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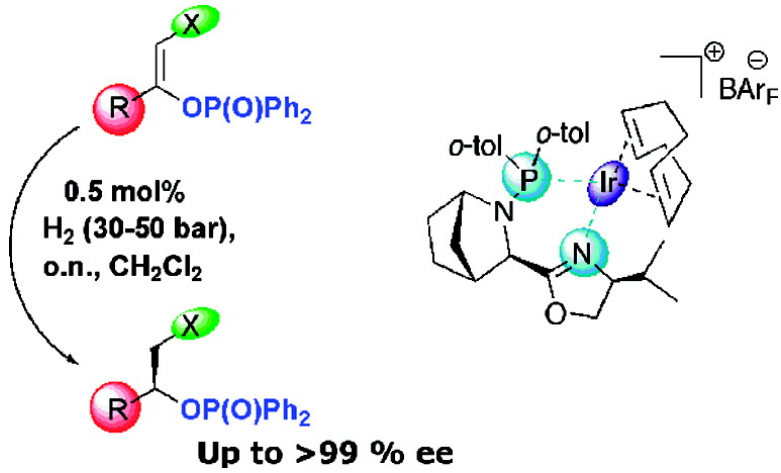
J. Am. Chem. Soc., **2008**, 130 (16), 5595-5599 • DOI: 10.1021/ja711372c • Publication Date (Web): 28 March 2008



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Asymmetric Hydrogenation of Di and Trisubstituted Enol Phosphinates with N,P-Ligated Iridium Complexes

Pradeep Cheruku, Jarle Diesen, and Pher G. Andersson*

Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, 751 24 Uppsala, Sweden

Received December 23, 2007; E-mail: Pher.Andersson@biorg.uu.se

Abstract: The iridium-catalyzed asymmetric hydrogenation of various di- and trisubstituted enol phosphinates has been studied. Excellent enantioselectivities (up to >99% ee) and full conversion were observed for a range of substrates with both aromatic and aliphatic side chains. Enol phosphinates are structural analogues of enol acetates, and the hydrogenated alkyl phosphinate products can easily be transformed into the corresponding alcohols with conservation of stereochemistry. We have also hydrogenated, in excellent ee, several purely alkyl-substituted enol phosphinates, producing chiral alcohols that are difficult to obtain highly enantioselectively from ketone hydrogenations.

Introduction

Enantiomerically enriched compounds and their preparation currently play a pivotal role in several important areas such as pharmaceuticals, agrochemicals, fine chemicals, and natural product chemistry.[1] As a result, the synthesis of useful chiral, nonracemic building blocks has become one of the most important topics in preparative organic chemistry, and various catalytic asymmetric methods have been developed for this purpose. Among these methodologies, asymmetric hydrogenation, the atom-economical addition of H_2 to a C=C or C=Y (Y = N or O) bond to obtain enantiomerically enriched compounds, has garnered much attention and become a very valued reaction.[2]

Early advances in asymmetric olefin hydrogenation were dominated by the introduction of the rhodium-diop[3] and ruthenium-BINAP catalysts,[4] and since then a vast number of chiral diphosphine ligands have been developed and used in the hydrogenation of functionalized olefins with good yields and excellent enantioselectivities.[5] However, the presence of a coordinating group, most often an enamide, in the immediate vicinity of the C=C double bond is a prerequisite for using these ruthenium- and rhodium-based catalysts because their chelation to the metal center governs the stereochemical outcome of the hydrogenation reaction.

The weaker coordination of ester moieties to metal centers generally makes them more difficult substrates for efficient asymmetric hydrogenation. There are considerably fewer reports in the literature describing the hydrogenation of enols than of enamides, which illustrates the difficulty in stereoselectively hydrogenating the former. However, the asymmetric hydrogenation of enol esters is of special interest because it would expand the reaction scope and allow access to compounds with many useful functionalities in the resulting chiral products. To date, the most successful results in asymmetric enol ester hydrogenations have been obtained using DIPAMP, DuPhos, KetalPhos, or TangPhos ligands on rhodium.[6]

As substrates without coordinating groups, or with less coordinating groups, are more challenging substrates for ruthenium- or rhodium-catalyzed asymmetric hydrogenation,[7] recent work has focused on iridium-based catalysts, which do not

(1) (a) Blaser, H. U., Schmidt, E. , Eds. *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*.; Wiley: Weinheim, Germany, 2003. (b) Ojima, I., Ed. In *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000. (c) Brown J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag:Berlin, 1999; Vol. I, pp 121–182. (d) Jacobsen, E. N., Pfaltz, A., Yamamoto, H. , Eds. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. *1–3*. (e) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; VCH: NewYork, 1993. (f) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(2) (a) Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291–1299. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366. (c) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277. (d) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998–2007. (e) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.

(3) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433.

(4) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922–924.

(5) (a) Enthaler, S.; Erre, G.; Junge, K.; Michalik, D.; Spannenberg, A.; Marras, F.; Gladiali, S.; Beller, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1288–1298. (b) Chi, Y.; Tang, W.; Zhang, X. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P., Ed.; Wiley-VCH, Verlag GmbH & Co. KGaA: Weinheim, 2005; pp 1–31. (c) Kitamura, M.; Noyori, Y. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I. , Ed.; Wiley-VCH, Verlag GmbH & Co. KGaA: Weinheim, 2004; pp 3–52. (d) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290. (e) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (f) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345–4353.

(6) (a) Zhang, W.; Zhang, X. *J. Org. Chem.* **2007**, *72*, 1020–1023. (b) Panella, L.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 4177–4180. (c) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205–207. (d) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489–3496. (e) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701–6704. (f) Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505–5508. (g) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519. (h) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 2362–2365.

(7) (a) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445–1446. (b) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int., Ed. Engl.* **1968**, *7*, 942.

operate via chelation control,[8] to overcome this limitation. In these studies, Crabtree's achiral complex[9] $[(COD)Ir(py)(PCy_3)]^+[PF_6]^-$ has served as a conceptual template, and the replacement of its monodentate pyridine and phosphine ligands with chiral bidentate N,P-ligands has yielded a number of stereoselective hydrogenation catalysts. Pioneering work by Pfaltz has clearly shown the potential of iridium catalysts with N,P-ligands for the asymmetric hydrogenation of unfunctionalized olefins.[10] These new Ir complexes have emerged as valuable tools for the asymmetric hydrogenation of mainly unfunctionalized substrates[11] and complement the ruthenium- and rhodium-catalyzed hydrogenation of chelating substrates.

Although admirable results have been obtained in the well-studied iridium-catalyzed asymmetric hydrogenation of unfunctionalized olefins, there have been very few successful hydrogenations of olefins bearing weakly coordinating functional groups.[11b,c,12]

Knochel et al. have demonstrated that amino acid derivatives can be obtained from enamides in 96% ee.[13] Chiral phosphine-oxazole ligands developed in our group[14c,d] have been employed in the iridium-catalyzed hydrogenation of allylic alcohols and the corresponding acetates. Pfaltz et al. have reported the hydrogenation of allylic esters[11a] using iridium-phosphinite-oxazolines and iridium-diaminophosphine-oxazolines.

In the past 4 years our laboratory has reported the development of several new types of chiral N,P-ligands for which the corresponding iridium complexes have successfully been employed in the asymmetric hydrogenation of various substrates, such as aryl imines (up to 92% ee) and di- and trisubstituted unfunctionalized olefins (>99% ee).[14] Recent work in our group has broadened the substrate scope of the iridium-N,P-ligand-based catalyst systems. As a part of this program, we have explored the class of olefinic substrates that have a heteroatom on the prochiral center. We have successfully hydrogenated several members of this substrate class, such as vinylsilanes[15] (up to 98% ee) and vinyl fluorides[16] (up to >99% ee), with excellent selectivities.

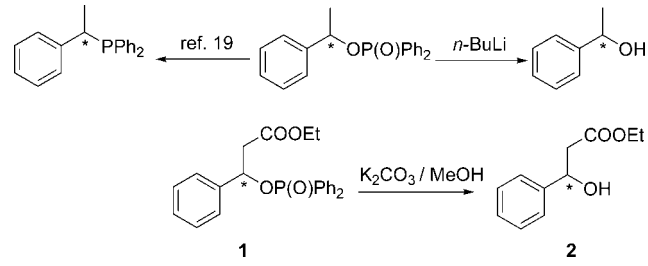


Figure 1. Applications of chiral alkyl phopshinates.

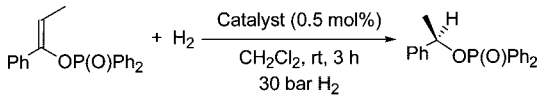
Enol phosphinates have been employed as substrates in rhodium-catalyzed asymmetric hydrogenation by Kumada and co-workers,[17] albeit with moderate ee values. We recently reported the hydrogenation of various terminal enol phosphinates using our N,P-ligated chiral iridium catalysts.[18] High conversions and excellent enantioselectivities (ee values ranging from 85 to >99) were achieved after a few hours.. Encouraged by these results, we wanted to explore this substrate class even further, because the phosphinate functional group is synthetically useful (Figure 1). All of the alkyl phosphinates we prepared were easily transformed to corresponding alcohols without any loss of enantioselectivity by treating with *n*-BuLi.[17] Alternatively, the phosphinate can be removed by transesterfication. Under mild conditions (3 equiv of K_2CO_3, dry MeOH), the phosphinate group of **1** was selectively cleaved to produce **2** in good yield. Chiral alkyl phosphinates can also be transformed into chiral phosphanes by displacement of the phosphityl group with diphenyl phosphine. In all cases, the chirality is retained.[19]

Bearing the utility of chiral alkyl phosphinates in mind, we sought to explore the asymmetric hydrogenation of enol phosphinates even further. We envisioned that the inclusion of various trisubstituted enol phosphinates would greatly expand the scope of the reaction. We were pleased to find that trisubstituted enol phosphinates were also stable toward degradation under our hydrogenation conditions, and were hydrogenated in higher yields and selectivities than the related 1,1-disubstituted compounds. We now give a full account of the asymmetric hydrogenation of trisubstituted enol phosphinates using iridium catalysts.

Results and Discussion

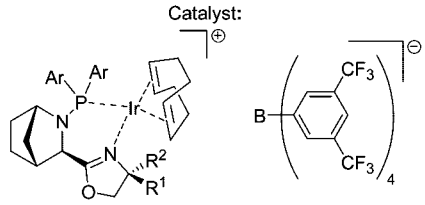
In our initial communication,[18] we reported the hydrogenation of various terminal enol phosphinates using complex **I**; this was therefore taken as a starting point for the present investigation. The hydrogenations of **3a** by catalyst **I** and two related catalysts, **II** and **III**, proceeded in quantitative yield after 3 h, whereas other catalysts gave inferior yields (Figure 2). Consistent with

(8) (a) Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 16688–16689. (b) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem.-Eur. J.* **2003**, *9*, 339–347.
(9) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331–337.
(10) (a) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem,. Int. Ed.* **1998**, *37*, 2897–2899. (b) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2003**, *346*, 497–537. (c) Källström, K.; Munslow, I.; Andersson, P. G. *Chem.-Eur. J.* **2006**, *12*, 3194–3200. (d) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296. (e) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.
(11) (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33–43. (b) Goulioukina, N. S.; Dolgina, T. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1397–1401. (c) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194–5197. (d) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943–946. (e) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.-Eur. J.* **2007**, *13*, 7162–7170. (f) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131. (g) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391–1393. (h) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8274–8276. (i) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642–644.
(12) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513–531.
(13) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941–3943.
(14) (a) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827. (b) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Chem.-Eur. J.* **2006**, *12*, 2318–2328. (c) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309. (d) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001. (e) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudörfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, 366–373.
(15) Källstrom, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575–2578.
(16) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537.
(17) Hayashi, T.; Kanehira, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4417–4420.
(18) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659–1661.
(19) Berens, U. Eur. Pat. Appl. Coden: EPXXDW EP 1582527 A1 20051005, 2005, 17.



3a

Catalyst:



Catalyst	Ar	R^1	R^2	Conv. (%)	*ee* (%)
I	***o*-Tol**	***i*Pr**	**H**	**>99**	**96**
II	Ph	*i*Pr	H	>99	74
III	Ph	Ph	Ph	>99	93

Figure 2. Asymmetric hydrogenation of substrate **3a** with several iridium-based catalysts.

the results for terminal enol phosphinates, the best stereoselectivity was obtained using **I**.

1. Asymmetric Hydrogenation of Trisubstituted Aryl-Alkyl and Ester-Functionalized Enol Phosphinates. Encouraged by the success of **I** in the hydrogenation of **3a**, we applied the catalyst to a variety of other trisubstituted enol phosphinates (Table 1). The hydrogenations of enol phosphinates **3a**-**3c** (Table 1, entries 1–3) revealed that increasing the bulk of the alkyl group decreased the conversion and enantioselectivity slightly. Thus, although the methyl-substituted substrate **3a** was completely hydrogenated in 96% ee after 3 h under 30 bar H_2 pressure, the hydrogenation of the corresponding ethyl- and *iso*-propyl-substituted analogues (**3b** and **3c**) under the same conditions produced alkyl phosphinates in 90 and 89% conversion and with 92 and 91% ee, respectively.[20]

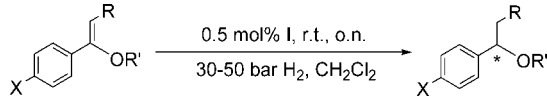
Replacing the alkyl group with a carboxylic ester to give **4a** lowered the reaction rate but boosted the enantioselectivity (90% conversion in 12 h, >99% ee). Increasing the hydrogen pressure from 30 to 50 bar led to full conversion in 6 h without affecting the ee. Therefore, we screened the remaining substrates using 50 bar H_2 pressure at room temperature overnight (o.n.) to ensure the maximum conversion.

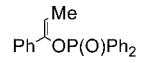
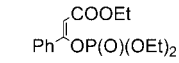
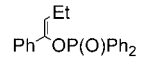
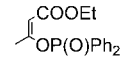
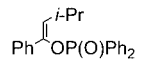
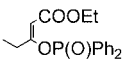
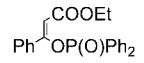
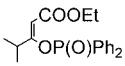
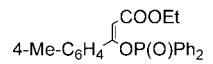
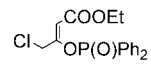
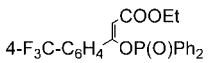
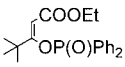
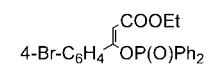
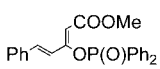
Aryl β-ketoester-derived enol phosphinates bearing electron-donating (**4b**) and electron-withdrawing (**4c** and **4d**) groups at the aryl moiety's para position were equally reactive, and were hydrogenated with similar selectivities (full conversion within 6 h, 98 → 99% ee).[21]

Substrate **4e**, which has a phosphorus triester rather than a phosphinate group, was hydrogenated in 99% ee and to full conversion. No cleavage of the phosphorus triester could be detected, even though the hydrogenolysis of this group was observed for the terminal enol phosphinate triester.[22]

Substrates with no aryl group near the double bond were also evaluated in the iridium-catalyzed hydrogenation. Compound

Table 1. Hydrogenation of Aryl-Alkyl Enol Phosphinates Using Complex **I**[a]



Entry	Substrate	Conv.[b] (%)	*ee*[c] (%)	Config.[d]	Entry	Substrate	Conv.[b] (%)	*ee*[c] (%)	Config.[d]
1	 **3a**	>99	96	*R*	8	 **4e**	**>99**	**99**[e]	*R*
2	 **3b**	90	92	*R*	9	 **5a**	**>99**	**>99**	*S*
3	 **3c**	89	90	*R*	10	 **5b**	**>99**	**99**	*S*
4	 **4a**	**>99**	**>99**	*R*	11	 **5c**	**>99**	**>99**	*S*
5	 **4b**	**>99**	**>99**	*R*	12	 **5d**	58 95[g]	92 93[g]	*R*
6	 **4c**	**>99**	**99**	*R*	13	 **5e**	98	93	*S*
7	 **4d**	**>99**	98	*R*	14[g]	 **5f**	50	58	+[f]

[a] Conditions: CH_2Cl_2 solution, 0.5 mol % catalyst, 30 bar H_2 (entries 1−3) or 50 bar H_2 (entries 4−14). [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Determined by hydrolyzing the product to the corresponding alcohol and comparing its optical rotation with that of the known alcohol. [e] Determined for the corresponding alcohol by chiral HPLC. [f] Absolute configurations were not determined. [g] 2 mol% catalyst loading.

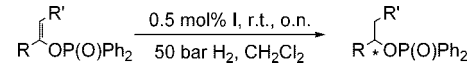
5a, in which the phenyl ring of **4a** has been replaced with a methyl group, was reduced highly enantioselectively (>99% ee, Table 1, entry 9). Increasing the size of the alkyl group did not affect the enantioselectivity significantly. Substrate **5e** (entry 13), which has a sterically demanding *tert*-butyl group, gave 98% conversion with 93% ee, whereas substrates **5b** and **5c** (entries 10 and 11) were completely hydrogenated with almost perfect enantiodiscrimination (≥99% ee). The chloroalkyl-substituted enol ether **5d** (entry 12) showed significantly lower conversion (58%) than the corresponding ethyl analogue (**5b**) and the ee (92%) was similar to that for the *tert*-butyl substrate (**5e**). Nevertheless, we were able to improve the conversion for **5d** from 58% to 95% by increasing the catalyst loading (from 0.5% to 2%). No lowering of the enantioselectivity occurred. Substrate **5f** (entry 14), possessing a conjugated double bond system, gave 50% conversion with moderate ee (58%). Interestingly, the enol double bond was reduced in preference to the *trans*-disubstituted double bond; we had expected both double bonds to be hydrogenated under the applied conditions.

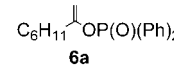
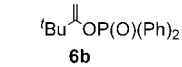
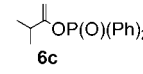
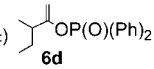
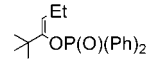
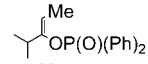
Comparing entries 4−7 with entries 9−13, we see no significant reactivity difference between alkyl- and aryl-substituted β-ketoester-derived enol phosphinates; both are hydrogenated to full conversion in 6 h with >99% ee using 0.5 mol % catalyst loading.[23]

2. Hydrogenation of Purely Alkyl-Substituted Enol Phosphinates. The asymmetric hydrogenation of prochiral alkyl–alkyl ketones to chiral alcohols by ruthenium and rhodium catalysts remains an exigent task due to the difficulty in differentiating two alkyl groups.[24] Apart from an article by Noyori,[25] which uses *tert*-alkyl ketones as substrates, there are few reports of purely alkyl-substituted ketones being hydrogenated with good enantioselectivity.[26] Hence, it remains a challenge to develop new methods for the asymmetric hydrogenation of alkyl–alkyl ketones to yield chiral alkanols.

Enol phosphinate hydrogenation can serve as an alternative to the ruthenium- and rhodium-catalyzed asymmetric ketone hydrogenations. The alkylketones were converted to enol phosphinates and subjected to hydrogenation by catalyst **I**. The resulting alkyl enol phosphinates were subsequently converted to the corresponding alcohols, without disturbing the ee, by the treatment with *n*-BuLi. For example, full conversion and 92% ee were obtained for substrate **6a** (Table 2, entry 1). Three other disubstituted alkyl enol phosphinates (Table 2, compounds **6b**–**6d**) were also hydrogenated in a highly enantioselective manner; the ee values obtained are among the highest reported for this class of compounds (92, >99, and 98%). Trisubstituted alkyl enol phosphinates were also reduced highly selectively. Particularly noteworthy are the hydrogenations of **6d**−**6f**, because the asymmetric hydrogenation of ketones to give the obtained chiral alcohols has not, to our knowledge, been reported in the literature; this report is the first to obtain them via hydrogenation.

Table 2. Hydrogenation Studies of Alkyl-Substituted Enol Phosphinates Using Complex **I**[a]



Entry	Substrate	Conv.[b] (%)	ee[c] (%)	Config.[d]
1	 **6a**	>99	92	*R*
2	 **6b**	**>99**	**>99**	*R*
3	 **6c**	>99	92	*R*
4	(±)  **6d**	**>99**	**98**	+[e]
5	 **6e**	>99	90[f]	+[e]
6	 **6f**	>99	91[f]	+[e]

[a] Conditions: 50 bar H_2, rt, CH_2Cl_2; 0.5 mol% catalyst. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Determined by hydrolyzing the product to the corresponding alcohol and comparing its optical rotation with that of the known alcohol. [e] Absolute configuration was not determined. [f] Determined after conversion to the corresponding 3,5-dinitrobenzoate.

The hydrogenation of the chiral, racemic substrate **6d** by complex **I** allowed us to study the effect of a pre-existing chiral center in the substrate. No kinetic resolution was detected, as both enantiomers of **6d** were hydrogenated with an enantioselectivity of 98%.

3. Highly Acid-Sensitive Substrates. While investigating the iridium-catalyzed asymmetric hydrogenation of enol phosphinates, we found it necessary to confront the atypical reactivity of especially acid-sensitive substrates during the reaction.[27,28] For example, the hydrogenation of substrate **7a** under standard conditions occurred with hydrogenolysis to produce (4-methoxyphenyl)ethane,[18] and we encountered the same problem with **7b** (Figure 3). To address this problem, we performed the

(20) Two aryl enol phosphinates could not be hydrogenated to alkyl phosphinates. The enol phosphinate derived from 1-tetralone decomposed under the hydrogenation conditions; whereas the tetrasubstituted enol phosphinate derived from *iso*-butyrophenone was unreactive, even at 40 °C and 100 bar H_2.

(21) Enol phosphinates in which the ester group of **4a** was replaced by a phenyl ketone or phenyl amide group were not hydrogenated, even at higher temperature and pressure, and neither was the analogue of **4a** that had a 3-furyl substituent in place of the phenyl group.

(22) The hydrogenation of *P*-(a-styryl) phosphonic acid diethyl ester with complex **I** results in ~50% hydrogenolysis. See ref 18.

(23) Note that the different absolute configurations of the products observed in Table 1, entries 1−8 vs entries 9−11 and 13 reflect a change in the priorities of the substituents, not in the sense of enantiodiscrimination.

(24) Ohkuma, T.; Noyori, R. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G. , Elsevier, C. J. , Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol. 3, pp 1105–1163.

(25) Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289. In this study, *tert*-butylmethylketone was hydrogenated in 97–98% ee.

(26) Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 11001103. In this study, *iso*-propylmethylketone and *tert*-butylmethylketone were hydrogenated by a Rh−PennPhos complex to give the corresponding alcohols in 84 and 94% ee, respectively.

(27) For example, Beletskaya and Pfaltz reported difficulty in hydrogenating diethyl 1-(6-methoxy-2-naphthyl)ethynylphosphonate with a catalyst that performed very well with other phosphonate esters. See ref 11b.

(28) Matsuda and co-workers reported that allylic alcohols could be substituted by various nucleophiles when treated with $[Ir(cod)(PPh_3)_2]PF_6$ that had been activated by H_2. They suggested that the reaction proceeded via activation of the alcohol to give an allylic cation that was subsequently attacked by the nucleophile to

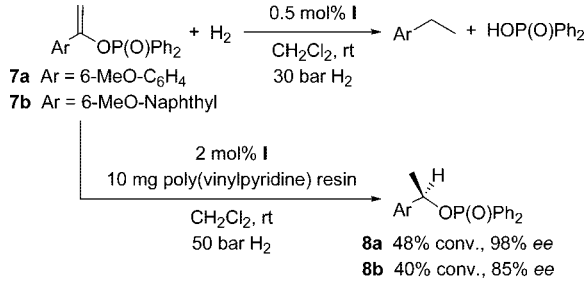


Figure 3. Asymmetric hydrogenation of particularly acid-sensitive enol phosphinates is accomplished in the presence of a proton scavenger.

asymmetric hydrogenation of the acid-sensitive substrates **7** in the presence of a small amount of proton scavenger (poly(4-vinylpyridine) resin). However, the addition of proton scavengers also deactivated the catalyst, so higher catalyst loadings (2 mol %) were used, and the conversions in these reactions were 40–50%. Therefore, although very acid-sensitive substrates present a challenge for the present system, they can still be hydrogenated with good or excellent ee values.

give the final product. In a control experiment, Matsuda observed similar reactivity using a catalytic amount of CF_3SO_3H instead of the iridium catalyst. Matsuda, I.; Wakamatsu, S.; Komori, K.; Makino, T.; Itoh, K. *Tetrahedron Lett.* **2002**, *43*, 1043–1046.

Conclusions

We have performed the asymmetric hydrogenation of various trisubstituted enol phosphinates using N,P-ligated iridium catalysts, and found catalyst **I** to give high conversions and excellent enantioselectivities in the reaction. Notably, purely alkyl-substituted enol phosphinates were reduced in high enantioselectivity.

Acknowledgment. This work was supported by grants from AstraZeneca, The Swedish Research Council (VR), and Ligbank. We are grateful to Dr. Tamara Church for her help in preparing the manuscript.

Supporting Information Available: Experimental procedures for the preparation of the substrates, hydrogenation procedures, characterization data, ^{1}H, ^{13}C, ^{31}P NMR spectra of new compounds and the chiral separation data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA711372C