

Fine-Tuning Monophosphine Ligands for Enhanced Enantioselectivity. Influence of Chiral Hemilabile Pendant Groups

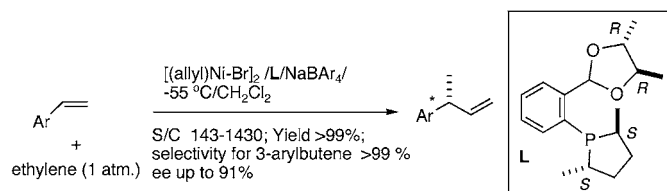
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ABSTRACT



* Efficiency and selectivity of the catalyst depends on the chirality of dioxalane C_4 and C_5

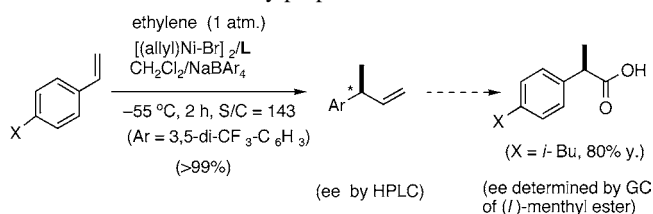
C_2 -Symmetric P -(2- X -aryl)-2,5-dialkylphospholanes (X = dioxolan-2-yl or dioxan-2-yl), designed on the basis of a working model for asymmetric induction, are effective ligands for the Ni(II)-catalyzed asymmetric hydrovinylation of styrenes. Excellent yields (>99%), selectivities for the desired 3-arylbutenes (>99%), high S/C ratios (>1200), and ee's (up to 91%) have been realized for a number of prototypical vinylarenes. In the dioxolane series, the selectivity depends on the configuration of the C_4 and C_5 carbons.

Use of chiral monophosphines as ligands goes back to some of the first discoveries in asymmetric catalysis. In 1968, Horner,^{1a} Knowles,^{1b} and their co-workers showed that replacement of Ph_3P in Wilkinson-type Rh-complexes produced asymmetric catalysts that gave varying degrees of selectivity in hydrogenation reactions. The enantioselectivities in these initial studies remained low, and interests in monophosphines as chiral ligands saw only sporadic interest until recently.² Many reactions failed to proceed, or gave unacceptably low enantioselectivities when bidentate ligands were employed. In one such example, we reported that bidentate phosphines inhibited the Ni(II)-catalyzed heterodimerization of ethylene and vinylarenes (step 1, Scheme 1).³ We showed that catalytic activity can be fully restored

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

(2) (a) For recent reviews dealing with this topic, see: (a) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315. (b) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (d) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (e) For a compilation of more recent references, see, Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156.

Scheme 1. Asymmetric Hydrovinylation and Synthesis of 2-Arylpropionic Acids



with a phosphine, carrying a hemilabile group at the optimum site (Table 1).⁴ Anecdotal evidence by way of the effect of variations of this hemilabile group, of its synergistic relation to various counterions, and NMR spectroscopy of the

(3) (a) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459. (b) RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68*, 8431. (c) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845.

(4) For use of hemilabile ligands in related reactions, see: Meking, S.; Keim, W. *Organometallics* **1996**, *15*, 2650 and references therein.

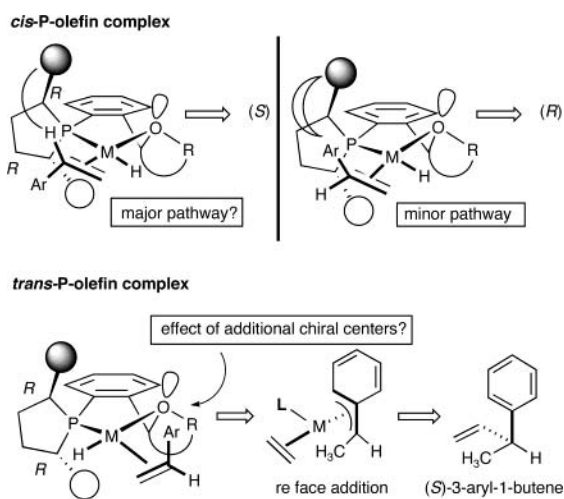
Table 1. Effect of Bidentate and Hemilabile Ligands in Hydrovinylation

yield/sel. ^a	0	93/99	0	95/99
enantiosel.	–	40 (S)	–	34 (S)

^a Selectivity for 3-arylbutene.

intermediates [(allyl)Ni⁺P X[–]] suggested the possibility that variation in this group could lead to an improvement of the selectivity in the asymmetric hydrovinylation reaction.⁵ Even though use of ligands with chiral side chains has been reported before,⁶ there is no explicit mention of the use of this as a control element in asymmetric catalysis. As a test case, we chose a commercially relevant substrate, 4-isobutylstyrene, for which the best selectivity reported to date has been only 74%.^{7,8} Our expectations of higher *selectivity* and *efficiency* have been met. Details of these studies are reported in this paper.

Based on a working model⁹ for asymmetric induction in this reaction (Figure 1), we decided to examine the effect of

**Figure 1.** Working model for asymmetric induction in the hydrovinylation reaction.

introducing additional elements of chirality at the hemilabile position. We prepared a series of C₂-symmetric P-(2-X-aryl)-

(5) Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899.

(6) For selected examples of monophosphines with chiral side chains, see: (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153. (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (c) Also see refs 2c and 3b. Many examples of the effects of chirality of one or other atom of a *chelating* ligand are known. For a recent example, see: Shintani, R.; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699.

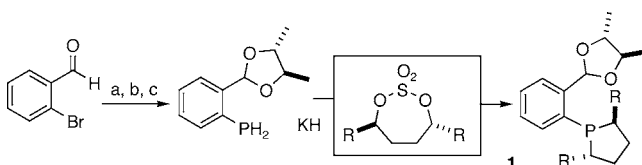
(7) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734.

Table 2. Asymmetric Hydrovinylation of 4-Isobutylstyrene

entry	ligand	conversion(%)	selectivity (%) ^a	ee (%)
1.		1a R = Me >99.5 1b R = Et 83	>99.5 >99.5	91 (R) 88 (R)
2.		>99.0	90 ^b	71 (R)
3.		>99.5	>99.5	85 (R)
4.		>99.5	>99.5	85 (R)
5.		>99.5	>99.5	90 (S)

^a Selectivity for 3-arylbutene. ^b The rest are *cis*- and *trans*-2-aryl-2-butenes.

2,5-dialkylphospholanes (X = dioxan-2-yl or dioxalan-2-yl, Table 2) via modification of a procedure published earlier (Scheme 2).^{5,10}

Scheme 2. Synthesis of a Prototypical Phospholane/Acetal Ligand 1^a

^a Key: (RR)-butane-2,3-diol, H⁺; (b) HP(O)(OEt)₂/Pd(OAc)₂, dppb, EtNPr₂, DMSO, 100 °C; (c) LAH/THF.

In scouting experiments, the hydrovinylation reaction was carried out using 0.007 equiv of Ni and the phosphine ligand in an atmosphere of ethylene at –55 °C.¹⁰ The results are tabulated in Table 2. The acetal-containing phospholanes (1–

(8) Feringa's phosphoramidites, a class of BINAPO-derived ligands useful for asymmetric hydrovinylation, give only a low yield of the product (28% yield, 68% ee) in the hydrovinylation of 4-isobutylstyrene. Franció, G.; Faraone, F.; Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736.

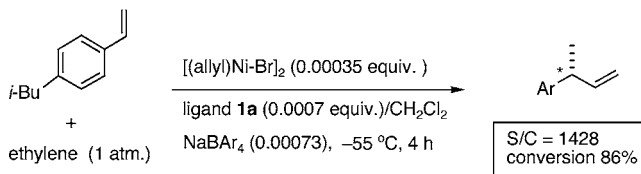
5), in general, are excellent ligands for asymmetric hydrovinylation, giving quantitative yields and selectivities for the expected 3-arylbutenes.

The combination of (*SS*)-2,5-dimethylphospholane and acetal derived from (*RR*)-2,3-butanediol (**1a**) gives the best selectivity (91% ee, entry 1). Increasing the size of the phospholane 2,5-substituents from Me to Et (**1b**) has a small effect on ee, but significantly, this results in a slower reaction (entry 1). A change in chirality of the 4,5-carbons of the 1,3-dioxalane (**2**, entry 2) leads to onset of isomerization of the primary product (up to 10%) and significant deterioration of the enantioselectivity (71% ee).¹⁰ Most notably, the ligand **3**, with an achiral acetal appendage, gives selectivity between that of the two diastereomers **1a** and **2** (entry 3). Structurally analogous ligands **4** and **5** with 1,3-dioxane side-chain behave in a similar fashion. In this case, as expected, the (*RR*)-phospholane/(*SS*)-dioxane combination (**5**) gives the best results (entry 5). An examination of the results from entries 1–5 shows that the stereoselectivity of the reaction is dictated by the chirality of the phospholane ring, with the (*RR*)-phospholane favoring (*S*)-3-arylbutene, in accordance with the proposed model.

Use of the ligand **1a** in hydrovinylation of other vinylarenes gave the following ee's under the typical reaction conditions (0.70 mol % Ni/-55 °C, >99.5% yield, unless specified otherwise): styrene (88); 4-methylstyrene (86); 4-bromostyrene (71); 4-methoxystyrene (73, 80% yield); 2-methoxy-6-vinylnaphthalene (86, 73% yield, 2.8 mol % Ni). Except for 4-bromostyrene, these are among the highest ee's reported for the asymmetric hydrovinylation of these substrates. Incidentally, diarylphosphinite⁷ and phosphor-

amidites⁸ are known to give excellent ee's for 4-halostyrenes. Thus, the advantages of the new ligands are complementary to the known ones with respect to substrates.

Finally, the catalytic efficiency of the reaction was examined using ligand **1a**. In a reaction carried out with 4-isobutylstyrene/Ni(II)**1a** ratio of 1428 (0.07 mol % catalyst) a yield of 86% (rest, starting material) was realized (see the equation below). Under these conditions, the enantioselectivity was only 72%, a clear indication that further process improvements will be needed for a practical synthesis of (*S*)-ibuprofen by this route.



In conclusion, using a heuristic model for induction of asymmetry in the hydrovinylation reaction, we have designed a new set of hemilabile ligands that give among the best ee's and turnover numbers for this exacting reaction. These ligands, and the principles envisioned in their design, may find broader applications in asymmetric catalysis of reactions where monophosphines are the only viable alternatives. We are currently examining other applications of these ligands.

Acknowledgment. This paper is dedicated to Professor Leo A. Paquette in recognition of his numerous scientific and other contributions to organic chemistry. Financial assistance for this research by US National Science Foundation (CHE-0308378) and the Petroleum Research Fund of the ACS (36617-AC1) is gratefully acknowledged.

Supporting Information Available: Full experimental details of various hydrovinylation reactions; spectroscopic and chromatographic data for characterization of compounds listed. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) This model assumes the involvement of diastereomeric (phosphorus/olefin) *cis* and *trans* square planar transition states for the Ni–H addition to the prochiral faces of the olefin. While the *cis*-P/olefin complex appears to have a clear choice for the *re*-face addition, for the *trans* P/olefin complex there is no such preference. Our conjecture is that additional elements of chirality at the hemilabile position would favor one or other of these addition modes leading to increased selectivity.

(10) See the Supporting Information for full experimental details, characterization, and analytical data including chromatographic traces of products.