

# Mono- versus Bidentate Ligands in Rhodium-Catalyzed Asymmetric Hydrogenation. A Comparative Rate Study

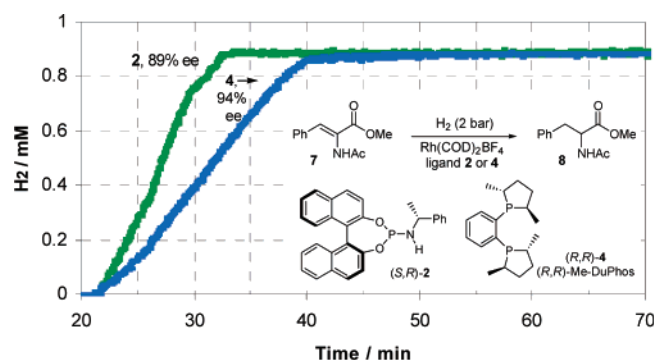
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## ABSTRACT



Bidentate chiral phosphines are no longer essential for achieving a fast and highly enantioselective hydrogenation of  $\alpha$ - or  $\beta$ -dehydroamino acid derivatives. In particular, a readily accessible and stable monodentate phosphoramidite can be highly effective in these asymmetric hydrogenations.

Monophosphines were the first chiral ligands employed in the pioneering studies on the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins.<sup>1</sup> Following the introduction of DIOP,<sup>2</sup> the field was soon taken over by chiral bidentate phosphorus ligands, and for more than thirty years, hundreds of these ligands were developed<sup>3</sup> on the basis of

the assumption that bidentate ligands were essential for achieving high enantioselectivities in the hydrogenation reaction.<sup>4</sup> However, this widespread notion has recently been challenged since monodentate phosphines,<sup>5a</sup> phosphonites,<sup>5b</sup> phosphites,<sup>5c</sup> and phosphoramidites<sup>5d</sup> have been successfully

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(1) (a) Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445. (b) Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem.* **1968**, 80, 1034. (c) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10. (d) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, 48, 315.

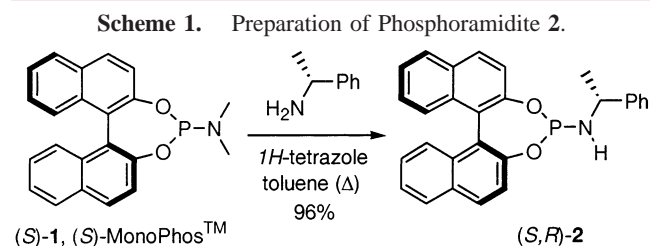
(2) Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481.

(3) (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, 41, 1998. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, 41, 2008. (c) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 5.1. (d) Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, 1994. (e) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, Germany, 1993.

(4) (a) Zhang, X. *Enantiomer* **1999**, 4, 541. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994; Chapter 2.

used in a number of asymmetric hydrogenation reactions with enantioselectivities up to 99%.<sup>6</sup> In the last three years, this small but rapidly expanding class of monodentate ligands has shown enantioselectivities comparable to or better than those reached with bidentate ligands reported so far.<sup>7</sup> Monodentate phosphonites, phosphites, and phosphoramidites have the advantage of being readily accessible, highly diverse, and extraordinarily inexpensive compared to various privileged bidentate ligands. Bearing in mind that asymmetric hydrogenation is continuously expanding as an important methodology in the industrial preparation of chiral building blocks, those characteristics mentioned above are vital features. However, to date, mono- and bidentate ligands have not been compared yet in terms of catalytic activity; another crucial parameter for implementation of asymmetric catalysis methodology. Herein we report a study demonstrating for the first time that a monodentate ligand can lead not only to higher enantioselectivities but also to faster asymmetric hydrogenations of prochiral olefins compared to several of the best bidentate ligands used so far.

MonoPhos (**1**)<sup>8</sup> is an extremely stable monodentate phosphoramidite that affords very good enantioselectivities when used as a ligand in the rhodium-catalyzed hydrogenation of  $\alpha$ -dehydroamino acid derivatives<sup>5d</sup> and enamides.<sup>6h</sup> This phosphorus ligand can be easily prepared from bis- $\beta$ -naphthol and HMPT in excellent yield.<sup>6j,9</sup> In the course of a study to find an efficient ligand for the enantioselective hydrogenation of  $\beta$ -dehydroamino acid derivatives,<sup>10</sup> we carried out a systematic optimization of the structure of MonoPhos by variations of the amine functionality via amine exchange (Scheme 1). In this way, ligand **2** was obtained from (S)-

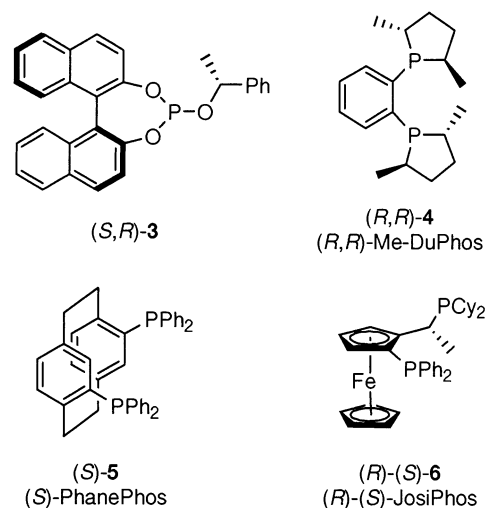


MonoPhos and commercial (R)- $\alpha$ -methylbenzylamine in 96% yield.

Initially, we tested monophosphoramidite **2** in the asymmetric hydrogenation of a benchmark substrate, methyl 2-acetamido cinnamate (dehydrophenylalanine methylester, **7**) under standard conditions.<sup>11</sup> Although the enantiomeric excess of **8** was somewhat lower compared to the value obtained with MonoPhos (90 vs 95% ee), the reaction appeared to be dramatically faster (5 min vs 4 h). To obtain an efficient ligand in the rhodium-catalyzed asymmetric hydrogenation, small R-groups on the amine unit of the

phosphoramidite appear to be necessary.<sup>5d,6g</sup> In this way, the presence in ligand **2** of a hydrogen attached to the nitrogen instead of a methyl group as in the case of MonoPhos should influence the rate of the hydrogenation. Nevertheless, the different enantioselectivities found with both phosphoramidites<sup>12</sup> suggest a more complex mechanistic picture. The differences in reaction rates and ees are probably based on the influence of the NH group present in **2**, as this is the major chemical difference between both ligands. Similar to its monophosphite analogue (S,R)-**3**,<sup>5c</sup> in this particular hydrogenation, the ee of the product when using ligand (S,R)-**2** only depends on the chirality of the bisnaphthol unit.<sup>10</sup>

Encouraged by these findings, we decided to compare the rate of the reaction of monophosphoramidites **1** and **2** and monophosphite **3**<sup>5c</sup> with some of the most successful and commercially available bidentate phosphines used in asymmetric hydrogenation, in particular DuPhos,<sup>13</sup> PhanePhos,<sup>14</sup> and JosiPhos<sup>15</sup> (Figure 1). For the rate comparison, we first



**Figure 1.** Ligands used in the comparison with phosphoramidites.

carried out parallel experiments using methyl 2-acetamido cinnamate (**7**), a common substrate normally hydrogenated

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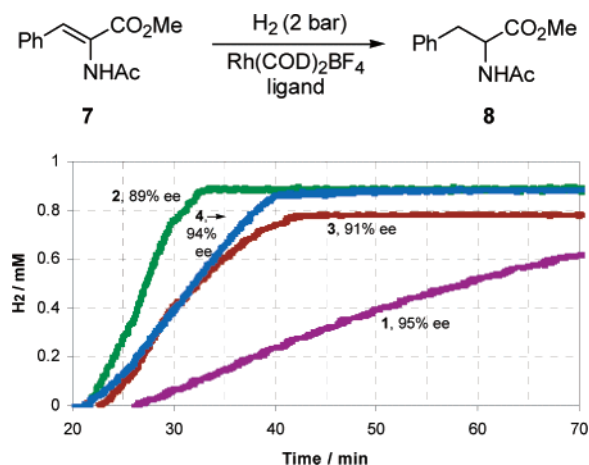
(6) For other recent examples: (a) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333. (b) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897. (c) Zeng, Q.; Liu, H.; Cui, X.; Mi, A.; Jiang, Y.; Li, X.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 115. (d) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*, 4977. (e) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480. (f) Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 5541. (g) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (h) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003. (i) Guillen, F.; Rivard, M.; Toffano, M.; Legros, J.-Y.; Daran J.-C.; Fiaud, J.-C. *Tetrahedron* **2002**, *58*, 5895. (j) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; 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*, 1.

(7) For a recent review, see: Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.

(8) Now commercially available through Strem Chemicals. See also: van den Berg, M.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. (DSM N. V.). World Patent WO 02/04466, 2002.

with excellent enantioselectivities. Ligands were compared using a standard 1 mmol of substrate **7** (0.2 M), 0.5 mol % Rh(COD)<sub>2</sub>BF<sub>4</sub>, and 2 bar of H<sub>2</sub>. Due to the fact that there is an important influence of the solvent used in the hydrogenation, we employed the best of the reported solvents for each ligand; DCM (**1** and **3**), EtOAc (**2**), or MeOH (**4**). To compensate for the influence of the rate on the catalyst formation or chelate effects on the global rate of hydrogenation,<sup>16</sup> we preformed all of the rhodium precatalysts prior to use.<sup>17</sup> Hydrogenation experiments were performed simultaneously in a parallel way using a semiautomated autoclave with eight reactors (Endeavor) that was purged twice with nitrogen and once with hydrogen.<sup>18</sup> Then, the autoclave was pressurized with H<sub>2</sub> to 2 bar and the reaction was monitored by the hydrogen consumption while being stirred at room temperature.

Typical results are depicted in Figure 2. Under these conditions, monophosphoramidite **2** (initial TOF = 1100 h<sup>-1</sup>,

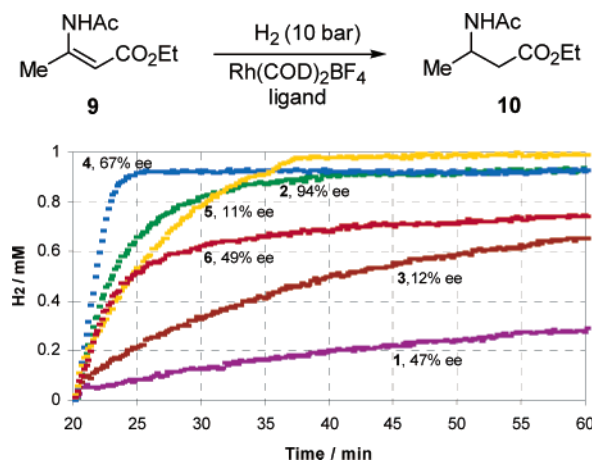


**Figure 2.** Asymmetric hydrogenation of methyl 2-acetamidocinnamate (**7**) using chiral ligands **1–4**.

green line) turned out to form the fastest catalyst among those tested in this study, twice as fast as its monophosphite analogue **3** (brown), five times faster than MonoPhos (**1**,

violet), and even faster than the most effective of the bidentate phosphines, DuPhos (**4**, blue).<sup>19</sup> To the best of our knowledge, this is the first time that a monodentate ligand has been reported to be faster than DuPhos in hydrogenation reactions. However, the enantioselectivity achieved with ligand **2** (89%) under these conditions was lower than that observed with MonoPhos (95% ee) or DuPhos (94% ee).<sup>20</sup>

Recently, Heller and Börner et al. have reported a comparison of the kinetics of the hydrogenation of  $\beta$ -dehydroamino acid derivatives using different bidentate phosphines.<sup>21</sup> We decided to compare monodentate ligands **1–3** with bidentate phosphines **4–6** in the hydrogenation of one example of this family of substrates, particularly (Z)-ethyl 3-acetamido-2-butenate (**9**, Figure 3).<sup>10,22</sup> These hydrogenation



**Figure 3.** Asymmetric hydrogenation of (Z)-ethyl 3-acetamido-2-butenate (**9**) using chiral ligands **1–6**.

tion experiments were carried out using 1 mmol of substrate **9** (0.2 M), 2 mol % Rh(COD)<sub>2</sub>BF<sub>4</sub>, and 10 bar of H<sub>2</sub>. Like in the hydrogenation of **7**, we preformed all of the rhodium precatalysts prior to use.<sup>23</sup> We employed *i*PrOH<sup>24</sup> (**1–3**) or MeOH<sup>25</sup> (**4–6**) as the solvent.

(9) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699.

(10) Peña, D.; Minnaard, A.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552.

(11) With 5% Rh(COD)<sub>2</sub>BF<sub>4</sub> as the catalyst precursor, 11% monodentate ligand in EtOAc at room temperature, and 1 bar of H<sub>2</sub>.

(12) The ee obtained using **1** as a ligand in the Rh-catalyzed hydrogenation of **7** is constant when increasing the hydrogen pressure (at least up to 60 bar), while it is enhanced when performing the reaction at lower temperatures (0 vs 25 °C; see ref 5d). On the contrary, in the case of ligand **2**, the ee drops when increasing the hydrogen pressure or when decreasing the reaction temperature.

(13) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.

(14) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.

(15) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(16) Heller et al. have extensively reported on these issues. For instance, see: (a) Börner, A.; Heller, D. *Tetrahedron Lett.* **2001**, *42*, 223. (b) Drexler, H.-J.; Baumann, W.; Spannenberg, A.; Fischer, C.; Heller, D. *J. Organomet. Chem.* **2001**, *621*, 89.

(17) The following procedure was used: Rh(COD)<sub>2</sub>BF<sub>4</sub> and 2 equiv (monodentates) or 1 equiv (bidentates) of the ligand were dissolved in DCM (20 mM). After the mixture was stirred under argon at room temperature for 15 min, volatiles were removed and the appropriate solvent was added (1 mM in the case of **2** due to the low solubility of the complex; 20 mM in the rest).

(18) Total purge time was 20 min.

(19) In our hands, preliminary runs had shown the superiority of DuPhos over PhanePhos and JosiPhos in the hydrogenation of **7** under our standard conditions. See Supporting Information for details.

(20) Higher enantioselectivities in the hydrogenation of **7** were reported for these ligands under different conditions: **1**, 98% ee (ref 5d); **4**, 98% ee (ref 13).

(21) Heller, D.; Drexler, H.-J.; You, J.; Baumann, W.; Drauz, K.; Krimmer, H.-P.; Börner, A. *Chem. Eur. J.* **2002**, *8*, 5196.

(22) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4169 and refs cited therein.

(23) In this case, the following procedure was used: Rh(COD)<sub>2</sub>BF<sub>4</sub> and 2 equiv (monodentates) or 1 equiv (bidentates) of the ligand were dissolved in DCM (20 mM). After the mixture was stirred under argon at room temperature for 15 min, volatiles were removed and DCM (**1–3**, 20 mM) or MeOH (**4–6**, 20 mM) was added.

(24) With ligands **1–3**, the preformed precatalysts were added in DCM solution, therefore the actual composition of the solvent was 4:1 *i*-PrOH/DCM.

On the basis of these experiments,<sup>26</sup> monophosphoramidite **2** (green line) turned out to be the fastest monodentate ligand compared to **1** (violet) and **3** (brown). When compared to bidentate phosphines, ligand **2** was found to be faster than JosiPhos (**6**, red) and as fast as PhanePhos (**5**, yellow), although slower than DuPhos (**4**, blue). However, phosphoramidite **2** is the only ligand of this group of mono- and bidentate ligands that leads to enantioselectivities exceeding 90% in this hydrogenation.<sup>27</sup>

In conclusion, in this competitive study we demonstrate that, compared to the *state of the art* bidentate ligands, readily accessible and stable monodentate phosphoramidites can lead

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(25) (a) MeOH is the best solvent for the hydrogenation of (Z)- $\beta$ -dehydroamino acid derivatives using DuPhos reported so far. See: (b) Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, *66*, 6816.

(26) Among these ligands, only **2** (ref 10) and **4** (ref 25b) have been previously reported in the asymmetric hydrogenation of  $\beta$ -dehydroamino acid derivatives.

(27) The ee reached with DuPhos depends on the H<sub>2</sub> pressure. Actually, at 1 bar, 87% ee can be reached with this ligand (see ref 25b).

to both higher rates and/or higher enantioselectivities in the asymmetric hydrogenation of  $\alpha$ - and  $\beta$ -dehydroamino acid derivatives. Therefore, bidentate chiral phosphines are no longer a *conditio sine qua non* for achieving a fast and highly enantioselective hydrogenation of amino acid precursors.

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**Supporting Information Available:** Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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