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Organocatalytic Enantioselective Synthesis of α-Hydroxyketones through a Friedel–Crafts Reaction of Naphthols and Activated Phenols with Aryl- and Alkylglyoxal Hydrates

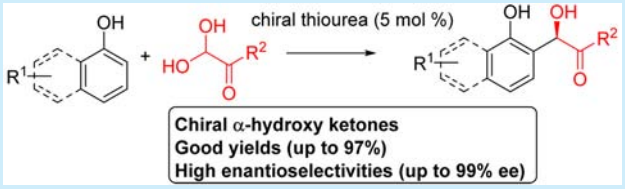
Carlos Vila,*[,†] Lucia Quintero,[†] Gonzalo Blay,[†] M. Carmen Muñoz,[‡] and José R. Pedro*[,†]

[†]Departament de Química Orgànica, Facultat de Química, Universitat de València, C/Dr. Moliner, 50, Burjassot, E-46100 València, Spain

[‡]Departament de Física Aplicada, Universitat Politècnica de València, C/Camí de Vera, s/n, E-46022 València, Spain

Supporting Information

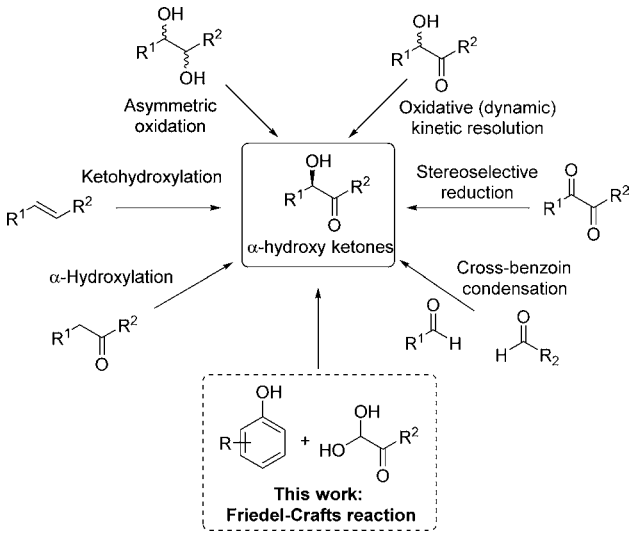
ABSTRACT: An efficient organocatalytic asymmetric synthesis of α-hydroxyketones has been developed. Quinine-derived thiourea catalyzed the enantioselective Friedel–Crafts alkylation of naphthols and activated phenols with aryl- and alkylglyoxal hydrates, providing the corresponding chiral α-hydroxyketones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



Chiral α-hydroxyketones are important building blocks for asymmetric synthesis of natural products, fine chemicals, and pharmaceutical compounds.[1] α-Hydroxyketones 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-hydroxyketones is the α-hydroxylation of ketones through enolate oxidation[4] or Sharpless asymmetric dihydroxylation of the corresponding silylenol ether.[5] Other oxidation methodologies that have been used are ketohydroxylation of olefins,[6] asymmetric mono-oxidation of 1,2-diols,[7] oxidative kinetic resolution,[8] and oxidative dynamic kinetic resolution[9] of racemic α-hydroxyketones. Some stereoselective reductions of 1,2-diketones[10] have been reported as well as traditional benzoin condensation.[11] Despite great advances in this area and in view of the importance of chiral α-hydroxyketones, development of new catalytic enantioselective methodologies for their synthesis in optically pure form is highly desirable.

Scheme 1. Several Methods for the Synthesis of Asymmetric α-Hydroxyketones



Catalytic enantioselective Friedel–Crafts reaction represents a powerful methodology to prepare chiral benzylic compounds.[12] 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-hydroxyketones, opening a valuable alternative for the synthesis of such important compounds, complementing existing methodologies. Arylglyoxals are a relevant class of compounds containing aldehyde and ketone functional groups with different reactivity, playing an important role in 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 asymmetric Friedel–Crafts reactions with naphthols and phenols[16,17] and the synthesis of optically pure α-hydroxycarbonyl compounds,[18] we describe the highly enantioselective organocatalytic addition of

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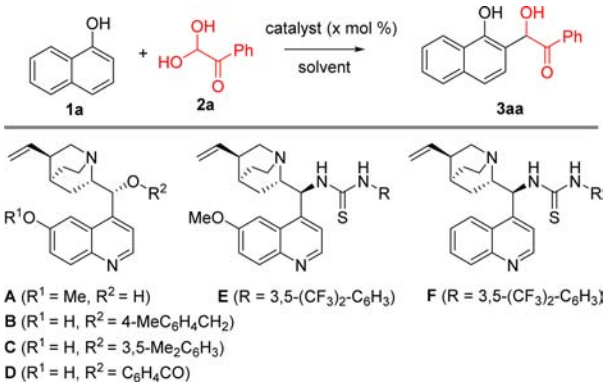
naphthols and activated phenols to aryl- and alkylglyoxal hydrates.

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

Quinine-derived thiourea **E**[20] exhibited excellent reactivity (80% yield after 6 h) with high enantioselectivity, affording **3aa** with 90% ee (entry 5). With cinchonidine-derived thiourea **F**, **3aa** was obtained with slightly lower enantioselectivity, so we decided to continue with **E** for further optimization of the reaction conditions. We tested different solvents, such as benzene, *o*-xylene, DCM, $CHCl_3$, diethylether, or THF (entries 7–12), with **E**. We observed that with aromatic solvents slightly better enantiomeric excesses were obtained, with toluene being the best solvent. Decreasing the temperature of the reaction to 4 °C (entry 13) did not improve the results obtained at rt. With **E** in toluene, we decreased 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) and obtained **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 (entries 16–18). The best yield and enantioselectivity were obtained when a mixture of 9:1 toluene/MTBE was used (entry 18), and **3aa** was obtained with 90% yield and 94% ee.

With the optimized reaction conditions established, the scope of the reaction was explored with respect to 1-naphthols **1** and arylglyoxal hydrates **2** (Scheme 2). The use of different substituted 1-naphthols with **2a** afforded the expected products **3aa**–**3fa** with 90–97% ee, independently of the electronic character of the substituents on the naphthol ring. Next, the effect of substitution on the aryl ring of **2** was evaluated in the reaction with **1a** (Scheme 2, **3ab**–**3ah**). Groups at the para position, such as methyl, fluoride, chloride, bromide, and nitro,

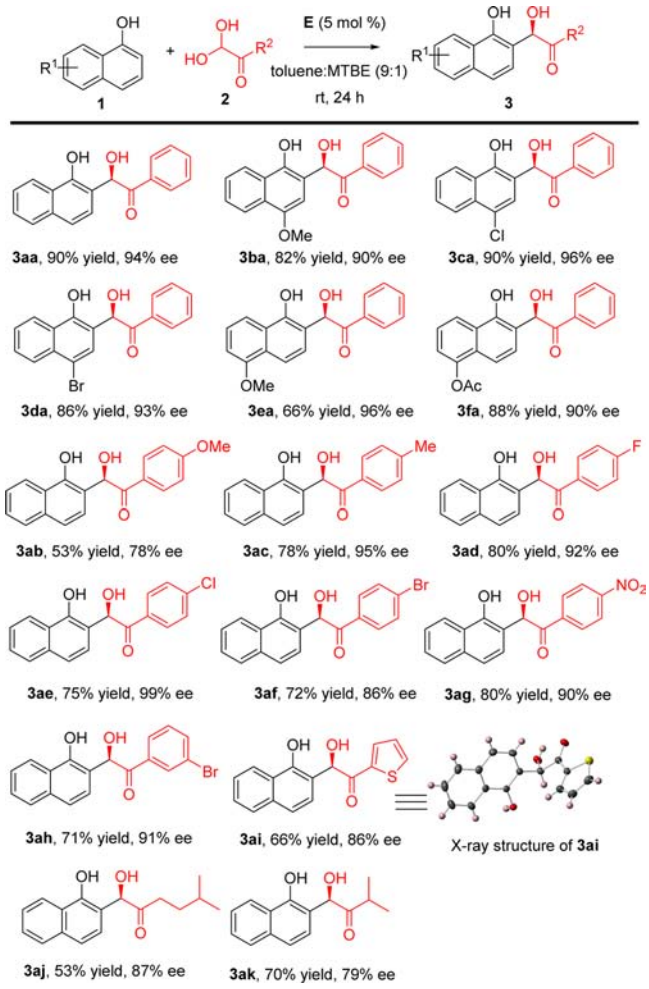
Table 1. Optimization of the Reaction Conditions[a]



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)	toluene/MTBE (7:3)	24	60	96
17	**E** (5)	toluene/MTBE (8:2)	24	68	94
18	**E** (5)	toluene/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 °C.

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 9:1 toluene/MTBE. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.

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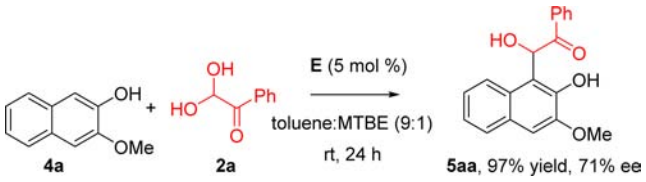
were well-tolerated, providing corresponding α-hydroxyketones **3** with 86−99% ee. However, the presence of a methoxy group at the para position had a detrimental effect on reactivity and enantioselectivity (53% yield, 78% ee). In addition, heterocyclic substrate **2i** gave good 66% yield and 82% ee (**3ai**).[21] The absolute configuration of the stereogenic center in **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. We extended our study to enolizable aliphatic alkylglyoxal hydrates (**2j,k**). We found that these were also suitable substrates for the reaction and gave good results (**3aj**−**3ak**), although they were less reactive than arylglyoxal hydrates.

Next, we focused our attention on the Friedel−Crafts reaction of 3-methoxy-2-naphthol (**4a**) with **2a**. α-Hydroxyketone **5aa** was obtained with an excellent 97% yield, although with a moderate 71% ee after 24 h (Scheme 3).[23] Our method could

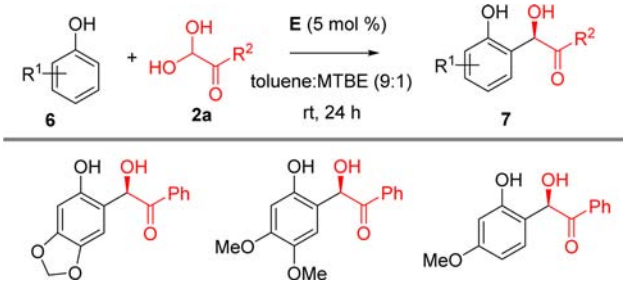
Scheme 3. Reaction of 4a[a]



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

also be applied to sesamol[24] (**6a**) and other activated phenols **6** as the nucleophiles (Scheme 4).[25] Sesamol reacted smoothly with

Scheme 4. Scope of Different Activated Phenols[a]

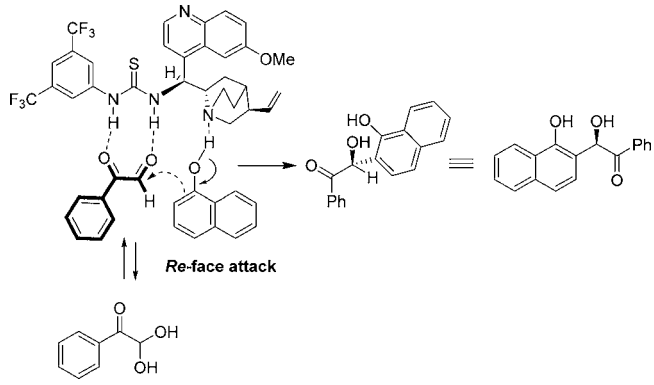


[a]Reaction conditions: **6** (0.1 mmol), **2a** (0.1 mmol), and **E** (5 mol %) in 1 mL of 9:1 toluene/MTBE. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase.

2a to give the corresponding α-hydroxyketone **7aa** with 92% yield and 96% ee. 3,4-Dimethoxyphenol **6b** and 3-methoxyphenol **6c**, with only one electron-donating group, gave corresponding chiral compounds **7ba**−**7ca** in a decreased yield.

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. 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

Scheme 5. Plausible Transition-State Model



bonding with the quinuclidine moiety of the catalyst.[26] The C-2 carbon atom of **1a** attacks the *Re* face of **2a**, thus accounting for the observed regio- and stereoselectivity.

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-hydroxyketones were obtained in 97% yields and up to 99% ee. This organocatalytic methodology features the use of bench-stable arylglyoxal hydrates with simple naphthols and phenols under mild reaction conditions and provides access to highly enantioenriched α-hydroxyketones, which are important chiral building blocks accessed through a simple Friedel−Crafts reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02893.

X-ray data for **3ai** (CIF)

Complete experimental procedures and characterization of new products, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: carlos.vila@uv.es.

*E-mail: jose.r.pedro@uv.es.

Notes

The authors declare no competing financial interest.

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