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Synthesis of new C_2-symmetrical diphosphines using chiral zinc organometallics

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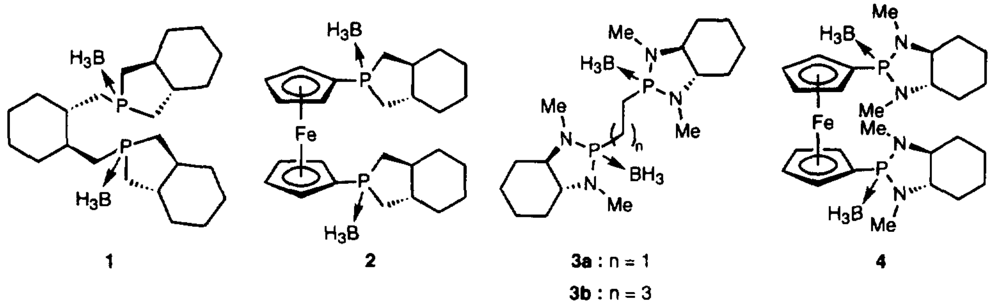
Abstract: The new C_2-symmetrical diphosphines **1–4** of potential interest for asymmetric catalysis were prepared in protected form by a convergent synthesis based on the use of readily available (*S,S*)-1,2-cyclohexanedicarboxylic acid **8** and the phosphorus reagent $(Et_2N)_2PLi{\cdot}BH_3$. © 1997 Elsevier Science Ltd

Chiral diphosphines are an important class of ligands for the performance of metal complexes catalyzed asymmetric transformations.[1] C_2-Symmetrical diphosphines[2] are especially interesting ligands. After complexation to a metal center, two homotopic space regions are defined so that the coordination of a reagent from the top or the bottom face leads to the same chiral intermediate. Recently, we have developed new general synthetic methods for the preparation of polyfunctional and chiral phosphines involving electrophilic phosphorus reagents $(R_{3-n}PCl_n)$[3] and nucleophilic phosphorus reagent $((Et_2N)_2PLi{\cdot}BH_3)$.[4] Herein, we wish to report the application of these methods to the preparation of the new C_2-symmetrical diphosphine–borane complex **1** as well as some related phosphine–borane complexes **2**, **3** and **4** (Scheme 1).



Scheme 1.

A convergent retrosynthesis of the diphosphine **1** involves the reaction of the chiral 1,4-dizinc reagent **5** with the tetrachlorodiphosphino derivative **6**. Both of these compounds are obtained in one step from a common precursor: (*S,S*)-1,2-di(iodomethyl)cyclohexane **7** which is available in a short sequence from the (*S,S*)-diacid **8** (Scheme 2). The diacid *rac*-**8** is readily available in two steps from commercially available *cis*-1,2-cyclohexanedicarboxylic anhydride.[6] The resolution of *rac*-**8** can be efficiently achieved using (*R*)-(+)-phenylethylamine (1.0 equiv) in ethanol. The resolution procedure affords pure (*S,S*)-**8** after three recrystallizations in toluene:ethanol (1:1) followed by an extraction of a 1N HCl solution with ether in ca. 40% yield ($[\alpha]_D^{25}=-64$ (c=5.0, acetone), 99% *ee*).

The enantiomeric excess was determined by converting the diacid **8** in the corresponding dibenzylester (DCC (2.0 equiv), DMAP cat, CH_2Cl_2) and performing an HPLC analysis on a chiral column (DAICEL chiralcel OD; 0.9 mL/min; *n*-heptane: 2-propanol (95:5)). The reduction of (*S,S*)-**8** with $LiAlH_4$ (2.2 equiv, ether, 36°C, 20 h) is furnishing the corresponding diol in 64% yield ($[\alpha]_D^{25}=+22$

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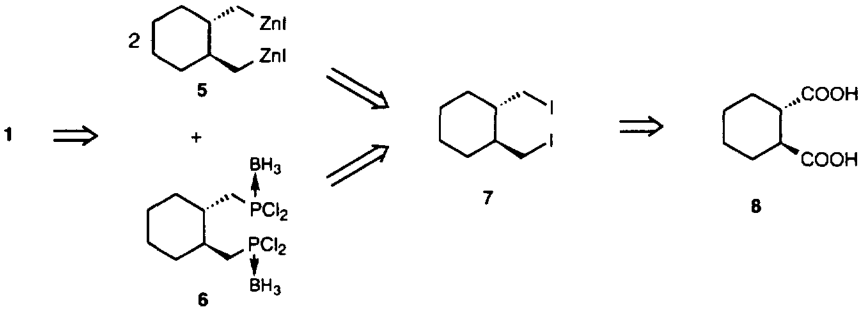


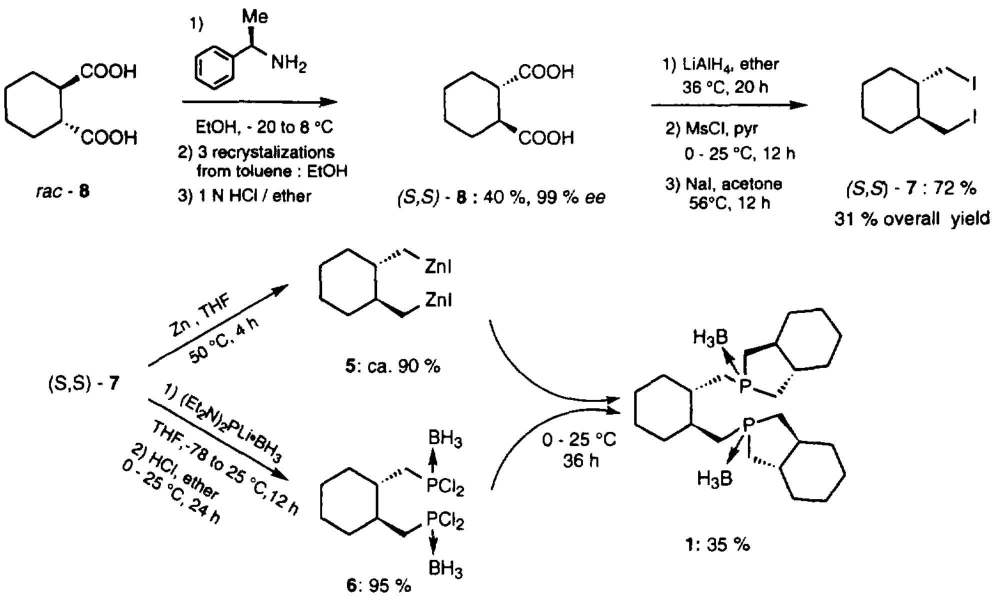
Scheme 2.

(c=5.6, $CHCl_3$)). Treatment with mesyl chloride (2.4 equiv) in pyridine (25°C, 12 h) gives the expected dimesylate in 69% yield ($[\alpha]_D^{25}=-21$ (c=4.8, $CHCl_3$)). Its reaction with sodium iodide (excess, acetone, 56°C, 12 h) affords the pure (*S*,*S*)-1,2-di(iodomethyl)cyclohexane **7** in 72% yield (31% overall yield; $[\alpha]_D^{25}=-54$ (c=2.6, $CHCl_3$)). The key diiodide (*S*,*S*)-**7** was converted to the corresponding dizinc reagent **5** by treatment with zinc dust (−325 mesh) in THF (50°C, 4 h) in 90% yield as determined by iodolysis and gas-chromatographic analysis.[5]

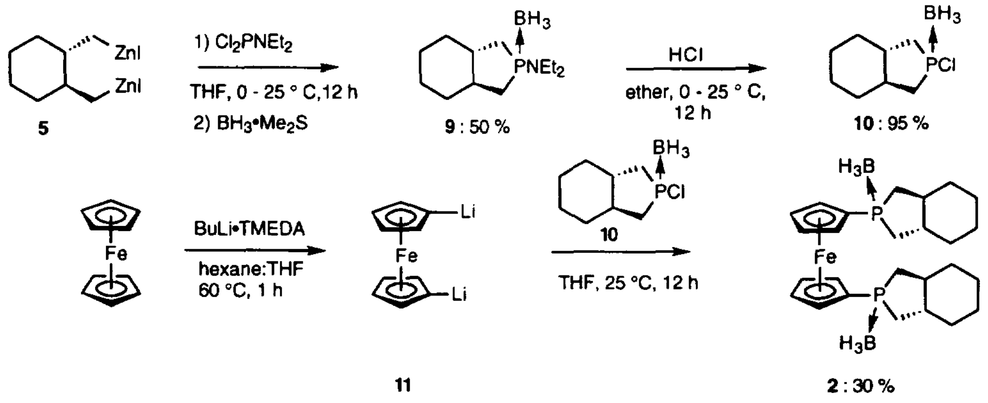
The reaction of (*S*,*S*)-**7** with $(Et_2N)_2PLi{\cdot}BH_3$[4] (8.0 equiv, THF, −80 to 25°C) furnishes by double substitution a diaminophosphine–borane complex in 80% yield. Its treatment with HCl (8.0 equiv) in ether provides the tetrachlorodiphosphine derivative **6** in 95% yield. Interestingly, the treatment of the (*S*,*S*)-zinc reagent **5** with $ClP(NEt_2)_2$ (2.0 equiv) furnishes the intermediate diaminophosphine–borane complex after BH_3 protection in only 20% yield. The mixing of the dizinc reagent **5** (2.0 equiv) with the *bis*-1,2-dichloro-phosphinocyclohexane **6** in THF (0–20°C, 36 h) leads to the desired *bis*-phosphacyclopentane derivative **1** in 35% isolated yield ($[\alpha]_D^{25}=-18.2$ (c=3.0, $CHCl_3$); Scheme 3). The related ferrocenyldiphosphine **2** can be prepared by a similar approach. Thus, the reaction of the (*S*,*S*)-dizinc compound **5** with Cl_2PNEt_2[3a,7] gives after complexation with borane the bicyclic aminophosphine–borane complex **9** (50% yield) which by the reaction with HCl in ether (0°C, 12 h) furnishes the chlorophosphine–borane complex **10** (95% yield; Scheme 4). Dilithiated ferrocene **11**[8] was reacted with **10** leading to the *bis*-phosphinoferrocene–borane complex **2** ($[\alpha]_D^{25}=-17.1$ (c=2.0, $CHCl_3$)) in 30% isolated yield.

As an extension of this work, we have also prepared related aminophosphine derivatives such as the bicyclic chlorophosphine–borane complex **12**[9] starting from the readily available (*R*,*R*)-1,2-*N*,*N*-dimethylaminocyclohexane **13**.[10] This sensitive chlorophosphine is prepared by the reaction of PCl_3 (1.0 equiv) with **13** in the presence of Et_3N (2.0 equiv, ether, 0°C, 12 h) in 78% yield (Scheme 5). The reaction of **13** with the dizinc reagent **14** or the dilithiated ferrocene **11** affords after borane protection[11] the diphosphine–borane complexes **3b** and **4** in respectively 55% and 56% yield. Alternatively, the diamine **13** can also be related with 1,2-*bis*-dichlorophosphinoethane in the presence of Et_3N (4.0 equiv) in ether resulting after borane protection in the formation of the diphosphinoethane derivative **3a** in 51% yield (Scheme 5). The aminophosphine–borane complexes **3b**, **4** and **3a** can be converted to the free aminophosphines by the treatment with morpholine[12] (3.0 equiv, 70°C, 12 h). The resulting free aminophosphines prove to be highly sensitive toward oxygen in contrast with the borane deprotected forms of **1** or **2**.

In summary, we have reported a convergent synthesis of new chiral C_2-symmetrical diphosphines using a convergent synthesis. The utility of ligands **1** and **2** in catalytic asymmetric reactions is currently evaluated in our laboratories.



Scheme 3.



Scheme 4.

Acknowledgements

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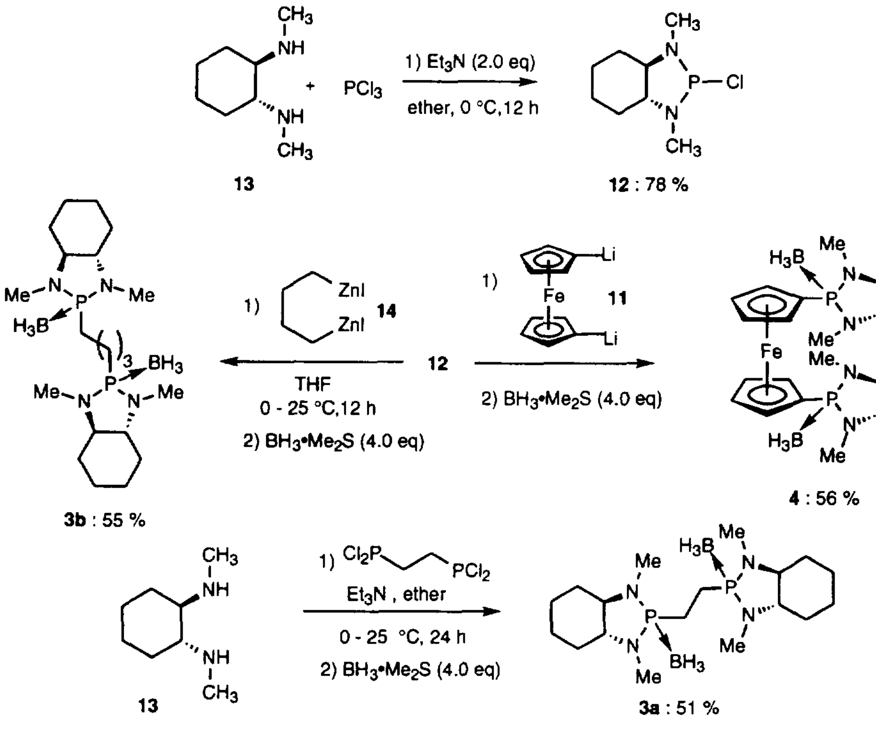

Scheme 5.

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