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Chiral diphosphine ligands based on camphor: synthesis and applications in asymmetric hydrogenations

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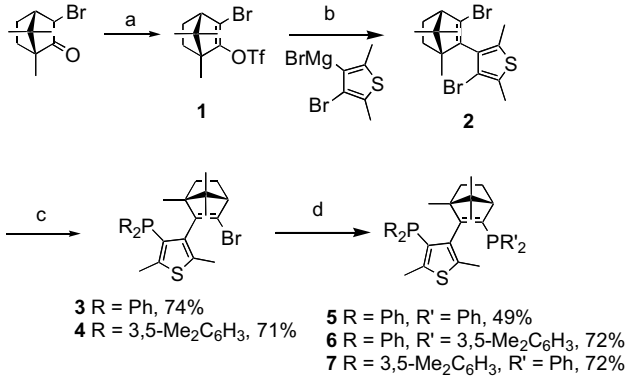
Abstract—The synthesis of a novel class of atropisomer chiral diphosphine ligands with a bornene framework is described. The new ligands showed in Rh catalyzed asymmetric hydrogenation of α- and β-enamides very high ee's (more than 99%).

The development of highly efficient chiral ligands plays a crucial role in expanding the utility of transition metal catalyzed asymmetric reactions. Considerable efforts have been taken in the design and synthesis of axially chiral biaryl ligands.[1] Most of them are readily available, easily modified to obtain various structural futures, and air stable. These advantages make this type of diphosphines very attractive for practical applications. Albeit, racemic resolution is required in most cases to obtain enantiomerically pure atropisomers. Knochel introduced a new type of planar chiral ligand by replacing one of the aryl moiety with a ferrocene unit using chiral ferrocenyl sulfoxide as starting compound.[2] By complexation to the metal, the conformation of the aryl group is locked generating axial chirality. We expanded this concept by replacing the ferrocenyl group with cycloolefinic unit having central chirality. The use of chiral, nonracemic components derived from readily available naturally occurring materials is obviously the most effective strategy to access the ligand in commercial scale. In this respect, terpenes routinely serve the desired chiral cycloolefinic scaffolds by applying sophisticated synthetic methods. Described herein are the first examples of this novel class of ligands containing a bornene backbone, which is combined with axial chirality.[3]

The general route for synthesis of the ligands is illustrated in Scheme 1. Commercially available 3-bromocamphor was converted to the corresponding vinyl triflate **1**. The key intermediate **2** was prepared by means of cross-coupling with a Grignard reagent. Applying the reaction conditions we optimized gave chemoselectively the desired product **2** in 78% isolated yield as a mixture of two atropisomers in 9:1 ratio. These atropisomers did not racemize even in boiling DMSO that is consistent with an activation barrier of 36 kcal/mol calculated using MMFF force field.[4] Assignment of the NMR signals was established by applying multidimensional



Scheme 1. Reagents and conditions: (a) (i) LDA, THF, −30 °C, (ii) *o*-$PyNTf_2$, 88%, (b) 3-bromo-2,5-dimethylthienyl-4-magnesium bromide, $Pd(PPh_3)_2Cl_2$, 50 °C, THF, 78%, (c) (i) *n*-BuLi, THF, −78 °C, (ii) $ClPR_2$, (d) (i) *t*-BuLi, THF, −90 °C, (ii) $ClPR'_2$.

Keywords: Asymmetric synthesis; Homogeneous catalysis; Phosphane ligands; Rhodium; Terpenes.
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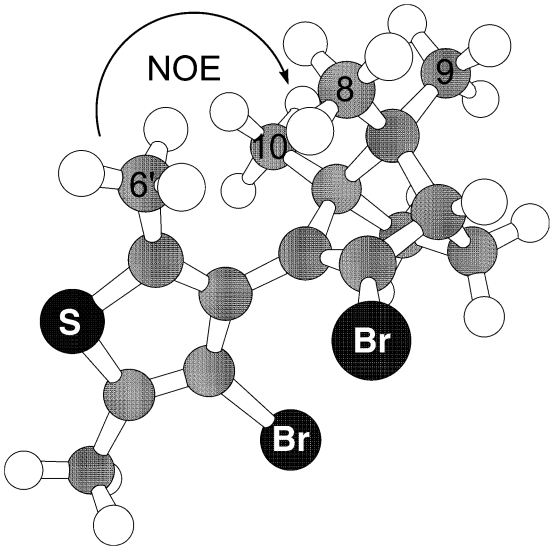


Figure 1. Optimized at pBP/DN* level geometry of major atropisomer of **2**.

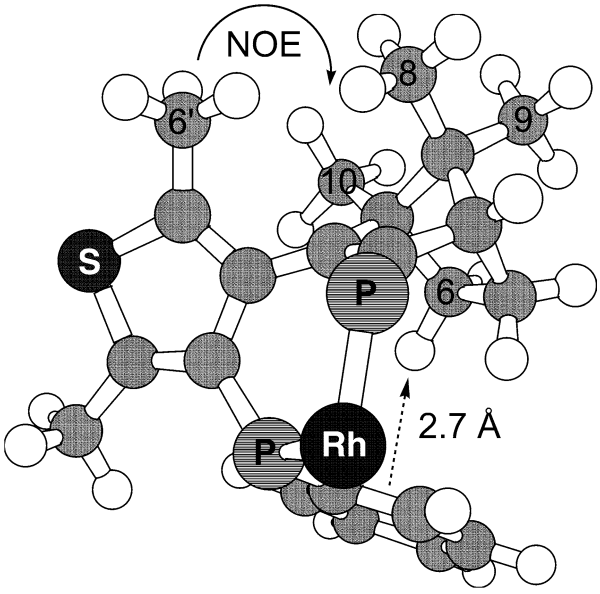


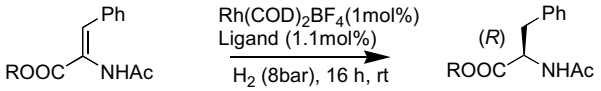
Figure 2. Optimized at pBP/DN* level geometry of the complex **8**. The cod-ligand at Rh and three P-phenyl groups are omitted for clarity.

NMR experiments. The (R_a)-configuration for the major isomer was deduced from NOE correlations observed between 6′-H, 8-H and 10-H as shown in computer-generated three-dimensional drawing (Fig. 1). It is not necessary to resolve the atropisomers for the large scale synthesis. The intermediary monophosphine derivatives **3** and **4** crystallize from the reaction mixture as a single isomer in 71% and 74% yields. This is achieved after bromine–lithium interconversion at the thienyl group followed by a reaction with the corresponding chlorophosphine. Next metalation with *t*-BuLi[5] and subsequent electrophilic phosphinylation with chlorodiarylphosphine delivered the desired diphosphine ligands **5**–**7** in satisfactory yields. The new compounds have a remarkable large coupling constants[5] J(P,P) (= 20–24 Hz).

The Rh(I) complex **8** ([Rh(**6**)(cod)]BF_4) was prepared from [Rh(cod)(acac)] and ligand **6** according to the known procedure.[6] The stereochemistry of the obtained products **6** and **8** was confirmed by multidimensional NMR experiments and has the same configuration around of the chiral axis as the starting dibromide **2**.[7] Noteworthy is the abnormally high field position (−0.30 ppm) in the ^{1}H NMR spectrum of **8** assigned to 6-H_{ax}. According to DFT-calculations, 6-H_{ax} is located at close-contact perpendicular distances of 2.7 Å above the face of one of the P-phenyl ring and thus experiences ring current shielding. A three-dimensional model of the optimized structure of complex **8** depicted in Figure 2 is consistent with the NOESY experiment.

We examined the performance of the novel ligands in asymmetric hydrogenation model substrates at standard conditions. Particularly promising results were achieved in the Rh-catalyzed hydrogenation of (*Z*)-α-(*N*-acetamido)cinnamates. All three ligands produced (*R*)-*N*-acylaminoacids and their esters with good to excellent enantioselectivities (Table 1).

Table 1. Enantioselective hydrogenation of (*Z*)-α-(*N*-acetamido)-cinnamates using Rh(I)-complexes with new ligands[a]



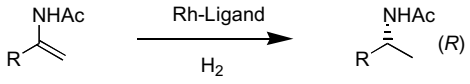
R	Ligand	Solvent	ee[b] (%)
H	**5**	MeOH	99.4
H	**6**	MeOH	96
H	**7**	CH_2Cl_2	99.6
Me	**5**	CH_2Cl_2	99.2
Me	**6**	CH_2Cl_2	97
Me	**7**	CH_2Cl_2	76

[a] Conditions: 0.2 mmol substrate, 2 μmol [Rh(COD)$_2$]BF_4, 2.2 μmol ligand, 1 mL solvent, 20 °C, 8 bar, 16 h. The reaction proceeds quantitatively.

[b] Enantiomeric excesses were determined by chiral HPLC on ChiralPak AD (hexane–2-PrOH, 75:25).

To explore the performance of new ligands, a variety of α-enamides were prepared according to the literature procedures.[8] The best results from screening various solvents are summarized in Table 2. In all cases the reaction proceeded smoothly with a substrate to catalyst ratio of S/C = 100 at ambient temperature to give the hydrogenation product in almost quantitative yield after 4 h. An enantiomeric excess of 84–99% was reached by employing ligands **5** and **6**. While the catalyst derived from **7** surprisingly gave lower asymmetric induction. The highest enantioselectivity of 99.7% was observed with ligand **6** in the hydrogenation of the *N*-acetyl-1-(3-nitrophenyl)-ethenamine. There are several electronically more rich alkylphosphine ligands[8,9] that are effective in hydrogenations of electron-rich enamides. However, in general, lower enantioselectivities are observed with ligands in the hydrogenation of α-arylenamides with electron-withdrawing substituents.[9b,10] When the isolated complex **8** was employed at S/C =

Table 2. Enantioselective hydrogenation of enamides using Rh(I)-complexes with new ligands[a]



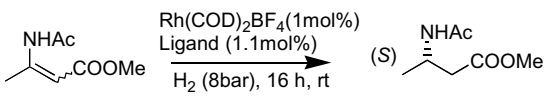
R[d]	Ligand	Solvent	H_2, bar	Time (h)	ee[b] (%)
t-Bu	**5**	CH_2Cl_2	50	3	87 (*S*)
t-Bu	**6**	CH_2Cl_2	50	3	84 (*S*)
t-Bu	**7**	Toluene	50	3	66 (*S*)
Ph	**5**	Toluene	50	4	88 (*R*)
Ph	**6**	MeOH	8	16	92 (*R*)
Ph	**7**	MeOH	8	16	46 (*R*)
4-ClC_6H_4	**5**	MeOH	50	3	84 (*R*)
4-ClC_6H_4	**6**	MeOH	50	3	85 (*R*)
4-ClC_6H_4	**7**	MeOH	50	3	56 (*R*)
2-$C_{10}H_7$	**5**	Toluene	50	4	94 (*R*)
2-$C_{10}H_7$	**6**	Toluene	50	4	98 (*R*)
2-$C_{10}H_7$	**7**	Toluene	50	4	44 (*R*)
3-$NO_2C_6H_4$	**5**	MeOH	50	3	97 (+)
3-$NO_2C_6H_4$	**8**	Toluene	5	1	99.7 (+)
3-$NO_2C_6H_4$	**8**	MeOH	60	1[c]	99 (+)
3-$NO_2C_6H_4$	**7**	MeOH	50	3	76 (+)

[a] Conditions: 0.2 mmol substrate, 2 μmol $[Rh(COD)_2]BF_4$, 2.2 μmol ligand, 1 mL solvent, 20 °C. The reaction proceeds quantitatively.
[b] Enantiomeric excesses were determined by chiral GC on CP Chirasil Dex-CB.
[c] The reaction was carried out in 2 mmol scale with S/C = 1000. Conversion 95% after 1 h.
[d] 2-$C_{10}H_7$ is naphthyl-2.

1000, 95% conversion was obtained within 1 h to afford the desired product in 99% ee. To the best of our knowledge, these results represent the highest enantioselectivity and activity achieved in Rh-catalyzed hydrogenation of this challenging substrate. The nitro-substituted phenylethylamines are important intermediates for pharmaceuticals,[11] particularly, the 3-nitro derivative is used in the synthesis of inhibitors of IMPDH enzyme.[11a]

In order to examine further the synthetic utility of the new ligands, β-dehydroaminoacids were used as test substrates. The hydrogenation results of (*Z*)- and (*E*)-methyl 3-acetylamino-but-2-enoates are summarized in Table 3. Excellent enantiomeric excesses of >99% were reached by the hydrogenation of *E*-isomer. With the more challenging *Z*-substrate, the catalysts based on ligand **6** provided high ee of 94%. The encouraging results of enantioselective hydrogenation presented herein indicate that the new ligands are able to form a suitable asymmetric environment around the metal, resulting in high asymmetric induction.

Table 3. Enantioselective hydrogenation of (*Z*)- and (*E*)-methyl 3-acetylamino-but-2-enoates using Rh(I)-complexes with new ligands



Configuration	Ligand	Solvent	ee[a] (%)
E	**5**	CH_2Cl_2	99 (*S*)
E	**6**	MeOH	99.3 (*S*)
E	**7**	THF	99 (*S*)
Z	**5**	CH_2Cl_2	81 (*S*)
Z	**6**	CH_2Cl_2	94 (*S*)
Z	**7**	MeOH	91 (*S*)

[a] Enantiomeric excesses were determined by chiral GC on CP Chirasil Dex-CB.

In conclusion, we have developed a new class of diphosphine ligands possessing a bornene backbone in combination with the axial chirality. Their catalytic potential has been demonstrated in the highly enantioselective Rh-catalyzed hydrogenation of α- and β-enamides. Full details of this survey along with further applications in new asymmetric reactions and the successful upscaling of the new ligands will be published shortly.[12]

Acknowledgements

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