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Asymmetric Synthesis of *N*-(Diphenylphosphinyl)-Ferrocenylamine by the Enantioselective Alkylation of Ferrocenylimine

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Abstract: Optically active *N*-(diphenylphosphinyl)ferrocenylamines with good to high e.e.'s were obtained by the enantioselective addition of dialkylzincs to ferrocenyl-diphenylphosphinylimine in the presence of chiral β-aminoalcohols. The subsequent hydrolysis afforded a chiral ferrocenylamine without racemization.

Optically active ferrocenylamines are important synthetic intermediates for the synthesis of chiral catalysts.[1] Optically active *N,N*-dimethylferrocenylalkylamine[2] has been derived from the ferrocenylalkanol.[3] Although asymmetric alkylation of imine seems to be a more direct approach to optically active ferrocenylalkylamine, only a few diastereoselective methods by the reduction of chiral imine[4] and by the alkylation of chiral hydrazone[5] have been reported. We[6] and others[7] have recently reported enantioselective alkylation of simple imines.

We now report asymmetric synthesis of *N*-(diphenylphosphinyl)ferrocenylamine by a highly enantio-selective alkylation of ferrocenyldiphenylphosphinylimine **1**. Dialkylzinc and imine **1**[8] were reacted in toluene in the presence of chiral β-aminoalcohol. The results are shown in Table 1. When (1*S*,2*R*)-2-morpholino-1-phenyl-1-propanol **2**[6] (MOPEP) was employed as a chiral ligand at room temperature, (+)-*N*-(diphenylphosphinyl)-1-ferrocenylpropylamine **5a** with 88% e.e. was obtained in 67% (Entry 1). (1*S*,2*R*)-*N*, *N*-Diallylnorephedrine **3** (DANE) and *N,N*-dibutylnorephedrine **4** (DBNE) as chiral ligands also afforded **5a** with 88% and 78% e.e., respectively (Entries 4 and 5). When the reaction was performed at 0 °C in the presence of **2**, the e.e. of **5a** increased to 90% e.e (Entry 2). On the other hand, when the ratio of **2** against imine **1** was varied from 1.0 to 0.5, the yield was reduced to half (34%), however, almost no decrease of the e.e. of **5a** was observed (86% e.e.) (Entry 3). This shows that only R_2Zn coordinated with **2** reacts with **1**. Dimethylzinc and di-*n*-butylzinc also afforded alkylated products **5b,c** with 76 and 87% e.e., respectively (Entries 6 and 7).

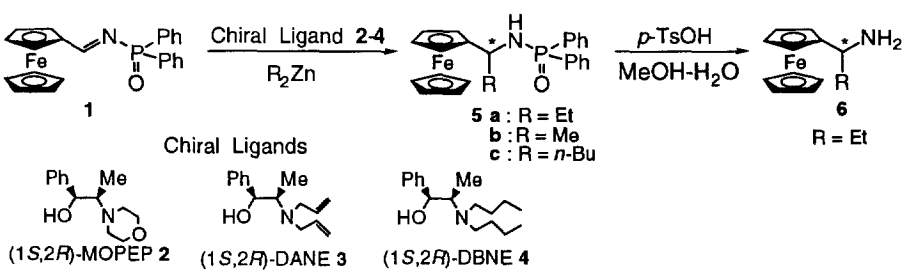

Table 1. Enantioselective Addition of Dialkylzincs to Ferrocenylimine **1** in the Presence of Chiral Aminoalcohol.

Entry[a]	R_2Zn	Chiral Ligand	Temp.(°C)	Time (h)	**5**	Yield (%)	E.e. (% e.e.)[b]
1	Et_2Zn	MOPEP	r.t.	50	**5a**	67	88
2	Et_2Zn	MOPEP	0	119	**5a**	44	90
3[c]	Et_2Zn	MOPEP	r.t.	70	**5a**	34	86
4	Et_2Zn	DANE	r.t.	65	**5a**	56	88
5	Et_2Zn	DBNE	r.t.	60	**5a**	44	78
6	Me_2Zn	MOPEP	r.t.	97	**5b**	13	76
7	$(n\text{-}Bu)_2Zn$	MOPEP	r.t.	66	**5c**	31	87

[a] Unless otherwise noted, molar ratio of imine : R_2Zn : Chiral Ligand was 1.0 : 3.5 : 1.0. [b] Determined by HPLC analyses using a chiral column (Chiralpak AS). [c] Imine : R_2Zn : Chiral Ligand = 1.0 : 3.0 : 0.5.

Subsequent hydrolysis of **5a** (88% e.e.) with *p*-TsOH in H_2O-MeOH afforded optically active (+)-1-ferrocenylpropylamine **6** (88% e.e., analyzed as *p*-toluene sulfonamide of **6**) without any racemization. In addition, the enantiomeric purity of compound **5a** (88% e.e.) was increased to >99% e.e. by the recrystallization (3 times) from a mixed solvent of hexane and ethyl acetate.

In a typical experiment (Table 1, entry 1), (1*S*,2*R*)-MOPEP (0.066g, 0.30 mmol) in toluene (3 ml) was added to a toluene solution (9 ml) of imine **1** (0.124g, 0.30 mmol) at room temperature and was stirred for 20 min. Diethylzinc (1.0 mmol, 1 M hexane solution 1.0 ml) was added at 0 °C and the mixture was stirred at 0 °C for 10 min and then at room temperature for 50 h. The reaction was quenched by adding satd. aq. NH_4Cl. The mixture was filtered using celite and the filtrate was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and was evaporated to dryness. Purification by silica gel TLC afforded **5a** (0.089g, 0.20 mmol) in 67%. Compound **5a** (0.089g, 0.20 mmol) was treated with *p*-toluenesulfonic acid hydrate (0.60 mmol) in a mixed solvent of MeOH (5 ml) and water (1.5 ml) at room temperature for 12 h. Satd. aq. Na_2CO_3 was added and the mixture was extracted with ether. The extract was dried over sodium sulfate and evaporated. Purification of the residue on alumina TLC (developed twice with EtOAc/MeOH=10/1) afforded amine **6** (0.025g, 0.10 mmol) in 50%.

As described, the present method directly provides optically active protected ferrocenylalkylamines.[9]

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