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The application of monodentate secondary phosphine oxide ligands in rhodium- and iridium-catalyzed asymmetric hydrogenation

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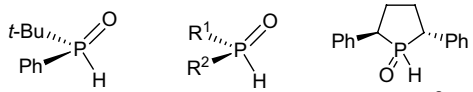
Abstract—Enantiopure secondary phosphine oxides have been tested as ligands in the rhodium- and iridium-catalyzed asymmetric hydrogenation of functionalized olefins. *tert*-Butylphosphinoyl benzene turned out to be a versatile ligand in the iridium-catalyzed hydrogenation of β-branched dehydroamino esters and in the rhodium-catalyzed hydrogenation of an enol carbamate.

1. Introduction

Recent analyses show that the use of asymmetric hydrogenation for the production of fine chemicals is limited, though expanding.[1,2] Two major factors that hamper its use are the cost of the catalysts, and in particular the ligands that are often prepared in a multistep synthesis. For this reason, we have embarked on a program aimed at the development of enantiopure ligands that are easily prepared in 1–3 synthetic steps.[3] A recent breakthrough in the field has been the development of monodentate phosphoramidites,[4] phosphonites,[5] phosphites,[6] and phosphines[7] for the highly enantioselective hydrogenation of α- and β-dehydroamino acids,[8] and enamides.[9] Other groups have developed monodentate ligands that also perform well in asymmetric hydrogenation. We recently reported on the successful use of monodentate secondary phosphine oxide ligands in iridium-catalyzed asymmetric imine hydrogenation.[10] This study was followed by a report of Haynes and co-workers applying secondary phosphine oxide ligands in palladium-catalyzed asymmetric allylic substitution reactions.[11]

Secondary phosphine oxide ligands such as **1** (Fig. 1) are air and moisture stable and their chiral members do not racemize easily. They are prepared in a two-step one-pot procedure from readily available starting materials and are thus suited to a modular or a combinatorial approach.[12] Until recently, chiral secondary phosphine oxides were used mainly as intermediates in the preparation of chiral phosphines and bisphosphines.[13] Achiral or racemic secondary phosphine oxides have been used as ligands in the platinum-catalyzed hydroformylation,[14] the hydrolysis,[15] and amination of nitriles[16] and in Pd-catalyzed coupling reactions.[17]



2 R^1= *i*-Pr, R^2=Ph
3 R^1= *t*-Bu, R^2=2-naphthyl
4 R^1= *t*-Bu, R^2=2-MeO-phenyl
5 R^1= *t*-Bu, R^2=3,5-di-Me-phenyl
6 R^1= *t*-Bu, R^2=2,4,6-tri-Me-phenyl
7 R^1= Ph, R^2=2-naphthyl

Figure 1. Secondary phosphine oxide ligands.

Herein we report our results on the application of enantiopure secondary phosphine oxides in the rhodium- and iridium-catalyzed asymmetric hydrogenation of functionalized olefins. As in our studies on imine hydrogenation, a series of enantiomerically pure ligands (Fig. 1), was obtained by preparative chiral HPLC.[18]

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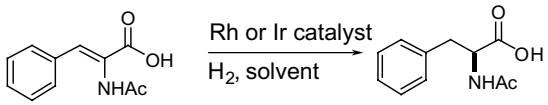
2. Results and discussion

As a first approach, the asymmetric hydrogenation of a series of *N*-acyl dehydroamino acids and esters was studied (Scheme 1).



Scheme 1. Asymmetric hydrogenation of **11** as a general example.

N-Acyl dehydroalanine **9**, *N*-acyl dehydrophenylalanine **11**, and especially their corresponding methyl esters **10** and **12** are benchmark substrates in the rhodium-catalyzed asymmetric hydrogenation (Fig. 2).[19] The related *Z*-β-dehydroamino esters **13** and **14** are considerably more challenging substrates and ee's higher than 90% have been reached only with a small set of ligands.[20]

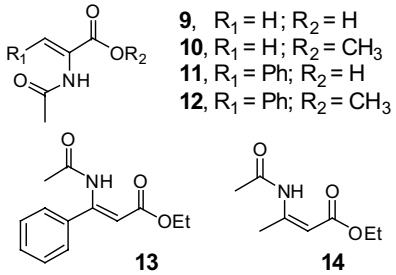


Figure 2. *N*-Acyl dehydroamino acids and esters.

Hydrogenation reactions were carried out under standard reaction conditions in an Endeavour system[21] using the cationic rhodium precursor $Rh(COD)_2BF_4$ (Table 1). Ligands **1** and **3** were chosen because of their performance in the earlier reported imine hydrogenations.

Although most reactions showed full conversion, the enantioselectivities obtained were disappointing. Remarkably, the hydrogenation of **9** in EtOAc gave the opposite enantiomer of the product compared to the same reaction in CH_2Cl_2. A similar effect was observed for **11** but not for its corresponding methyl ester **10**. The reason is unknown, though the effect is reminiscent of the solvent effect in the asymmetric hydrogenation of itaconic acid and its methyl ester using a rhodium-phosphoramidite catalyst.[22] An attempt using a cationic iridium complex led to low ee (entry 9).

Next, the asymmetric hydrogenation of a series of β-branched dehydroamino esters was studied (Fig. 3). Contrary to the substrates mentioned before, only a few ligands have been described that afford high ee's and acceptable reaction rates with these substrates.[23] Remarkably, successful results using monodentate ligands have not yet been reported. Substrates **15**, **17**, and **18** were prepared by condensation of the corresponding keto esters with acetamide[24] whereas **16** was synthesized using the procedure of Schmidt and co-workers.[25] Using a cationic rhodium precursor, all hydrogenation reactions went to completion whereas ee's were low to moderate (Table 2). Surprisingly, however, when the iridium precursor $[Ir(COD)Cl]_2$ was used, high ee's and full conversions were reached in the hydrogenation of methyl *N*-acyl dehydrocyclohexylglycine **18**. Ligands **1** and **3** performed similar, **1** being slightly superior and affording methyl *N*-acyl cyclohexylglycine in 85% ee.

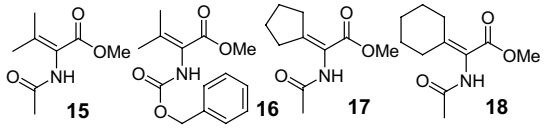


Figure 3. β-Branched dehydroamino esters.

Iridium, though far less applied than rhodium and ruthenium, has been used very successfully in the asymmetric hydrogenation of unfunctionalized alkenes. Initiated by Pfaltz and co-workers[26] and elaborated upon by Cui and Burgess[27] and Zhang and co-work-

Table 1. Asymmetric hydrogenation of *N*-acyl dehydroamino acids and esters[a]

Entry	Substrate	Ligand	Solvent	Time (h)	Conv (%)	Ee (%)
1	**9**	**1**	EtOAc	46	100	53
2	**9**	**1**	CH_2Cl_2	21	75	−38
3	**10**	**1**	CH_2Cl_2	21	100	39
4	**10**	**3**	CH_2Cl_2	19	100	30
5	**11**	**1**	CH_2Cl_2	21	75	−51
6	**11**	**1**	EtOAc	46	95	28
7	**12**	**1**	CH_2Cl_2	19	100	25
8	**12**	**1**	EtOAc	46	100	30
9[b]	**12**	**1**	CH_2Cl_2	69	100	27
10[c]	**13**	**1**	CH_2Cl_2	69	100	36
11	**14**	**1**	CH_2Cl_2	21	41	20
12[c]	**14**	**1**	CH_2Cl_2	69	100	6

[a] General procedure; see Experimental section. 2 mol% of $Rh(COD)_2BF_4$, 4 mol% of ligand, 5 bar H_2. Conversion and ee were determined by GC. Use of ligand (*R*)-**1** and (*R*)-**3** afforded the (*S*)-products for **9**–**12** and the (*R*)-products for **13** and **14** unless otherwise noted.
[b] $Ir(COD)_2BF_4$, 10 bar H_2.
[c] 10 bar H_2.

Table 2. Asymmetric hydrogenation of β-branched dehydroamino esters[a]

Entry	Substrate	Ligands	*t* (h)	Conv (%)	Ee (%)
1	**15**	**1**	69	100	27
2[b]	**15**	**3**	69	75	30
3	**16**	**1**	69	100	58
4	**17**	**1**	69	100	15
5	**17**	**2**	69	100	19
6[c]	**17**	**2**	69	100	7
7	**18**	**1**	69	100	31
8[d]	**18**	**1**	46	100	−25
9[b]	**18**	**1**	69	100	**85**
10[b]	**18**	**3**	69	100	81

[a] General procedure; see Experimental section. 2 mol% of $Rh(COD)_2BF_4$, 4 mol% of ligand, 10 bar H_2 in CH_2Cl_2 at rt. Conversion and ee were determined by GC. Use of ligand (*R*)-**1** and (*R*)-**3** afforded the (*S*)-products for **15**, **17**, and **18** unless otherwise noted. The absolute configuration of the product from **16** is not known.
[b] $[Ir(COD)Cl]_2$.
[c] $Ir(COD)_2BF_4$.
[d] 5 bar H_2 in EtOAc.

ers,[28] excellent ee's have been obtained using phosphorus–nitrogen ligands also for unsaturated acids, alcohols, and esters. To the best of our knowledge, dehydroamino acids and their esters have not been used as substrates. As people regularly resort to iridium when catalysts based on rhodium or ruthenium fail, this might also hold for the hydrogenation of sterically encumbered dehydroamino esters, as shown here.

As *N*-acyl enamide **19**, itaconic acid **20**, and its dimethyl ester **21** are frequently used substrates in rhodium-catalyzed hydrogenation, also these substrates were applied in a screening (Fig. 4). Using standard conditions, **19**, **20**, and **21** were hydrogenated in either dichloromethane or EtOAc as solvent (Table 3). With ligand **1**, that performed best in the previous studies, full conversions were again obtained using $Rh(COD)_2BF_4$ as the metal precursor. Enantioselectivities, however, are moderate at best. Changing to a cationic iridium precursor afforded racemates.

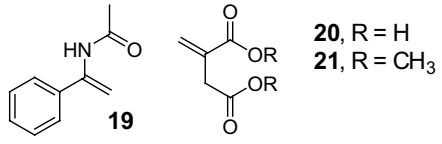


Figure 4. *N*-(1-Phenylethyl)acetamide and itaconic acid (ester).

As enantiopure alcohols are very important building blocks in organic synthesis, the rhodium-catalyzed hydrogenation of enol esters, in analogy to *N*-acyl enamides, is a logical extension. Therefore, enol ester **22** (Fig. 5) has been used several times as a benchmark substrate in rhodium-catalyzed asymmetric hydrogenation. Contrary to the corresponding *N*-acyl enamide **19** however, reports of the successful hydrogenation of **22** are scarce. High ee's have been obtained using DuPhos[29] or TangPhos[30] as a ligand whereas monodentate phosphites have also been successful.[31]

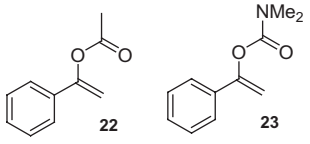


Figure 5. The enol acetate and enol carbamate of acetophenone.

We decided to introduce enol carbamates as a new class of substrates to obtain enantiomerically enriched alcohols by asymmetric hydrogenation. In order to enhance the coordination of the carbonyl group to the rhodium, according to the established mechanisms essential for enantioselectivity,[32] the methyl group in **22** is replaced by a dimethylamino group giving **23**. This mimics the coordination of the corresponding *N*-acyl enamide. Enol

Table 3. Asymmetric hydrogenation of *N*-acyl enamide and itaconic acid[a]

Entry	Substrate	Solvents	*t* (h)	Conv (%)	Ee (%)
1	**19**	EtOAc	46	100	61
2	**19**	CH_2Cl_2	24	100	30
3	**20**	CH_2Cl_2	21	100	45
4	**20**	EtOAc	46	100	7
5[b]	**20**	EtOAc	72	95	2
6	**21**	CH_2Cl_2	21	100	36
7[b]	**21**	EtOAc	72	50	1

[a] General procedure, see Experimental section. 2 mol% of $Rh(COD)_2BF_4$, 4 mol% of ligand **1**, 5 bar H_2 at rt. Conversion and ee were determined by GC. Use of ligand (*R*)-**1** afforded the (*S*)-products.
[b] $Ir(COD)_2BF_4$.

carbamate **23** can be prepared by reaction of the sodium enolate of acetophenone with dimethylcarbamyl chloride in moderate yield.

Hydrogenation of **23** using 2 mol% of the metal precursor $Rh(COD)_2BF_4$ and **1** as the chiral ligand in different solvents clearly showed that ethyl acetate is the preferred solvent in this reaction (Table 4). Using a ligand to metal ratio of 2 and 1 bar of hydrogen, 81% ee was obtained. Although the reaction is slow, it runs to completion. Attempts to speed up the reaction were not very successful. Increasing the hydrogen pressure led to a considerable decrease in ee, whereas a higher ligand to metal ratio slowed down the reaction somewhat but gave a slight increase in ee. Carrying out the reaction at a slightly elevated temperature with a higher ligand to catalyst ratio accelerated the reaction but a slight drop in ee was noticed. The use of other rhodium precursors or $Ir(COD)_2BF_4$ led to incomplete conversion and low ee.

Based on this result a series of different enantiopure secondary phosphine oxide ligands was screened in the hydrogenation of **23** (Table 5). It turned out that ligand **1** performs best in terms of ee and conversion. For most other ligands the hydrogen pressure had to be increased in order to get a good conversion, but this led invariably to lower ee's.

3. Conclusion

The results of this study show that monodentate secondary phosphine oxides are suitable ligands for rhodium- and iridium-catalyzed hydrogenation of functionalized olefins. In terms of chiral induction, ligand **1** gives the best results, a conclusion that was also drawn from our studies in the asymmetric imine hydrogenation. The fact that **1** can be easily prepared in a one-pot two-step procedure, and can be resolved efficiently either by chiral HPLC or classical resolution, adds significantly to its versatility. Especially in the iridium-catalyzed asymmetric hydrogenation of β-branched dehydroamino esters and in the rhodium-catalyzed hydrogenation of enol carbamate **23**, ligand **1**

Table 4. Asymmetric hydrogenation of enol carbamate **23**[a]

Entry	Solvent	L/Rh	H_2 (bar)	*t* (h)	Conv (%)	Ee (%)
1	EtOAc	2	1	64	100	**81**
2	EtOAc	4	1	65	65	**84**
3	CH_2Cl_2	2	5	24	100	32
4	*i*-PrOH	2	1	65	18	70
5	THF	2	1	26	3	67
6	Toluene	2	1	95	40	7
7	EtOAc	3	5	44	100	57
9	EtOAc	4	5	44	95	61
10	EtOAc	8	5	44	89	62
11[b]	EtOAc	3	1.5	45	100	76
12[b]	EtOAc	6	1.5	45	100	76
13[c]	EtOAc	1	1.5	45	81	1
14[d]	EtOAc	1	1.5	45	18	−15
15[e]	EtOAc	2	5	44	34	9

[a] General procedure; see Experimental section. 2 mol% of $Rh(COD)_2BF_4$, 4 mol% of ligand **1**, at rt. Conversion and ee were determined by GC. Use of ligand (*R*)-**1** afforded the (*S*)-product.
[b] At 40 °C.
[c] $[Rh(NBD)Cl]_2$.
[d] $Ir(COD)_2BF_4$.
[e] $[Rh(COD)Cl]_2$.

Table 5. Asymmetric hydrogenation of enol carbamate **23** using different ligands[a]

Entry	Ligands	L/Rh	H_2 (bar)	*t* (h)	Conv (%)	Ee (%)
1	**1**	1	5	92	75	52
2	**1**	3	5	44	100	57
3[b]	**2**	2	10	69	100	5
4	**3**	3	5	44	100	53
5	**4**	2	2	92	65	2
6[b]	**4**	2	10	69	82	9
7	**5**	2	5	92	96	3
8	**5**	2	2	92	86	11
9	**6**	2	5	92	43	2
10	**6**	2	2	92	42	1
11	**7**	2	2	92	100	21
12	**8**	2	1	90	55	56

[a] General procedure; see Experimental section. 2 mol% of $Rh(COD)_2BF_4$, 4 mol% of ligand, in EtOAc at rt. Conversion and ee were determined by GC.
[b] In CH_2Cl_2.

shows high enantioselectivities. As for these substrate classes few alternative versatile ligands are available, further studies using this new class of ligands are certainly desirable.

4. Experimental

The preparation and resolution of ligands **1**–**8** has been previously described.[10] Substrate **9**, **11**, **20**, and **21** were purchased from commercial suppliers and used as received. Substrate **10**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19**, and **22** were prepared according to literature.[8a,b,9a] To ensure accurate determination of enantioselectivities, racemic mixtures of all products were prepared by hydrogenation of the substrates using Wilkinson's catalyst or Pd/C. The absolute configuration of the products was assigned by comparing the retention times on GC with commercially available compounds or derivatives thereof (for the products from **9**, **10**, **11**, **12**, **19, 20**, **21**, and **23**) or with the literature (for the products from **13** and **14**[8b] and from **15**, **17**, **18**[33]). All hydrogenation products, except for the product of **23**, have been described in the literature. *N*-Acylalanine, *N*-acylphenylalanine, and methylsuccinic acid were transformed into their corresponding methyl esters using (trimethylsilyl)diazomethane ($(CH_3)_3SiCHN_2$) before GC analysis.[34] Hydrogenation experiments were performed in an Endeavor™ multireactor autoclave,[35] the eight reactors being equipped with glass liners and stirring paddles. Each reactor was charged with 0.002 mmol of iridium or rhodium catalyst precursor, 0.004 mmol of ligand, 0.2 mmol of substrate, and 5 mL of solvent. The autoclave was purged three times with N_2, three times with H_2, and then pressurized with H_2. After the reaction, a sample was taken, which was filtered over a short silica column and subjected to conversion and ee determination by means of chiral GC.

4.1. Enantioselectivity determinations

Methyl *N*-acylalanine (from **9** and **10**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 110 °C, 15 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 1.3:1; $t_R = 3.38$ min, $t_S = 3.92$ min, $t_{SM} = 4.15$ min.

Methyl *N*-acylphenylalanine (from **11** and **12**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 160 °C, 12.5 min, 10 °C/min increase to 180 °C. $T_{ini.} = T_{det.} = 250$ °C, split ratio 25:1; $t_R = 6.74$ min, $t_S = 7.42$ min, $t_{SM} = 15.36$ min.

Ethyl 3-(acetylamino)-3-phenylpropanoate (from **13**): CP-Chirasil-Dex-CB column (25 m × 0.25 mm × 0.25 μm); init. temp: 100 °C, 5 min, 10 °C/min increase to 170 °C, 30 min. $T_{det.} = T_{inlet} = 250$ °C, split ratio 10:1; $t_S = 37.50$ min, $t_R = 38.10$ min, $t_{SM} = 33.09$ min.

Ethyl 3-(acetylamino)butanoate (from **14**): CP-Chirasil-Dex-CB column (25 m × 0.25 mm × 0.25 m); init. temp: 100 °C, 5 min, 10 °C/min increase to 170 °C, 18 min. $T_{det.} = T_{inlet} = 250$ °C, split ratio 10:1; $t_1 = 11.77$ min, $t_2 = 11.96$ min, $t_{SM} = 10.7$ min.

Methyl 2-(acetylamino)-3-methylbutanoate (from **15**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 m); init. temp: 140 °C, 16 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 25:1; $t_R = 2.48$ min, $t_S = 2.65$ min, $t_{SM} = 4.52$ min.

2-Benzyloxycarbonylamino-3-methyl-butyric acid methyl ester (from **16**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 140 °C, 16 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 25:1; $t_1 = 19.36$ min, $t_2 = 19.58$ min, $t_{SM} = 22.43$ min.

Methyl 2-(acetylamino)-2-cyclopentylacetate (from **17**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 140 °C, 16 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 25:1; $t_R = 7.22$ min, $t_S = 8.12$ min, $t_{SM} = 13.36$ min.

Methyl 2-(acetylamino)-2-cyclohexylacetate (from **18**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 140 °C, 16 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 25:1; $t_R = 10.7$ min, $t_S = 12.27$ min, $t_{SM} = 19.17$ min.

N-(1-Phenylethyl)acetamide (from **19**): CP-Chirasil-Dex-CB column (25 m × 0.25 mm × 0.25 m); 140 °C, 45 min isothermic, $T_{det.} = T_{inlet} = 250$ °C; $t_1 = 13.78$ min, $t_2 = 14.92$ min, $t_{SM} = 16.53$ min.

Dimethyl methylsuccinate (from **20** and **21**): Chiraldex G-TA column (25 m × 0.25 mm × 0.25 μm); init. temp: 80 °C, 50 min, 10 °C/min increase to 150 °C. $T_{det.} = T_{inlet} = 250$ °C; $t_R = 19.27$ min, $t_S = 20.55$ min, $t_{SM} = 29.42$ min.

1-Phenylethyl dimethylcarbamate (from **23**): CP Chiracel-L-Val column (25 m × 0.25 mm × 0.25 μm); init. temp: 100 °C, 10 min, 10 °C/min increase to 180 °C. $T_{det.} = T_{inlet} = 250$ °C, split ratio 75:1; $t_R = 9.76$ min, $t_S = 10.12$ min, $t_{SM} = 13.17$ min.

4.2. 1-Phenylvinyl dimethylcarbamate 23[36,37]

Sodium hydride (8.8 g, 220 mmol, 60% suspension in oil) was added in portions to DMSO (500 mL, freshly distilled under reduced pressure from calcium hydride). After stirring for 2 h at 50 °C hydrogen evolution ceased and the mixture was cooled to room temperature. To the gray solution acetophenone (23.3 mL, 200 mmol) in 50 mL DMSO was added dropwise in 30 min, the addition being slightly exothermic and changing the color of the solution to yellow. This solution was left stirring for 15 min before dimethylcarbamyl chloride (20.3 mL, 220 mmol) in 50 mL of DMSO was added dropwise in 30 min, while maintaining rt. After stirring for 45 min, water (500 mL) was carefully added to the orange solution. The mixture was extracted with hexane (5 × 500 mL) and the combined extracts were washed with brine and dried over magnesium sulfate.

Purification by column chromatography (silica gel, ethyl acetate/hexane 4:1) afforded the product as a colorless oil (37%). ^{1}H NMR (200 MHz, $CDCl_3$) 2.92 (s, 3H), 3.06 (s, 3H), 4.99 (d, $J = 1.8$ Hz, 1H), 5.38 (d, $J = 1.8$ Hz, 1H), 7.25–7.46 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 36.2, 36.5, 101.4, 124.7, 128.3, 128.5, 134.9, 153.2, 154.3; ESI-MS m/z 51 (6), 72 (100), 103 (7), 191 (34) [M^+]; HRMS (ESI$^+$) calculated for $C_{11}H_{13}NO_2$: 191.09461, found: 191.09530.

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