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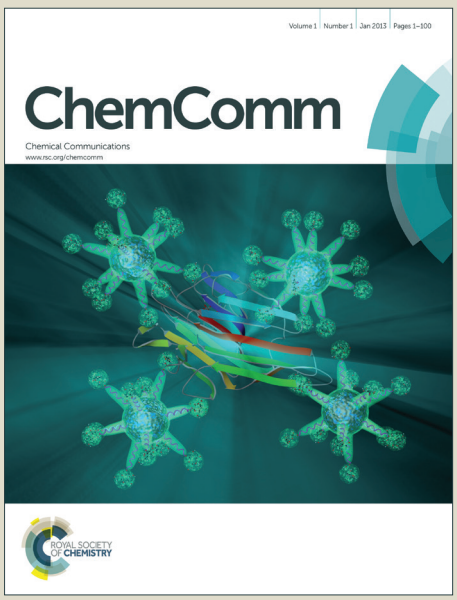

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ARTICLE TYPE

Enantio- and chemoselective Brønsted-acid/Mg(^{n}Bu)$_2$ catalysed reduction of α-keto esters with catecholborane †

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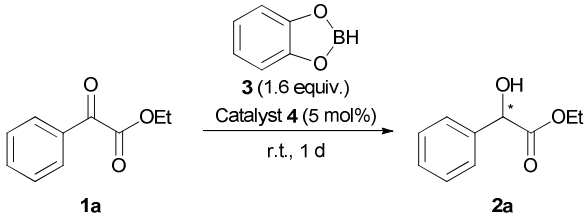
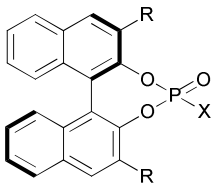
The first enantio- and chemoselective Brønsted-acid catalysed reduction of α-keto esters with catecholborane has been developed. The α-hydroxy esters were obtained under mild reaction conditions in virtually quantitative yields and excellent enantioselectivities. With slight modifications both enantiomers can be obtained without any loss of selectivity.

Enantiomerically pure α-hydroxy acids and their derivatives are an important class of substances and play a significant role as chiral building blocks in the pharmaceutical and the chemical industry.[1] Therefore various synthetic methods have been developed including enzymatic and biomimetic methods,[2] Canizzaro reactions,[3] Friedel-Crafts reactions,[4] kinetic resolutions[5] and the synthesis of cyanohydrins as precursors.[6] However, the most convenient method for the asymmetric synthesis of α-hydroxy esters is the reduction of prochiral α-keto esters by chiral boranes,[7] diastereoselective reductions with chiral auxiliaries,[8] homogeneous hydrogenations and hydrogen transfer reactions[9] as well as heterogeneous enantioselective hydrogenations.[10] Although achiral boranes are widely used in the CBS-reduction of ketones and trichloromethyl ketones[11] they have not been applied to multifunctionalized substrates so far. Despite its high reactivity, catecholborane shows a significant tolerance for several functional groups like esters, sulfonates, and even terminal alkenes,[12] but its tremendous potential in the field of asymmetric catalysis has not been recognized for a long time.[13] To the best of our knowledge no asymmetric reduction of α-keto esters employing an achiral borane has been developed so far without requiring toxic transition metals. Recently we have developed the asymmetric reduction of imines and α-imino esters by chiral BINOL based phosphorylborates and catecholborane.[14] Herein we want to describe the first transition metal-free reduction of α-keto esters employing chiral phosphoric acid catalysts and catecholborane. We started our investigations by screening several Brønsted acids **4** for the reduction of the commercially available ethyl benzoylformate (**1a)** at room temperature (Table 1). Although first attempts with the phenyl substituted acid **4a** were not very promising, the desired

Table 1 Evaluation of the chiral Brønsted acids **4**[a]





4a X = OH, R = Ph
4b X = OH, R = 4-$NO_2C_6H_4$
4c X = OH, R = 3,5-$(CF_3)_2C_6H_3$
4d X = OH, R = $SiPh_3$
4e X = OH, R = 2,4,6-$(^iPr)_3C_6H_2$
4f X = OH, R = 9-phenanthryl
4g X = NHTf, R = 9-phenanthryl

Entry	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**4a**	5	-
2	**4b**	93	61
3	**4c**	94	65
4	**4d**	91	23
5	**4e**	22	–33
6	**4f**	56	–87
7	**4g**	56	37
8[d]	**4f**	94	73

[a] The reaction was conducted on a 0.1 mmol scale of **1a** in 1.0 mL of toluene. [b] Yield of isolated **2a** after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Catalyst not washed with HCl after purification by flash column chromatography.

α-hydroxy ester **2a** was obtained in high yield and moderate selectivity of 61% *ee* with stronger acids **4b** and **4c** (Table 1, entries 1-3). Increasing the steric demand of the aryl substituents on the BINOL backbone with the catalysts **4d** and **4e** caused the enantioselectivity to decrease dramatically to 23% *ee* and 33% *ee* respectively, however, with only a low yield of 22% and a change in the absolute configuration of **2a** (Table 1, entries 4, 5). Finally, the best results were obtained with the more sterically demanding acid **4f**, furnishing the α-hydroxy ester **2a** in 87% *ee* and moderate yield of the opposite enantiomer.

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†Electronic Supplementary Information (ESI) available. Experimental procedures, characterization data of all products, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. See DOI: 10.1039/b000000x/

Table 2 Optimization of the metal additive[a]

Entry	Additive (mol%)	Yield[b] (%)	*ee*[c] (%)
1	-	56	–87
2	^{n}BuLi (5.0)	78	0
3	Ca(OMe)$_2$ (2.5)	56	26
4	Mg(^{n}Bu)$_2$ (2.5)	89	16
5	Mg(^{n}Bu)$_2$ (0.3)	39	–4
6	Mg(^{n}Bu)$_2$ (0.9)	67	72
7	Mg(^{n}Bu)$_2$ (1.3)	94	78
8	Mg(^{n}Bu)$_2$ (1.9)	99	80

[a] The reaction was conducted on a 0.1 mmol scale of **1a** in 1.0 mL of toluene with 5 mol% of catalyst **4f**. [b] Yield of isolated **2a** after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

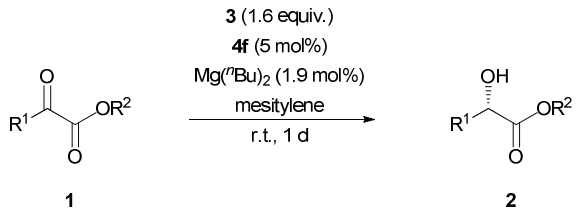
Changing to the more acidic and thus more reactive triflylamide **4g** was ineffective (Table 1, entries 6-7). Interestingly, the use of acid **4f** contaminated with metal salt impurities gave very good results with an excellent yield and good enantioselectivity of 73% *ee*. Since phosphoric acid metal salts have already been reported to be effective in numerous organic transformations[15] we investigated the influence of several main group metal sources in our reduction (Table 2). Among the most common main group metals tested in our reduction magnesium showed the best results in yield with an enantioselectivity of 16% *ee* (Table 2, entry 4). Because the selectivity of the pure phosphoric acid magnesium salt was rather low compared to previous results we examined different amounts of the metal source resulting in 1.9 mol% as the optimum with 99% yield and 80% *ee*. Interestingly, we could also observe a change in the absolute configuration of our product by increasing the amount of the metal species. Therefore a high purity of the established chiral phosphoric acid and thus its thorough washing with HCl is required after the purification by flash column chromatography. Having identified chiral phosphoric acid **4f** in combination with 1.9 mol% dibutyl magnesium to be the best catalytic system we investigated the influence of the solvent on our asymmetric reduction (Table 3). Since polar solvents have proven to be unsuitable reaction media

Table 3 Influence of the solvent and temperature[a]

Entry	Solvent	Yield[b] (%)	*ee*[c] (%)
1	toluene	99	80
2	benzene	98	67
3	*o*-xylene	98	82
4	mesitylene	94	87
5	^{n}hexane	56	72
6[d]	mesitylene	94	86

[a] The reaction was performed on a 0.1 mmol scale of **1a** in 1.0 mL of toluene with 5 mol% of catalyst **4f** and 1.9 mol% Mg(^{n}Bu$_2$). [b] Yield of isolated **2a** after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at 0 °C.

Table 4 Substrate scope of the reduction of α-keto esters[a]



1 2

Entry	2	R^1	R^2	Yield[b] (%)	*ee*[c] (%)
1	**a**	Ph	Et	94 (56)[d]	87 (–87)[d]
2	**b**	Ph	^{i}Pr	93 (21)[d]	91(–89)[d]
3[e]	**c**	Ph	^{t}Bu	48	81
4	**d**	Ph	Bn	97	66
5	**e**	4-Me-C$_6$H$_4$	^{i}Pr	94	97
6	**f**	3-Me-C$_6$H$_4$	^{i}Pr	>99	95
7	**g**	2-Me-C$_6$H$_4$	^{i}Pr	97	97
8	**h**	4-MeO-C$_6$H$_4$	^{i}Pr	>99 (85)[f]	98 (97)[f]
9	**i**	2-MeO-C$_6$H$_4$	^{i}Pr	>99	96
10	**j**	4-F-C$_6$H$_4$	^{i}Pr	95	97
11	**k**	4-Cl-C$_6$H$_4$	^{i}Pr	97	95
12	**l**	4-Br-C$_6$H$_4$	^{i}Pr	>99	91
13	**m**	3-F-C$_6$H$_4$	^{i}Pr	>99	93
14	**n**	3-Cl-C$_6$H$_4$	^{i}Pr	88	89
15	**o**	2-F-C$_6$H$_4$	^{i}Pr	90	95
16	**p**	2-Cl-C$_6$H$_4$	^{i}Pr	94	83
17	**q**	3,5-F$_2$-C$_6$H$_3$	^{i}Pr	>99	88
18	**r**	1-Naphthyl	^{i}Pr	>99	90
19	**s**	2-Naphthyl	^{i}Pr	97	94
20	**t**	6-MeO-2-naphthyl	^{i}Pr	>99	97
21	**u**	Thienyl	^{i}Pr	97	96
22	**v**	Cyclohexyl	^{i}Pr	97	70
23	**w**	^{t}Bu	^{i}Pr	99	74

[a] The reaction was performed on a 0.15 mmol scale of **1** in 1.5 mL of mesitylene. [b] Yields of isolated **2** after flash column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was conducted without the addition of Mg(^{n}Bu)$_2$. [e] The reaction was performed at 0 °C. [f] The reaction was conducted on a 1.0 mmol scale.

for our catalytic system[14] and ^{n}hexane gave only moderate results, only the aromatic non-polar solvents were assumed to be beneficial. By increasing the hydrophobic character of the solvent we achieved an enantioselectivity of 82% with *o*-xylene and finally 87% *ee* accompanied by almost quantitative yield performing the reaction in mesitylene at room temperature. Lowering the reaction temperature to 0 °C was ineffective leading to a slightly lower selectivity of 86% *ee*. With the optimized reaction conditions in hand we finally examined the substrate scope of the enantioselective, Brønsted-acid catalysed reduction of α-keto esters (Table 4). Various electron-rich as well as electron-deficient aromatic α-keto esters with different

substitution patterns were reduced with excellent enantioselectivities and almost quantitative yields. The absolute configuration has been determined to be (*S*) by comparing the optical rotation values of the α-hydroxy esters **2a-d**, **2p** and **2w** with those reported in the literature. While the more flexible benzyl ester **2d** was obtained only in moderate selectivity of 66% *ee*, the more sterically demanding isopropyl ester was reduced with 91% *ee* (Table 4, entries 2 and 4). Although better results have been expected for the *tert*-butyl ester, the corresponding α-hydroxy ester could only be obtained in moderate yield and good enantioselectivity even at 0 °C presumably caused by the lability of the ester moiety under the optimized conditions (Table 4, entry 3). The newly developed method was highly efficient and appeared to be independent from the substitution pattern as well as the substituent. Remarkably, both enantiomers can be obtained in excellent enantioselectivities with the same catalyst only by adding a metal source (Table 4, entries 1, 2). Even heteroaromatic systems could be reduced with excellent results of 97% yield and 96% *ee* (Table 4, entry 21). Aliphatic α-hydroxy esters were also obtained in high yield, albeit with only good selectivities of 70% *ee* and 74% *ee*, respectively. Finally our protocol was conducted on a 1.0 mmol scale furnishing hydroxyl ester **2h** with almost the same yield and stereoselectivity (Table 4, entry 8, values in brackets).

Conclusion

In conclusion, a new efficient and highly enantioselective Brønsted-acid catalysed reduction of α-keto esters has been developed employing catecholborane as reducing agent and an *in situ* generated chiral phosphoryl borate as the catalyst. The scalable protocol furnished the α-hydroxy esters in almost quantitative yields and excellent enantioselectivities. Additionally, the opposite enantiomer is accessible with only slight modifications and without a loss in enantioselectivity, albeit, in only moderate yields. Further investigations utilizing this catalytic system are ongoing in our laboratories.

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