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Hammett ^{13}C NMR and X-ray studies of π-allylpalladium phosphinooxazoline chiral ligand complexes

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Abstract—The transmission of substituent effects across the palladium center to the allyl carbons is monitored by ^{13}C NMR and X-ray crystallography as a way to probe electronic asymmetry in chiral ligand design. Based on their similar chemical shift trends and X-ray structures, the π-allylpalladium intermediates provide a good model for early transition state reactions, which are less sensitive to electronic perturbations. Hammett analysis supports an electronic basis for enantioselection that increases as the transition state becomes later.
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Phosphinooxazoline (PHOX) chiral ligands have proven extremely effective at inducing asymmetry in palladium-catalyzed allylic-substitution reactions.[1] These ligands are proposed to function by controlling the ratio of the *exo* to *endo* π-allylpalladium intermediates and then directing nucleophilic addition *trans* to phosphorus (the better acceptor ligand) in the favored *exo* intermediate. The low-temperature NMR structure of the initially formed alkene–palladium complex has established this '*trans* to phosphorus in *exo*' addition as the major pathway.[2] Nonetheless, this does not preclude other explanations for its favorability (e.g., steric interactions with the nucleophile or in the product alkene complex) nor does it provide any information about the pathway(s) leading to the minor enantiomer.

Our Hammett studies of the enantioselectivity with electronically modified PHOX ligands (**1a**–**f**) provided additional support for the electronic basis of the *trans* to phosphorus addition mechanism, but they also demonstrate that the nucleophile plays an important role in determining the enantioselectivity.[3] In particular, for reactions with sodiodimethyl malonate as the nucleophile the ee's were less sensitive to the backbone substituent (X) (**1a**–**f**: 89–93% ee). In contrast, for reactions with benzylamine as the nucleophile the ee's showed a great sensitivity to the backbone substituent (X) (**1a**–**f**: 16–67% ee). These results suggest that the position of the transition state also influences the enantioselectivity.

To gain further insight into the basis for enantioselectivity and the position of the transition state, we measured the ^{13}C NMR chemical shifts and examined several X-ray structures of the π-allylpalladium intermediates themselves (**2a**–**f**), which are regarded as good models for an early transition state structure.[4] ^{13}C NMR chemical shifts have been successfully correlated to both positive charge density[5] and regioselectivity of nucleophilic attack with substituted 1,3-diphenylallylpalladium complexes with achiral ligands by Hammett analysis.[6] In the case of ligands **1a**–**f** the electron donating or withdrawing substituent is on the ligand backbone and should show Hammett correlations via electronic transmission across the palladium center to the allyl termini. Based on the proposed mechanism for enantioselection, the biggest effect was expected on C_3 in the *exo* diastereomer.

Palladium complexes **2a**–**f** were prepared from the corresponding chiral ligands (**1a**–**f**)[3] and 1,3-diphenylallylpalladium chloride dimer by reaction with silver tetrafluoroborate in acetone (Scheme 1).[6b,7] The complexes were obtained in essentially quantitative yield

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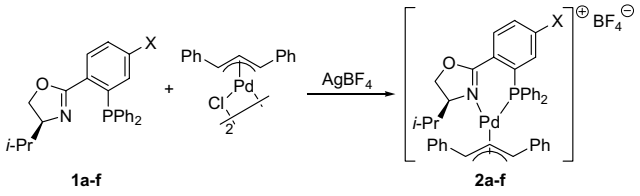


Scheme 1. Synthesis of π-allylpalladium complexes **2a**–**f**: X = NMe_2, OMe, Me, H, F, Cl (only *exo* diastereomer shown).

and sufficient purity for NMR spectroscopy. Analytically pure samples and crystals suitable for X-ray crystal diffraction (see below) were grown by slow vapor diffusion of diethyl ether into a solution of the complex in acetonitrile. The ^1H and ^{13}C NMR assignments for **2a**–**f** were made based on the literature data for the analogous hexafluoroantimonate salt of **2d** (X = H)[8] and confirmed by ^1H NMR and ^{13}C HMQC NMR experiments (Table 1). The *exo*:*endo* ratio was determined by integration of the ^1H NMR spectra. The signals for the major diastereomer were assigned to the *exo* complex, which is known to predominate in solution.[1a,8,9]

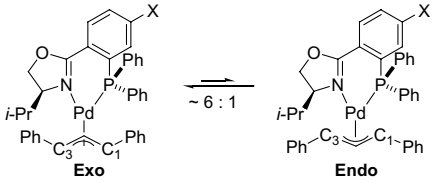
The ratio of *exo* to *endo* diastereomers is believed to play a role in the enantioselectivity of PHOX ligands despite their rapid equilibration in solution.[1,10] Since nucleophilic attack *trans* to phosphorus in the *endo* complex gives the opposite (minor) enantiomer and would, presumably, also be electronically favored, this pathway must be disfavored by some other means. A change in the *exo*:*endo* ratio as a function of substituent would be one possibility; however, complexes **2a**–**f** show a constant, approximately 6:1 *exo*:*endo* ratio for all the substituents investigated. Consequently, the substituent's effect on the ligand's enantioselectivity must have another origin.[11,12]

In contrast to the *exo*:*endo* ratios, the chemical shifts of the allyl carbons do change with different substituents and show the expected downfield trend with electron withdrawing groups. The increased deshielding does correlate with higher observed enantioselectivity (increasing **1a** to **1f**).[3] Contrary to our expectations though, no pronounced changes in the chemical shifts of C_3 are observed in the *exo* diastereomer relative to the others; the chemical shifts of C_1 and C_3 change by about the same amount for both diastereomers. Likewise, the differences between the two allyl termini ($\Delta(\delta C_3 - \delta C_1)$) remain constant at 30.1 ppm for the *exo* complex and 20.4 ppm for the *endo* complex. The larger $\Delta\delta$ for the *exo* diastereomer has been reported in 1,3-dialkylallyl complexes of **2d** and related ligands.[13] In addition, this $\Delta\delta$ difference has been proposed to correlate to diastereomer reactivity for several S,N- and P,N-ferrocene ligand palladium complexes.[14] Therefore, it seems reasonable to conclude that the *exo* complexes of **2a**–**f** are either more reactive or more selective (or both) than the *endo* complexes.[15] This provides an explanation for how the enantioselectivity obtained with these ligands (>98% ee in THF[1]) can exceed the *exo*:*endo* ratio (~8:1 in THF[12]).[16]

These $\delta\Delta$ trends can also be seen in the similar slopes of the Hammett plots of σ_p and σ_m versus the ^{13}C NMR shifts of C_1 (*trans* to N) and C_3 (*trans* to P) in both the *exo* (solid symbols) and *endo* (open symbols) complexes (Fig. 1 and 2).[17] The data fits better to σ_p than σ_m, as judged by R^2.[18] The better fit to σ_p could suggest a more significant substituent influence via N; however, the uniformity of the chemical shift changes of both C_1 and C_3 indicates a similarity in the effects transmitted via N (*para* to X and *trans* to C_1) and P (*meta* to X and *trans* to C_3). Thus, the Hammett fit to σ_p is perhaps best interpreted as a general electron donating/withdrawing effect with a strong resonance component. This makes sense as the allyl fragment is π-conjugated to the ligand via Pd and σ_p is known to have a strong resonance component.[17]

The similarities of **2a**–**f** by ^{13}C NMR in terms of chemical shift changes and $\Delta\delta$ led us to examine some of their X-ray structures to see if any bond length or angle differences could be detected that might explain their differing enantioselectivities. Suitable crystals were obtained for

Table 1. ^{13}C NMR chemical shifts of π-allylpalladium complexes **2a**–**f**



X	*exo*:*endo*[a]	C_1 (*exo*)	C_3 (*exo*)	$\Delta\delta^b$ (*exo*)	C_1 (*endo*)	C_3 (*endo*)	$\Delta\delta^b$ (*endo*)
NMe_2	85:15	69.87	100.03	30.16	73.91	94.22	20.31
OMe	86:14	70.57	100.65	30.08	74.62	95.02	20.40
Me	85:15	70.58	100.80	30.22	74.61	95.18	20.57
H	86:14	70.74	100.85	30.11	74.73	95.14	20.41
F	86:14	71.19	101.26	30.07	75.32	95.63	20.31
Cl	83:17	71.28	101.26	29.98	75.32	95.81	20.49

[a] Ratio determined by integration of ^1H NMR spectra taken in CD_2Cl_2 and based on the average of all resolved peaks for each complex.
[b] $\Delta\delta = \delta C_3 - \delta C_1$.

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