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Brønsted Acid Mediated Direct α-Hydroxylation of Cyclic α-Branched Ketones

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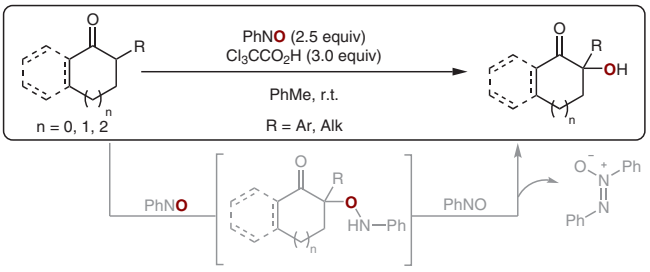

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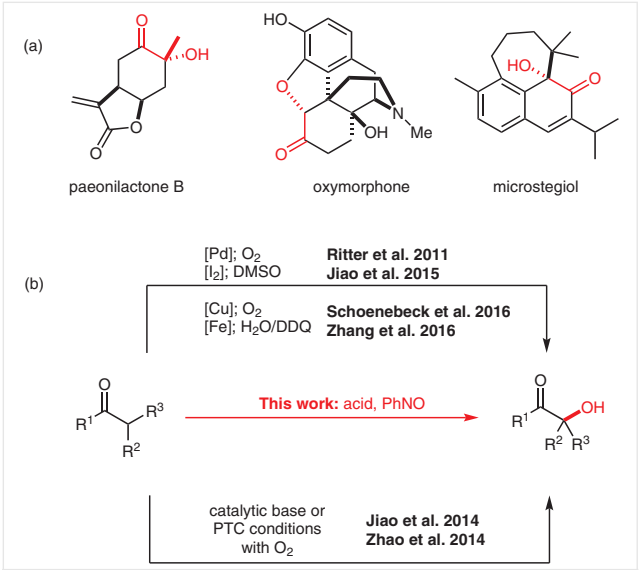
Abstract We report a Brønsted acid mediated direct α-hydroxylation of cyclic α-branched ketones via a tandem aminoxylation/N–O bond-cleavage process. Nitrosobenzene is used as the oxidant and subsequently promotes the liberation of the free alcohol. The desired products could be isolated in moderate to good yields at a maximum tested scale of 10 mmol. Derivatizations of the obtained products are presented.

Key words α-branched ketones, α-hydroxylation, aminoxylation, α-functionalization of ketones, enolization, Brønsted acid mediated

The direct α-hydroxylation of carbonyl compounds represents an efficient approach towards α-hydroxy carbonyls, a ubiquitous motif in pharmaceuticals and natural products (Scheme 1, a).[1] Although α-hydroxylations of linear aldehydes and ketones are well established, such reactions of their branched derivatives still remain a challenge.[2] α-Branched ketones are particularly difficult substrates because of the added challenge of controlling the branched vs. unbranched regioselectivity. It is therefore not surprising that a general solution does not exist and common synthetic strategies towards α-hydroxy carbonyls rely on the oxidation of prefunctionalized substrates, e.g., enol ethers and enol esters.[3] Few direct methods, which combine catalytic/substoichiometric amounts of (transition) metals, iodine, or strong bases with oxygen, DDQ, or DMSO as the corresponding oxidant, were recently reported (Scheme 1, b).[4]

Nitrosobenzene has been used as an oxidant in organocatalytic aminoxylations of aldehydes and ketones.[5] In fact, in the presence of a Brønsted acid, a second equivalent of nitrosobenzene can additionally act as a reductant, giving direct access to the desired hydroxy carbonyl compounds via a tandem aminoxylation/N–O bond-cleavage process with azoxybenzene as the side product.[6]



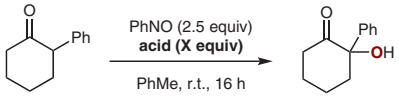
Scheme 1 (a) Natural products and pharmaceuticals containing the α-hydroxy ketone motif. (b) Previous approaches for the direct α-hydroxylation of branched ketones.

Given the dearth of direct α-hydroxylation methods and based on our current interest in α-functionalizations of branched ketones via Brønsted acid catalyzed enolizations (enol catalysis),[7] we pursued a complementary method for the direct α-hydroxylation of branched ketones using nitrosobenzene. This reaction presents several challenges, i.e., i) controlling the regioselectivity of the enolization, as well as the ii) chemoselectivity (enol addition to *O* vs. *N* of nitrosobenzene) and finally, iii) successfully completing the tandem sequence.

We began our investigations using 2-phenylcyclohexanone (**1a**) as the model substrate (Table 1, for more details, see the Supporting Information). Optimization of the reac-

tion conditions showed that an overstoichiometric amount of a strong acid is necessary for the reaction to proceed, with 3 equiv of trichloroacetic acid (TCA) giving the best result (Table 1, entry 4, 60% yield). Interestingly, weaker acids, e.g. acetic acid, did not show any reactivity (Table 1, entry 1). While the yield remained the same, higher amounts of TCA required additional purification steps to remove the excess of acid (Table 1, entry 7). Since clean reaction profiles were observed, we suspect the moderate yields to result from the formation of an uncharacterized polymer in the course of the reaction.

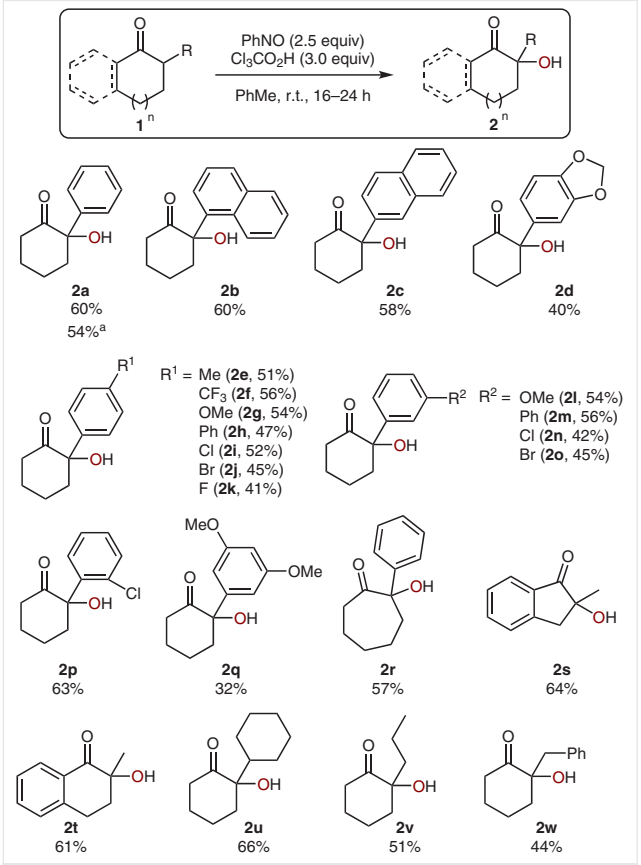
Table 1 Optimization of Reaction Conditions[a]



1a **2a**

Entry	Acid	equiv	Yield (%)[b]
1	AcOH	3	0
2	$ClCH_2CO_2H$	3	traces
3	$Cl_2CH_2CO_2H$	3	28
4	Cl_3CCO_2H	3	(60)
5	F_3CCO_2H	3	(37)
6	Cl_3CCO_2H	1	27
7	Cl_3CCO_2H	5	(60)

[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), acid, nitrosobenzene (0.63 mmol, 2.5 equiv) in dry PhMe (2.5 mL).
[b] Determined by ^1H NMR spectroscopy using Ph_3CH as internal standard. Isolated yield in parentheses.

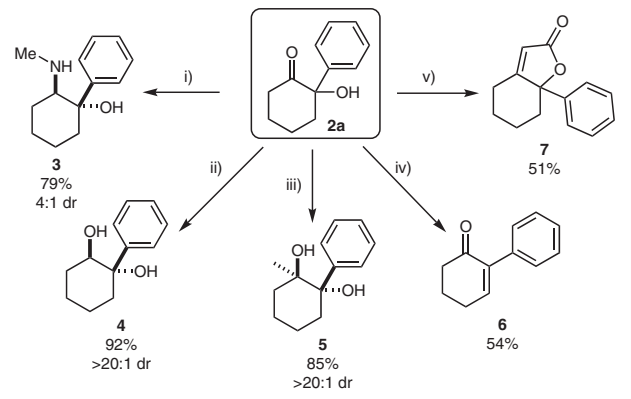


Scheme 2 Scope of the α-hydroxylation of 2-substituted cyclic ketones, indanone and tetralone. If not otherwise indicated the reactions were performed using 0.25 mmol of **2**. [a] Performed using 10 mmol of **2a**.

With the optimized conditions in hand, we turned our attention towards the scope of this transformation. Various α-aryl cyclohexanones reacted readily under the reaction conditions giving the desired products in moderate to good yields (Scheme 2, 2a–q). Interestingly, no significant electronic effect was observed (**2f**, 56% yield vs. **2g**, 54% yield). To our delight, challenging *ortho*-substituted α-aryl cyclohexanones (**2b** and **2p**), a cycloheptanone (**2r**) and 2-alkyl cyclohexanones (**2u–w**) could be transformed to their corresponding 2-hydroxy derivatives in similar yields. Furthermore, 2-methyl-indanone and 2-methyl-tetralone gave the desired products with similarly good results (**2s**, 64% and **2t**, 61%). However, when cyclopentanones or acyclic ketones were used as substrates, no desired products were obtained. Finally, the robustness of the method was demonstrated by scale-up experiments of the model substrate. Gratifyingly, **2a** was obtained at a maximum tested scale of 10 mmol without deterioration of yield.

To demonstrate the utility of our developed method, product **2a** was derivatized to a variety of synthetically useful functionalities (Scheme 3). Namely, amino alcohol **3** was obtained via reductive amination. Reduction of ketone **2a** using K-Selectride® gave diol **4** in excellent yield and diastereoselectivity. Notably, using $NaBH_4$ as the reductant resulted in similar yields, however, a dr of only 4:1 of the resulting diol was observed. Treatment of product **2a** with methyl magnesium chloride resulted in the formation of diol **5** as a single diastereomer. Elimination under acidic conditions gave enone **6** in 54% yield, in addition to 16% of the corresponding regioisomeric enone (see the Supporting Information for details). Finally, treatment with the Bestmann ylide[8] afforded lactone **7**, providing an efficient access to dihydroactinidiolide-type structures.[9]

In summary, we have developed a simple and practical Brønsted acid mediated direct hydroxylation of branched ketones using nitrosobenzene as the oxygen source.[10] The scope includes various 2-aryl and 2-alkyl cyclohexanones, which were converted into the corresponding products in



Scheme 3 Chemical derivatization of obtained products. i) $MeNH_2$, $Ti(OiPr)_4$, PhMe, reflux, 24 h then $NaBH_4$, MeOH, 0 °C, 1 h. ii) K-Selectride®, THF, −78 °C to 0 °C, 2 h then NaOH, H_2O_2, r.t., overnight. iii) MeMgCl, THF, −78 °C to r.t., overnight, the product was obtained as a mixture with unreacted starting material (^{1}H NMR ratio: 5.6:1). iv) *p*TsOH, PhMe, reflux, overnight. v) Ph_3PCCO, PhMe, reflux, 3 d.

moderate to good yields. The method is complementary to published systems, easy to execute, and scalable and therefore might find application in chemical synthesis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610292.

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(10) **Exemplary Procedure**
In a GC vial 2-phenylcyclohexanone (**1a**, 43.6 mg, 0.25 mmol, 1.0 equiv) was dissolved in a solution of trichloroacetic acid (0.75 mmol, 3.0 equiv) in dry PhMe (2.5 mL) and nitrosobenzene (0.625 mmol, 2.5 equiv) was added. The vial was closed with a screw cap, and the resulting mixture was stirred at r.t. for 16 h. The crude reaction mixture was directly purified by flash column chromatography (SiO_2, hexanes/EtOAc = 100:0 then 10:1) to give 2-hydroxy-2-phenylcyclohexan-1-one (**2a**) as an orange oil (28.7 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 2 H), 7.35–7.29 (m, 3 H), 5.04 (s_{br}, 1 H), 3.06–2.99 (m, 1 H), 2.59–2.51 (m, 1 H), 2.48–2.39 (m, 1 H), 2.11–2.02 (m, 1 H), 1.91–1.83 (m, 2 H), 1.82–1.68 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.9, 139.8, 129.3, 128.6, 126.5, 80.3, 39.0, 38.9, 28.5, 23.2. HRMS (ESI+): *m/z* calcd for $C_{12}H_{14}O_2Na$ [M + Na]$^+$: 213.0886; found: 213.0885.