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Chemo- and Enantioselective Brønsted Acid-Catalyzed Reduction of α-Imino Esters with Catecholborane

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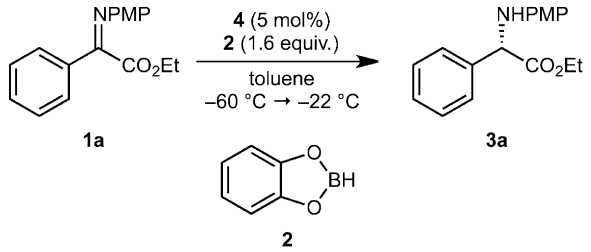
Abstract: The chemo- and enantioselective reduction of α-imino esters with catecholborane has been developed employing 10 mol% of an enantiopure BINOL-based phosphoric acid as organocatalyst. Various differently substituted aromatic α-amino acid derivatives can be achieved in almost quantitative yields and very good to excellent enantioselectivities of up to 96% *ee* under mild reaction conditions.

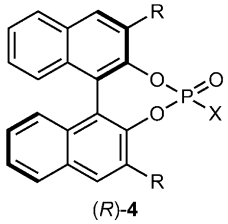
Keywords: amino acids; Brønsted acids; catecholborane; organocatalysis; phosphoric acids; reduction

Enantiomerically pure α-amino acids belong to one of the most important classes of organic molecules and as the building blocks of life play a key role in modern protein and peptide research.[1] Therefore and due to their central role in organic chemistry the enantioselective synthesis of amino acids has gained great attention and is still the focus of intensive current research.[2] Besides their application as enantiopure substrates for auxiliaries, ligands and catalysts, α-amino acids are also utilized as chiral building blocks in total synthesis.[3] An interesting class of such compounds is the chiral arylglycines because of their intriguing role in various pharmaceutical agents such as glycopeptide antibiotics, ß-lactam antibiotics, antibacterial agents and cardiovascular drugs.[4] Due to their great importance, a variety of methodologies has been developed,[5a] including asymmetric catalysis,[5] enzymatic resolution[6] and chiral auxiliary-mediated induction.[7] In recent years especially asymmetric Strecker reactions,[8] alkylations of glycine derivatives and α-imino esters have attracted great attention.[5c,9] The organocatalytic biomimetic transamination of α-keto esters has been published just recently.[10] Among these methods the most direct approach to enantiomerically enriched α-arylglycines is the catalytic asymmetric direct reduction of prochiral α-enamides and α-imino esters, employing both metal-based catalysts and organocatalysts. Although only few examples of metal-catalyzed hydrogenation reactions of α-imino esters are known due to the low reactivity of these substrates,[11] some organocatalytic protocols have been developed employing Hantzsch esters,[12] benzothiazolines[13] or trichlorosilane[14] as hydride source. However, the reduction with Hantzsch esters as well as with benzothiazolines occasionally suffers from difficulties in the purification of the products, albeit, in the latter case these problems have been overcome by developing novel benzothiazolines bearing hydroxy groups.[13] In contrast, the use of achiral boron hydrides as reducing agents in organocatalysis is less investigated. Whereas the Corey–Bakshi–Shibata (CBS) reduction is well known for the reduction of ketones,[15] aromatic imines,[16] oximes,[17] stable N–H imines[18] or cyclic *N*-sulfonylimines,[19] to the best of our knowledge, only the hydroboration of chiral α-imino esters has been reported utilizing L-selectride.[20] To some extent this might result from the low chemoselectivity of most of the common boron hydrides. Hence, just recently catecholborane was successfully utilized in the organocatalytic reduction of ketones employing either thiourea catalysts or chiral phosphoric acids[21] and in the reduction of ketimines *via* Brønsted acid catalysis by our group.[22]

Chiral Brønsted acid catalysis has gained great attention in the last decade since the pioneering work of Akiyama and Terada and is a rapidly growing subfield of organocatalysis. BINOL-based phosphoric acids have successfully been employed in several organic transformations.[23] Because of the tremendous potential of this class of organocatalysts and the fact that catecholborane does not reduce ester groups even at elevated temperatures,[24] we envisaged a Brønsted acid-catalyzed chemoselective reduction of α-imino esters by applying catecholborane as hydride source.

Table 1. Evaluation of the chiral Brønsted acids **4** in the reduction of imino ester **1a** with catecholborane (**2**).[a]





(*R*)-**4**

4a X = OH, R = 9-phenanthryl
4b X = OH, R = $SiPh_3$
4c X = OH, R = 3,5-$(CF_3)_2C_6H_3$
4d X = OH, R = 4-$NO_2C_6H_4$
4e X = OH, R = 3,4,5-$F_3C_6H_2$
4f X = OH, R = 2,4,6-(*i*-Pr)$_3C_6H_2$
4g X = NHTf, R = 2,4,6-(*i*-Pr)$_3C_6H_2$
4h X = OLi, R = 2,4,6-(*i*-Pr)$_3C_6H_2$

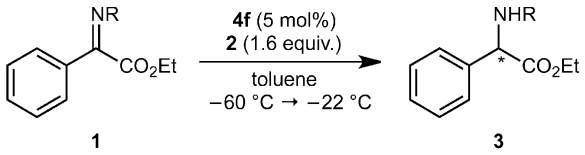
Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**4a**	70	20
2	**4b**	35	0
3	**4c**	49	23
4	**4d**	91	21
5	**4e**	95	45
6	**4f**	95	77
7	**4g**	95	37
8	**4h**	25	0

[a] The reactions were performed on a 0.1-mmol scale of imino ester **1a** using 1.6 equiv. of catecholborane (**2**) and 5 mol% of catalyst **4** at −22 °C in 1.0 mL toluene for 2 d. Before the addition of **1a** the reaction mixture was pre-cooled to −60 °C.
[b] Yield of isolated **3a**.
[c] Determined by chiral stationary phase HPLC analysis.

In continuation to our efforts in the asymmetric synthesis of amino acids,[5c,25] herein we wish to report the first chemo- and enantioselective hydroboration of α-imino esters employing a chiral phosphoric acid as catalyst. Preliminary experiments using achiral diphenyl phosphate as catalyst in the reduction of *p*-methoxyphenyl (PMP)-protected ethyl imino ester **1a** revealed high reactivity and almost full conversion within two hours at room temperature. Therefore we started our investigations with a survey of different chiral phosphoric acids at −22 °C with pre-cooling to −60 °C before the addition of **1a** (Table 1). Initial tests with 5 mol% of sterically demanding chiral phosphoric acids **4a** and **4b** gave amino ester **3a** only in moderate yield and low enantioselectivity or even as a racemic mixture (Table 1, entries 1 and 2). A change to the less demanding acid **4c** led to a slight increase of the selectivity to 23% *ee*, however, still with only moderate yield (Table 1, entry 3). We assumed a low reactivity of the chiral phosphoric acid borate formed *in situ* by the reaction of the acid with catecholborane. Therefore, we then examined the more acidic chiral acids **4d** and **4e** bearing a nitro function or fluorine atoms at the aryl substituent of the BINOL backbone (Table 1, entries 4 and 5). To our delight this led to an increase in yield to more than 90% as well as a slight increase of the enantioselectivity to 45% (Table 1, entry 5). Further screening of phosphoric acids showed that the well known TRIP phosphoric acid **4f** furnished the product **3a** in 95% yield accompanied with an increased selectivity of 77% *ee* (Table 1, entry 6).[26] In the reduction of ketimines, investigated by our group, the more acidic *N*-triflylphosphoramide **4g** gave the best results.[22] In the case of the reduction of **1a**, **4g** also gave the amino ester **3a** in almost quantitative yield, albeit with a dramatic decrease of enantioselectivity (Table 1, entry 7). Use of a chiral lithium salt has been reported in the reduction of ketones, furnishing the corresponding alcohols in high yield and selectivity.[21b] In our case upon utilizing the chiral lithium salt **4h** only racemic **3a** was obtained (Table 1, entry 8).

Having identified chiral phosphoric acid **4f** to be the best catalyst we next examined the influence of the aromatic *N*-protecting group on the yield and enantioselectivity (Table 2). Although amino esters **3** could be isolated in high yields independently from the *N*-protecting group, its effect on the selectivity of the reduction was remarkable. In the presence of an unsubstituted phenyl group on the imine moiety, **3b** was achieved with only moderate selectivity of 32% *ee* (Table 2, entry 1). While the PMP-protecting group gave the best result with 77% *ee*, moving the methoxy group to the *ortho* position decreased the enantiose-

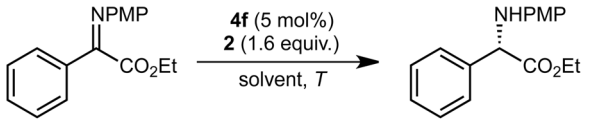
Table 2. Influence of the *N*-protecting group on the asymmetric reduction of α-imino esters **1**.[a]



Entry	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**3b**	90	32
2	OMP[d]	**3c**	88	19
3	PMP	**3a**	95	77
4	TMP[e]	**3d**	84	4

[a] Unless otherwise specified the reactions were performed on a 0.1-mmol scale of imino ester **1a** using 1.6 equiv. of catecholborane (**2**) and 5 mol% of catalyst **4f** at −22 °C in 1.0 mL toluene for 2 d. Before the addition of **1a** the reaction mixture was pre-cooled to −60 °C.
[b] Yield of isolated **3a**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] OMP = 2-methoxyphenyl.
[e] TMP = 3,4,5-trimethoxyphenyl.

Table 3. Evaluation of the solvent and the temperature in the reduction of imino ester **1a** with catecholborane (**2**).[a]



1a **3a**

Entry	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	DCM	−60→−22	98	59
2	Et_2O	−60→−22	98	5
3	*n*-hexane	−60→−22	98	55
4	petroleum ether	−60→−22	98	63
5	*o*-xylol	−22	88	72
6	toluene	r.t.	91	18
7	toluene	0	81	3
8	toluene	−22	99	39
9	toluene	−60→−22	95	77
10[d]	toluene	−60→−22	95	70
11[e]	toluene	−60→−22	98	83
12[f]	toluene	−60→−22	98	83

[a] Unless otherwise specified the reactions were performed on a 0.1-mmol scale of imino ester **1a** using 1.6 equiv. of catecholborane (**2**) and 5 mol% of catalyst **4f** at −22 °C in 1.0 mL toluene for 2 d. Before the addition of **1a** the reaction mixture was pre-cooled to the given temperature.
[b] Yield of isolated **3a**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] Reaction was performed in 2.0 mL solvent.
[e] Reaction was performed with 10 mol% **4f** for 24 h.
[f] Reaction was performed with 15 mol% **4f** for 24 h.

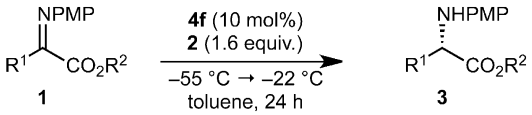
lectivity to 19% (Table 2, entries 2 and 3). The introduction of a more electron-rich arene as protecting group, such as TMP, furnished the corresponding amino ester **3d** almost as a racemic mixture (Table 2, entry 4). In the latter case it might be assumed that the steric hindrance in the corresponding transition state is too big to allow a considerable enantiodifferentiation.

Next we investigated the effect of the solvent and the temperature on the reduction of α-imino esters **1** (Table 3). Although the solvent seemed not to have any influence on the yield of isolated **3a**, screening polar or coordinating solvents like DCM or diethyl ether revealed inferior selectivities compared to toluene (Table 3, entries 1 and 2). Therefore, in all further experiments exclusively non-polar and non-coordinating solvents are evaluated. Whereas *n*-hexane only leads to a moderate enantioselectivity of 55%, conducting the reaction in petroleum ether furnished α-amino ester **3a** with 63% *ee* (Table 3, entries 3 and 4). However, aromatic non-polar solvents gave better results compared to the aliphatic ones. Although the reaction mixture with *o*-xylol could only be cooled to −22 °C due to its higher melting point the enantioselectivity was increased to 72% (Table 3, entry 5). Conducting the reaction in toluene under the same conditions, instead, the selectivity clearly decreases to 39% *ee* and even more at 0 °C and room temperature (Table 3, entries 6–8). But we were pleased that the enantioselectivity was increased to 77%, when the reaction mixture was pre-cooled to −60 °C before the addition of **3a** and then further stirred at −22 °C for 48 h (Table 3, entry 9). While decreasing the concentration of the imino ester led to a slight decrease in enantioselectivity (Table 3, entry 10), increasing the catalyst loading to 10 mol% provided the amino ester **3a** in 98% yield and a very good enantioselectivity of 83%. A further increase of the catalyst loading had no effect on the reaction (Table 3, entries 11 and 12).

During our investigations in the asymmetric reduction of imino esters we recognized a strong dependence of the enantioselectivity on the pre-cooling temperature. For this reason we finally did a survey of the reaction temperature before adding **1a** to the reaction mixture. Interestingly pre-cooling to −70 °C and −50 °C had a clear effect on the selectivity and led to only 60% *ee* and 80% *ee*, respectively. It might be assumed that at these temperatures the formation of a borane imine adduct gets more favourable leading to a potential uncatalyzed and thus unselective reduction. To our delight we were able to improve the conditions further by pre-cooling to −55 °C before the addition of **1a** and further stirring at −22 °C for 24 h. Applying these conditions **3a** is obtained in almost quantitative yield and 86% *ee* (Table 4, entry 2).

With the optimized conditions in hand we finally investigated the substrate scope of the enantioselective reduction of α-imino esters. Various electron-rich as well as electron-deficient aromatic α-imino esters with different substitution patterns were reduced with very good to excellent enantioselectivity and overall almost quantitative yield (Table 4). The absolute configuration of the amino esters **3a** and **3e–3h** has been determined to be (*S*) by comparing the optical rotation values with those reported in the literature.[12a,b,13] With small or flexible ester moieties like methyl or benzyl esters only moderate enantioselectivities up to 66% were obtained (Table 4, entries 1 and 5). In contrast, the more sterically demanding *tert*-butyl ester delivered the corresponding amino ester **3g** in almost quantitative yield and excellent enantioselectivity of 96% *ee* (Table 4, entry 4). Thus exclusively *tert*-butyl esters were used in the following experiments. Interestingly electron-rich 4-substituted imino esters only gave moderate enantioselectivties but still in excellent yield (Table 4, entries 6 and 7), whereas halogenated substrates gave better results. With decreasing size of the halogen atom in the 4-position of the aromatic moiety the enantioselectivity increased from 72% for bromine to 91% for fluorine substituted ester **1k** (Table 4, entries 8–10). Assuming that the substituent

Table 4. Susbtrate scope for the enantioselective reduction of α-imino esters.[a]



Entry	R^1	R^2	**3**	Yield [%][b]	*ee* [%][c]
1	C_6H_5	Me	**3e**	93	63
2	C_6H_5	Et	**3a**	93	86
3	C_6H_5	*i*-Pr	**3f**	97	92
4	C_6H_5	*t*-Bu	**3g**	87	96
5	C_6H_5	Bn	**3h**	86	66
6	4-MeC_6H_4	*t*-Bu	**3i**	97	67
7	4-$MeOC_6H_4$	*t*Bu	**3j**	88	70
8	4-FC_6H_4	*t*-Bu	**3k**	94	91
9	4-ClC_6H_4	*t*-Bu	**3l**	97	78
10	4-BrC_6H_4	*t*-Bu	**3m**	90	72
11	3-MeC_6H_4	*t*-Bu	**3n**	97	77
12	3-ClC_6H_4	*t*-Bu	**3o**	91	84
13	3-FC_6H_4	*t*-Bu	**3p**	97	89
14	2-MeC_6H_4	*t*-Bu	**3q**	97	94
15	2-FC_6H_4	*t*-Bu	**3r**	99	92
16	2-ClC_6H_4	*t*-Bu	**3s**	97	90
17	2-naphthyl	*t*-Bu	**3t**	92	84
18	2-thienyl	*t*-Bu	**3u**	81	86
19	cyclohexyl	*t*-Bu	**3v**	95	57

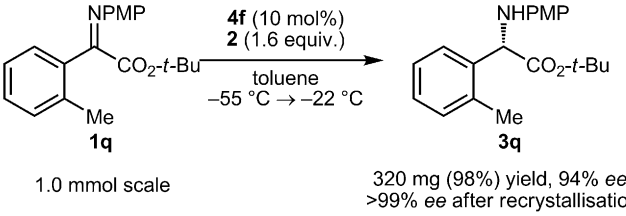
[a] The reactions were performed on a 0.1-mmol scale of imino ester **1a** using 1.6 equiv. of catecholborane (**2**) and 10 mol% of catalyst **4f** at −22 °C in 1.0 mL toluene for 24 h. Before the addition of **1** the reaction mixture was cooled to −55 °C.

[b] Yield of isolated **3**.

[c] Determined by chiral stationary phase HPLC analysis.

in the 4-position directly points to one of the TRIP moieties in the transition state structure, resulting in lower selectivities with increasing steric demand of the substituent, other substitution patterns should give better results. To our delight 3-substituted aromatic imino esters were reduced in high yield with very good selectivities for both electron-rich and electron-deficient aromatic substrates in up to 89% *ee* (Table 4, entries 11–13).

Furthermore, aromatic amino esters bearing a substituent in the 2-position were isolated in excellent yield and enantioselectivities ranging from 90% to 94%, respectively (Table 4, entries 14–16). Particularly this is the first time an enantioselective reduction of *ortho*-substituted imino esters is reported giving very good results. Similar reductions with trichlorosilane as hydride source only gave moderate results in this case. Finally also the naphthyl moiety revealed to be a good substituent with 92% yield of isolated **3t** and 84% *ee* as well as heteroaromatic compounds like thienyl with 86% enantioselectivity (Table 4, entries 17 and 18). The reduction of alkyl-substituted imino esters could also be achieved in almost quantitative yield, but only moderate enantioselectivity (Table 4, entry 19). In the end, the scalability of the newly investigated method was proven with a 1.0-mmol scale experiment (Scheme 1). α-Amino ester **3q** was obtained in 98% yield and excellent enantioselectivity of 94%, which was further improved to >99% *ee* by a single recrystallization from *n*-pentane.



Scheme 1. Enantioselective reduction of α-imino ester **1q** in a 1.0-mmol scale experiment.

In summary, we have developed the first enantioselective reduction of α-imino esters with catecholborane employing a chiral phosphoric acid as catalyst. Several electron-rich and halogenated aromatic substrates with various substitution patterns have been reduced in almost quantitative yields and very high enantioselectivities.

Experimental Section

General Procedure for the Asymmetric Reduction of α-Imino Esters

In a dry, argon-flushed Schlenk tube chiral phosphoric acid **4f** (8 mg, 0.01 mmol, 10 mol%) was dissolved in dry toluene (1.0 mL) and catecholborane **2** (19.7 mg, 0.16 mmol) was added *via* syringe. After stirring at room temperature for 20 min the solution was cooled to −55 °C by a dry ice/acetone bath and the solid α-imino ester was added in one portion. After stirring at −22 °C for 24 h the reaction was stopped with an ethanolamine/water mixture (1:2, 0.8 mL) and was warmed to room temperature. After further addition of 1 N NaOH (2.0 mL) the brown solution was extracted three times with diethyl ether. The combined organic phases were dried over Na_2SO_4 and filtered. After evaporation of the solvent the residue was purified *via* flash column chromatography over silica gel (diethyl ether:*n*-pentane = 1:10 to 1:4) to furnish the corresponding α-amino esters. Racemic samples were prepared using diphenyl phosphate (5 mol%) as catalyst in dry toluene for 1.5 h at room temperature.

Acknowledgements

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