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Enantioselective Rh-Catalyzed Hydrogenation of Enol Acetates and Enol Carbamates with Monodentate Phosphoramidites

Lavinia Panella,[†] Ben L. Feringa,*[,†] Johannes G. de Vries,*[,†,‡] and Adriaan J. Minnaard*[,†]

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands, and DSM Research, Life Sciences-Advanced Synthesis, Catalysis & Development, P.O. Box 18, 6160 MD Geleen, The Netherlands

b.l.feringa@rug.nl; hans-jg.vries-de@dsm.com; a.j.minnaard@rug.nl

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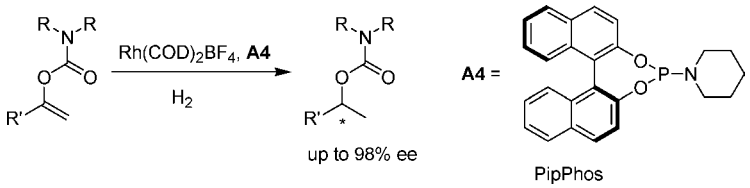
ABSTRACT



Monodentate phosphoramidites, in particular PipPhos and its octahydro analogue, are excellent ligands for the rhodium-catalyzed asymmetric hydrogenation of aromatic enol acetates, enol carbamates, and 2-dienol carbamates up to 98% ee. These latter substrates were hydrogenated selectively to the carbamates of the allyl alcohol.

In the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins,[1] bidentate phosphine ligands were long considered to be essential for high enantioselectivities.[2] However, in the past few years, monodentate phosphines,[3a] phosphonites,[3b] phosphites,[3c,e] and phosphoramidites[3d] were shown to be excellent and sometimes superior alternatives to bidentate ligands,[4] in terms of enantioselectivity, simplicity of synthesis, and ease of structural variation. The use of a monodentate phosphoramidite in a large-scale production of an α-alkyl cinnamate was recently announced by DSM.[5]

The asymmetric hydrogenation of enol acetates gives access to chiral esters, which makes this method an interesting alternative to the enantioselective hydrogenation of prochiral ketones for the preparation of chiral alcohols. Very few ligands have been reported to be successful for this transformation despite the structural similarity with enamides, the majority of which can be hydrogenated with high enantioselectivity.[2,4] In one of the most recent examples, enantioselectivities up to 99% ee were achieved using Rh-

[†] University of Groningen.
[‡] DSM Research.

(1) For reviews, see: (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (c) Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, 1994. (d) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1.

(2) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) (a) Guillen, F.; Fiaud, J.-C. *Tetrahedron Lett.* **1999**, *40*, 2939. (b) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961. (c) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (d) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (e) Hua, Z.; Vassar, V. C.; Ojima, I. *Org. Lett.* **2003**, *5*, 3831.

(4) For reviews, see: (a) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (b) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101. (c) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315.

(5) (a) de Vries, A. H. M.; Lefort, L.; Boogers, J. A. F.; de Vries, J. G.; Ager, D. J. *Chim. Oggi* **2005**, *23* (2), Supplement on Chiral Technologies, 18. (b) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209.

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TangPhos for the hydrogenation of aromatic acyclic enol acetates.[6b] Catalysts such as Ru-Tunaphos and Rh-PennPhos were found to be more efficient for cyclic enol acetates (up to 99% ee).[6c,f] The only example of a successful use of monodentate ligands was recently reported by Reetz, who found enantioselectivities up to 94% ee for the more difficult alkenyl carboxylates, using a Rh-monophosphite catalyst.[7] Previously, using bidentate Duphos, 64% ee was obtained in the hydrogenation of a comparable enol acetate.[6g] In most cases, reaction times between 12 and 14 h have been reported.[8]

A possible explanation for the slow development in this area might be the weaker coordination of the acyl group of the enol ester to the metal as compared to the enamides (Figure 1). It is well-known that this secondary coordination is important in the enantiodiscrimination.[9]

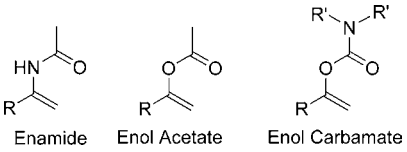


Figure 1. Substrates with bidentate structural features.

In view of the excellent results we have previously obtained with BINOL-derived monodentate phosphoramidites in the Rh-catalyzed hydrogenation of a variety of olefins,[3d,5,10] we became intrigued with the idea of applying these ligands for the more challenging enol acetates. We also envisioned the use of enol carbamates, in the hope that the increased electron density would improve the binding capabilities of the substrate to the metal center and make it more akin to an enamide (Figure 1). To establish the activity and selectivity of phosphoramidite-based catalysts, we performed initial hydrogenation experiments on aromatic enol acetates[11] using a selection of phosphoramidite ligands (Figure 2).

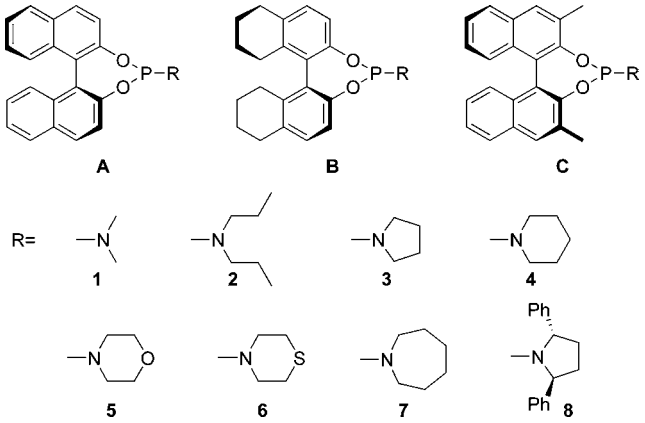
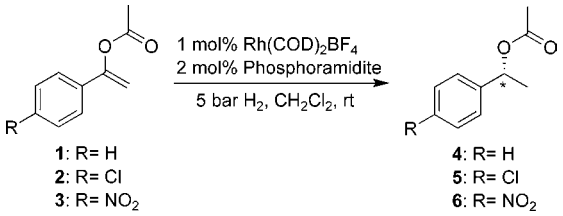


Figure 2. Monodentate phosphoramidites used in this study.

To our surprise MonoPhos (**A1**, Table 1, entry 1) induced a very low ee in the hydrogenation of **1**. On the contrary, a high 90% ee was obtained by using ligand **A4** (entries 2 and 3), while ligand **A5** gave again a modest result (entry 4). Solvent screening indicated that CH_2Cl_2 was the best in terms of enantioselectivity, similar to most phosphoramidite-based hydrogenations.[12] Using MeOH as solvent, the opposite enantiomer (26% ee) was obtained. Good selectivity but somewhat lower reactivity was observed by using ligand **A4** on 1-*p*-Cl-phenyl-vinyl acetate (entries 5 and 6),[13] whereas an excellent 98% ee, with higher reactivity (entry 8), was obtained with 1-*p*-NO_2-phenyl-vinyl acetate. Small structural

Table 1. Asymmetric Hydrogenation of Enol Acetates[a]



entry	substrate	product	ligand	conversion[b] (%)	ee[c,d] (%)
1	**1**	**4**	**A1**	89	10 (*R*)
2	**1**	**4**	**A4**	97	**90** (*R*)
3	**1**[e]	**4**	**A4**	100	**90** (*R*)
4	**1**	**4**	**A5**	90	66 (*R*)
5	**2**	**5**	**A4**	74	78 (*R*)
6	**2**[f]	**5**	**A4**	92	**90** (*R*)
7	**2**	**5**	**A5**	32	29 (*R*)
8	**3**	**6**	**A4**	100	**98** (*R*)

[a] Reactions were performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol % catalyst at room temperature for 16 h. [b] Conversions determined by ^{1}H NMR and GC. [c] ee's determined by chiral GC. [d] In all cases, the (*S*)-enantiomer of the ligand was used. [e] Reaction carried out at 10 bar H_2. [f] Reaction carried out at 20 bar H_2.

(6) (a) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, 646. (b) Tang, W.; Liu, D.; Zhang, X. *Org. Lett.* **2003**, *5*, 205. (c) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495. (d) Chi, Y.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 4849. (e) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489. (f) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 516. (g) Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505. (h) Le Gendre, P.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453. (i) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357. (j) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.

(7) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099.

(8) The only exception was reported by Boaz: 2 h reaction time for 1-alkyl-enol acetates and dienyl esters.[6g]

(9) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J. *J. Mol. Catal.* **1983**, *19*, 159.

(10) For some recent examples, see: (a) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943. (b) Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, *6*, 1433. (c) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552.

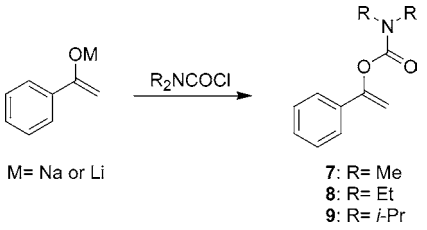
(11) For the preparation of enol acetates, see: (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. (b) Noyce, D. S.; Pollack R. M. *J. Am. Chem. Soc.* **1969**, *91*, 119.

(12) van den Berg, M.; Minnaard, A. J.; Haak R.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308.

changes (ligands **A4** and **A5**) induced remarkably different results (entries 2 vs 4, 5 vs 7). The outcome of this preliminary investigation showed that monodentate phosphoramidites are indeed suitable ligands for the Rh-catalyzed asymmetric hydrogenation of vinyl carboxylates. At this point we decided to test our assumptions regarding the superiority of vinyl carbamates with the same catalysts.

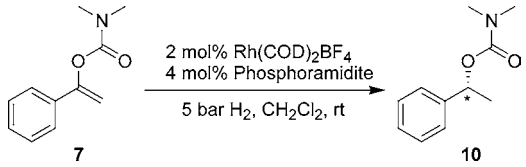
Simple 1-phenylvinyl *N*,*N*-dialkylcarbamates are accessible from ketones by reacting the corresponding enolates with carbamoyl chlorides (Scheme 1).[14,15]

Scheme 1. Synthesis of 1-Phenylvinyl *N*,*N*-Dialkylcarbamates



In this way *N*,*N*-dimethyl (**7**), *N*,*N*-diethyl (**8**), and *N*,*N*-diisopropyl (**9**) substituted vinyl carbamates were prepared. Hydrogenation of **7** confirmed our assumptions, as evidenced by an increase of enantioselectivity from 90% for **4** to 94% ee for **10** using ligand **A4** (Table 2, entry 4). Very good

Table 2. Asymmetric Hydrogenation of 1-Phenylvinyl *N*,*N*-Dimethylcarbamate **7**[a]



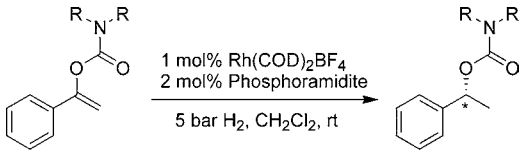
entry	ligand	conversion[b] (%)	ee[c,d] (%)
1	**A1**	100	19 (*R*)
2	**A2**	100	64 (*R*)
3	**A3**	100	14 (*R*)
4	**A4**	100	**94** (*R*)
5	**A5**	100	**93** (*R*)
6	**A6**	6	22 (*R*)
7	**A7**	100	76 (*R*)
8	**A8**	3	**92** (*R*)
9	**B4**	100	**94** (*R*)
10	**C4**	77	15 (*R*)

[a] Reactions were performed in 4 mL of solvent with 0.2 mmol of substrate and 2 mol % catalyst at room temperature for 16 h. [b] Conversions determined by ^{1}H NMR or GC. [c] ee's determined by chiral GC. [d] In all cases, the (*S*)-enantiomer of the ligand was used.

activities were obtained in almost all cases, except when a sterically demanding amine (**A8**, entry 8) or BINOL moiety (**C4**, entry 10) were used. The variety of enantioselectivities obtained demonstrates the influence of the ligand structural features. Other heterocyclic ring sizes in the ligand (**A3** and **A7**) resulted in poorer enantioselectivities compared to **A4**. Changing the backbone of the ligand from BINOL to octahydro-BINOL (**B4**) produced no change in the enantioselectivity, as 94% ee was achieved in both cases. In view of the superior performance of ligands **A4** and **B4**, they were selected as the ligands of choice for further studies.

Table 3 shows the results obtained in the hydrogenation

Table 3. Asymmetric Hydrogenation of 1-Phenylvinyl *N*,*N*-Dialkylcarbamates[a]



entry	substrate	product	ligand	ee[b–d] (%)
1	**7**[e]	**10**	**A4**	94 (*R*)
2	**8**[e]	**11**	**A4**	**96** (*R*)
3	**8**[f]	**11**	**A4**	**98** (*R*)
4	**8**[g]	**11**	**B4**	96 (*R*)
5	**9**	**12**	**A4**	95 (*R*)

[a] Reactions were performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol % catalyst at room temperature for 16 h. [b] All reactions went to full conversion. [c] ee's were determined by chiral GC. [d] In all cases, the (*S*)-enantiomer of the ligand was used. [e] Reaction completed after 4 h. [f] Reaction carried out at −20 °C and 20 bar H_2. [g] Reaction completed after 2 h.

of 1-phenylvinyl *N*,*N*-dialkylcarbamates, varying the substitution pattern on the nitrogen. A small increase in ee from 94% to 96% was noted in the hydrogenation of the *N*,*N*-diethyl carbamate **8**, with both ligands **A4** and **B4** (entries 2 and 4). An excellent 98% ee (entry 3) was also obtained by decreasing the temperature to −20 °C. On the other hand, no further improvement was achieved using substrate **9**. It should be emphasized that the catalyst loading for this set of reactions was reduced to 1 mol %, without effecting reactivity or enantioselectivities (entry 1). A closer look at the reaction rate revealed a very efficient catalytic system and a substantial difference between ligands **A4** and **B4**, as the reactions were found to be finished in around 4 and 2 h, respectively.[16] In view of these excellent results, we decided to expand the substrate scope further (Figure 3).

Modifications of literature procedures, based on the multigram-scale synthesis and α-lithiation of the simple vinyl carbamate **19** (Scheme 2),[17] allowed the preparation of substrates **14**−**17** with perfect control over the regioselectivity in good yields.[18]

It should be noted that the preparation of substrate **13** was not possible using the conditions described in Scheme 1. The

(13) Lower reactivity for this substrate was also observed using a Ru-Tunaphos catalyst (48 h).[6c]

(14) (a) Olofson, R. A.; Cuomo, J.; Bauman, B. A. *J. Org. Chem.* **1978**, *43*, 2073. (b) Jiang, X.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2004**, *15*, 2223.

(15) For an alternative synthesis, see also: Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe D. *Synthesis* **2002**, *3*, 381.

(16) The use of an Endeavor allows one to follow the uptake of H_2 during the reaction: Peña, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 475.

(17) (a) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, *43*, 3791. (b) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

(18) (a) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680. (b) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 6057.

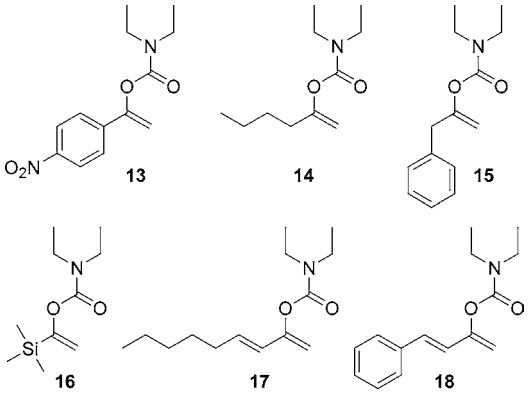
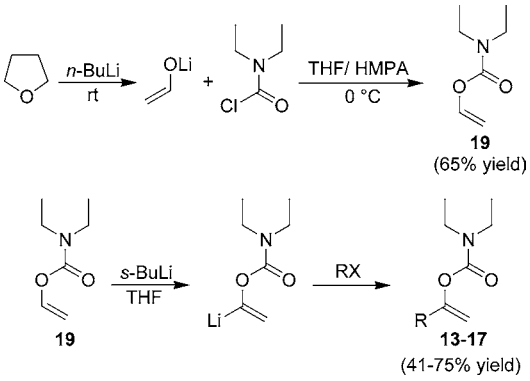


Figure 3. Enol carbamate hydrogenation substrates.

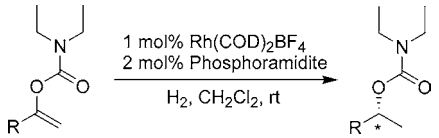
same conditions would prevent the selective preparation of substrates such as **14** or **15**, since a mixture of the internal (*E*/*Z*) and the desired terminal double bond would be obtained. Hence, the method presented in Scheme 2 is very versatile. Substrate **18** was instead synthesized following Scheme 1.[11a]

Scheme 2. Regiocontrolled Synthesis of Enol *N*,*N*-Diethylcarbamates[19]



The results of the asymmetric hydrogenation of substrates **13**−**18** are depicted in Table 4. An excellent 98% ee (entry 1) was obtained for substrate **13**, confirming also for enol carbamates the importance of an electron-withdrawing group on the aromatic moiety. Moreover, this substituent had a beneficial influence also on the activity, as the reaction was finished after around 1 h. According to Burk, the presence of electron-withdrawing groups enhances metal olefin binding, resulting in higher rates and enantioselectivities.[6j] As shown for substrate **15** (entry 4), the presence of a benzyl group causes a decrease in enantioselectivity (73% ee), although full conversion was achieved with 5 bar H_2 using **A4**. When the substituent is an alkyl group (substrate **14**), a further decrease in enantioselectivity (63% ee, entry 2) was observed and a higher pressure was necessary in order to reach full conversion. We were pleased to see an increase both in terms of enantioselectivity (69% ee) and reactivity

Table 4. Asymmetric Hydrogenation of Enol *N*,*N*-Diethylcarbamates **13**−**18**[a]



entry	substrate	product[b]	ligand	pressure H_2 (bar)	ee[c,d] (%)
1	**13**	**20**	**A4**	5	**98** (*R*)
2	**14**	**21**	**A4**	25	63 (*S*)
3	**14**	**21**	**B4**	10	69 (*S*)
4	**15**	**22**[e]	**A4**	5	73
5	**16**	**23**[e]	**A4**	5	43
6	**17**	**24**	**A4**	10	**97** (*R*)
7	**18**	**25**	**A4**	15	76 (*R*)
8	**18**	**25**	**B4**	10	77 (*R*)

[a] Reactions were performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol % catalyst at room temperature for 16 h. [b] Conversions determined by ^{1}H NMR or GC; all reactions went to completion. [c] ee's were determined by chiral GC. [d] In all cases, the (*S*)-enantiomer of the ligand was used. [e] The absolute configuration has not been established.

(only 10 bar H_2 were used) for this substrate when using ligand **B4** (entry 3).[20] Interestingly the sterically hindered substrate **16** could also be hydrogenated to full conversion (entry 5), although the enantioselectivity was modest. To our surprise, an excellent 97% ee was achieved for the dienyl substrate **17** (entry 6), and only 10 bar H_2 was necessary to achieve complete conversion to the product.[21] On the other side, lower enantioselectivity was observed for the dienyl carbamate **18** (entries 7 and 8). It should be mentioned that in both cases the catalytic system showed very good selectivity as the hydrogenation proceeded leaving the extra internal double bond intact.

In conclusion, we have shown that monodentate phosphoramidites, in particular PipPhos (**A4**) and its octahydro analogue (**B4**), are excellent ligands for the rhodium-catalyzed asymmetric hydrogenation of aromatic enol acetates, aromatic enol carbamates, and 2-dienyl carbamates with excellent enantioselectivities up to 98%. Fast reactions were achieved, making the combination of enol carbamates and monodentate phosphoramidites very competitive compared to the existing systems.

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Supporting Information Available: Experimental data, spectral data for new or not described substrates and products, and methods for enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) See Supporting Information for more details.

(20) The results on substrates **14** and **15** are comparable with those obtained by using Duphos on similar enol acetates; see ref 6g.

(21) A similar phenomenon was previously observed by using Duphos on a similar enol acetate; see ref 6g.