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Enantioselective hydrogenation with inexpensive, easily available monodentate phosphite ligands

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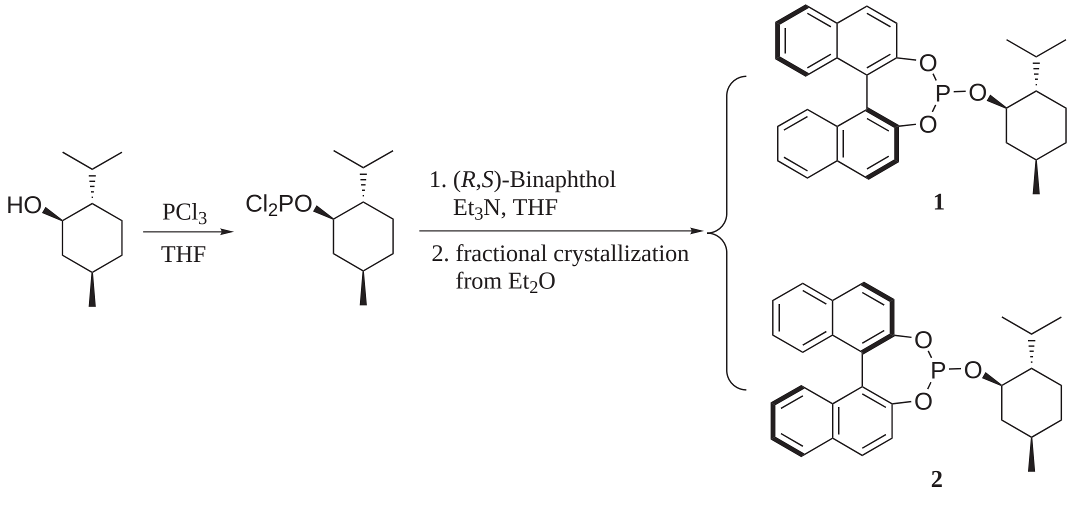
Abstract—Diastereomerically pure menthyl binaphthylphosphite ligands, easily accessible from the inexpensive, racemic binaphthol, L-menthol and PCl_3, are shown to be effective in the rhodium-catalysed enantioselective hydrogenation of prochiral olefins. © 2001 Published by Elsevier Science Ltd.

Rhodium-catalyzed asymmetric hydrogenation is almost exclusively effected in the presence of bidentate phosphine ligands, of which renowned examples include BINAP, DuPHOS and DIPAMP.[1–3] Very recently, however, monodentate phosphonites and phosphites have been shown to be excellent ligands in the rhodium catalysed asymmetric hydrogenation of unsaturated carboxylic acids and dehydroamino acids by the research groups of Pringle,[4] Reetz,[5,6] and Feringa.[7] For instance, the hydrogenation of itaconic acid dimethyl ester by rhodium in the presence of the enantiomerically pure alkyl binaphthylphosphites afforded the saturated product with ee values up to 97.6%.[5] High enantioselectivities have also been observed with similar phosphonite ligands, which, in some cases, even outperform their bidentate analogues.[4] In the reactions affected by such ligands, the enantiodiscrimination appears to be controlled by the biaryl moieties, of which binaphthyl has attracted the most attention. In the publications that have appeared, binaphthyl is introduced by the reaction of phosphorus or phosphine chlorides with optically pure binaphthol. We here report that chiral binaphthylphosphite ligands can be accessed from the much less expensive, racemic binaph-



Scheme 1. Synthesis of menthyl binaphthylphosphites **1** and **2**. For details of reaction conditions, see reference 8.

Keywords: asymmetric hydrogenation; monodentate phosphites; rhodium catalysts; racemic binaphthol; menthol.

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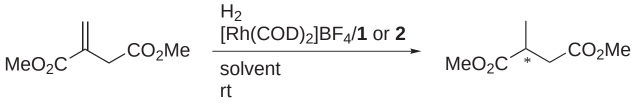
thol and the ligands so generated are effective in the asymmetric hydrogenation of unsaturated carboxylic acid derivatives.

Our approach is based on the observation that racemic binaphthol readily forms separable phosphite diastereoisomers upon treatment with PCl_3 and one of the cheapest chiral alcohols, L-menthol, both of which are industrial products.[8] Thus, the reaction of PCl_3 with 1 equiv. of (1*R*,2*S*,5*R*)-(−)-menthol in THF yields quantitatively menthyl phosphorodichloridite, and the addition of racemic 1,1′-binaphthalene-2,2′-diol to a THF solution of the menthol derivative in the presence of NEt_3 affords the diastereomerically pure phosphites **1** and **2** upon fractional crystallisation in diethyl ether, with **1** derived from (*S*)-binaphthol and **2** from (*R*)-binaphthol (Scheme 1).[9] This reaction sequence was originally designed by Buono for the optical resolution of binaphthol; the two enantiomerically pure binaphthols were obtained on the oxidation of **1** and **2** followed by reduction.[8,10] Ligands **1** and **2** are surprisingly resistant towards oxidation. Thus, leaving a chloroform solution of **1** in air for one week resulted in less than 10% oxidation.

The two ligands have been found to be good ligands in the rhodium-catalysed asymmetric hydrogenation of prochiral olefins such as itaconic acid dimethyl ester and methyl-2-acetamido acrylate. The rhodium catalyst was formed in situ by combining $[Rh(COD)_2][BF_4]$ with **1** or **2** in a chosen solvent. In a typical hydrogenation reaction involving itaconic acid dimethyl ester (Eq. (1)), $[Rh(COD)_2][BF_4]$, 2 equiv. of **1** and the olefinic substrate, with olefin/Rh (S/C) molar ratio = 2000, were mixed under an atmosphere of argon in CH_2Cl_2. The hydrogenation was started by replacing the argon with 10 bar H_2.[11] Pre-generation of the active catalyst in the absence of the substrate is unnecessary, as it appears to have little effect on the enantioselectivity. Table 1 summarises the results obtained. As can be seen, overnight hydrogenation afforded 100% conversion of the olefin and an ee value of 95.2% in favour of the *S*-configured product. This value compares favourably with those obtained with the monodentate phosphoramidite ligand[7] and the analogous phosphonites,[4,6] or phosphites[5] in which the menthyl in **1** is replaced with such groups as methyl and substituted phenyls, although it is lower than the value of 97.6% when using isopropyl binaphthylphosphite.[5] Switching from ligand **1** to **2**, the opposite enantiomer was obtained, at 90.5% ee, indicating that the binaphthyl moiety is decisive for enantioselectivity and the combination of (*S*)-binaphthol with L-menthol represents the matched case for this substrate.



(1)

Table 1 also shows that solvents play an important role in affecting the enantioselectivity. Thus, when carried out in solvents other than CH_2Cl_2, not only were the ee values lowered substantially but the conversions decreased as well. For example, the hydrogenation in THF afforded a conversion of 42.5% and an ee value of only 31.1% under conditions otherwise identical to those with CH_2Cl_2. The dramatic effect of MeOH on both the conversion and ee may suggest that phosphite dissociation takes place during the hydrogenation. Similar solvent effect on ee was noted with the monodentate phosphoramidite, albeit to a lesser degree.[7]

Pressure appears to have little effect on the enantioselectivity. As can be seen from the table, increasing the hydrogen pressure from 10 to 50 or 100 bar was accompanied only by a slight decrease in ee, from 95.2 to 94.6 or 93.6%. However, higher pressure favours faster reactions. Thus, at 100 bar, the hydrogenation was complete within 2 h reaction time. The aforementioned phosphoramidite appears to behave similarly in the hydrogenation of dehydroamino acids. Of practical interest, the S/C ratios can be substantially increased without much detrimental effect on ee values when high pressure is applied. For example, at S/C = 10000 and 50 bar H_2 with **1** as ligand, a complete conversion was achieved after overnight hydrogenation, with an ee value of 94.4%, which is only slightly lower than that observed at S/C = 2000 and 10 bar H_2 and about the same as that observed at S/C = 2000 and 50 bar H_2.

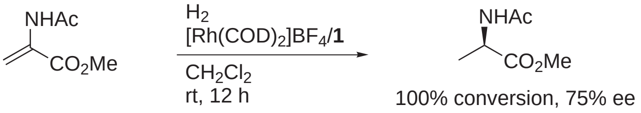
We also examined the ligands **1** and **2** for the hydrogenation of methyl 2-acetamido acrylate (Eqs. (2) and (3)). Under conditions identical to those for the itaconic

Table 1. Rh-catalysed asymmetric hydrogenation of itaconic acid ester in the presence of the ligand **1** or **2**[a]

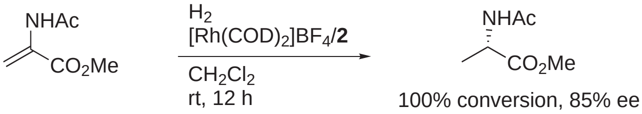
Ligand	Solvent	S/C	P_{H2} (bar)	Time (h)	Conversion (%)	% Ee
1	CH_2Cl_2	2000	10	12	100	95.2 (*S*)
2	CH_2Cl_2	2000	10	12	100	90.5 (*R*)
1	Toluene	2000	10	12	55.2	78.9 (*S*)
1	EtOAc	2000	10	12	40.5	67.5 (*S*)
1	THF	2000	10	12	42.5	31.1 (*S*)
1	MeOH	2000	10	12	9.0	7.6 (*S*)
1	CH_2Cl_2	2000	50	5	100	94.6 (*S*)
1	CH_2Cl_2	2000	100	2	100	93.6 (*S*)
1	CH_2Cl_2	10000	50	12	100	94.4 (*S*)

[a] Reactions were carried out at room temperature, with conversion and ee values determined by GC.

acid ester (10 bar H_2, in CH_2Cl_2), complete conversion was observed and the *R*-configured alanine derivative obtained in 75% ee with ligand **1**. Somewhat surprisingly, a higher ee was obtained when **2** was employed, indicating that the combination of $[Rh(COD)_2][BF_4]$ with **2** instead of **1**, as in the case of itaconic acid ester, now represents the matched case. The ee values are lower than those presented in Table 1 for the itaconic acid ester, but comparable with those obtained using methyl or phenyl binaphthylphosphite as ligand.[5]



(2)



(3)

In summary, we have shown that menthol-derived monodentate binaphthylphosphites can act as efficient chiral ligands in the rhodium-catalysed hydrogenation. The advantage for using such ligands is that they can be made from cheap, racemic binaphthol by extremely easy crystallisation upon the introduction of the optically active menthol. Our results on the hydrogenation reactions corroborate the recent reports,[4–7] showing monodentate ligands can be equally effective in enantiodiscrimination.

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9. The two ligands, L-menthyl-(*S*)-1,1′-binaphthalene-2,2′-diyl phosphite **1** and L-menthyl-(*R*)-1,1′-binaphthalene-2,2′-diyl phosphite **2**, were prepared in accordance with the procedures described in reference 8, except with the sequence of reagent addition in preparing menthyl phosphorodichloridite being modified; L-menthol, used as received (Lancaster, 99%), was added to a THF solution of PCl_3, instead of the reverse, as originally reported. Ligand **1** could very easily be crystallised from diethyl ether, but the crystallisation of **2** appeared not to be as easy as reported in reference 8. Nonetheless, pure **1** and **2** could be obtained reproducibly, with their ^{31}P NMR spectra each showing only one singlet, at δ 147.9 and 151.0, respectively.
10. This method was also used in the optical resolution of racemic, substituted binaphthols: Bähr, A.; Droz, A. S.; Püntener, M.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1998**, *81*, 1931.
11. The product was analysed by a Varian CP-3380 GC after passing through a short silica column. A Chiraldex G-TA (40 m×0.25 mm) column and a Chrompack Chirasil-Dex CB (25 m×0.25 mm) column were used for determining ee values for the hydrogenation of itaconic acid ester and methyl 2-acetamido acrylate, respectively.