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Organocatalytic Asymmetric β-Hydroxylation of α,β-Unsaturated Ketones

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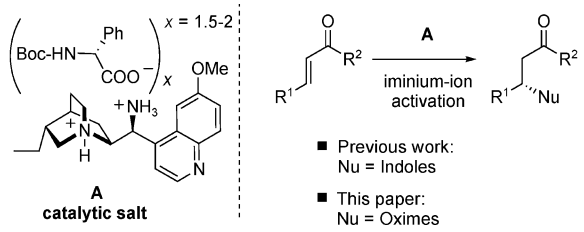
The highly enantioselective organocatalytic β-hydroxylation of α,β-unsaturated ketones was accomplished by using oximes as the oxygen-centered nucleophile. Optically active products are obtained with enantioselectivity up to 94%. Central to these studies was the use of catalytic primary amine salt **A**, in which both the cation and the anion are chiral. Amine **A** exhibits high reactivity and selectivity for iminium-ion catalysis with enones. The potential interest of this novel transformation was demonstrated with the easy conversion of the Michael adducts in enantioenriched *anti* and *syn* 1,2-diols without erosion of the optical purity.

Introduction

In recent years asymmetric organocatalysis has become a field of central importance for the stereoselective preparation of chiral interesting compounds.[1] Novel modes of substrate activation have been achieved that can deliver unique, orthogonal, or complementary selectivities in comparison to metal-catalyzed processes. In particular, chiral secondary amine catalysis has proven to be a powerful procedure for the enantioselective transformations of carbonyl compounds. By exploiting distinct catalytic activation modes such as enamine,[2] SOMO,[3] iminium-ion,[4] and dienamine[5] activation, aminocatalysis has enabled the asymmetric α-, β-, and γ-functionalization of aldehydes with a wide range of electrophiles and nucleophiles.[6] In comparison, little progress has been achieved in the corresponding asymmetric functionalization of ketones, probably due to the inherent difficulties of generating congested covalent intermediates from ketones and chiral secondary amines.

Recently, some reports have demonstrated the ability of chiral primary amine derivatives to efficiently activate ketones, owing to reduced steric constraints.[7] Meanwhile, List and coworkers have introduced asymmetric counterion directed catalysis (ACDC)[8] as an efficient strategy for enantioselective transformations that proceed via cationic species, including iminium-ion intermediates. In this vein, we have developed a new catalyst primary amine salt, in which both the cation and the anion are chiral, that exhibits high reactivity and selectivity for iminium-ion catalysis with α,β-unsaturated ketones.[9] In particular, we have shown that salt **A**, made by combining the easily available 9-amino(9-deoxy)*epi*-hydroquinine[10] with D-*N*-Boc phenylglycine as the chiral counteranion, can function as a highly efficient catalyst for the asymmetric conjugate addition of indoles to simple enones;[9] the efficient activation relies on the proven ability of primary amines to form iminium-ion intermediates from ketones combined synergistically with the benefits of asymmetric counterion directed catalysis.



Herein, we report the first highly chemo- and enantioselective oxygen-centered addition of oximes to α,β-unsaturated ketones catalyzed by chiral salt **A**, demonstrating the generality and efficiency of this catalytic system as an iminium-ion activator of simple enones

Results and Discussion

β-Hydroxy ketones and the corresponding alkoxy analogues constitute highly valuable chiral building blocks in organic synthesis and structural recurring motifs in a variety of natural products. They are generally synthesized either by aldol chemistry or the sequential epoxidation and reduction of enones.[11] In contrast, the direct asymmetric conjugate addition of O-centered nucleophiles to α,β-unsaturated ketones has proven a challenging task[12] mainly as a consequence of the relative weakness of such nucleophiles

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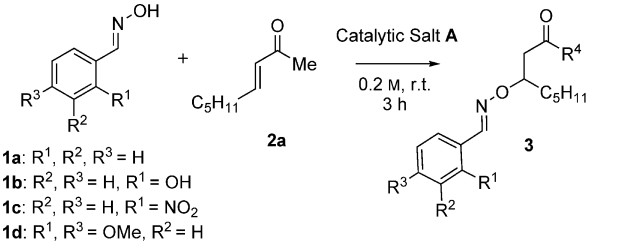
coupled with problems associated with reaction reversibility.

Recently, oximes have been identified as suitable nucleophiles for a range of highly enantioselective catalytic oxa-Michael addition to electron deficient olefins.[13] Moreover, the oxime ethers resulting from this type of conjugate addition contain a labile N–O bond, which enables reductive cleavage to afford formal hydration products.

With this in mind, a series of commercially available oximes, **1**, was screened in the addition to *trans*-3-nonen-2-one (**2a**) in the presence of catalytic salt **A** (1:2 ratio of amine to acid); the results of this survey are reported in Table 1. Despite the fact that (*E*)-benzaldehyde oxime (**1a**) afforded the desired product with high enantioselectivity, the reaction of commercially available 2,4-dimethoxybenzaldoxime (**1d**) with **2a** in toluene was complete within 3 h to yield the β-addition product with superior chemical and optical yield (89% *ee*; Table 1, Entry 4).

Table 1. Screening results for the organocatalytic addition of aromatic oximes to enone **2a**.[a]



1a: R^1, R^2, R^3 = H
1b: R^2, R^3 = H, R^1 = OH
1c: R^2, R^3 = H, R^1 = NO_2
1d: R^1, R^3 = OMe, R^2 = H

Entry	Oxime	Solvent	Catalytic salt **A** % amine	% acid	Yield [%][b]	*ee* [%][c]
1	**1a**	toluene	20	40	22	86
2	**1b**	toluene	20	40	75	32
3	**1c**	toluene	20	40	31	66
4	**1d**	toluene	20	40	55	89
5[d]	**1d**	toluene	20	40	50	50
6[e]	**1d**	toluene	20	40	49	80
7[f]	**1d**	toluene	20	40	48	82
8[g]	**1d**	toluene	20	40	56	81
9	**1d**	CH_2Cl_2	20	40	52	76
10	**1d**	AcOEt	20	40	46	86
11	**1d**	hexane	20	40	42	72
12	**1d**	Et_2O	20	40	52	90
13[g]	**1d**	Et_2O	20	40	53	90
14[h]	**1d**	Et_2O	10	20	55	90
15[i]	**1d**	Et_2O	20	40	49	91
16[j]	**1d**	Et_2O	10	20	49	80
17[k]	**1d**	Et_2O	10	10	31	90
18[k]	**1d**	Et_2O	10	15	52	90

[a] Reactions were carried out at room temperature by using 3 equiv. of oxime on a 0.1 mmol scale. [b] Yield of isolated product. [c] The *ee* value of **3** was determined by HPLC analysis. [d] TFA was used as counteranion. [e] L-*N*-Boc phenylalanine was used as chiral counteranion. [f] L-*N*-Boc phenylglycine was used as chiral counteranion. [g] Reaction time: 24 h. [h] Reaction time: 18 h. [i] Reaction carried out at 0 °C for 18 h. [j] Reaction carried out at reflux for 18 h. [k] Reaction time: 40 h.

The results obtained with different counteranions (e.g., trifluoroacetic acid, L-*N*-Boc phenylalanine; Table 1, Entries 5, 6) did not bring any appreciable improvement.[14] Remarkably, as previously observed,[9] employment of the opposite enantiomeric counteranion (L-*N*-Boc phenylglycine) afforded the same enantiomeric product **3** with lower reactivity and selectivity (Table 1, Entry 7), illustrating a marked case of a matched/mismatched catalyst–ion pair combination. On the basis of these studies, catalytic salt **A** was chosen as the best system and used for further optimizations.

Interestingly, prolongation of the reaction time did not improve the conversion, probably as a consequence of the reversibility of the process. Moreover, the products formed in toluene slowly racemized after reaching the thermodynamic equilibrium (Table 1, Entry 8). In order to circumvent this problem, an extensive study of the standard reaction parameters was performed, indicating solvent choice, catalyst loading, and catalytic salt composition as the crucial factors. Evaluation of the reaction media (Table 1, Entries 9–12) led to the observation that carrying out the reaction in Et_2O provided comparable results in terms of both yield and enantioselectivity with respect to toluene (Table 1, compare Entries 4 and 12) but, more importantly, without erosion of the enantiomeric purity during time (Table 1, Entry 13). This condition allowed the catalyst loading to be reduced to 10 mol-% (1:2 ratio of amine to acid) without affecting the efficiency of the system (Table 1, Entry 14). In addition, variation of the reaction temperature with the aim to improve the yield and enantiopurity did not provide useful results (Table 1, Entries 15, 16).

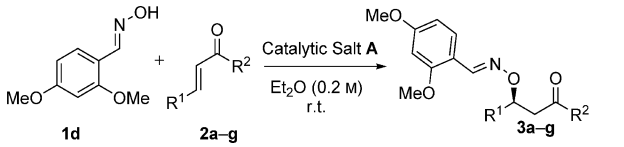
Importantly, a survey of the catalytic salt composition revealed that whereas a 1:1 ratio of 9-amino(9-deoxy)*epi*-hydroquinine to D-*N*-Boc phenylglycine had a detrimental impact on reactivity, a 1:1.5 ratio represented the best compromise between catalyst loading and catalytic efficiency (Table 1, Entries 17, 18).

After optimization of the catalytic system, the scope of this novel organocatalytic β-hydroxylation was explored by using the conditions reported in Table 2. Different linear α,β-unsaturated ketones underwent the reaction smoothly to afford optically active oxime addition products **3** in moderate-to-good yields and high enantioselectivities (up to 94% *ee*). Notably, the mild reaction conditions adopted are tolerant of the silyl ether functionality (Table 2, Entry 7).

Variation in the steric contribution of the R^2 ketone substituents revealed that the more encumbered ethyl group engenders higher stereoselectivity, albeit with slightly lower reactivity (Table 2, Entries 1, 2 and 3, 4). Practical limitations of the method include prohibitively slow reaction rates with enones bearing aromatic or highly hindered β substituents.

A demonstration of the synthetic utility of this novel organocatalytic reaction is presented in the stereoselective preparation of optically active *syn*- or *anti*-configured 1,3-diols (Scheme 1), highly valuable chiral structural motifs present in many polyketide-derived natural products of proven biological activity.[15] The asymmetric oxime addition to **2e** under our catalytic conditions, followed by simple reductive cleavage, provided formal hydration product **4** with minimal erosion of the optical purity (88% *ee*). This process enabled the verification of the absolute configuration of the β-hydroxy ketone **4** by comparison of the mea-

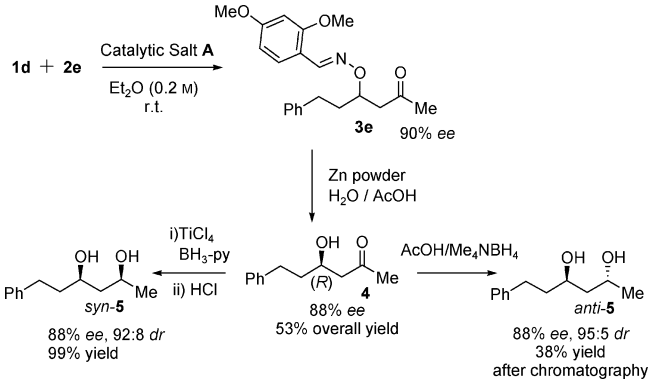
Table 2. Scope of the organocatalytic asymmetric β-hydroxylation of α,β-unsaturated ketones with the use of oxime **1d**.[a]



Entry	R^1	R^2	Catalytic salt **A** % amine	% acid	*t* [h]	Yield [%][b]	*ee* [%][c]
1	pentyl	Me, **2a**	10	15	40	(**3a**)52	90
2	pentyl	Et, **2b**	20	30	48	(**3b**)56	94
3	Me	Me, **2c**	10	15	40	(**3c**) 53	80
4	Me	Et, **2d**	20	30	60	(**3d**)46	88
5	$PhCH_2CH_2$	Me, **2e**	10	15	40	(**3e**) 55	90
6	propyl	Et, **2f**	20	30	55	(**3f**) 55	92
7[d]	CH_2OTIPS	Et, **2g**	20	30	60	(**3g**)35	80

[a] Reactions were carried out at room temperature by using 3 equiv. of **1d** on a 0.2 mmol scale. [b] Yield of isolated product. [c] The *ee* value of **3** was determined by HPLC analysis. [d] TIPS: triisopropylsilyl.

sured optical rotation with the value reported in the literature.[16,17] The stereoselective *syn* or *anti* reduction[18] of **4** furnished corresponding 1,3-diols **5** with preserved optical purity (88% *ee*) and the desired relative stereochemistry.



Scheme 1. Stereoselective route to optically active *syn*- or *anti*-configured 1,3-diols.

Conclusions

We have disclosed the first catalytic and highly enantioselective β-hydroxylation of α,β-unsaturated ketones by using aromatic oximes as the O-centered nucleophiles and catalyzed by primary amine salt **A**, in which both the cation and the anion are chiral. Besides establishing the generality and the efficiency of this new catalytic system as an iminium-ion activator of simple enones, this novel organocatalytic transformation shows potential applicability to the synthesis of polyketide-derived natural products.

Experimental Section

General Procedure for the Organocatalytic β-Hydroxylation of α,β-Unsaturated Ketones: All the reactions were carried out in undistilled Et_2O without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-amino(9-deoxy)epi-hydroquinine (10 or 20 mol-%) and D-*N*-Boc phenylglycine (15 or 30 mol-%) as the chiral counteranion were dissolved in Et_2O (1 mL). The solution was stirred for 20 min at room temperature to allow the formation of catalytic salt **A**. After the addition of α,β-unsaturated ketones (0.2 mmol), the mixture was stirred at room temperature for 10 min. Then, oxime (0.6 mmol, 3 equiv.) was added in one portion. The tube was then closed with a rubber stopper and stirring was continued for the indicated time. The crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica (hexane/Et_2O, 1:1). The solvent was removed in vacuo, and the residue was purified by flash chromatography to yield the desired product.

2,4-Dimethoxybenzaldehyde *O*-[1-(2-Oxopropyl)hexyl]oxime (3a): The reaction was carried out at room temperature for 40 h following the general procedure (Table 2, Entry 1). The title compound was isolated by column chromatography (hexane/acetone, 95:5) in 52% yield and 90% *ee*. The *ee* was determined by HPLC analysis by using a Chiralcel OD-H column (hexane/*i*PrOH, 80:20; flow rate 0.75 mL min^{-1}; λ = 214, 254 nm; τ_{minor} = 6.2 min; τ_{major} = 6.5 min). $[\alpha]_{r.t.}^{D}$ = +2.8 (*c* = 1.2, $CHCl_3$, 90% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.21–1.50 (m, 6 H), 1.52–1.75 (m, 2 H), 2.20 (s, 3 H), 2.56 (dd, *J* = 7.4, 15.6 Hz, 1 H), 2.86 (dd, *J* = 4.8, 15.6 Hz, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 4.55–4.61 (m, 1 H), 6.41 (d, *J* = 2.4 Hz, 1 H), 6.48 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 8.34 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 22.5, 25.0, 30.9, 31.7, 34.0, 48.6, 55.4, 55.5, 79.4, 98.1, 105.4, 113.9, 127.2, 144.2, 158.7, 162.3, 207.7 ppm. HRMS: calcd. for $C_{18}H_{27}NO_4$ 321.1940; found 321.1943.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full characterization.

Acknowledgments

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