

# Unprecedented Electronic and Steric Effects in Palladium-Catalyzed Asymmetric Allylation: Switching of Enantioselectivity with a Single Chiral Backbone

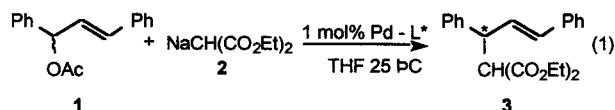
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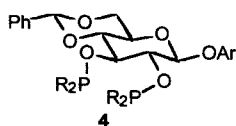
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**Abstract:** In the palladium-catalyzed asymmetric substitution reaction between 1,3-diphenylallyl acetate and sodium salt of diethyl malonate, electron-withdrawing and electron-rich *P*-substituents in a *single chiral back-bone* give products of opposite stereochemistry. Sterically bulky substituents have the same effect as electron-rich ones.

Asymmetric, palladium-catalyzed nucleophilic allylic substitution reaction is an important carbon-carbon bond forming reaction.<sup>1</sup> The mechanisms of the individual steps and the origin of enantioselectivity have been the subject of intense research.<sup>2,3</sup> One of the prototypical reactions which has been studied in considerable detail is the nucleophilic addition of stabilized anions to 1,3-diphenylallyl system (Eq. 1). High enantioselectivity has been



achieved by the use of  $C_2$  symmetric ligands<sup>2a-c,h</sup> and ligands that have chelating atoms with different donor-acceptor properties.<sup>2d-g</sup> In general, four different mechanistic arguments based on the supposition<sup>3</sup> that nucleophilic attack occurs at the diastereotopic allyl termini in the thermodynamically more stable intermediate (Scheme 1. 5), have been proposed for the observed sense of chiral induction: (i) the interaction of the incoming nucleophile with a ligand pendant groups<sup>1b</sup> (ii) distortion of the allylic unit caused by the steric repulsion of one of the ligand substituents and the allylic system<sup>2a-c</sup> (iii) electronic differentiation by trans influence due to different chelating atoms in the square planar Pd-complex<sup>2d,e,g</sup>, and (iv) stability of the Pd-olefin  $\pi$ -complex resulting from the addition of the nucleophile to the  $\pi$ -allyl complexes.<sup>2f</sup> Our interest in this reaction was prompted by the belief that systematic changes in the electronic and steric properties of a *given ligand frame* might provide new insights into these various mechanistic possibilities, and this could lead to new control elements for the enhancement of enantioselectivity. We have successfully used this approach in the discovery of unprecedented electronic amplification of enantioselectivity in asymmetric hydrocyanation<sup>4a-c</sup> and hydrogenation<sup>4d</sup> reactions. In sharp contrast to these two reactions, where the origin of enantioselectivity has been attributed to a difference in the reactivities of diastereomeric intermediates,<sup>5</sup> a direct correlation between the structures of the well-characterized intermediates and the chirality of the products has been established for the Pd-catalyzed allylation reaction.<sup>2,3</sup> The question is, could we alter the equilibrium composition of the relevant diastereomeric intermediates (and possibly the factors listed under ii - iv above) by changes in ligand electronics alone? Can this be parlayed into high enantioselectivity?



In trying to answer these questions we have used a series of pseudo- $C_2$  symmetric ligands **4** which are easily available from carbohydrates.<sup>4</sup> The results are shown in Table 1. Bidentate phosphinites are excellent ligands for this reaction and all of the

chemical yields are nearly quantitative (>95 %). To our surprise, we obtained both (*R*)- and (*S*)-selectivities just by changing the substituents on the aromatic ring of the phosphorus atom. The following features are characteristic of the system: (1) bis-diphenylphosphinite and the corresponding 3,5-dimethyl derivatives gave ~0 %ee (enantiomeric excess) (entries 1 and 2). (2) Phosphinites with large 3,5-substituents in aromatic ring<sup>6</sup> gave (*R*)-selectivity (entries 3-5). (3) Electron-withdrawing groups in aromatic ring generally gave the (*S*)-enantiomer (entries 6-8). (4) In the case of 3,5-bis-(trifluoromethyl)phenyl derivative<sup>7</sup> (entry 5) steric effects seem to take precedence over electronic effects. (5) Aliphatic phosphinites gave (*R*)-selectivity; a larger group (cyclohexyl) giving better ee than a smaller (ethyl) one (entries 9, 10).

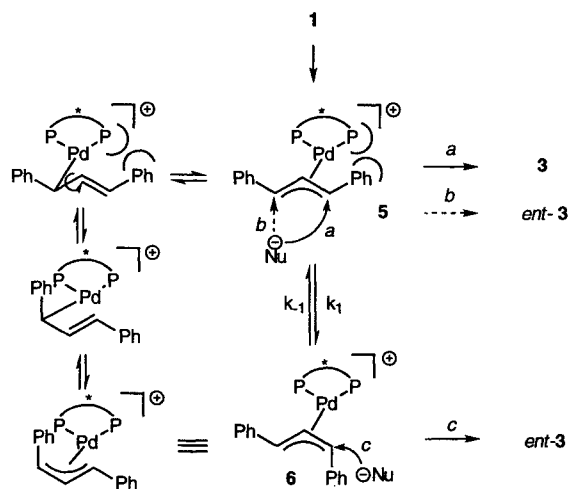
**Table 1.** Electronic and steric effects for asymmetric allylation using various substituents on phosphorus

entry	R <sup>a</sup>	<sup>31</sup> P NMR, ppm <sup>b</sup>	ee, % <sup>c</sup>	config. <sup>d</sup>
1	Ph	118.6, 113.9	~ 0	—
2		121.7, 115.4	~ 0	—
3		122.1, 115.3	16	( <i>R</i> )
4		127.4, 124.5	25	( <i>R</i> )
5		110.6, 108.8	39	( <i>R</i> )
6		116.9, 113.7	17	( <i>S</i> )
7		112.5, 110.5	41	( <i>S</i> )
8		114.0, 111.4	55	( <i>S</i> )
9	Et	146.8, 143.9	18	( <i>R</i> )
10	Cy	151.9, 148.1	59	( <i>R</i> )

<sup>a</sup> Ar of **4** was phenyl except entry 1 in which 2-naphthyl was applied.

<sup>b</sup> Chemical shifts of the ligands in CDCl<sub>3</sub>. 85% H<sub>3</sub>PO<sub>4</sub> was a reference standard. <sup>c</sup> Determined by HPLC analysis with a chiral column (Daicel OJ). <sup>d</sup> Determined by the major peak of HPLC analysis from an authentic (*R*) major sample by the reaction with (*S,S*)-CHIRAPHOS.

At present we do not have an adequate mechanism for this remarkable reversal of enantioselectivity by a remote electron-withdrawing groups.<sup>8</sup> For an explanation, one could argue that the ligand electronics affect the Pd-C bond distances in the intermediate allyl complex and the *syn/anti* equilibrium ( $k_1/k_{-1}$ ) might be different for different phosphinites. Nucleophilic addition at the carbon carrying the *anti*-phenyl group (6, Scheme 1, c) will now lead to the observed product. Surprisingly all reports<sup>9</sup> that propose the induction mechanisms<sup>2,3</sup> assume that enantioselectivity is induced by preferential attack of the nucleophile at one of the diastereotopic allylic termini of 5 (Scheme 1, a vs b), although equilibration of *syn/syn* 5 and *syn/anti* 6 isomers has been recognized.<sup>10</sup> In the context of a C<sub>2</sub> or pseudo-C<sub>2</sub> symmetric ligand it is hard to see how a remote group such as 4-CF<sub>3</sub> on the phosphorus-aromatic ring can bring about a reversal of regiochemistry of nucleophilic addition (Scheme 1, 5 a vs b) to a *syn/syn* intermediate,<sup>11</sup> as has been argued so far. Further studies are in progress.



**Scheme 1.** A plausible mechanism for switch of enantioselectivity with a C<sub>2</sub> or pseudo-C<sub>2</sub> symmetric ligand.

#### Experimental Procedure

All reactions were carried out at 25 °C under a nitrogen atmosphere in a Vacuum Atmosphere drybox. To a solution of  $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$  (1.0 mg, 2.7  $\mu\text{mol}$ ; 0.55 mol%) in THF (1 mL) was added a solution of the phosphinite 4 (6.5  $\mu\text{mol}$ ; 1.3 mol%) in THF (3 mL). A solution of 1 (125 mg, 0.50 mmol) in THF (2 mL) was treated successively with this catalyst solution, and a solution of 2 (109 mg, 0.60 mmol) in THF (4 mL). After the conversion was complete according to TLC analysis, the reaction mixture was taken out of the drybox. Then a saturated NH<sub>4</sub>Cl solution (10 mL) was added, and the organic material was extracted with Et<sub>2</sub>O (20 mL). The extract was dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to afford 3 in nearly quantitative yield.

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