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Chiral Ion-Pair Organocatalyst-Promoted Efficient Enantioselective Reduction of α-Hydroxy Ketones

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Abstract. The enantioselective reduction of α-hydroxy ketones with catecholborane has been developed employing 5 mol% of an 1,1'-bi-2-naphthol (BINOL)-derived ion-pair organocatalyst. This methodology provides a straightforward access to the corresponding aromatic 1,2-diols in high yields (up to 90%) with excellent enantioselectivities (up to 97%). Furthermore, the α-amino ketones also could be reduced with moderate ee values under mild reaction condition.

Keywords: α-hydroxy ketone; ion-pair; catecholborane; organocatalysis; reduction

Catalytic asymmetric reduction of carbonyl compounds is one of the most sophisticated methods in organic synthesis.[1] Although Significant progress has been made in the asymmetric transfer hydrogenation of aromatic ketones,[2] the development of a general and asymmetric catalytic method applicable to the synthesis of optically active 1,2-diols still meets a great challenge. These compounds are known as substructures of many naturally occurring or pharmaceutical compounds such as carisbamate,[3a] reboxetine,[3b] and many other biologically active substances.[3c-d]

Chiral 1,2-diols have commonly been synthesized by direct asymmetric dihydroxylation of alkenes,[4] asymmetric hydrolysis of epoxides,[5] enzymatic reactions,[6] and asymmetric hydrogenation of α-hydroxy ketones.[7-9] Among various synthetic methods, the last one represents the most direct and promising approaches for the generation of valuable terminal, vicinal 1,2-diols. While many highly enantioselective processes catalyzed by transition-metal complexes based on Ir,[7] Rh,[8] and Ru[9] have been reported, additional studies using organocatalyst to achieve highly enantioselective hydrogenation of α-hydroxy ketones are still warranted.

Although achiral boranes are already widely used in the CBS-reduction,[10] the use of achiral boron hydrides as reducing agents in organocatalysis is still less investigated. So far, catecholborane has proved to be one of the most versatile and robust achiral boron hydrides,[11] which also shows a significant tolerance for many functional groups. There are only a few examples of asymmetric organocatalysis processes using catecholborane as reductant. In 1998, Fujisawa[12] developed a method of the asymmetric reduction of (trifluoroacetyl)biphenyl derivatives using oxazaborolidine catalyst and catecholborane. In 2000, Umani-Ronchi[13] demonstrated the use of $Zn(OTf)_2$-bisoxazoline complexes for the catalytic enantioselective reduction of α-alkoxy ketones. A few years ago, Falck and Antilla successfully utilized catecholborane in the reduction of ketones employing either thiourea catalysts or chiral phosphoric acids, respectively.[14] Later on, Enders and co-workers reported the use of catecholborane in the organocatalytic asymmetric transfer hydrogenation of a range of ketimines[15] and α-ketone esters[16] with good results via Brønsted acid catalysis. To the best of our knowledge no asymmetric reduction of α-hydroxy ketones employing achiral borane hydrides has been developed.

Over the last decade, along with the rapid development of organocatalysis, chiral-ion pair have emerged as a new and efficient type of organocatalysts.[17] Inspired by previous work,[18] and also in conjunction with our ongoing interest in the asymmetric reduction,[19] we present herein a chiral ion-pair organocatalyst-promoted enantioselective hydroboration of α-hydroxy ketones.

We started our investigations with evaluation of representative chiral phosphoric acids **4** and **5** for the reduction of the commercially available 2-hydroxy-1-phenylethan-1-one **1a** at room temperature. Initial tests with the SPINOL-derived phosphoric acids **4** were not very promising, the desired 1-phenylethane-1,2-diol **6a** was mostly obtained in moderate yields and low enantioselectivities. We then examined BINOL-derived phosphoric acids (**5a, 5d, 5e** etc.) in this reaction, which unfortunately also gave diol **6a** in low enantioselectivities or even as racemic mixtures (Table 1). Increasing the steric demand of the aryl

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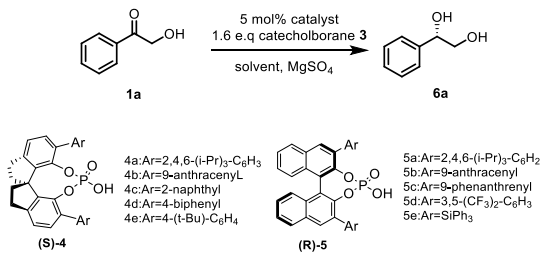
Table 1. Optimization of the reaction conditions.[a)]



Entry	catalyst	Solvent	T(°C)	Yield(%)[b)]	ee(%)[c)]
1	**(R)-5a**	toluene	r.t	55	0
2	**(R)-5b**	toluene	r.t	85	75
3	**(R)-5c**	toluene	r.t	73	55
4	**(R)-5d**	toluene	r.t	62	0
5	**(R)-5e**	toluene	r.t	47	5
6	**(S)-4a**	toluene	r.t	68	-3
7	**(S)-4b**	toluene	r.t	65	-12
8	**(S)-4c**	toluene	r.t	70	-15
9	**(S)-4d**	toluene	r.t	32	-10
10	**(S)-4e**	toluene	r.t	53	-23
11	**(R)-5b**	Et_2O	r.t	45	60
12	**(R)-5b**	DCM	r.t	76	53
13	**(R)-5b**	c-hexane	r.t	23	5
14	**(R)-5b**	o-xylol	r.t	80	72
15	**(R)-5b**	toluene	-20	72	79
16	**(R)-5b**	toluene	-55	58	81
17	**(R)-5b**	toluene	-78	<5	-

[a)] Reaction condition: **1a** (0.1 mmol), catalyst (5 mol %), $MgSO_4$ (100 mg) and 1.6 e.q catecholborane **3** in 1 mL solvent. Unless otherwise noted, the reaction was carried out under nitrogen for 12 h. [b)] Yield of isolated product after column chromatography. [c)] Determined by HPLC analysis.

substituents on the BINOL backbone using catalysts **5c** caused the enantioselectivity to increase dramatically to 55%. Finally, the best result was obtained with BINOL-derived phosphoric acid **5b**, furnishing the product in 85% yield and 75% ee. Screening polar or inert solvent like DCM or diethyl ether revealed inferior enantioselectivities compared to toluene (Table 1, entries 11–12). Whereas using c-hexane as solvent only led to a low enantioselectivity of 5% (Table 1, entries 13), conducting the reaction in o-xylol furnished diol **6a** with 72% ee. The best result was obtained using toluene as solvent under the same condition, instead, the selectivity clearly increased to 75% ee and even more when the reaction mixture was cooled to -20°C and -55°C (Table 1, entries 15–16). But when the reaction temperature reached -78°C, catalyst **5b** show very low catalytic activity due to low temperature. Later on, we found out that when DMAP was added, the reaction proceeded smoothly even at -78°C with good yields and ee values (Table 2, entry 4).

Since phosphoric acid metal salts and phosphoric acid derived ion-pair catalysts have already been reported to be effective in numerous organic trans-

Table 2. Optimization of the additive.[a)]

Entry	Additive (mol %)	Yield (%)[b)]	ee(%)[c)]
1	-	85	75
2	$Ca(OMe)_2$ (2.5)	87	54
3	$Mg(t\text{-}Bu)_2$ (2.5)	89	66
4	DMAP (5.0)	88	83
5 [d)]	DMAP (5.0)	90	95
6 [d)]	N,N-diethylpyridin-4-amine (5.0)	78	90
7 [d)]	4-(pyridin-4-yl)morpholine (5.0)	62	57
8 [d)]	N,N-diphenethylpyridin-4-mine (5.0)	67	68
9	Phenylboronic Acid (5.0)	63	81
10	p-Tolylboronic Acid (5.0)	56	70
11	4-Chlorophenylboronic Acid (5.0)	54	65

[a)] Reaction condition: **1a** (0.1 mmol), catalyst **(R)-5b** (5 mol %), additive (x mol %), $MgSO_4$(100 mg) and 1.6 e.q catecholborane **3** in 1 mL toluene. Unless otherwise noted, the reaction was carried out under nitrogen at r.t for 4 h. [b)] Yield of isolated product after column chromatography. [c)] Determined by HPLC analysis. [d)] Reaction was run at -78°C for 4h.

formations,[17, 20] an investigation on the influence of different types of additives in the reaction was commenced (Table 2). Firstly, phosphoric acid metal salts of calcium and magnesium showed the results of good yields with enantioselectivities decreased to 54% and 66%, respectively. Excellent enantioselectivity was obtained when combining chiral phosphate acid with 4-(dimethylamino)pyridine (DMAP) (Table 2, entry 4–5), which has been proved to be an efficient combination in previous work.[14b] However, other potential candidates for cation moiety, such as N,N-diethylpyridin-4-amine, 4-(pyridin-4-yl)morpholine and N,N-diphenethylpyridin-4-mine, did not further improve the ee value (Table 2, entries 6–8). Furthermore, boronic acids were also evaluated as additives,[21] which seem to have a negligible effect on enantioselectivities (Table 2, entries 9–11).

With the optimal anionic and cationic moiety of the catalyst identified, we further examined the influence of the amount of catecholborane **3** in the reaction (Table 3). Drawing on the experience of other reduction protocols employing catecholborane as the reducing agent,[13-16] we found the use of 1.8 equiv of hydride source provided the best result with 96% ee (Table 3, entry 4), while lowering the amount of borane led to a significant decrease of yield and ee value. Especially under low temperature, an extra amount (more than 1.6 equiv) of catecholborane **3** is very important to maintain the enantioselectivity in this reaction.

With the optimized conditions in hand, the scope of the reaction was studied. Various electron-rich as well as electron-deficient aromatic α-hydroxy ketones **1** with different substitution patterns furnished the resulting diols **6** with good yields and enantioselectivities. The absolute configuration of the

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Table 3. Influence of the amount of catecholborane **3** on reduction.[a)]

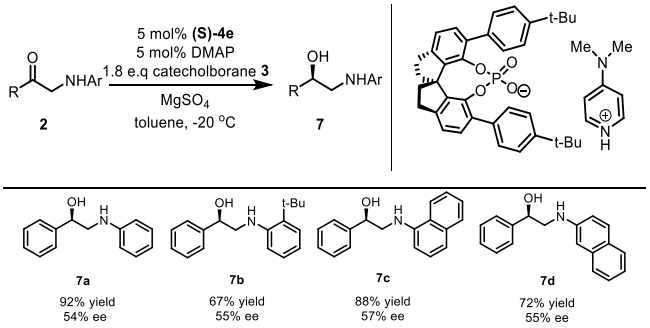
Entry	**3** (equiv)	Yield (%)[b)]	ee(%)[c)]
1	1.0	50	30
2	1.4	65	57
3	1.6	90	95
4	1.8	89	96
5	2.0	86	92

[a)] Reaction condition: **1a** (0.1 mmol), catecholborane **3** (x equiv), DMAP (5 mol %), catalyst **(R)-5b** (5 mol %), $MgSO_4$ (100 mg) in 1 mL toluene at -78°C for 4h. [b)] Yield of isolated product after column chromatography. [c)] Determined by HPLC analysis.

aromatic 1,2-diols **6** has been determined to be (S) by comparing the optical rotation values with those reported in the literature.[4e, 9f] Interestingly, electron-rich α-hydroxy ketones (**1d** and **1e**) gave inferior enantioselectivties but still in good yields, halogenated, substrates gave better results. Moreover, ketones bearing halogen substituents in both 3 and 4-position of the aromatic ring gave slightly higher enantioselectivities than other substitution patterns (Table 4, **6p**–**6r**). With decreasing size the halogen atom in the 4-position of the phenyl ring the enantioselectivity increased from 60% for iodine (see in SI) to 95% for chlorine substituted α-hydroxy ketone **1i**. To our delight more sterically demanding ketones (**1l** and **1m**) were reduced in high yields with very good selectivities (90% ee). Labile functional groups, such as nitrile, trifluoromethyl, and trifluoromethoxy were well tolerated (Table 4, **6p**–**6r**). Heteroaromatic systems could be reduced smoothly with good yields, albeit with only moderate selectivities of 71% ee and 57% ee, respectively.

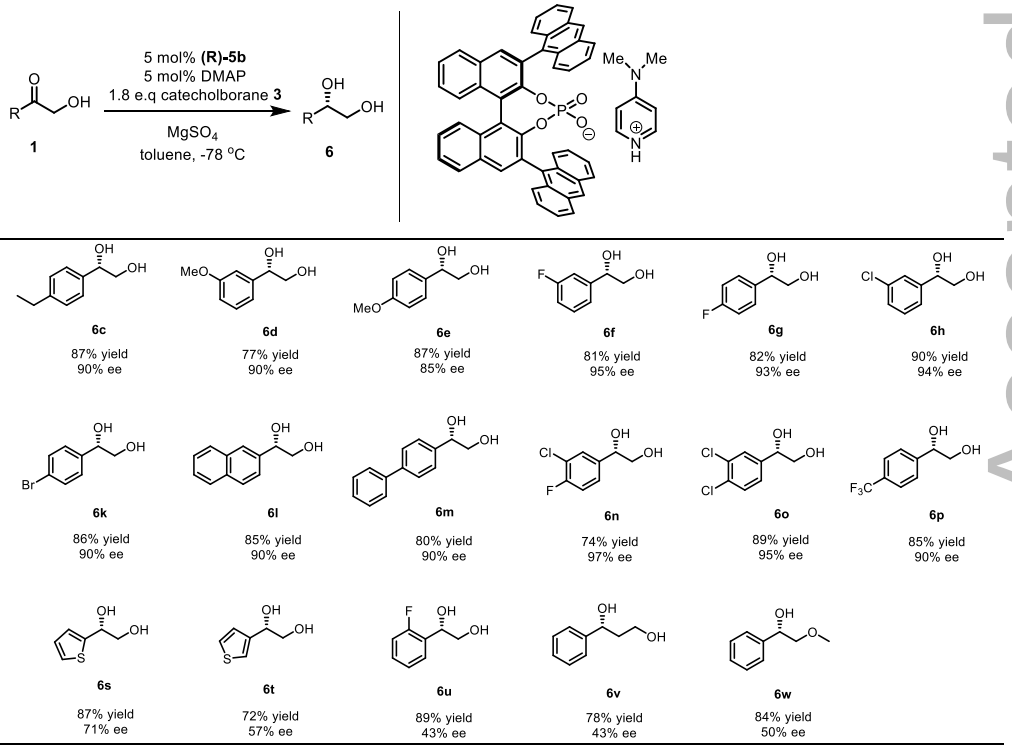
Furthermore, aromatic diol **6u** bearing a substituent in the 2-position were isolated in moderate enantioselectivity. We suspected that the ortho substituents might interfere with the preferred coordination of the carbonyl group to the boron cen-

Table 5. Substrate scope of α-amino ketones. [a)]



[a)] Reaction condition: **2** (0.1 mmol), catecholborane **3** (1.8 equiv), DMAP (5 mol %), catalyst **(S)-4e** (5 mol %), $MgSO_4$ (100 mg) in 1 mL toluene. Unless otherwise noted, the reaction was carried out under nitrogen in toluene at -20 °C for 2 h, yields referred to isolated yields, ee values were determined by HPLC.

Table 4. Substrate scope of α-hydroxy ketones. [a)]

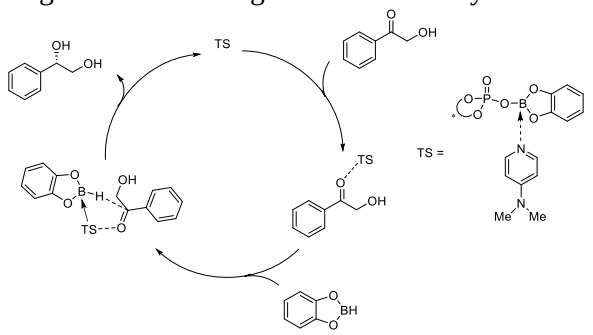


[a)] Reaction condition: **1** (0.1 mmol), catecholborane **3** (1.8 equiv), DMAP (5 mol %), catalyst **(R)-5b** (5 mol %), $MgSO_4$ (100 mg) in 1 mL toluene. Unless otherwise noted, the reaction was carried out under nitrogen at -78 °C for 2 h, Yields referred to isolated yields, ee values were determined by HPLC. [b)] Reaction was run at -20°C.

ter and lead to low selectivity. When employing the optimal conditions, moderate selectivity was obtained for 3-hydroxy-1-phenylpropan-1-one **1v**, but still in good yield. Finally we use methylated ketone **1w** asubstrate, albeit with only moderate selectivity. The OH group of the α-hydroxy ketones might be essential to control the enantioselectivity under the existing conditions of this reaction.

We next turned our attention to asymmetric reduction of α-amino ketones **2**, and the results were presented in Table 5. Unfortunately, the corresponding products **7a-7d** were obtained in moderate enantioselectivities (Table 5).[22]

On the basis of aforementioned results and previous reports,[13b, 14a] a possible mechanism for this reaction is proposed (Scheme 1). On the basis of the fact that the hydrogen evolution is observed after mixing the chiral ion-pair catalyst with catecholborane **3**, therefore, a chiral phosphoryl borate intermediate (TS) is thought to be formed. While the boron of the intermediate can act as a Lewis acid coordinating to the ketone, the P=O moiety the catalyst coordinates to another catecholborane molecule. The hydride of this catecholborane can be added in a chiral environment of the α-hydroxy ketones, providing the (S)-configured diols and regenerated the catalyst.



Scheme 1. Proposed reaction mechanism.

In summary, we have found that chiral ion-pair (comprised of chiral phosphoric acid and DMAP) can act as an efficient organocatalyst for asymmetric reduction of α-hydroxy ketones. The scalable protocol furnished the chiral diols in good yields and excellent enantioselectivities. Further investigations utilizing this catalytic system are ongoing in our lab.

Experimental Section

General procedure for asymmetric reduction：

To a flame-dried test tube was added catalyst (2r,6s)-2,6-di(anthracen-9-yl)-4-hydroxydinaphtho[1,3,2]dioxaphosphepine 4-oxide **(R)-5b** (3.5 mg, 0.005 mmol, 5 mol %), 4-(dimethylamino)-pyridine (DMAP, 1.2 mg, 0.005 mmol, 5 mol %) and 1.0 mL dry CH_2Cl_2, stirred for 1h and then concentrated in vacuo to form the ion-pair catalyst. 2-Hydroxy ketone **1** (0.10 mmol) and $MgSO_4$ (100 mg) were added in the tube. The vessel was placed under vacuum and the atmosphere exchanged with nitrogen three times before the addition of dry toluene (1.0 mL). The mixture was allowed to stir for 30 min before being cooled to -78 °C. Catecholborane **3** (1.8 equiv) was added subsequently. After stirring for 2 h at -78 °C, MeOH (0.5 mL) followed by 1N NaOH solution (1 mL) were added. The mixture was allowed to warm to room temperature gradually and stirred for another 1 h and then extracted with EtOAc (10 mL ×3), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography.

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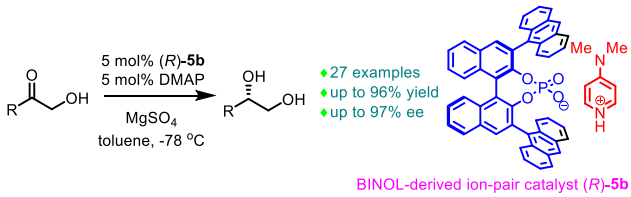

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