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Enantioselective hydrogenation of enamides catalyzed by chiral rhodium–monodentate phosphite complexes

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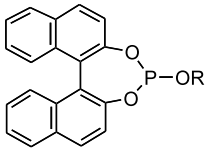
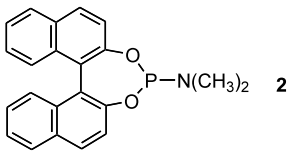
Abstract—Chiral monophosphites derived from BINOL are cheap and efficient ligands in the Rh-catalyzed hydrogenation of *N*-acyl enamides, providing amines with high degrees of enantioselectivity (up to 97.0% ee).

Recently, we reported the surprising finding that chiral monodentate phosphites **1** are highly efficient ligands in the Rh-catalyzed hydrogenation of prochiral olefins such as itaconic acid ester and 2-acetamido acrylic acid esters (ee = 95–99%).[1] In an independent study Feringa, de Vries and co-workers described similar results using the monophosphoramidite **2**.[2] Moreover, Pringle[3] and our group[4] independently reported on the use of chiral phosphonites **3** as ligands in Rh-catalyzed olefin hydrogenation, reactions in which the degree of enantioselectivity is somewhat lower than in the case of **1** and **2**. Taken together the results clearly demonstrate that the traditional use of chelating ligands is not necessary in order to obtain high enantioselectivities in a general manner.[5] The fact that ligands **1**–**3** are readily available accounts for their industrial interest.[6]

In a further development of this chemistry Chan recently described the use of **2** as a ligand in the Rh-catalyzed hydrogenation of enamides **4**,[7] the ee values ranging between 55% and 87% at room temperature (up to 96% ee at −20°C).[8] Zhou independently



1 **a** R = CH_3 (*S*-BINOL)
b R = $CH(CH_3)_2$ (*S*-BINOL)
c R = c-C_5H_9 (*S*-BINOL)
d R = CH_2Ph (*S*-BINOL)
e R = $CH_2CH(CH_3)_2$ (*R*-BINOL)
f R = $CH_2CH(C_2H_5)_2$ (*R*-BINOL)
g R = $CH_2C(CH_3)_3$ (*S*-BINOL)
h R = (*S*)-$CH(CH_3)(C_2H_5)$ (*S*-BINOL)
i R = (*S*)-$CH(CH_3)(C_2H_5)$ (*R*-BINOL)
j R = (*R*)-$CH(Ph)(CH_3)$ (*S*-BINOL)
k R = $CH_2CH_2N[CH(CH_3)_2]_2$(*S*-BINOL)
l R = $CH_2CH_2OCH_3$ (*S*-BINOL)
m R = CH_2CH_2Cl (*R*-BINOL)
n R = CH_2CCl_3 (*R*-BINOL)



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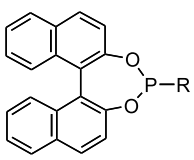

3 **a** R = Me (*R*-BINOL)
b R = Et (*R*-BINOL)
c R = *t*-Bu (*R*-BINOL)
d R = Ph (*R*-BINOL)

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Table 1. Rhodium-catalyzed asymmetric hydrogenation of enamide **4a** using chiral phosphites **1** (solvent: CH_2Cl_2; Rh:substrate = 1:500; ligand:Rh = 2:1; 60 bar H_2; 20 h; 30°C)

Entry	Ligand	Conversion (%)	% ee (configuration of product)
1	**1a**	100	76.0 (*R*)
2	**1b**	100	89.4 (*R*)
3	**1c**	100	93.7 (*R*)
4	**1d**	100	94.2 (*R*)
5	**1e**	100	93.1 (*S*)
6	**1f**	100	93.7 (*S*)
7	**1g**	100	95.3 (*R*)
8	**1h**	100	92.0 (*R*)
9	**1i**	100	94.1 (*S*)
10	**1j**	100	94.9 (*R*)
11	**1k**	20	0 (–)
12	**1l**	100	86.0 (*R*)
13	**1m**	100	92.7 (*S*)
14	**1n**	<5	n.d.

substantiated this result, and also reported on a novel monophosphoramidite having a *spiro*-type structure which leads to higher enantioselectivities (ee typically 95–99%).[9] These two publications prompt us to report our preliminary results concerning the Rh-catalyzed hydrogenation of substrates **4** using ligands **1** and **3**.

One of the advantages of phosphites **1** as ligands in Rh-catalyzed hydrogenation is their modular nature which allows for easy variation of the R group in the alcohol portion (ROH) of the compounds.[1,10,11] This makes simple ligand tuning possible. We have therefore started to evaluate some of the ligands **1** available in our laboratory, specifically in a test reaction involving substrate **4a**. In all cases $Rh(COD)_2BF_4$ (COD = cyclooctadiene) was used as the precursor, which leads to the displacement of one COD by two monophosphites. Although only 14 of the 60 in our laboratory currently available ligands were tested so far, the results summarized in Table 1 show that, as expected, the ee varies considerably as a function of the nature of the R group in the ligand. Among the best ligands are those derived from cyclopentanol (entry 3), benzyl alcohol (entry 4) and neopentyl alcohol (entry 7). Chiral alcohols such as 2-butanol or 1-phenylethanol also lead to high enantioselectivities, whereby the absolute configuration seems to play only a small role (cf. entries 8–10). Amino moieties in the phosphites shut down the reaction, possibly due to chelation (entry 11), and strongly electron-withdrawing groups also lower the hydrogenation rate (entry 14).

The results of experiments using monophosphonites **3** turned out to be less encouraging (solvent: CH_2Cl_2; ligand:Rh = 2:1; substrate:catalyst = 250:1; 60 bar H_2; 30°C; 1 h; 100% conversion): **3a** (ee = 74% *S*); **3b** (ee = 67.2% *S*); **3c** (ee <1%); **3d** (ee = 58% *S*). Interestingly, at 1.5 bar H_2 similar results were obtained. Catalysts based on phosphonites **3** appear to be more active than those based on phosphites **1**, although enantioselectivities are usually considerably lower.

Following these results we started to hydrogenate other *N*-acyl enamides **4** using selected phosphite ligands **1**. Although this study has not been completed, the preliminary results summarized in Table 2 demonstrate the generality of the method. Thus, each substrate can be matched with the best ligand in a simple process of screening (which has not yet been performed for all substrates). This possibility constitutes a major advantage of the method.

In summary, we have developed a simple and efficient method for the Rh-catalyzed asymmetric hydrogenation of *N*-acyl enamides which provides chiral amines with high enantioselectivities.[12] Since the BINOL-derived monophosphites are cheap (e.g. only 2% of the cost of BINAP), the method is likely to be of industrial interest.[6] Moreover, catalyst optimization for a given substrate is possible by simple variation of the alcohol ROH which is incorporated in the synthesis of the modular ligands **1**.

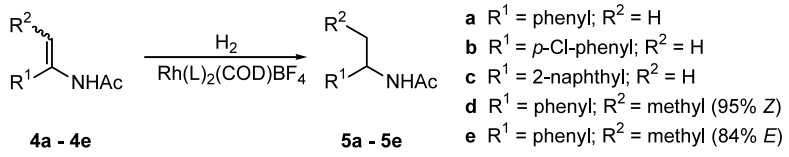

Table 2. Rhodium-catalyzed asymmetric hydrogenation of enamides **4b–e** (solvent: CH_2Cl_2; Rh:substrate = 1:500; ligand:Rh = 2:1; 60 bar H_2; 20 h; 30°C)

Entry	Enamide	Ligand	Conversion (%)	% ee (configuration of product)
1	**4b**	**1j**	100	95.8 (*R*)
2	**4c**	**1d**	100	94.3 (*R*)
3	**4c**	**1e**	100	>92.0 (*S*)
4	**4c**	**1f**	100	>93.0 (*S*)
5	**4c**	**1g**	100	93.7 (*R*)
6	**4c**	**1h**	99.0	90.6 (*R*)
7	**4c**	**1i**	99.5	>93.4 (*S*)
8	**4d**	**1j**	100	97.0 (*R*)
9	**4e**	**1j**	69	76.2 (*R*)

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12. Typical procedure for Rh-catalyzed hydrogenation of *N*-acyl enamides **4** using chiral phosphites: A mixture consisting of 0.5 mL of a 2 mM solution of $Rh(COD)_2BF_4$ in dry CH_2Cl_2 and 0.5 mL of a 4 mM solution of a phosphite **1** in CH_2Cl_2 is prepared, which causes a color change from orange to yellow. Following addition of substrate **4a** (80.6 mg, 0.5 mmol) in 1 mL of CH_2Cl_2, the reaction flask is brought into an autoclave. A H_2 pressure of 60 bar is applied and the contents is stirred at 30°C for 20 h. GC analysis provides the ee values and degree of conversion.