Pergamon

Tetrahedron Letters 42 (2001) 8737–8740

TETRAHEDRON LETTERS

Asymmetric activation of conformationally flexible monodentate phosphites for enantioselective hydrogenation

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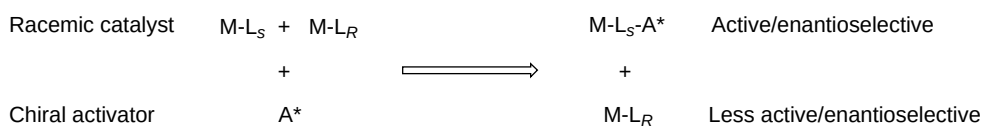
Received 22 August 2001; revised 26 September 2001; accepted 5 October 2001

Abstract—A new method is presented with which achiral, conformationally flexible biphenylphosphites can be activated by easily available chiral alcohols to give monodentate phosphite ligands that are effective in rhodium-catalysed enantioselective hydrogenation.

Racemic catalysts can be made enantioselective by the introduction of chiral activators capable of selectively activating one of the enantiomers of the catalyst (Scheme 1). This process has been termed asymmetric activation and has proven its utility with a number of catalysts based on bidentate ligands.[1,2] For example, by using an enantiomerically pure diamine, Noyori, Mikami and co-workers showed that ketones can be hydrogenated in the presence of the racemic $[RuCl_2(TolBINAP)(dmf)_n]$ catalyst to give alcohols with enantiomeric purity close to that attainable with a catalyst containing the enantiomerically pure TolBINAP ligand and the same diamine.[3] Mikami has further extended this concept to Ru(II) complexes containing the conformationally flexible, proatropisomeric biphenylphosphine (BIPHEP) ligands.[4] While the latter cannot be isolated in enantiopure forms, their Ru(II) complexes can be obtained in a diastereomerically enriched form upon complexation with a chiral diamine activator, which controls chirality of BIPHEP through epimerisation and leads to asymmetric activation of the complexes to give enantioselective catalysts for the hydrogenation of ketones. The advantage of such an approach to asymmetric catalysis is that the physical separation of a racemic catalyst is circumvented, provided that a matching chiral activator can be identified. In the examples that have appeared, the asymmetric activation begins with a racemic metal catalyst, where one of the enantiomers combines preferentially with a chiral activating molecule, producing a more catalytically active and enantioselective species. We present herein a method that leads to asymmetric activation of conformationally flexible monodentate phosphite ligands and our preliminary results on the use of these ligands in the rhodium catalysed enantioselective hydrogenation of an unsaturated carboxylic acid derivative.

Monodentate phosphonites and phosphites have recently been shown to be excellent ligands in the rhodium catalysed asymmetric hydrogenation of unsaturated carboxylic acids and dehydroamino acids.[5–8] We have also reported that diastereomerically pure binaphthylphosphites can be obtained from the inexpensive, racemic binaphthol, (L)-menthol and PCl_3 and the phosphites so generated are excellent ligands in the enantioselective hydrogenation of some unsaturated carboxylic acid derivatives.[9] In this approach, one may consider L-menthol to be a chiral activator, generating two easily separable chiral ligands out of a racemic chiral building block.



Scheme 1. Asymmetric activation of racemic catalysts via chiral molecules.[1,2]

Keywords: asymmetric activation; asymmetric hydrogenation; monodentate phosphites; biphenyl ligands; rhodium catalysts.

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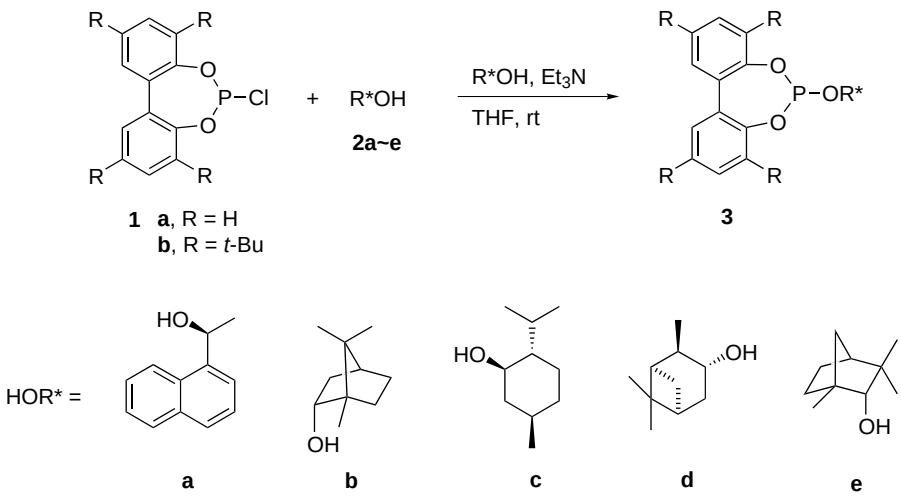
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01895-0

Our new approach is concerned with the asymmetric activation of conformationally flexible biphenyl scaffolds to give chiral phosphite ligands.[10] Thus, by reacting the conformationally flexible, proatropisomeric biphenyl phosphorochloridites **1**[11] with 1 equiv. of a chiral activator, the optically pure alcohol **2**, in THF in the presence of NEt_3 at room temperature, the phosphites **3** could be isolated in over 90% yield (Scheme 2).[12] Unlike their precursors, compounds **3aa**–**ae** are mixtures of diastereoisomers consisting of *S*-**3** and *R*-**3** (*R* and *S* refers to axial chirality). And as such, they need not be equal molar mixtures. However, the ^{31}P NMR spectra of **3aa**–**ae** obtained in $CDCl_3$ at ambient temperature each displayed two singlets with ca the same intensities, which did not appear to change with time. This observation suggests that the steric bias of the chiral activator may not be significant enough to distinguish the conformations adopted by the biphenyl moiety and the two diastereoisomers of each phosphite exist in approximately equal concentrations. A similar observation was made with a 2,2′-bis(diarylphosphino)biphenyl complex of ruthenium containing a chiral activator, *S*,*S*-1,2-diphenylethylenediamine, where two diastereoisomers of equal concentrations were formed.[4a] The difference is that, in the latter case, one of the diastereoisomers was enriched at the expense of the other upon standing or heating for a short period of time. We anticipated that, by placing bulky *t*-Bu groups at the 3,3′ and 5,5′ positions of **1a**, the balance between the two diastereoisomers could be disturbed because of increased steric interactions. This is not the case, however, as the ^{31}P NMR spectrum of **3ba**–**be** showed again two singlets of ca 1:1 ratio

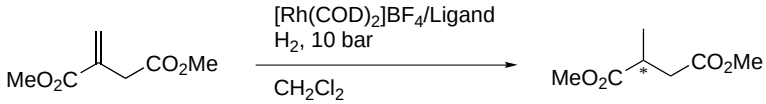
The balance between the two diastereoisomers of **3** did break down upon the introduction of a rhodium complex. Thus, the 1:1 mixture of *S*-**3ae** and *R*-**3ae** reacted with half an equivalent of $[Rh(COD)_2][BF_4]$ to give two compounds in a molar ratio of 1:5, as indicated by ^{31}P NMR at room temperature. Only two doublets appeared in the ^{31}P NMR spectrum, indicating the formation of two compounds, probably $[Rh(S\text{-}\mathbf{3ae})_2(COD)]^+$ and $[Rh(R\text{-}\mathbf{3ae})_2(COD)]^+$ (δ 119.9, $J_{Rh-P}=258.5$ Hz; δ 120.7, $J_{Rh-P}=258.8$ Hz). However, it is not clear at this stage which of the two is the more stable. The complex $[Rh(S\text{-}\mathbf{3ae})(R\text{-}\mathbf{3ae})(COD)]^+$, which would be expected to give rise to two doublet doublets or an AB multiplet in the ^{31}P NMR spectrum, did not appear to be formed.

Having established that the metal complexes of **3** exist as a non-equimolar mixture in solution, we then applied the ligands to the rhodium catalysed enantioselective hydrogenation of dimethyl itaconate. The catalyst was formed in situ by combining $[Rh(COD)_2][BF_4]$ with 2 equiv. of a ligand in CH_2Cl_2. Table 1 summarises the results obtained. As can clearly be seen, the chirally activated biphenylphosphites are capable of face discrimination and hence creating handedness in the product. With the **3a** series of ligands, all the reactions went to completion under the conditions of substrate/catalyst (S/C) = 2000, 20°C and 12 h reaction time, with enantioselectivities ranging from 29% to 57% ee. The ee values for **3ae** could be increased when the temperature was lowered. Thus, ee's rose to 68% at 0°C and 75% at −15°C. It is not clear whether the major enantiomers of these products are due to *S*-**3a** or *R*-**3a** coordinated rhodium catalyst. However, if the configuration of the hydrogenation product is determined by the axial chirality of the ligands, one might expect the *S* configured product to arise from *S*-**3**, as with the same reaction catalysed by L-menthol binaphthylphosphite-Rh(I) complexes, where (*S*)-binaphthyl affords the *S* dominated enantiomer.[9] The conformationally more flexible **3a** ligands gave rise to higher ee values. With the **3b** series of ligands, not only were the enantioselectivities lower but the reactions were in general slower as well. Also, worthy of note is the observation that with some of these ligands, the configuration of the favoured enantiomers of the product is reversed. Thus, while **3ae** gave the *S* configured product with 60% ee, **3be** afforded the opposite enantiomer with 19% ee and a much lower conversion (Table 1), indicating that the enhanced steric bulkiness on going from **3a** to **3b** affects the relative stability of the diastereoisomers of **3**-Rh(I) and/or alters the kinetic profile of each diastereoisomer in the hydrogenation.[13]



Scheme 2. Synthesis of chiral alcohol activated biphenylphosphites. For detailed reaction conditions, see Ref. 12.

Table 1. Enantioselective hydrogenation of dimethyl itaconate by Rh(I) and chirally activated monodentate phosphites[a]



Ligand	S/C	Temp. (°C)	Time (h)	Conversion (%)	% ee
3aa	2,000	20	12	100	29 (*R*)
3ab	2,000	20	12	100	46 (*S*)
3ac	2,000	20	12	100	35 (*S*)
3ad	2,000	20	12	100	31 (*S*)
3ae	2,000	20	12	100	57 (*S*)
3ae	200	20	0.5	100	60 (*S*)
3ae	200	0	2	100	68 (*S*)
3ae	200	−15	2	100	75 (*S*)
3ba	200	20	0.5	16.1	11 (*R*)
3bb	200	20	0.5	100	13 (*S*)
3bc	200	20	0.5	81.4	9 (*R*)
3bd	200	20	0.5	72.6	2 (*S*)
3be	200	20	0.5	2.1	19 (*R*)

[a] Ligand/Rh = 2. S/C: molar ratio of substrate/catalyst. Conversion and ee values were determined by a Varian CP-3380 GC equipped with a Chiraldex G-TA (40 m×0.25 mm) column.

We have also examined these ligands in a limited, combinatorial way, aiming to find a more matched ligand pair that would be more effective towards enantioselective hydrogenation of the itaconate. Combinatorial approaches for identifying lead homogeneous asymmetric catalysts have seen considerable progress in the last few years.[14] Comformationally flexible monodentate phosphites can be ideal candidates for use in such methods, as libraries of these ligands can easily be generated, no chiral separation is needed, and the easy dissociation of monodentate ligands from a metal atom could lead to favourable diastereoisomers out of a mixture of ligands. The few experiments that we have carried out to date are summarised in Table 2. These results seem to suggest that catalysts containing mixed ligands such as [Rh(**3ad**)(**3bd**)(COD)]$^+$ were not formed and the observed enantioselectivities resulted from the aforementioned catalysts. However, a more detailed investigation would be needed to clarify this.

In summary, our results demonstrate that asymmetric activation of conformationally flexible biphenyl-based ligands by coupling with easily available chiral molecules is feasible and the monodentate phosphites so generated are capable of enantioselection in rhodium-catalysed hydrogenation. This method could provide an easy entry to libraries of chiral ligands without invoking resolution.

Table 2. Enantioselective hydrogenation of dimethyl itaconate by Rh(I) and mixed phosphite ligands[a]

Ligand 1	Ligand 2	Conversion (%)	% ee
3ad	**3ae**	100	58 (*S*)
3bb	**3ae**	100	46 (*S*)
3ab	**3ae**	100	55 (*S*)
3ac	**3ad**	100	33 (*S*)
3bd	**3ad**	100	27 (*S*)

[a] Reactions were carried out under 10 bar H_2 in CH_2Cl_2 at room temperature for 30 min. S/C = 200. Ligand 1:Ligand 2:Rh = 1:1:1.

Acknowledgements

We thank the EPSRC for a postdoctoral research fellowship (WC) and the industrial partners (Synetix, Johnson Matthey, Catalytica, Air Products, Syntroleum) of the Leverhulme Centre for Innovative Catalysis for support. We also thank Dr. Nick Greeves and P. M. R. Borges for assistance in computer modelling.

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