Substituent Effect in Asymmetric Hydroformylation of Olefins Catalyzed by Rhodium(I) Complexes of (*R*,*S*)-BINAPHOS Derivatives: A Protocol for Improvement of Regio- and Enantioselectivities

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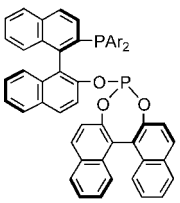
Received July 6, 2000; Accepted September 12, 2000

Keywords: asymmetric catalysis; homogeneous catalysis; hydroformylation; rhodium; P ligands

Asymmetric hydroformylation of prochiral olefins is recognized as a potentially useful method for the synthesis of optically active aldehydes, known as versatile intermediates for pharmaceuticals and agrochemicals.[1] In 1993, we reported that a Rh(I) complex of the chiral phosphine-phosphite (*R*,*S*)-BINAPHOS (**1a**) serves as a truly efficient catalyst for asymmetric hydroformylation of styrene and vinyl acetate, affording the corresponding *iso*-aldehydes regioselectively and enantioselectively.[2a] Later, the catalyst has been applied to the asymmetric hydroformylation of various kinds of olefins with the highest enantiomeric excesses ever reported.[2] Derivatization of the ligand is naturally of much interest if one expects even higher efficiency.[2d] In this study, we have incorporated substituents on the phenyl groups of (*R*,*S*)-BINAPHOS (**1a**) aiming to accomplish the best performance of the catalyst system. With the 3-methoxy-substituted ligand **1b**, hydroformylation of styrene (**2a**) gave *iso*-aldehyde **3a** with higher regioselectivity than with **1a**. The catalyst system Rh(I)-**1b** has been successfully applied to other olefins **2b–d** with remarkable improvements of enantioselectivities.

Ligands **1b–1g** are readily accessible from commercially available aryl bromides according to the reported procedures.[2b] The asymmetric hydroformylation of several olefins was examined with the newly developed ligands **1b–1g** and the results are summarized in Table 1. In all runs, no other products other than aldehydes **3a** and **4a** were detected. Styrene (**2a**) was first selected as a substrate for tuning the ligand (runs 1–11). With all of the ligands **1b**-**1g**, styrene was completely converted into aldehydes **3a** and **4a** under the conditions of substrate/catalyst ratio of 2000, at 60 °C for 20 h. With 3-methoxy-substituted **1b**, the regioselectivity to *iso*-aldehyde **3a** has been improved to 92.5%, maintaining the highest enantiomeric excess of 95.0% (compare runs 1 and 3). Lowering the reaction temperature to 23 °C resulted in the highest selectivities, *iso*-selcetivity of 95.0 % with 97.5% ee of **3a**, at the expense of the conversion (run 4). With **1c** bearing a larger substituent, an *iso*-propoxy group, selectivities similar to those with **1b** were achieved (runs 5 and 6). Very recently, Leitner et al. reported that a BINAPHOS derivative with 3-*n*-$C_6F_{13}CH_2CH_2$-substituted phenyls (**1d**) is effective to improve the regioselectivity, although a slight loss of % ee was observed (run 8).[3] Addition of two methoxy groups on the 3- and 5-positions (**1e**) maintained the regioselectivity (93.4%), similar to that with mono-substituted **1b** (run 9). In contrast, neither substitution with methoxy at the 4-position (**1f**) nor with methyl at the 3-position (**1g**) caused any improvement in selectivities compared to **1a** (runs 10 and 11).



1a: Ar = Ph
1b: 3-MeO-C_6H_4-
1c: 3-^{i}PrO-C_6H_4-
1d: 3-$C_6F_{13}CH_2CH_2$-C_6H_4-
1e: Ar = 3,5-(MeO-)$_2C_6H_3$-
1f: 4-MeO-C_6H_4-
1g: 3-Me-C_6H_4-

The catalyst system of Rh(I)-**1b** has been applied to other prochiral olefins as also shown in Scheme 1 and Table 1. When employing **1b** in place of **1a**, another mono-substituted ethene, 1-hexene (**2b**), was transformed into the corresponding aldehydes with

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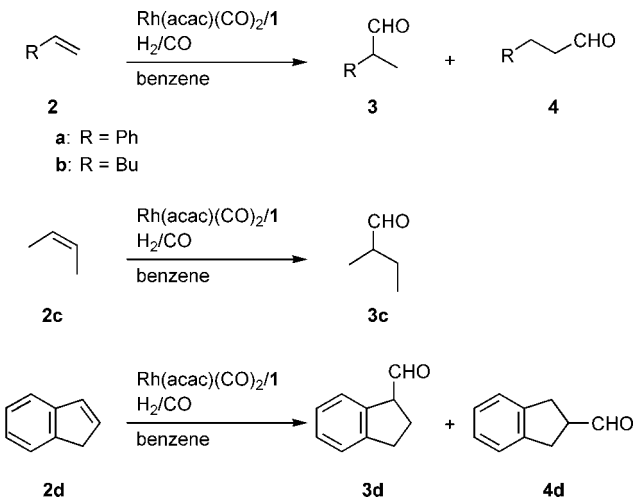
Table 1. Asymmetric hydroformylation of olefins catalyzed by Rh(I)-(*R*,*S*)-BINAPHOS derivatives

Run	Olefin	Ligand **1**	H_2/CO (MPa/MPa)	Temp. (°C)	Time (h)	Conv. to **3** + **4** (%)	*iso* (**3**) selectivity (%)	%ee[a] of **3**
1[b]	Styrene (**2a**)	**1a**	1/1	60	20	>99	88.0	93.2 (*R*)
2		**1a**	1/1	23	22	21	90.6	95.2 (*R*)
3		**1b**	1/1	60	20	>99	92.5	95.0 (*R*)
4		**1b**	1/1	23	22	34	95.0	97.5 (*R*)
5		**1c**	1/1	60	20	>99	91.1	95.7 (*R*)
6		**1c**	1/1	23	22	25	94.0	98.3 (*R*)
7		**1c**	1/1	23	112	>99	93.9	94.5 (*R*)
8[c]		**1d**	5/5	60	17	>99	92.7	90.6 (*R*)
9		**1e**	1/1	60	20	>99	93.4	93.1 (*R*)
10		**1f**	1/1	60	20	>99	87.5	92.2 (*R*)
11		**1g**	1/1	60	20	>99	88.8	91.7 (*R*)
12	1-Hexene (**2b**)	**1a**	1/1	30	40	34	24.3	80.2 (*R*)
13		**1b**	1/1	30	40	66	29.8	90.0 (*R*)
14	(*Z*)-2-Butene (**2c**)	**1a**	1.6/1.6	60	8	(23)[d]	–	82.0 (*S*)
15		**1b**	1.6/1.6	60	9	(7.6)[d]	–	89.9 (*S*)
16	Indene (**2d**)	**1a**	1/1	60	20	34	89.6	83.3 (–)[e]
17		**1b**	1/1	60	20	49	91.3	88.9 (–)[e]

[a] Absolute configuration is shown in parentheses.
[b] With H_2/CO = 50/50, after 43 h, values >99% conv., *iso/normal* = 88/12, 94% ee were reported in ref. [2b].
[c] Data taken from ref. [3] for comparison.
[d] Turnover frequency (h^{-1}).
[e] Absolute configuration is not determined. Optical rotation sign is given.

an improvement in regio- and enantioselectivities (runs 12 and 13), although the *normal*-aldehyde **4b** was still the major product over **3b**. With **1b**, higher enantioselectivities were observed in the asymmetric hydroformylation of 1,2-disubstituted ethenes. From (*Z*)-2-butene (**2c**), (*S*)-2-methylbutanal [(*S*)-**3c**] was obtained with complete chemo- and regioselectivities and 89.9% ee, the highest value ever reported for this substrate (run 15). Indene (**2d**), another disubstituted olefin, was successfully hydroformylated to the corresponding aldehyde **3d**, again with the highest selectivities (run 17). A substrate/catalyst ratio of 250 was employed for this substrate. The product, 1-formyldihydroindene, is known as an important intermediate for the synthesis of 1-aminomethyldihydroindene with hypotensive activity.[1e]



Scheme 1.

In the hydroformylation of 1-alkenes, the electronic effect of unsymmetrical bisphosphine ligand was discussed by Casey in relation to the regioselectivity of the reaction,[4] while an influential steric effect was emphasized by van Leeuwen.[5] Unfortunately, at this moment, the current 3-methoxy group effect is clearly explained by neither electronic nor steric factors. The electronic effect may be rather small in this particular case, because substitution at the 3-position of the phenyl group seems not to affect the electron density of the phosphine phosphorus, significantly. On the other hand, **1c**, **1e**, and **1g** are sterically very different, for example, but give very similar results. A theoretical study[6] is now in progress in our laboratory to clear the substituent effect in **1b**.

Experimental Section

Asymmetric Hydroformylation of Olefins Catalyzed by Rh(I)-Ligand 1[2b]

A solution of olefin (10.0 mmol), $Rh(acac)(CO)_2$ (1.3 mg, 5.0 μmol), and ligand **1** (0.020 mmol) in benzene (0.5 mL) was treated with CO/H_2. For (*Z*)-2-butene (**2c**), a large excess amount of the olefin was charged and the catalytic activity was evaluated with turnover frequency. For indene (**2d**), a substrate/catalyst ratio of 250 was employed. Details of reaction conditions are listed in Table 1. Conversion to aldehydes and regioselectivity of the reaction were determined by ^{1}H NMR. After oxidation of the aldehydes with CrO_3/aq.H_2SO_4-acetone, the enantiomeric excess of the *iso*-carboxylic acid was determined by GLC analysis using a chiral capillary column (Chirasil-DEX CB, 0.25 mm×25 m, 150 °C, He 2 kg · cm^{-2}). When a highly volatile olefin, e. g., (*Z*)-2-butene, was employed, an excess amount (*ca.*

5.0 mL) of olefin was subjected to the reaction. In such a case, Ph_2CH_2 (5–10 equivalents to the catalyst) was added as an internal standard in order to calculate the turnover number by ^1H NMR.

Acknowledgments

We are grateful to Sumikin Chemical Co. Ltd. for the generous gift of (S)-binaphthol. TH thanks the Ministry of Education, Science, Sports and Culture, Japan, for the Grants-in-Aid for COE Research on Elements Science, No. 12CE2005. Financial support for KN from the Ministry of Education, Science, Sports and Culture, the Grant-in-Aids for Scientific Priority Area No. 403 is gratefully acknowledged.

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