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Hammett Studies of Enantiocontrol by PHOX Ligands in Pd-Catalyzed Allylic Substitution Reactions

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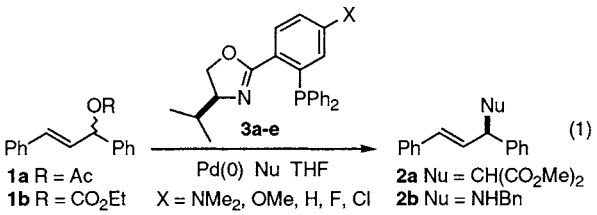
ABSTRACT



Electronically modified PHOX ligands 3a–e were synthesized to probe the mechanism of the enantioselective palladium-catalyzed allylic alkylation and amination reactions. Alkylation with dimethyl sodiomalonate produced only a small variation in the ee (89.3% to 93.4%), but amination with benzylamine gave a much wider variation in the ee (16.4% to 66.6%). Hammett analysis suggests that the substituents interact more significantly with phosphorus and supports a combined electronic and steric basis for enantioselection.

The enantioselective palladium-catalyzed allylic substitution reaction (eq 1) is a powerful method for the construction of carbon−carbon and carbon−heteroatom bonds.[1] Among the myriad types and classes of chiral ligands designed for this and other enantioselective reactions, the phosphinooxazoline (PHOX) ligands (**3**) have attracted considerable synthetic and mechanistic interest.[2] The observed stereochemistry of the products (**2**) is consistent with either nucleophilic attack trans to phosphorus in the **exo** intermediate or trans to nitrogen in the **endo** intermediate (Figure 1). The former pathway is generally favored for the following reasons. Both solution ^{1}H NMR and X-ray crystallographic studies show that the **exo** diastereomer predominates.[3] The π-acceptor nature of the phosphorus ligand should make the trans allylic carbon more electron-deficient and therefore more susceptible to nucleophilic addition.[4] Most definitively, low-temperature ^{1}H NMR studies of the initially formed product, the alkene−palladium complex, show the nucleophile oriented away from phosphorus, suggesting it arose from a least-motion rotation following nucleophilic addition trans to phosphorus in the **exo** η^3-allylpalladium intermediate.[5]

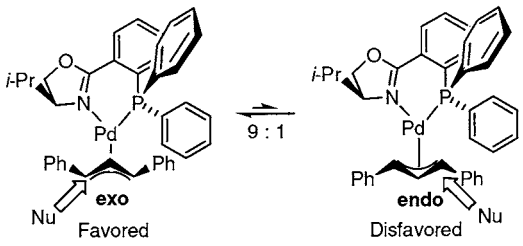


Figure 1. The two modes of nucleophilic attack on the η^3-allylpalladium intermediates consistent with the observed product stereochemistry.

(1) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(2) (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Helmchen, G. *J. Organmet. Chem.* **1999**, *576*, 203. (c) Williams, J. M. J. *Synlett* **1996**, 705.

(3) (a) Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913. (b) Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **1996**, *79*, 803. (c) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523.

(4) Szabo, K. J. *Organometallics* **1996**, *15*, 1128.

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Although the PHOX ligands seem like a clear case of electronic control of enantioselectivity (i.e., nucleophilic attack trans to the better π-acceptor ligand phosphorus rather than the donor ligand nitrogen), steric interactions between the chiral ligand and product alkene complex can also explain the enantioselectivity (Figure 2).[6] With a series of *N*,*S*-chiral

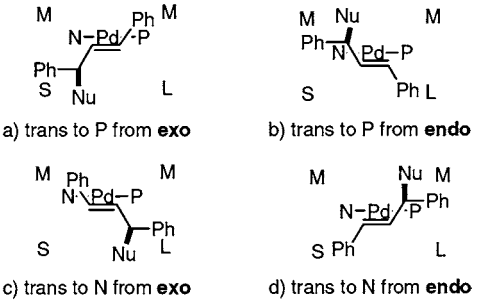
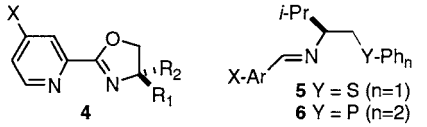


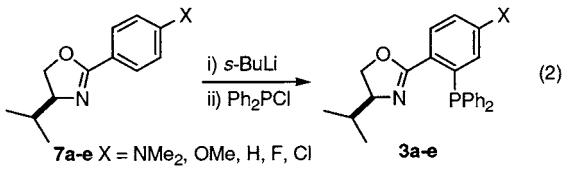
Figure 2. "Sector model"[6a] for the four possible alkene−palladium complexes arising from the nucleophilic addition pathway indicated. Hydrogen is the small group (S), the *i*-Pr and axial-like Ph are considered medium groups (M) and the equatorial-like Ph is considered large (L). Pathways a and d give the major enantiomer and pathways b and c give the minor enantiomer.

ligands nucleophilic attack trans to the arguably harder nitrogen was observed and the chiral recognition was specifically attributed to steric interactions rather than electronic differences in the ligand.[7] Additionally, theoretical calculations of several types of *P*,*N*-chiral ligands attributed the enantioselectivity to steric interactions with nucleophilic attack occurring trans to nitrogen in some cases.[8]

Previous studies of electronic differences between other types of chiral ligands have produced disparate results in the alkylation of **1a**.[9,10] A large difference in reactivity was observed for different substituents (X) with 4′-substituted pyridinyloxazolines (**4**) but the enantioselectivity was "scarcely affected".[11] Whereas imine-sulfide ligands **5** showed almost no variation in ee with changing substituents,[7] the analogous phosphine ligand system (**6**) showed a dramatic change in the ee as the substituents were varied.[12] These results have been used to argue for either steric or electronic origins for enantiocontrol, respectively.



The objective of this study is to investigate whether the trans to phosphorus transition state for the PHOX ligands is primarily electronic or steric in origin. Toward that goal, we undertook the synthesis and Hammett study of ligands **3a,b,d,e**, which are electronically different but sterically identical (around the sites of ligation) to the parent PHOX ligand (**3c**). The modified ligands were prepared according to literature protocols starting from the corresponding 4-substituted acids or acid chlorides and (*S*)-valinol.[13] Directed lithiation of the 4′-substituted 2-aryloxazolines and coupling with chlorodiphenylphosphine provided the desired chiral ligands (eq 2).[2a,14]



The electronic differences between the ligands became apparent during the synthesis. Both electron-donating (**a,b**) and electron-withdrawing (**d,e**) groups gave higher chemical yields in the directed-lithiation/coupling step than **3c**. The ligands with electron-withdrawing groups (**3d,e**) also proved more sensitive to decomposition and were repurified by flash chromatography directly before use in the palladium-catalyzed reactions. Attempts to study the X = CF_3 PHOX ligand have thus far been unsuccessful for this reason.

The electronically modified PHOX ligands were first tested in what has become the standard test reaction: the alkylation of **1a** with dimethyl sodiomalonate to give **2a** (eq 1a).[15] In contrast to the dramatic results observed with Morimoto's phosphine-imine ligand **6**,[12] much less variation in the ee of **2a** was observed over a similar range of substituents (Table 1). The trend toward higher ee's with more electron-withdrawing substituents is likely real (i.e., ee differences are greater than error range for **3a** to **3e**) but not definitive.

(5) (a) Junker, J.; Reif, B.; Junker, B.; Felli, I. C.; Reggelin, M.; Griesinger, C. *Chem. Eur. J.* **2000**, *6*, 3281. (b) Steinhargen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2108.

(6) (a) Kollmar, M.; Steinhagen, H.; Janssen, J. P.; Goldfuss, B.; Malinovskaya, S. A.; Vazquez, J.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2002**, *8*, 3103. (b) von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Ruegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (c) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.

(7) Adams, H.; Anderson, J. C.; Cubbon, R.; James, D. S.; Mathias, J. P. *J. Org. Chem.* **1999**, *64*, 8256.

(8) (a) Windhalm, M.; Nettekoven, U.; Kalchhauser, H.; Mereiter, K.; Calhorda, M. J.; Felix, V. *Organometallics* **2002**, *21*, 315. (b) Blochl, P. E.; Tongi, A. *Organometallics* **1996**, *15*, 4125.

(9) For an example where the major enantiomer reverses with changing electronics, see: Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; RajanBabu, T. V. *J. Org. Chem.* **1999**, *64*, 7601.

(10) For examples of electronic ligand tuning in other asymmetric reactions, see: (a) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A.; Nomura, N.; Jin, J.; Park, H.; Nandi, M. *Curr. Org. Chem.* **2003**, *7*, 301. (b) Casey, M.; Smyth, M. P. *Synlett* **2003**, 102. (c) Morimoto, T.; Nakajima, N.; Achiwa, K.; *Tetrahedron: Asymmetry* **1995**, *6*, 23. (d) Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.

(11) Chelucci, G.; Deriu, S. P.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457.

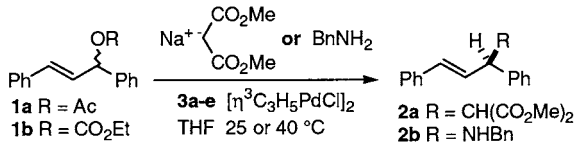
(12) Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227.

(13) (a) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (b) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprintz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547.

(14) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Pretot, R.; Schaffner, S.; Schnider, P.; von Matt, P. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 206.

(15) See Supporting Information for full experimental details of palladium-catalyzed allylic-alkylations and aminations of **1a,b**.

Table 1. Enantioselective Alkylation/Amination Results



		2a		2b	
ligand	X	% ee[a]	error[b]	% ee[c]	error[b]
3a	NMe_2	89.3 (*S*)[d]	±2.21	16.4 (*R*)[e,f]	±4.14
3b	OMe	89.7 (*S*)	±1.11	22.7 (*R*)	±2.81
3c	H	89.9 (*S*)	±1.86	28.4 (*R*)	±2.61
3d	F	93.0 (*S*)	±1.15	44.9 (*R*)	±3.96
3e	Cl	93.4 (*S*)	±0.55	66.6 (*R*)	±4.03

[a] HPLC Chiralpak AD 90:10 hexane/2-propanol, 1.0 mL/min. [b] One standard deviation based on 5−7 trials. [c] HPLC Chiralcel OJ 85:15 hexane/2-propanol, 0.5 mL/min. [d] Determined from (−) sign of optical rotation, ref 16a. [e] Determined from (−) sign of optical rotation, ref 16b. [f] (*R*)-**2b** has the same "sense" of chirality as (*S*)-**2a**, but the priority rules reverse.

Using benzylamine as the nucleophile (eq 1b), however, produced a much larger variation in the ee of **2b** with the same trend as the malonate alkylations (both (*S*)-**2a** and (*R*)-**2b** have the same "sense" of chirality[16]). In neither reaction was a dramatic effect on reactivity observed with varying substituents, although the amination reactions were slower than the malonate alkylations on the whole and required heating to 40 °C.

The substituent (X) in the modified PHOX ligands (**3**) is both meta to phosphorus and para to the nitrogen-containing oxazoline ring. To ascertain which interaction (with P or N), if either, is more significant, Hammett analysis of the enantioselectivity with respect to both σ_P and σ_M was carried out (Figures 3 and 4).[17] For comparative and interpretive purposes the literature data for ligand **6** was also included in this analysis.[12,18] The log of the enantiomeric ratio (er)[19] was used for these plots because log(er) relates directly to the free energy difference between the diastereomeric transition states.[20]

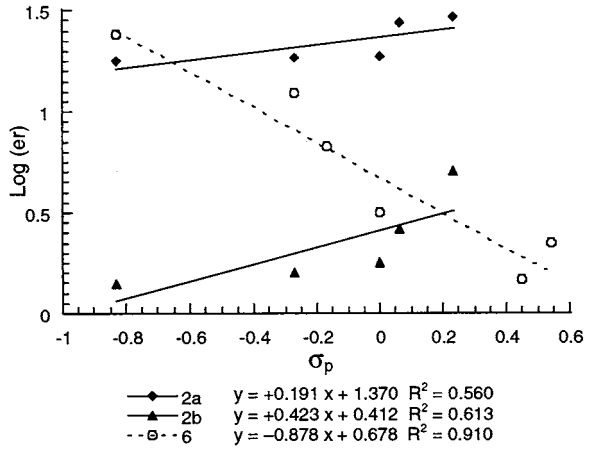


Figure 3. Hammett plot of log(er) data vs σ_P for ligands **3a**−**e** giving **2a** (♦) and **2b** (▲) and ligand **6** (○) (also giving **2a**).

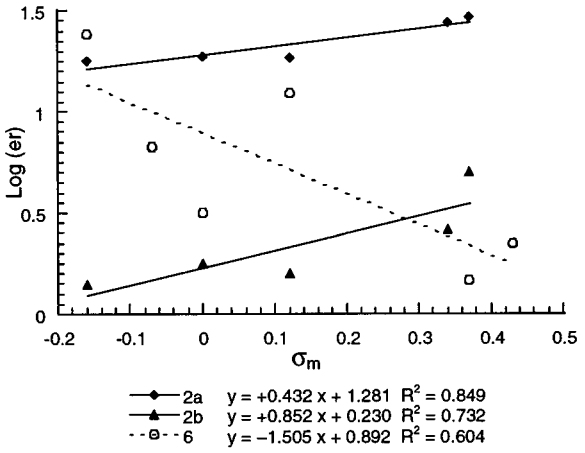


Figure 4. Hammett plot of log(er) data vs σ_M for ligands **3a**−**e** giving **2a** (♦) and **2b** (▲) and ligand **6** (○) (also giving **2a**).

The Hammett plots for alkylations with ligand **6** are the most straightforward to interpret. Structurally, all substituents in ligand **6** are para (i.e., imines of 4-substituted benzaldehydes) and only conjugated with nitrogen. So it is not surprising that the log(er) data fit σ_P ($R^2 = 0.910$) much better than σ_M ($R^2 = 0.604$). The negative slope of the plot suggests that electron-donating groups increase the er by making nitrogen a stronger donor ligand (accentuating the difference between nucleophilic attack trans to P or N), whereas electron-withdrawing groups lower the er by making nitrogen a weaker donor ligand (minimizing the electronic difference between nucleophilic attack trans to P or N).[21]

For the data with ligands **3a**−**e** giving **2a** and **2b**, the log(er) data fit σ_M (Figure 4) better than σ_P (Figure 3) with a positive slope in both cases. The overall quality of the fits is lower than with **6**.[22] The substituents in **3** likely affect both phosphorus (meta) and nitrogen (para) to some extent. Nonetheless, it appears that the substituents in ligand **3** affect

(16) For absolute configuration determinations and optical rotation correlations, see: (a) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191. (b) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(17) All substituent constants (σ_P and σ_M) taken from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(18) The raw ee data for the dimethyl malonate alkylation of **1a** to give **2a** was taken from ref 12. Those authors did not undertake the formal Hammett analysis shown here, nor are these interpretations and conclusions about functioning of ligand **6** necessarily supported by those authors.

(19) Since **2a** and **2b** have opposite (*R*/*S*) configurations, the enantiomeric ratio (er) is defined here as the relative amount of the major enantiomer divided by the relative amount of the minor enantiomer (e.g., 80% ee gives an er of 9.0).

(20) The er reflects the net ratio of rates of formation of the (*R*) and (*S*) products through the four pathways shown in Figure 2.

(21) For an example of a similar electronic trend with several *P*,*N*-ligands see: Porte, M. A.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180.

(22) Regression analysis with other types of substituent constants (e.g., σ^+, σ^o, etc.) or dual-parameter fits (e.g., F/R, σ_I/σ_R, etc.) did not provide better data fits. Considering the "simple" system (**6**) only gave an $R^2 = 0.91$ it is not clear that better fits should be expected.

phosphorus more than nitrogen. This agrees with the prediction that electron-withdrawing groups increase the er by making phosphorus a better acceptor ligand (accentuating the electronic difference between nucleophilic attack trans to P or N) and electron-donating groups decrease the er by making phosphorus a weaker acceptor ligand (minimizing the difference between nucleophilic attack trans to P or N). That is, the electronic effects of ligand **3** are opposite in nature to those of ligand **6**.

The changes in enantioselectivity could also be explained by a change in the **exo** to **endo** ratio of intermediates resulting in an increased (or decreased) rate of formation of the minor enantiomer via nucleophilic addition trans to phosphorus in the **endo** intermediate (Figure 2, path b).[23] However, a change in the **exo** to **endo** ratio based on electronics seems unlikely as this ratio is reported to be steric in origin and varies with the size and structure of the allyl moiety and the size of the groups on phosphorus.[2,24] Thus, it seems reasonable to conclude that the ligand substituents (X) do affect the ratio of nucleophilic attack trans to phosphorus or nitrogen. This effect would apply to both the **exo** and **endo** complexes, but because the major enantiomer arises from the more abundant **exo** complex,[5] changing the reactivity for attack trans to phosphorus or nitrogen would be amplified by the **exo** to **endo** ratio and thus alter the net enantioselectivity.

Finally, the differing susceptibilities of the alkylation and amination reactions to electronic influences on the enantioselectivity (i.e., ee data or slopes of the Hammett plots) suggest some differences in the origin of the enantioselectivities.[25] These reactions differ in both the size and charge of the nucleophile. The less electronically sensitive nature of the alkylation reaction (eq 1a) suggests that it is more influenced by sterics either in the transition state due to the bulkier malonate anion nucleophile or in the product alkene-palladium complex (Figure 2). Conversely, the more electronically sensitive amination reaction (eq 1b) seems more influenced by the electronic structure (i.e., phosphorus vs nitrogen) of the η^3-allylpalladium intermediate (Figure 1) and less influenced by sterics. Similarly, the differing positions of the transition states may influence the transmission of electronic effects. A later transition state is expected for the less reactive amine nucleophile. Although a late transition state has generally been used to argue for the increased importance of steric interactions in the product alkene−palladium complex,[6c] the greater degree of bond formation may accentuate the electronic differences between the allylic termini as well.

In conclusion, these Hammett studies of modified ligands **3a**−**e** support a mechanism whereby the PHOX ligands direct nucleophilic attack trans to phosphorus in the **exo** intermediate for electronic reasons but suggest that steric interactions may also play a role in determining the enantioselectivity that can vary with the nature of the nucleophile.

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Supporting Information Available: Experimental conditions for **2a,b**, experimental procedures and full characterization data for **3a,b,d,e** and **7a,b,d,e**, and tables of data used for Hammett analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) This explanation could avoid any involvement of nucleophilic addition trans to nitrogen.

(24) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047.

(25) The difference between 89.3% ee and 93.4% ee corresponds to a ΔG of 0.30 kcal/mol, while the difference between 16.4% ee and 66.6% ee corresponds to a ΔG of 0.75 kcal/mol.