Asymmetric Hydroformylation of 1,2-Disubstituted Olefins Catalysed by Chiral Phosphinephosphite–Rhodium(I) Complexes

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Hydroformylations of internal olefins such as (E)- and (Z)-but-2-ene, (E)- and (Z)-1-phenylprop-1-ene, indene, and 1,2-dihydronaphthalene catalysed by (R,S)-binaphos–Rh[I] complex {(R,S)-binaphos = (R)-[2-(diphenylphosphino)-1,1'-binaphthalen-2'-yl][(S)-1,1'-binaphthalen-2,2'-diyl]phosphite} or its enantiomer gave the corresponding oxo-aldehydes in up to 97% enantiomeric excess, e.e.

Asymmetric hydroformylation provides a potential synthetic tool for the preparation of enantiomerically pure aldehydes useful as precursors of many biologically active compounds.[1] Highly enantioselective hydroformylations of arylethenes catalysed by chiral diphosphine–Pt[II] complexes have been reported.[2] On the other hand, high enantioselectivities have rarely been attained in hydroformylation of 1,2-disubstituted olefins.† Recently, we reported that Rh[I] complexes of a new chiral phosphinephosphite ligand, (R,S)-binaphos [(R,S)-1] and its enantiomer (S,R)-binaphos [(S,R)-1], are highly efficient catalysts for asymmetric hydroformylation of mono-substituted olefins such as arylethenes, vinyl acetate, and N-vinylphthalimide.[4] We report here the first example of highly enantioselective hydroformylation of 1,2-disubstituted olefins catalysed by Rh[I] complexes of (R,S)- and (S,R)-1.

The catalyst precursor Rh(acac) (1) (with excess 1) has been prepared *in situ* by the reaction of Rh(acac)(CO)$_2$ and 4.0 equiv. of (R,S)- or (S,R)-1. Thus, a degassed solution of (Z)-but-2-ene (2a) (2.5 ml), Rh(acac)(CO)$_2$ (5.00 × 10^{-3} mmol), and (R,S)-1a (2.00 × 10^{-2} mmol) in benzene (0.5 ml) prepared in a Schlenk tube was transferred into a 50 ml autoclave and stirred at 60 °C for 67 h under hydrogen and

carbon monoxide pressure (1:1, total 100 atm). ^{1}H NMR analysis of the reaction mixture using Ph$_2$CH$_2$ as internal standard showed that (S)-2-methylbutanal [(S)-3a] was formed as an exclusive product. Any byproducts such as butane and pentanal were not detected by ^{1}H NMR and GLC analysis. The turnover number calculated based on the yield of 3a was 9.84 h^{-1} (Table 1, run 1). The enantiomeric excess of (S)-3a (82% e.e.) was determined by GLC analysis, using a chiral capillary column, of the acid obtained by Jones oxidation of product 3a. This value is, to our knowledge, the highest level ever reported for the hydroformylation of simple aliphatic olefins. When (E)-but-2-ene (2b) was used as substrate in the presence of (R,S)-1-Rh[I], the reaction proceeded more slowly to give (S)-3a with lower enantio-selectivity [eqn (1), run 2]. The absence of pentanal in the reaction mixtures indicates that no isomerization of but-2-ene into but-1-ene occurred during the present catalysis. This seems very important for obtaining high e.e.s, since the absolute configurations of the product 3a obtained in the hydroformylation of but-1-ene catalysed by the same catalysts (30 °C, turnover number h^{-1} = 23.3, 3a/4a = 21/79, 83% e.e.) were the reverse to those derived from (E)- and (Z)-but-2-ene.‡ This is in sharp contrast with the fact that the hydroformylation of but-2-ene catalysed by chiral diphos-phine–Pt[II] systems gave pentanal in up to 13% yield.[2a] Asymmetric hydroformylation has also been applied to other internal olefins 2c,d and 5a,b and some representative results are given in Table 1. All of the reactions with volatile olefins were conducted in the presence of large excesses of olefins and the catalytic activites were shown in turnover number h^{-1}. Hydroformylation of (E)-1-phenylprop-1-ene 2c also proceeded slowly at 60 °C to afford 2-phenylbutanal in high regioselectivity (>97%) and in 92% e.e. Reaction at higher temp. gave an enhanced reaction rate, but resulted in a decrease of e.e. Use of a 1:1 mixture of (E)- and (Z)-prop-1-enylbenzene (2c,d) afforded 3c in only a slight decrease in enantioselectivity, but in considerably lower regioselectivity. Hydroformylations of cyclic olefins 5a,b gave aldehydes 6a,b, respectively, in high regio- and enantio-selectivities [eqn. (2)].† Longer reaction time for 5a, however, resulted in a slight racemization of the product 6a. When reaction of 5b was conducted at 60 °C for 6 h [substrate/catalyst (S/C) = 100], 6b was obtained in a reasonable conversion (70%) and in 97% e.e. A longer reaction time (S/C = 300, 60 °C, 20 h) brought about higher conversion (79%) of 5b to give 6b in 96% e.e. A prolonged reaction time (S/C = 250, 60 °C, 72 h, 100% conversion), however, resulted in a much decreased e.e. (84%) which suggests that 6b also racemizes slowly in the absence of the starting olefin 5b.§

The above results show that the present catalysis provides a new powerful means for the synthesis of a variety of

(R,S)-1 [(R,S)-BINAPHOS]

2
a R^1 = Me, R^2 = H, R^3 = Me
b R^1 = Me, R^2 = Me, R^3 = H
c R^1 = Me, R^2 = Ph, R^3 = H
d R^1 = Me, R^2 = H, R^3 = Ph

5
a n = 1
b n = 2

Table 1 Hydroformylations of olefins **2** and **5** catalysed by phosphinephosphite–Rh[I] complexes[a]

Substrate[b]	T/°C	t/h	S/C	Turnover/h	3/4 or 6/7[c]	3 or 6 % e.e.[d]	Config[e]
2a	60	44	—[f]	9.84	—	82	S-(+)
2b	60	45	—[f]	0.50	—	48	S-(+)
2c	60	50	250	0.50	97/3	92	R-(−)
2c	80	61	1000	7.87	98/2	80	R-(−)
2c + 2d[g]	80	38	1000	13.95	78/22	79	R-(−)
5a	60	20	250	3.13	92/8	83	(−)
5a	60	41	500	4.51	92/8	78	(−)
5b	60	6	100	11.70	95/5	97	(−)
5b	60	20	300	11.85	96/4	96	(−)

[a] Reactions were carried out in benzene (solvent:substrate ratios were 0.5–1 unless otherwise stated) in a 50 ml autoclave under 1:1 mixture of H_2 and CO at initial total pressure of 100 atm. [b] Ligand = (R,S)-1. Ligand/[Rh] ratios were 4.0. [c] Yields and 3:4 or 6:7 ratios were determined based on ^{1}H NMR using Ph_2CH_2 as internal standard. [d] Determined by GLC analysis with a chiral capillary column (CHROMPACK Cp-Cyclodex β 236M or Astec Chiraldex B-PH) of acids derived by Jones oxidation of the products **3a–c** and **6a, 6b**. [e] Determined by the signs of optical rotation, which were given in parentheses where possible. [f] Substrates **2a** and **2b** were used in large excesses. [g] A 1:1 mixture of **2c** and **2d** was used.

physiologically active compounds. For example, aldehyde (S)-**3a** is a precursor of (2S,3S)-isoleucine and **3c** is the starting material for antitussive butethamate and anti-inflammatory indoprofen.[1a] Compound **6a** can be converted to the amines with hypotensive activity in a single step by reductive amination with Ni or Pt catalyst,[5] while **6b** is known as an intermediate of vasoconstrictor tetrahydrozoline.[1a]

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Footnotes

† Hydroformylation of indene (**5a**) and acenaphthylene catalysed by PtCl₂–SnCl₂–(R,R)-{(bicyclo[2.2.2]octane-2,3-diyl)bis(methylene)}bis(5H-benzo[b]phosphindole) gave the corresponding aldehydes in 45 and 48% e.e., respectively, see ref. 3.

‡ A similar stereochemical relationship has been reported for the reaction of but-2-ene and but-1-ene catalysed by chiral Pt[II] com-

plexes.[2a] Hydroformylations of (Z)- and (E)-but-2-ene, and but-1-ene catalysed by PtCl₂–SnCl₂–(R,R)-{(bicyclo(2.2.2]octane-2,3-diyl) bis(methylene)}bis(5H-benzo[b]phosphindole) gave 2-methylbutanal **3a** in 30% (R, **3a**:**4a** = 87:13), 29% (R, **3a**:**4a** = 87:13), and 67% e.e. (S, **3a**:**4a** = 14:86), respectively.[2a]

§ In fact, treatment of (−)-**6b** (66% e.e.) in benzene (benzene:**6b** = 5) with (R,S)-binaphos–Rh(acac)(CO)₂ (3:1) under hydrogen and CO pressure (1:1, 100 atm) at 60 °C for 110 h resulted in recovery of (−)-**6b** with only 3% e.e.

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