Pergamon

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Tetrahedron Letters 44 (2003) 9025–9028

TETRAHEDRON LETTERS

Electronic and steric effects of ligands as control elements for rhodium-catalyzed asymmetric hydrogenation

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Received 28 August 2003; revised 29 September 2003; accepted 29 September 2003

Abstract—Electronic and steric effects in the rhodium diphosphinite catalyzed asymmetric hydrogenation were investigated. A series of electronically and sterically modified (*S*)-BINOL and (*S*)-H_8-BINOL ligands was synthesized and effects on the catalytic performance were studied. Phosphinite basicity was varied by using *p*-CH_3O, *p*-CH_3, *p*-H, *p*-CF_3, 3,5-$(CH_3)_2$, 3,5-$(CF_3)_2$ substituents on the diphenylphosphine moieties. In the hydrogenation of dimethyl itaconate and methyl (*Z*)-α-acetamido cinnamate an increase in enantioselectivity and activity was observed with increasing phosphine basicity.

Rhodium-catalyzed asymmetric hydrogenation is one of the most important applications of homogeneous catalysis in industry.[1] While a rational understanding of how ligand structure can steer the selectivity in the hydrogenation is now unfolding,[2] only limited attention has been paid to the electronic properties of phosphine[3] and phosphinite ligands[4] and their influence on catalytic performance.

Very recent research has shown that the chiral catalysts derived from 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl ligands exhibit higher activities and enantioselectivities for asymmetric reactions[5] than those prepared from their parent ligands due to the steric and electronic modulation in binaphthyl backbone.[6] A simple modification, namely the reduction of the unsubstituted rings of the BINOL, provides a superior catalyst for the enantioselective hydrogenation.

In addition to the binaphthyl moieties, the phosphorus groups can be modified through the phenyl groups. The introduction of substituents can modify the electron density of the aromatic rings, and this, in turn, alters the electron density at phosphorus. Catalysts prepared from these modified systems can have different reaction rates and selectivities when compared to the parent ligand system. To study the exact nature of the electronic effect in rhodium diphosphinite catalyzed asymmetric hydrogenation,[7] we synthesized a series of (*S*)-BINOL and (*S*)-H_8-BINOL based diphosphinite ligands with varying basicities.

The novel ligands (**3a**, **3b**, **3d**, **4a**, **4b**, **4d**, **4f**) were prepared by reacting (*S*)-BINOL (1,1′-bi-2-naphthol) or (*S*)-H_8-BINOL (H_8-BINOL = 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) with the corresponding chlorodiarylphosphine in the presence of dry triethylamine in diethyl ether under an argon atmosphere at room temperature.[8,9] (*S*)-H_8-BINOL can be readily derived from BINOL using the protocol of Cram.[10] For a comparative study, the diphosphinites[8] (**3c**, **3e**, **4e**) already described have also been synthesized.

The precatalysts were prepared as usual by the reaction of diphosphinites with $[Rh(cod)_2]BF_4$ in CH_2Cl_2. For all diphosphinite ligands, the formation of the [(diphosphinite)Rh(COD)]BF_4 complexes was evidenced by the appearance of a doublet in their ^{31}P NMR spectra. NMR spectroscopic analysis showed that complexes with two coordinated phosphorus in the *cis* positions were formed.[11] We have found that decreasing the phosphine basicity gave increasing rhodium/phosphorus ^1J(Rh,P) coupling constants and increasing coordi-

Keywords: asymmetric hydrogenation; diphosphinites; rhodium; dimethyl itaconate; methyl(*Z*)-α-acetamido cinnamate.
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doi:10.1016/j.tetlet.2003.09.217

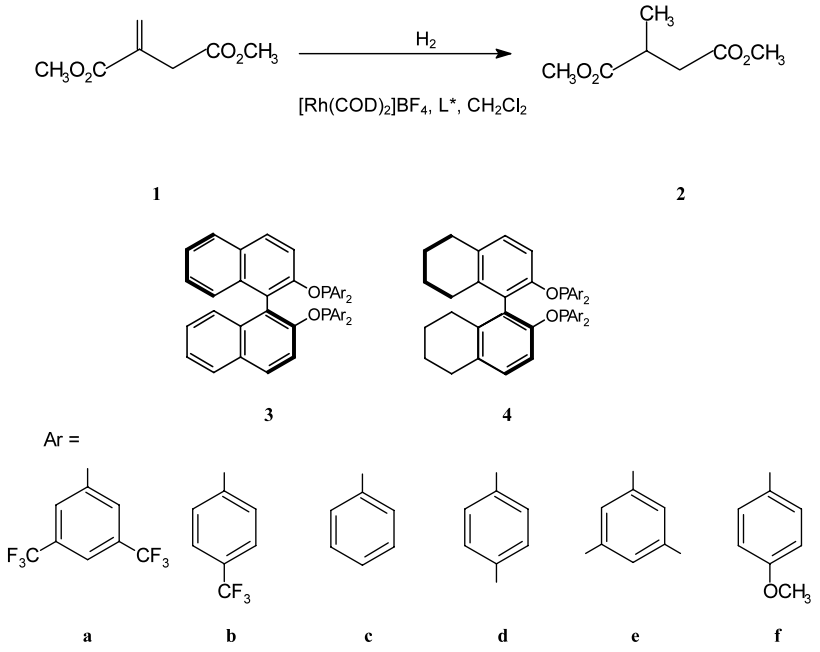
nation shifts (δP for complex – δP for free ligand). Unlike the other parameters, the chemical shift values for the [(diphosphinite)Rh(COD)]BF_4 complexes are very similar.

We carried out asymmetric hydrogenation of electron-deficient olefins, dimethyl itaconate **1** (Scheme 1), and methyl (*Z*)-α-acetamido cinnamate **5**, using the Rh-complexes of the series of electronically modified (*S*)-BINOL and (*S*)-H_8-BINOL diphosphinite ligands. These complexes are useful in terms of quantifying the electronic as well as steric influences of the ligands. The conditions used for the hydrogenation are given in Table 1.[12]

A comparison of the experimental results from entries 1, 2 and 4, 5 (Table 1) revealed the detrimental effect on enantioselectivity and catalytic activity caused by electron-withdrawing substituents. These results are not consistent with the expectation that the electronic effect is less significant when compared to the steric hindrance effect in influencing the enantioselectivity of the reaction. An analysis of the results from entries 2, and 4, 6 indicated that the electron-withdrawing *para* substituent on the phenyl rings decreases enantioselectivity, while electron-donating substituents were found to increase the enantioselectivities of the desired product and the activities of the catalysts. The highest ee, 93.9%, was achieved at atmospheric pressure (entry 7). Increased hydrogen pressure accelerated the reaction but played a minor role in enantioselectivity.

Other interesting features can be noted from Table 1. While the (*S*)-BINOL based system provided hydrogenated products with moderate to good ee values, the partially hydrogenated BINOL based catalysts gave higher activities and ee values for all ligands studied in the hydrogenation of dimethyl itaconate **1**, giving further support to the beneficial effect of the 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl backbone.[5]

The catalytic hydrogenation can be applied successfully to methyl (*Z*)-α-acetamido cinnamate **5** (Scheme 2). The experimental results revealed that rhodium catalysts bearing these diarylphosphinite ligands gave very different enantioselectivities and activities (Table 2).

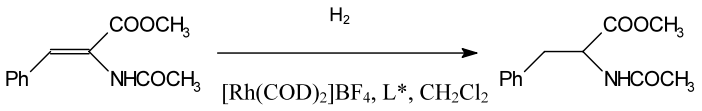


Scheme 1.

Table 1. Asymmetric hydrogenation of **1**[a]

Entry	Ligand	Ar	React. time (min)	Conv (%)	ee (%)	Config.
1	**4a** (**3a**)	3,5-$(CF_3)_2C_6H_3$	90 (90)	87.7 (82.3)	51.6 (50.9)	(*R*)
2	**4b** (**3b**)	4-$CF_3C_6H_4$	20 (30)	100 (100)	72.9 (65.6)	(*R*)
3	(**3c**)	C_6H_5	(17)	(100)	(81.3)	(*R*)
4	**4d** (**3d**)	4-MeC_6H_4	7 (10)	100 (100)	89.5 (81.0)	(*R*)
5	**4e**	3,5-$(CH_3)_2C_6H_3$	9	100	91.5	(*R*)
6	**4f**	4-$MeOC_6H_4$	5	100	92.2	(*R*)
7	**4f**	4-$MeOC_6H_4$	25	100	93.9[b]	(*R*)

[a] General conditions:[12] substrate:catalyst (s:c) = 500, pH_2 = 20 atm, room temperature.
[b] pH_2 = 1 bar.



5 6

Scheme 2.

Table 2. Asymmetric hydrogenation of **5**[a]: influence of the structure of the ligand

Entry	Ligand	Ar	React. time (min)	Conv (%)	ee (%)	Config.
1	**4a**	3,5-$(CF_3)_2C_6H_3$	105	29.3	30.9	(S)
2	**4b**	4-$CF_3C_6H_4$	50	81.8	48.7	(*S*)
3	**4d**	4-MeC_6H_4	25	100	92.5	(*S*)
4	**4e** (**3e**)	3,5-$(CH_3)_2C_6H_3$	13 (25)	100 (100)	95.4 (93.9)	(*S*)
5	**4f**	4-$MeOC_6H_4$	6	100	96.8	(*S*)
6	**4f**	4-$MeOC_6H_4$	25	97.5	98.6[b]	(*S*)

[a] General conditions:[12] substrate:catalyst (s:c) = 500, $pH_2 = 7$ bar, room temperature, 2 mmol of **5** was used.
[b] $pH_2 = 1$ bar.

When the aryl groups on the phosphorus of the phosphinite ligand having an electron-withdrawing group were replaced by aryl groups with electron-donating groups the enantioselectivity and the activity of the catalyst enhanced greatly. For example, 48.7% ee was obtained with **4b**. On replacing CF_3 in **4b** by an Me group in **4d** the enantioselectivity increased to 92.5%. The enantioselectivity was further increased to 96.8% with the methoxy-substituent in the *para* position **4f**. The highest ee, 98.6%, was achieved at atmospheric pressure. Comparison of the sense of asymmetric induction by **3b**, **3c**, and **3d** or **4b**, **4d**, and **4f** suggested that the electronic effect is one of the key elements that controls enantioselectivity. The electronic nature of the *para* substituents in phosphinites has a significant effect not only on the enantioselectivity but also on the activity of the catalysts. Phosphinites with electron-donating substituents (**4d–f**, entries 3–6 in Table 2) gave higher catalytic activities than those with electron-withdrawing substituents (**4a–b**, entries 1–2).

(*S*)-H_8-BINOL based diphosphinites, **4** possessing more electron-rich and bulkier backbone uniformly gave higher ee values than the analogous (*S*)-BINOL based diphosphinites; however, the effect is small. The effect is particularly impressive when the electronic nature of the substituents is changed, enantioselectivities range from 30.9% with **4a** to 95.4% with **4e**. The special '3,5-dialkyl *meta* effect' is well demonstrated in the literature.[8c,13] The (*S*)-BINOL and (*S*)-H_8-BINOL diphosphinite ligands **3d**, **4d–f** bearing both *para* electron-donating groups and *meta*-methyl groups proved to be more efficient than those bearing electron-withdrawing groups in the *para* or *meta* positions **3a–b**, **4a–b**.

In summary, we have developed a highly efficient method for improving the enantiomer discriminating power of the catalytic system. Electronic effects employed as a control element for enantioselectivity and the electronically modified ligands produced a remarkable improvement in the activity and selectivity of the hydrogenation of electron-deficient olefins (**1**, **5**). Since the BINOL and H_8-BINOL based ligands have been widely used in catalytic reactions, the substantial improvements of enantioselectivities and catalytic activities by simply changing the basicity of the ligands clearly indicate the high potential of this new strategy, which, we believe, can be applied to other catalytic reactions. A more detailed study of this new approach with different kinds of catalysts is underway.

Acknowledgements

Support from Hungarian National Science Foundation (OTKA T 032 004) is gratefully acknowledged. We thank Mr. Béla Édes for skillful assistance in the synthetic and catalytic experiments.

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9. ^{31}P NMR (121.42 MHz, $CDCl_3$, 25°C) of **3** and **4**: **3a** δ 104.0, **3b** 106.6, **3d** 111.9, **4a** 101.8, **4b** 104.4, **4d** 108.8, **4e** 109.1, **4f** 109.1 ppm (s).
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11. $[Rh(cod)_2]BF_4$ with **3** and **4**: ^{31}P NMR (202.45 MHz, $CDCl_3$, 25°C): **3a** δ 129.6 (d, ^1J(P,Rh) = 177.4 Hz), **3b** 128.3 (d, ^1J(P,Rh) = 172.3 Hz), **3d** 128.9 (d, ^1J(P,Rh) = 170.0 Hz), **4a** 129.7 (d, ^1J(P,Rh) = 175.9 Hz), **4b** 127.1 (d, ^1J(P,Rh) = 170.2 Hz), **4d** 129.1 ppm (^1J(P,Rh) = 167.6 Hz), **4e** 130.4 (d, ^1J(P,Rh) = 163.2 Hz), **4f** 128.1 (d, ^1J(P,Rh) = 166.2 Hz).
12. **A typical procedure for the catalytic asymmetric hydrogenation**: reactions were carried out in a 20 ml stainless steel autoclave. The catalysts were made in situ by mixing phosphinite (0.011 mmol) with $[Rh(cod)_2]BF_4$ (4.1 mg, 0.01 mmol) in 10 mL of CH_2Cl_2 under argon. The solution was stirred for 15 min and then the substrate (0.7 mL, 5 mmol of **1**) was added. The mixture was transferred into the autoclave under argon atmosphere. The autoclave was pressurized with H_2 and then shaken at a frequency of 180/min, 75° from the upright position, with horizontal amplitude of 3 centimeters. The reaction was monitored by the change in pressure. The reaction mixture and the distilled products were analyzed by gas chromatography. The enantiomeric excess of the product (**2**) was determined by GC analysis of the distilled product (Hewlett-Packard HP 4890 gas chromatograph, split/spitless injector, β-DEX 225, 30 m, internal diameter 0.25 mm, film thickness 0.25 μm, carrier gas: 100 kPa nitrogen, F.I.D. detector; the retention times of the enantiomers are 30.5 min (*R*), 32.1 min (*S*)). In the case of **6** the reaction mixture was passed through a short silicagel column to remove the catalyst. The enantiomeric excess was determined on CP-CHIRASIL-L-VAL column (25 m, internal diameter 0.25 mm, film thickness 0.12 μm, carrier gas: 100 kPa nitrogen, F.I.D. detector; the retention times of the enantiomers are 32.5 min (*R*), 34.2 min (*S*)). The configuration of the prevailing enantiomer in the products was determined by the sign of optical rotation of the hydrogenated product. Conversions were determined by GC (SPB-1).
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