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Enantioselective Oxidation of 1,2-Diols with Quinine-Derived Urea Organocatalyst

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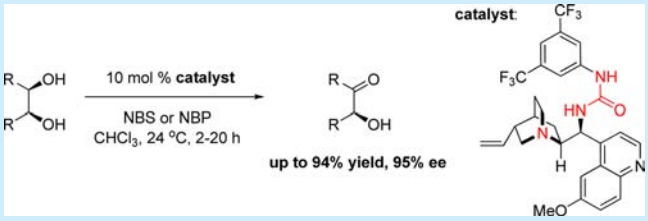
Supporting Information

ABSTRACT: Quinine-derived urea has been identified as a highly efficient organocatalyst for the enantioselective oxidation of 1,2-diols using bromination reagents as the oxidant. This simple procedure utilizes readily available reagents and operates at ambient temperature to yield a wide range of α-hydroxy ketones in good yield (up to 94%) and excellent enantioselectivity (up to 95% ee).



Catalytic asymmetric transformations of alcohol substrates such as kinetic resolution of racemic alcohols or desymmetrization of *meso*-diols have proven to be a powerful approach to access valuable enantioenriched materials in organic synthesis.[1] Along these lines, enantioselective oxidation of alcohols has been one of the most explored reaction types, in addition to asymmetric group transfer reactions.[2] Among the different catalytic strategies developed for enantioselective oxidation, almost all the efficient and highly stereoselective systems were based on transition-metal catalysis, which mainly includes asymmetric dehydrogenation catalyzed by Ru or Ir complexes,[3] Pd-,[4] V-[5] or Fe-catalyzed[6] oxidation with O_2, aerobic oxidation catalyzed by Ru(salen) or Fe(salan) complexes,[7] and Mn(salen)[8] or Cu-bisoxazoline-catalyzed[9] oxidation with $PhI(OAc)_2$ or NBS (*N*-bromosuccinimide) as the oxidant. Organocatalytic method for enantioselective oxidation of alcohols remains scarce, with only examples reported that are catalyzed by chiral TEMPO derivatives[10] or with Shi's oxazolidinone dioxiranes.[11] We report here our finding of highly stereoselective quinine urea-catalyzed oxidation of 1,2-diols using bromination reagents as the oxidant.

Our group has been interested in the use of modified cinchona alkaloids as bidentate ligand or catalyst in enantioselective catalysis (utilizing the highly basic quinuclidine nitrogen and another Lewis basic group as illustrated by model **A** in Scheme 1).[12] Recently, we reported highly diastereo- and enantioselective addition of allyltrichlorosilane to aldehydes catalyzed by quinine amides such as **4b** (Table 1).[13] As another proof-of-principle system for transition-metal catalysis, we evaluated the performance of quinine amides **4a**,**b** as potential bidentate ligands for Cu-catalyzed oxidative desymmetrization of *meso*-diols using NBS as the oxidant (Table 1).

Scheme 1. Different Catalysis Modes by Quinine-Amide

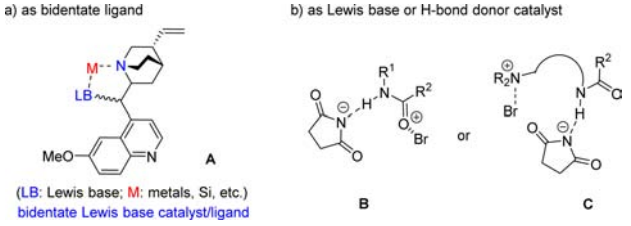
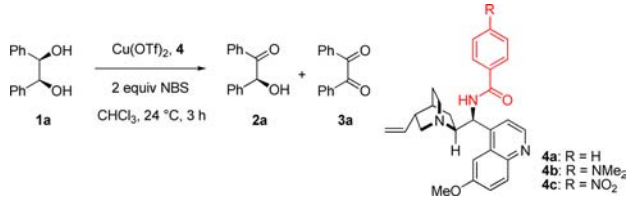


Table 1. Validating the Role of Quinine-Derived Amide[a]



entry	Cu (mol %)	**4** (mol %)	**2a** yield[b] (%)	**3a** yield[b] (%)	**2a** ee[c] (%)
1	0	0	7[d]	93[d]	
2	10	**4a** (10)	86	<5	48
3	10	**4b** (10)	91	<5	33
4	0	**4a** (10)	70	<5	70
5	0	**4b** (10)	70	<5	60
6	0	**4c** (10)	89	<5	73

[a]Reaction conditions: **1a** (0.10 mmol), NBS (2.0 equiv), 0 or 10 mol % $Cu(OTf)_2$, 0 or 10 mol % **4** in $CHCl_3$ (1.0 mL) at 24 °C for 3 h. [b]Isolated yield. [c]Determined by HPLC (Chiracel Daicel OJ-H). [d]3 h reaction.

As shown by data in entry 1, oxidation of **1a** with NBS alone proceeded smoothly to yield the overoxidized dione **3a** as the major product. Gratifyingly, addition of $Cu(OTf)_2$ in combination with **4a** or **4b** led to the formation of **2a** in high yield (with <5% **3a**) with moderate level of enantioselectivity, implying significant acceleration over the background reactivity

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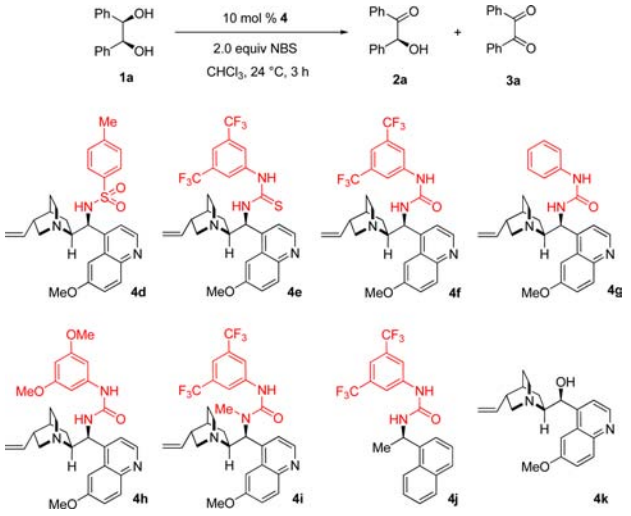
by the Cu-quinine amide complex (entries 2 and 3). Intriguingly, however, in the absence of Cu salt, oxidation catalyzed by **4a** alone produced **2a** in improved enantioselectivity of 70% (entry 4). Again the side product **3a** was produced in <5% yield, indicating that the catalytic process was selective toward diol oxidation. Inspired by the work of peptide-catalyzed asymmetric bromination reported from the Miller group[14] and asymmetric halolactonization[15] reported from the Borhan group,[16] the Tang group,[17] the Jacobsen group,[18] and the Yeung group,[19] we surmised that the amide or the quinuclidine nitrogen in the catalyst may be involved in the bromonium formation leading to an enantioselective oxidation (models **B** or **C** in Scheme 1). Furthermore, the results obtained from catalysts **4b** and **4c** (entries 5 and 6) showed that more electron-deficient amide moiety led to higher efficiency and selectivity, implying the possibility of amide serving as H-bond donor in the interaction with succinimide.

Following this promising lead, much experimentation was carried out on the optimization of quinine amides that, unfortunately, led to no further improvement in the reaction outcome. We then moved on to screen quinine-derived molecules incorporated with related Lewis basic groups or H-bond donor units (Table 2). While quinine sulfonamide **4d** or

Table 2. Catalyst Optimization for Oxidation of 1a[a]



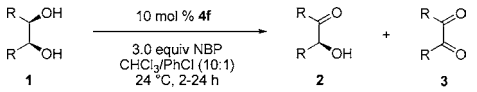
entry	4	yield[b] (%)	ee[c] (%)	entry	4	yield[b] (%)	ee[c] (%)
1	**4d**	83	32	5	**4h**	90	70
2	**4e**	52	7	6	**4i**	93	77
3	**4f**	94	91	7	**4j**	92	<2
4	**4g**	92	84	8[d]	**4k**	82	<2

[a]Reaction conditions: **1a** (0.10 mmol), NBS (2.0 equiv), 10 mol % of **4** in $CHCl_3$ (1.0 mL) at 24 °C for 3 h. [b]See Table 1. [c]See Table 1. [d]16 h reaction.

quinine thiourea **4e** led to poor enantioselectivities, the use of quinine urea **4f** interestingly produced **2a** in 94% yield with 91% ee (entry 3 vs entries 1 and 2). The electronic property of the urea moiety was examined next, which followed the same trend as in the quinine amide series (entries 3−5). Monomethylated urea catalyst **4i** proved much less selective (77% ee, entry 6). These data seem to support the hypothesis that urea moiety is serving as the H-bond donor. Finally, the importance of urea as well as the quinuclidine nitrogen was supported by the fact that utilizing catalyst **4j** bearing only a chiral urea moiety or quinine (**4k**) led to the formation of racemic product.

Further screening of solvents showed that chloroform was the best choice for the reaction of **1a** (see the Supporting Information, Table 1). *N*-Bromophthalimide (NBP) was identified as the optimal oxidant from the examination of various halogenation reagents (NCS, NIS, DBDMH (1,3-dibromo-5,5-dimethylhydantoin), etc.), the loading of which had some effect on the enantioselectivity as well, with 3 equiv providing optimal enantioselectivity. Under the optimized conditions, **2a** could be obtained in 94% yield with 95% ee (entry 1, Table 3).

Table 3. Enantioselective Oxidative Desymmetrization of *meso*-Diols Catalyzed by 4f[a]



				product 2	
entry	R	product	time (h)	yield[b] (%)	ee[c] (%)
1	Ph	**2a**	3	94	95[d]
2	2-ClC_6H_4	**2b**	24	90	81[d,e]
3	3-ClC_6H_4	**2c**	3	92	66
4	4-FC_6H_4	**2d**	3.5	83	84[d]
5	4-ClC_6H_4	**2e**	3	90	74
6	4-BrC_6H_4	**2f**	2	91	86
7	4-$CH_3C_6H_4$	**2g**	2	94	91
8	4-$OMeC_6H_4$	**2h**	2.5	85	82
9	1-naphthyl	**2i**	2	65	83[e]
10	CH_2OBn	**2j**	18	50	54[d,f]

[a]Reaction conditions: **1** (0.1 mmol), NBP (3.0 equiv), 10 mol % of **4f** in $CHCl_3$/PhCl (10:1; 1.0 mL) at 24 °C unless noted otherwise. [b]Isolated yield. [c]Determined by HPLC. [d]$CHCl_3$ (1.0 mL). [e]20 mol % of **4f**. [f]2.0 equiv of NBS instead of NBP was used.

The substrate scope of this catalytic system was then explored. A mixed solvent system (10:1 $CHCl_3$/PhCl) was discovered to be beneficial for most substrates. As shown in Table 3, a wide range of diaryl-substituted *meso*-1,2-diols could be oxidized selectively to mono-oxidation product **2** with excellent yield and good to excellent enantioselectivity. Different *para*-, *meta*- and even *ortho*-substitution on the aryl unit could be well-tolerated (entries 1−9). When we tried dialkyl-substituted diols such as **1j**, however, both the efficiency and selectivity of the system dropped dramatically, with **2j** obtained in only 54% ee (entry 10).

While the low efficiency in the oxidation of dialkyl substituted-diols represents the limitation of this catalytic system, we demonstrate here that it serves well for the resolution of racemic *syn*-diols. As illustrated in Scheme 2, both chemo- and enantioselectivities are involved for the oxidation of racemic diol **5** bearing different substituents. If both high enantio- and chemoselectivity (i.e., oxidation of benzylic alcohol only) can be achieved for this reaction; hydroxy ketone **6** will be the sole product, and this will result in the kinetic resolution of racemic **5**.[20] In another related scenario where the reaction shows no chemoselectivity, both **6** and *ent*-**7** can be obtained in high enantioselectivity, which will result in a divergent reaction on a racemic mixture,[21] according to the nomenclature of Vedejs.[1c]

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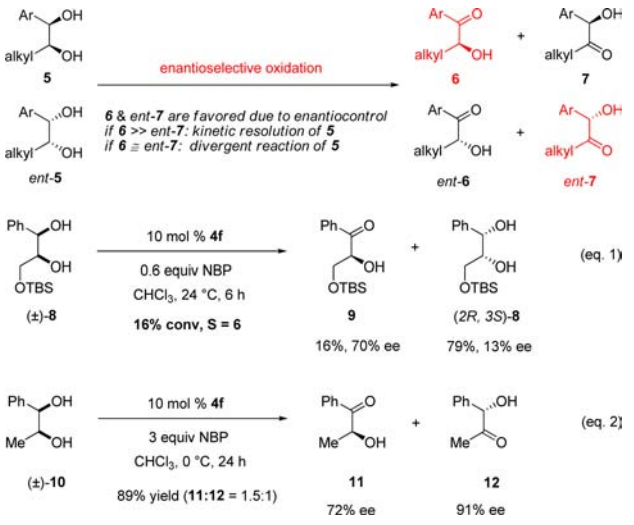
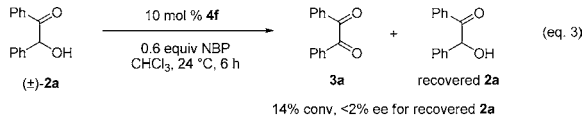
Scheme 2. Extension to Kinetic Resolution or Divergent Reaction on Racemic Diol 5



When we tested the enantioselective oxidation of racemic **8** catalyzed by **4f** (eq 1, Scheme 2), only one α-hydroxy ketone product **9** was produced, indicating perfect chemoselectivity. The level of catalytic efficiency and enantioselectivity for this kinetic resolution process, however, was only moderate (s = 6). When diol **10** bearing phenyl and methyl substituents were tested, interestingly, products **11** and **12** were formed in a ratio of 1.5:1 with good to high enantioselectivities (72% and 91% ee, respectively), representing an example of divergent reaction on racemic mixture.

The diol functionality is believed to be essential for the catalytic reaction to proceed efficiently with high enantioselectivity. While a small amount of dione **3** could be formed in our reaction (up to 5%), we showed that oxidation of α-hydroxy ketone (racemic **2a**) to dione was not enantioselective (eq 3). It is also noteworthy that while HBr is formed as the



side product, addition of external base is not necessary for the high catalytic activity of the system. We speculate that the quinuclidine nitrogen of the catalyst is involved in complexation with NBP (model **C**, Scheme 1), which transfers the bromonium species to diol substrate and turns over by complexation with another molecule of NBP, instead of being trapped by HBr. Considering the identity of oxidant has a profound effect on the enantioselectivity of the reaction as well, we propose that H-bonding interactions among the urea moiety from the catalyst, the phthalimide and diol (serving as H-bond donor) are key factors for a well-organized transition state that accounts for the enantioselectivity of this catalytic system.

In conclusion, quinine-based urea has been identified as a highly efficient and stereoselective catalyst for oxidation of 1,2-diols. This reaction utilizes commercially available reagents, operates at ambient temperature, and therefore represents a practical method to produce α-hydroxy ketones in good to high enantioselectivity. Efforts to extend the scope of this catalytic system to other types of alcohols are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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