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New Chiral Aminophosphines and Their Use in Asymmetric Catalysis

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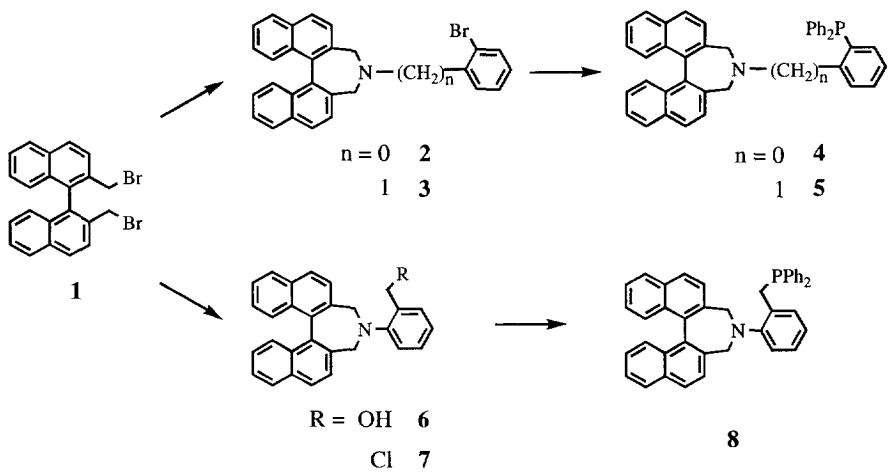
Abstract: Chiral aminophosphines **4**, **5** and **8** were synthesized from **1** in 34%, 57% and 42% overall yield, respectively. The new ligands were investigated with respect to their efficiency in the allylic alkylation of 1,3-diphenyl-1-acetoxy-2-propene with sodium malonate, the cross-coupling reaction of phenethylmagnesium chloride with vinyl bromide, and asymmetric hydrogenations of unsatured mono- and dicarbonic acids. The highest asymmetric inductions were observed with **4** (dimethyl 1,3-diphenyl-allyl-propandioate, 96% e.e.) and **5** (N-acetyl-phenylalanine, 77% e.e.; methylsuccinic acid, 56% e.e., 3-phenyl-1-butene 47% e.e.).

Besides diphosphine ligands especially aminophosphines have drawn considerable attention as chiral auxiliaries in asymmetric catalysis[1]. Only recently attempts have been made to utilize the axial-chiral binaphthyl unit in a bidentate aminophosphine ligand[2]. From a practical point of view compounds such as **4**,**5** and **8** were attractive candidates as the chiral precursor **1** is easily accessible[3,4].

Scheme 1[5]



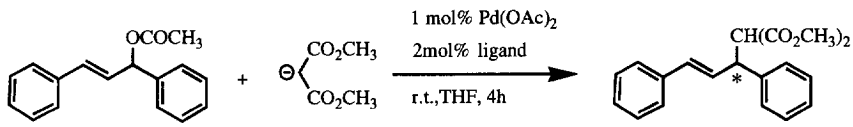
1→**2**: 2-Bromoaniline, Et_3N, toluene, reflux, 48h, 48%. **1**→**3**: 2-Bromobenzylamine, Et_3N, toluene, reflux, 24h, 80%. **2**→**4**: a) n-BuLi, THF, -40°C, 2.5h; b) Ph_2PCl, 71%. **3**→**5**: a) n-BuLi, THF, -40°C, 2.5h; b) Ph_2PCl, 71%. **1**→**6**: 2-Aminobenzyl alcohol, Et_3N, toluene, reflux, 20h, 79%. **6**→**7**: a) HCl/EtOH; b) $SOCl_2$/benzene[6]; c) Δ, 81%. **7**→**8**: Ph_2PLi/THF, 0°C, 65%.

Since the length and rigidity of the P-N connecting carbon back bone will determine the "bite-angle" and thus influencing the catalytic activity and enantioselectivity we chose C_2 and C_3 fragments of moderate flexibility to connect the heteroatoms (scheme 1). Haloazepines **2** and **3** were prepared by the reaction of **1** with bromoamines while **7** was accessible via alcohol **6**. The corresponding aminophosphines were synthesized either by metal - halogen exchange and subsequent treatment with chlorodiphenylphosphine (**4,5**) or by reaction of chloride **7** with lithiumdiphenylphosphide (**8**)[5]. Optically active ligands (+)-**4**, (+)-**5** and (+)-**8** were obtained similarly from (-)-(S)-**1**[3a].

The chiral aminophosphines **4,5** and **8** were tested as auxiliaries in some well known enantioselective catalytic model reactions which are frequently investigated to check scope and limitations of new catalysts.

Asymmetric allylic alkylation: Results of the alkylation of 1,3-diphenyl-2-propenyl-1-acetate with sodium dimethylmalonate catalysed by Pd complexes of **4,5** and **8** are listed in table 1. In all cases the chemical yields were excellent but only **4** exhibited high enantioselectivity. Since the e.e. dropped - especially with **8** - we suspect the presence of monocoordinated intermediates in this case.

Table 1: Allylic alkylation[a]

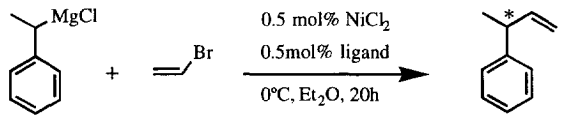


entry	catalyst[b]	isolated yield [%]	% e.e.[c]	product configuration
1	(S)-**4** /$Pd(OAc)_2$	95	96	S
2	(S)-**5** /$Pd(OAc)_2$	93	79	S
3	(S)-**8** /$Pd(OAc)_2$	97	18	S

[a] Typical procedure: To a solution of ligand (2mmol), $Pd(OAc)_2$ (1mmol) and 1,3-diphenyl-2-propenyl-1-acetate (1mmol) in 4ml of $THF_{abs.}$ was added a suspension of sodium malonate (1.5mmol) prepared from NaH (55% dispersion in oil) and dimethyl malonate in 4ml of THF[7]. [b] Prepared in situ. [c] Determined by ^1H NMR using $Eu(hfc)_3$ in $CDCl_3$.

Asymmetric cross-coupling reaction: We investigated the cross coupling of phenethylmagnesium chloride with vinyl bromide in the presence of Ni and Pd catalysts (table 2). Only with **5** a moderate enantioselectivity (46% e.e.) was observed with acceptable reaction rate at 0°C for 20h (entry 5). In the other cases reactivity was low and formation of styrene became a dominant side reaction. The same is true for Pd complexes (not included in table 2).

Table 2: Cross-coupling reaction[a]

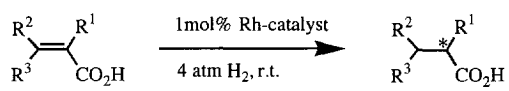


entry	catalyst	isolated yield [%]	styrene[c]	% e.e.[d]	product configuration
4	(S)-**4** /$NiCl_2$	55	28	9	R
5	(S)-**5** /$NiCl_2$	67	2	46	R
6	(S)-**8** /$NiCl_2$	13	34	3	S

[a] Reactions were performed in Et_2O on a 7mmol scale following standard procedures[8]. [b] Prepared in situ. [c] Estimated by ^1H NMR. [d] A commercially available GC column was used: FS-Lipodex-C® (Macherey-Nagel, 50m x 0.25mm i.d.)[9].

Asymmetric hydrogenation reactions (table 3) of (Z)-acetamidocinnamic acid (entry 7), itaconic acid (entry 8, 11), mesaconic acid (entry 9) and citraconic acid (entry 10) were catalysed by Rh complexes of **5** and **8** in presence of triethylamine.

Table 3: Hydrogenation[a]



entry	catalyst[b]	R^1	R^2	R^3	conversion	$[\alpha]_D$	% e.e.[d]	product configuration
7	[**5**Rh(COD)]X[e]	NHAc	H	Ph	100	+35.4	77	S
8	[**5**Rh(COD)]ClO_4	CH_2CO_2H	H	H	100	+9.3	55	R
9	[**5**Rh(COD)]ClO_4	CH_3	CO_2H	H	67	-6.7	59	S
10[f]	[**5**Rh(COD)]ClO_4	CH_3	H	CO_2H	85	-1.9	13	S
11	**8**Rh(COD)Cl	CH_2CO_2H	H	H	100	-7.6	45	S

[a] Reactions were run on a 0.5 - 1.0mmol scale with 1mol% of catalyst and Et_3N (1 equivalent per carboxyl group) in 10ml CH_2Cl_2/MeOH (1:1) (neutral complexes) or MeOH (cationic complexes) at 4 atm H_2 and room temperature for 22h unless otherwise noted; work-up procedures as given in the literature were applied[10]. [b] Prepared from ligands with (S)-chirality and $[Rh(COD)Cl]_2$, $[Rh(COD)]ClO_4$ or $[Rh(COD)]BF_4$, respectively. [c] Estimated by ^1H NMR (MeOD-d_4 or DMSO-d_6). [d] Estimated on the basis of highest reported values for specific rotations: (S)-N-acetyl-phenylalanine: $[\alpha]_D^{20}$ +46.0 (c: 1.0, EtOH)[11]; (R)-2-methyl-succinic acid: $[\alpha]_D^{20}$ +16.88 (c: 1.8, $EtOH_{abs}$)[12]. [e] X = ClO_4 or BF_4. [f] 100h.

Only cationic complexes of **5** revealed moderate optical yields up to 77% e.e. (entries 7-9). Among the isomeric dicarbonic acids citraconic acid was found to be a poor substrate giving only 13% e.e. at a low reaction rate (entry 10). From ligand **8** only a neutral Rh complex could be obtained which exhibited low reactivity and enantioselectivity as shown in entry 11.

Optimization experiments and the extension to other asymmetric reactions are presently under progress.

Acknowledgements

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2 During the preparation of this manuscript two papers were published; one of which reports the synthesis of 2-dimethylaminomethyl-2'-diphenylphosphino-1,1'-binaphthyl (Y. Uozumi, N. Suzuki, A. Ogiwara, T. Hayashi, *Tetrahedron* **1994**, 50, 4293) and the other one describes the syntheses of 4-(2-diphenylphosphinoethyl)-4*H*-dinapth[2,1-c:1',2'-e]azepine and 4-(3-diphenylphosphinopropyl)-4*H*-dinaphth[2,1-c:1',2'-e]azepine and their use in asymmetric catalysis (H. Kubota, K. Koga, *Tetrahedron Lett.* **1994**, 35, 6689).
See also: H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis,* VCH, Weinheim, **1993**.

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