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Asymmetric Isomerisation of a Cyclic Diene: a Comparative Study of BINAP and BIPNOR–Rhodium(I) Catalysts

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Abstract—The asymmetric isomerisation of 5,7-dibenzyloxy-6-(trialkylsilyloxy)cyclohepta-1,3-diene **1** to the corresponding 1,6-dibenzyloxy-7-(trialkylsilyloxy)cyclohepta-1,3-diene **2** can be accomplished at 90°C in a 75/25 mixture of toluene and DME in the presence of a $[Rh(BIPNOR)(cod)]^+$ catalyst with 92% ee. A much lower ee is observed with BINAP. In both cases, the observed ee's increase with temperature. A mechanism involving an η^5-pentadienyl–rhodium complex is proposed.

Introduction

Among the various processes relying on enantioselective catalysis, the asymmetric isomerisation of alkenes is certainly one of the most useful as illustrated by the industrial synthesis of (−)-menthol.[1] This reaction has been performed on various substrates such as allylamines,[2] allyl ethers,[3] and allyl acetals.[4] In most cases, the chiral catalyst was a BINAP–rhodium(I) complex.[5] To our knowledge, this type of transformation has never been applied to a conjugated diene. In the course of our work on the total synthesis of calystegines,[6] the key intermediate **1** appeared to be a potential substrate to test the efficiency of such an asymmetric isomerisation process (Scheme 1). Recently, we found BIPNOR[7] to be a very promising bis-phosphine ligand for enantioselective catalysis. In BIPNOR the chiral information is located on two non-racemisable bridgehead phosphorus centres (Fig. 1). We report here on the efficient asymmetric isomerisation of diene **1** in the presence of the BIPNOR–rhodium(I) catalyst which was shown to be largely superior to the classical BINAP–rhodium(I) catalyst.

Results and Discussion

The cyclic diene **1** readily isomerises to a racemic product **2** under acidic conditions or in the presence of the Wilkinson catalyst. Full conversion was observed in toluene at 80°C after 12 h in the presence of *para*-toluenesulfonic acid. Isomerisation was also complete at 50°C after 4 h in the presence of 20% of $[RhCl(PPh_3)_3]$. On this basis, it was clear that reproducible results in asymmetric isomerisation experiments could only be obtained in aprotic solvents. Therefore all reactions were conducted in the presence of solid anhydrous sodium bicarbonate. It was possible to efficiently separate (+)-**2** and (−)-**2** on a CHIRALCEL® OD stationary phase. Preliminary experiments were carried out at 50°C in a 1:1 mixture of toluene and THF in the presence of 15% of $[Rh(S,S)\text{-}(-)\text{-BIPNOR})(cod)]^+PF_6^-$ as a catalyst. Addition of THF was necessary to solubilise the catalyst. A careful kinetic study showed that the isomerisation of **1** to (+)-**2** and (−)-**2** can be viewed as the superimposition of two first-order reactions with rate constants $k_+=1.71\times10^{-5}\ s^{-1}$ and $k_-=5.49\times10^{-5}\ s^{-1}$, respectively, showing that the (−)-BIPNOR catalyst favours the hydrogen [1,5] shift leading to (−)-**2**. Full conversion of **1** into (−)-**2** was observed after 32 h with a 53% ee. Similar tests with (+)-BIPNOR led to (+)-**2** with the same enantiomeric excess. Comparative experiments were carried out with (*R*)-(+)-BINAP under identical conditions. The isomerisation of **1** proceeded more rapidly with BINAP than with BIPNOR, yielding 97.5% versus 32% of (+)-**2**, after only 1 h. However the enantiomeric excess was lower (31% ee).

In order to determine the influence of the temperature, we repeated the experiments with (−)-BIPNOR at 20°C. As expected, the reaction was much slower with rate constants $k_+=2.71\times10^{-6}\ s^{-1}$ and $k_-=3.27\times10^{-6}\ s^{-1}$. To our surprise, the enantioselectivity was lower with an ee of only 9.4%. Similar experiments with (*R*)-(+)-BINAP also showed a decrease of ee to 11%. It had been observed earlier by others that an increase of ee with increasing temperature could be observed when the chiral recognition step is entropy-controlled.[8] In our case, entropy certainly plays a major role in the transformation of the highly symmetrical

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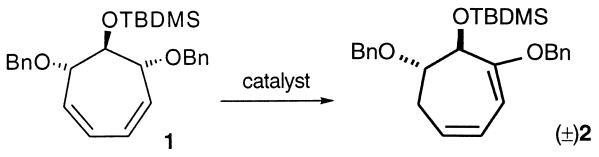
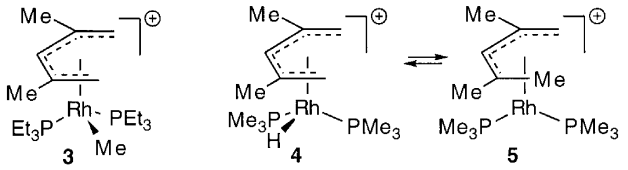


Scheme 1.

diene **1** to its isomer of lower symmetry **2**. Very recently, a similar positive effect of the temperature on the ee has been found in the BINAP–[Ni(cod)$_2$]-catalysed reductive ring opening of oxabicyclo[3.2.1]alkenes to give related cyclohexenols.[9]

On the basis of these preliminary observations, we decided to carefully optimise the conditions for the enantioselective conversion of **1** into (+)- or (−)-**2** using the more efficient BIPNOR-based catalyst. Since the ee appeared to increase with the temperature, we decided to conduct the reactions at temperatures higher than 50°C. Therefore, we replaced THF by other cosolvents of higher boiling points such as 1,4-dioxane, 1,2-dimethoxyethane (DME) or diethyleneglycol dimethylether (DGE). Our experiments are summarised in Table 1. A 3:1 mixture of toluene and DME at 90°C was found to give the best results. The cosolvent appeared to play a decisive role in the enantioselectivity. Indeed, the use of chlorobenzene or 1,2-dichloroethane led to no selectivity (ee=0%). A coordinating solvent such as pyridine in a 25:75 ratio with toluene at 90°C gave an 8% ee. Adding a catalytic amount of an optically active diamine such as (*S*)-(−)-*N*,*N*-dimethyl-1-phenylethylamine did not improve the selectivity with the BIPNOR catalyst. Finally, the ratio of catalyst to substrate was found to be crucial: high selectivities were obtained with 15% of catalyst. Additional quantities of catalyst did not improve the ee's. Even with these optimised conditions (15% catalyst, DME/toluene 25:75, 90°C), the BINAP-based catalyst again gave poor ee (11%).

Two experimental observations are essential to any discussion of the mechanism of isomerisation of **1** to **2**: (a) an oxygen containing cosolvent is necessary for good enantioselectivity; (b) 1,4-dienes were never observed. The first observation militates against a possible intervention of the oxygen substituents of **1** for ligation to rhodium during stereodifferentiation, as had been proposed by Otsuka for the mechanism of asymmetric isomerisation of allylamines.[2] The second observation suggests a direct [1,5] migration of hydrogen without formation of η^3-allyl intermediates. Also, Bleeke and Donaldson[10] have observed stable η^5-pentadienyl–rhodium complexes such as **3** which were characterised by X-ray diffraction. When the rhodium atom bears a hydride ligand, there is an equilibrium between structure **4** and a η^4-diene complex **5**.



On this basis, we propose a mechanism involving the formation of a rhodium complex **6** by η^4-coordination of diene **1** on the face opposite to the benzyloxy substituents. This would be followed by the insertion of Rh into one of the *syn* sp^3-C–H bonds giving the η^5-pentadienyl complex **7**. Hydride transfer to the other terminus of the pentadienyl ligand would then give the isomerised η^4-complex **8** (Scheme 2). This mechanism easily explains the observed enantioselectivities. The net result of the transformation of **6** to **8** via **7** is a rotation of the molecule around its coordination axis to rhodium. If (*S*,*S*)-BIPNOR occupies the two

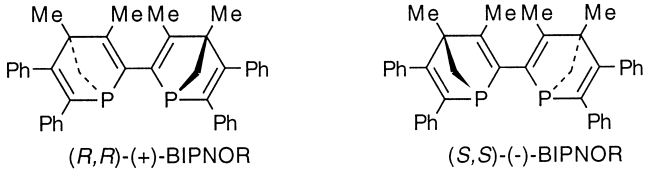
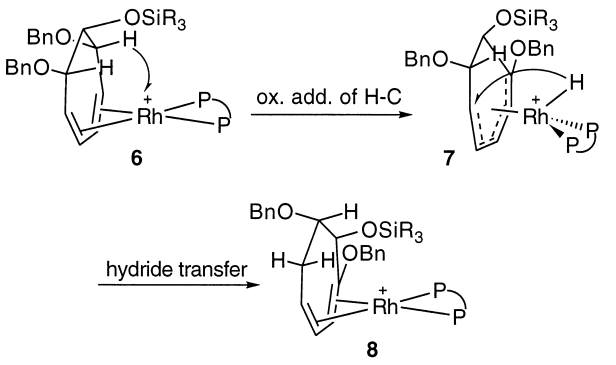


Figure 1. BIPNOR.

Table 1. Influence of the cosolvent on the asymmetric isomerisation of diene **1** in the presence of 15% of [Rh(BIPNOR)(cod)]$^+$PF$_6^-$ as the catalyst

Entry	Cosolvent	Ratio:toluene	Time (min) 100% conversion	Temperature (°C)	ee %
1	Dioxane	100:0	<2	90	36
2	Dioxane	50:50	15	90	57
3	Dioxane	25:75	15	90	71
4	Dioxane	10:90	30	90	63
5	DME	100:0	<2	90	36
6	DME	75:25	<2	90	82
7	DME	50:50	15	90	79
8	DME	25:75	<2	90	92
9	DME	10:90	<2	90	85
10	DGE	25:75	15	90	26
11	DGE	10:90	15	90	22
12	DGE	50:50	<2	110	37
13	DGE	25:75	<2	110	40
14	DGE	10:90	<2	110	39
15	DGE	2:98	<2	110	17



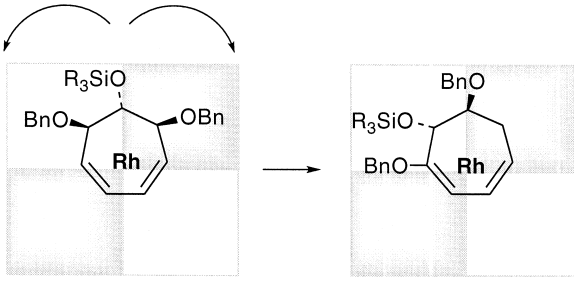
Scheme 2. Proposed mechanism for the isomerisation of **1** into **2**.

shaded quadrants of the space around rhodium,[11] the bulky siloxy substituent would prevent the rotation of the molecule to the right (Scheme 3). The role of oxygen-containing cosolvents would be to block the competitive H^+-catalysed isomerisation mechanism which would lead to a racemic product.[12] Solvents such as chlorobenzene or 1,2-dichloroethane would be inefficient for that purpose. Solvents with too high coordination ability such as pyridine or, to a lesser extent, DGE would prevent an efficient coordination of **1** to rhodium. This is in complete agreement with the experimental evidence presented above.

Experimental

NMR spectra were recorded in $CDCl_3$ on Bruker WP 200 and AM 400 spectrometers. The chemical shifts δ are reported in ppm (TMS as internal standard $\delta=0$). Coupling constants J are reported in Hz. ^{13}C NMR spectra were recorded on the same instruments. ^{13}C NMR chemical shifts are expressed in ppm, reported from the central peak of deuterochloroform (77.1 ppm). IR spectra were recorded on a Perkin–Elmer FT 1600 instrument and are reported in terms of frequency of absorption ν, cm^{-1}. High resolution mass spectra (HR-MS) were recorded on a ZAB HFQ VG apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1 dm cell.

All reactions were carried out under argon. Dry solvents were freshly distilled before use. Dichloromethane and chlorobenzene were distilled from P_2O_5. Toluene, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and diethyleneglycol dimethylether were distilled from sodium/benzophenone. 1,2-Dichloroethane was distilled from calcium hydride, and pyridine from BaO.



Scheme 3. Origin of enantioselectivity with (*S*,*S*)-BIPNOR (the [Rh(BIPNOR)] unit stands behind the cycloheptadiene; the two occupied quadrants are shaded).

Reactions were monitored by thin layer chromatography (TLC) carried out on Merck silica gel plates (ref. 5549) using 5% ethanolic phosphomolybdic acid/heat as the developing agent. Merck silica gel (ref. 9385) was used for flash chromatography. Reaction rates and enantiomeric excesses were determined using a CHIRALCEL® OD column (elution with a mixture 2:1000 of propan-2-ol/hexane) equipped with a UV-detector. (5*R*,6*S*,7*S*)-5,7-Dibenzyloxy-6-[(*t*-butyldimethylsilyl)oxy]cyclohepta-1,3-diene (**1**), $[Rh(BIPNOR)(cod)]^+PF_6^-$ and $[Rh(BINAP)(cod)]^+PF_6^-$ were prepared as previously reported.[6,7]

Procedure for isomerisation of 1 in the presence of Wilkinson's catalyst: synthesis of racemic 1,6-dibenzyloxy-7-[(*t*-butyldimethylsilyl)oxy]-cyclohepta-1,3-diene 2

A solution of **1** (200 mg, 458 μmol, 1 eq.) in 20 mL of dry toluene containing Wilkinson's catalyst (85 mg, 92 μmol, 0.2 eq.) was left for 4 h at 50°C. According to TLC, the isomerisation was complete. The solution was filtered through Celite®, washed twice with dichloromethane, dried ($MgSO_4$) and concentrated to give an oil which was purified by flash chromatography (ethyl acetate/cyclohexane=7:93) to yield **2**: 0.164 g (82%).

^1H NMR (400 MHz): 7.41–7.28 (m, 10H, phenyl); 6.11 [ddd, ^3J(H-3, H-4)=10.9, ^4J(H-3, H-2)=7.8, ^4J(H-3, H-5)=2.7, 1H: H-3]; 5.82 [ddd, ^3J(H-4, H-3)=10.9, ^3J(H-4, H-5a)=6.6, ^3J(H-4, H-5b)=5.1, 1H: H-4]; 5.28 [d, ^3J(H-2, H-3)=7.8, 1H: H-2]; 4.82 [d, ^2J(H-1″a, H-1″b)=11.5, 1H: H-1″a]; 4.73 [d, ^2J(H-1″b, H-1″a)=11.5, 1H: H-1″b]; 4.64 [d, ^2J(H-1′a, H-1′b)=12.4, 1H: H-1′a]; 4.52 [d, ^2J(H-1′b, H-1′a)=12.4, 1H: H-1′b]; 4.39 [d, ^3J(H-7, H-6)=5.7, 1H: H-7]; 3.95 [ddd, ^3J(H-6, H-7)=5.7, ^3J(H-6, H-5b)=5.1, ^3J(H-6, H-5a)=3.1, 1H: H-6]; 2.95 [ddd, ^2J(H-5a, H-5b)=15.1, ^3J(H-5b, H-6)=5.1, ^3J(H-5b, H-4)=5.1, 1H: H-5b]; 2.69 [ddd, ^2J(H-5a, H-5b)=15.1, ^3J(H-5b, H-4)=6.6, ^3J(H-5a, H-6)=3.1, 1H: H-5a]; 0.94 [s, 9H: $(CH_3)_3CSi$]; 0.09 [s, 6H: $(CH_3)_2Si$]. ^{13}C NMR (100 MHz): 159.4 (C-1); 124.4 (C-4); 122.7 (C-3); 98.7 (C-2); 76.1 (C-6); 74.0 (C-7); 72.2 (C-1′); 69.4 (C-1″); 28.7 (C-5); 26.0 [$(CH_3)_3CSi$]; −4.4, −5.1 [$(CH_3)_2Si$]. IR (film): 3029 (=C–H); 1652 (C=C–O); 1618 (C=C–C=C); 1252 (C–Si); 1168, 1139, 1085 (C–O–C); 837 (C–Si). HRMS: Calc. for $C_{27}H_{36}O_3Si$: 436.2433; found: 436.2433.

General procedure for asymmetric catalytic isomerisation of 1 into a mixture of (6*R*,7*S*)- and (6*S*,7*R*)-1,6-dibenzyloxy-7-[(*t*-butyldimethylsilyl)oxy]-cyclohepta-1,3-diene 2

The $[Rh(P^*–P^*)(cod)]^+PF_6^-$ catalyst (10 μmol, 0.15 eq.) was dissolved in 2 mL of a mixture of dried and degassed solvents (see Table 1). A small amount of anhydrous $NaHCO_3$ crystals was added to neutralise any acid. The *meso* diene **1** (30 mg, 66.7 μmol, 1 eq.) was dissolved in 2 mL of the same mixture of solvents, also in the presence of $NaHCO_3$. Both solutions were brought separately to the

desired temperature, then quickly mixed (addition of diene to catalyst). After completion (TLC) of the reaction, the mixture was filtered through Celite®, washed twice with dichloromethane, dried ($MgSO_4$) and concentrated to give an oil which was purified by flash chromatography (ethyl acetate/cyclohexane=7:93) to give enantiomerically enriched **2**. Yield: 29 mg (97%).

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