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Synthesis of Chiral Phosphine Ligands with Aromatic Backbones and Their Applications in Asymmetric Catalysis

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Abstract: A general strategy for the synthesis of new chiral phosphine ligands has been discovered. A common feature of these ligands is that they contain rigid aromatic backbones which can be used to restrict conformational flexibility. The bite angle of P-M-P can be changed systematically depending on the aromatic backbone. Many asymmetric reactions can potentially be catalyzed by transition metal complexes of these ligands. Moderate selectivity has been realized in the reaction between 1,3-diphenyl-2-propenyl acetate and dimethyl malonate using palladium complexes of these ligands.

Asymmetric phosphine ligands have played a critical role in the development of novel transition metal catalyzed asymmetric reactions and the discovery of effective new chiral phosphines remains a challenging task. Over 1000 chiral diphosphines[1] have been made for asymmetric catalysis, yet only a few of these ligands provide the efficiency and selectivity required for commercial applications. Some successful chiral bidentate phosphines include DIPAMP,[2] DIOP,[3] Chiraphos,[4] BINAP,[5] and Duphos.[6] While high selectivities were observed in a variety of reactions, there are many cases where these ligands are not very efficient in terms of activity and selectivity. Herein we report a general strategy for the synthesis of new chiral phosphine ligands of the type depicted in Figure 1.

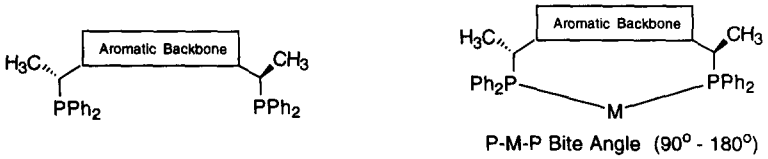


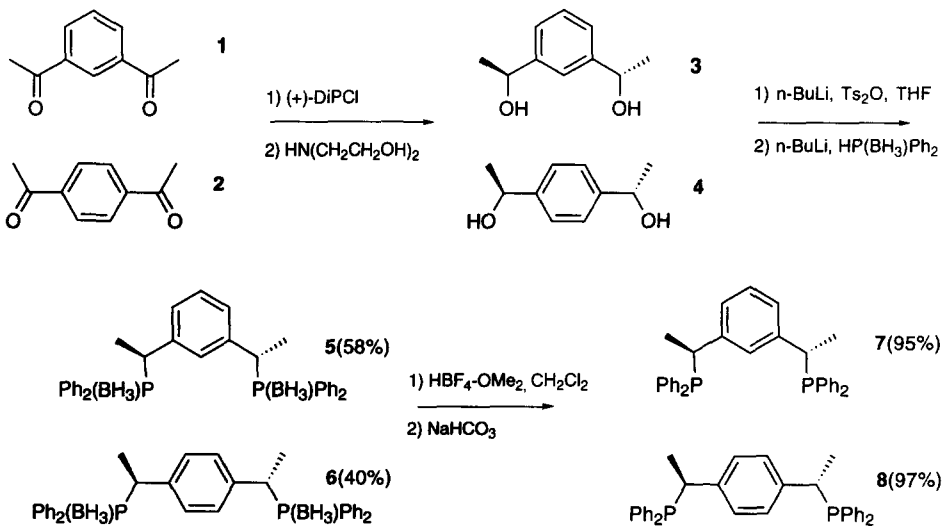
Figure 1

Compared with ligands previously reported, there are several potential advantages to our ligands: 1) these ligands can be easily prepared from readily accessible diketones and; 2) the aromatic backbones are rigid and the efficiency of chiral transfer can be enhanced through this rigidity and; 3) the bite angle of P-M-P can be systematically changed by varying the aromatic backbone.

There are several reports on the synthesis of aromatic aliphatic chiral phosphines which have a structure similar to that illustrated in Figure 1. One system relies on ferrocene as the aromatic backbone in which substitution by HPR_2 can be carried out with retention of configuration at the stereogenic carbon center.[7] Another method utilizes nucleophilic attack of chiral epoxides by $LiPR_2$.[8] In a previous communication,[9a] we reported the synthesis of a chiral tridentate ligand with pyridine as the backbone. However, this method is not general for the synthesis of ligands with the structure depicted in Figure 1. There are two major problems associated with the ligand synthesis. One is the difficulty in forming the ditosylate or dimesylate species and the other is the racemization which occurs during attack by $LiPR_2$. The conventional methods for synthesizing ditosylates and

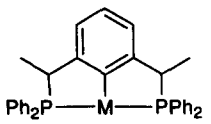
dimesylates often fail when the corresponding hydroxy groups are at benzylic positions. For our system, the tosylate species is formed *in situ* using a literature procedure[10] (Ts_2O + BuLi). Strong bases such as BuLi or $LiPPh_2$ can remove the acidic protons of these ligands and racemization can occur. We have decreased the basicity of the phosphine nucleophile by converting it to the borane protected form. Not only do we prevent the possible racemization during the nucleophilic attack, but also the BH_3 protected phosphines are air-stable and can be purified easily. Deprotection generates a variety of chiral phosphines for asymmetric catalysis. In this preliminary study, we have made two chiral phosphine ligands from commercially available 1,3-diacetylbenzene (**1**) and 1,4-diacetylbenzene (**2**) (Scheme 1).

Scheme 1



Asymmetric reduction of **1** and **2** using (+)-DiPCl gave (1S,1S′)-1,3-bis(1-hydroxyethyl)benzene (**3**, 99% ee with 7% meso diol)[11a] and (1S,1S′)-1,4-bis(1-hydroxyethyl)benzene (**4**, 100% ee after recrystallization from EtOAc and no meso diol)[11b] according to a literature procedure.[12] Tosylations of **3** and **4** were performed *in situ* and nucleophilic attack of $Li(BH_3)PPh_2$ to the tosylates generated the borane protected phosphines **5** and **6**. Single recrystallization of **5** from EtOAc was effective at removing the meso compound. In the final step, BH_3 was removed with HBF_4•OMe_2[13] and enantiomerically pure chiral phosphines **7**[14] and **8** were obtained.

The chiral phosphine **7** is particularly attractive for asymmetric catalysis because it can adopt PCP tridentate coordination with transition metals (Figure 2). Venanzi has prepared racemic ligand **7** and its PCP tridentate coordination complexes with several transition metals.[15,16] Venanzi and Togni made a similar chiral ligand and used it for the asymmetric aldol reaction,[17] while recently, van Koten et al. demonstrated that ruthenium complexes with this type of tridentate ligand are excellent catalysts for transfer-hydrogenation.[18] We have prepared **7** from readily available starting materials and will conduct asymmetric catalytic reactions in this direction.

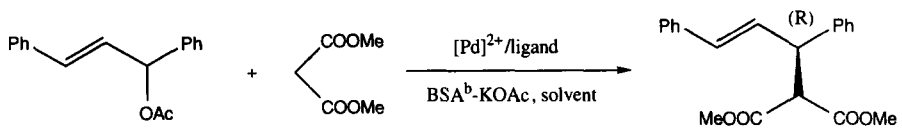


M = Ru, Rh, Ir, Pd, Ni, and Pt

Figure 2

Asymmetric allylic alkylation[19] has been investigated using palladium complexes of the aforementioned ligands **7** and **8** (Table 1). The reaction of dimethylmalonate with 1,3-diphenyl-2-propenyl acetate **9** proceeded smoothly to form the optically active alkylation product **10**.

Table 1. Palladium-catalyzed Asymmetric Allylic Alkylation



9 **10**

Entry[a]	Ligand	Solvent	Cat.	T(°C)	Time(h)	Yield(%)[c]	%ee[d]
1	**8**	CH_2Cl_2	$Pd(OAc)_2$	25	24	63	72
2	**8**	THF	$Pd(OAc)_2$	25	24	62	74
3	**8**	THF	$Pd_2(dba)_3$	25	5	90	57
4	**8**	CH_2Cl_2	$Pd_2(dba)_3$	25	1	95	61
5	**8**	CH_2Cl_2	$[Pd(C_3H_5)Cl]_2$	25	2	99	59
6	**7**	THF	$Pd(OAc)_2$	25	48	18	50
7	**7**	THF	$[Pd(C_3H_5)Cl]_2$	25	18	98	52
8	**7**	CH_2Cl_2	$[Pd(C_3H_5)Cl]_2$	25	1	99	67
9	**7**	CH_2Cl_2	$[Pd(C_3H_5)Cl]_2$	0	8	98	74
10	**7**	CH_2Cl_2	$[Pd(C_3H_5)Cl]_2$	-20	24	94	79

a. 2 mol% Pd, 2.5 mol% ligand; b. BSA= *N,O*-Bis(trimethylsilyl)acetamide; c. isolated yield; d. determined by HPLC analysis using a Chiracel-OD column; the R absolute configuration was determined by comparing the optical rotation with literature values (ref. 17).

Asymmetric catalytic reactions based on **7**, **8** and related ligands are being explored and will be reported in due course.

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