Substituent Effects of Ligands on Asymmetric Induction in a Prototypical Palladium-Catalyzed Allylation Reaction: Making Both Enantiomers of a Product in High Optical Purity Using the Same Source of Chirality

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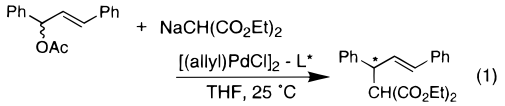
The substituent effects of the ligands **1** through **8** play a crucial role in determining the enantioselectivity in the palladium-catalyzed asymmetric allylation reaction between 1,3-diphenylprop-2-en-1-yl acetate and the sodium salt of diethyl malonate. For a given chirality of the backbone, electron-deficient and electron-rich ligands generally gave opposite enantiomers, while sterically hindered ligands had the same enantioselectivity as electron-rich ligands. In the case of flexible backbones with ligands of comparable size, a variation of the enantioselectivity with the electronic properties of the ligand is predictable. In ligands with rigid backbones, the steric effects of the substituents appear to play a more decisive role, and caution should be exercised in interpreting the role of electronic effects in such cases. Examples are provided for maximizing both the chemical yield and the enantioselectivity of the allylation reaction through the tuning of the electronic properties of the ligands. In selected cases, the major sense of the asymmetric induction could be reversed solely by changing the electronic properties of the ligands. Bisphosphinites from (*R*)-(+)-1,1′-bi-2-naphthol (BINOL) can be tuned to produce both (*R*)- and (*S*)-products in 80 and 87% ee, respectively. Stoichiometric reaction of complexes **10e*** and **10j*** with the sodium salt of diethyl malonate gave malonate adducts with enantiomeric excesses in agreement with those obtained under the catalytic conditions. Also reported are the details of an NMR study of the Pd-(η^3-1,3-diphenylallyl)bis-diphenylphosphinite and the corresponding bis-dicyclohexylphosphinite complexes **10e*** and **10j***.

Introduction

Until recently, strategies for controlling enantioselectivity in metal-catalyzed asymmetric reactions have depended largely on the design and application of chiral ligands that would provide optimum steric matching between the catalyst and the substrate(s).[1] Increasingly, new examples of asymmetric reactions which employ electronic tuning of ligands as a control element are beginning to appear in the literature.[2−5] We have successfully used this approach in several key asymmetric reactions including hydrocyanation,[2d,3] hydrogenation,[4] and hydroformylation[5] reactions. The origin of the enhanced enantioselectivity remains uncertain in these cases due to the problems associated with studying the catalytically relevant intermediates.[6] In contrast, for the palladium-catalyzed asymmetric allylation reaction (eq 1), a direct correlation between well-characterized intermediates and the chirality of the products has been established.[7] With the hope that a study of the role of



(1)

ligand electronic effects in this reasonably well-delineated system could have broader implications for the design of asymmetric catalysts, we undertook a systematic study of a variety of chiral backbones which could be modified with chelating atoms of varying electron density.

The palladium-catalyzed asymmetric allylation has been employed for a variety of C−C and C−N bond-

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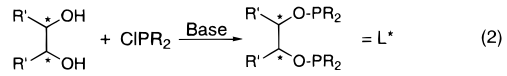
forming reactions. Using carefully designed chiral ligands, high enantioselectivities have been achieved for the reactions with a prototypical substrate, 1,3-diphenylallyl acetate, and a number of soft nucleophiles.[7−18] Even though chelating ligands with widely different donor−acceptor properties (e.g., P/P, N/N, P/S, P/N) have been successfully employed for this reaction, a systematic study of the variation of electronic effects in truly C_2-symmetric ligands has not been carried out before. In this context, note that our goal was to keep the two ligating atoms in strictly identical steric environments, so that the variations in enantioselectivity could be reliably attributed to electronic effects. We have examined the electronic effects for a variety of chiral backbones with the goal of achieving practical levels of asymmetric induction by electronic tuning of readily available ligands, prototypes of which are diethyl tartrate and binaphthol. We report here the first examples of the predictable dependence of enantioselectivities on ligand electronic effects in Pd-catalyzed allylation reactions. Also reported is a rare example of the switching of the sense of chiral induction by changes in the nonchiral substituents of a C_2-symmetric ligand. A careful structural investigation of the intermediates by NMR rules out at least one principal mechanism, viz., the intermediacy of geometric isomers arising via π-σ-π interconversion, for this dichotomy. The finding that the π-allyl Pd intermediates produced under stoichiometric or catalytic conditions react with the malonate nucleophile to give essentially identical enantioselectivity further supports the relevance of such a mechanistic investigation.

Results and Discussion

We examined several C_2- or pseudo-C_2-symmetric diols as precursors of the chiral backbones (Figure 1). These were easily converted into bisphosphinites by reaction with a chlorophosphine (eq 2). Reactions of (*E*)-1,3-



(2)

diphenylprop-2-en-1-yl acetate with sodium diethyl malonate were carried out in THF at 25 °C in the presence of a mixture of 0.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and 1.2−1.4 mol % of the corresponding bisphosphinite (eq 1), and the products were analyzed by HPLC. The bisphosphinites are in general excellent ligands for the allylation reaction. In many cases the yields of the reaction are nearly quantitative.

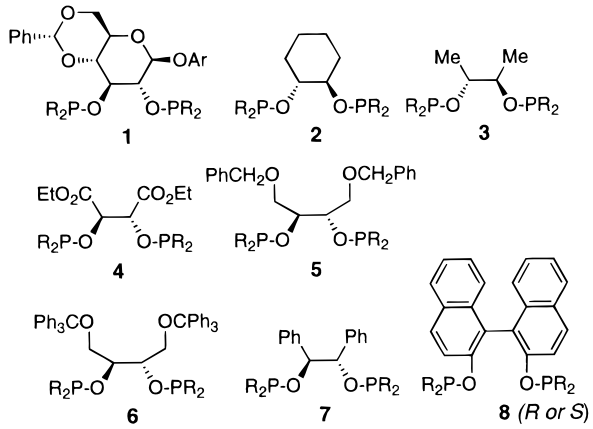


Figure 1. Chiral phosphinites.

entry	R
a	3,5-$(CF_3)_2C_6H_3$
b	3,5-$F_2C_6H_3$
c	4-$(CF_3)C_6H_4$
d	4-FC_6H_4
e	Ph
f	3,5-$Me_2C_6H_3$
g	3,5-$(TMS)_2C_6H_3$
h	3,5-(t-Bu)$_2$-4-(MeO)C_6H_2
i	Et
j	Cy

Figure 2. Substituents on phosphorus.

Table 1. Electronic and Steric Effects on Enantioselectivity using Various Substituents on Phosphorus with Ligand 1

entry	R[a]	ee (%)[b]	config.[c]
1	3,5-$(CF_3)_2C_6H_3$	39	(*R*)
2	3,5-$F_2C_6H_3$	41	(*S*)
3	4-$(CF_3)C_6H_4$	55	(*S*)
4	4-FC_6H_4	17	(*S*)
5	Ph	∼0	
6	3,5-$Me_2C_6H_3$	∼0	
7	3,5-$(TMS)_2C_6H_3$	16	(*R*)
8	3,5-(t-Bu)$_2$-4-(MeO)C_6H_2	25	(*R*)
9	Et	18	(*R*)
10	Cy	59	(*R*)

[a] Ar of **1** was phenyl except entry 1 in which 2-naphthyl was applied. [b] Determined by HPLC analysis with a chiral column (Daicel OJ). [c] Determined by comparison with an authentic (*R*) sample prepared by a reaction with (*S*,*S*)-CHIRAPHOS.

First, we examined the role played by electronic effects on the enantioselectivity of the reaction using rigid pseudo-C_2-symmetric, glucose-derived ligands represented by the generic structure **1** (Figure 1).[17] In previous work, this ligand backbone had been successfully used in asymmetric hydrocyanation and hydrogenation reactions.[3,4] Systematic changes of the nonchiral substituents of **1** at the phosphorus atoms (Figure 2) leads to both (*R*)- and (*S*)-enantioselectivities, although the enantioselectivity remains modest (Table 1). The unsubstituted diphenylphosphinite and the corresponding 3,5-$Me_2C_6H_3$-substituted phosphinite gave almost racemic product

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Table 2. Electronic and Steric Effects for Enantioselectivity Using 2−8 with Various Substituents on Phosphorus[a]

	substituent	backbone						
entry	R[b]	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	3,5-$(CF_3)_2C_6H_3$	21 (*S*)	19 (*S*)	73 (*R*)	∼0	77 (*R*)	48 (*S*)	11 (*S*)
2	4-$(CF_3)C_6H_4$	25 (*R*)	8 (*R*)	51 (*R*)	31 (*S*)	45 (*R*)	23 (*R*)	47 (*R*)
3	Ph	7 (*S*)		13 (*S*)				63 (*R*)
4	Cy	18 (*R*)	15 (*R*)	41 (*S*)	∼0	54 (*R*)	∼0	66 (*S*)

[a] Each result contains enantioselectivity of the product (absolute configuration) as determined by HPLC analysis with a chiral column (Daicel OJ). [b] The R substituents are placed in the increasing order of ligand electron density.

(∼0% ee, Table 1, entries 5 and 6), while the ligands with aromatic rings having electron-withdrawing groups generally yielded (*S*)-enantioselectivity (Table 1, entries 2−4), with an exception of the 3,5-$(CF_3)_2C_6H_3$-substituted phosphinite (Table 1, entry 1). Since there is good correlation between electron-deficiency of the ligands and the (*S*)-enantioselectivity, we suspect that in the case of the 3,5-$(CF_3)_2$-substituted aromatic rings, the electronic effects could play a secondary role to steric effects. A trifluoromethyl group is reasonably large, having roughly the same size as an isopropyl group.[19] To probe the effect of bulky meta-substituents we prepared the 3,5-$(TMS)_2C_6H_3$ and 3,5-(*t*-Bu)$_2$-4-(MeO)C_6H_2 ligands which are electronically different from the CF_3-substituted ligand. As expected, these ligands showed the same sense of asymmetric induction (Table 1, entries 7 and 8) as the 3,5-$(CF_3)_2C_6H_3$ ligand. In light of these results, we believe the steric bulkiness of the trifluoromethyl group led to (*R*)-enantioselectivity rather than the (*S*)-enantioselectivity predicted for an electron-deficient ligand. We have previously observed such abnormal behavior for the bis-3,5-(trifluoromethyl)phenyl substituents in Rh-catalyzed hydrogenation reactions.[4] A clear indication that electronic effects can be used to enhance the selectivity of the (*R*)-enantiomer is shown in entries 9 and 10 in Table 1. Diethylphosphinite (Table 1, entry 9), which is presumably smaller than diphenylphosphinite (*A* values Et = 1.8; Ph = 2.8), yet more electron-rich, gave a modest (*R*)-enantioselectivity. Making the ligand electron-rich and bulkier leads to better enantioselectivity, for example, in the dicyclohexylphosphinite (*A* value 2.2, Table 1, entry 10). These initial results prompted us to examine the generality of these electronic effects using a number of well-known and readily available ligand scaffolds. The results are shown in Table 2.

As shown in Table 2, in each case, the enantioselectivity is affected by the substituents on phosphorus. The phosphinites **2** derived from (1*R*,2*R*)-cyclohexane-1,2-diol were examined as a simpler analogue of **1**. Considering this backbone has the opposite configurations at its chiral centers in comparison to **1**, we obtained selectivities similar to **1**, except for the dicyclohexyl phosphinite. Even though the selectivities are poor in the case of **2**, since both (*R*)- and (*S*)-products are obtained, these results confirm that the unexpected electronic effects are not simply caused by the pseudo-C_2-symmetric nature of the sugar backbone. On the basis of our previous studies on asymmetric hydrogenation of dehydroamino acids we had indeed expected, lower enantioselectivities with the cyclohexyl-1,2-phosphinites (**2**) vis-à-vis the sugar phosphinites (**1**).[4c] The selectivity observed with the 3,5-$(CF_3)_2C_6H_3$-substituted bisphosphinite ligand (**2a**) was opposite to what was seen for the other electron-deficient ligands, indicative of the dominance of steric effects over electronic effects for the 3,5-$(CF_3)_2C_6H_3$ substituents.

Table 3. Electronic and Steric Effects for Enantioselectivity Using 4 and 8 with Various Substituents on Phosphorus[a,b]

		substituent	backbone	
entry	label[c]	R[d]	**4**	**8**
1	a	3,5-$(CF_3)_2C_6H_3$	96% 73% ee (*R*)	6% 11% ee (*S*)
2	b	3,5-$F_2C_6H_3$	90% 71% ee (*R*)	35% 52% ee (*R*)
3	c	4-$(CF_3)C_6H_4$	38% 51% ee (*R*)	>99% 47% ee (*R*)
4	d	4-FC_6H_4	22% 5% ee (*S*)	>99% 48% ee (*R*)
5	e	Ph	46% 13% ee (*S*)	92% 63 (80) % ee (*R*)[e]
6[f]	f	Ph		81% 64% ee (*S*)[f,g]
7	g	3,5-$(TMS)_2C_6H_3$	96% 58% ee (*R*)	>99% 34% ee (*S*)
9	h	Et	49% 53% ee (*S*)	95% 30% ee (*S*)
10	i	Cy	94% 41% ee (*S*)	>99% 66 (87) % ee (*S*)[e]
11[f]	j	Cy		82% 73% ee (*R*)[f,g]

[a] Each result contains enantioselectivity of the product (absolute configuration) and the isolated yield of the product **1**. [b] The enantioselectivity was determined by HPLC analysis using a CHIRALCEL OJ column (Daicel). [c] See Figure 2 for substituents. [d] The R substituents are placed in the increasing order of ligand electron density. [e] The numbers in the parentheses were obtained at −30 °C. [f] The stoichiometric reactions were performed with (*S*)-BINAPO as the backbone. [g] The reaction was performed using a stoichiometric amount of [Pd(η^3-PhCHCHCHPh)(L*)]SbF_6 complex.

Of the other readily available ligands, L-(+)-diethyl tartrate based phosphinites **4** and (*R*)-(+)-binaphthol based phosphinites **8** gave the most promising results and these ligands were chosen for a detailed study of electronic and steric effects in the allylic alkylation reaction.

Diethyl tartrate is one of the most abundantly available chiral precursors. Both enantiomers have been used extensively in asymmetric synthesis. It is more flexible than backbones **1** and **2** (and possibly **8**), and the electronic effects appear to be more pronounced and predictable in this system.[20] The diphenylphosphinite substituted ligand gave 13% ee (*S*) (Table 3, ligand 4, entry 5). In comparison with this result, electron-withdrawing substituents on aromatic rings consistently increased the proportion of the (*R*)-enantiomer (Table 3, entries 1−5) in a predictable fashion as the electron density[3a] at the phosphorus decreased. The 3,5-$(CF_3)_2$ phenyl phosphinite (Table 3, entry 1) gave the highest

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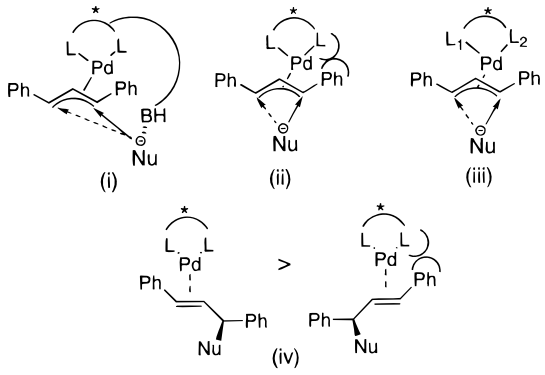
(20) We have previously seen that in Rh-catalyzed asymmetric hydrogenation of dehydroamino acids, conformationally flexible ligands show more pronounced, and often predictable, electronic effects. See refs 4b and 4c.

ee. Note the switch of the sense of chiral induction and enhancement of the enantioselectivity in going from the diphenyl derivative (13% ee *S*) to the 3,5-$(CF_3)_2C_6H_3$ derivative (73% ee *R*). Thus by tuning the electronic properties of this readily available ligand system, one is able to get better yields and nearly the same selectivity achieved by the unstable and synthetically more complex tartrate-derived TADDOP ligand.[15] Note that the 3,5-$(CF_3)_2$-substituted aromatic rings did not appear to cause a switching of the sense of enantioselectivity with this backbone compared to the electronically similar 3,5-F_2-substituted ligand, as was seen with ligands **1** and **2**. The trifluoromethyl groups therefore function as true electron-withdrawing groups with much less steric interference in the case of this ligand with a flexible backbone. In contrast, electron-rich dialkylphosphinites (Table 3, entries 9 and 10) gave increased (*S*)-enantioselectivity, up to 53% ee. The marginal difference between the bulky cyclohexyl-substituted ligand as compared to that of the ethyl derivative is more difficult to interpret. These results clearly indicate that by tuning the electronic properties of the ligands alone, the enantioselectivity of a reaction can be switched. However, the unexpected (*R*)-selectivity shown by bulky 3,5-$(TMS)_2$-substituted aromatic ligands demonstrate that caution should be exercised in exceptional cases.

The (*R*)-binaphthol-derived phosphinites[21] are excellent ligands for the catalytic allylation reaction, often giving quantitative yields of the products, except for the very electron-deficient ligands (entries 1 and 2 under **8**, Table 3). As in the case of ligand **1**, electron-deficient and electron-rich ligands gave opposite enantioselectivities (Tables 1 and 3). Some of the electron deficient ligands gave lower selectivities, (**8a**−**d**), and in some cases lower yields (**8a** and **8b**) as compared to the diphenylphosphinite (**8e**). The binaphthyl backbone is itself electron-withdrawing, and in the presence of additional electron-withdrawing substituents on phosphorus, coordination ability of the ligand may have been reduced resulting in poor reactions. This suggests that the appropriate electron density at phosphorus is a requirement for this reaction. Dicyclohexylphosphinite gave an ee of 66% (*S*), the highest of all electron-rich phosphinites. Note that the sense of asymmetric induction was opposite to what was observed with the corresponding diphenylphosphinite. Since these ligands impart high activity for the catalysts, we can carry out the reaction at temperatures as low as −30 °C to achieve one of the highest levels of enantioselectivity for C_2-symmetric chelating phosphine ligands (Table 3, entries 5 and 10).[9] Note that both enantiomers of the product were produced by a single chiral backbone in ee's of 80% and 87%, respectively (Table 3, ligand **8**, entries 5 and 10).

These results are summarized as follows: (a) In using ligands with flexible backbones, electronic effects can be used to enhance the enantioselectivity of an inherently poor ligand. The sense, and the extent of enantioselectivity are predictable, especially with ligands of similar steric bulk. Ligands having bulky substituents can give unpredictable results. (b) In ligands with rigid backbones, caution should be exercised in predicting the electronic effects. In these instances, bulky substituents appear to have the determining role. (c) In a given series, catalysts with electron-deficient ligands give the opposite enantiomer in comparison to catalysts with electron-rich ligands. Thus enantioselectivity can be switched by changing the electronic properties of the chelating atoms, even when the chirality of the backbone remains the same.

Scheme 1. Mechanisms for Chiral Induction in Pd-Catalyzed Allylation



Stoichiometric Allylation Reactions with Complexes 10e* and 10j*. Studying the ground-state structures of reaction intermediates would be irrelevant if it cannot also be shown that the same intermediates are involved under catalytic and stoichiometric conditions. Therefore we undertook a study of the stoichiometric allylation of complexes **10e*** and **10j*** (vide infra, eq 4). [The asterisk indicate that the (*S*)-binaphthol-derived phosphinites were used in these reactions]. The complexes **10e*** and **10j*** were prepared according to eq 4 and then reacted with an equivalent amount of sodium diethyl malonate under conditions similar to those used in the catalytic studies. The reaction with the Pd-allyl complex **10e*** proceeded to give predominantly the (*S*)-enantiomer of the malonate adduct in 64% ee (Table 3, entry 6) at room temperature. The reaction of the allyl complex **10j*** with sodium diethyl malonate gave the (*R*)-enantiomer in 73 % ee (Table 3, entry 11). The catalytic and the stoichiometric results are consistent, yielding the same products in approximately the same enantioselectivity, thus giving further credence to the structural studies reported below.

Asymmetric Induction Mechanisms. It is believed that soft nucleophiles, such as the malonate anion, directly attack one of the terminal carbons of the allyl moiety from the face opposite to the coordinated palladium.[7] Thus, the chiral ligands are remote from the reacting center of the molecule and, a priori, difficulties in obtaining high enantioselectivity should be anticipated. Nevertheless, remarkable enantioselectivity has been achieved in this reaction. Mechanistic rationale for the observed enantioselectivity can be summarized as follows (Scheme 1): (i) an interaction of a ligand pendant group with the incoming nucleophile which results in preferential attack at one of the allyl terminal carbon atoms,[8] (ii) a distortion of the allylic unit caused by a steric repulsion of a ligand substituent with the allylic system,[22] (iii) an electronic differentiation of the terminal allyl carbon atoms by the trans effect resulting from

(21) Indeed diphenylphosphinite from binaphthol was one of the first chiral ligands used for enantioselective allylation of malonates. Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. These workers were also among the first to prepare the 3,5-bis-TMS-aryl derivative. It is not apparent whether the switching of the enantioselection occurred with the allylation of the cyclic substrate that was studied, the increase in selectivity notwithstanding.

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different donor−acceptor properties of the chelating atom in the square planar Pd-complex,[10,11,23] and (iv) the relative stabilities of the intermediate Pd(0)-olefin π-complexes resulting from the addition of the nucleophile to the π-allyl complexes.[13]

Mechanism i applies to only specially designed ligands, whereas mechanism ii depends on intramolecular steric effects and the attendant charge separation in the Pd−C bonds of the π-allyl Pd intermediate(s) to differentiate the π-allyl termini. In the case of mechanism iii steric as well as electronic effects are important. A lack of C_2-symmetry in the ligands can give rise to more than one intermediate complex whose reactivities determine the enantioselection. It should be noted that rationalizations ii and iii rely on typical ground-state arguments and are valid only for nucleophilic attack proceeding through an early-transition state. On the other hand, mechanism iv is based on the assumption that the reaction has a late-transition state. Although the asymmetric induction explanations conclude that the enantioselectivity is reflected in the site-selectivity of the allyl terminal carbons of thermodynamically stable (syn,syn)-allyl complexes, some uncertainty remains as to which diastereomers of the π-allyl complexes are catalytically relevant, especially when the enantioselectivity is low. For example, NMR studies have revealed that in some cases diastereomeric syn/syn and syn/anti isomers of the π-allyl intermediates can coexist in solution and these can be attacked at different rates (vide infra).[18,24,27]

After careful inspection of a series of the malonate alkylation reactions with various Pd(0)L_2 complexes and the X-ray structures of the putative intermediates, Seebach[15] proposed the following generalization: for a reaction that proceeded through the λ-conformation[26] for the allyl intermediate, the (*S*)-isomer of the product was likely to be the major one, whereas for the reaction proceeding through the δ-conformation, the (*R*)-enantiomer (Figure 3) was likely to predominate. In a recently completed study we have shown that seven-membered 1,2-bis-diarylphosphinite ligands form C_2-symmetric Ni(II) or Rh(I)-complexes whose conformations can be clearly defined by the λ/δ convention (Figure 4).[4c] We expect the Pd-complexes presented here also to behave accordingly, and the λ/δ models for the intermediates should provide a basis for the discussion of the origin of enantioselectivity in reactions of these complexes. The bis-diarylphosphinite from (*R*)-binaphthol should form a well-defined δ-chelate (Figure 3),[28] and in accordance with the empirical generalizations, the major allylation product should be the (*R*)-isomer, as has been observed. However, difficulties arise in providing a satisfactory explanation as to how, for a given chiral backbone, a ligand substituent quite removed from the coordination

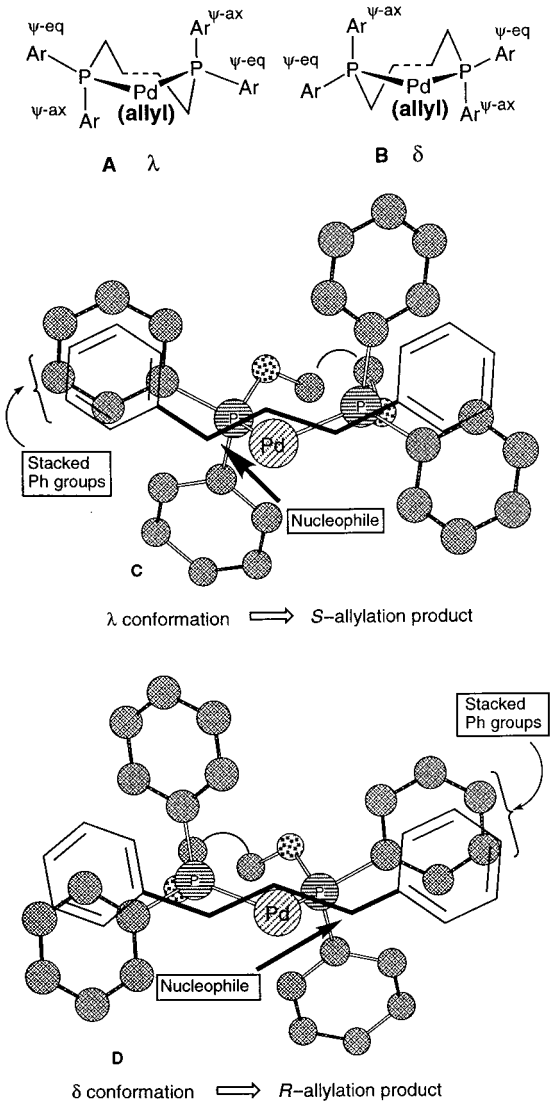

Figure 3. **A** and **B** are conformations of η^3-allylPd(II) complexes.[15] **C** and **D** are λ- and δ-conformations of C_2-symmetric [diarylphosphinite]Pd(II) complexes leading to (*S*) and (*R*) adducts.

sphere (for example, a 4-fluoro- or 3,5-difluoro-substituent on a P-aromatic ring), or a change from P-phenyl (*A* value 2.8) to P-cyclohexyl (*A* value 2.2) can bring about conformational change of a reactive diastereomer. Thus for the dramatic reversal of the selectivity, for example, in going from complex **10e** (80% (*R*)) to complex **10j** (87% (*S*)), one should look elsewhere for an explanation. Two alternate explanations can be offered for this observation. (i) The reactivities of the two allyl termini (Scheme 2, see the syn,syn complex) are different for the two different ligands. (ii) The (syn,syn)/(syn,anti) equilibrium could be different for the phenyl and cyclohexyl phosphinites (Scheme 2).[18,24,27] Nucleophilic addition at the carbon carrying an anti-phenyl group in the (syn,anti) complex would lead to the opposite enantiomer to that obtained from attack of the same carbon atom in the

(23) (a) Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679. (b) Åkermark, B.; Krakenberger, B.; Hansson, S.; Vitagliano, A. *Organometallics* **1987**, *6*, 620.

(24) Barbaro, P.; Pregosin, P. S.; Salzmann, R.; Albinati, A.; Kunz, R. W. *Organometallics* **1995**, *14*, 5160.

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(26) For definitions of λ- and δ-conformations, see: (a) Kagan, H. B. Asymmetric Synthesis Using Organometallic Catalysts. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 463. (b) Pavlov, V. A.; Klaunovskii, E. I.; Struchkov, Y. T.; Voloboev, A. A.; Yanovsky, A. I. *J. Mol. Catal.* **1988**, *44*, 217.

(27) Herrmann, J.; Pregosin, P. S.; Salzmann, R.; Albinati, A. *Organometallics* **1995**, *14*, 3311.

(28) Note that for a given backbone chirality, the δ/λ-conformations alternate in going from a seven-membered to a nine-membered chelate. Thus (*R*)-BINAP-metal chelates exhibit a λ-conformation and (*R*)-BINAPO-phosphinite complexes a δ-conformation. The same has been seen before in going from five- to seven-membered chelates. For a compilation, see ref 15. Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.

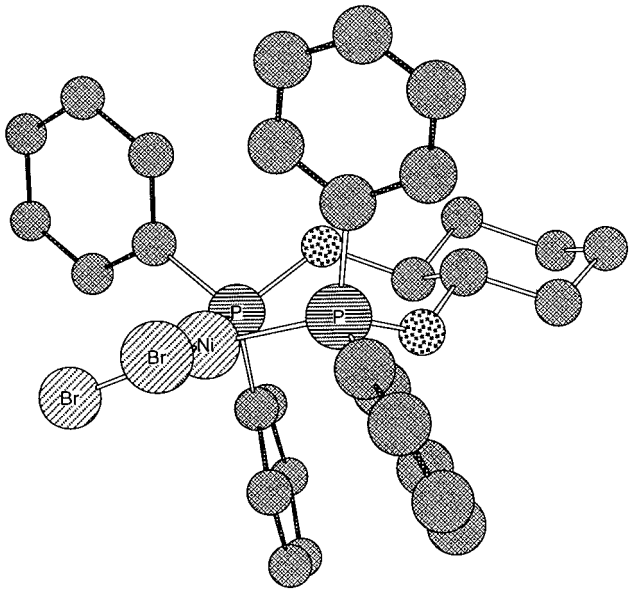
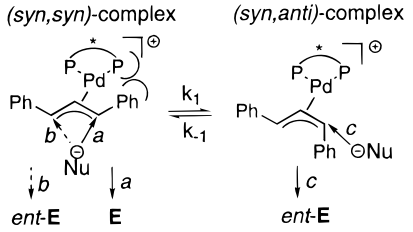
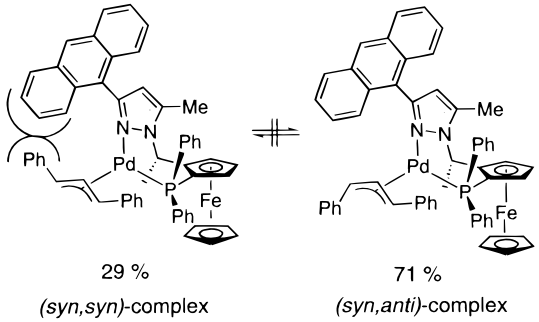


Figure 4. Crystal structure of a prototypical 1,2-bis-diarylphosphinite complex.[4c]

Scheme 2. Role of syn,syn/syn,anti Isomerization in Switching of the Enantioselectivity



Scheme 3. Formation of a syn,anti Pd(allyl) Complex



(syn,syn) complex. Each diastereomeric intermediate could react at a different rate. As long as the rate of nucleophilic addition is slower than syn,syn/syn,anti equilibration, the ratio of diastereomers need not reflect the enantiomeric ratio of the products. In one case reported by Togni (Scheme 3), a series of substituted ferrocenyl pyrazole ligands were used in a palladium-catalyzed asymmetric allylic amination reaction.[25] The reaction with a bulky 9-anthryl ligand gave 40% ee for the (*S*)-product, a result opposite to that of the other ligands substituted with methyl, phenyl, cyclohexyl, 1-naphthyl, or 2-naphthyl groups. They attributed this inversion of enantioselectivity for the 9-anthryl-substituted case to a major steric influence of the bulky substituent on the configuration of the allyl-palladium intermediate. In an NMR study of the [Pd(η^3-PhCHCHCHPh)(L*)]PF_6 complex with the 9-anthryl-substituted ligand, a mixture of two isomers was observed in solution. The minor isomer (29%) was determined to be a (syn,-syn) allyl-complex while the major isomer (71%) was a (syn,anti) allyl-complex. The ratio of the two configurational isomers (29:71) reflected the observed ratio of the enantiomers for the product of the catalytic amination (30:70). It was assumed that the nucleophile attacks the same terminal allyl carbon trans to the phosphorus in both cases. Since there was no equilibration of diastereomeric complexes on the NMR time-scale, the conclusion was reached that the ratio of the intermediate complexes did reflect the enantioselectivity of the reaction. Two other cases of the existence of syn,syn/syn,anti isomerism have also been reported.[18,24] In these cases the reactions appeared to proceed under Curtin−Hammett conditions, and the observed ratio of the diastereomers as determined by NMR (∼4:1) did not correspond to the enantioselectivity (∼95:5) of the reaction.

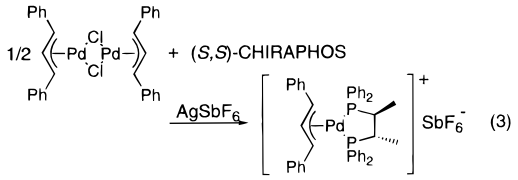
NMR Study of Allyl Palladium Bis-phosphine and Bis-phosphinite Complexes. Since the catalytic and stoichiometric reactions lead to the same level of asymmetric induction (but in opposite absolute sense) for the complexes **10e** and **10j**, it should be possible to explore, by NMR, whether differing syn,syn/syn,anti ratios of intermediates is responsible for this unusual mechanistic dichotomy and the following studies address this issue.

In enantioselective Pd-catalyzed allylation reactions, analysis of ground-state properties of intermediates has been used successfully to predict the sense, if not the absolute value, of the enantioselectivity.[7] In this connection, NMR methods have been used extensively. The analysis of the data from a variety of 1- and 2-D NMR experiments giving both scalar (*J*, in hertz) and through-space coupling (NOE) information can provide a remarkably clear picture of the solution structure of the intermediate Pd-complex(es).[7d,29] We undertook a detailed NMR study of the solution structures of the bis-phosphinite complexes **10e*** ([Pd(η^3-PhCHCHCHPh)((*S*)-**8e**)]-SbF_6) and **10j*** ([Pd(η^3-PhCHCHCHPh)((*S*)-**8j**)]SbF_6) in order to probe the origin of the unprecedented switching in the alkylation selectivity when the P-substituent of the BINAPO ligand was changed from phenyl to cyclohexyl [(Table 3, ligand **8**, entries 6 and 11); note that the stoichiometric reactions and the NMR studies were carried out with the (*S*)-BINAPO series of ligands, and that these ligands and their complexes are indicated by an asterisk (for example, **8e***, **8j*** and **10e***, **10j***) next to the number.] For comparison purposes, and to ascertain our ability to detect all diasteromeric Pd(II)-complexes (including any syn,anti isomers of the η^3-1,3-diphenylallyl complex) involved in the reaction, we also studied the intermediate(s) from (*S*,*S*)-CHIRAPHOS, a ligand that provided ee's comparable to our system.[30] When we started this work, there was only one report of a [Pd(η^3-PhCHCHCHPh)(L*)]X complex with a C_2-symmetric chiral phosphine ligand.[24] Several systems described previously had an asymmetric allyl component

(29) (a) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev.* **1996**, *115*, 35. (b) Pregosin, P. S.; Trabesinger, G. *J. Chem. Soc., Dalton Trans.* **1998**, 727.

(30) Since there was a discrepancy in the ee values reported for the allylation of dimethyl malonate (22%[7b] vs 90%[9]) using (*S*,*S*)-CHIRAPHOS as a ligand, we repeated the reaction (with diethyl malonate, the substrate under our study) and observed ee's of 75% (*R*) in THF at room temperature.

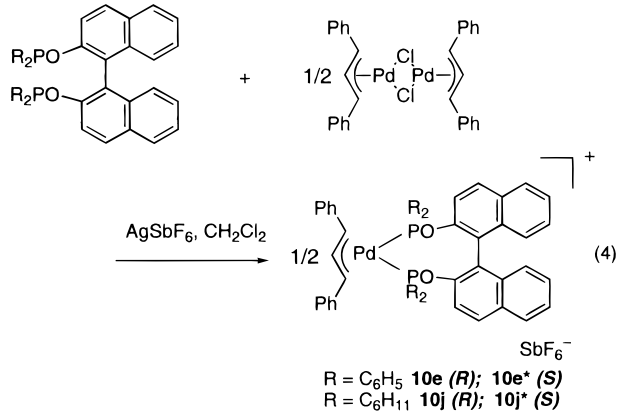
like η^3-β-pinene,[31−34] η^3-methylallyl,[35] or an η^3-exomethylenecyclopentene allyl moiety.[32] Alternatively, the reported complexes contained an asymmetric, mixed chelate ligand with P/S,[36] N/S,[37] or P/N donor atoms.[7d,11]



9

The complex **9** ([Pd(η^3-PhCHCHCHPh)[(*S*,*S*)-CHIRAPHOS]SbF_6), a red solid, was prepared according to eq 3. The ^{1}H, ^{13}C, and ^{31}P NMR spectra are included in the Supporting Information. Surprisingly, the coupling pattern, and to some extent, the chemical shifts in both the ^{31}P and ^{1}H spectra of this complex are highly dependent on the solvent and the concentration of the complex in solution. For example, the ^{31}P{^{1}H} NMR spectrum of the crude material (32 mg) in $CDCl_3$ solution (ca. 1 mL) at 30 °C contained a singlet at 49.14 ppm. The crude complex **9** was purified by reprecipitation from dichloromethane. Visible in the ^{31}P{^{1}H} NMR spectrum of this pure complex (ca. 10 mg in 1 mL) was an AB quartet ($\Delta\nu = 0.58$, $J_{PP} = 67.2$ Hz) with $\nu_A = 49.26$ and $\nu_B = 48.68$ ppm. It was determined that a low concentration of complex **9** was essential in obtaining well-resolved ^{31}P-{^{1}H} NMR spectra. Curiously a larger $\Delta\nu$ (1.32 ppm) was observed for the two ^{31}P chemical shifts at 30 °C in C_6D_6 ($\nu_A = 49.10$ and $\nu_B = 47.78$, $J_{PP} = 66.1$ Hz) as compared to the value in $CDCl_3$, while under similar conditions of concentration and temperature, in THF-d_8, a singlet was observed at 49.73 ppm.[38] The ^{1}H [$CDCl_3$ δ 0.91−1.15 (m, 6H), 2.09−2.27 (m, 1H), 2.42−2.60 (m, 1H), 4.79−4.92 (ddd, J = 13.0, 9.1, 3.9, 1H), 5.07−5.23 (ddd, J = 13.0, 8.8, 4.1, 1H), 6.49 (t, J = 13.0, 1H), 6.55−6.75 (m, 2H, aromatic), 6.85−7.75 (m, aromatic)] and ^{13}C NMR spectrum [$CDCl_3$ inter alia 112.8 (dm, $J_{CP} = 12.0$, C_2), 91.21 (dd, $J_{CP} = 22.6$, 7.8, C_1 or C_3), 89.14 (dd, $J_{CP} = 24.0$, 11.0 C_3 or C_1, allylic fragment)] was also consistent with the proposed structure. These data is in agreement with a syn,syn configuration for the allyl unit, and there is no indication of a syn,anti isomer in any of the solvents examined. On the basis of previous results,[24] we expected to see an additional set of ^{31}P signals if any of the syn,-anti isomer was present in solution. From these studies we conclude that in all probability the two enantiomers arise via alkylation at the different allyl termini of the coordinated unit, and not as a result of syn,syn to syn,-anti isomerization followed by reactions of each of these isomers. The major product arises via a δ-conformation[15] of the π-allyl complex (Figure 3) where the nucleophilic attack takes place at the C-terminal carrying the stacked Ph group.[29]

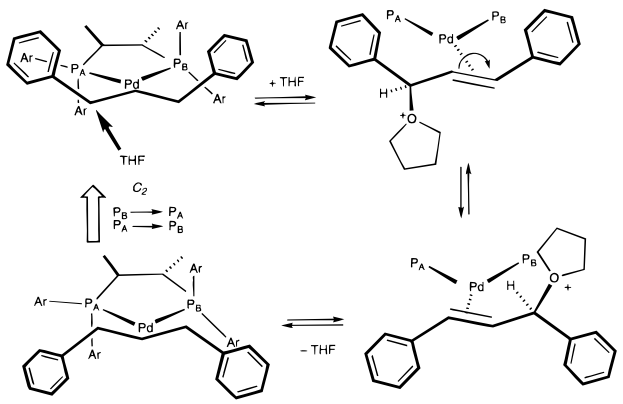
The [Pd(η^3-PhCHCHCHPh)(L*)]SbF_6 bisphosphinite complexes **10e*** and **10j*** were prepared by the reaction of [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ with $AgSbF_6$ and the bisphosphinite ligands **8e*** and **8j*** (eq 4). Purification



by precipitation from a benzene solution with hexane gave the desired complexes as orange solids.

The aromatic region (6.64−8.06 ppm) of the ^{1}H NMR spectrum of **10e*** in THF-d_8 contained signals for the protons of the binaphthalene backbone, the phenyl substituents of the allyl moiety and the phenyl substituents on phosphorus (see Supporting Information for spectra). Interestingly, one pair of the aromatic protons was shielded and visible at δ 5.91 (dd, $J_{PH} = 11.5$, $J_{HH} = 7.5$). The allyl methine proton signals were visible at δ 6.29 (dd, J = ∼13, 13, 1H), 5.85 (dd, br, 1H), and 4.96 (dd, J = ∼12, 12, 1H) ppm. The ^{31}P{^{1}H} spectrum of **10e*** contained two doublets at 142.64 and 126.99 ppm with J_{PP} of 79.5 Hz and a $\Delta\delta$ of 15.65 ppm (Table 4). Only one set of phosphorus signals were observed at room temperature indicating that either several rapidly equilibrating complexes were present, or alternatively only a single isomer of the complex of **10e*** was present. Attempts to locate minor isomers by a 2-D NOESY spectrum[27] were not successful. The topology of the complex is determined by the chirality of the binaphthyl backbone and the attached phenyl groups, with different diastereomeric complexes

(38) One intriguing possibility is that THF is involved in a $\pi-\sigma-\pi$ equilibration process which renders the two phosphorus nuclei identical. Initial attack by THF will be followed by a rotation around a Pd-olefin complex, which has been identified as a viable intermediate by Reggellin and Helmchen in reactions of Pd-allyl complexes with nucleophiles. See ref 7d.



(31) Rüegger, H.; Kunz, R. W.; Ammann, C. J.; Pregosin, P. S. *Magn. Reson. Chem*. **1991**, *29*, 197.
(32) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 5040.
(33) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 83.
(34) Pregosin, P. S.; Salzmann, R.; Togni, A. *Organometallics* **1995**, *14*, 842.
(35) Pregosin, P. S.; Salzmann, R. *Magn. Reson. Chem*. **1994**, *32*, 128.
(36) Barbaro, P.; Currao, A.; Herrmann, J.; Nesper, R.; Pregosin, P. S.; Salzmann, R. *Organometallics* **1996**, *15*, 1879.
(37) Boog-Wick, K.; Pregosin, P. S.; Trabesinger, G. *Organometallics* **1998**, *17*, 3254.

Table 4. Selected ^{1}H and ^{31}P Chemical Shifts for Complexes 10e and 10j in THF-d_8[a]

nucleus	10e	10j
P_A	126.99	178.99
P_B	142.64	173.86
H_1	4.96	4.85
H_2	6.29	6.62
H_3	5.85	5.61
H_{Aax} (on P_{Aax})	6.77	2.05−2.30
H_{Aeq} (on P_{Aeq})	7.15	
H_{Bax} (on P_{Bax})	5.91	1.25−1.96
H_{Beq} (on P_{Beq})	7.84	
C_1	89.95	81.46
C_2	112.92	111.78
C_3	103.03	103.48

[a] Chemical shifts in ppm relative to TMS [^{1}H] and H_3PO_4 [^{31}P]. See text.

resulting from geometric isomers of the coordinated allyl moiety (Scheme 2). The (syn,syn) configurations of the allyl moiety are generally preferred, unless ligands with exceptional steric demands are involved.[25,32] In a series of ^{1}H and ^{31}P DNMR experiments with **10e*** in THF-d_8, no evidence for the presence of more than one complex was observed at temperatures as low as 210 K. Thus, the possibility of the rapid equilibration of diastereomeric complexes was eliminated and we believe that a single complex of **10e*** is present in solution.[39]

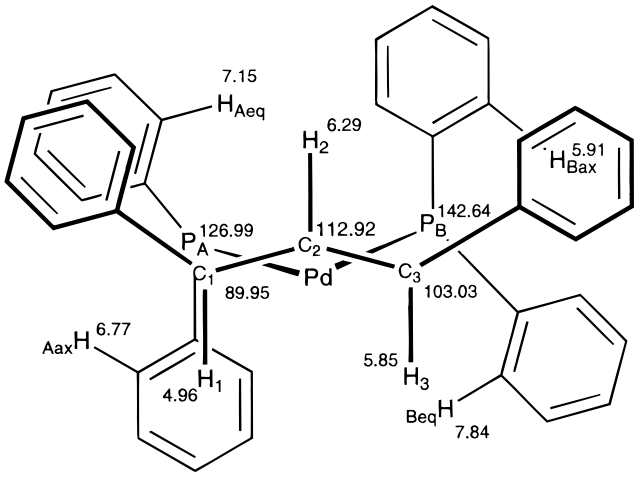
The allyl methine proton signals of **10e*** were assigned on the basis of ^{1}H decoupling and COSY NMR experiments. Based on a series of experiments (vide infra) the signal at 6.29 ppm was assigned to the central allyl proton H_2 and the signals at 4.96 and 5.85 ppm to the terminal protons H_1 and H_3. This chemical shift trend has been observed in other complexes of this type.[36,37] The H_2 signal was a dd with $^3J_{HH} = \sim 13$ Hz which is typical for a trans H−H arrangement. In a series of ^{1}H NOE experiments, NOEs were observed between protons H_1 and H_3, but not between H_2 and either H_1 or H_3. These data is consistent with the 1,3-diphenylallyl moiety having the (syn,syn) configuration, eliminating the (syn,-anti) complexes as likely structures for complex **10e***.

It is known that for a metal-coordinated allyl group, coupling occurs through the metal between the phosphorus atom and a trans allyl proton.[40] This trans P−H coupling is large while the corresponding cis coupling is small (ca. 0 Hz). The ortho protons of the phosphorus phenyl substituents are also coupled to the phosphorus. These "reporter" proton signals[29] are extremely useful in determining the overall 3-D structures of these complexes and can be identified with ^{1}H{^{31}P} experiments.

Irradiation at 126.99 (P_A) allowed for the assignment of the trans H_3 at 5.85 ppm and H_{Aax} and H_{Aeq}, the ortho hydrogen atoms of the phenyl substituents on P_A at 6.77 and 7.15 ppm, respectively. Similarly, irradiation of the 142.64 ppm phosphorus signal (P_B) identified P_B as trans to H_1 at δ 4.96. Also assigned were signals at δ 5.91 and 7.84 for H_{Bax} and H_{Beq} the ortho hydrogen signals of the phenyl substituents on P_B. The ortho hydrogen atoms of the axial phenyl substituents are typically shielded relative to the equatorial substituent.[31,32,35,40] Thus the 6.77 ppm and the 5.91 ppm signals were assigned to the ortho hydrogen atoms H_{Aax} and H_{Bax}, respectively.

(39) Of course, because of the C_2-symmetric nature of the ligand, the two (syn,syn) complexes derived from the two enantiomeric allyl acetates are identical.

(40) Ammann, C. J.; Pregosin, P. S.; Rüegger, H.; Albinati, A.; Lianza, F.; Kunz, R. W. *J. Organomet. Chem.* **1992**, *423*, 415.



nOe observed: H_1 to H_{Aax}, H_3, *not* to H_2; H_3 to H_1, H_{Beq}, *not* to H_2
H_1 coupled to P_B and H_3 coupled to P_A
H_1 coupled to C_1, H_2 coupled to C_2 and H_3 coupled to C_3

Figure 5. ^{1}H, ^{13}C, and ^{31}P NMR data for **10e***.

The orientation of the allyl moiety relative to the bisphosphinite ligand was determined through ^{1}H NOE experiments, where through space relationships between the allyl and the phosphorus phenyl ortho protons were established. Irradiation at 5.85 ppm (H_3) gave an NOE of the H_{Beq} ortho hydrogen signal, while irradiation of H_1 (δ 4.96) gave an NOE of the H_{Aax} signal at δ 6.77. This NMR data is consistent with the (syn,syn) configuration of the allyl complex shown in Figure 5. Examination of this structure shows stacking of the P_A equatorial phenyl group and the phenyl group attached to C_1 of the allyl moiety. It is likely that the proximate position of the C_3-allyl phenyl group results in the shielding of the ortho-hydrogens of the axial P_B-phenyl group resulting in an upfield shift (5.91 ppm). Further verification of the relative orientation of the P_B-phenyl groups come from the strong NOE observed for the ortho hydrogen at δ 7.84, when H_3 at δ 5.85 is irradiated. The shielding of H_1 relative to H_3 (δ 4.96 and 5.85 respectively, see Figure 5) also confirms these assignments.

Through selective proton decoupling in the ^{13}C NMR of **10e*** at −40 °C, the chemical shifts for the allylic carbon resonances were established at δ 89.95 (C_1, coupled to H_1 at δ 4.96), 112.92 (C_2, coupled to H_2 at δ 6.29), and 103.03 (C_3 coupled to H_3 at δ 5.85).

The major product observed, i.e., the (*S*)-isomer results from attack of the nucleophile at C_1 (Figure 3). Note that this carbon carries the phenyl group that encounters maximum steric repulsion from one of the P-aryl groups, in this case, the P_A-equatorial phenyl group.[41]

A similar series of NMR experiments were performed with **10j*** to determine the solution structure of this complex. The aromatic region of the ^{1}H NMR spectrum of **10j*** in THF-d_8 contains signals for the protons of the binaphthalene backbone and the phenyl substituents of the allyl moiety between 7.06 and 8.22 ppm. The allyl methine proton signals, all of which appear to be much broader than those of **10e***, are seen at δ 6.62, 5.61, and 4.85 ppm. The highest field signal (δ 4.85) appears as a broad multiplet. As the solution is cooled evolution of some fine structure is seen, and at 270 K the signal at δ 4.85 is a broad doublet of doublets (J = 10.4, 10.4 Hz).

Clearly the dicyclohexylphosphinites appear to be much more fluxional than the diphenylphosphinites. The aliphatic region of the spectrum contains broad signals for the cyclohexyl substituents on phosphorus between 0 and 2.65 ppm. The $^{31}P\{^1H\}$ spectrum of **10j*** contains two doublets at δ 178.99 and 173.86 ppm with J_{PP} of 53.5 Hz and a $\Delta\delta$ of 5.13 ppm (Table 4). Only one set of phosphorus signals were observed for **10j*** in THF-d_8 at temperatures as low as 210 K. As in the case of **10e***, this is consistent with a single diastereomeric complex of **10j*** present in solution.[39]

The allyl methine proton signals of **10j*** were assigned on the basis of ^1H decoupling and COSY NMR experiments. The signal at δ 6.62 ppm was assigned to allyl proton H_2, and the signals at δ 4.85 and 5.61 ppm were assigned to the terminal hydrogens H_1 and H_3. The H_2 signal was a dd with a $^3J_{HH}$ of 11.4 Hz which is typical for a trans H−H arrangement. An NOE was observed between the H_1 and H_3 protons but not between H_2 and the other allyl protons. These data is consistent with the 1,3-diphenylallyl moiety having a (syn,syn) configuration.

Irradiation of the 178.99 ppm phosphorus signal (P_A) in a $^1H\{^{31}P\}$ experiment at −20 °C identified P_A as trans to H_3 at 5.61 ppm. Also identified were signals at 2.30 and 2.05 ppm (all greater than δ 2.00) in the aliphatic region for protons of the P_A-cyclohexyl substituents. On account of the small chemical shift difference between P_A and P_B, the decoupler power in these experiments had to be very carefully set in order to irradiate each of the ^{31}P nuclei selectively. Irradiation of P_B at 173.86 ppm allowed for the assignment of the trans H_1 at 4.85 ppm, and also signals between 1.25 and 1.96 ppm (most notably none greater than δ 2.00) for protons on the cyclohexyl substituents. The line shape of the aliphatic region of the ^1H spectrum of **10j*** was very complex and overlapping, and the unambiguous assignment of signals in this region was not possible.

Irradiation of the allyl protons of **10j*** in NOE experiments gave data that was consistent with the relative orientation of the allyl and the bisphosphinite ligand moieties determined by $^1H\{^{31}P\}$ measurements. Irradiation of H_1 which is cis to P_A, gave an enhancement of the signals at 2.30 and 2.05 ppm for protons on the P_A-cyclohexyl substituents. Irradiation of H_3 gave an NOE to signals below 2.00 ppm.

Due to the high degree of signal overlap in the aliphatic region of the ^1H NMR spectrum, an unambiguous assignment of signals from each of the four cyclohexyl substituents, and hence the identification of reporter atoms in each quadrant of **10j*** was not possible. This is in contrast to complex **10e*** where the phenyl ortho hydrogen atom signals were used to determine the overall 3-D structure of the complex.

Through selective proton decoupling in the ^{13}C NMR of **10j*** at −40 °C, the chemical shifts for the allylic carbon resonances were established at δ 81.46 (C_1, coupled to H_1 at δ 4.85), 111.78 (C_2, coupled to H_2 at δ 6.62), and 102.48 (C_3 coupled to H_3 at δ 5.61). An HMQC experiment at −20 °C confirmed these assignments.

The structure of **10j*** could not be rigorously established on the basis of these NMR experiments. However, with the syn,syn configuration of the allyl moiety confirmed, these NMR results are consistent with a conformation of **10j*** which is similar to that of **10e***. If the basic assumption is made that both **10e*** and **10j*** have the same λ-conformation, nucleophilic attacks at two different allylic terminal carbons have to be invoked in order to explain the opposite selectivities observed. How this depends on whether the phosphorus atoms carry a phenyl or a cyclohexyl substituent is not entirely clear. One possible explanation is that the stacking effects that have been proposed for the P-phenyl ligands are not possible with cyclohexyl-substituted phosphinites. In addition, cyclohexyl derivatives are sterically bulkier (for example, the cone angle for tricyclohexylphosphine is larger than that of triphenylphosphine: 185° vs 145°). These effects may have attendant consequences such as differing Pd−C_{allyl} bond lengths, and hence differing electrophilicities for the associated carbons in the relevant diasteromers.[42] One measure of such differences is the relative chemical shifts of the phosphorus atoms and the associated trans allylic carbon atoms. Curiously, in the case of the diphenylphosphinites, the low-field carbon is trans to the high-field phosphorus and in the case of the dicyclohexylphosphinites the high field carbon is trans to the high-field phosphorus. The relevance of this observation remains to be clarified. For example, the difference in donor−acceptor properties of the two chelating phosphorus atoms of a C_2-symmetric ligand could be responsible for the preferred site of attack by a nucleophile. A more likely scenario is that a synergistic effect of the electrophilicities of the terminal allyl carbons and the electronic properties of the relevant trans-chelating atom is responsible for the observed selectivity. In the BINAPO system, assuming the same conformation for both the diphenylphosphinite and the dicyclohexylphosphinite complexes, the major product in each case arises from the attack of the nucleophile trans to the more deshielded phosphorus. Our IR studies with [1,2-bis(diarylphosphinite)Ni$(CO)_2$ complexes[3a] support the suggestion that the more electron-withdrawing the phosphorus, the better the back-bonding from the metal as judged by the carbonyl (ν_{A1} and ν_{B1}) frequencies. In Pd-catalyzed allylation reactions, a number of highly successful chelating ligands have been designed on the basis of preferential nucleophilic attack on the allylic carbon trans to the better π-acceptor.[7]

Conclusions

Our results can be summarized as follows. Even when the bisphosphinite ligands are C_2-symmetric, in the formation of complexes (e.g., **10e*** or **10j***), this symmetry is broken, as indicated by the AB-nature of the ^{31}P NMR. On the basis of the NMR experiments, we propose a λ-conformation for the complex **10e***. The 1,3-diphenylallyl unit exists exclusively, as the (syn,syn) isomer. Attack by a malonate anion preferentially occurs at the carbon that carries the phenyl group which is eclipsed (stacked) with respect to one of the P-aryl groups. In the case of the cyclohexyl substituted phosphinite complex **10j***, which gave the opposite enantiomer as the major product, the conformation of the chelate could not be determined with certainty. The results of these NMR studies clearly rule out one of the possible mechanisms for this unusual stereochemical result: the one involving

(41) It should be noted this is counter to the notion that the most deshielded carbon of the allyl unit is the one that undergoes the nucleophilic attack. However, the ^{13}C chemical shift criterion for reactivity[24] as well as Pd−C bond strength[42] has been labeled "suspect".

(42) For an example of what appears to be a steric acceleration of a Pd−C bond cleavage in an allyl complex, see: Breutel, C.; Pregosin, P. S.; Salzmann, R.; Togni, A. *J. Am. Chem. Soc.* **1994**, *116*, 4067.

a syn,syn to syn,anti interconversion. Nucleophilic attack at the allylic carbon which is trans to the more deshielded and π-acceptor phosphorus atom provides a satisfactory explanation for the observed reversal of selectivity in going from the diphenylphosphinite to the dicyclohexylphosphinite BINAPO complex. Whatever be the origin of the reversal of stereoselectivity, in selected cases it has been shown to be possible to reverse the outcome of an enantioselective reaction simply by changing the nonchiral substituents on a ligand.

Experimental Section

General Methods. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere inside a Vacuum Atmospheres drybox. Analytical TLC were performed on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted with silica gel 40 (Scientific Adsorbents Incorporated, 40 Microns Flash).[43] NMR spectra were obtained on $CDCl_3$ solutions unless otherwise stated. Splitting patterns are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Low-resolution mass spectra were recorded in fast atom bombardment mode (MSFAB). Enantiomeric excesses were determined by HPLC using a Daicel Chiralcel OJ column and eluting with 5% 2-propanol in hexane as eluant. Tetrahydrofuran, diethyl ether, and hexane were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. The solvents in the drybox were stored over activated molecular sieves after distillation as described above. The bisphosphinites **1**−**8** (Figures 1 and 2) were synthesized according to the methods A−C. The cationic (phosphine)Pd(allyl) complexes were synthesized by the method D. Representative examples are given below. Characterization data for other bisphosphinites are included in the Supporting Information. Air-sensitive trivalent phosphorus containing compounds give poor microanalyses. The purity of the ligands were ascertained by ^{1}H and ^{31}P{^{1}H} NMR. In most instances the ligands were >95% pure.

The precursor diol for bisphosphinite **1** and the O-substituted pyranose bisphosphinites **1a**−**g** were prepared by the method of RajanBabu and co-workers.[3a] The precursor diol for bisphosphinite **2** was purchased from Fluka. The precursor diols for bisphosphinites **3**, **4**, **7**, and **8** and (L)-threitol used in the preparation of bisphosphinites **5** and **6** were purchased from Aldrich. Backbone **5** was prepared according to the method of Mash and co-workers.[44] The chlorophosphines were prepared according to known procedures.[45,46] The [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ complex was prepared according to the method of Bosnich and co-workers.[47]

Chemical Methods. Preparation of the Phosphinites. (1*R*,2*R*)-1,2-Cyclohexylene Bis[3,5-bis(trifluoromethyl)-phenylphosphinite] (2a), Method A. To 1.0 equiv of (1*R*,2*R*)-*trans*-cyclohexane-1,2-diol (22.4 mg, 0.190 mmol) in dichloromethane (1 mL) were added pyridine (0.5 mL), a catalytic amount of DMAP (4-(dimethylamino)pyridine), and chlorobis-[bis-3,5-(trifluoromethyl)phenyl]phosphine (209 mg, 0.425 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 10 h, and the solvent was evaporated in vacuo. The residue was extracted with dry diethyl ether and filtered through Celite. Concentration of the filtrate and removal of excess reagents under vacuum overnight gave the bisphosphinite **2a** (207 mg, 0.202 mmol, crude). ^{1}H NMR: δ 1.20−1.45 (m, 2H), 1.46−1.65 (m, 2H), 1.66−1.85 (m, 2H), 1.86−2.10 (m, 2H), 4.15−4.28 (m, 2H), 7.58−8.26 (m, 16H). ^{31}P{^{1}H} NMR: δ 102.1 (s).

Diethyl (2*R*,3*R*)-2,3-Bis[(diphenyphosphino)oxy]succinate (4e), Method B. To a solution of diphenylchlorophosphine (196 mg, 0.888 mmol) in toluene (3 mL) was added DMAP (112 mg, 0.917 mmol) in toluene (1 mL) and L-diethyl tartrate (73 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 3 h and filtered through Celite. Concentration of the filtrate and removal of excess reagents under vacuum overnight gave the bisphosphinite **4e** (248 mg, 0.432 mmol, crude). ^{1}H NMR: δ 0.91 (t, J = 7.1 Hz, 6H), 3.78 (dq, J = 7.1, 10.8 Hz, 2H), 3.96 (dq, J = 7.1, 10.8 Hz, 2H), 5.20 (d, J_{P-H} = 9.0 Hz, 2H), 7.13−7.66 (m, 20H). ^{31}P{^{1}H} NMR: δ 119.5 (s).

(1*R*,2*R*)-1,2-Cyclohexylene Bis(diphenylphosphinite) (2e), Method C. To a solution of (1*R*,2*R*)-*trans*-cyclohexane-1,2-diol (42 mg, 0.37 mmol) in THF (5 mL) at −30 °C was added a solution of *n*-butyllithium in hexane (280 μL, 0.730 mmol). The reaction mixture was stirred with warming to room temperature over 20 min, and diphenylchlorophosphine (160 μL, 0.730 mmol) was added. The reaction mixture was stirred at room temperature for 9 h. The solvent was evaporated in vacuo, and the residue was extracted with diethyl ether and filtered through Celite. Concentration of the filtrate and removal of excess reagents under vacuum overnight gave the bisphosphinite **2e** (195 mg, 0.401 mmol, crude). ^{1}H NMR: δ 1.20−1.30 (m, 2H), 1.47−1.51 (m, 2H), 1.61−1.67 (m, 2H), 2.03−2.08 (m, 2H), 3.99−4.04 (m, 2H), 7.17−7.53 (m, 20H). ^{31}P{^{1}H} NMR: δ 106.4 (s).

Backbone 6. To L-threitol (56.9 mg, 0.466 mmol) in dichloromethane (10 mL) were added triphenylmethyl chloride (300.0 mg, 1.076 mmol), triethylamine (2 mL), and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 16 h, poured into crushed ice, and extracted with dichloromethane. The organic extracts were sequentially washed with saturated ammonium chloride solution, water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Column chromatography of the residue with 6% ethyl acetate in hexane as eluant gave backbone **6** (149 mg, 52%). ^{1}H NMR: δ 2.62−2.67 (m, 2H), 3.11 (dd, J = 5.6, 9.6 Hz, 2H), 3.35 (dd, J = 4.5, 9.6 Hz, 2H), 3.74−3.85 (m, 2H), 7.18−7.41 (m, 30H).

Preparation of Pd-Allyl Complexes. [Pd(η^3-PhCHCH-CHPh)((*S*,*S*)-CHIRAPHOS)]SbF$_6$ (9), Method D. [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ complex (11.5 mg, 0.0172 mmol) and silver antimony hexafluoride (17.6 mg, 0.0512 mmol) were stirred in CH_2Cl_2 (5 mL) for 15 min. The mixture was filtered through Celite into a solution of (*S*,*S*)-CHIRAPHOS (14.8 mg, 0.0347 mmol) and stirred for an additional 45 min. The reaction was concentrated and the resultant solids were dissolved in benzene, transferred, and precipitated with hexane. The precipitate was filtered with Celite and washed with hexane. The precipitate was dissolved with CH_2Cl_2, eluted through Celite and concentrated to give complex **9** (19.1 mg, 58%) as a red solid. ^{1}H NMR: δ 0.91−1.15 (m, 6H), 2.09−2.27 (m, 1H), 2.42−2.60 (m, 1H), 4.79−4.92 (ddd, J = 13.0, 9.1, 3.9 Hz, 1H), 5.07−5.23 (ddd, J = 13.0, 8.8, 4.1 Hz, 1H), 6.49 (t, J = 13 Hz, 1H), 6.55−6.75 (m, 2H, aromatic), 6.85−7.75 (m, aromatic). ^{13}C NMR (75 MHz): allylic carbons 89.14, 91.21, 112.8. ^{31}P{^{1}H} NMR (101 MHz): δ 48.68 (d, J_{P-P} = 67.2 Hz), 49.26 (d, J_{P-P} = 67.2 Hz). MSFAB (SIMS(+)) m/z (rel intensity): 726 ($C_{43}H_{41}P_2Pd$, M^+, 35), 725 ($M^+ - 1$, 100).

[Pd(η^3-PhCHCHCHPh)(8e*)]SbF$_6$ (10e*), Method D. The reaction of [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ complex (10.2 mg, 0.0152 mmol), silver antimony hexafluoride (16.2 mg, 0.0472 mmol) and bisphosphinite **8e*** (20.2 mg, 0.0309 mmol) gave complex **10e*** (28.8 mg, 80%) as an orange-red solid. ^{1}H NMR (THF-d_8): δ 4.96 (dd, J = 12.1, 12.1 Hz, 1H), 5.85 (br dd, 1H), 5.91 (dd, J = 7.5, 11.5 Hz, 2H), 6.29 (dd, J = 12.7, 12.7 Hz, 1H), 6.64−6.85 (m, 12H), 6.97−7.48 (m, 20H), 7.64−7.73 (m, 4H), 7.83 (d, J = 11.1 Hz, 1H), 7.85 (d, J = 11.7 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 9.1 Hz, 1H). ^{13}C NMR (125 MHz, THF-d_8, −40 °C): allylic carbons 89.95, 103.03, 112.92. ^{31}P{^{1}H} NMR (THF-d_8): δ 126.99 (d, J_{P-P} = 79.5 Hz), 142.64 (d, J_{P-P} = 79.5 Hz). MSFAB (SIMS(+)) m/z (rel intensity): 954 ($C_{59}H_{45}O_2P_2Pd$, M^+, 34), 953 ($M^+ - 1$, 65), 453 (100).

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[Pd(η^3-PhCHCHCHPh)(8j*)]SbF$_6$ (10j*), Method D. The reaction of [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$ complex (8.1 mg, 0.012 mmol), silver antimony hexafluoride (12.7 mg, 0.0370 mmol), and bisphosphinite **8j*** (16.8 mg, 0.0247 mmol) gave complex **10j*** (21.5 mg, 73%) as an orange-red solid. ^{1}H NMR (THF-d_8): δ 0.00−2.35 (m, 44H), 4.85 (br dd, J = 10.4, 10.4 Hz, 1H), 5.61 (br dd, J = 10.9, 10.9 Hz, 1H), 6.62 (br dd, J = 11.4, 11.4 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.31 (t, J = 8.2 Hz, 1H), 7.36−7.41 (m, 11H), 7.56−7.61 (m, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 9.5 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, THF-d_8, −40 °C): allylic carbons 81.46, 102.48, 111.78. ^{31}P-{^{1}H} NMR (THF-d_8): δ 173.86 (d, J_{P-P} = 48.9 Hz), 178.99 (d, J_{P-P} = 48.9 Hz). MSFAB (SIMS(+)) m/z (rel intensity): 978 ($C_{59}H_{69}O_2P_2Pd$, M^+, 50), 977 ($M^+ - 1$, 100).

Diethyl 1-(1,3-Diphenylprop-2-enyl)malonate (11). (a) Reaction of Diethyl Malonate Anion Mediated by a Catalytic Amount of a Palladium Bisphosphinite Complex. To a solution of [Pd(η^3-C_3H_5)(μ-Cl)]$_2$ (1.0 mg, 2.7 mmol; 0.55 mol %) in THF (1 mL) was added a solution of the corresponding bisphosphinite (6.5 mmol, 1.3 mol %) in THF (3 mL). A solution of 1,3-diphenylprop-2-en-1-yl acetate (125 mg, 0.495 mmol) in THF (2 mL) was treated successively with this catalyst solution and a solution of diethyl malonate sodium salt (109 mg, 0.598 mmol) in THF (4 mL). After the conversion was complete according to TLC analysis, the reaction mixture was removed from the drybox, and the reaction was quenched with saturated ammonium chloride solution (10 mL). The organic material was extracted with diethyl ether (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Column chromatography of the residue with 10% ethyl acetate in hexane as eluant gave malonate adduct **11**. ^{1}H NMR: δ 1.02 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 3.98 (d, J = 10.9 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.28 (dd, J = 8.2, 10.9 Hz, 1H), 6.38 (dd, J = 8.2, 15.7 Hz, 1H), 6.49 (d, J = 15.7 Hz, 1H), 7.20−7.32 (m, 10H).

(b) Reaction of Diethyl Malonate Anion with a Stoichiometric Amount of [Pd(η^3-PhCHCHCHPh)(8j*)]SbF$_6$ Complex (10j*). A solution of sodium diethyl malonate (3.6 mg, 0.020 mmol) in THF (3 mL) was added to a solution of **10j*** (19.0 mg, 0.0156 mmol) in THF (2 mL), and the resulting mixture was stirred at room temperature for 10 h. The deep-red reaction solution was removed from the drybox, diluted with diethyl ether, washed with saturated ammonium chloride solution and brine, and dried over anhydrous $MgSO_4$. The reaction was filtered and concentrated in vacuo. Column chromatography of the residue with 2% ethyl acetate in hexane as eluant gave adduct **11** as a colorless oil (4.5 mg, 82%).

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Supporting Information Available: Experimental details and characterization data for bisphosphinite ligands, NMR spectra for complexes **9**, **10e**, and **10j** as well as two typical HPLC chromatograms used in determining the enantioselectivity of the allylation reaction with bisphosphinites **8e** and **8j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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