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Direct Asymmetric α-Hydroxylation of Cyclic α-Branched Ketones through Enol Catalysis

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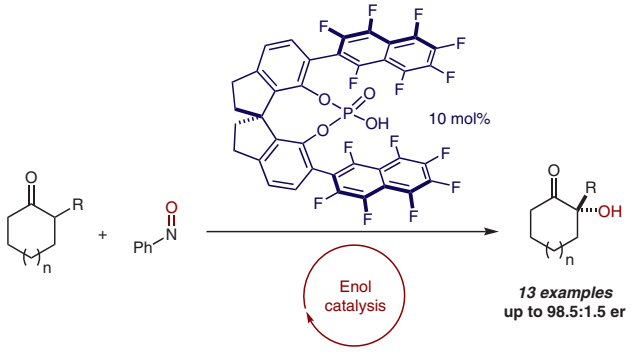

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Abstract Enantiopure α-hydroxy carbonyl compounds are common scaffolds in natural products and pharmaceuticals. Although indirect approaches towards their synthesis are known, direct asymmetric methodologies are scarce. Herein, we report the first direct asymmetric α-hydroxylation of α-branched ketones through enol catalysis, enabling a facile access to valuable α-keto tertiary alcohols. The transformation, characterized by the use of nitrosobenzene as the oxidant and a new chiral phosphoric acid as the catalyst, delivers a good scope and excellent enantioselectivities.

Key words enol catalysis, α-hydroxy ketones, Brønsted acid catalysis, hydroxylation, chiral phosphoric acid

α-Hydroxy carbonyl compounds and their derivatives are versatile building blocks and can be found in numerous bioactive molecules and drugs (Figure 1, a).[1] Over the last decades, numerous synthetic strategies towards these motifs have been developed; however, they have almost exclusively relied on nature's chiral pool,[2] chiral auxiliaries,[3] or chiral reagents (e.g. Davis oxaziridine).[4] More recently, catalytic methods initially developed for the dihydroxylation/epoxidation of olefins, e.g. Sharpless dihydroxylation,[5] Jacobsen–Katsuki,[6] and Shi epoxidations[7] were successfully applied to the oxidation of preformed enol ethers and esters. Moreover, Yamamoto et al. employed tin enolates and silyl enol ethers as reactants in the Lewis acid-catalyzed α-hydroxylation with nitrosobenzene as the oxidant.[8] High *O*/*N* selectivity was obtained and subsequent reduction gave the desired α-hydroxy carbonyl compounds.[8c] Nevertheless, all these indirect methodologies require an additional step to pre-functionalize the starting material toward the corresponding enolate.

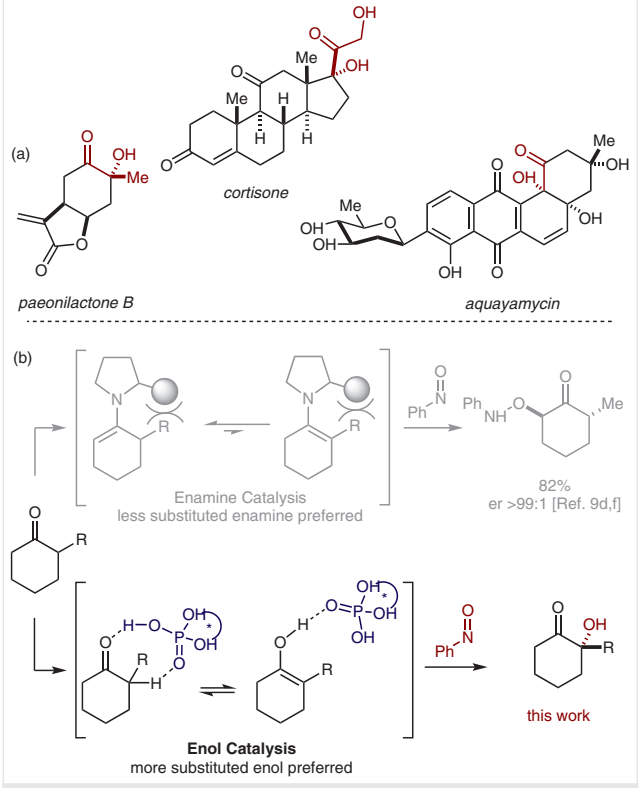


Figure 1 (a) Natural products and drugs bearing the α-hydroxy ketone moiety; (b) direct catalytic routes toward enantioenriched α-hydroxy ketones

Efficient direct asymmetric aminoxylation reactions of linear aldehydes and cyclic ketones have been reported in the context of enamine catalysis with use of chiral secondary amines as the catalysts and nitrosobenzene as the reagent.[9,1c] However, because of the steric constrains of enamines, α-branched ketones exclusively react through

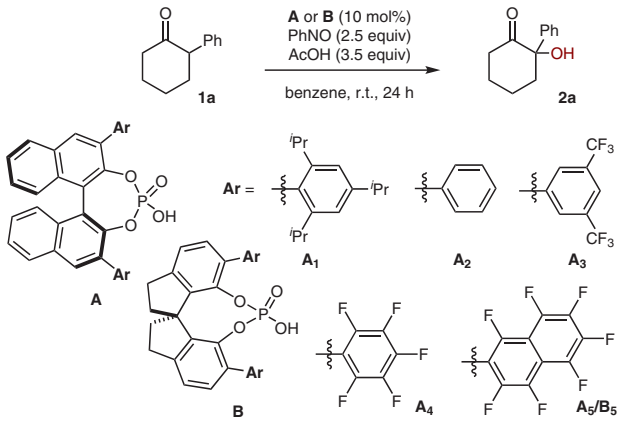
the least-substituted enamine intermediate, thus precluding access to synthetically challenging tetrasubstituted stereocenters (Figure 1, b).[9d,e] An alternative phase-transfer catalytic approach has also been reported for the hydroxylation of α,α'-trisubstituted ketones, yet the regioselectivity challenge was not addressed.[9i] We recently proposed a solution for the direct functionalization of branched ketones through enol catalysis.[10] In the presence of catalytic amounts of a chiral phosphoric acid, the more substituted enol is formed thus enabling highly selective and enantioselective α-functionalizations. By employing this new activation mode, C–C[10a,11] and C–N[12] and bond forming reactions were successfully developed. Recently, we disclosed the direct aryloxylation of α-branched cyclic ketones; however, additional synthetic modifications were required in order to access the corresponding α-hydroxy ketones.[13] We therefore hypothesized that we could apply *enol catalysis* in the presence of an excess of nitrosobenzene thus directly accessing highly valuable tetrasubstituted α-hydroxy ketones through a tandem asymmetric aminoxylation/deprotection sequence (Figure 1, b).[14]

The chiral Brønsted acid catalyst should play multiple roles in this designed scenario and enable: the enolization (nucleophile activation), the enantioselective functionalization (electrophile activation through protonation of the nitrogen atom), and ultimately the cleavage of the N–O bond to deliver the free alcohol. This transformation presents, however, multiple challenges: (i) regioselectivity (more vs. less substituted enol), (ii) *N*/*O* selectivity of the attack on nitrosobenzene, (iii) enantioselectivity, and (iv) the tandem sequence of the α-oxidation and reductive cleavage. Nevertheless, if successful, this approach would represent the first direct, catalytic, and asymmetric α-oxidation of branched ketones, and provide a single step access to enantioenriched α-hydroxy ketones.

We started our investigation (Table 1) by employing commercially available 2-phenyl cyclohexanone (**1a**) as a model substrate. When a reaction of **1a** was performed with an excess of nitrosobenzene in the presence of a chiral phosphoric acid catalyst such as (*S*)-TRIP (**A1**), the desired α-hydroxy ketone **2a** was indeed obtained albeit in low yields and very low enantioselectivities (entry 1, 14% yield, 58.5:41.5 er). Initial experiments had immediately shown that aromatic solvents and the addition of over stoichiometric amounts of acetic acid were beneficial in terms of yield and enantioselectivity (see Supporting Information for details). More importantly, when electron-withdrawing groups were included in the 3,3'-positions of the catalyst, the enantioselectivity increased dramatically. For example, catalyst $\mathbf{A_3}$ afforded 44% of product **2a** with an enantiomeric ratio of 82.5:17.5. We screened other nitrosobenzene derivatives, but these resulted only in lower enantioselectivities. Interestingly, fluorinated catalyst $\mathbf{A_4}$ outperformed $\mathbf{A_3}$ raising the enantioselectivity to 89:11 er. Indeed, when new catalysts bearing perfluorinated naphthalene substituents were tested ($\mathbf{A_5}$), higher enantioselectivities were obtained (entry 5). Finally, by changing the backbone from BINOL to SPINOL ($\mathbf{B_5}$),[15] we were able to isolate **2a** in 56% yield and 98:2 er (entry 6). Noteworthy in all cases, hydroxylation of the nonsubstituted α-carbon of the ketones only occurred in traces.

In all cases 6-*oxo*-6-phenylhexanoic acid was obtained as side product, presumably through two successive oxidations of the substrate (see Supporting Information for details). However, this could be strongly suppressed by slow addition of nitrosobenzene without influencing the yield of the product. Further optimization attempts (e.g. temperature, equivalents, and concentration) did not further improve the yields while maintaining in all cases very high enantioselectivities. Control experiments showed that the desired products were stable under the reaction conditions. Although kinetic resolution of the starting material is present (see Supporting Information for details), this does not solely account for the moderate yields, and we believe that the formation of an uncharacterized polymer may be an additional cause.

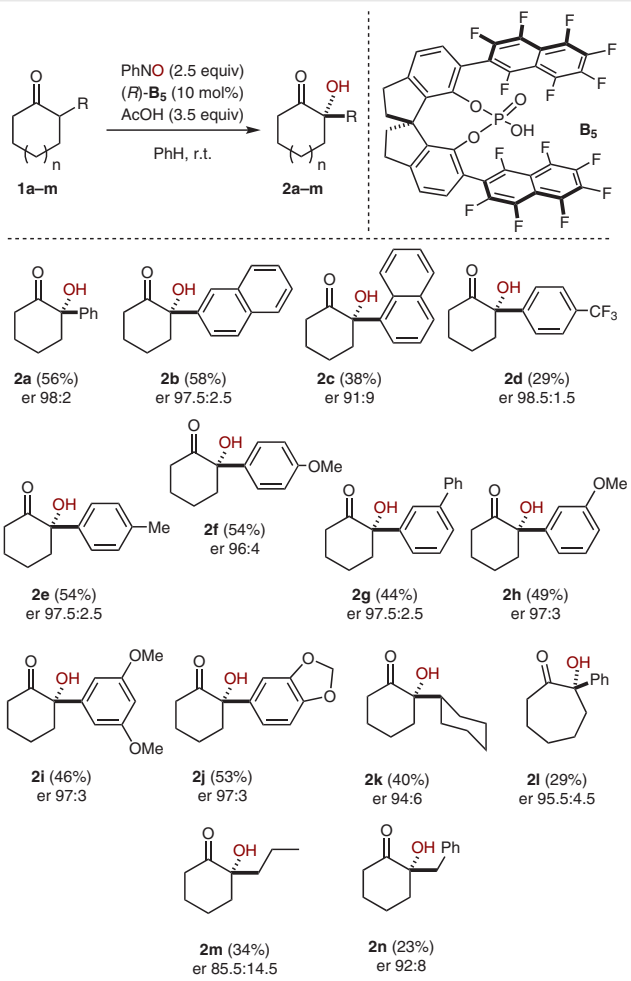
Table 1 Optimization of the Catalyst Structure for the Asymmetric α-Hydroxylation of α-Branched Ketones[a]



Entry	Catalyst	Yield (%)[b]	er[c]
1	$\mathbf{A_1}$	14	58.5:41.5
2	$\mathbf{A_2}$	47	55:45
3	$\mathbf{A_3}$	44	82.5:17.5
4	$\mathbf{A_4}$	55	89:11
5	$\mathbf{A_5}$	43	92.5:7.5
6	$\mathbf{B_5}$	56[d]	98:2
7	$\mathbf{B_5}$	17[e]	98:2

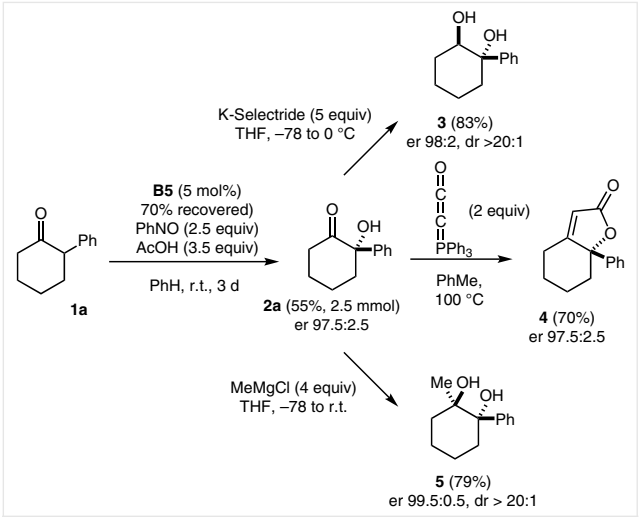
[a] Reactions were performed on a 0.025 mmol scale. For full optimization see Supporting Information.
[b] Determined by ^{1}H NMR with use of Ph_3CH as an internal standard.
[c] Determined by HPLC on a chiral stationary phase.
[d] Isolated yield.
[e] No acetic acid added.

Having the best conditions in hands, we turned our attention towards the generality of the transformation (Scheme 1). Various cyclohexanones bearing an electron-neutral, -rich or mildly -poor aromatic substituents in the 2-position were hydroxylated in moderate to good yields and very high enantioselectivities (**2a–j**). More electron-deficient substituents on the aromatic ring (-CF_3) resulted in lower yields yet extremely high enantiomeric ratios (**2d**). Despite its strong steric hindrance, 2-(1-naphtyl) cyclohexanone was also compatible with the protocol (**2c**, 38% yield, 91:9 er). To our delight, cycloheptanone **2l** was also tolerated (29% yield, 95.5:4.5 er). Finally, 2-alkyl-substituted cyclohexanones delivered the desired products in lower yields and enantioselectivities (**2k**, **2m**, and **2n**). Interestingly, indanone- and tetralone-derived substrates, which performed well in previous enol catalysis reports,[11a] either did not react or resulted in racemic product. Products derived from 2-substituted cyclopentanones were not stable under the reaction conditions and decomposed. Acyclic ketones did not show any reactivity even at higher temperatures (up to 40 °C tested). The absolute configuration was confirmed by X-Ray spectroscopic analysis of **2a** and assigned by analogy for the other substrates.



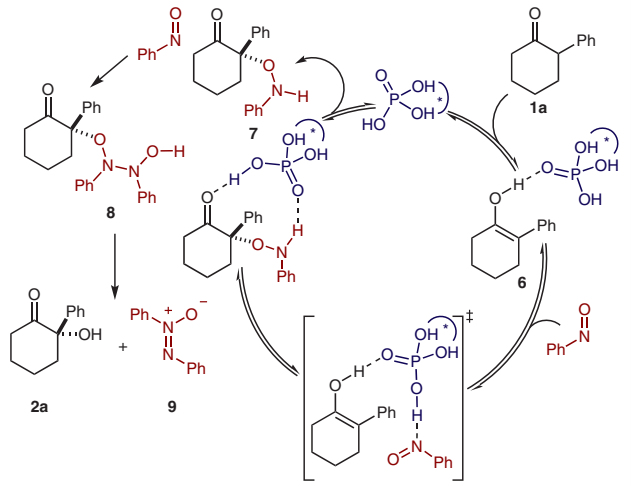
Scheme 1 Substrate scope of the catalytic asymmetric α-hydroxylation of α-branched ketones. Reactions were performed on a 0.2 mmol scale and run for 24 or 48 h at room temperature. Absolute configurations of the products were assigned according to the crystal structure of **2a**.

The robustness of the method was further highlighted by a scale-up experiment with our model substrate, and **2a** was obtained without deterioration in yield or enantioselectivity by employing a lower catalyst loading (Scheme 2, 5 mol%, 70% recovered). To illustrate the utility of the developed method, hydroxy ketone **2a** was derivatized to diols **3** and **5** by stereoselective reduction or Grignard addition, respectively. Furthermore, reaction with the Bestmann ylide[16] afforded lactone **4**, giving a straightforward and highly enantioselective access to dihydroactinidiolide-type structures.[17] In all cases, no deterioration in enantioselectivity was observed.



Scheme 2 Scale-up reaction and derivatization of the products

On the basis of our previous studies[10–13] and literature reports[14] we propose the reaction to proceed through the catalytic cycle depicted in Scheme 3. Phosphoric acid-promoted enolization gives catalyst/enol complex **6**. The observed kinetic resolution of the starting material suggests that this step is rate-determining (see Supporting Information for details). Subsequent attack of the enol onto nitrosobenzene gives aminoxylated ketone **7**, which reacts with a second equivalent of nitrosobenzene to give the targeted α-hydroxy ketones alongside with azoxybenzene (**9**)[18] presumably through intermediate **8**.[14] Initial mechanistic studies suggest the reversibility of the initial attack of the enol onto nitrosobenzene and support the existence of aminoxylated ketone **7** as a reaction intermediate (see Supporting Information for details).



Scheme 3 Proposed catalytic cycle

In summary, we have developed the first direct asymmetric α-hydroxylation of α-branched ketones through enol catalysis.[19] By employing nitrosobenzene as both the oxidant and reductant in a tandem process, various valuable cyclic α-hydroxy ketones were obtained in moderate to good yields and excellent enantioselectivities. We believe that the presented findings will further broaden the scope of enol catalysis thus inspiring other highly enantioselective transformations.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611084.

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(18) Azoxybenzene **9** was both observed by ^{1}H NMR spectroscopy and isolated from the crude reaction mixture (purification by FCC).

(19) **General Procedure:** Catalyst $\mathbf{B_5}$ (16.4 mg, 0.02 mmol, 10 mol%) and 2-phenyl cyclohexanone (**1a**, 0.2 mmol, 1.0 equiv) were placed in a plastic GC vial. After the addition of benzene (0.8 mL) and acetic acid (40 µL, 0.7 mmol, 3.5 equiv), nitrosobenzene (21.4 mg, 0.2 mmol, 1.0 equiv) was added in one portion and the reaction mixture was stirred for 2 h. Then, additional nitrosobenzene (32.1 mg, 0.3 mmol, 1.5 equiv) was added and stirring was continued for additional 22 h. The crude reaction mixture was directly purified by flash column chromatography (hexanes/EtOAc gradient 100:0 to 10:1) to give hydroxy ketone **2a** (21.5 mg, 56%, 98:2 er) as an orange oil. ^{1}H NMR (500 MHz, C_6D_6): δ = 7.18–7.12 (m, 2 H), 7.11–7.01 (m, 3 H), 4.61 (s, 1 H), 2.73 (dq, *J* = 14.3, 3.2 Hz, 1 H), 2.19 (dddd, *J* = 13.5, 4.1, 2.7, 1.6 Hz, 1 H), 1.95 (td, *J* = 13.5, 6.3 Hz, 1 H), 1.69–1.61 (m, 1 H), 1.34 (ddt, *J* = 12.5, 6.3, 3.1 Hz, 1 H), 1.29–1.07 (m, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 211.9, 141.2, 129.1, 126.8, 80.1, 39.2, 38.8, 28.2, 23.1 ppm (one aromatic signal missing because of overlap with solvent). HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}O_2Na$: 213.0886; found 213.0885. HPLC (Chiralpak AD-3, *n*-Hept/EtOH = 80:20, flowrate: 1.0 ml/min, λ = 206 nm): $t_{r(major)}$ = 6.88 min, $t_{r(minor)}$ = 9.73 min. $[\alpha]_D^{25}$: +166.0 (c 0.20, $CHCl_3$, 98:2 er).