Organocatalytic Enantioselective Synthesis of α-Hydroxy Ketones through a Friedel-Crafts Reaction of Naphthols and Activated Phenols with Aryl- and Alkylglyoxal Hydrates.

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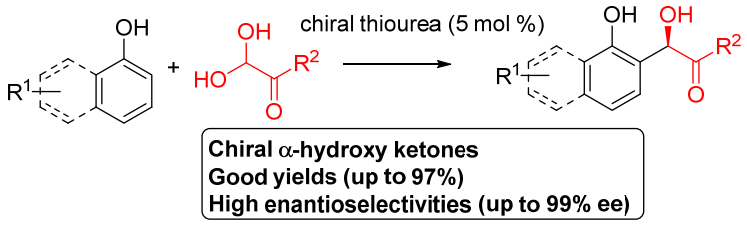
Supporting Information Placeholder



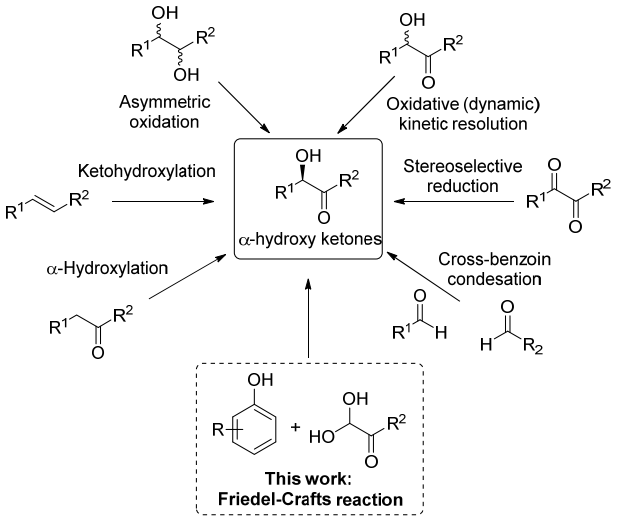
ABSTRACT: An efficient organocatalytic asymmetric synthesis of α-hydroxyketones has been developed. Quinine derived thiourea catalyzed the enantioselective Friedel-Crafts alkylation of naphthols and activated phenols with aryl- and alkylglyoxal hydrates providing the corresponding chiral α-hydroxy ketones with high yields (up to 97%) and excellent enantioselectivities (up to 99% ee).

Chiral α-hydroxy ketones are very important building blocks for asymmetric synthesis of natural products, fine chemicals and pharmaceutical compounds.[1] Moreover, α-hydroxy ketones are precursors for the synthesis of chiral 2-amino alcohols or 1,2-diols.[2] For these reasons, their enantioselective synthesis is of great interest for organic chemistry and several synthetic methodologies have been reported for this purpose (Scheme 1).[3]

One of the most used chemical approaches for the preparation of chiral α-hydroxy ketones is the α-hydroxylation of ketones through the enolate oxidation,[4] or the Sharpless asymmetric dihydroxylation of the corresponding silylenol ether.[5] Other oxidation methodologies that have been used are the ketohydroxylation of olefins,[6] the asymmetric mono-oxidation of 1,2-diols,[7] the oxidative kinetic resolution[8] and the oxidative dynamic kinetic resolution[9] of racemic α-hydroxy ketones. Furthermore, some stereoselective reductions of 1,2-diketones[10] have been reported as well as the traditional benzoin condensation.[11] Despite the great advances in this area and in view of the great importance of chiral α-hydroxy ketones, the development of new catalytic enantioselective methodologies for their synthesis in optically pure form is highly desirable.

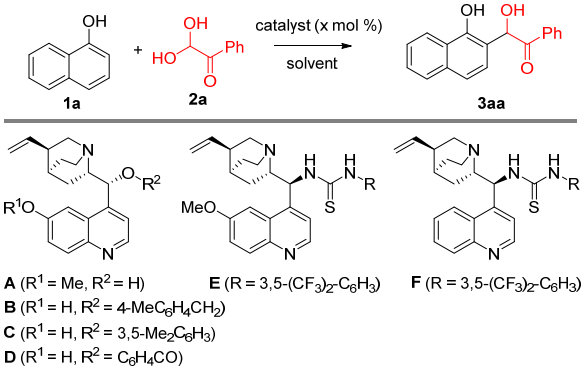
On the other hand, the catalytic enantioselective Friedel-Crafts reaction represents a powerful methodology to prepare chiral benzylic compounds.[12] In this context, the Friedel-Crafts reaction with carbonyl compounds provides chiral benzylic alcohols. We envisioned that the corresponding enantioselective addition of electron-rich arenes to arylglyoxals should afford the corresponding chiral α-hydroxy ketones opening a valuable alternative for the synthesis of such important compounds, complementing the existing methodologies. Arylglyoxals are a relevant class of compounds containing both aldehyde and ketone functional groups with different reactivity, playing an important role for the synthesis of different important building blocks.[13] Arylglyoxals usually are sticky oily or semisolid compounds that are difficult to handle and prone to dimerize or polymerize. Nevertheless, these compounds are normally prepared and stored as their corresponding monohydrates, which are stable solids. Despite the versatility of arylglyoxals as electrophiles in organic synthesis, their use in asymmetric Friedel-Crafts reactions has not been explored as far as we know.[14,15] As a part of our ongoing interest in the asymmetric Friedel-Crafts reactions with naphthols and phenols[16,17] and the synthesis of optically pure α-hydroxy carbonyl compounds,[18] here we described the highly enantioselective organocatalytic addition of naphthols and activated phenols to aryl- and alkylglyoxal hydrates.

Scheme 1. Several methods for the synthesis of asymmetric α-hydroxy ketones.



We initiated our studies by evaluating the reaction between 1-naphthol (**1a**) and phenylglyoxal hydrate (**2a**) in the presence of a series of *Cinchona* alcaloid derived bifunctional organocatalysts.[19] As shown in Table 1, when 10 mol % of quinine (**A**) was used in toluene, the α-hydroxy ketone **3aa** was obtained with low yield and low enantioselectivity after 24 hours (entry 1, Table 1). Catalysts **B**, **C** and **D**, were more effective and the corresponding product **3aa** was obtained with better yields and enantioselectivities, although the results were not satisfactory (entries 2-4).

Table 1. Optimization of the reaction conditions[a]

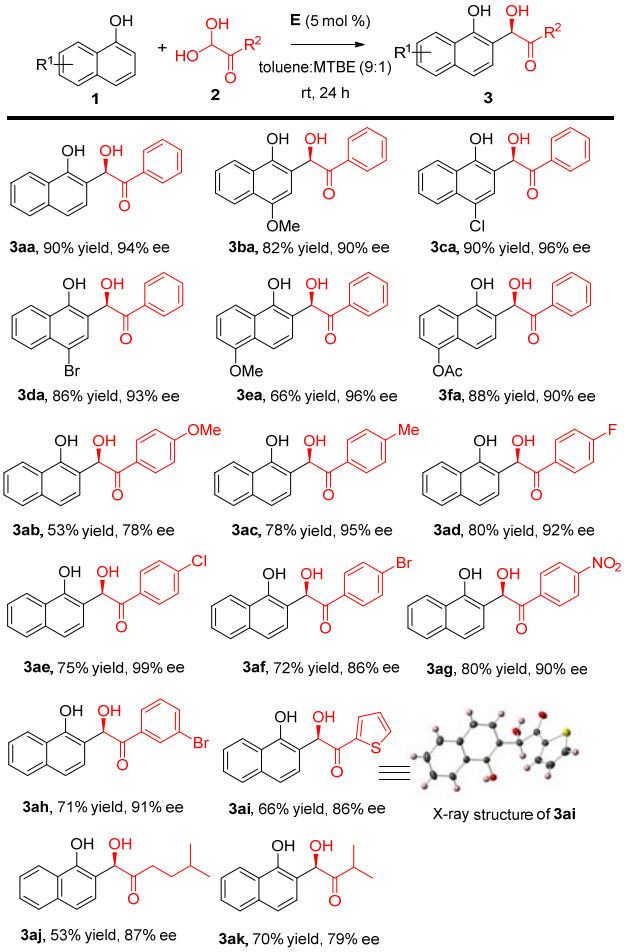


entry	catalyst (x mol %)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	**A** (10)	toluene	24	14	29[d]
2	**B** (10)	toluene	24	40	38
3	**C** (10)	toluene	24	47	28
4	**D** (10)	toluene	24	25	60
5	**E** (10)	toluene	6	80	90
6	**F** (10)	toluene	20	95	88
7	**E** (10)	benzene	4	84	89
8	**E** (10)	o-xylene	2	80	87
9	**E** (10)	CH_2Cl_2	2	81	83
10	**E** (10)	$CHCl_3$	3	83	78
11	**E** (10)	Et_2O	5	84	79
12	**E** (10)	THF	5	87	75
13[e]	**E** (10)	toluene	10	81	89
14	**E** (5)	toluene	18	79	89
15	**E** (5)	MTBE	17	47	96
16	**E** (5)	tol.:MTBE (7:3)	24	60	96
17	**E** (5)	tol.:MTBE (8:2)	24	68	94
18	**E** (5)	tol.:MTBE (9:1)	24	90	94

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (x mol %) in 1 mL of solvent at rt. [b] Isolated yield after column chromatography. [c] Determined by HPLC using chiral stationary phase. [d] Opposite enantiomer was obtained. [e] The reaction was performed at 4 ºC.

To our delight, quinine derived thiourea **E**,[20] exhibited excellent reactivity (80% yield after 6 hours) with high enantioselectivity, affording product **3aa** with an enantiomeric excess of 90% (entry 5). With cinchonidine derived thiourea **F**, product **3aa** was gained with slightly lower enantioselectivity, so we decided to continue with catalyst **E** for further optimization of the reaction conditions. Therefore, we tested different solvents such as benzene, *o*-xylene, DCM, $CHCl_3$, diethyl ether or THF (entries 7-12) with catalyst **E**. We observed that with aromatic solvents slightly better enantiomeric excess were obtained, being toluene the best solvent. Lowering the temperature of the reaction to 4 ºC (entry 13) did not improve the results obtained at room temperature. With catalyst **E** in toluene, we could decrease the catalyst loading to 5 mol% without compromising the yield and enantiomeric excess, although we observed a diminished reactivity (entry 14). Next, we tried MTBE as a solvent with 5 mol % of **E** (entry 15), obtaining product **3aa** with an excellent 96% ee, however the yield was moderate (47%). At this point, we decided to try different toluene/MTBE mixtures as solvent (entry 16-18). The best result in terms of yield and enantioselectivity was obtained when a mixture of toluene:MTBE 9:1 was used (entry 18), and the product **3aa** was gained with 90% yield and 94% ee.

Scheme 2. Scope of the addition of 1-naphthol derivatives to aryl- and alkylglyoxal hydrates.[a]

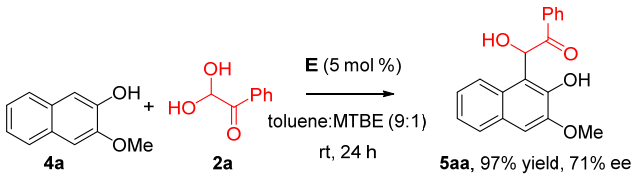


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol) and **E** (5 mol %) in 1 mL of toluene:MTBE (9:1). Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.

With the optimized reaction conditions stablished, the scope of the reaction was explored with respect to both the 1-naphthols **1** and the arylglyoxal hydrates **2** (Scheme 2). The use of different substituted 1-naphthols with **2a** afforded the expected products **3aa–3fa** with excellent results (90–97% ee), independently of the

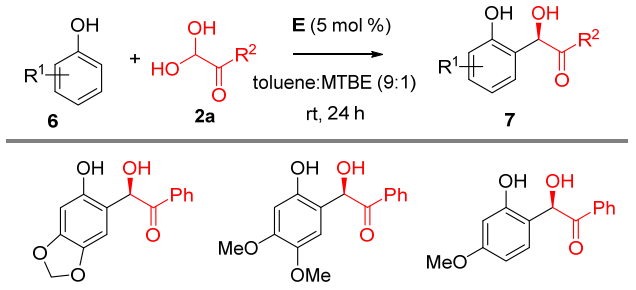
electronic character of the substituents on the naphthol ring. Next, the effect of substitution in the aryl ring of **2** was evaluated in the reaction with **1a** (Scheme 2, **3ab-3ah**). Groups at para position such as methyl, fluoride, chloride, bromide and even, nitro were well tolerated providing the corresponding α-hydroxy ketones **3** with high to excellent enantioselectivities (86-99% ee). However, the presence of a methoxy group at the para position had a detrimental effect in both reactivity and enantioselectivity (53% yield, 78% ee). In addition, heterocyclic substrate **2i** gave good yield and enantiomeric excess (**3ai**, 66% yield and 82% ee).[21] The absolute configuration of the stereogenic center in compound **3ai** was determined to be *R* on the basis of X-ray crystallographic analysis;[22] the configuration of the other products **3** was assigned on the assumption of a uniform mechanistic pathway. Moreover, we extended our study to enolizable aliphatic alkylglyoxal hydrates (**2j-k**). We found that these were also suitable substrates for this reaction and gave good results (**3aj-3ak**) although were less reactive than arylglyoxal hydrates.

Scheme 3. Reaction of 3-methoxy-2-naphthol (4a).[a]



[a] Reaction conditions: **4a** (0.1 mmol), **2a** (0.1 mmol) and **E** (5 mol %) in 1 mL of toluene:MTBE (9:1). Isolated yield after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.

Scheme 4. Scope for different activated phenols.[a]

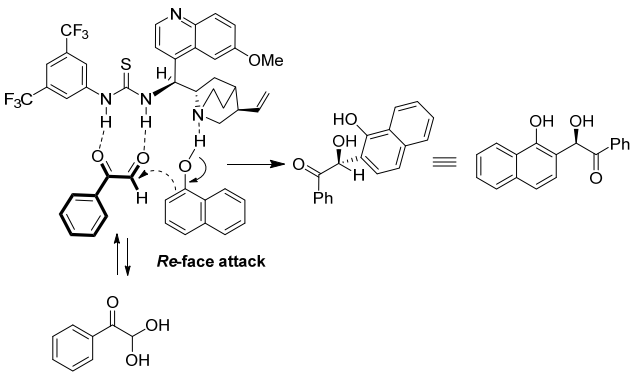


[a] Reaction conditions: **6** (0.1 mmol), **2a** (0.1 mmol) and **E** (5 mol %) in 1 mL of toluene:MTBE (9:1). Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.

Next, we focused our attention on the Friedel-Crafts reaction of 3-methoxy-2-naphthol (**4a**) with phenylglyoxal hydrate (**2a**). α-hydroxy ketone **5aa** was obtained with an excellent 97% yield, although with a moderate ee (71%) after 24 h (Scheme 3).[23] Remarkably, our method could also be applied to sesamol[24] (**6a**) and other activated phenols **6** as the nucleophiles (Scheme 4).[25] Sesamol reacted smoothly with phenylglyoxal hydrate (**2a**) to give the corresponding α-hydroxy ketone **7aa** with 92% yield and excellent enantiomeric excess (96% ee). 3,4-Dimethoxyphenol **6b** and even 3-methoxyphenol **6c**, bearing only one electron-donating group, gave the corresponding chiral compounds (**7ba–7ca**), although a decrease in the yield was observed.

A plausible transition-state model for the enantioselective reaction is shown in Scheme 5. Phenylglyoxal hydrate is in equilibrium with the corresponding aldehyde form. The thiourea catalyst is responsible for the preorientation and activation of the substrates acting as a bifunctional organocatalyst. The phenylglyoxal is activated upon formation of hydrogen bonds between the thiourea moiety and the carbonyl groups of **2a**, while the 1-naphthol undergoes nucleophilic activation by hydrogen bonding with the quinuclidine moiety of the catalyst.[26] The C-2 carbon atom of the 1-naphthol **1a** attacks to the *Re*-face of the aldehyde **2a**, thus accounting for the observed regio- and estereoselectivity.

Scheme 5. Plausible transition-state model.



In conclusion, we have successfully developed an enantioselective addition of naphthols and electron-rich phenols to aryl and alkylglyoxal hydrates catalyzed by a quinine derived thiourea. The corresponding α-hydroxy ketones were obtained in good yields (up to 97%) and good to excellent enantioselectivities (up to 99% ee). This organocatalytic methodology features the use of bench-stable arylglyoxal hydrates in combination with simple naphthols and phenols, under mild reaction conditions, and provides access to highly enantioenriched α-hydroxy ketones, which are an important chiral building blocks accessed through a simple Friedel-Crafts reaction.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products, X-ray data for enantiopure products **3ai** (CIF), ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) We only observed the alkylated product at *ortho* position in all cases.

(22) CCDC-1505242 contains the supplementary crystallographic data for **3ai**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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