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Facile axial chirality control by using a precursor with central chirality. Application to the preparation of new axially chiral diphosphine complexes for asymmetric catalysis

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A diastereoselective synthesis of a new chiral diphosphine with planar chirality is performed in 2 steps from (*S*)-*p*-tolylferrocenyl sulfoxide with 60% overall yield. The ligand gives enantioselectivities up to 98% *ee* in Pd(0)-catalyzed allylic substitution reactions.

Molecules having axial chirality have found important applications as ligands in asymmetric catalysis.[1] The enantioselective synthesis of axially chiral compounds can be troublesome,[2] however, an elegant approach for the synthesis of axially chiral binaphthyls has been recently reported by Lipshutz[3] and Bringmann.[4] Herein, we report the synthesis of a new class of planar chiral diphosphines such as **1** using the chiral building block **2**.[5] The diphosphine **1** forms, upon complexation to a metallic salt, axially chiral complexes such as **3**. Due to steric hindrance, the complexation of a metal with ligand **1** will only occur on the upper face away from the bulky ferrocenyl moiety. Furthermore, the diphenylphosphinyl group attached to the upper Cp-ring (see complex **3**) will allow a further right–left differentiation, so that the metallic moiety (L_2M) will be in a well defined steric environment (see Fig. 1).

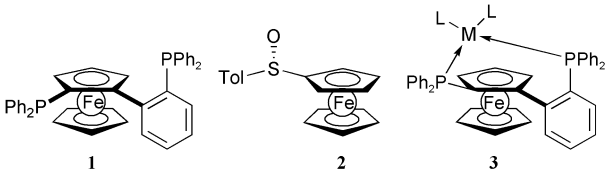


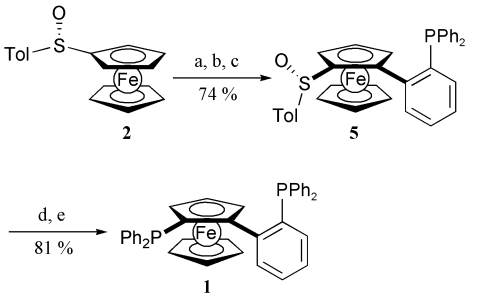
Fig. 1 Structures of the diphosphine **1** and complexes **2** and **3**.

The complexation to the metal center locks the conformation of the aryl ring attached to the ferrocene and thus creates a chirality axis.

The ferrocenyl sulfoxide **2** can be readily prepared in optically pure form according to Kagan.[5] Its *ortho*-lithiation using LDA (−78 °C to room temp., 1 h) followed by transmetallation with $ZnBr_2$ furnishes the corresponding zinc reagent. Negishi cross-coupling[6] of this intermediate ferrocenylzinc derivative with (2-iodophenyl)diphenylphosphine (**4**) in the presence of $Pd(dba)_2$ (5 mol%), tris-*o*-furylphosphine (tpf, 10 mol%) in THF (65 °C, 16 h) afforded the chiral sulfoxide **5** in 74% yield. Sulfoxide–lithium exchange of **5** with *t*-BuLi in THF (−78 °C, 5 min) and trapping of the lithium intermediate with $ClPPh_2$ provides the diphosphine **1** in 81% yield. Thus, the diphosphine **1** was obtained in 2 steps from the sulfoxide **2** in *ca.* 60% overall yield (Scheme 1).

The mode of complexation of the new ligand **1** was verified by forming complex **6** with $[Pd(C_3H_5)Cl]_2$ (0.5 equiv) and $LiClO_4$. The X-ray structure[7] of **6** indicates that only the predicted diastereomeric complex is formed. Therefore, the ferrocenyl moiety efficiently shields the bottom side and the back side (Fig. 2).

The diphosphine **1** was tested in several reactions.[8] Allylic substitution[9] of 1,3-diphenylallyl acetate (**7**) with dimethyl malonate in the presence of $[Pd(C_3H_5)Cl]_2$ (1 mol%) and the chiral ligand **1** (2 mol%) provides the expected allylic



Scheme 1 Synthesis of ligand **1**. Reagents and conditions: (a) LDA (1.1 equiv), THF, −78 °C, 30 min; (b) $ZnBr_2$ (1.3 equiv), THF, −78 °C to room temp., 1 h; (c) $Pd(dba)_2$ (5 mol%), tfp (10 mol%), THF, 65 °C, 16 h, (2-iodophenyl)diphenylphosphine (**4**; 0.7 equiv); (d) *t*-BuLi (2.0 equiv), THF, −78 °C, 5 min; (e) $ClPPh_2$ (3.5 equiv), −78 °C to room temp.

substitution product (**8**) in high yield and 92–98% *ee* depending on the temperature. The highest enantiomeric excess is obtained at −20 °C (98% *ee*) (Scheme 2).

Similarly, the substitution of 1,3,3-triphenylprop-2-enyl acetate (**9**)[10] with dimethyl malonate furnishes with complete regioselectivity the triphenyl derivative **10** in 94% yield and 85% *ee* (Scheme 2). Pd(0)-catalyzed substitution reactions with amine derivatives have also been examined. Thus, the reaction of the potassium salt of benzoylhydrazine leads to the product **12b** in 86% *ee* at 20 °C and in 95% *ee* at −20 °C in 96–98% yield. Finally, benzylamine furnishes at 20 °C the allylic amine **12c** under the standard conditions in 71% yield and 82% *ee*. Only very little conversion was observed, when the same reaction was attempted at −20 °C (Scheme 3).

In summary, we have developed a new simple synthesis of axially chiral diphosphine complexes. The presence of the planar chiral ferrocenyl unit avoids the need of resolution since

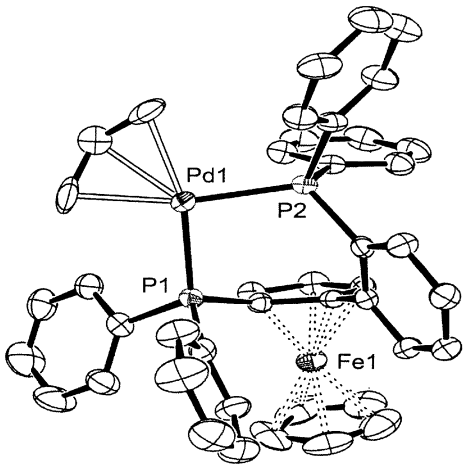


Fig. 2 ORTEP-Plot of the molecular structure of Pd-complex **6** (anion and H-atoms were omitted for clarity). The thermal ellipsoids represent a 50% probability.

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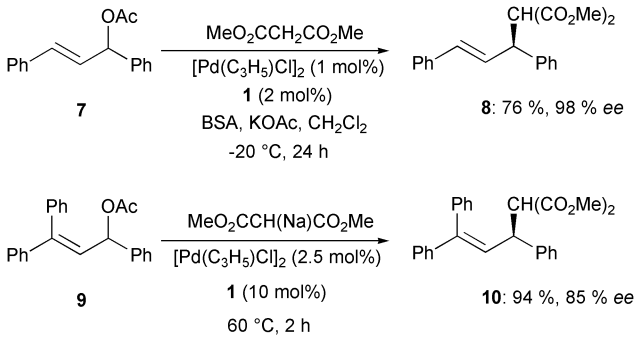
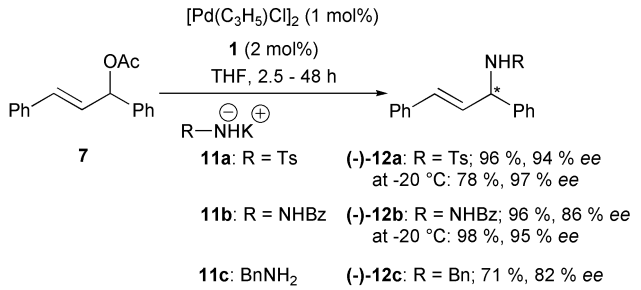


Scheme 2 Pd-catalyzed allylic substitution of acetates **7** and **9** using ligand **1**.



Scheme 3 Pd-catalyzed allylic amination of acetate **7** using ligand **1**.

only one diastereomer is formed in a metal complexation. From central chirality (sulfoxide) we were able to generate stereoselectively a chirality plan and a chirality axis. The new ligand is useful for asymmetric allylic substitutions with malonates and amino derivatives.[10–12] Further applications in asymmetric catalysis are currently underway.

We thank Degussa AG for financial support and for the generous gift of chemicals.

Notes and references

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7 **6**: $C_{43}H_{37}ClFeO_4P_2Pd$, M_r = 877.42 g mol^{-1}, yellow needle, 0.32 × 0.06 × 0.04 mm, orthorhombic, $P2_12_12_1$, a = 9.74630(10), b = 18.7721(2), c = 20.4955(2) Å, α = 90, β = 90, γ = 90°, V = 3749.83(7) Å^3, Z = 4, ρ = 1.55421(3) g cm^{-3}, T = 200(2) K, μ(MoKα) = 1.066 mm^{-1}, numerical absorption correction, 'KappaCCD', λ(MoKα) = 0.71073, θ range: 3.17–27.47, 59657 refls., 8570 independent and used in refinement, 7195 with $I \geq 2\sigma(I)$, R_{int} = 0.0619, mean $\sigma(I)/I$ = 0.0419, C-bonded H are refined with a riding model. The center-C-atom of the allyl ligand is disordered, 468 parameters, $R(F_{obs})$ = 0.0400, $R_w(F^2)$ = 0.1100, S = 1.111, Flack parameter: −0.04(2), min. and max. residual electron density: −1.024, 0.650 e Å^{-3}, max. shift/error: 0.002, programs used: 'SIR97 (Cascarano *et al.*, *Acta Crystallogr., Sect A*, 1996, C79)', 'SHELXL-97 (G. M. Sheldrick. University of Gottingen, 97-2 version)', ORTEP (M. N. Burnett, C. K. Johnson, ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996). CCDC 190672. See http://www.rsc.org/suppdata/cc/b2/b207399d/ for crystallographic data in CIF or other electronic format.
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11 Preparation of diphosphine **1**. (a) Preparation of sulfoxide **5**: LDA (2 M in THF, 1.35 mL, 2.70 mmol, 1.1 equiv) was added dropwise at −78 °C to a solution of (*S*)-ferrocenyl-*p*-tolylsulfoxide (**2**) (793 mg, 2.45 mmol) in THF (15 mL). After 30 min of stirring, $ZnBr_2$ (1.3 M in THF, 2.51 mL, 3.26 mmol, 1.3 equiv) was slowly added and the mixture allowed to warm to room temperature. After 1 h the solvent was evaporated *in vaccuo* and the resulting residue was dissolved in THF (10 mL). $Pd(dba)_2$ (61.2 mg, 5 mol%) and tfp (49.2 mg, 10 mol%) were dissolved in THF (3 mL) and stirred for 10 min. A solution of (2-iodophenyl)diphenylphosphine (**4**) (633 mg, 1.63 mmol, 0.67 equiv) in THF (2 mL) was added and the mixture stirred for an additional 10 min. The solution of the ferrocenyl zinc compound was added and the reaction mixture was stirred at 65 °C for 16 h. The solution was quenched with water, the aqueous phase was extracted with Et_2O (3 × 50 mL), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, pentane/Et_2O 1:2) affording **5** (707 mg, 1.21 mmol, 74 %) as a yellow solid (mp = 198 °C). (b) Phosphorylation of **5** leading to **1**. To a solution of ferrocenyl sulfoxide **5** in THF (8 mL) was slowly added *t*-BuLi (1.6 M in pentanes, 0.64 mL, 1.03 mmol, 2.0 equiv) at −78 °C. After stirring for 5 min, chlorodiphenylphosphine (0.32 mL, 1.80 mmol, 3.5 equiv) was added dropwise, the mixture stirred for 5 min at −78 °C and for 30 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, the aqueous phase was extracted with Et_2O (3 × 50 mL), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, pentane/Et_2O 50:1) affording **1** (260 mg, 0.41 mmol, 81%) as a yellow solid (mp = 187 °C).
12 Typical procedure for the allylic amination of **7**. To a suspension of KH (36.5 mg, 0.91 mmol) in THF (4 mL) was added portionwise *p*-tolylsulfonamide **11a** (200 mg, 1.17 mmol) and the mixture was stirred for 2 h at room temperature. Allylpalladium chloride (dimer, 2.3 mg, 1.0 mol%) and ligand **1** (8.1 mg, 2.0 mol%) were dissolved in THF (1 mL), stirred for 15 min at room temperature and then cooled to −20 °C. Acetate **6** (168 mg, 0.64 mmol) and the suspension of **11a** were added and the reaction mixture was stirred at −20 °C for 48 h. The reaction was quenched with saturated aqueous NH_4Cl solution, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, pentane/Et_2O 2:1) affording **12a** (181 mg, 0.50 mmol, 78%, 97% *ee*) as a white solid.