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Ligand Tuning in Asymmetric Catalysis: Mono- and Bis-Phospholanes for a Prototypical Pd-Catalyzed Asymmetric Allylation Reaction

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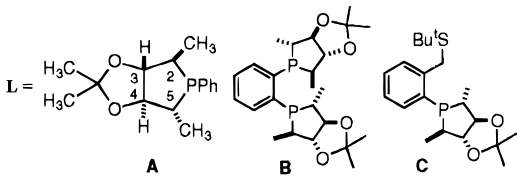
ABSTRACT



• Also diastereomers of **A**, **B** and **C** with C_2 and C_5 centers inverted. Excellent isolated yields (up to 99%) and ee's (up to >99%) in the asymmetric allylation.

Enantioselectivities and yields comparable to the best catalysts reported previously can be achieved in the addition of potassium dimethyl malonate to diphenylallyl acetate by the use of Pd(0) complexes of bis-phospholanes prepared from D-mannitol. By appropriate changes in the C_2–C_5 substituents, rare example of a useful *monophosphine* can also be prepared by a similar route. In both instances chirality of C_3 and C_5 oxygen seems to play a crucial role in the asymmetric induction.

By virtue of their relative abundance in enantiomerically pure form and their immense stereochemical diversity, monosaccharide derivatives continue to attract attention as ligand precursors.[1−3] A number of recent publications[2,3] have dealt with the utility of D-mannitol as a valuable starting material for the synthesis of a variety of phospholanes including analogues of the versatile DuPhos ligands.[4,5] We also reported[3] the synthesis of a number of C_2-symmetric monophospholanes, some carrying hemilabile groups.[6] In this paper we disclose the applicability of these ligands for Pd-catalyzed asymmetric allylation reactions. The enantioselectivity imparted by these ligands depends critically on the nature and relative stereochemistry of the various substituents

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(5) For other modifications of the phospholane scaffolding, see: (a) Hitchcock, P. B.; Lappert, M. F. Yin, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1598. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131. (c) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (d) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813 and references therein. See also ref 2.

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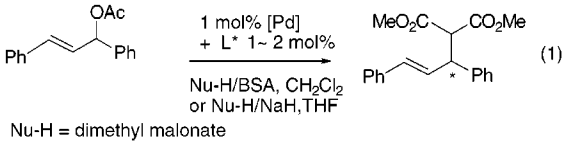
on the phospholane ring. By judicious choice of these groups, enantioselectivities approaching 100% can be achieved in a prototypical allylation reaction. Significantly, we also find that for this reaction a similar functionalization of simple monodentate 1-phenyl-2,5-dimethylphospholane leads to a set of ligands with activity and selectivity comparable to the best *monophosphines* known previously. The importance of this discovery is highlighted by the fact that with a few notable exceptions[7] monodentate ligands generally perform poorly in enantioselective catalysis. Yet, several useful asymmetric reactions[8] such as formate reduction of allylic esters,[8a] hydrosilylation,[8b] heterodimerization of olefins,[8c,d] and enantioselective acylation[5d] are carried out with monodentate ligands.

For the initial evaluation of the new ligands we chose the palladium(0)-catalyzed addition of dimethyl malonate to (*E*)-1,3-diphenylprop-2-enyl acetate (eq 1),[9] principally for two



reasons: (a) this transformation is the best known allylation reaction, whose mechanistic and synthetic aspects have been studied in considerable detail; (b) the reaction has been carried out with a wide variety of mono- and bidentate ligands carrying phosphorus, nitrogen, and other donor groups, thus enabling a direct comparison of the efficacy of different ligand systems. Besides, many successful ligands developed for this reaction have been found to have broader applicability in other related reactions.[10]

A list of functionalized phospholane ligands readily prepared from D-mannitol is shown in Figure 1.[3,11] They fall into three categories: C_2-symmetric bis-phospholanes (**2** and **3**), C_2-symmetric monophospholanes (**5** and **6**), and monophospholanes with a pendant SBu^t group (**8** and **9**). To gauge the effect of the substituents on the phospholane ring, the enantioselectivity obtained with the parent ligand systems without the oxygen substituents (**4**, **7, 10**) was also examined. From one of the readily available intermediates we also

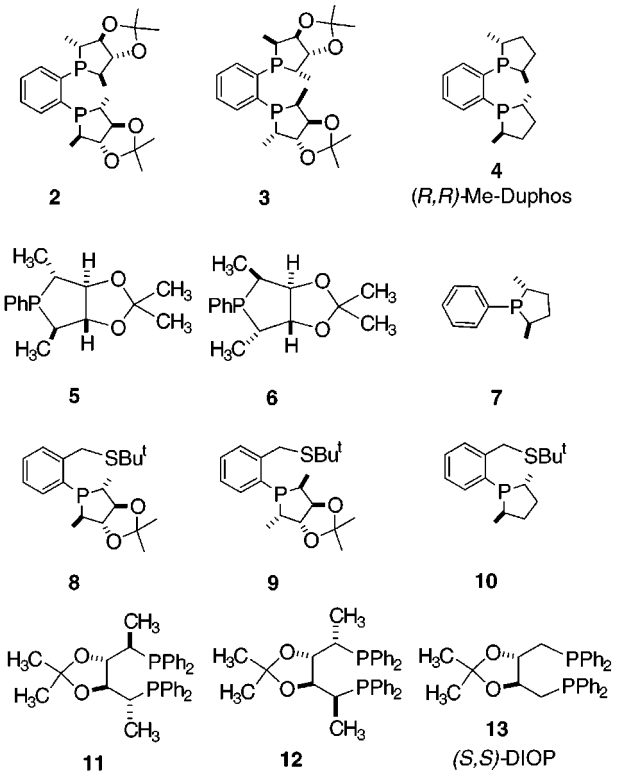


Figure 1. Functionalized phospholanes and phosphines for Pd(0)-catalyzed allylation.

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(10) For a complete listing of the ligands used, see refs 9a−c.

(11) While our studies were in progress, Zhang et al.[2c] reported the synthesis of ligand **3** and application of one of its derivatives to Rh(1)-catalyzed asymmetric hydrogenation.

prepared a new dimethyl analogue (**11**) of the historically important DIOP ligand (**13**)[12] in order to probe the effect of substituents on the carbon α to the chelating phosphorus atoms.

The new phospholanes and phosphines are excellent ligands for the Pd(0)-catalyzed allylation of dimethyl malonate with isolated yields of products greater than 95% in most cases. Typically the reaction is carried out with 1 mmol of the substrate, 3 equiv of dimethyl malonate, and bis-(trimethylsilyl)acetamide in the presence of a catalytic amount of potassium acetate and 1 mol % of Pd (as $[Pd(allyl)Cl]_2$) using a ligand-to-metal ratio of 1:2. Under these conditions[13] the reaction was complete in less than 2 h at room temperature. The enantioselectivities (ee) of the product were determined by HPLC analysis on a Daicel Chiracel-OD-H column where base-line separation of the enantiomers was observed. The enantioselectivity depends on the substitution pattern of the phospholane ring and to some extent on the reaction conditions.[13] Selected values are shown in Table 1, and a more complete listing is included in the Supporting Information.

Table 1. Enantioselectivity in Pd(0)(L)-Catalyzed Allylations of Dimethyl Malonate. Effect of Substituents on Phospholane and DIOP Ligands[a]

no.	ligand	solvent	L/Pd	yield, %	% ee[b]
		Bisphospholanes			
1.	**2** (*RSSR*)	THF	1.6	98	94 (*S*)
2.	**2** (*RSSR*)	toluene	1.6	99	85 (*S*)
3.	**3** (*SSSS*)	CH_2Cl_2	1.6	98	>99 (*R*)[e]
4.	**3** (*SSSS*)	THF	1.6	99	>99 (*R*)[e]
5.	**4** (*RR*)	THF	2	99	97 (*S*)
		Monophospholanes			
6.	**5** (*RSSR*)	THF	1	96	29 (*R*)
7.	**5** (*RSSR*)	THF	4	98	79 (*R*)
8.	**5** (*RSSR*)	toluene	2	99	94 (*R*)[c]
9.	**6** (*SSSS*)	toluene	2	98	93 (*S*)[c]
10.	**7** (*RR*)	toluene	2	96	37 (*R*)
		Monophospholanes with Pendant *t*-BuS Group			
11.	**8** (*RSSR*)	CH_2Cl_2	1.1	99	44 (*S*)
12.	**9** (*SSSS*)	CH_2Cl_2	1.1	98	60 (*R*)
13.	**10** (*RR*)	CH_2Cl_2	1.1	97	31 (*S*)
		DIOP Analogues			
14.	**11** (*RSSR*)	CH_2Cl_2	2	98	~0
15.	**12** (*SSSS*)	CH_2Cl_2	2	92	63 (*S*)
16.	**13** (*SS*)	CH_2Cl_2	1.3	95	~0[d]

[a] See eq 1, text, and Supporting Information for experimental details. [b] ee's determined by HPLC on Daicel Chiracel OD-H column, hexane/2-propanol 98:2, 0.5 mL/min flow. [c] Reaction done at −15 °C, 18 h. [d] From the literature, see refs 12c−e. [e] $[\alpha]^{20}_D = +22.3$ ($c = 1.8$, $CHCl_3$); lit. $[\alpha]^{20}_D = +22.4$ ($c = 1.8$, $CHCl_3$). [Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769].

Among this series, the bis-phospholanes **2** and **3** are the best ligands for the allylation, giving ee's of 94% (*S*) and >99% (*R*), respectively. The (*RSSR*)-ligand **2** gives the major product having the same absolute configuration as the unsubstituted 2,5-dimethylphospholane, (*RR*)-DuPhos (**4**). The sense of asymmetric induction appears to be dictated by the absolute stereochemistry of the *P*-carrying carbons. Thus, the (*SSSS*)-ligand **3** gives the major product of opposite configuration. It is gratifying to note that *both* enantiomers of the product can thus be produced from ligands that originate from natural D-mannitol. Thus, in the case of the bis-phospholanes, the additional substitution around the phospholane brings about only marginal improvement (entries 4 and 5, **3** vs **4**, for example) in selectivity. In sharp contrast, for the monophospholanes, a substantial improvement of ee was observed when the 3,4-positions of the parent **7** are substituted with oxygen (entries 7−9 vs entry 10). The selectivity improves from 37% ee to 94% ee! Curiously, the sense of asymmetric induction is opposite to what has been observed for the configurationally related bis-phospholanes **2** and **3**. In all cases, the sense of induction is controlled by the chirality of the C2 and C5 atoms. As expected, a 2:1 stoichiometry of ligand to metal is absolutely essential when the monophosphines are employed (entries 6 vs 7 or 8). Of all the *monophosphines* described in the literature, only Zhang's phosphabicyclo[2.2.1]heptane ligand[7c] gives enantioselectivity better than what is observed with **5** or **6**.

Hybrid ligands containing chelating phosphorus and heteroatoms (N, S) have been used with remarkable success in asymmetric Pd-catalyzed allylation reactions.[9] Almost invariably, chirality of these ligands has its origin in the backbone of the ligand. In this context ligand **10** represents a new structural motif with the chirality resident on the phosphorus atom. As shown in entries 11−13, no substantial improvement of the parent ligand **10** was observed with the type of structural changes described earlier for **7**. In sharp contrast, improvements in the classical ligand DIOP (which gives nearly 0% ee in allylation reactions[12c−e]) can be achieved, if the appropriate diastereotopic α-hydrogens (i.e., α to the

(12) (a) DIOP (2,2-dimethyl-1,3-dioxalane-4,5-diylbismethylene)bis-diphenylphosphine): Dang, T.-P.; Kagan, H. B. *J. Chem. Soc., Chem Commun.* **1971**, 481. See also: Kagan, H. B. Chiral Ligands for Asymmetic Catalysis. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, pp 1−39. (b) Another analogue, **12**, has already been described in the literature: Kagan, H. B.; Fiaud, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923. DIOP itself gave nearly racemic products in the allylation reaction, see: (c) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (d) Robert, F.; Gaillard, N.; Sinou, D. *J. Mol. Catal. A.; Chem.* **1999**, *144*, 473. (e) Reference 9o.

(13) **General Procedure for Palladium-Catalyzed Allylic Alkylation.** Reaction conditions adapted from ref 9e. In the drybox, a mixture of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.8 mg, 1 mmol %) and the ligand (**5**, 5.3 mg, 2 mmol %) in 1 mL of anhydrous toluene was stirred at room temperature. After 30 min, a solution of 1,3-diphenylprop-3-en-1-yl acetate (252 mg, 1 mmol) in 1 mL of the same solvent was added, and stirring was continued for 20 min. Then dimethyl malonate (0.34 mL, 3 mmol), *N*,*O*-bis(trimethylsiyl)-acetamide (BSA, 0.74 mL, 3 mmol) and a catalytic amount of potassium acetate (KOAc) were subsequently added. The resulting solution was stirred at room temperature and monitored by TLC for the disappearance of 1,3-diphenylprop-3-en-1-yl acetate. After reaction, the mixture was taken out of the drybox. Then 10 mL of Et_2O was added and the organic layer was washed twice with saturated NH_4Cl solution and dried over $MgSO_4$. After evaporation, the crude product was purified by column chromatography on silica gel (CH_2Cl_2/hexane, 1/1, v/v) to afford the malonate product in nearly quantitative yield. The enantiomeric excess was determined by HPLC. For dimethyl (1,3-diphenylprop-2-en-1-yl)malonate: Chiralcel OD-H column, eluent hexane/PrOH 98/2, flow rate 0.5 mL/min. For diethyl (1,3-diphenylprop-2-en-1-yl)malonate: OJ column, eluent hexane/PrOH 95/5, flow rate 0.5 mL/min. Some variations of ee's as a function of solvent, temperature, and the nature of the nucleophile were observed. For a more complete listing of reactions examined, see Supporting Information.

chelating phosphorus) are substituted by methyl groups. The (*RSSR*)-derivative **11** is no better than the parent **13** (~0% ee); yet the (*SSSS*)-derivative **12** gives 63% ee.

Even though the modifications of **10** and **13** are of marginal synthetic value in the present context, the principles they illustrate may have broader implications for the design of better catalysts for other reactions.

We are currently exploring other applications of these ligands and their derivatives.

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Supporting Information Available: Tables of data detailing the effects of solvent, temperature, stoichiometry of reagents, and the nature of the nucleophile on the enantioselectivity in allylation reactions using ligands **2**, **3**, **5**, **6**, **8**, **9**, **11**, and **12**. Typical chromatograms of *crude* products. This material is available free of charge via the Internet at http://pubs.acs.org.

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