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Direct organocatalytic asymmetric α-oxidation of ketones with iodosobenzene and *N*-sulfonyloxaziridines

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Abstract—The novel, direct amino acid-catalyzed α-oxidation of ketones with iodosobenzene and *N*-sulfonyloxaziridines is presented. A screen of several synthetically common oxidants revealed that iodosobenzene and *N*-sulfonyloxaziridines act as electrophiles in the direct organocatalytic asymmetric α-hydroxylation of ketones. The direct proline-catalyzed asymmetric α-oxidation of ketones with iodosobenzene yielded the corresponding α-hydroxylated ketones with up to 77% ee. Furthermore, several amino acid derivatives catalyze the stereoselective α-oxidation of ketones with *N*-sulfonyloxaziridines. For example, the direct diamine-catalyzed enantioselective α-hydroxylation of ketones with *N*-sulfonyloxaziridines furnished the corresponding α-hydroxylated products in moderate yield with up to 63% ee.

One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of optically active functional molecules from simple readily available starting materials. There are several methods for the preparation of enantiomerically pure compounds and among these asymmetric catalysis is a highly active research field.[1]

Optically active α-hydroxy carbonyl moieties are commonly found in numerous important natural products.[2] This has led to extensive research to find new diastereoselective and enantioselective routes for their syntheses.[3] One way of preparing these compounds is by asymmetric α-hydroxylation of enolates employing chiral auxiliaries or substrates.[4] Recently, Momiyama and Yamomoto reported a more efficient catalytic system based on AgX/BINAP-complexes that mediate indirect α-oxidation of activated tin enolates with nitrosobenzene as the electrophile.[5]

Organocatalysis has experienced a renaissance in organic chemistry.[6] In this context, we and other researchers have reported that amino acids and their derivatives catalyze the direct Yamamoto-type α-aminoxylation reaction with excellent stereoselectivities.[7] These initial reports by Zhong,[7c] MacMillan and co-workers,[7d] Hayashi and co-workers[7e–g] and us[7a,b] were later followed up by the excellent studies of Yamamoto,[8] Blackmond and others.[9] Furthermore, we recently demonstrated that amino acids catalyze the biomimetic asymmetric aerobic α-oxidation of aldehydes and ketones.[10] Based on this research and our interest in amino acid-catalyzed asymmetric reactions,[11] we became interested in whether other oxidants could be employed in transformations with catalytically generated chiral enamines. Herein, we disclose the first examples of direct organocatalytic α-oxidation of ketones with iodosobenzene and *N*-sulfonyloxaziridines yielding α-hydroxylated ketones and diols with up to 77% ee.

In an initial screen of different oxidants for the α-oxidation of cyclohexanone **1a** in the presence of a catalytic amount of L-proline (20 mol %), we found that iodosobenzene (PhIO) and *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine **3** furnished the corresponding α-hydroxylated ketone **2a** in 27% and 44% yields with 67% and 29% ee's, respectively.[12] On standing the α-hydroxy ketone **2a** dimerized and oligomerized and was therefore reduced in situ with excess $NaBH_4$ to the corresponding diol **4a** (Eq. 1).

Encouraged by these preliminary results we carried out a catalyst and solvent screen on the direct asymmetric

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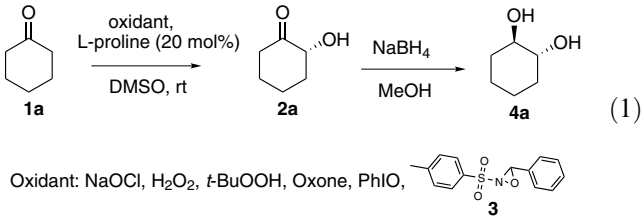


(1)

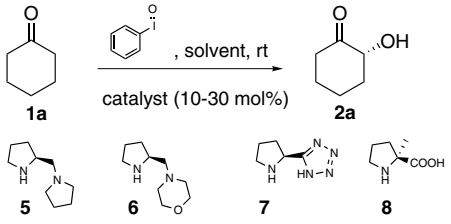
α-hydroxylation of **1a** with PhIO and *N*-sulfonyloxaziridine **3** as the oxidants (Tables 1 and 2).

The catalyst screen of the direct organocatalytic α-oxidation of ketone **1a** with PhIO revealed that L-proline provided ketone **2a** with the highest enantioselectivity in comparison to catalysts **5**–**8** (Table 1). In fact, organic catalysts **5**–**8** only furnished trace amounts of **2a** (entries 2–5). Conducting the α-oxidation of **1a** with PhIO in DMF improved the enantioselectivity of the transformation and the corresponding diol **4a** was obtained in 29% yield (*trans*/*cis* 5:1) with 77% ee after in situ reduction of **2a** (entry 6). Attempts to increase the enantioselectivity by decreasing the reaction temperature from room temperature to 0 °C were unsuccessful (entry 8). Potential background oxidation of the enamine intermediates may occur, however, the initial oxidant screen indicates that it was not significant under the reaction conditions.[12]

Next, we investigated the direct stereoselective reaction between *N*-sulfonyloxaziridine **3** and ketone **1a** in DMSO utilizing the proline-derived catalysts **5**–**9** (Table 2). We found that diamine catalyst **5** provided the α-hydroxylated ketone *ent*-**2a** with the highest ee (entry 2). The most efficient catalyst was 5-(pyrrolidin-2-ylmethyl)tetrazole **7**, which furnished **2a** in 69% yield with 17% ee (entry 4).[13] We also investigated the possibility of adding a substoichiometric amount of acid in the diamine-catalyzed reactions, which has previously been shown to accelerate the reaction rate as well as increase the enantioselectivity in enamine-catalyzed asymmetric reactions.[6g,14] We found that the yield of **2a** was augmented by addition of 0.3 equiv of TFA, however the ee of **2a** did not significantly increase (entry 7). We also performed the novel amine-catalyzed asymmetric α-oxidation of **1a** with **3** in different solvents. The solvent screen revealed that the efficiency and enantioselectivity of the reactions catalyzed by diamines **5** and **6** significantly improved in THF and $CHCl_3$. For example, diamine **6** furnished the corresponding *ent*-**2a** in 29% yield with 52% ee (entry 10). We also investigated the possibility of adding water to the diamine-catalyzed reaction in the hope of increasing the hydrophobic interactions of the substrate and the catalyst, however, no significant enhancement of the rate or enantioselectivity was observed. Furthermore, decreasing the reaction temperature did not improve the enantioselectivity of the reaction (entry 9). The diamine-catalyzed reactions with *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine furnished the α-hydroxy ketones with similar ee's to the reactions with **3**.

We next investigated the organocatalytic enantioselective α-hydroxylation reactions for a set of different ketones (Table 3).[15] The proline-catalyzed asymmetric α-oxidation of ketones **1a**–**c** with PhIO proceeded

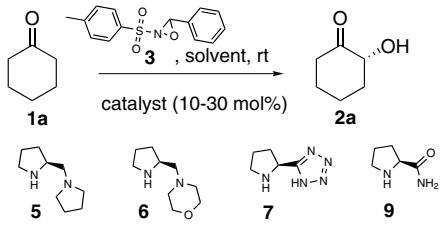
Table 1. Direct organocatalytic asymmetric α-oxidations of **1a** with PhIO[a]



Entry	Catalyst	Solvent	Yield[b] (%)	Ee[c] (%)
1	L-Proline	DMSO	27 (32)[d]	67 (65)[d]
2	**5**	DMSO	Traces	ND
3	**6**	DMSO	Traces	ND
4	**7**	DMSO	Traces	<5
5	**8**	DMSO	10	<5
6	L-Proline	DMF	29	77
7	L-Proline	CH_3CN	Traces	5
8	L-Proline	DMF	22[e]	70[e]
9	L-Proline	Dioxane	10	50
10	L-Proline	$CHCl_3$	Traces	ND

[a] To PhIO (1 mmol) in 4 mL of organic solvent in the presence of organic catalyst (10–30 mol %) was added ketone **1a** (3 mmol). After stirring for 16–24 h at room temperature the reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish α-hydroxy ketone **2a** or by in situ reduction with excess $NaBH_4$ (15 mmol) at 0 °C to afford the corresponding optically active crude diol **4a**.
[b] Yield of the isolated pure diol **4a**.
[c] The ee of *trans*-**4a** as determined by chiral-phase GC analyses.
[d] 10 equiv of **1a** was used.
[e] Temperature = 0 °C.

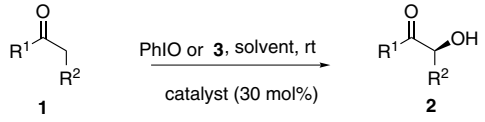
Table 2. Direct organocatalytic asymmetric α-oxidations of **1a** with **3**[a]

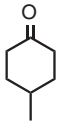
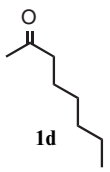


Entry	Catalyst	Solvent	Product	Yield[b] (%)	Ee[c] (%)
1	L-Proline	DMSO	**2a**	44	29
2	**5**	DMSO	*ent*-**2a**	35	39
3	**6**	DMSO	*ent*-**2a**	Traces	10
4	**7**	DMSO	**2a**	69	17
5	**9**	DMSO	**2a**	Traces	0
6	**5**·AcOH (0.3 equiv)	DMSO	*ent*-**2a**	Traces	ND
7	**5**·TFA (0.3 equiv)	DMSO	*ent*-**2a**	50	33
8	**5**	THF	*ent*-**2a**	46	37
9	**5**	THF	*ent*-**2a**	11[d]	15[d]
10	**6**	THF	*ent*-**2a**	29	52
11	**6**	$CHCl_3$	*ent*-**2a**	44	45

[a] To **3** (1 mmol) in 4 mL of organic solvent in the presence of catalyst (10–30 mol %) was added ketone **1a** (3 mmol). After stirring for 16–24 h at room temperature the reaction was quenched either by addition of brine followed by extraction with EtOAc to furnish α-hydroxy ketone **2a** or by in situ reduction with excess $NaBH_4$ (15 mmol) at 0 °C to afford the corresponding optically active crude diol **4a**.
[b] Yield of isolated pure diol **4a**.
[c] The ee of *trans*-**4a** as determined by chiral-phase GC analyses.
[d] Temperature = 0 °C.

Table 3. Direct organocatalytic asymmetric α-oxidations of ketones with PhIO and **3**

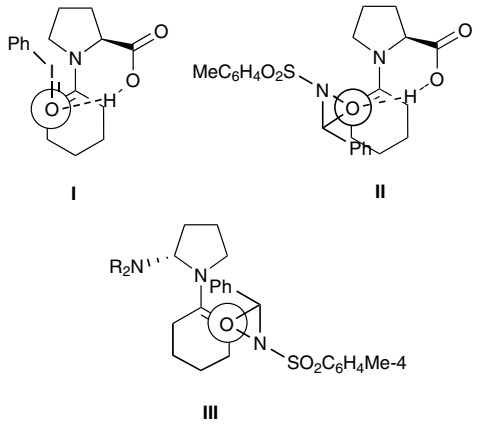


Entry	Catalyst	Ketone	Oxidant	Solvent	Product	Yield[a] (%)	Ee[b] (%)
1	L-Proline	**1a**	PhIO	DMF	**2a**	29 (48)[c]	77 (76)[c]
2	L-Proline	 **1b**	PhIO	DMSO	**2b**	20	70
3	L-Proline	**1b**	PhIO	DMF	**2b**	22	68
4	L-Proline	 **1c**	PhIO	DMSO	**2c**	21	65
5	L-Proline	 **1d**	PhIO	DMSO	**2d**	10	ND
6	**6**	**1a**	**3**	THF	*ent*-**2a**	29	52
7	**6**	**1b**	**3**	THF	*ent*-**2b**	28	63
8	**6**	**1c**	**3**	THF	*ent*-**2c**	27	34
9	**7**	**1b**	**3**	DMSO	**2b**	92	21

[a] Yield of isolated pure diol **4** following in situ reduction.
[b] The ee of *trans*-**4** as determined by chiral-phase GC analyses.
[c] 45 μL Water was added to the reaction.

smoothly furnishing the corresponding ketones **2a**–**c** in low yield with up to 77% ee. Attempts to increase the yield by addition of the PhIO in small portions were not successful. The diamine **6**-catalyzed α-oxidation of ketones **1a**–**c** with oxaziridine **3** proceeded smoothly and furnished the corresponding ketones *ent*-**2a**–*ent*-**2c** in low yields with up to 63% ee (entries 6–8). The low yields could be due to decomposition of the electrophiles. However, addition of water (100 mmol) or employing catalyst **7** increased the yield (entries 1 and 9). In addition, the reactions can be readily scaled-up and are operationally simple. The reactions with acyclic ketones **1** were slow and provided only small amounts of the corresponding α-hydroxylated ketones **2**.

The stereochemistry of the reaction was determined by synthesis and by comparison with the previously reported *trans*-diol **4a**. The stereochemical outcome of the proline-catalyzed reaction is explained by *re*-facial attack on the catalytically generated enamine by the oxygen of PhIO or *N*-sulfonyloxaziridine **3**, which is protonated by the acid moiety of L-proline to furnish the α-hydroxylated ketone **2a** (**I** and **II**). This is in accordance with the previous proline-catalyzed α-oxidations with nitrosobenzene and molecular oxygen.[8–10] The stereochemical outcome of the diamine-catalyzed reaction is opposite to that of the proline-catalyzed reactions. In this case, *si*-facial attack on the catalytically generated diamine by the oxygen of *N*-sulfonyloxaziridine **3** occurs and yields α-hydroxy ketone *ent*-**2a** (**III**). This proposed transition state is favored due to hydrophobic interactions.[16]



In summary, we present the first examples of direct organocatalytic asymmetric α-oxidation of ketones with iodosobenzene and *N*-sulfonyloxaziridines. In comparison to singlet molecular oxygen as the oxidant,[10] the amino acid-catalyzed α-oxidations with PhIO and *N*-sulfonyloxaziridine exhibited similar stereoselectivity yielding α-hydroxylated ketones with up to 77% ee. The large degree of variation in the synthesis of chiral amine- and amino acid-derived catalysts makes the likelihood of finding highly enantioselective catalysts a real possibility for the α-oxidation of carbonyl compounds with readily available oxidants. Efforts in this area are in progress.

Acknowledgements

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12. In a typical experiment, the ketone **1a** (1 mmol) was dissolved in DMSO (4 mL) and the oxidant (10 mmol) was added to the reaction mixture. In the cases of α-oxidation with PhIO and **3**, 1 mmol of the oxidant was used and 3 mmol of ketone **1a**. After 16–24 h of vigorous stirring at room temperature, the reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish α-hydroxy ketone **2a** or by in situ reduction with $NaBH_4$ at 0 °C to afford the corresponding optically active crude diol **4a**. The crude α-hydroxy ketone **2a** existed as an oligomeric mixture that upon standing formed the dimer, which was isolated by silica-gel column chromatography (EtOAc–pentane 1:20) and the ee was determined by chiral-phase GC-analysis. GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL/min, T_i = 60 °C (9 min), rate = 85 °C/min, T_f = 200 °C (5 min); retention times of **2a**: t_{maj} = 10.64 min, t_{min} = 10.66 min. The *trans*-**4a** and *cis*-**4a** diols were isolated by silica-gel column chromatography (EtOAc–pentane 1:1) and the ee of the pure *trans*-**4a** diol was determined by GC analyses. (1*R*,2*R*)-*trans*-Cyclohexane-1,2-diol: $[\alpha]_D$ −21 (*c* 0.2, $CHCl_3$); GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL/min, T_i = 110 °C (2 min), T_f = 200 °C, rate = 80 °C/min; retention times of the acetylated compound: t_{min} = 9.75 min, t_{maj} = 9.61 min. The results from the α-oxidation screen of **1a** with different oxidants for the diol **3a** was: aq NaOCl (traces, 0% ee), H_2O_2 (traces, 4% ee), *t*-BuOOH (traces, 0%), oxone (traces, 0% ee), PhIO (27% yield, 67% ee), *m*-CPBA (traces, 5% ee), oxaziridine **3** (44% yield, 29% ee).
13. For previous use of catalyst **7**, see: (a) Refs. 8a,b,10, and Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558; (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983; (c) Hartikaa, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.
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15. In a typical experiment, the ketone **1** (3 mmol) was dissolved in organic solvent (4 mL) and PhIO or **3** (1 mmol) was added to the reaction mixture. After 16–24 h of vigorous stirring at room temperature, the reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish α-hydroxy ketone **2a** or by in situ reduction with excess $NaBH_4$ (15 mmol) at 0 °C to afford the corresponding optically active crude diol **3**. The enantiomeric excess was determined by chiral-phase GC analyses.
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