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Kinetic Resolution of Oxaziridines via Chiral Bifunctional Guanidine-Catalyzed Enantioselective α-Hydroxylation of β-Keto Esters

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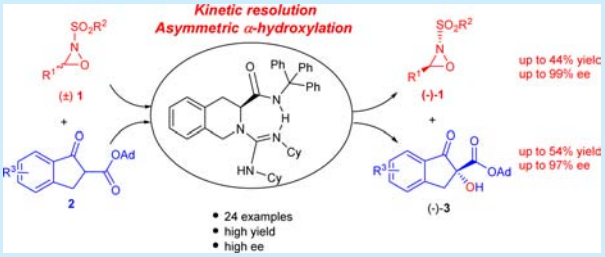
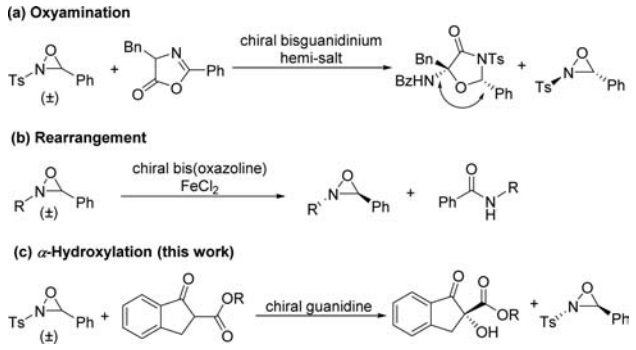
Supporting Information

ABSTRACT: An efficient kinetic resolution of racemic oxaziridines has been realized via catalytic asymmetric α-hydroxylation of available β-keto esters. In the presence of a chiral bifunctional guanidine catalyst, a variety of optically active oxaziridines and chiral α-hydroxy β-keto esters were generated with excellent results (ee's of up to 99% and 97% and yields of up to 44% and 54%, respectively).



Oxaziridines, compounds containing O, N, and C atoms in a three-membered ring, are important synthons, such as oxygen- or nitrogen-transfer reagents[1] and 1,3-dipoles.[1f] Optically active oxaziridines could directly participate in stereoselective oxidation[1f,2] and cycloaddition reactions.[3] In the past few years, methods related to the asymmetric synthesis of nonracemic oxaziridines were reported. Asymmetric oxidation of imines provides direct access to enantiopure oxaziridines.[4] Moreover, kinetic resolution[5] (KR) of racemic oxaziridines provides an alternative approach.[3,6] For instance, our group developed an efficient KR of oxaziridines via organocatalytic oxyamination of azlactones (Scheme 1a).[3]

Scheme 1. Kinetic Resolution of Oxaziridines



Subsequently, the Yoon group reported an iron-catalyzed kinetic resolution of *N*-sulfonyl oxaziridines via rearrangement of one enantiomer of the oxaziridine to the corresponding *N*-sulfonyl imide (Scheme 1b).[6b] However, the relative rate (*s* factor) should be improved so much more. Our previous study on KR of oxaziridines via oxyamination was hampered by the diastereomer differentiation induced by the chiral catalyst and oxaziridine. Given the extensive use of oxaziridines as electrophilic oxygen donors,[1a−c,e,f] we sought to follow a double purpose: asymmetric α-hydroxylation and KR of oxaziridines (Scheme 1c).

The asymmetric α-hydroxylation reaction of 1,3-dicarbonyl compounds provides direct access to α-hydroxy dicarbonyl compounds. A number of chiral metal complex catalysts have been successfully employed for this purpose using oxaziridines as the oxidants.[7] In addition, Wang, Qu, and co-workers developed a chiral guanidine featuring a tartaric acid skeleton to promote the α-hydroxylation reaction.[8] Although moderate to good enantioselectivity of α-hydroxylation was achieved, in these cases enantiomeric discrimination of oxaziridines was not studied. Chiral guanidines, which play a prominent role in organocatalysis,[9] have attracted increasing attention during the past two decades. Our group has developed a class of bifunctional chiral guanidine catalysts from amino acids.[9d] They have been widely applied to various organocatalyzed asymmetric reactions[3,10] because of their strong basicity[11] and capacity to form multiple intermolecular hydrogen bonds[12] between the catalyst and substrates.[13] Herein we utilized an acyclic guanidine−amide catalyst to achieve KR of oxaziridines and asymmetric α-hydroxylation of β-keto esters simultaneously. The reactions performed well for a wide range of oxaziridines and indanone-derived β-keto esters, providing excellent yields and enantioselection.

In our initial study, we chose racemic *N*-sulfonyl oxaziridine (±)-**1a** and 0.5 equiv of β-keto ester **2a** as the starting substrates. A complete transformation occurred once the two reactants were mixed at room temperature. Therefore, evaluation of the chiral organocatalysts for the asymmetric α-hydroxylation reaction was carried out at −78 °C, and post-treatment was run until β-keto ester **2a** was consumed. Chiral bisguanidinium hemisalt **BGs**, which is efficient in oxyamination reaction of oxaziridines, provided α-hydroxy β-keto

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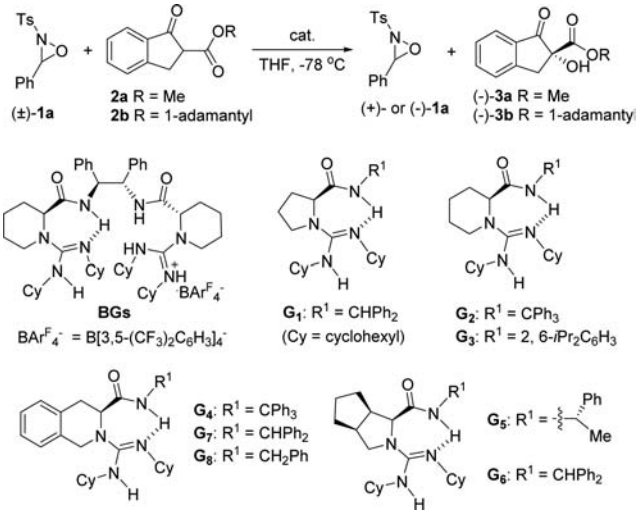
ester **3a** with 54% ee and the recovered (*R*,*R*)-oxaziridine **1a** with 50% ee (Table 1, entry 1). The subunits of the chiral

Table 1. Optimization of the Reaction Conditions[a]



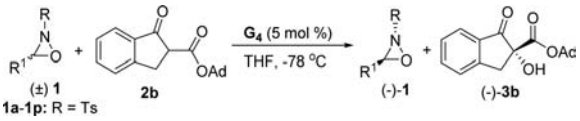
		1a (%)	3 (%)
entry	cat.	yield[b]; ee[c]	yield[b]; ee[c]
1	**BGs**	47; 50 (*R*,*R*)	49; 54 (*R*)
2	$\mathbf{G_1}$	45; 7 (*R*,*R*)	49; 25 (*R*)
3	$\mathbf{G_2}$	47; 21 (*S*,*S*)	48; 11 (*S*)
4	$\mathbf{G_3}$	47; 0	48; 0
5	$\mathbf{G_4}$	47; 75 (*S*,*S*)	49; 74 (*R*)
6	$\mathbf{G_5}$	45; 0	49; 19 (*R*)
7	$\mathbf{G_6}$	46; 25 (*S*,*S*)	48; 7 (*R*)
8	$\mathbf{G_4}$	47; 90 (*S*,*S*)	49; 97 (*R*)
9[d]	$\mathbf{G_4}$	44; 99 (*S*,*S*)	54; 95 (*R*)
10[d,e]	$\mathbf{G_4}$	44; 99 (*S*,*S*)	54; 95 (*R*)
11[d,f]	$\mathbf{G_4}$	42; 96 (*S*,*S*)	54; 94 (*R*)
12[d,e]	$\mathbf{G_7}$	44; 92 (*S*,*S*)	54; 91 (*R*)
13[d,e]	$\mathbf{G_8}$	44; 75 (*S*,*S*)	54; 71 (*R*)

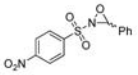
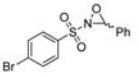
[a]Unless otherwise noted, all reactions were carried out with catalyst (10 mol %), **1a** (0.20 mmol), and **2** (0.10 mmol) in THF (1.0 mL) at −78 °C for 72 h (entries 1−7, **2a**; entries 8−13, **2b**). [b]Isolated yields according to the amount of **1a**. [c]The ee values were determined by HPLC analysis and the absolute configurations by comparison with refs 3 and 7d. [d]**2** (0.11 mmol). [e]$\mathbf{G_4}$ (5 mol %). [f]$\mathbf{G_4}$ (2 mol %).

guanidines, including the amide and the amino acid backbone, are crucial for its basicity and the stereoenvironment.[10,13] The choice of catalyst has a major impact on the selectivity of hydroxylation (entries 2−7). It was found that chiral guanidine−amides $\mathbf{G_1}$−$\mathbf{G_3}$, $\mathbf{G_5}$, and $\mathbf{G_6}$ derived from L-proline, L-pipecolic acid, and L-ramipril all failed in terms of enantioselectivity. To our delight, an obvious increase in enantioselectivity was observed when chiral guanidine $\mathbf{G_4}$ derived from (*S*)-tetrahydroisoquinoline-3-carboxylic acid was used, and the reaction performed well with 75% ee for the recovered (*S*,*S*)-oxaziridine **1a** and 74% ee for the product **3a** (entry 5). With the purpose of improving the ee value of the recovered oxaziridine **1a**, next we investigated the influence of the ester group of the *β*-keto ester.[7b−e] Steric hindrance of the *β*-keto ester turned out to be an important factor. When *β*-keto ester **2b** bearing an adamantyl group was subjected to the catalytic system, the corresponding product **3b** and the oxaziridine **1a** were given in 97% and 90% ee, respectively (entry 8). Moreover, the application of 0.55 equiv of **2b** gave the best results (54% yield with 95% ee for the product **3b** and 44% yield with 99% ee for the recovered **1a**; entry 9). When the catalyst loading of $\mathbf{G_4}$ was reduced to 5 mol %, the good results were maintained (entry 10). The enantioselectivity of the recovered oxaziridine had a slight drop at 2 mol % catalyst loading (entry 11). Further modification of the amide substituent with smaller steric hindrance resulted in reduced enantioselection (entries 12 and 13). Thus, this system of $\mathbf{G_4}$ was selected to probe the scope of asymmetric hydroxylation and KR of oxaziridines.

We next explored the scope of oxaziridines **1** that participate in the *α*-hydroxylation of *β*-keto ester **2b**, with a focus on KR of the oxaziridines (Table 2). Racemic oxaziridines containing *C*-

Table 2. Scope of Oxaziridines[a]



		1 (%)		3b (%)	
entry	R^1	yield[b]	ee[c]	yield[b]	ee[c]
1[d]	**1a**: C_6H_5	44	99	54	95
2	**1b**: 4-FC_6H_4	44	97	54	95
3	**1c**: 4-ClC_6H_4	43	98	54	94
4	**1d**: 4-BrC_6H_4	42	99	53	95
5	**1e**: 4-MeC_6H_4	39	98	52	90
6	**1f**: 4-$F_3CC_6H_4$	40	92	53	90
7	**1g**: 3-FC_6H_4	44	99	54	93
8	**1h**: 3-ClC_6H_4	44	99	54	90
9	**1i**: 3-BrC_6H_4	42	99	53	91
10	**1j**: 3-MeC_6H_4	42	98	54	92
11	**1k**: 3-$F_3CC_6H_4$	42	95	52	92
12	**1l**: 3-$MeOC_6H_4$	44	99	53	94
13	**1m**: 3,4-$Cl_2C_6H_3$	39	99	53	92
14	**1n**: 2-MeC_6H_4	39	63	54	79
15	**1o**: 1-naphthyl	28	76	53	75
16[e]	**1p**: cyclohexyl	42	83	53	83
17	**1q**: 	31	72	51	88
18	**1r**: 	38	99	54	94

[a]Unless otherwise noted, the reactions were performed with $\mathbf{G_4}$ (5 mol %), **1** (0.20 mmol) and **2b** (0.11 mmol) in THF (1.0 mL) at −78 °C for 72 h. Ad = 1-adamantyl. [b]Isolated yields according to the amount of **1**. [c]Determined by chiral HPLC analysis. [d]With **1a** (6.0 mmol) and **2b** (3.3 mmol) in THF (30 mL). [e]At −60 °C.

aryl substituents with various electronic properties at the *para* and *meta* positions gave the corresponding enantiomerically enriched isomers in excellent yields (39−44% yield with 92−99% ee; entries 1−13). Meanwhile, *α*-hydroxy *β*-keto ester **3b** was given in 52−54% yield with 90−95% ee. However, the reaction of oxaziridine **1n** bearing a 2-methylphenyl substituent resulted in decreased enantioselectivity due to the steric hindrance, and the substrate **1n** was recovered with 63% ee

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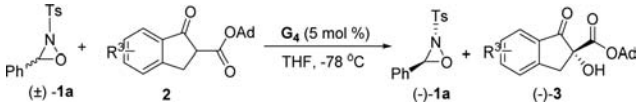
(entry 14). 1-Naphthyl-substituted oxaziridine **1o** was obtained with moderate ee in lower yield (entry 15). Oxaziridine **1p** with a *C*-cyclohexyl substituent underwent the asymmetric α-hydroxylation smoothly, and the KR process gave the corresponding oxaziridine with 83% ee at an increased reaction temperature (−60 °C; entry 16). The resolution of 4-bromo-substituted *N*-benzenesulfonyl oxaziridine **1r** was more selective than that of 4-nitro-substituted *N*-benzenesulfonyl oxaziridine **1q** (entries 17 and 18). Notably, oxaziridines **1e**, **1m**, **1n**, **1o**, **1q**, and **1r** decomposed gradually during the reaction, which resulted in lower recovered yields (entries 5, 13−15, 17, and 18). We also examined the large-scale resolution of a racemic oxaziridine and found that this protocol is readily scalable. The KR of racemic oxaziridine **1a** on a gram scale was as efficient as the model reaction without any decrease in yield and enantioselectivity, as optically pure oxaziridine **1a** was obtained in 44% yield along with α-hydroxy β-keto ester **3b** with 95% ee in 54% yield (entry 1).

Next, the scope of β-keto esters **2** was probed through α-hydroxylation with oxaziridine **1a** (Table 3). A representative

Table 3. Substrate Scope of β-Keto Esters[a]



		1a (%)		3 (%)	
entry	R^3	yield[b]	ee[c]	yield[b]	ee[c]
1	6-Cl	43	96	50 (**3c**)	96
2[d]	6-Me	43	93	54 (**3d**)	93
3	6-MeO	43	95	54 (**3e**)	93
4	5-Cl	43	94	52 (**3f**)	96
5	5-F	40	99	54 (**3g**)	95
6	4-Br	44	90	49 (**3h**)	97

[a]Unless otherwise noted, the reactions were performed with $\mathbf{G_4}$ (5 mol %), **1a** (0.20 mmol), and **2** (0.11 mmol) in THF (1.0 mL) at −78 °C for 72 h. Ad = 1-adamantyl. [b]Isolated yields according to the amount of **1a**. [c]Determined by chiral HPLC analysis. [d]At −60 °C.

selection of inden-1-one-derived β-keto esters with different substituent at C4, C5, and C6 (**2c**−**h**) were used in the reaction. The related α-hydroxylation products **3c**−**h** were obtained in 49−54% yield with excellent enantioselectivity (93−97% ee), and the unreacted (−)-oxaziridine **1a** was recovered in reasonable yields (40−44%) with 90−99% ee. The reaction of β-keto ester **2d** bearing a 6-methyl substituent had to be conducted at −60 °C (entry 2). Comparatively, the 4-bromo substituent of substrate **2h** had an effect on the resolution of the oxaziridine, although the highly enantioselective product **3h** was generated (49% yield with 97% ee; entry 6). Unfortunately, a tetralone-derived β-keto ester underwent the reaction without enantioselection at 35 °C (see the Supporting Information for details).

The absolute configurations of the recovered oxaziridine **1a** and the α-hydroxylation product **3b** were determined to be (*S*,*S*) and (*R*), respectively, by comparison of the optical rotations with those reported in the literature.[3,7d] On the basis of previous studies employing guanidine−amides as bifunctional organocatalysts,[10a] a possible catalytic model was proposed. As depicted in Figure 1, the guanidine subunit of catalyst $\mathbf{G_4}$ acts as a base, on which strong zwitterionic hydrogen bonds with β-keto ester **2b** can be tied. The *Si* face of

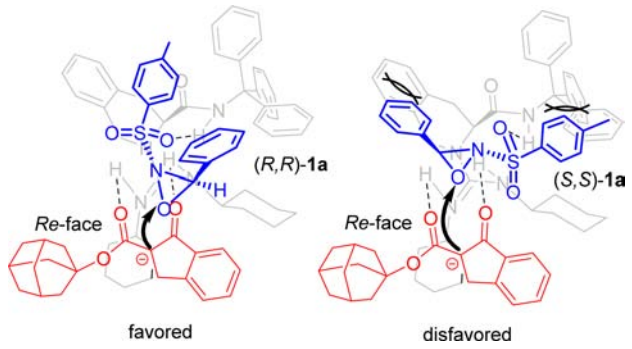


Figure 1. Proposed asymmetric induction models.

2b is blocked by the amidine backbone, and the oxygen-transfer reagent has to approach from the less hindered *Re* face, generating (*R*)-**3b**. The enantiomeric recognition of the oxaziridine is controlled by the amide subunit of the catalyst. An intermolecular hydrogen bond between the Ts group of oxaziridine **1a** and the amide of the catalyst occurs. (*R*,*R*)-**1a** gets close more easily than its enantiomer and is consumed in the α-hydroxylation reaction. Nevertheless, steric hindrance between the catalyst and the oxidant is generated when the (*S*,*S*) isomer is used, between the *C*-aryl substituent of **1a** and the tetrahydroisoquinoline backbone of $\mathbf{G_4}$ and also between the Ts group of **1a** and the triphenylmethanamine substituent of $\mathbf{G_4}$. Therefore, (*S*,*S*)-**1a** is inactive and can be recovered enantioselectively.

To summarize, we have developed a chiral bifunctional guanidine-catalyzed synchronous α-hydroxylation of β-keto esters and kinetic resolution of oxaziridines. A variety of oxaziridines and β-keto esters are well-tolerated, affording the corresponding oxaziridines and α-hydroxy β-keto esters in excellent yields and enantioselectivities. The resolution could easily be performed on a gram-scale preparation without loss of selectivity or yield. The performance of this type of bifunctional organocatalyst in asymmetric transformations will stimulate further efforts to explore new applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01614.

Experimental details and analytical data (NMR, HPLC, and ESI-HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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