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On the Nature of the Asymmetric Induction in a Palladium Catalyzed Allylic Alkylation

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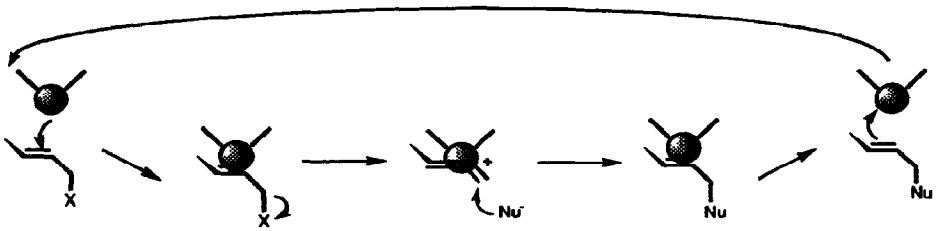
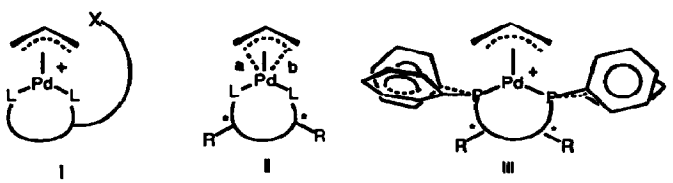
Summary. The source of the asymmetric induction using chiral ligands comprising bis(2-diphenylphosphinobenzoyl) derivatives of chiral diamines and diols in palladium(0) catalyzed allylic alkylations is probed.

While great strides are being made in achieving practical asymmetric induction in a number of reactions, developing models to understand the source of the asymmetric induction, which is so important for prediction and rational design, remains a major challenge. Asymmetric induction in palladium catalyzed allylic alkylations differs from most metal catalyzed reactions in that the bond forming and/or breaking events in any enantiodiscriminating step occur outside the coordination sphere of the metal and therefore far from any chiral ligands coordinated to the metal as outlined in Scheme 1.[1]

Scheme 1. Catalytic Events for the Pd Catalyzed Allylic Alkylation



In order to influence events so distal to the ligands, three concepts have been forwarded; 1) attaching a substituent to the ligand via a tether long enough to reach the other side of the π-allyl unit to interact with any incoming nucleophile as in I[2], 2) effecting electronic dissymmetrization wherein different C-Pd bond lengths **a** and **b** in II lead to a bias to attack at one enantiotopic terminus over another,[3,4] and 3) immersing the substrate in chiral space as illustrated in III for the case of a chiral propellor created by the conformational bias for edge--face interactions of the phenyl groups of the diarylphosphino moieties

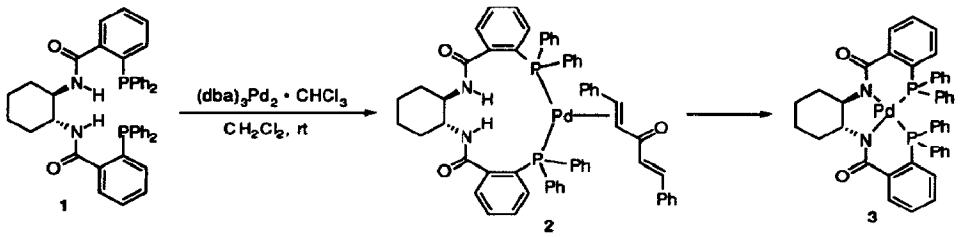


I II III

induced by the primary stereogenic centers.[5,6] Among the ligands reported to date, 2-diphenylphosphinobenzoyl derivatives of chiral diamines have proven to be the most general in giving

high ee's in both ionization[7] and alkylation[8] reactions. In proceeding with developing a suitable working hypothesis, most investigators assume bis-phosphines (or other ligands bearing two potential coordinating sites) function as chelating ligands in the catalytic cycle. Even in those cases where x-ray structures of isolated complexes demonstrate the feasibility of such chelation, the relevance of these isolated complexes to the catalytic cycle is unclear at best in most cases. This issue is particularly thorny with respect to our recently developed ligands since their functioning in a bidentate mode involving the two phosphines requires the formation of a 13 membered ring. We, therefore, undertook studies to define the importance of chelation in the catalytic cycle and to probe how the chiral scaffold, which is so distant from the site of bond making or breaking, can influence these steps.

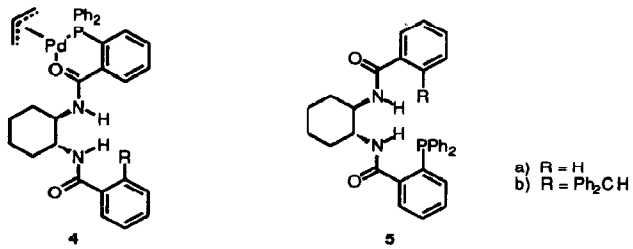
In a throroughly deoxygenated solvent composed of 4:1 THF: C_6D_6, the ^{31}P nmr spectrum of a mixture of ligand **1** and $(dba)_3Pd_2 \cdot CHCl_3$ in a ratio such that P:Pd = 4:1 was recorded. In addition



1 2 3

to the signal for the free ligand at δ -8.9, a clean AB system appeared with δ_A 24.86, δ_B 22.46 and J_{AB} = 14.6 Hz in accord with olefin complex **2**.[9] Thus, non-coordinated ligand does not exchange with coordinated ligand on the nmr time scale and the coupling clearly indicates that the bis-phosphine functions as a bidentate ligand. Exposing the olefin complex to air rapidly converts it to a new complex subsequently identified as **3**.

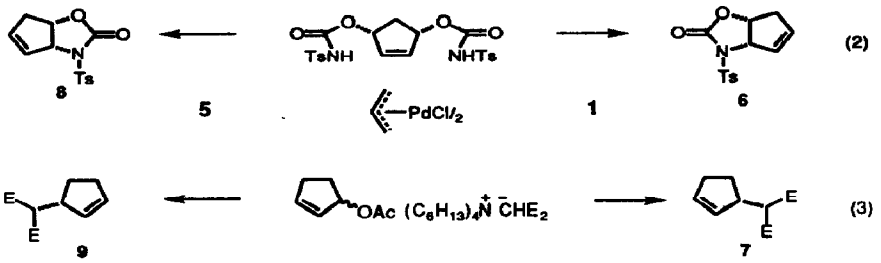
While formation of **2** proves that the bis-phosphine ligand can serve as a chelator involving both phosphines, it does not establish such is the case under the conditions of the alkylation. During the alkylation in addition to bidentate coordination as in **2**, this ligand may function as a monodentate one or possibly as a bidentate one involving the amide as in **4**. To probe these questions, we prepared ligands **5a,b** which cannot serve as bidentate ligands involving two phosphines, but may function



4 5

a) R = H
b) R = Ph_2CH

identically to **1** in any other possible binding mode. In our test reaction of oxazolidin-2-one formation (eq 2), the ee dropped precipitously from 80% with **1** to 40% with **5a** and only 12% with **5b**. A similar dramatic change occurred in the test reaction of alkylation (eq 3) where the ee dropped from 99% with **1**



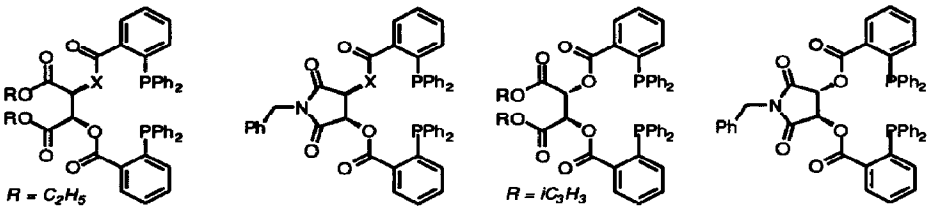
(2)

(3)

to only 19% with **5a**. *More significantly, the sense of chirality in both cases was opposite--favoring 6 and 7 with 1 but their enantiomers 8 and 9 with 5a or 5b.*

If the second phosphino moiety did not play a role in the enantiodiscriminating step, then the nature of the induction in this step should be similar among the three ligands. While any differences observed between **5a** and **1** may be attributed to steric differences associated with the absence of the diphenylphosphino moiety, this argument disappears with **5b** which contains a sterically equivalent benzhydryl group as the replacement of the diphenylphosphino group. The observations that both the magnitude and the sense of the induction between **1** and **5** changes dramatically in spite of the fact that they possess the same chiral scaffold strongly supports the contention that both phosphines of **1** coordinate in the enantiodiscriminating step, a conclusion that could not be reached by an x-ray structure of an isolated π-allylpalladium complex.

With strong evidence implicating ligands like **1** functioning in a bidentate fashion with coordination through phosphorus, we examined the influence of the chiral scaffold. The tartrate derivatives **10** (X=O) and **11** (X=O) are meso and, by definition, must give racemic product.



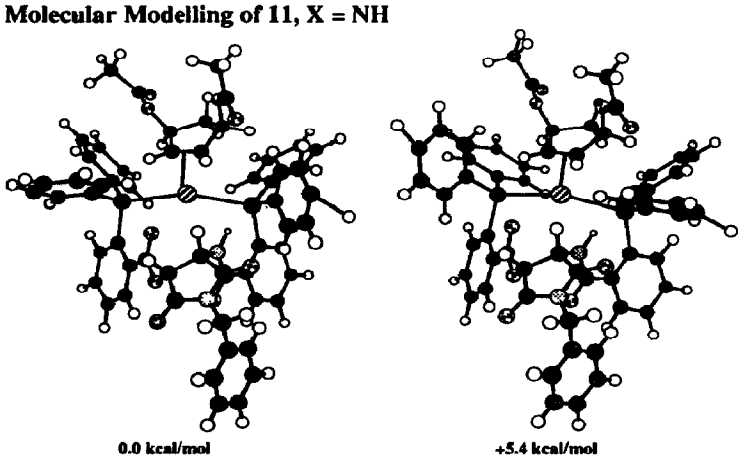
10 **11** **12** **13**

Desymmetrizing these ligands by changing only X should also give ee's approaching zero if the chiral scaffold was directly responsible for the asymmetric induction (e.g., through an effect as in II). In stark contrast to this reasonable expectation, ligand **10**, X = NH (54% ee) significantly *increased* the ee for eq 2 compared to the R,R-tartrate **12** (33% ee) and ligand **11**, X = NH (78%ee) gave a similar ee to the normal R,R-tartrimide **13** (75% ee).

How can a meso-like scaffold give rise to enhanced asymmetric induction quite distant from the scaffold as in the case of allylic alkylation? While the meso tartaric acid derivatives **10** and **11** lack molecular chirality, the bis(diphenylphosphino) moieties still adopt the conformationally chiral right and left handed propellor arrays. Racemic product results from the fact that both conformers will be equal in energy as a result of the achiral scaffold. On the other hand, desymmetrization by simply changing X in **10** and **11** removes the energetic degeneracy between the two propellors. Molecular modelling using the

CAChe system suggests that the two propellors for **11** as depicted in Fig. 1 differ by 5.4 kcal/mol, more than enough to account for the observed ee.

Fig. 1. CAChe Molecular Modelling of 11, X = NH



The picture that emerges using 2-diphenylphosphinobenzoyl derivatives of chiral diols and diamines strongly supports their involvement as bidentate ligands involving both phosphines. Amide or ester coordination is not important in the catalytically active species. Combining this fact with the observation that a meso-like chiral scaffold results in high enantiomeric excess supports the concept that the source of the chiral recognition resides in the conformational chirality of the diphenylphosphino moieties and supports model III as the working hypothesis.

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