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Highly Enantioselective Transfer Hydrogenation of α-Imino Esters by a Phosphoric Acid

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Abstract: Chiral phosphoric acids have been identified as highly efficient organocatalysts for the asymmetric transfer hydrogenation of α-imino esters and amide. Utilizing Hantzsch esters as the hydrogen donor, versatile highly enantioenriched α-amino esters and their derivatives were obtained with up to 98% *ee*.

Keywords: amino esters; asymmetric catalysis; asymmetric transfer hydrogenation; Hantzsch esters; imino esters; organic catalysis

The synthesis of optically pure α-amino acids and their derivatives constitutes an important task in organic synthesis because of their broad utility in all disciplines of biology, medicine and chemistry.[1] Among the currently existing catalytic asymmetric approaches,[2] the transition metal-catalyzed enantioselective hydrogenation of α-dehydroamino acids has been one of the most efficient methods to synthesize α-amino acids and their derivatives.[3] However, arylglycines, an important class of α-amino acids that has found wide applications in the synthesis of biologically active compounds,[4] have to be prepared *via* hydrogenation of the α-imino esters instead of the α-enamides. In spite of the fact that asymmetric hydrogenation of the corresponding α-imino acid and derivatives is a direct way to deliver the glycine derivatives, there has been very limited success in this transformation mainly due to the poor reactivity of these substrates towards hydrogenation.[5] Recently, an excellent report from Zhang's group shows that an Rh-tangphos catalyst could catalyze the asymmetric hydrogenation of α-arylimino esters affording α-arylamino esters with high *ee*s up to 95%.[6] As part of our program is the search for applications of chiral phosphoric acids[7–8] and since the these compounds are used as efficient catalysts for asymmetric transfer hydrogenations of C=N double bonds with Hantzsch esters as the hydrogen donors,[9–10] we envisaged that chiral phosphoric acids would be efficient organocatalysts for the hydrogenation of α-imino esters and their derivatives (Figure 1). In this communication, we report a highly enantioselective synthesis of α-amino esters and their derivatives with a focus on α-arylimino esters by chiral phosphoric acids-catalyzed transfer hydrogenation with Hantzsch esters as the hydrogen donor (up to 98% *ee*).

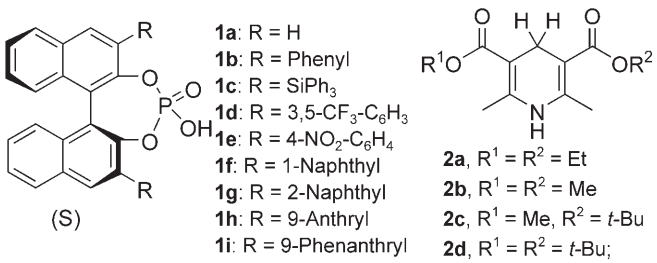
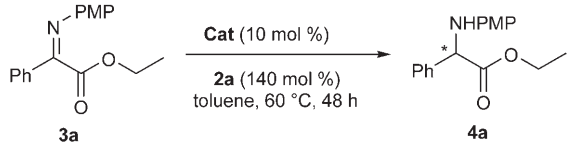


Figure 1. Chiral phosphoric acids and Hantzsch esters.

We first examined the hydrogenation of **3a** with 1.4 equivalents of Hantzsch ester **2a** in toluene (Table 1). With 10 mol% of **1**, all the phosphoric acids could catalyze the reduction at 60 °C, affording phenylglycine ethyl ester **4a** with variable degrees of enantioselectivity. Phosphoric acid **1h** gave the product **4a** with 82% conversion in 48 h with the best enantioselectivity (88% *ee*, entry 8, Table 1). Surprisingly, phosphoric acid **1c** led to a low conversion and gave a nearly racemic product in spite of its excellent performance for the reductive amination between aryl ketones and anilines.[9c]

With 10 mol% of **1h** as the catalyst at 60 °C or under reflux (when the boiling point of the solvent is below 60 °C), various solvents have been examined for this reaction, as summarized in Table 2. The asym-

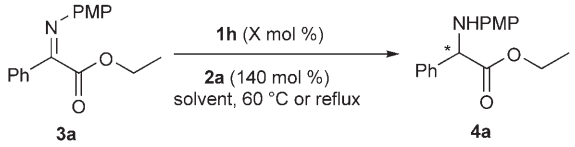
Table 1. Optimization of the reaction conditions for the asymmetric transfer hydrogenation of **3a**.[a]



Entry	Catalyst	Conversion [%][b]	*ee* [%][c]
1	**1a**	82	3
2	**1b**	69	45
3	**1c**	20	<1
4	**1d**	39	32
5	**1e**	85	36
6	**1f**	84	66
7	**1g**	56	40
8	**1h**	82	88
9	**1i**	61	70

[a] *Reaction conditions:* 10 mol% of **1**, 140 mol% of **2a**, 0.05 mol/L of **3a** in toluene at 60°C.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H). PMP = *para*-methoxyphenyl.

Table 2. Screening of solvents.



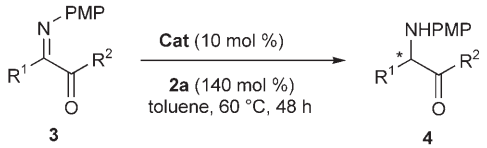
Entry[a]	X [mol%]	Solvent	Time [h]	Conversion [%][b]	*ee* [%][c]
1	10	Toluene	48	82	88
2	10	Benzene	48	76	89
3	10	Xylene	48	82	89
4	10	$CHCl_3$	48	79	91
5	10	DCM	48	61	92
6	10	Dioxane	48	78	90
7	10	THF	48	94	91
8	10	AcOEt	48	91	92
9	10	*t*-BuOMe	3	>95	90
10	10	Bu_2O	16	91	89
11	10	Et_2O	16	>95	92
12[d]	10	Et_2O	20	>95	92
13[d]	5	Et_2O	20	>95	93
14[d]	2	Et_2O	36	93	91
15[d]	1	Et_2O	36	91	92

[a] *Reaction conditions:* 10 mol% of **1h**, 140 mol% of **2a**, 0.05 mol/L of **3a** in solvent at 60°C or under reflux.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).
[d] Reaction was carried out at 25°C.

metric transfer hydrogenation reactions could be carried out smoothly in several conventional solvents such as benzene (89% *ee*), xylene (89% *ee*), dioxane (90% *ee*), THF (91% *ee*), AcOEt (92% *ee*), $CHCl_3$ (91% *ee*), CH_2Cl_2 (92% *ee*), *t*-BuOMe (90% *ee*), *n*-Bu_2O (89% *ee*) and Et_2O (92% *ee*). Et_2O was chosen as the optimal solvent since the reaction in Et_2O led to complete conversion in 16 h (entry 11, Table 2). Interestingly, running the reaction at room temperature did not show any effect on either the conversion or the enantioselectivity (entry 12, Table 2). Further studies on the catalyst loadings disclosed that high reaction conversion and enantioselectivity were obtained even with 1 mol% of **1h** (91% conversion, 92% *ee*, entry 15, Table 2).

Several Hantzsch esters have been tested and the results are summarized in Table 3. Hantzsch ester **2a** was found to be the optimal in terms of both reaction conversion and *ee* of the product.

Table 3. Investigation of Hantzsch esters.

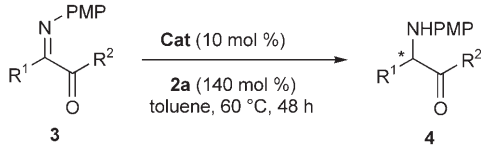


Entry[a]	**2**	Time [h]	Conversion [%][b]	*ee* [%][c]
1	**2a**	36	91	92
2	**2b**	36	39	94
3	**2c**	36	48	92
4	**2d**	36	73	91

[a] *Reaction conditions:* 1 mol% of **1h**, 140 mol% of **2**, 0.05 mol/L of **3a** in Et_2O at 25°C.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H).

In presence of 1 mol% of **1h** and 1.4 equivs. of **2a**, a variety of α-imino esters have been reduced in Et_2O to examine the reaction scope. The results are summarized in Table 4. The effect of different esters was first examined. We found that the enantioselectivity was highly dependent on the steric size of the ester group. High *ee*s were obtained for the substrates bearing bulky ester groups such as Bn (95% *ee*), *i*-Pr (97% *ee*) and *t*-Bu (97% *ee*), whereas only 33% *ee* was given for the methyl ester substrate **3b** (entries 1–5, Table 4). For the scope of R^1, several substituted phenyl isopropyl esters containing either electron-donating or electron-withdrawing groups all led to good yields and excellent ees (97–98% *ee*, entries 6–11, Table 4). In addition, enantiopure **4f** was obtained by one simple recrystallization, and a single crystal X-ray analysis disclosed its absolute configuration as *S*.[11] Asymmetric transfer hydrogenation of 2-naphthyl-bearing imino ester **3l** afforded the corresponding amino ester in 93% yield with 98% *ee* (entry 12, Table 4). A low reactivity towards the alkyl-substitut-

Table 4. Asymmetric transfer hydrogenation of α-imino esters and amide **3**.[a]

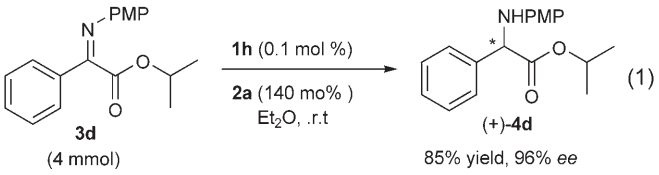


Entry	R^1	R^2	Product	Yeld [%][b]	*ee* [%][c]	Configuration
1	C_6H_5 (**3a**)	OEt	**4a**	88	92	(+)
2	C_6H_5 (**3b**)	OMe	**4b**	85	33	(+)
3	C_6H_5 (**3c**)	OBn	**4c**	86	95	(+)
4	C_6H_5 (**3d**)	O-*i*-Pr	**4d**	87	97	(+)
5	C_6H_5 (**3e**)	O-*t*-Bu	**4e**	78	97	(+)
6	4-BrC_6H_4 (**3f**)	O-*i*-Pr	**4f**	92	97(>99 %)[d]	*S* (+)[e]
7	4-ClC_6H_4 (**3g**)	O-*i*-Pr	**4g**	95	98	(+)
8	4-FC_6H_4 (**3h**)	O-*i*-Pr	**4h**	82	97	(+)
9	4-$CH_3C_6H_4$ (**3i**)	O-*i*-Pr	**4i**	90	98	(+)
10	4-$MeOC_6H_4$ (**3j**)	O-*i*-Pr	**4j**	94	97	(+)
11	3-$CH_3C_6H_4$ (**3k**)	O-*i*-Pr	**4k**	89	98	(+)
12	2-naphthyl (**3l**)	O-*i*-Pr	**4l**	93	98	(+)
13[f]	cyclohexyl (**3m**)	O-*i*-Pr	**4m**	46	88	(−)
14[g]	thienyl (**3n**)	O-*i*-Pr	**4n**	78	84	(+)
15	C_6H_5(**3o**)	NH-*t*-Bu	**4o**	85	96	(+)

[a] *Reaction conditions:* 1 mol % of **1h**, 140 mol % of **2a**, 0.05 mol/L of **3** in Et_2O at room temperature unless noted otherwise.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] After one recrystallization.
[e] Determined by single crystal X-ray diffraction analysis.
[f] With 5 mol % of **1h** under reflux.
[g] With 5 mol % of **1h**.

ed imino ester was observed. For instance, only 46 % yield was obtained for imino ester **3m** having a cyclohexyl group with 88 % *ee* (entry 13, Table 4). It should be noted that thienyl-derived **3n** also underwent the reduction and afforded the desired product in 84 % *ee* (entry 14, Table 4). In addition, substrate **3o** with a carboxyl amide group is also well tolerated to afford the hydrogenated product **4o** in 85 % yield with 96 % *ee* (entry 15, Table 4).

To test the practicality of the current method for the synthesis of α-amino acid derivatives, the asymmetric transfer hydrogenation of α-imino ester **3d** in a gram-scale was carried out using 0.1 mol % of **1h** [Eq. (1)]. With 140 mol % of Hantzsch ester **2a** in Et_2O at room temperature, α-amino ester **4d** was obtained in 85 % yield and 96 % *ee* (1.19 g, 4 mmol of **3d**).



In summary, we have identified chiral phosphoric acids as highly efficient organocatalysts for the asymmetric transfer hydrogenation of α-imino esters. The advantages include good yields, excellent *ee*s, mild reaction conditions, as well as an operationally simple and environmentally benign procedure. All these features together with tolerability of α-imino carboxylamides warrant the wide application of the current methodology for the synthesis of highly enantioenriched α-amino esters and their derivatives.

Experimental Section

General Procedure for the Asymmetric Transfer Hydrogenation of α-Imino Esters

In a dry Schlenk tube, α-imino ester **3** (0.2 mmol) and phosphoric acid **1** (0.002 mmol) were dissolved in Et_2O (4 mL) under argon. The solution was stirred for 10 min at room temperature. Subsequently, Hantzsch ester **2** (0.28 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/8 to 1/50) to afford the respective α-amino ester **4**.

Acknowledgements

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[11] CCDC 643978 contains the supplementary crystallographic data for **4f**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif.

