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Chiral Brønsted Acid-Catalyzed Enantioselective α-Hydroxylation of β-Dicarbonyl Compounds

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α-Hydroxy-β-dicarbonyl compounds are key structural functionalities throughout natural products and pharmaceuticals.[1] Chiral α-hydroxy-β-keto esters are particularly promising molecules in the field of medicinal chemistry, as represented by the antibiotic kjellmanianone.[2] Moreover, this functional unit appears in key intermediates in many multistep reaction sequences, such as the *Aspidosperma* alkaloids 11-demethoxyvindoline and vindoline.[3] The first straightforward enantioselective α-hydroxylation of β-keto esters was the reaction of enolate salts with stoichiometric amounts of enantiopure *N*-sulfonyloxaziridines, as developed by Davis and co-workers almost three decades ago.[4] However, despite considerable efforts in the area of synthetic methods toward α-hydroxy-β-keto esters,[1] to the best of our knowledge there are only three examples[5] dealing with asymmetric catalysis. The remaining challenges lie in broadening the scope of substrates to include those bearing simple and small ester groups, for which enantioselectivities are at present not satisfactory (9−72% ee). Since the oxygen sources of such transformations are basically oxaziridines and peroxides, the development of practical, asymmetric synthetic procedures to access enantiopure α-hydroxy-β-keto esters with less sterically demanding ester groups and the discovery of novel oxygen sources are highly desirable.

During the past few years, the field of asymmetric catalysis has been expanded by the development of chiral Brønsted acids[6] as a powerful tool. In 2004, the research groups of Akiyama[7] and Terada[8] independently reported a different type of activation of electrophiles by way of protonation with strong phosphoric acids derived from chiral BINOLs, which thereafter have been widely employed in the design of novel asymmetric processes.[6]

Most of the phosphoric acid-catalyzed reactions reported to date involve imine or iminium ion electrophiles,[6−8] while the application of chiral phosphoric acid catalysis to other electrophiles is in imperious demand. Given our long-standing work in aminoxylation chemistry,[9,10] which proved to be a useful route to highly enantiopure α-hydroxycarbonyl compounds, we envisioned that by protonation of the basic nitrogen atom of nitroso compounds, aminoxylation of β-keto esters followed by N−O bond heterolysis[10c] could offer direct access to enantioenriched α-hydroxy-β-keto esters (Scheme 1). Herein we describe the first chiral phosphoric acid-catalyzed α-hydroxylation of β-dicarbonyl compounds through a tandem aminoxylation/N−O bond heterolysis sequence using nitroso compounds as the oxygen source.

Central to the utility of this new catalysis is the mechanistic requirement that selective protonation of the nitrogen atom instead of the oxygen atom in the transition state (i.e., TS-1 instead of TS-2 in Scheme 1) should be realized by the judicious choice of Brønsted acids[11] and that a chiral environment sufficient to ensure high levels of asymmetric induction for the overall process should be established.[12] To test this activation concept, an initial survey of suitable Brønsted acids was carried out, as summarized in Table 1.[13] As expected, when phosphoric acid (*R*)-**5a** was used, the proposed strategy was indeed facile at room temperature and could be accomplished within 12 h (entry 1). The reaction course could be easily monitored by observation of its color change from green to dark-brown and furnished the desired product **3a** in 88% yield with almost complete O-selectivity (O/N = 98:2) accompanied by promising enantioselectivity (60:40 er), which exemplified the first case of the activation of nitrosobenzene as an electrophilic oxygen source.[14]

Screening of other phosphoric acids revealed that (*R*)-**5e** provided the best enantio- and O/N selectivity (entry 5). Solvent examination showed that the apolar, nonprotic aromatic solvents were superior with respect to chemical yield and optical purity (entries 6 and 7). Performing the reaction with 4-chloronitrosobenzene (**2b**) induced

Scheme 1. Projected Synthesis of Chiral α-Hydroxy-β-keto Ester **1**

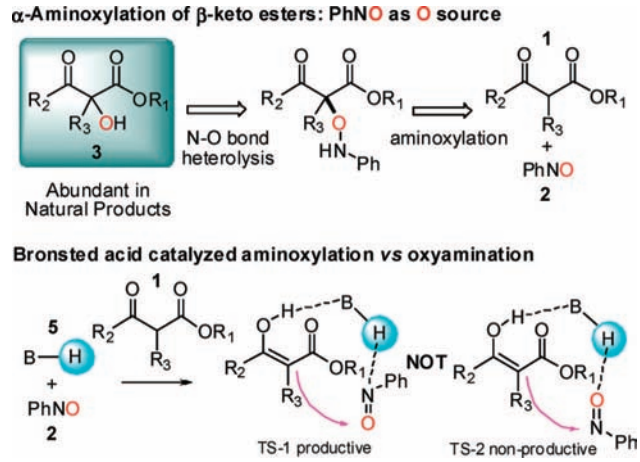
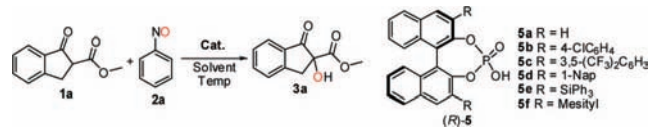


Table 1. Screening of Reaction Conditions[a]



entry	**5** (mol %)	solvent	time (h)	O/N[b]	% yield[c]	er[d]
1	**5a** (10)	$CHCl_3$	12	98:2	88	60:40
2	**5b** (10)	$CHCl_3$	12	98:2	89	70:30
3	**5c** (10)	$CHCl_3$	48	10:90	7	64:36
4	**5d** (10)	$CHCl_3$	48	6:94	4	62:38
5	**5e** (10)	$CHCl_3$	16	93:7	85	75:25
6	**5e** (10)	toluene	16	95:5	80	94:6
7	**5e** (10)	benzene	16	98:2	81	95:5
8[e]	**5e** (10)	benzene	16	98:2	80	96:4
9[e,f]	**5e** (10)	benzene	24	95:5	81	97:3
10[e,f]	**5e** (1)	benzene	30	94:6	80	99:1
11[e,f]	**5e** (0.5)	benzene	36	94:6	79	99:1
12[e,f,g]	**5e** (1)	benzene	22	94:6	81	>99:1

[a] For screening details, see the Supporting Information. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Determined by chiral HPLC. [e] 4-Chloronitrosobenzene (**2b**) was used. [f] Reaction conducted at 4 °C. [g] Using 0.25 M **1a**.

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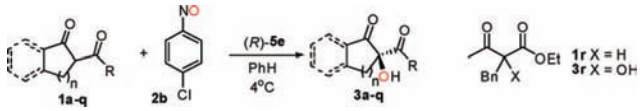
the reaction with better enantiocontrol (entry 8). Notably, although a prolonged reaction time was required at 4 °C, efficient catalytic performance with improved er was shown (entry 9). Remarkably, catalyst loadings as low as 0.5 mol % could be utilized without any decrease in er or O/N selectivity (entry 11). In terms of operational convenience, the use of 1 mol % **5e** ensured high levels of reaction efficiency and enantioselectivity while maintaining expedient reaction times (entry 10). Moreover, it is noteworthy that the concentration of the reaction mixture also played an important role, as a thorough exploration showed that a **1a** concentration of 0.25 M gave excellent results (entry 12).

Experiments that probed the scope of the β-keto ester component in this reaction are summarized in Table 2. There appears to be

Table 2. Substrate Scope



entry[a]	R	n	1	% yield[b]	er[c]
1	OMe	1	C_6H_4 (**1a**)	81 (**3a**)	>99:1
2	OEt	1	C_6H_4 (**1b**)	83 (**3b**)	>99:1
3	O*i*Pr	1	C_6H_4 (**1c**)	80 (**3c**)	>99:1
4	O*t*Bu	1	C_6H_4 (**1d**)	73 (**3d**)	>99:1
5	OBn	1	C_6H_4 (**1e**)	80 (**3e**)	>99:1
6	OMe	1	5-ClC_6H_4 (**1f**)	85 (**3f**)	>99:1
7	OMe	1	6-MeOC_6H_4 (**1g**)	83 (**3g**)	>99:1
8	OMe	1	H (**1h**)	75 (**3h**)	95:5
9	OEt	1	H (**1i**)	83 (**3i**)	96:4
10	OBn	1	H (**1j**)	82 (**3j**)	99:1
11[d]	OEt	2	H (**1k**)	88 (**3k**)	92:8
12	Me	1	H (**1l**)	75 (**3l**)	93:7
13	Me	1	C_6H_4 (**1m**)	68 (**3m**)	92:8
14	Me	1	5-ClC_6H_4 (**1n**)	67 (**3n**)	91:9
15	Me	1	6-MeOC_6H_4 (**1o**)	65 (**3o**)	90:10
16	Me	2	C_6H_4 (**1p**)	49 (**3p**)	84:16
17[d]	OMe	3	H (**1q**)	51 (**3q**)	75:25
18[e]	OEt	1	H, Ph (**1r**)	48 (**3r**)	70:30

[a] Conditions: 0.1 mmol of **1**, 0.3 mmol of **2b**, and 1 mol % **5e** in 0.4 mL of benzene at 4 °C, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC or chiral GC analysis. [d] Using 2 mol % **5f**. [e] Using 10 mol % **5f** and 10 mol % $Cu(OTf)_2$.

substantial latitude in the steric demand of the ester moiety. Substrates bearing methyl or ethyl groups afforded products in high enantioselectivities (entries 1 and 2); however, more sterically hindered *i*Pr or *t*Bu derivatives were less reactive and underwent α-hydroxylation with comparable er's (entries 3 and 4); furthermore, the electronically more demanding benzyl group was also tolerated (entry 5). Systematic tuning of electron-withdrawing and electron-donating substituents at the para and meta positions of the aromatic ring, respectively (entries 6 and 7), demonstrated broad access to a variety of substituted α-hydroxybenzo-β-keto esters. Moreover, our protocol can also be applied effectively to simple β-keto esters, as good yields and er's were obtained independent of the ester group (entries 8−11) for five- and six-membered-ring systems. In the case of inert seven-membered-ring and acyclic substrates (entries 17 and 18), diminished results were obtained.[13] The absolute configuration of **3f** was determined by comparing the optical rotation with literature data,[15] and the stereochemistries of the other α-hydroxy-β-keto esters were tentatively assigned by analogy.

To highlight the anticipated further synthetic utility of this novel activation mode, we present preliminary results for the enantioselective α-hydroxylation of β-diketones.[13] Although the α-hydroxy-β-diketone functional unit[1] is an important structural motif found in many antibiotics, such as doxycycline,[16] no catalytic asymmetric synthesis of it has been documented to date. Specifically, exposure of 2-acetyl-cyclopentanone (**1l**) to our Brønsted acid activation conditions unraveled the feasibility of the first catalytic α-hydroxylation of a β-diketone with useful levels of yield and a good er (entry 12). The benzo-β-diketones with varied substituents and substitution patterns were able to undergo this transformation smoothly (entries 13−15), while in the case of 2-acetyl-1-tetralone (**1p**), erosion of reactivity and enantioselectivity was observed (entry 16).

In summary, we have developed a facile, practically appealing, highly enantioselective Brønsted acid-catalyzed α-hydroxylation of β-dicarbonyl compounds using nitroso compounds as the oxygen source. The results disclosed herein considerably extend the substrate scope for the α-aminoxylation, allowing expeditious, straightforward, and efficient access to valuable α-hydroxy-β-dicarbonyl compounds with the highest levels of enantiocontrol. This discovery is likely to find immediate synthetic applications, given that it is the first example of the activation of nitroso compounds catalyzed by a chiral phosphoric acid. Additional investigations to clarify the reaction mechanism[14] and its application to other enantioselective reactions are underway.

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Supporting Information Available: Experimental details, DFT calculations, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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