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Synthesis and Potential Application of Novel C_2-Symmetrical Bis(ferrocenyl) P_2N Ligand

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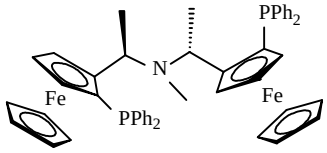
Abstract: A novel chiral bis(ferrocenyl) P_2N ligand **1** with C_2-symmetry was synthesized through a four-step procedure from (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine. In a model reaction of Pd-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate **6** with dimethyl malonate, good enantioselectivity (86% e.e.) was obtained.

Keywords: Synthesis, C_2-symmetry, bis(ferrocenyl) P_2N ligand, Pd-catalyzed allylic alkylation.

Since the pioneering work of Ugi and coworkers on the preparation and the resolution of N,N-dimethyl-1-ferrocenylethylamine and its derivatives nearly three decades ago, various types of chiral ferrocenes have been prepared and successfully applied in the asymmetric organic synthesis[1, 2]. Further development of new ferrocenyl skeletons is still in progress. Recently, great progress has been made in preparing novel chiral C_2-symmetrical bis(ferrocenyl) ligands which include diphosphines[3,4], bis(ferrocenyl)P_2N_2[5], and others[6, 7]. Most of these ligands have been tested with a great success in a number of the catalytic asymmetric reactions[2] such as hydrogenation, hydrosilylation, allylic substitution, cyclopropanation, and so on. Prompted by these observations, we have attempted the preparation of novel C_2-symmetrical nitrogen-bridged bis(ferrocenyl) diphosphine ligand **1**.



1

Starting from optically active (*R*)-N,N-dimethyl-1-ferrocenylethylamine **2** that was achieved from the resolution of the racemate using the well-known Ugi's procedure[8], the target product **1** was synthesized according to the procedure outlined in **Scheme 1**. The highly diastereoselective *ortho*-lithiation of amine **2** followed by treatment with $ClPPh_2$

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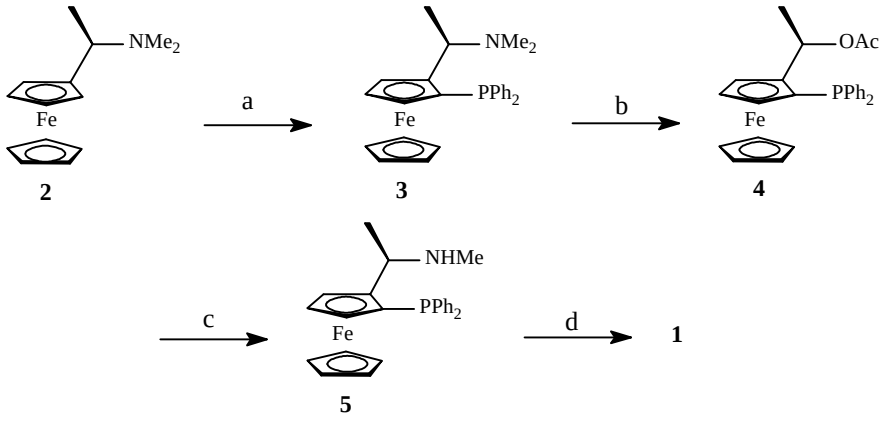
gave phosphine-amine compound **3** [(*R*)-(*S*)-PPFA] in 67% yield. Subsequent acetylation of (*R*)-(*S*)-PPFA **3** with Ac_2O at 100°C gave acetate **4**, which can be directly used for following transformation without purification. Substitution of acetoxy group with methylamino group was carried out by treatment of **4** with an excess of methylamine in CH_3CN yielding methylamino substituted compound **5**. The nitrogen-bridged bis(ferrocenyl) ligand **1**[9] was then synthesized by the substitution reaction of methylamino substituted compound **5** with acetate **4** in refluxing methanol in 51% yield.

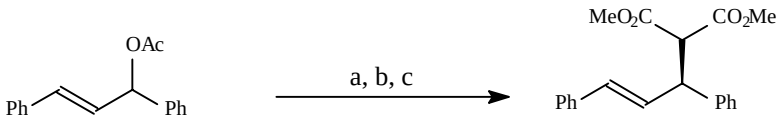
Scheme 1



Reagent and conditions: (a) *n*-BuLi / Et_2O, r.t.; $ClPPh_2$ / Et_2O, reflux; (b) Ac_2O, 100°C; (c) H_2NMe / MeOH, 80-90°C; (d) acetate **4**, MeOH, reflux.

To examine the catalytic efficiency of **1** as chiral ligand in the catalytic asymmetric reaction, a model reaction of Pd-catalyzed allylic substitution of *rac*-1,3-diphenylprop-2-enyl acetate **6** with dimethyl malonate was examined. The reaction was carried out in the presence of 2.0 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 8.0 mol% of chiral ligands, and a mixture of N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate in CH_2Cl_2 (**Scheme 2**). Good enantioselectivity (86% e.e.) was achieved. Further modification and application of ligand **1** are still in progress.

Scheme 2



6 **7**

61% yield, 86% e.e.

Reagents and conditions: (a) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ / ligand **1**, CH_2Cl_2; (b) allylic acetate **6**; (c) $CH_2(CO_2Me)_2$, BSA / KOAc, rt.

Acknowledgments

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References and Notes

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9. Selected data for compound **1**: ^{1}H NMR (DMSO-d_6) δ ppm 1.22-1.24 (d, 6 H, J = 6.4 Hz), 1.33 (s, 3 H), 3.75 (s, 10 H), 3.82-3.83 (m, 4 H), 4.06-4.08 (m, 4 H), 7.17-7.61 (m, 20 H); ^{31}P NMR δ ppm -24.6.

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