P Ligands

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Primary and Secondary Aminophosphines as Novel P-Stereogenic Building Blocks for Ligand Synthesis**

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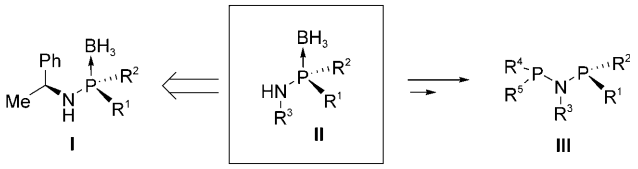
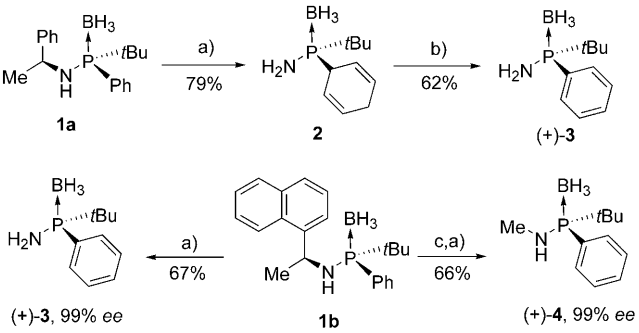
Chiral phosphine ligands are central to asymmetric metal catalysis.[1] The effect of the majority of these ligands arises from the chirality of their backbones; however, P-stereogenic (P*) ligands have garnered renewed interest.[2] After the decisive work of Knowles and co-workers with PAMP and DIPAMP ligands, several efficient syntheses of all-carbon P* compounds have been reported.[3,4] In contrast, P* compounds that contain heteroatoms directly linked to the phosphorus center are scarce, and have found little application in catalysis. This class of substances includes secondary phosphine oxides, which exist in equilibrium with their trivalent phosphinite form.[5] P* aminophosphines, which are the corresponding nitrogen analogues, are even more rare,[6] as free primary aminophosphines tend to dimerize with the evolution of ammonia.[7] However, Kolodiazhnyi et al. have reported that borane aminophosphines of type **I** are stable and that they can be obtained in diastereomerically pure form using 2-phenylethylamine as a chiral amine (Scheme 1).[8] Nonetheless, type **I** compounds do not have any reported applications in asymmetric catalysis, nor has their hydrogenolysis been described. We envisioned that reductive cleavage of the arylethyl fragment should provide borane-protected primary aminophosphines of type **II**, which would be amenable to further transformations and become useful P* building blocks in catalysis. Herein, we report the synthesis of enantiopure P-chiral primary and secondary aminophosphines (**II**) and diphosphinoamines (**III**).



Scheme 1. Strategy explored to synthesize P*-aminophosphine building blocks.

We began by investigating the hydrogenolysis of the known compound **1a**, which contains a *tert*-butyl(phenyl)phosphinamine moiety (Scheme 2), under various



Scheme 2. Synthesis of primary and secondary aminophosphines **3** and **4**. Reagents and conditions: a) Li/NH_3, *t*BuOH, −78 °C, THF; b) $KMnO_4$, Al_2O_3, 0 °C, acetone; c) *n*BuLi, MeI, THF.

reaction conditions; however, all initial attempts failed. We were pleased to find that reaction of **1a** with lithium in ammonia afforded the desired cleavage of the benzylic fragment. Although the phenyl group attached to phosphorus underwent concomitant Birch-type reduction to form the phosphinodiene **2** (Scheme 2), oxidation of **2** with $KMnO_4$ on alumina resulted in **3**; to the best of our knowledge, this is the first report of this compound.[9,10] We were able to circumvent the undesired Birch-type reduction by preparing the naphthyl derivative **1b**. Reductive cleavage of the naphthylethyl fragment in **1b** occurs before the undesired Birch reduction of the phosphine phenyl group. This behavior, which may be attributed to the difference between the reduction potentials of the naphthalene and benzene rings,[11] enabled the efficient syntheses of the primary and secondary aminophosphines **3** and **4**, respectively, from **1b** (Scheme 2). Notably, no isomerization of the phosphorus center was detected under these conditions. Thus, the use of diastereomerically pure **1a** or **1b**

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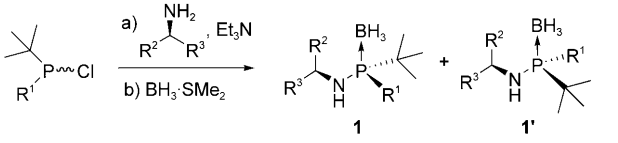
provided optically pure P* aminophosphines (as determined by HPLC on a chiral stationary phase). Most gratifyingly, compounds **3** and **4** were stable crystalline solids.

Having optimized the hydrogenolysis, we then sought to develop a practical and useful methodology for the diastereoselective synthesis of aminophosphines. Substitution reactions of racemic chlorophosphines with chiral alcohols and amines are known to occur under dynamic kinetic resolution at the phosphorus center to produce an uneven mixture of the diastereomers **1** and **1′**.[12] Thus, we tested several commercially available chiral amines with (±)-*t*BuPhPCl and (±)-*t*BuMePCl (Table 1). Among the amines tested, use of

Table 1: Diastereoselective synthesis of bulky aminophosphine boranes.

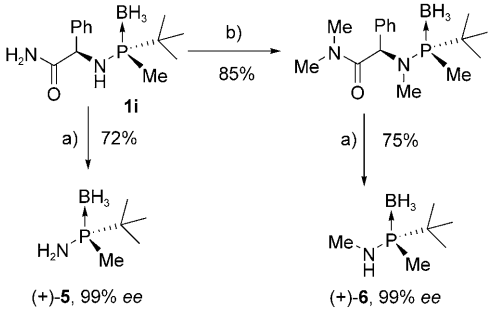


Entry	R^1	R^2, R^3	Yield [%][a]	d.r.[b]	Product
1	Ph	Ph, Me	87	5:1	**1a**,**1a′**
2	Ph	1-naph, Me	91	6:1[c]	**1b**,**1b′**
3	Ph	*p*-tol, Me	88	4:1[c]	**1c**,**1c′**
4	Ph	*p*-$MeOC_6H_4$, Me	90	4:1[c]	**1d**,**1d′**
5	Ph	*p*-ClC_6H_4, Me	88	4.5:1[c]	**1e**,**1e′**
6	Ph	Ph, $CONH_2$	95	1:1	**1f**,**1f′**
7	Me	Ph, Me	91	1:2[d]	**1g**,**1g′**
8	Me	1-naph, Me	90	1:3[d]	**1h**,**1h′**
9	Me	Ph, $CONH_2$	98	1.5:1[d]	**1i**,**1i′**

[a] Yields correspond to product mixtures purified by flash chromatography. [b] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy. [c] Absolute configuration at the phosphorus center was determined by comparison with data in Ref. [8]. [d] Absolute configuration at the phosphorus center was determined from the X-ray crystal structure of the resulting Rh complex **14**.

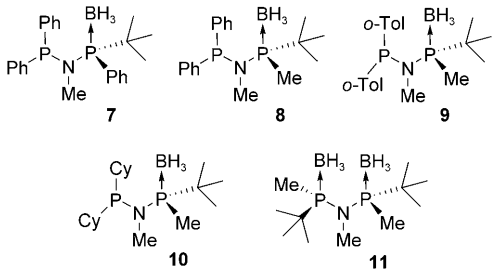
1-naphtylethylamine resulted in the highest selectivities for both chlorophosphines (Table 1, entries 2 and 8). Phenylglycinamide was also found to be a highly efficient resolving agent. Although we encountered low diastereoselectivities, we were able to readily separate both sets of diastereomers (**1f**/**1f′** and **1i**/**1i′**) by chromatography, and, more importantly, these products were highly crystalline, which facilitated their purification. Thus, based on reactivity and separability, we chose 1-naphtylethylamine for the preparation of **3** and **4** (Scheme 2). Alternatively, we found phenylglycinamide to be the most effective resolving agent for the syntheses of **5** and **6** (Scheme 3). Diastereomerically pure **1i** and **1i′** (> 99 % *de*) were obtained by flash chromatography (SiO_2, CH_2Cl_2/EtOAc 1:1). Multigram quantities of **1i** were obtained by crystallization in EtOH.[13] Reductive cleavage of **1i** provided ready access to optically pure aminophosphine **5** (as determined by GC on a chiral support; Scheme 3). Alternatively, exhaustive methylation of **1i** with NaH and MeI followed by treatment with Li/NH_3 afforded the *N*-methyl secondary aminophosphine **6**.

The aminophosphines **3**–**6** are attractive building blocks for the construction of chiral ligands. The reactivity of the amino group should permit further functionalization that can



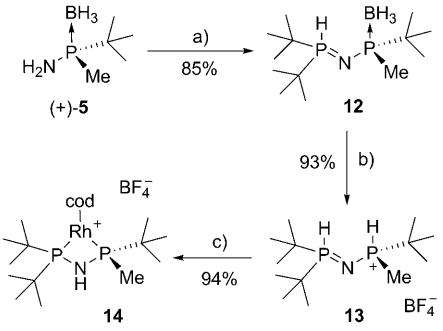
Scheme 3. Synthesis of primary and secondary aminophosphines **5** and **6**. Reagents and conditions: a) Li/NH_3, *t*BuOH, −78 °C, THF; b) NaH, MeI, RT, DMF.

result in novel structures that preserve the original P chirality. A straightforward application of these P* aminophosphines is the preparation of chiral aminodiphosphine (PNP) ligands. Although many PNP ligands have been reported, they have met little success in asymmetric catalysis,[14] as most chiral PNP ligands reported to date derive from chiral amines, and therefore, the chiral center remains far away from the metal center. Thus, the aminophosphines **3**–**6** are ideally suited for the synthesis of PNP* and P*NP* ligands. As a proof of principle, we synthesized a series of diphosphine ligands from the *N*-methylaminophosphines **4** and **6** (Scheme 4). Formation of the anion with *n*BuLi and reaction with R_2PCl provided the C_1-symmetric ligands **7**–**10** with identical optical purity as the starting phosphinoamine. The enantiomeric excess for ligands **7** and **8** was determined to be greater than 99 % by HPLC on a chiral stationary phase, thus ruling out racemization at this point. Alternatively, reaction of **6** with racemic *t*BuMePCl provided a mixture of the *meso* compound and the C_2-symmetric ligand **11** in 41 and 32 % yield respectively.[15] Ligand **11** is a nitrogen analogue of the ligand miniPHOS reported by Imamoto and co-workers.[16]



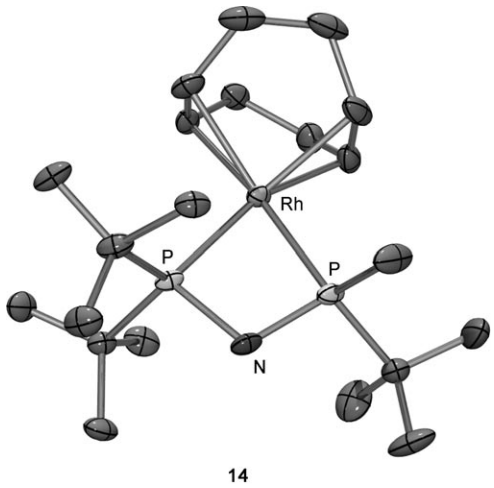
Scheme 4. P-stereogenic aminodiphosphine ligands derived from (+)-**4** and (+)-**6**. Cy = cyclohexyl; Tol = tolyl.

The presence of an alkyl group on the nitrogen atoms generally stabilizes the resulting PNP ligands. However, the free primary aminophosphine is required for reaction with the bulky tBu_2PCl. Thus, reaction of optically pure (+)-**5** with tBu_2PCl provided the bisphosphinamine **12** (Scheme 5). Compound **12** was found to exist exclusively as its P–H tautomer, which prevented the oxidation of phosphorus.[17] Removal of the borane moiety with HBF_4 in MeOH at 60 °C



Scheme 5. Synthesis of the aminodiphosphine rhodium complex **14**. Reagents and conditions: a) NaH, tBu$_2$PCl, 60 °C, THF. b) HBF$_4$, 65 °C, MeOH. c) [Rh(cod)$_2$]BF$_4$, Na$_2$CO$_3$, THF. cod = 1,5-cyclooctadiene.

provided the air-stable phosphonium salt **13** in 93% yield.[18] Compound **13** is a nitrogen-containing analogue of the trichickenfootPHOS (TCFP) ligand reported by Hoge et al.; this compound is one of the most efficient ligands ever developed for asymmetric hydrogenation reactions.[19] Finally, reaction with [Rh(cod)$_2$]BF$_4$ in the presence of sodium carbonate provided the corresponding cationic complex **14**. The X-ray structure of **14** is shown in Figure 1.[20] The solid-



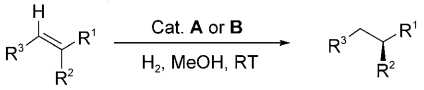
14

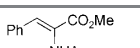
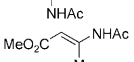
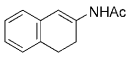
Figure 1. Crystal structure of complex **14** (ORTEP drawing showing thermal ellipsoids at 50% probability). The BF$_4^-$ counterion is omitted for clarity.

state structure confirmed that the aminodiphosphine ligand worked as a C_1-symmetric P–P ligand. The P-N-P angle in **14** is 103.04°, which is wider than the P-C-P angle in TCFP. However, the P–N bonds (1.701 and 1.688 Å) in **14** are shorter than those in TCFP, thus resulting in a bite angle of 70.0°, which is slightly smaller than that of TCFP (72.6°).[19a]

We undertook a preliminary study of the performance of **14** in asymmetric hydrogenation reactions in order to check whether aminodiphosphines could be efficient ligands in catalysis (Table 2). (*Z*)-α-Acetamidocinnamate and (*E*)-β-acetamidobutanoate were reduced with complete selectivity using 0.3 mol% of **14** as catalyst (Table 2, entries 1 and 3). Alternatively, the active ligand–metal species can be conveniently generated in situ by mixing [Rh(cod)$_2$]BF$_4$, **13**, and an organic base. High levels of selectivity were also achieved by following this procedure (Table 2, entry 2). Finally, reduction of *N*-(3,4-dihydronaphthalen-2-yl)acetamide provided the corresponding amine in 99% *ee* (Table 2, entry 4). This pharmaceutically relevant intermediate is known to be a difficult substrate for asymmetric hydrogenation reaction.[21] To the best of our knowledge, our result represents the highest enantioselectivity ever reported for this compound.[22]

Table 2: Asymmetric hydrogenation reactions using either phosphonium salt **13** or rhodium complex **14**.



Entry	Substrate	Cat.[a] (mol%)	H_2 [bar]	*ee*[b] [%]
1		A (0.3)[c]	3	99
2		B (1.0)	3	99
3		A (0.3)	3	99
4		B (3.0)	10	99

[a] Catalyst A: complex **14**. Catalyst B: Rh complex formed in situ by mixing iPr$_2$EtN or Et$_3$N, **13** and [Rh(cod)$_2$]BF$_4$, in a 2.4/1.2/1 ratio. All hydrogenation reactions resulted in greater than 99% conversion. [b] Enantiomeric excess was determined by GC or HPLC on a chiral stationary phase. [c] Reaction time less than 9 h.

In summary, we have reported the first synthesis of optically pure, borane-protected primary and secondary aminophosphines. These compounds were found to be valuable P-stereogenic building blocks in catalysis, as demonstrated with the synthesis of new, chiral asymmetric aminodiphosphine ligands. These building blocks are easily prepared in optically pure form, and, owing to their distinct structural and electronic characteristics, are ideal for exploitation in catalysis.

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