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An axially chiral phosphine ligand based on restricted rotation in *N*-arylimides

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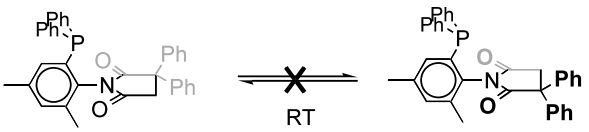
Abstract—Described is the preparation, resolution, and absolute configuration of a new axially chiral monodentate phosphine ligand. The chirality of the ligand is derived from restricted rotation about a central N_{imide}–C_{aryl} bond, resulting in enantiomeric atropisomers that are stable and separable up to >120°C. Finally, the ability of the new axially chiral phosphine ligand is demonstrated in a Pd-catalyzed allylic alkylation reaction.

Chiral phosphines are important molecules in effecting asymmetric transformations as ligands for transition metal catalysts and as chiral nucleophilic catalysts.[1,2] One of the most successful classes of chiral phosphines have been the axially chiral biaryls, as exemplified by the monodentate MOP[3] and the bidentate BINAP.[4] The synthesis of new axially chiral biaryls, however, remains a challenge due to the difficulties in forming the central sterically hindered C_{aryl}–C_{aryl} bond.[5] Therefore, we have set out to develop the chemistry of more synthetically accessible axially chiral molecules based on the restricted rotation in *N*-arylimides.[6,7] Presented, herein, is the synthesis, resolution, structural analysis, and asymmetric transformations of axially chiral monophosphine **1** based upon an *N*-arylimide framework.



(R)-(-)-**1** *(S)*-(+)-**1**

The chirality in monophosphine **1** arises from restricted rotation about the central C_{aryl}–N_{imide} single bond. This structurally hindered bond is readily synthesized by condensation of an *ortho*-substituted aniline and a cyclic anhydride. The resulting *N*-arylimide rotamers are highly stable and are axially chiral enantiomers. Ligand **1** was designed to place its phosphine atom in a highly asymmetric environment. The steric repulsion of the phenyl groups of the diphenylphosphine and the adjacent imide group orient the phosphine lone pair toward the imide surface. This conformation is beneficial as the coordination of a metal center by the phosphine atom would 'enshroud' it in the highly asymmetric environment over the imide ring in which one face would be shielded by the phenyl substituents that project up from the imide surface. In contrast, a structurally similar axially chiral monophosphine reported by Virgil et al. positions the phosphine lone pair over a relatively flat aromatic surface.[8]

One of the primary advantages of monophosphine **1** is that it can be rapidly synthesized from common starting materials (Scheme 1).[9] In contrast to the biaryls, the central bond is readily formed by heating an appropriately substituted aniline with a cyclic anhydride. For example, condensation of aminophosphine **4** with 2,2-diphenylsuccinic anhydride **5** proceeds in high yield (81%) to give (±)-**1** simply be heating the neat components together in vacuo at 150°C.[10] The requisite aminophosphine **4** was synthesized from the corresponding chloroaniline **2** via a nickel-mediated phosphination and reduction with Na/naphthalene.[11]

Racemic phosphine **1** was resolved by coordination with enantiomerically pure (+)-di-μ-chlorobis[(*R*)-2-[1-(dimethylamino)ethyl]phenyl-C^2,*N*]dipalladium(II) (**6**) (Scheme 1).[12] The resulting diastereomeric Pd-complexes (*R*,*R*)-**7** and (*S*,*R*)-**7** were kinetically stable and readily separable by flash chromatography.[13] In fact, a large difference in polarity of the diastereomers was observed ($\Delta R_f = 0.20$), yielding evidence of the highly asymmetric environment present in phosphine **1**. The

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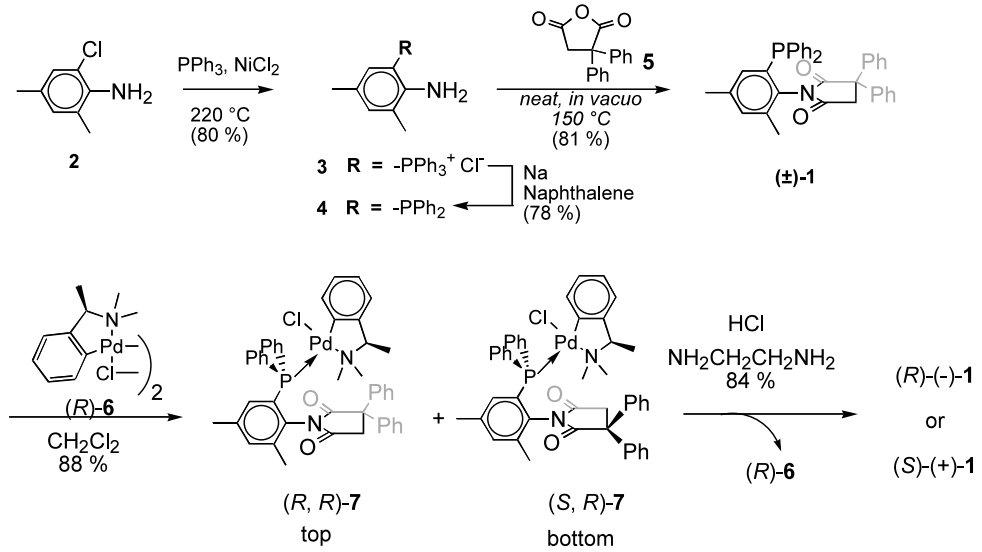
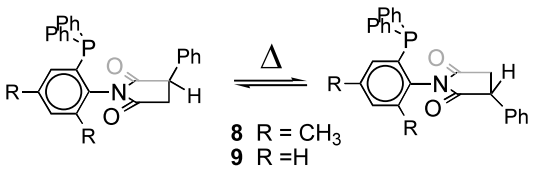


Scheme 1. Synthesis and resolution of monophosphine (±)-**1**.

individual diastereomers of **7** were treated with $NH_2CH_2CH_2NH_2$ to release the enantiomerically pure (*R*)-(−)-**1** or (*S*)-(+)-**1**. Acidification of the aqueous extracts with HCl allowed recovery of the valuable enantiomerically pure Pd-complex (*R*)-**6** in >80% yield.

The conformational stability of phosphine **1** was evaluated by examination of the monophenyl analogs **8** and **9**. Restricted rotation in **8** and **9** is more easily observed as the atropisomers are diastereomers (phenyl up and phenyl down) and are easily separable by flash chromatography (silica gel) and differentiated on the basis of ^{1}H NMR. Models suggest that the missing phenyl group is too far away from the *N*-aryl group to significantly alter the rotational barrier.



Phosphine **8** is directly analogous to phosphine **1**, having both a diphenyl phosphine and a methyl group *ortho* to the imide ring. The diastereomers of phosphine **8** were highly stable and no interconversion was seen even on heating at 110°C (toluene reflux) for 2 days. This sets a lower limit of the rotational barrier of >40 kcal/mol.[14] By comparison the diastereomers of phosphine **9**, which lacks an *ortho*-methyl group, rotates slowly a room temperature. The diastereomers of **9** were initially separable at room temperature (23°C) but rapidly began to interconvert on standing for >10 min, corresponding to a rotational barrier of only 21 kcal/mol.

The three-dimensional structure of phosphine **1** was established by X-ray crystallography (Fig. 1).[15] Enantiomerically pure crystals were obtained by recrystallization of the resolved enantiomers from acetone. Two conformationally independent molecules were observed in the unit cell, which differ slightly in the dihedral angle about the C_{aryl}–P bonds. The observed conformations are almost identical to those calculated by molecular modeling. The cyclic imide and aryl planes are nearly perpendicular (89.7 and 86.0°). Both conformers also maintain the indented orientation in which the phosphine lone pair is pointing into the asymmetric over the imide ring. This leads to a chirally enshrouded environment in which approach from one face of the phosphine is hindered by the steric bulk of the 3,3-diphenyl groups.

The high quality of the X-ray data set and the presence of the phosphorous heavy atom enabled determination of the absolute stereochemistry from the anomalous X-ray scattering data.[16] The (+)-enantiomer was assigned an (*S*)-stereochemistry with a corresponding Flack parameter of 0.01(5).[17] For completeness, the

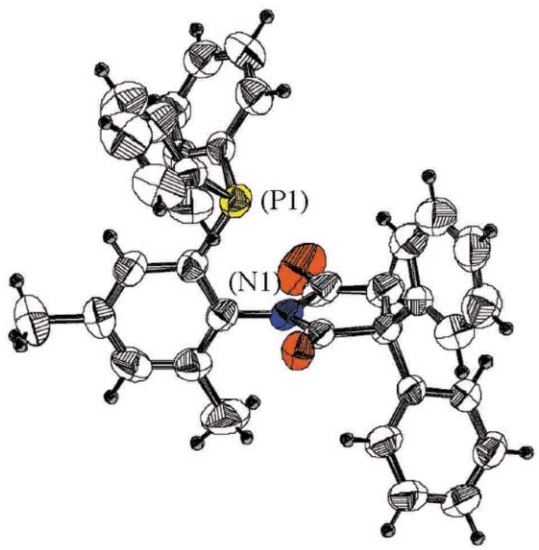
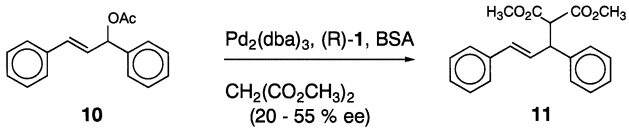


Figure 1. X-Ray crystal structures of (±)-**1**.

Table 1. Reaction conditions and results of the Pd-catalyzed allylic alkylation using (−)-**1**[a]

Entry	Pd (mol%)	(*R*)-**1** (mol%)	Nuc. (equiv.)	BSA[b] (equiv.)	Solvent (mL)	Conversion (%)	Time (h)	ee %[c]
1	5	40	5	10	THF (0.2)	36	64	9
2	5	40	3	6	CH_2Cl_2 (0.2)	99	48	32
3	5	20	3	6	CH_2Cl_2 (0.2)	71	47	42
4	5	20	3	6	CH_2Cl_2 (0.2)	23	24	52
5	5	20	3	4	CH_2Cl_2 (0.2)	14	24	55

[a] Reactions were all carried out using 200 μL of acetate **10** at rt.
[b] *N*,*O*-Bis(trimethylsilyl)acetamide.
[c] ee was measured by chiral HPLC (ChiralPak AD).



Scheme 2.

(−)-enantiomer was likewise crystallized and assigned as the (*R*)-enantiomer with a Flack parameter of 0.08(9).

The ability of monophosphine **1** to effect asymmetric transformations was tested in the well studied Pd-catalyzed allylic alkylation reaction (Scheme 2).[18] Monophosphine **1** is able to induce moderate enantioselectivity with a high of 55% ee (Table 1, entry 5). Higher reactivity and selectivity was observed in CH_2Cl_2 as opposed to THF. In addition, it was found that the reaction appeared to give higher selectivities at lower conversions. While overall the selectivity is moderate using monophosphine in comparison to bidentate phosphine ligands, it is on par with that observed other chiral monodentate phosphine ligands.[3,19] We are currently in the process of surveying the selectivity of monophosphine **1** in other asymmetric reactions in which monodentate phosphine ligands have out performed their bidentate cousins.[3,20,21]

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15. Crystal data for phosphine (+)-**1**: $C_{36}H_{30}NO_2P$, space group $P2_1$, $a=12.8739(7)$, $b=12.8245(7)$, $c=17.8403(10)$ Å, $\beta=94.5560(10)°$, volume = 2936.1(3) Å^3, $Z=4$. A yellow plate crystal of approximate dimensions 0.45 mm× 0.36 mm×0.11 mm was used for X-ray crystallographic analysis. The X-ray intensity data were measured at 293 K using a Bruker SMART APEX CCD-based diffractometer system equipped with a Mo target X-ray tube ($\lambda=0.71073$ Å). The structure was solved and refined using the Bruker SHELXTL (Version 5.1) software package. The final anisotropic full-matrix least-squares refinement converged at $R_1=0.0438$, $wR_2=0.0644$ ($I>2\sigma I$), using 11588 independent reflections. Hydrogen atoms were refined using a riding model. Refinement of the absolute structure parameter (Flack parameter) indicated the compound to be enantiomerically pure.
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