ORGANIC LETTERS

2000
Vol. 2, No. 26
4137−4140

Ligand Substituent Effects on Asymmetric Induction. Effect of Structural Variations of the DIOP Ligand on the Rh-Catalyzed Asymmetric Hydrogenation of Enamides

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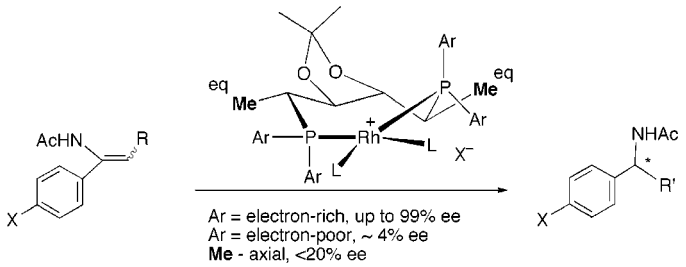
Received September 14, 2000

ABSTRACT



Substituent changes in the ligand (L*) backbone and the chelating phosphorus atoms of the classical DIOP ligand result in dramatic changes in the enantioselectivity of $Rh^{+}L^{*}$-catalyzed enamide hydrogenations.

A select few prototypical transformations such as Rh-catalyzed hydrogenation of α-acylaminoacrylic acid derivatives[1] and Pd-catalyzed alkylation of stabilized carbanions[2] are used as benchmark reactions for evaluating new phosphine ligands. A large number of diverse, often structurally unrelated, ligand scaffoldings have been successfully employed for these reactions, and newer ones continue to emerge. Yet, there is a dearth of information on the effect of systematic, deep-seated structural variations within a specific ligand frame, the recent advances in combinatorial approaches to ligand design notwithstanding.[3,4] Such information would be immensely valuable in developing working models for the asymmetric induction process and, eventually, for the de novo design of highly selective catalysts. In an earlier paper,[5a] we reported a modest effort to make structural changes in the well-known DIOP [**1**, (2,2-dimethyl-1,3-dioxolane-4,5-diylbis-methylene)bisdiphenylphosphine], which, as the first chelating phosphorus ligand to be used in

(1) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 121. (b) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37, and references therein. (c) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 1.

(2) (a) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 833. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(3) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 1389. Burgess, K.; Porte, A. M. In *Advances in Catalytic Processes*; Doyle, M., Ed.; JAI Press: Greenwich, 1998; p 69.

(4) For notable exceptions, see the following. (a) Salen complexes for epoxidation and epoxide opening reactions: Jaobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 649, 1309. (b) Sugar phosphinite ligands for hydrocyanation and hydrogenation reactions: RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A. In *Advances in Catalytic Processes*; Doyle, M., Ed.; JAI Press: Greenwich, 1998; p 1.

(5) (a) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900. (b) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199.

10.1021/ol006591f CCC: $19.00
Published on Web 12/01/2000

asymmetric catalysis, occupies a historic place in organic chemistry.[6] A report on the use of these ligands for the Pd-catalyzed allylation of dimethyl malonate with 1,3-diphenylallyl acetate followed.[5b] Since then we have completed the synthesis of a number of additional analogues, including a few that would permit an evaluation of electronic effects on enantioselectivity of a given reaction. In this paper we present our recent findings on the synthesis and use of these ligands for the Rh-catalyzed asymmetric hydrogenation of α-arylenamides, a reaction that has attracted considerable attention recently.[7]

The ligands involved in this study are shown in Figure 1. Of these, **1** ((*RR*)-DIOP) is commercially available, the

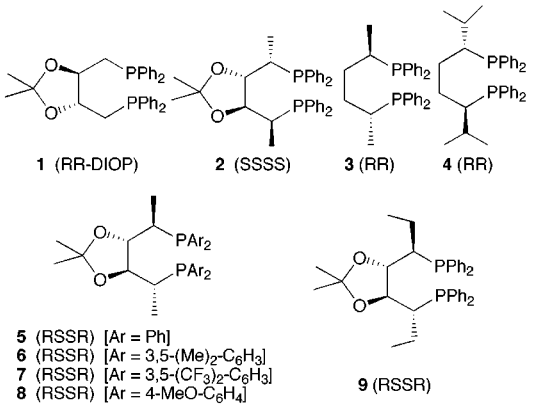
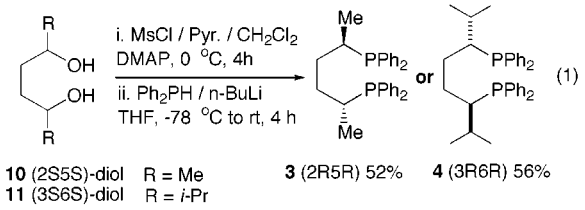


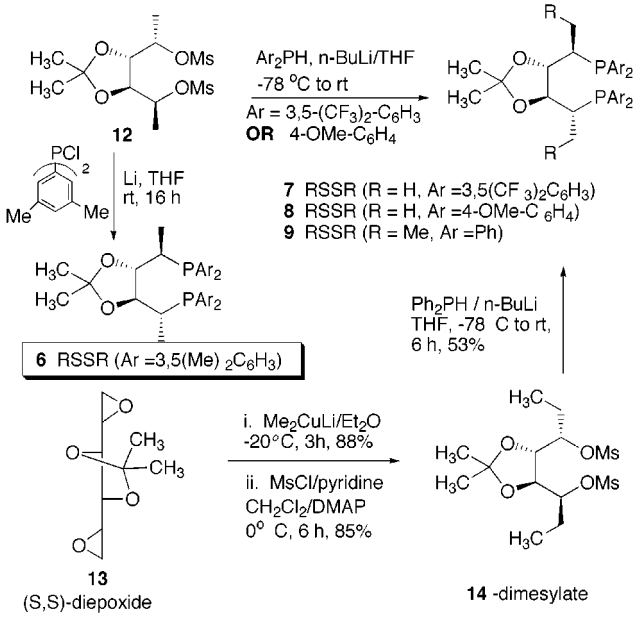
Figure 1. Derivations of DIOP used for enamide hydrogenations.

synthesis of **2** was originally described by Kagan,[8] and we reported the synthesis of **5**.[5a,9] Syntheses of ligands **3** and **4** starting with the corresponding alcohols (**10** and **11**)[10] are shown in eq 1. Ligands **6**, **7**, and **8** were prepared by simple



S_N2 reaction of the mesylate **12** with the corresponding lithium diarylphosphide (Scheme 1).[11,12] Ligand **9** was prepared by dialkylcuprate opening of the known epoxide **13**, mesylation, and formation of the C−P bonds by S_N2 displacements.[12]

Scheme 1. Synthesis of Ligands **6**−**9**



Hydrogenation of a prototypical substrate, *N*-(1-phenylvinyl)acetamide, was examined in detail, and the results are shown in Table 1. Reactions were carried out using isolated cationic Rh complexes prepared by reacting stoichiometric amounts of the ligand with $Rh^+(COD)_2\ X^-$ where X = BF_4, SbF_6, or PF_6.[13] In each case, quantitative yield of the hydrogenation product was obtained with ee's approaching 99% in several instances. In our hands, use of BF_4, SbF_6, or PF_6 salt in CH_2Cl_2 appears to be the method of choice for carrying out this reaction.[14] This is a surprising finding in view of the fact that CH_2Cl_2 has been reported to have a delirious effect on the selectivity of this reaction when a $[Rh(COD)_2Cl]_2$ precursor was used.[7f] Use of the isolated cationic salts in a noncoordinating solvent permits the reaction to be conducted under milder conditions (20 psi/10 h vs 140 psi and 48−60 h[7f]) with consistently high enantioselectivities.

(6) (a) Kagan, H. B. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 9. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(7) (a) Burk, M. J.; Wang, Y.; M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142, and references therein. (b) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (c) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808. (d) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590. (e) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (f) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871.

(8) Kagan, H. B.; Fiaud, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923.

(9) While our paper was being readied for publication, Zhang reported an alternate synthesis of **5** and its use in enamide reduction.[7f] The analytically pure **5** is a white solid.

(10) We thank Dr. M. J. Burk (Chirotecch) for the gift of these alcohols.

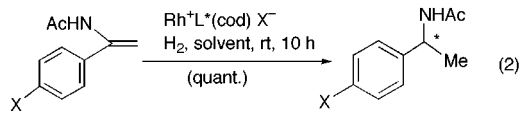
(11) Syntheses of the diarylphosphines were accomplished by LAH reduction of the corresponding chlorophosphine[11a] according to a published procedure.[11b] (a) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869. (b) Casey, C. P.; Paulsen, E. L.; Beuttenmueller, W.; Proft, B. R.; Petrovich, L. M.; Matter, B. A.; Powell, D. R. *J. Am. Chem. Soc.* **1997**, *119*, 11817.

(12) See Supporting Information for details of experimental procedure and full characterization of the compounds.

(13) The hydrogenation reactions were carried out as follows. In a drybox, a Fisher−Porter tube was charged with the enamide substrate (0.1 mmol), the appropriate solvent (2 mL), and preformed $Rh^+L^*(COD)\ X^-$ (1 mol %). After sealing, the tube was removed from the drybox and placed behind proper shielding. After five vacuum-refilling cycles with hydrogen, the tube was brought to the appropriate pressure (20 or 40 psi) of H_2 and the mixture was vigorously stirred for 10 h. After removing the catalyst on a plug of silica gel, the ee's of the products were determined by chiral GC (Chirasil-L-Val on WCOT fused silica 25 m × 0.25 mm).

(14) For other results, see: Sinou, D.; Kagan, H. B. *J. Organomet. Chem.* **1976**, *114*, 325, and ref 7f.

Table 1. Hydrogenation of α-Acetamidostyrene (eq 2)[a]



(X = H, Me, F)

entry	ligand/X/solvent	pressure	% ee[b] (confign)
1	**1**/BF_4/CH_2Cl_2	20	53 (*S*)
2	**2**/SbF_6/CH_2Cl_2	20	20 (*S*)
3	**3**/BF_4/CH_2Cl_2	20	91 (*R*)
4	**4**/BF_4/CH_2Cl_2	20	95 (*S*)
5	**5**/BF_4/MeOH	40	94 (*R*)
6	**5**/BF_4/CH_2Cl_2	20	98 (*R*)
7	**5**/BF_4/CH_2Cl_2	40	98 (*R*)
8	**5**/BF_4/$PhCH_3$	40	86 (*R*)[c]
9	**5**/SbF_6/MeOH	20	88 (*R*)
10	**5**/SbF_6/THF	20	92 (*R*)
11	**5**/SbF_6/CH_2Cl_2	20	98 (*R*)
12	**5**/PF_6/CH_2Cl_2	20	98 (*R*)
13	**6**/BF_4/CH_2Cl_2	40	82 (*R*)
14	**7**/BF_4/CH_2Cl_2	40	~4 (*R*)
15	**8**/BF_4/CH_2Cl_2	20	97 (*R*)
16	**9**/BF_4/CH_2Cl_2	20	99 (*R*)

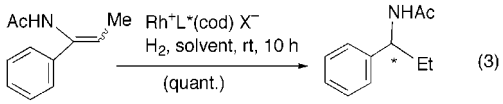
[a] See footnote 13 and Supporting Information for details. [b] Determined by GC. [c] 74% conversion.

Under our reaction conditions, (*RR*)-DIOP (**1**) gave 53% ee (*S*) of the hydrogenation product *N*-acetyl-1-phenylethylamine.[14] The (*SSSS*)-dimethyl analogue **2**[8] is a poorer ligand, giving only 20% ee. Removal of the two oxygen atoms from DIOP restores some of the selectivity as indicated by the 91% ee observed for **3** (entry 3). In the dideoxy analogues, increasing the size of the α-substitituents improves the selectivity (compare entries 3 and 4). The (*RSSR*)-dimethyl analogue **5** is one of the best ligands for the asymmetric reduction of an enamide, giving up to 98% ee in CH_2Cl_2 and slightly lower values in other solvents under our reaction conditions (entries 5−12). The reaction appears to be slower in a hydrocarbon solvent such as toluene. Comparison of the sense of asymmetric induction imparted by ligands **2**, **3**, **4**, and **5** shows that the chirality of the α-substituent (α to the phosphorus atom) is the key control element in the reaction. Since **3** is a better ligand than either **2** or **1**, it is reasonable to assume that the two oxygens in **2**, by virtue of their cis relationship to the methyl groups, contributes to unfavorable interactions in the diasteromeric complexes leading to the (*S*) product (vide infra). No such interactions are present in the relevant intermediate leading to the (*R*) product from **5** (the methyl groups and the dioxolane oxygens are trans to each other). Thus, (*RR*)-**3** and (*RSSR*)-**5** give high selectivities for the *R* product. Increasing the size of the α-substituent in **5** has little impact on the selectivity or reactivity. Thus, (*RSSR*)-**9** gave 99% ee (entry 16) under the standard conditions, not unlike (*RSSR*)-**5**.

Electronic effects of ligands can have profound influence on the rate and selectivity of asymmetric catalyzed reactions.[4a,15] No report of ligand electronic effects have been recorded for the Rh-catalyzed enamide reductions. Entries 6, 13, 14, and 15 in Table 1 address this issue in the context of the "best" DIOP derivative (**5**). Our synthetic strategy allows for the preparation of an electron-deficient ligand, **7**, and two electron-rich ones, **6** and **8**. The data clearly show the dramatic effect of an electron-deficient phosphorus on the selectivity. As with the Rh-catalyzed hydrogenation of α-acetamidoacrylic acid derivatives,[15c] the ee drops off precipitously with electron-withdrawing ligand **7**.

Data in Table 2 show how the new ligands affect the enantioselectivity of other Rh-catalyzed enamide hydrogenations. The selectivity for the 4-methylphenyl and 4-fluorophenyl enamide derivatives[16] (eq 2) parallels the behavior of the unsubstituted compound for each of the ligands. Since the preparation of isomerically pure *E*- or *Z*-enamides is difficult, reduction of a mixture in high ee is of significant practical interest. Indeed, a mixture of the *Z*- and *E*-enamides (*Z*:*E* = 1.0:2.4) is readily converted into the hydrogenation products in excellent ee's under the standard conditions (eq 3, Table 2, column 5). Gratifyingly, the dependence of enantioselectivity on the structure of the ligand is entirely predictable on the basis of studies of the prototypical system (eq 2, Table 1). For all substrates, the electron-rich (*RSSR*) ligand systems **5**, **8**, and **9** gave quantitative yields and

Table 2. Hydrogenation of Enamides Using DIOP Analogs[a]



		substrates (% ee,[b] configuration)		
no.	L	X = Me (eq 2)	X = F (eq 2)	*Z* + *E* enamide (eq 3)
1	**1**	68 (*S*)	71 (*S*)	92 (*S*)
		57 (*S*)[c]	50 (*S*)[c]	87 (*S*)[c]
2	**2**	~0	11 (*S*)	6 (*R*)
3	**3**	93 (*R*)	97 (*R*)	96 (*R*)
4	**4**	93 (*S*)	94 (*S*)	77 (*S*)
5	**5**[d]	99 (*R*)	98 (*R*)	96 (*R*)
6	**6**	81 (*R*)	88 (*R*)	76 (*R*)
		74 (*R*)[c]		
7	**7**	4 (*R*)	2 (*R*)	6 (*S*)
8	**8**	98 (*R*)	96 (*R*)	98 (*R*)
9	**9**	99 (*R*)	99 (*R*)	98 (*R*)

[a] See footnote 13 and Supporting Information for details. In CH_2Cl_2 at 20 psi with BF_4^- as the counterion, unless otherwise specified. [b] ee determined by GC. [c] In MeOH. [d] SbF_6 and PF_6 ions also gave comparable ee's.

(15) For Rh-catalyzed reactions, see: (a) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169. (b) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931. (c) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012. (d) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429. Hydrocyanation reactions: Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869.

(16) Prepared according to the procedure described by Burk et al.: Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084.

excellent selectivities where as the (*SSSS*)-**2** and the electron-deficient (*RSSR*)-**7** produced near-racemic products.

The striking deterioration of enantioselectivity in the case of **7** (*RSSR*) as compared to **6** (*RSSR*) deserves further comment. While **6** is one of the better ligands (highest ee, 88%), **7** uniformly gives low ee's (<4%). Since the chirality of the backbone is the same in both cases, and both aromatic substituents have bulky groups in the *m*-positions (P[(3,5-Me_2-C_6H_3)]$_3$ and P[3,5-$(CF_3)_2$-C_6H_3]$_3$), one has to necessarily invoke an electronic effect as the cause of this deterioration of selectivity. The exact nature of this effect, whether it is a consequence of equilibrium shifts among the diastereomeric Rh−enamide complexes[15d] or of changes in kinetics of oxidative addition of hydrogen to these complexes, remains to be established. The latter assumes the Halpern mechanism[17] for enamide reduction, in which oxidative addition of H_2 to the initially formed diastereomeric complexes(s) is the rate-determining step. In itaconate reduction, the ligand electronic effects appear to alter the equilibrium between the olefin−Rh complexes.[15d]

A very simple-minded explanation for the low selectivity of **2** compared to that of **1** or **5** would start with an examination of the ground state confirmation of the Rh^+-(L)(**1**) X^-.[18] The methyl groups in **5** (*RSSR*) are in a quasiequatorial orientation and reinforce *one* stable ground state conformation for the corresponding precatalyst (Figure 2). In **2** (*SSSS*), the quasiaxial orientation of the two methyl groups destabilize this conformation, possibly resulting in the intervention of others. Attendant effects would be felt in the key diastereomeric Rh−enamide complexes and ensuing transition states. Unless there are *huge* differences in the rates of oxidative addition of hydrogen between these diastereomers, the reduction of the intrinsic differences in the energies among these intermediates could result in a deterioration of selectivity.

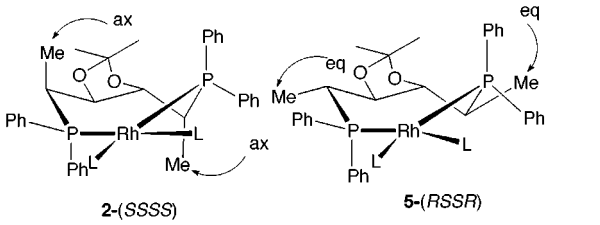


Figure 2. Effect of α-substitution in (*SS*)-DIOP ligand(s). The λ-conformations are based on known X-ray structures of (*SS*)-DIOP complexes.[18]

In summary, we have evaluated the effect of various electronic and steric parameters on the ability of DIOP to function as a ligand in an important Rh-catalyzed asymmetric hydrogenation reaction. Introduction of methyl or ethyl groups, in an orientation where the conformational flexibility of the precatalyst is diminished, seems to result in a dramatic improvement (53 to 99% ee in a typical case) on the enantioselectivity of the reaction. An electron-deficient phosphorus, even on the best ligand scaffolding, leads to nearly racemic products.

Acknowledgment. This work was supported by EPA/NSF Program for Environmentally Benign Synthesis (R826120-01-0) and NSF (CHE-9706766 and CHE-0079948).

Supporting Information Available: Details of the synthesis of ligands **3**, **4**, **5**, **6**, **7**, **8**, and **9**. Typical chromatograms of *crude* products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. For a highly readable summary of the mechanism of Rh-catalyzed asymmetric hydrogenation, see: Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 121.

(18) Based on X-ray structures of Rh^+(DIOP)(norbornadiene)[18a] and Pd-(DIOP)(ethylene).[18b] (a) Knowles, W. S.; Vineyard, B. D.; Sabacky, M. J.; Stults, B. R. In *Fundamental Research in Homogeneous Catalysis*; Ishii, Y.; Tsutsui, Eds.; Plenum: New York; Vol. 3, p 537. (b) Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *Organometallics* **1988**, *7*, 1761. For a discussion of a related conformational change due to an α-substituent in an aminophosphine ligand, see: Pavlov, V. A.; Klabunovskii, E. I.; Struchkov, Y. T.; Voloboev, A. A.; Yanovsky, A. I. *J. Mol. Catal.* **1988**, *44*, 217, especially pp 218−220.