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Highly Enantioselective Hydrogenation of Enamides Catalyzed by Chiral Phosphoric Acids

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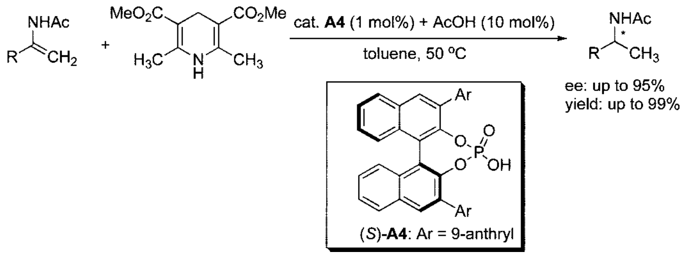
ABSTRACT



A highly enantioselective hydrogenation of enamides catalyzed by a dual chiral−achiral acid system was developed. By employing a substoichiometric amount of a chiral phosphoric acid and acetic acid, catalyst loadings as low as 1 mol % of the chiral catalyst were sufficient to provide excellent yield and enantioselectivity of the reduction product.

Enantioselective hydrogenation is one of the key transformations to produce chiral compounds in academia and in the chemical industry.[1] As a new direction in this research field, enantioselective hydrogenation catalyzed by organocatalysts with Hantzsch esters as the reducing agent has emerged as an attractive strategy due to its environmentally benign nature.[2] Recently, chiral Brønsted acids[3] were reported as highly efficient catalysts for the hydrogenation of ketimines, α,β-unsaturated aldehydes, and nitroolefins by the research groups of Rueping, List, MacMillan, and others.[4] Likewise, our recent interest in chiral phosphoric acid catalysis[5] included a report whereby α-imino esters could be reduced in the presence of a VAPOL phosphoric acid catalyst (**A2**) to prepare chiral α-amino acid esters with excellent enantioselectivities.[5a]

Although the reductive amination of ketones and the hydrogenation of ketimines catalyzed by chiral Brønsted acids were achieved in high enantioselectivities, these reactions were limited primarily to reactants derived from aniline and its analogues. As a result, the deprotection of the aromatic group to reveal the amino group can be relatively difficult, requiring somewhat harsh reaction conditions such as those methods that use ceric ammonium nitrate (CAN), rendering these methods less synthetically appealing (eq 1, Scheme 1). Attractive features of enamides are their relative stability and ease in handling. Additionally, when considering *N*-acyl enamide substrates, the acyl group of the reduction product can be easily removed under standard procedures in good yield. Therefore, due to these considerations, such enamide precursors have become popular substrates for preparing chiral amines through standard metal-catalyzed hydrogenation.[1] Herein we report our results on the asymmetric hydrogenation of enamides with high enantioselectivity using chiral phosphoric acid catalysis (eq 2, Scheme 1).

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[1] (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Jaekel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912. (c) Brown, J. M. *Mechanism of enantioselective hydrogenation. Handbook of Homogeneous Hydrogenation*; De Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007.

[2] For reviews, see: (a) Ouellet, G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (b) You, S. -L. *Chem. Asian J.* **2007**, *2*, 820. (c) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407.

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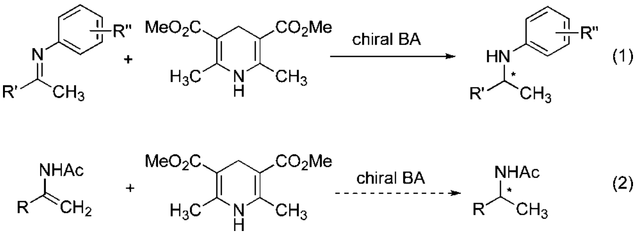
Scheme 1



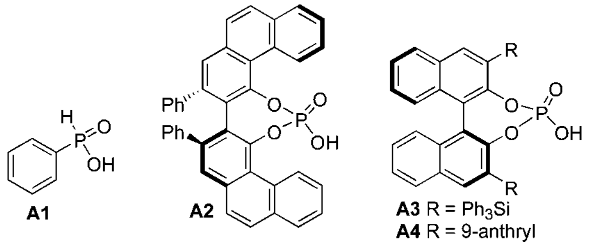
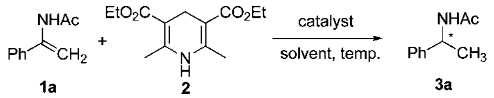


Figure 1. Phosphorus-based acid catalysts.

We initiated our studies on the hydrogenation of enamide **1a** by using the achiral phenylphosphinic acid (**A1**) as the catalyst, with 1.1 equiv of Hantzsch ester dihydropyridine **2** as the reducing agent. We were pleased to find that in the presence of 10 mol % of **A1**, at ambient temperature, the reaction took place smoothly in an argon atmosphere to provide a 95% isolated yield of the desired product amide **3a** (entry 1, Table 1). However, when we replaced the achiral catalyst **A1** with chiral phosphoric acids (**A2**−**A4**) under similar conditions (5 mol % catalyst, rt), the reactions were sluggish and no product was detected by TLC after 24 h (not shown in Table 1). However, when we raised the temperature to 50 °C, we were pleased to find that catalyst **A3** allowed for a 92% isolated yield of amine **3a** with 91% ee (entry 4), while acids **A2** and **A3** gave very low yields of the desired product (<15% yield by ^{1}H NMR, entries 2 and 3). Further screening of solvents showed that noncoordinating solvents like toluene were ideal (entry 4), while other coordinating solvents such as ether, THF, and the protic solvent methanol gave very sluggish reactions (entries 5−8).

Table 1. Reaction Conditions for the Asymmetric Reduction of Enamides



entry	catalyst (mol%)	solvent	*T* (°C)	time (h)	yield (%)^a	ee (%)
1	**A1** (10)	toluene	rt	17	95	0
2	**A2** (5)	toluene	50	36	<15^b	nd
3	**A3** (5)	toluene	50	36	<10^b	nd
4	**A4** (5)	toluene	50	15	92	91
5	**A4** (5)	Et$_2$O	50	22	<13^b	nd
6	**A4** (5)	THF	50	22	<5^b	nd
7	**A4** (5)	EtOAc	50	48	<15^b	nd
8	**A4** (5)	MeOH	50	48	<5^b	nd
9	**A4** (2)	toluene	50	41	85	91
10	**A4** (1)	toluene	50	117	39	90
11	**A4** (1) + AcOH (10)	toluene	50	15	97	91
12	AcOH (10)	toluene	50	17	0^b	nd

^{a} Isolated yields. ^{b} Yield determined by ^{1}H NMR. ^{c} Ee values determined by Chiral-HPLC (see the Supporting Information).

Efforts toward decreasing the catalyst loading led to lower yields but no loss in ee was found. For example, with 2 mol % of catalyst **A3**, the yield of **3a** was 85% (entry 9), but with a catalyst loading of 1 mol %, the yield of **3a** decreased to 39% even with a longer reaction time (entry 10). Believing that a reactive iminium was the intermediate of this reaction

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(3) For reviews with considerable chiral phosphoric acid coverage, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Chem. Commun.* **2008**, 4097. For recent reports, see: (e) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (f) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119. (g) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399. (h) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411. (i) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458. (j) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2840. (k) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652. (l) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (m) Zhang, G.-W.; Wang, L.; Nie, J.; Ma, J.-A. *Adv. Synth. Catal.* **2008**, *350*, 1457. (n) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (o) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (p) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731. (q) Giera, D.; Sickert, M.; Schneider, C. *Org. Lett.* **2008**, *10*, 4259. (r) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (s) Sickert, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3631. (t) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016. (u) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (v) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836. (w) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (x) Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem.—Eur. J.* **2008**, *14*, 3539. (y) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (z) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 10090.

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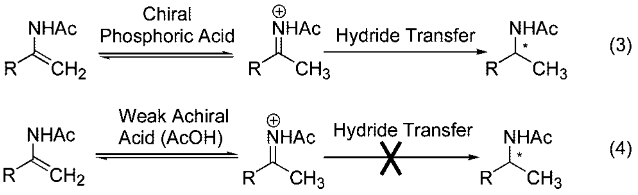
we reasoned that decreasing the catalyst loading probably lead to a low concentration of iminium, and thus a slow reaction. Our working hypothesis assumed therefore that this iminium formation was the rate determining step (eq 3, Scheme 2). In order to develop an efficient hydrogenation reaction with a low catalyst loading, we considered the use of a dual catalytic chiral−achiral acid system. We believed that a suitable achiral acid should be able to facilitate iminium formation, while being inactive in the hydrogenation step, where our chiral phosphoric acid, which had already demonstrated enantioselectivity, could remain active (eq 4, Scheme 2).

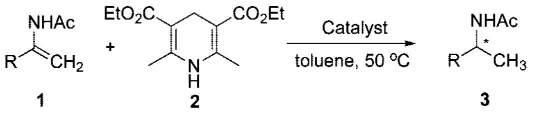
Scheme 2. Function of a Dual-Acid Catalyst System



As expected, with 1 mol % of catalyst (*S*)-**A4** and 10 mol % of acetic acid as a cocatalyst, the reaction was completed within 15 h to provide the desired product **3a** in 97% isolated yield and with 91% ee (entry 11, Table 1). A study on the background reaction with acetic acid as the only catalyst further confirmed our hypothesis that the acetic acid was inactive for the hydrogenation of enamide **1a** (entry 12). We would like to note that a similar strategy was also reported by Rueping's group. Rueping and co-workers successfully utilized two Brønsted acids as the catalyst for the asymmetric synthesis of isoquinuclidines.[6]

Our optimized reaction conditions for the enantioselective organocatalytic hydrogenation of enamides were determined to be the following: 1 mol % of chiral phosphoric acid **A4**, 10 mol % of AcOH, 50 °C, with a ratio of enamide **1** and Hantzsch ester **2** set at 1/1.1 equiv and toluene as the solvent. Under the general conditions above, we evaluated various enamide substrates, and the results are summarized in Table 2. In order to demonstrate the advantages of the dual-acid catalytic system, we also conducted the corresponding reactions catalyzed by the single chiral phosphoric acid (*S*)-**A4**. As shown in Table 2, the dual-acid catalytic system significantly accelerated the hydrogenation reaction. For example, enamide **1b** bearing a *p*-methyl group on the phenyl ring gave only 53% yield and 91% ee of the product **3b** even when the reaction was run for 3 days (entry 3), while with the addition of 10 mol % of acetic acid, the reaction provided a 93% isolated yield and 90% ee of the product in 24 h (entry 4). In other cases, the dual-acid catalytic system was also highly efficient; for instance, with aromatic enamides bearing electron-withdrawing groups such as *p*-chloro (entries 5 and 6), *p*-fluoro (entries 7 and 8), and *p*-*trifluoromethyl groups (entries 9 and 10) provided similar rate acceleration with good enantioselectivities (87−92% ee). Likewise, the p-methoxy (95% ee; entry 11) and β-naphthyl enamide substrates (92% ee; entry 13) were excellent reaction partners.*

Table 2. Studies on the Substrate Scope



entry	R	catalyst[a]	time (h)	yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	A	117	39	91 (*R*) (+)
2	Ph (**1a**)	B	15	**97**	91 (*R*) (+)
3	4-MeC$_6$H$_4$ (**1b**)	A	72	53	91 (*R*) (+)
4	4-MeC$_6$H$_4$ (**1b**)	B	24	**93**	90 (*R*) (+)
5	4-ClC$_6$H$_4$(**1c**)	A	48	71	92 (*R*) (+)
6	4-ClC$_6$H$_4$(**1c**)	B	17	**88**	91 (*R*) (+)
7	4-FC$_6$H$_4$ (**1d**)	A	72	90	90 (*R*) (+)
8	4-FC$_6$H$_4$ (**1d**)	B	17	**96**	89 (*R*) (+)
9	4-CF$_3$C$_6$H$_4$ (**1e**)	A	69	74	87 (*R*) (+)
10	4-CF$_3$C$_6$H$_4$ (**1e**)	B	40	**96**	87 (*R*) (+)
11	4-MeOC$_6$H$_4$ (**1f**)	A	15	96	95 (*R*) (+)
12	β-naphthyl (**1g**)	A	48	91	94 (*R*) (+)
13	β-naphthyl (**1g**)	B	14	**99**	92 (*R*) (+)
14	α-naphthyl (**1h**)	A	94	31	89 (*S*) (−)
15	α-naphthyl (**1h**)	B	44	**43**	78 (*S*) (−)
16	3-MeOC$_6$H$_4$ (**1i**)	A	47	90	74 (*R*) (+)
17	3-MeOC$_6$H$_4$ (**1i**)	B	18	**98**	71 (*R*) (+)
18	2-MeOC$_6$H$_4$ (**1j**)	A	40	90	42 (*S*) (−)
19	2-MeOC$_6$H$_4$ (**1j**)	B	15	**96**	41 (*S*) (−)
20	*t*-Butyl (**1k**)	A or B	48	NR[d]	ND[e]

[a] Catalyst A = **A4** (1 mol %); catalyst B = **A4** (1 mol %) + AcOH (10 mol %). [b] Isolated yield. [c] Determined by chiral HPLC; see the Supporting Information for details. [d] No desired product was detected. [e] Not analyzed.

A lower enantioselectivity was noted with the α-naphthyl enamide **1h** (78% ee; entry 15). It is interesting that in this case the addition of the cocatalyst resulted in a slightly diminished ee. This phenomenon suggested that steric hindrance is an important factor in this hydrogenation reaction, and it was further confirmed by other examples. Enamides **1i** and **1j**, *meta*- and *ortho*-substituted arenes, gave even lower enantioselectivities as the steric hindrance increased (71% ee and 41% ee, entries 17 and 19, respectively. Finally, it should be noted that while these conditions allow for the highly selective hydrogenation of aromatic enamides they are ineffective for aliphatic enamides, such as enamide **1k** (entry 20). The absolute stereochemistries of all the products were assigned by comparing the optical rotation with the corresponding known amides (see the Supporting Information for details).

In order to support our hypothesis that the iminium is an important intermediate of this reduction, a series of ^{1}H NMR experiments was performed. To a solution of **1a** in C$_6$D$_6$ was added catalyst **A4**. It was apparent that new NMR signals grew in after 5 min at room temperature. These peaks were assigned to the following species: acetophenone, acetamide,

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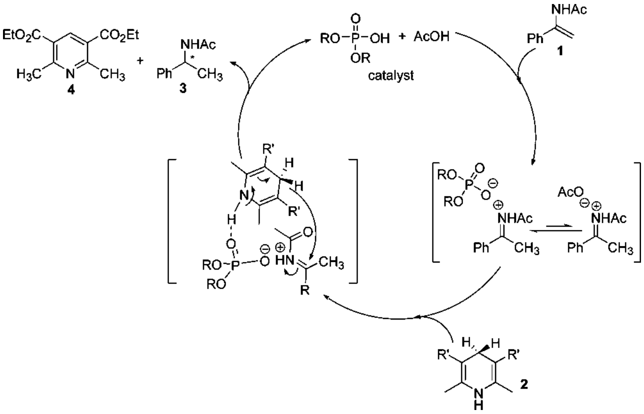
(6) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832.

Scheme 3. Proposed Mechanism for the Asymmetric Hydrogenation of Enamides Catalyzed by a Dual Acid System



and the corresponding iminium. It was therefore apparent that catalyst **A4** can tautomerize the enamide **1a** to its imine and then partially decompose this imine. In a separate experiment using acetic acid instead of catalyst **A4**, nothing happened at room temperature. However, at 50 °C, the corresponding iminium was observed after 3 h, and only a very small amount of enamide **1a** was decomposed. These experiments comfirmed the hypothesis in Scheme 2. Based on the experiments above, a reasonable dual-activation mechanism similar to that reported recently by Goodman is proposed in Scheme 3.[7] In the presence of catalyst **A4** and the cocatalyst acetic acid, the enamide **1** was tautomerized to the corresponding imine, which was activated by the acid via an iminium intermediate. In the following step, only chiral phosphoric acid **A4** was active enough to catalyze the hydrogenation of the imine, while the acetic acid role was probably only to help keep a sufficient concentration of iminium intermediate present since **A4** was used in such small quanitities.

In conclusion, we have developed a highly enantioselective hydrogenation reaction of enamides catalyzed by a dual-acid catalyst system. By using a chiral phosphoric acid combined with a catalytic amount of acetic acid as the catalyst, the loading of the chiral phosphoric acid can be as low as 1 mol % but still provide excellent yield and enantioselectivity for the process. Additionally, we confirmed that the iminium is the intermediate generated and that the achiral coacid can be used to generate a suitable concentration of iminium for a facile reaction.

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Supporting Information Available: Experimental procedures, characterization, chiral HPLC conditions, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For an excellent theoretical study on a related mechanism, see: Simon, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.