J|A|C|S ARTICLES

Published on Web 05/22/2009

Iridium-N,P-Ligand-Catalyzed Enantioselective Hydrogenation of Diphenylvinylphosphine Oxides and Vinylphosphonates

Pradeep Cheruku, Alexander Paptchikhine, Tamara L. Church, and Pher G. Andersson*

Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, 751 23 Uppsala, Sweden

Received February 24, 2009; E-mail: Pher.Andersson@biorg.uu.se

Abstract: Diphenylvinylphosphine oxides and di- and trisubstituted vinylphosphonates have been employed as substrates in iridium-catalyzed asymmetric hydrogenations. Complete conversions and excellent enantioselectivities (up to and above 99% *ee*) were observed for a range of substrates with both aromatic and aliphatic groups at the prochiral carbon. We have also hydrogenated electron-deficient carboxyethylvinylphosphonates with excellent stereoselectivity (up to and above 99% *ee*). The hydrogenated products of both classes of substrates are synthetically useful intermediates.

Introduction

Chiral organophosphorus compounds have gained much attention in recent decades because of their extensive applications in various fields of chemistry.[1,2] They are crucial as ligands in the rapidly developing field of asymmetric catalysis, as evinced by numerous reports in the literature.[3] Chiral phosphines are generally prepared by resolution or use of stochiometric amounts of chiral auxiliaries;[4] highly effective, enantioselective routes to these compounds are extremely desirable. 1-Arylphosphonic acid derivatives are widely used as key composites in drugs used for treatment of various bone and calcium-metabolism diseases.[4] Phosphonic acid derivatives are also useful as enzyme inhibitors and drugs for viral and bacterial infections as well as for neurological disorders.[5] For example, glutamic acid analogues are well-known for the treatment of neurological disorders such as Parkinson's and Huntington's diseases.[6] α-Aryl-substituted fosmidomycin analogues have shown promising antimalarial activity.[7] Because of their ability to chelate to metals, there is considerable interest in the chemistry of carboxyalkylphosphonates as well.[2] The substitu-

(1) (a) Engel, R. In *The Role of Phosphonates in Living Systems*; Hinderbrand, R. L., Ed.; CRC Press: Boca Raton, FL, 1983; p 93. (b) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215. (c) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931. (d) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH, Weinheim, Germany, 2004. (e) Savignac, P.; Iorga, B. In *Modern Phosphorus Chemistry*; CRC Press: New York, 2003 p 319. (f) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (g) Afarinkia, K.; Vinader, M. V. In *Comprehensive Organic Functional Group Transformations*; Moody, C. J., Ed.; Pergamon: London, 1995, Vol. 5, p 393. (h) Kalir, A.; Kalir, H. H. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: Chichester, U.K., 1996; Vol. 4, p 767. (i) Corbridge, D. E. C. In *Phosphorus: An Outline of its Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: New York, 1995; Chapter 3.

(2) (a) Frey, S. T.; Horrocks, W. D., Jr. *Inorg. Chem.* **1991**, *30*, 1073–1079. (b) Schneppensieper, T.; Finkler, S.; Czap, A.; van Eldik, R.; Heus, M.; Nieuwenhuizen, P.; Wreesmann, C.; Abma, W. *Eur. J. Inorg. Chem.* **2001**, 491–501. (c) Gardner, S.; Motevalli, M.; Shastri, K.; Sullivan, A. C.; Wyatt, P. B. *New J. Chem.* **2002**, *26*, 433–439. (d) Clearfield, A. *Prog. Inorg. Chem.* **1998**, *47*, 371–510. (e) Thompson, M. E. *Chem. Mater.* **1994**, *6*, 1168–1175. (f) Distler, A.; Sevov, S. C. *Chem. Commun.* **1998**, 959–960. (g) Alberti, G.; Costantino, U.; Casciola, M.; Vivani, R.; Peraio, A. *Solid State Ionics* **1991**, *46*, 61–68. (h) Burwell, D. A.; Thompson, M. E. *Chem. Mater.* **1991**, *3*, 730–737.

(3) (a) Otero, I.; Börner, A. In *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008; p 307. (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581–593. (c) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290. (d) Halterman, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I. (e) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070. (f) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151.

(4) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2003.

(5) (a) Bellucci, C.; Gualtieri, F.; Scapecchi, S.; Teodori, E.; Budriesi, R.; Chiarini, A. *Farmaco* **1989**, *44*, 1167–1191. (b) Bondarenko, N. A.; Lermontova, I. N.; Bondarenko, G. N.; Gulyukina, N. S.; Dolgina, T. M.; Bachurin, S. O.; Beletskaya, I. P. *Pharm. Chem. J.* **2003**, *37*, 226–228. (c) Gulyukina, N. S.; Dolgina, T. M.; Bondarenko, G. N.; Beletskaya, I. P.; Bondarenko, N. A.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Russ. J. Org. Chem.* **2002**, *38*, 573–587. (d) Jung, K. W.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2281–2282.

(6) (a) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158–169. (b) Cull-Candy, S. G.; Donnelan, J. F.; James, R. W.; Lunt, G. G. *Nature* **1976**, *262*, 408–409. (c) Hemmi, K.; Takeno, H.; Hashimoto, M.; Kamiya, T. *Chem. Pharm. Bull.* **1982**, *30*, 111–118. (d) Jane, D. E.; Jones, P. L. St. J.; Pook, P. C.-K.; Tse, H.-W.; Watkins, J. C. *Br. J. Pharmacol.* **1994**, *112*, 809–816. (e) Moonen, K.; Van Meenen, E.; Verwée, A.; Stevens, C. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7407–7411. (f) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.

(7) (a) Devreux, V.; Wiesner, J.; Jomaa, H.; Rozenski, J.; Van der Eycken, J.; Van Calenbergh, S. *J. Org. Chem.* **2007**, *72*, 3783–3789. (b) Haemers, T.; Wiesner, J.; Van Poecke, S.; Goeman, J.; Henschker, D.; Beck, E.; Jomaa, H.; Van Calenbergh, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1888–1891. (c) Schlüter, K.; Walter, R. D.; Bergmann, B.; Kurz, T. *Eur. J. Med. Chem.* **2006**, *41*, 1385–1397. (d) Kurz, T.; Schlüter, K.; Kaula, U.; Bergmann, B.; Walter, R. D.; Geffken, D. *Bioorg. Med. Chem.* **2006**, *14*, 5121–5135.

tion of a carboxylic acid group by a phosphonic one increases receptor selectivity.[8] As biological activity depends strongly on optical purity, the development of enantioselective routes to these molecules is important.

Catalytic asymmetric hydrogenation of prochiral unsaturated compounds is now a key methodology in enantioselective organic synthesis, and we imagined that appropriate unsaturated precursors could be hydrogenated to elegantly obtain optically active phosphines. Early reports on olefin hydrogenations were dominated by ruthenium and rhodium catalysts, but highly selective reductions using these catalysts are strictly limited to olefins that contain a polar coordinating group close to the double bond.[3c−e,9,10] Chiral N,P-ligated iridium catalysts for olefin reduction,[11] on the other hand, generally do not operate via chelation control[12,13] and thus are used for substrates without coordinating groups or with less strongly coordinating groups.[14] Many research groups have contributed to the development of chiral N,P-ligated iridium catalysts for this purpose.[11] However, iridium-catalyzed asymmetric hydrogenation is strongly substrate-dependent and must be tested with new substrate classes before it can become a widely accepted methodology.[11i,14a]

We have reported several classes of chiral N,P ligands that are highly effective in the iridium-catalyzed asymmetric hydrogenations of imines and unfunctionalized trisubstituted olefins.[15] Several olefinic substrate classes with heteroatoms at the prochiral centers have also been hydrogenated.[16] Recently, while examining the asymmetric reduction of various protected enols, we found that diphenylphosphine oxide protecting groups produced stable substrates that were hydrogenated highly enantioselectively.[17] This inspired us to explore diphenylvinylphosphine oxides, in which diphenylphosphine oxides are directly attached to the prochiral carbons, as a substrate class. Diphenylvinylphosphine oxides can be hydrogenated directly to give protected chiral phosphines, which can be readily converted to chiral phosphines upon reduction.[18] To our knowledge, only one catalytic asymmetric reduction of diphenylvinylphosphine oxides has been reported: Matteoli and co-workers[18] synthesized the chiraphos ligand via asymmetric hydrogenation of 2,3-bis(diphenylphosphinoyl)buta-1,3-diene.

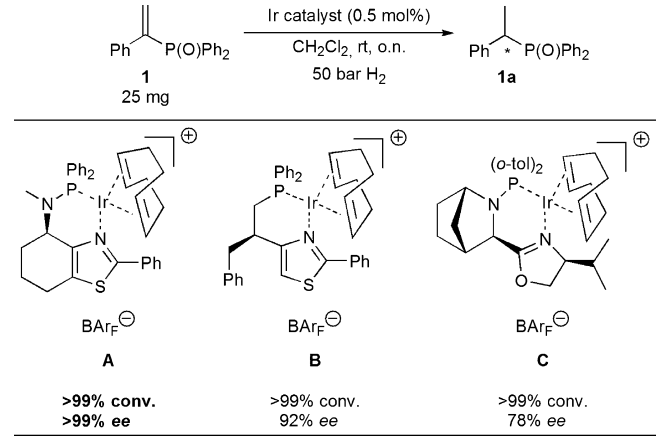


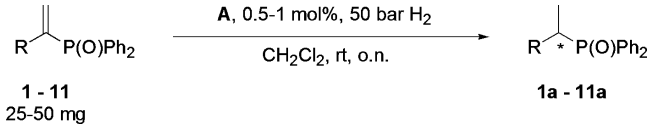
Figure 1. Asymmetric hydrogenation of substrate **1** with several iridium-based catalysts.

Results and Discussion

1. Reduction of Diphenylvinylphosphine Oxides. Initially, we screened three iridium catalysts in the hydrogenation of diphenyl(1-phenylvinyl)phosphine oxide (**1**) (Figure 1). All three catalysts completely converted **1** to the desired product overnight using 50 bar H_2 and 0.5 mol % catalyst loading at room temperature (rt). In general, complexes **A** and **B** were superior to complex **C** (Figure 1). Complex **C**, which had been an excellent catalyst for enol phosphinate hydrogenation, was unsatisfactory in this study, producing **1a** in only 78% *ee*.

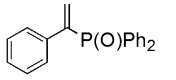
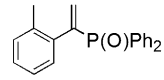
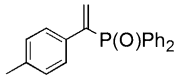
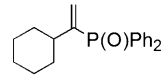
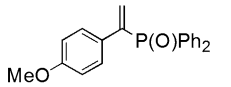
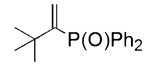
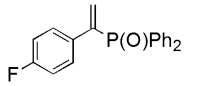
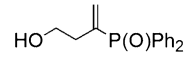
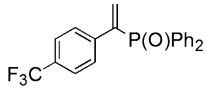
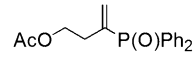
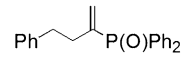
(8) Frank, A. W. *Crit. Rev. Biochem.* **1984**, *16*, 51–101.
(9) (a) Enthaler, S.; Erre, G.; Junge, K.; Michalik, D.; Spannenberg, A.; Marras, F.; Gladiali, S.; Beller, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1288–1298. (b) Chi, Y.; Tang, W.; Zhang, X. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 1. (c) Kitamura, M.; Noyori, Y. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004; p 3. (d) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345–4353.
(10) (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. (i) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445–1446. (j) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942.
(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) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194–5197. (c) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 943–946. (d) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.—Eur. J.* **2007**, *13*, 7162–7170. (e) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131. (f) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391–1393. (g) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8274–8276. (h) Källström, K.; Munslow, I.; Andersson, P. G. *Chem.—Eur. J.* **2006**, *12*, 3194–3200. (i) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296. (j) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411. (k) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, *350*, 979–983.
(12) (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.
(13) Burgess and co-workers have recently shown that chelation control is operative in certain iridium-catalyzed asymmetric hydrogenations. See ref 11d and: Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 8894–8895.
(14) (a) For a recent review, see: Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513–531. (b) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941–3943. (c) 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.
(15) (a) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudörfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366–373. (b) Verendel, J. J.; Andersson, P. G. *Dalton Trans.* **2007**, 5603–5610. (c) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem.—Eur. J.* **2006**, *12*, 2318–2328. (d) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309. (e) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001. (f) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827.
(16) (a) Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575–2578. (b) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537. (c) Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. *Tetrahedron Lett.* **2008**, *49*, 7290–7293. (d) Baeza, A.; Pfaltz, A. *Chem.—Eur. J.* **2009**, *15*, 2266–2269.
(17) (a) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659–1661. (b) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599.
(18) (a) Matteoli, U.; Beghetto, V.; Schiavon, C.; Scrivanti, A.; Menchi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 1403–1409. (b) Beghetto, V.; Matteoli, U.; Scrivanti, A. *Chem. Commun.* **2000**, 155–156.

Table 1. Catalytic Asymmetric Hydrogenation of Diphenylvinylphosphine Oxides by Complex **A**[a]



1 - 11
25-50 mg

1a - 11a

Entry	Substrate		Conv.[a] (%)	*ee*[b] (%)	Entry	Substrate		Conv.[a] (%)	*ee*[b] (%)
1		**1**	>99	>99 (*R*)[c]	6		**6**	>99	>99 (+)
2		**2**	>99	>99 (+)	7		**7**	>99	99 (+)
3		**3**	>99	>99 (+)	8		**8**	98	90 (+)
4		**4**	>99	>99 (+)	9		**9**	80 >99[d,e]	92 (-) >99 (-)
5		**5**	>99	93 (+)	10		**10**	>99[e]	>99 (-)
					11		**11**	>99	>99 (+)

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC (see the Supporting Information for details). Optical rotations are given in parentheses. [c] Determined by comparing optical rotation with a literature value.[19] [d] Using 1 mol % catalyst loading. [e] $P(H_2) = 100$ bar.

Complex **B** gave 92% *ee,* whereas the hydrogenation of **1** by complex **A** occurred in >99% *ee* (*R*).[19] Therefore, we chose to screen the rest of the diphenylvinylphophine oxide substrates in this study using catalyst **A**.

Having obtained encouraging results in the hydrogenation of **1**, we investigated the substrate scope of this transformation. A wide range of diphenylvinylphosphine oxide substrates were hydrogenated to provide the corresponding protected phosphines with perfect enantioselectivity (Table 1). Introduction of an electron-donating group at the para position of the *C*-phenyl ring impacted neither the reactivity nor the enantioselectivity, as substrates **2** and **3**, bearing methyl and methoxy groups, respectively, were also hydrogenated to the corresponding alkyldiphenylphosphine oxides in almost quantitative conversion with excellent enantioselectivity (>99% *ee*).

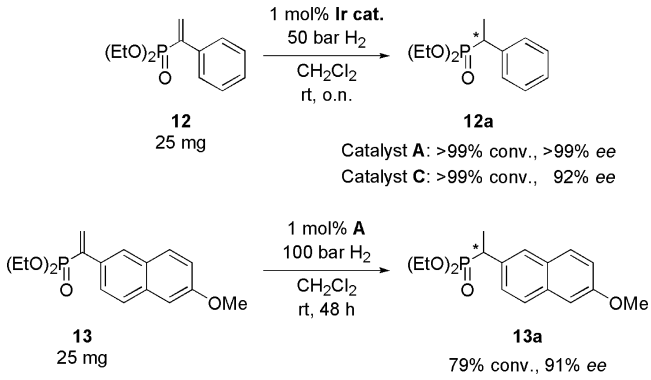
Substrates having electron-withdrawing groups at the para position of the *C*-phenyl ring were as reactive as the unsubstituted analogue **1** (complete conversion in 3 h) but showed different selectivities. Para-fluoro-substituted **4** gave a very high *ee* (>99%; Table 1, entry 4), whereas substrate **5**, bearing a trifluoromethyl group at the para position, was slightly less selectively reduced (93% *ee*; entry 5). Thus, both the reactivity and stereoselectivity of hydrogenation were highly tolerant of para substituents on the *C*-phenyl ring, regardless of their electronic properties. Additionally, a methyl group at the ortho position of the *C*-phenyl ring did not alter the reaction; substrate **6** was hydrogenated to the same conversion and *ee* as its para-substituted analogue (>99% conversion, >99% *ee*; entry 6).

Substrates without aryl groups at the prochiral carbon were also selectively hydrogenated and generally behaved similarly to their aryl cohorts. (1-Cyclohexylvinyl)diphenylphosphine oxide (**7**) was hydrogenated to full conversion with >99% *ee* (Table 1, entry 7). Increasing the size of the alkyl group affected the conversion slightly: (1-*tert*-butylvinyl)diphenylphosphine oxide (**8**) was hydrogenated to 98% conversion with >90% *ee* (entry 8).

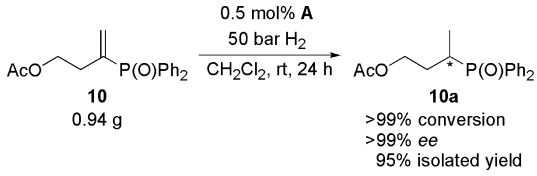
To broaden the synthetic utility of this reaction, we hydrogenated **9**, which bears a hydroxyl-terminated alkyl chain. The terminal hydroxyl group in the product, chiral alkyl diphenylphoshine oxide **9a**, can be further modified to access diverse chiral precursors. Higher catalyst loading was required to achieve good conversion and *ee* in the hydrogenation of **9**. Under the standard conditions with 0.5 mol % catalyst, **9** was hydrogenated to only 80% conversion in 92% *ee*, whereas the hydrogenation of **9** using 1 mol % catalyst and 100 bar H_2 resulted in >99% conversion and *ee*. The lower conversion at lower catalyst loading was likely due to the ability of the alcohol to coordinate the metal and deactivate the catalyst. On the other hand, 0.5 mol % catalyst loading was sufficient to hydrogenate the acetyl-protected alcohol **10** to full conversion with perfect enantiodiscrimination (>99% *ee*) (entry 10). The hydrogenated product **10a** could easily be deprotected, with retention of enantioselectivity, to give the corresponding alcohol **9a** by treatment with M_2CO_3 (M = Na, K) in ethanol. The hydrogenation of 1-phenylethyl-substituted diphenylvinylphosphine oxide **11** was also almost complete using 0.5 mol % catalyst and 50

(19) (a) Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517–6518. (b) Naylor, R. A.; Walker, B. J. *J. Chem. Soc., Chem. Commun.* **1975**, 45–47.

Scheme 1. Hydrogenation of Two Diethyl 1-Arylvinylphosphonates



bar H_2, and gave **11a** in >99% *ee* (entry 11). Finally, when the hydrogenation of **10** was performed using the standard conditions but on a larger scale (eq 1), **10a** was isolated in 95% yield with >99% *ee*.

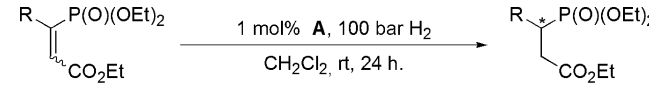


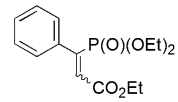
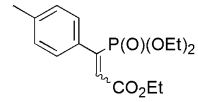
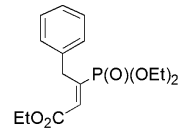
(1)

2. Reduction of Vinylphosphonates. Keeping the excellent results for diphenylvinylphosphine oxides in view, we extended the substrate scope further. Replacing the diphenylphosphine oxide group with a diethyl phosphonate group at the prochiral center provided access to a different class of substrates: vinylphosphonates. The asymmetric hydrogenation of 1-arylvinylphosphonates using Ir catalysts was reported by Beletskaya, Pfaltz, and co-workers.[14c] They reported good enantioselectivities (up to 95%), though only diethyl 1-arylethenylphosphonates were studied. The enantioselective hydrogenation of ester-functionalized vinylphosphonates (carboxyethylvinylphosphonates) has barely been explored. Kadyrov et al.[20] reported the hydrogenation of terminal and internal 3-phosphonobutenoates using a Rh(bppm) catalyst. The terminal substrate was hydrogenated much faster and with higher enantioselectivity than its internal isomer, highlighting the importance of chelation in rhodium-catalyzed hydrogenations. To the best of our knowledge, this is the only example of carboxyethylphosphonate hydrogenation. Here, we report the iridium-catalyzed asymmetric hydrogenation of both carboxyethylvinylphosphates and 1-arylvinylphosphonates.

We chose **12** as a model substrate to optimize the hydrogenation conditions. We screened two catalysts (**A** and **C**) and found that catalyst **A** was again the better catalyst. Hydrogenation of **12** with complexes **A** and **C** led to full conversion within 6 h using 50 bar H_2 at rt (Scheme 1). Complex **A** reduced **12** in >99% *ee*, whereas complex **C** gave a lower *ee* (92%) and required higher catalyst loading (1 mol %). At less than 50 bar pressure, prolonged reaction times were required, although no considerable effect on *ee* was observed. The enantioselectivity obtained in our study (>99% *ee*) is the best ever reported for this substrate. The hydrogenation of **13** was more demanding;[14c] it required 100 bar H_2 and 1 mol % catalyst to reach 79% conversion in 48 h. The hydrogenation product, which is the phosphorus analogue of naproxen, was obtained in 91% *ee*. Encouraged by these results, we extended our study to trisubstituted vinylphosphonates. We chose carboxyethylvinylphosphonic acid esters as substrates because the carboxylate group can undergo post-hydrogenation functional group interconversion (FGI) to provide a variety of chiral precursors with wide potential utility.

Table 2. Catalytic Asymmetric Hydrogenation of Carboxyethylvinylphosphonates by Complex **A**



Entry	Substrate		Isomer	Conv.[a] (%)	*ee*[b] (%)
1		**14**	*E*	<10	90
2			*Z*	>99	>99
3			*E*/*Z* (1:4)	>99	>99
4		**15**	*Z*	>99	>99
5			*E*/*Z* (1:6)	>99	>99
6		**16**	*E*	>99	>99

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC (see the Supporting Information for details).

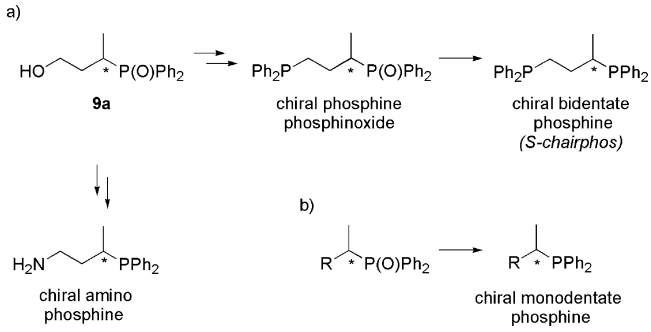
Carboxyethylvinylphosphonates are highly electron-deficient, so the hydrogenation reaction was sluggish: 100 bar H_2 and 1 mol % catalyst loading were required to ensure full conversions. Hydrogenation of (*E*)-**14** using 100 bar H_2 at rt for 24 h gave <10% of the desired product (Table 2). Increasing the temperature and reaction time did not augment the conversion; however, the observed *ee* was good (90%). (*Z*)-**14**, on the other hand, was hydrogenated to full conversion with >99% *ee*. Under similar reaction conditions, a 1:4 mixture of (*E*)- and (*Z*)-**14** was completely hydrogenated to the desired product and gave only a single enantiomer (>99% *ee*). Interestingly, the hydrogenation of both substrates led to the same enantiomer. This phenomenon was observed earlier for the Ru-catalyzed asymmetric hydrogenation of fluorinated olefins[21] but had not been observed for Ir catalysts. The lower reactivity of the pure *E* isomer of **14** might be due to substrate binding to the metal in a fashion that deactivates the catalyst. Curiously, the *E* isomer was also hydrogenated to lower *ee* in the absence of the *Z* isomer; further investigations are required to understand this result. Substrate (*Z*)-**15** was completely hydrogenated to give a single enantiomer of the product (>99% *ee*), as was a 1:6 mixture of (*E*)- and (*Z*)-**15**. When the phenyl ring on the prochiral carbon was replaced by a benzyl group (**16**), full conversion was still achieved with >99% *ee*. To our surprise, the *E* isomer of **16** was hydrogenated to full conversion with excellent enantioselectivity (>99%).

3. Functional-Group Elaboration. Hydrogenation of diphenylvinylphosphine oxides gives direct access to protected chiral phosphines, which can readily be converted to the corresponding

(20) Kadyrov, R.; Selke, R.; Giernoth, R.; Bargon, J. *Synthesis* **1999**, 1056–1062.

(21) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem.* **1994**, *69*, 5–6.

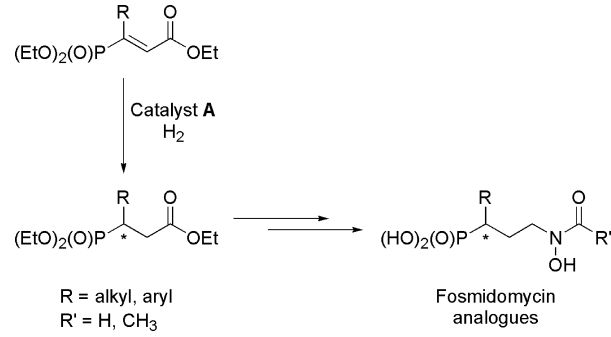
Scheme 2. Elaboration of **9a** To Produce a Range of ω-Functionalized Chiral Phosphines



chiral phosphines upon reduction.[18] Subjecting **9a** to simple manipulations afforded chiral O,P (phosphine, phosphinoxide), N,P (aminophosphine), and P,P (bisphosphine) ligands (Scheme 2). For example, the chairphos ligand was originally produced in a tedious synthesis starting from optically pure malic acid.[22] Using our methodology, we reached the key intermediate, protected phosphine alcohol **9a**, in two steps with >99% *ee* and good isolated yield (87%). Recently, several groups have independently reported syntheses of chiral oxophosphonates via organocatalytic asymmetric phosphonylation and hydrophosphination of α,β-unsaturated aldehydes.[23] Good *ee* values were obtained, but high catalyst loading, low temperatures, and additives to increase the reaction rate were required.

α-Aryl-substituted fosmidomycin analogues (FR9000098) show higher antimalarial activity than fosmidomycin. However, most have been tested only as racemates.[7] In the current study, the hydrogenations of **14**−**16** provide access to both β-aryl and β-alkyl precursors of FR9000098 as single enantiomers (>99% *ee*), and these can be transformed into their corresponding chiral fosmidomycin analogues (Scheme 3).[24] Therefore, Ir-catalyzed asymmetric hydrogenation can also be adopted to synthesize these compounds. This would not only serve as a synthetic methodology but also expand the utility of Ir-based hydrogenation catalysis.

Scheme 3. Iridium-Catalyzed Asymmetric Hydrogenation in the Synthesis of Fosmidomycin Analogues



Conclusions

We have synthesized and hydrogenated a wide range of diphenylvinylphosphine oxides and vinylphosphonates to the corresponding chiral products via N,P-ligated-iridium-catalyzed asymmetric hydrogenation. Catalyst **A** gave the best conversions and enantioselectivities in the hydrogenation. Furthermore, we have demonstrated the enantioselective hydrogenation of highly electron-deficient carboxyethylvinylphosphonates with excellent enantioselectivity. We have also extended the substrate scope of iridium-catalyzed asymmetric hydrogenation to include di- and trisubstituted vinylphosphonates. For most substrates, exclusive enantioselectivities and good conversions were observed. Notably, the *Z* isomer of **14** was hydrogenated much faster than the *E* isomer, but both isomers gave the same enantiomer as the major product. This phenomenon is new to Ir-catalyzed asymmetric hydrogenation.

Acknowledgment. This work was supported by grants from AstraZeneca, The Swedish Research Council (VR), and Ligbank. T.L.C. thanks Wenner-Gren Stiftelserna for a postdoctoral fellowship. The authors are grateful to Dr. Adolf Gogoll for his help in interpreting NMR spectra.

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

JA901437T

(22) MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273–2280.
(23) (a) Maerten, E.; Cabrera, S.; Kjærsgaard, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 8893–8903. (b) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504–4506. (c) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4507–4510.
(24) The esters formed in the asymmetric reduction of carboxyethylvinylphosphonates can be converted to the corresponding aldehydes using a simple reduction−oxidation sequence. The resulting aldehdyes can be converted to fosmidomycin analogues. See refs 7b−d.