group were well-tolerated (**5a**–**5d**), although an electron-withdrawing substituent did lead to a diminished yield and selectivity: product **5c** could only be isolated as an inseparable 5:1 mixture of 1,6- and 1,4-addition products. Unfortunately, only traces of the targeted products could be obtained when ketones of different ring sizes were employed as starting materials.[6] Interestingly, an indanone-derived β-keto ester gave exclusively the oxidized 1,4-addition product **6** as an inseparable mixture with 1,4-hydroquinone. The stereoelectronic properties of the quinone partner also proved to be important for the outcome of the reaction. Electron-poor quinones such as 2,6- and 2,5-dichlorobenzoquinone readily reacted to form the corresponding aryloxylated products (**5e** and **5f**). In contrast, electron-rich quinones such as 1,4-naphthoquinone or 2,6-dimethylbenzoquinone did not result in any conversion of the starting material. Additionally, chloranil, a strong oxidizing agent, gave no conversion of the starting material, presumably because of steric repulsions. Full, albeit unselective, conversion was observed with DDQ; however, no detectable amount of the desired

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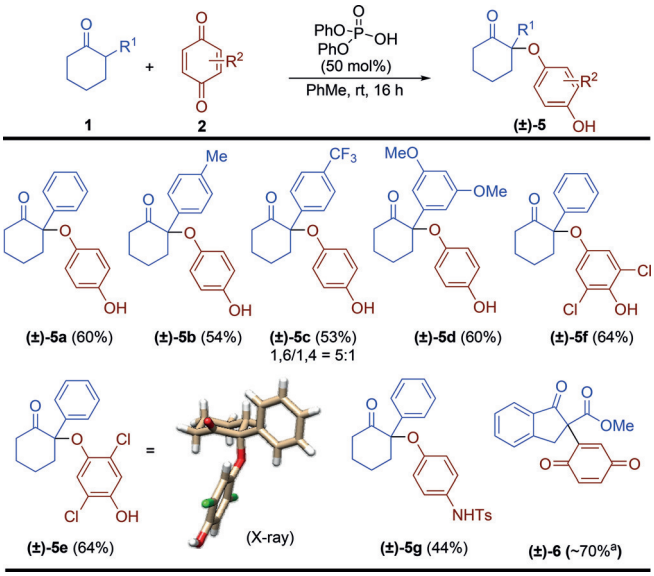
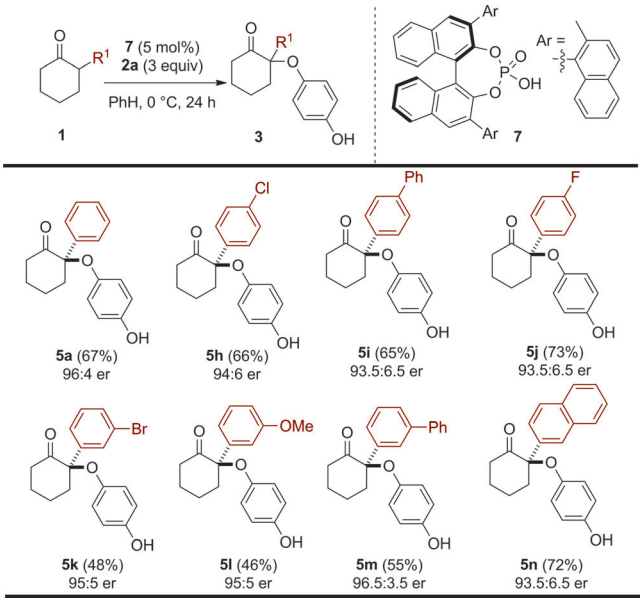


Scheme 1. Scope of the α-aryloxylation of α-branched ketones. Yields of isolated products are reported. Reactions were performed using ketone **1** (0.2 mmol), diphenyl phosphate (0.1 mmol), and quinone **2** (0.6 mmol) in anhydrous toluene at room temperature. [a] Isolated as an inseparable mixture with the corresponding hydroquinone.



Scheme 2. Scope of the asymmetric 1,6-addition of α-branched ketones to 1,4-benzoquinone. Yields of isolated products are reported. If not otherwise indicated, reactions were performed using ketone **1** (0.2 mmol), (*R*)-**7** (5 mol%), and 1,4-benzoquinone (**2a**; 0.6 mmol) in anhydrous benzene at 0°C.

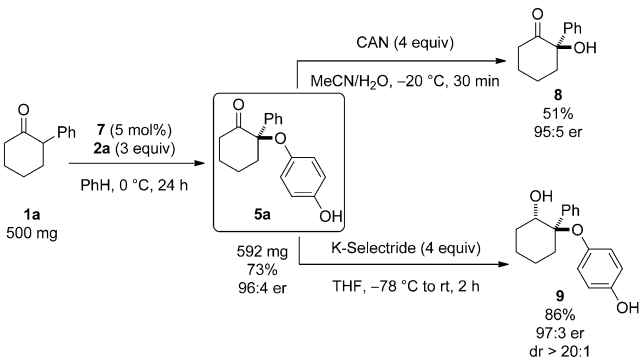
product was formed. Gratifyingly, the reaction with the 4-aminophenol-derived quinone formed exclusively the desired C–O bond, and product **5g** could be isolated in 44% yield.

In light of the uniqueness and potential utility of the method, we then attempted to develop an asymmetric variant of the transformation, with 2-phenylcyclohexanone (**1a**) and 1,4-benzoquinone (**2a**) employed as model substrates.[6] Gratifyingly, by using 1,1′-binaphthol (BINOL) derived phosphoric acids, the catalyst loading could successfully be reduced to 5 mol%. Further screening of reaction conditions and catalysts led to catalyst **7**, which gave the desired product **5a** in 67% yield and 96:4 er.[6,7] In all cases, products resulting from 1,4-conjugate addition were only obtained in trace amounts, and the lower yields of product **5a** observed in some cases can be attributed to the formation of uncharacterized side products.

With the optimized conditions in hand, we shifted our attention towards the scope of this asymmetric α-aryloxylation with 1,4-benzoquinone (**2a**; Scheme 2). Similar to the non-enantioselective transformation depicted in Scheme 1, α-aryl ketones were the preferred substrates and readily reacted under the optimized conditions. Substituents in the *para* position of the α-aryl group were well-tolerated and the corresponding products could be isolated in similar yields as with the model substrate **1a**, but with a slight erosion of enantioselectivity (**5h**–**5j**). Substituents in the *meta* position caused a decrease in yield, but a slight increase in the enantioselectivity (**5k**–**5m**). 2-(2-Naphthyl)cyclohexanone was also well-tolerated under the reaction conditions (**5n**, 72% yield, 93.5:6.5 er). In contrast, *ortho*-substituted α-aryl ketones did not result in any conversion of the starting material, presumably because of increased steric interaction with the catalyst.

A scale-up experiment using 500 mg of ketone **1a** proceeded smoothly and without deterioration of the yield or enantioselectivity (Scheme 3). As anticipated, the introduced hydroquinone moiety can be converted into a synthetically useful hydroxy group under oxidative conditions similar to those required to remove *p*-methoxyphenyl (PMP) protecting groups.[8] Furthermore, a diastereoselective reduction of ketone **3a** gave alcohol **9** as a single diastereomer. Both reactions proceeded without any erosion of enantioselectivity.

A plausible reaction pathway is depicted in Figure 2. The catalytic cycle is initiated by the phosphoric acid catalyzed enolization of the ketone. This step is less likely to be rate-limiting due to the absence of a kinetic resolution and the change in the kinetic profile with different quinone concentrations.[6] Subsequent coordination of the quinone derivative through hydrogen bonding gives complex **A**.[9] This complex presumably undergoes a proton-coupled electron transfer (PCET) to furnish diradical complex **B**.[10–12] Subsequent



Scheme 3. Scale-up and derivatization of the products.

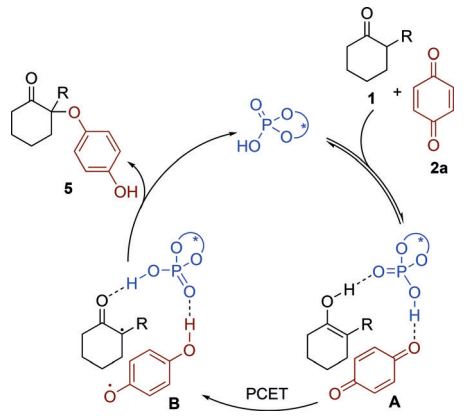
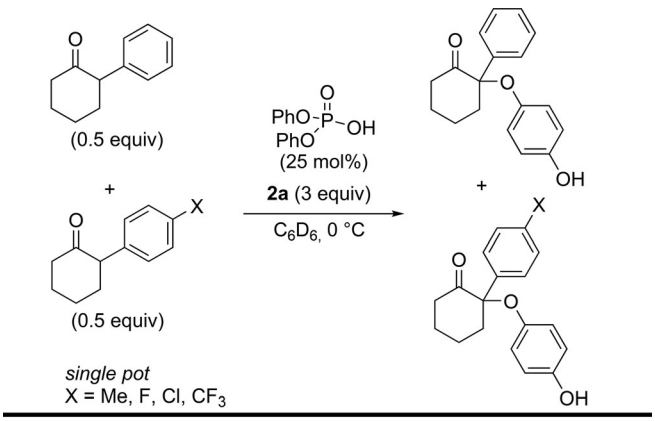


Figure 2. Proposed reaction mechanism.

formation of the product and release of the catalyst occurs by radical recombination.

An ionic mechanism is less likely, as a negative ρ value in a Hammett plot was obtained, which is in agreement with an oxidation being the rate-limiting step (Figure 3).[6] A hydrogen atom transfer (HAT) mechanism is less likely on the grounds of the thermochemistry of the proposed mechanism: The O–H bond dissociation free energy (BDFE) of a phenol, as an extreme case of an enol, is 88.3 kcal mol^{-1} and the semiquinone O–H BDFE is 65.2 kcal mol^{-1} (both values in DMSO), thus making the proposed PCET highly favorable.[13] Furthermore, the proposed mechanism is in good agreement with extensive kinetic studies by Mayr et al. which showed that the formation of similar intermediates presumably proceeds by a SET/inner-sphere electron-transfer mechanism (INES).[5c]

In conclusion, we have serendipitously discovered and further developed the first direct, catalytic, and asymmetric α-aryloxylation of cyclic α-branched ketones. Various α-substituted ketones underwent selective formal 1,6-additions to benzoquinones in moderate to good yields and with good to excellent enantioselectivities. Preliminary mechanistic studies are in good agreement with a PCET mechanism. Our findings significantly broaden the scope of enol catalysis and inspire various other enantioselective transformations involving enol-derived radical intermediates.



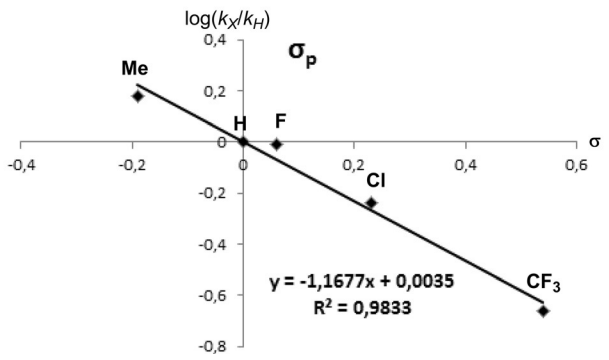


Figure 3. Hammett analysis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: α-aryloxylation · Brønsted acid catalysis · enol catalysis · proton-coupled electron transfer · quinones

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