On the efficacy of propeller-shaped, C_3-symmetric triarylphosphines in asymmetric catalysis

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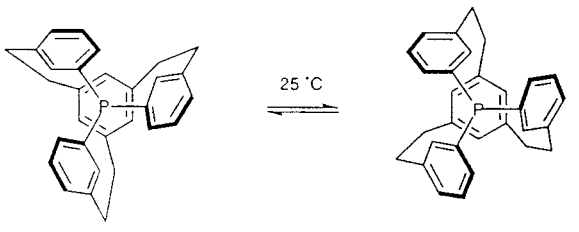
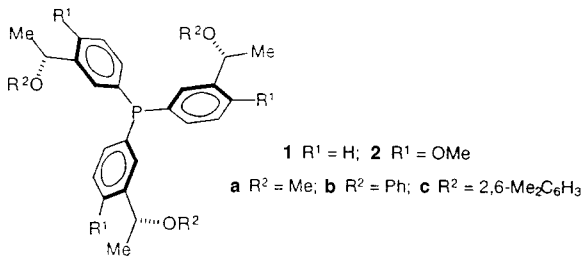
Ligand sets 1 and 2 were prepared and examined for evidence of C_3-symmetric propeller-shaped conformations in solution, and for their ability to induce enantioselectivity in an allylation reaction.

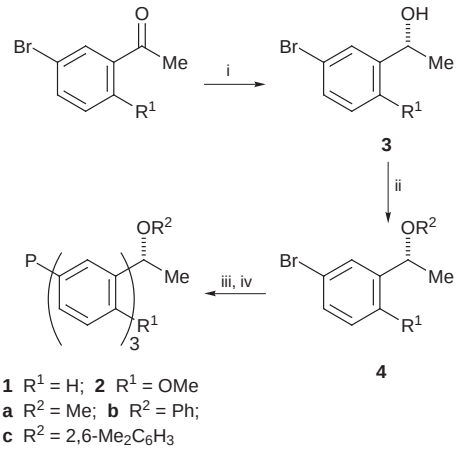
There are conflicting arguments with regard to the potential of optically pure, C_3-symmetric triarylphosphines in asymmetric syntheses. Some researchers may correctly point to the value of C_2-ligands[1] and claim that application of C_3-ligands is a logical extrapolation of the field. C_3-Symmetric arrangements of three aromatic groups around a central atom can adopt stable enantiomeric propeller-shaped conformations that might provide chiral pockets to facilitate enantiodiscrimination.[2] However, the contrary argument is also convincing. Asymmetric induction cannot increase indefinitely with the symmetry of the chiral directing group because a perfectly spherical object would be useless for inducing a chiral environment.

Experimentally, the value of optically active, propeller-shaped, C_3-symmetric phosphines is hard to assess. This is because of synthetic difficulties associated with obtaining the requisite ligands, and due to a lack of techniques to recognize rigid propeller conformations in solution. Sharpless and co-workers, for instance, prepared triarylphosphine cage structures (an example is shown below) by relatively difficult synthetic routes.[3,4] They then found that in an optically active complex, this ligand stereomutates between enantiomeric propeller-shaped conformations at room temperature. This ligand design therefore did not facilitate a test of the efficacy of propeller-shaped C_3-symmetric ligands, hence their value remained questionable. The work described in this manuscript deals with attempts to address this issue using phosphines **1** and **2**. The tenet of this project is that a chiral substituent on the aromatic rings could be easily installed, and may lead to stable C_3-symmetric propeller-shaped aryl arrays in the ligand.



an easily racemized C_3 ligand from Sharpless





Scheme 1 *Reagents and conditions*: i, $BH_3{\cdot}SMe_2$, 5 mol% 4,5,6,7-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2]-[1,3,2]oxazaborolebornane (CBS),[8] CH_2Cl_2, −25 °C, 12 h (94% and 96.2% ee for **1**; 85%, 99% ee for **2**); ii, alkylation (yields range from 70 to 99%, *e.g.* MeI, NaH, DMF for **1a**); iii, ^{t}BuLi, Et_2O, −30 °C, 1 h; iv, PCl_3, Et_2O, −30 to 25 °C (yields typically 30–50% for steps iii and iv)

Scheme 1 outlines the route by which the ligand set **1a–1c** (and later **2a–2c**) was obtained. The route diverges from the common chiral alcohol intermediate **3** hence this strategy is more efficient than ones that rely on different starting materials for each phosphine prepared.

Evidence for preferred stereoisomeric propeller-shaped conformations in solution is hard to obtain. Crystallographic studies of derivatives such as complex **5a** (Fig. 1) indicated the desired conformations exist in the solid state, but these observations can give no indication of their dynamic behavior in solution. Consequently, a set of circular dichroism (CD) spectra was recorded to elucidate solution state conformations. Chiral ordering of the aromatic groups should be accompanied by

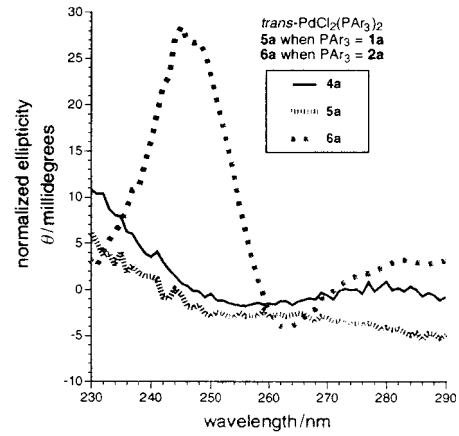


Fig. 1 Comparison of normalized ellipticities (*i.e.* ellipticities per mole of aromatic ring) for compounds **4a**, **5a** and **6a**

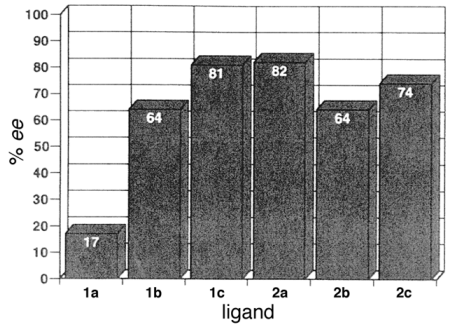
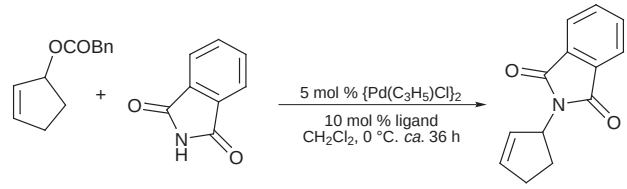


Fig. 2 Phosphines **1** and **2** in an allylation reaction (unoptimized yields, measured by GC using an internal standard: **1a**, 72%; **1b**, 33%; **1c**, 54%; **2a**, 50%; **2b**, 51%; **2c**, 47%)

increased molar ellipticities at wavelengths corresponding to aromatic absorptions for palladium complex **5a** relative to the aryl bromide starting material **4a**.[5] Fig. 1 shows that an increased ellipticity was not observed for complex **5a** derived from ligand **1a**. This led us to suppose that conformational rigidity could be increased by incorporation of a *para*-substituent to disfavor free rotation about the bond to the *meta*-chiral center. Consequently, ligand set **2** was prepared and selected derivatives were examined by CD. Fig. 1 indicates that complex **6a** derived from ligand **2a** does indeed show an enhanced ellipticity relative to intermediate **4a**.

High throughput parallel screens[6] were used to test ligands **1** and **2** in the palladium mediated allylation reaction illustrated below. Thus reactions were run simultaneously in wells contained in a cooled aluminium block, then analyzed using an autosampler/chiral HPLC apparatus. Details of this approach applied in other studies from our group have been documented.[7] Fig. 2 shows the data obtained. The enantioselectivities reached an optimum value of 82%. We think that this level of induction by the distal chiral *meta*-substituents would not be possible unless ordering of the aromatic rings were operative. Enhanced ellipticities when a *para*-substituent is present (*i.e.* **2a** *vs.* **1a**) correlates with dramatically increased enantioselectivities. On average, higher enantioselectivities tend to be observed for the ligands **2** than for series **1**.



The data presented here suggest that phosphines **2** can exist in conformations in which the aromatic groups are ordered in propeller-shaped arrays, and that these same phosphines give significant induction in an allylation reaction. However, it is unlikely that perfectly C_3-symmetric conformations predominate for ligand **2** in complexes because the *meta*-substituent can adopt orientations that are *exo* and *endo* with respect to the metal. Work now in progress concerns a ligand system for which this is not a possibility.

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