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Synthesis of new chiral monodentate phosphines and their use in asymmetric hydrogenation

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Abstract—A general synthesis of chiral 4,5-dihydro-3*H*-dinaphthophosphepines **1a**–**g** is described. The resulting ligands represent a new class of monodentate chiral phosphines. First applications of **1a**–**g** in the rhodium-catalyzed asymmetric hydrogenation of unsaturated carboxylic acid derivatives demonstrate the usefulness of our ligands. Enantioselectivities up to 95% ee for the hydrogenation of methyl α-acetamidocinnamate were obtained in the presence of **1d**. This result represents one of the highest enantioselectivities reported for asymmetric hydrogenation in the presence of monodentate phosphines.

The synthesis of new chiral phosphines is of major importance for organic synthesis. In general, bidentate phosphine ligands have been found to give excellent control in a number of catalytic asymmetric reactions. Nevertheless, there is a continuing interest in new, simpler phosphine ligands, which can be modularly designed.

Among the different transition metal-catalyzed reactions enantioselective hydrogenations are probably the most important class of catalytic asymmetric reactions in industry.[1] In the past optically active diphosphines were essential as chiral ligands in order to achieve high selectivities in these reactions.[2] Attempts to develop chiral monodentate phosphine ligands for asymmetric hydrogenation reactions which would afford high enantioselectivities met only with limited success.[3] To the best of our knowledge the highest enantioselectivity (90% ee) has been reported already in 1972 with CAMP ($R^1R^2R^3P$, R^1 = *c*-Hex, R^2 = *o*-Anisyl, R^3 = Me) as ligand for the hydrogenation of (*Z*)-α-acetamidocinnamic acid derivatives.[3c,4] Very recently however, more efficient monodentate phosphoramidates were introduced by de Vries and Feringa et al.[5] as well as by Zhou et al.[6] for asymmetric hydrogenation reactions. Monodentate phosphites and phosphines giving high enantioselectivities were reported by Reetz et al.,[7] by Orpen and Pringle[8] and by Helmchen et al.[9]

Due to the often easier synthesis of monophosphines compared to diphosphines as well as the possibility of a simple biphasic recycling of chiral phosphines by introducing water-soluble groups we became interested in the synthesis of chiral monodentate phosphines, which are easily accessible, and would give improved enantioselectivities in asymmetric hydrogenation reactions.

At the start of our investigations we envisioned the use of different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]-phosphepine ligands **1**. Surprisingly, these monodentate atropisomeric ligands have been only scarcely investigated.[10,11] With the exception of a more complicated resolution reaction by Gladiali and co-workers, there has been no synthesis of enantiomerically pure ligands **1** described.[10] As shown in Scheme 1, seven different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **1** were synthesized in a simple and straightforward manner from homochiral 2,2′-dimethylbinaphthyl.[12]

On the one hand double metallation of 2,2′-dimethylbinaphthyl with *n*-butyl lithium in the presence of TMEDA (tetramethylethylendiamine) and quenching with commercially available dichlorophosphines gives ligands **1a**–**d** in 60–83% yield.[13] On the other hand double metallation, quenching with diethyl-

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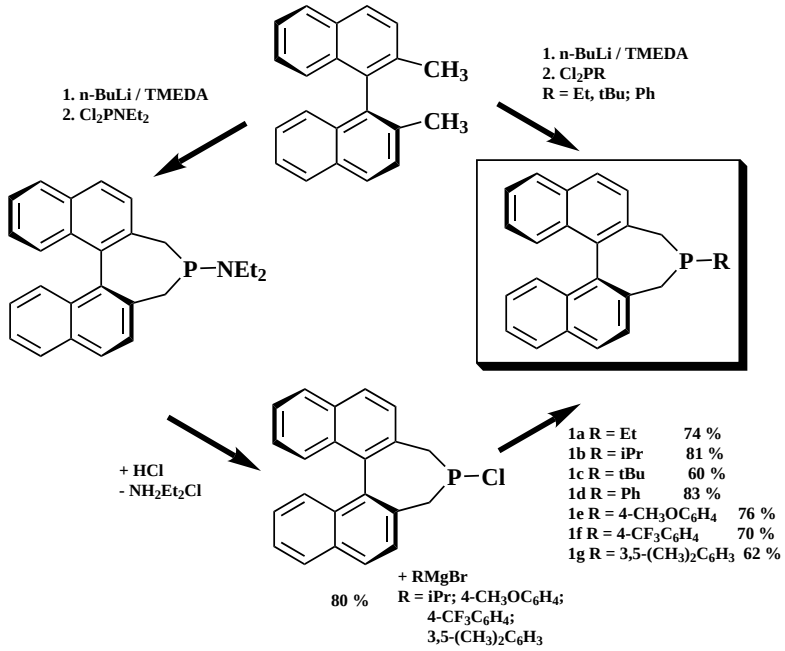


Scheme 1. Synthesis of 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **1**.

aminodichlorophosphine and subsequent reaction with HCl gives the corresponding chlorophosphepine in 80% yield. It is worthwhile mentioning that this chlorophosphepine is an extremely useful building block for the synthesis of a variety of substituted 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **1** by uncomplicated Grignard reaction. Hence, ligands **1e**–**g** were prepared without optimization in 62–76% yield. It is easily foreseen that the described procedure will not only allow the preparation of other chiral monodentate phosphepines, but is useful also for the synthesis of bidentate phosphepines.

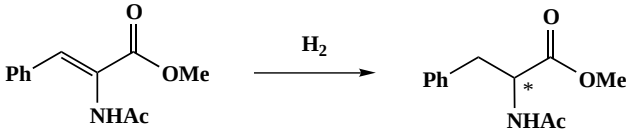
With a number of chiral monodentate ligands in hand we were interested in their catalytic behavior. Initially as a model reaction the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate **2a** was studied at ambient pressure (Table 1).[14] This reaction is generally accepted as a benchmark test for new chiral ligands.

Although there is a close structural relationship between ligands **1a**–**c** and the recently synthesized MonoPhos ligand of de Vries and Feringa[5] the alkyl-substituted phosphepine ligands give only disappointing enantioselectivities in the model reaction. However, the aryl-substituted phosphepines **1d**–**g** proved to be quite selective ligands. Using 1 mol% $[Rh(COD)_2]BF_4$ in the presence of 2 mol% ligand in 15 ml toluene enantioselectivities up to 90% ee are obtained.

Next a screening of solvents and conditions was applied to the 'best' ligand **1d**. As shown in Table 2 the use of ethyl acetate, THF, acetone, and methanol significantly speeds up considerably the hydrogenation reaction. Turnover frequencies (TOF) up to 500 h^{-1} were observed at 50% conversion. Improved enantioselectivities are obtained in THF (92% ee) and ethyl acetate (93% ee). However, the best selectivity is achieved in toluene with SDS (SDS = sodium dodecyl sulfate) as additive (95% ee). *This result seems to be one of the highest enantioselectivities ever reported for a monodentate phosphine in the hydrogenation benchmark test for chiral ligands*. While most of the hydrogenation reactions were performed in the presence of 1 mol% of catalyst, it is possible to decrease the catalyst concentration to 0.1 mol% without observing a negative effect on yield and selectivity.

$[Rh(COD)_2]BF_4$/**1d** was also used as catalyst precursor in asymmetric hydrogenations of substituted dehydroamino acid methyl esters and methyl itaconate (Table 3). In all reactions excellent yields and good

Table 1. Asymmetric hydrogenation of methyl α-acetamidocinnamate[a]

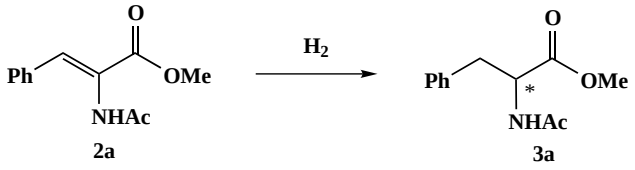


2a **3a**

Entry	Ligand	ee (%) (R)	*t*/2 (min)
1	**1a**	47	6
2	**1b**	46	4
3	**1c**	20	52
4	**1d**	90	50
5	**1e**	74	12
6	**1f**	82	36
7	**1g**	67	17

[a] Conditions: 1.0 mmol substrate; 0.01 mmol $[Rh(COD)_2]BF_4$; cat.:ligand = 1:2; 15 ml solvent; 25°C, 1 bar H_2; solvent: toluene; conversion: 100%.

Table 2. Solvent screening in asymmetric hydrogenation of methyl α-acetamidocinnamate for ligand **1d**

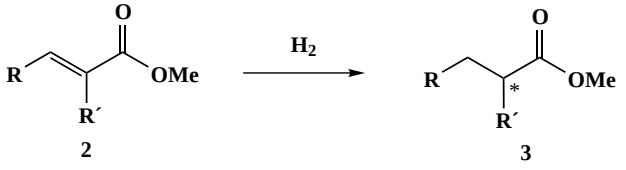


2a 3a

Entry	Solvent	ee (%) (R)	$t/2$ (min)
1[a]	Ethyl acetate	90	5
2[b]	Ethyl acetate	90	8
3[c]	Ethyl acetate	93	8
4[d]	Ethyl acetate	92	77
5[a]	THF	92	15
6[a]	Methanol	89	2
7[a]	Acetone	88	3
8[a]	CH_2Cl_2	86	4
9[e]	Toluene/SDS	95	36

[a] Conditions: 1.0 mmol substrate; 0.01 mmol $[Rh(COD)_2]BF_4$; cat.:ligand = 1:2; 15 ml solvent; 25°C, 1 bar H_2.
[b] Rh:**1d** = 1:1.
[c] Rh:**1d** = 1:4.
[d] Rh:**1d** = 0.1:1.
[e] Conditions like [a] +0.2 mmol SDS; conversion: 100%.

Table 3. Substrate screening in asymmetric hydrogenation for ligand **1d** in toluene



2 3

Entry	Substrate	ee (%)
1[a]	R = 4-CH_3-C_6H_4; R′ = NHAc	90
2[a]	R = 4-Br-C_6H_4; R′ = NHAc	84
3[a]	R = 4-NO_2-C_6H_4; R′ = NHAc	90
4[b]	R = H; R′ = CH_2COOMe	78

[a] Substrate:Rh:**1d** = 2 mmol:0.01 mmol:0.02 mmol; 5 bar H_2; toluene as solvent.
[b] Substrate:Rh:**1d** = 1 mmol:0.01 mmol:0.02 mmol; solvent: ethyl acetate; yield: >99%.

enantioselectivities (78–90% ee) are obtained using the standard reaction protocol in toluene as solvent.

In conclusion, a general synthesis of optically pure monodentate dinaphthophosphepine ligands is presented. A variety of new chiral ligands are now available on g-scale. Aryl-substituted dinaphthophosphepine ligands lead to very good enantioselectivities in the rhodium-catalyzed hydrogenation of (*Z*)-α-acetamidocinnamic acid derivatives. Even though more selective bidentate phosphines are known for the shown asymmetric hydrogenation reactions, the here presented ligands demonstrate that simple monodentate phosphines are close to the selectivity level of the more prominent chiral diphosphines. Further optimization of the ligand structure and the synthesis of water-soluble ligands are currently explored.

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13. Metallation[15] of enantiomerically pure 2,2′-dimethylbinaphthyl with *n*-BuLi/TMEDA affords the crystalline dilithio species in 70–80% yield. Starting from 12 mmol dilithium salt of homochiral 2,2′-dimethylbinaphthyl in 35 ml hexane 13.6 mmol phenyl dichlorophosphine in 15 ml hexane was added at 0°C. After 2 h refluxing, the reaction mixture was quenched with water/toluene. The organic layer was separated and dried over $MgSO_4$. The ligand **1d** was purified by column chromatography (83%). **4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepin** (**1d**): ^{1}H NMR (25°C, CD_2Cl_2): δ 2.81–2.87 (m, CH_2, 3H), 3.05 (dd, CH_2, 1H, $J=16.8$ Hz), 6.93 (d, 1H), 7.18–7.30 (m, 9H), 7.43 (m, 2H), 7.71 (t, 1H), 7.87–7.98 (m, 4H). ^{13}C NMR (25°C, CD_2Cl_2): δ 31.5 ($J=17.2$ Hz), 32.6 ($J=22.9$ Hz), 125.2, 125.4, 125.7, 126.2, 126.4, 126.8, 127.7, 128.2, 128.5, 128.6, 128.7, 129.3, 131.6, 132.3, 132.7, 133.1, 133.2, 134.0, 134.1, 134.8, 136.9, 138.3, 138.5.). ^{31}P NMR (25°C, CD_2Cl_2): δ 7.8. MS (ES, 70 eV): $m/z=388$ [M^+], 282 [M^+–P–C_6H_5], 265, 183, 153, 107, 77; $[\alpha]^{23}=-14.2$ (*c* 1, toluene).
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