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Asymmetric Hydroformylation of Allylic Alcohols Catalyzed by Rh(I)-(*R*,*S*)-BINAPHOS

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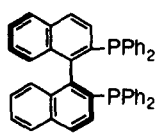
Abstract: Chiral lactones **4a–e** were synthesized by the asymmetric hydroformylation of allylic alcohols **1a–e** and **5** catalyzed by a rhodium(I) complex of a chiral phosphine-phosphite, (*R*,*S*)-BINAPHOS, followed by the silver(I) oxidation. © 1997 Elsevier Science Ltd.

Regio- and enantioselective preparation of substituted tetrahydrofurans and γ-butyrolactones has been an attractive subject since these heterocycles are important subunits for biologically important compounds including natural products. Cyclocarbonylation of allylic alcohols is a direct method for the synthesis of γ-butyrolactones,[1] and palladium complexes with chiral ligands have been developed for asymmetric processes.[1b,f] Asymmetric hydroformylation of allylic alcohols followed by oxidation is of much interest as an alternative.[2] In contrast to the extensive efforts devoted to this subject using achiral catalysts,[3] only a few reports have appeared on the asymmetric hydroformylation of allylic alcohols.[4] We recently have developed a new Rh(I) catalyst system for asymmetric hydroformylation using chiral phosphine-phosphite[5] and phosphine-phosphinite ligands.[6] Here we report an asymmetric synthesis of γ-butyrolactones via rhodium-catalyzed hydroformylation of allylic alcohols.

Cinnamyl alcohol (**1a**) was first employed as a substrate and the reaction conditions were examined. Hydroformylation of **1a** gave the lactol **2a** as an exclusive product and the regioisomer **3a** was not detected by ^{1}H NMR spectroscopy. Introduction of the formyl group at the α-position to the aromatic substituent is common in Rh-catalyzed hydroformylation of aryl-substituted olefins.[7] The crude lactol was converted to the lactone **4a** by oxidation with silver carbonate[8] and the *ee* was determined by HPLC. The results are summarized in Table 1. In a series of chiral ligands tested, the phosphine-phosphite ligand (*R*,*S*)-BINAPHOS gave the best results (runs 2–4). Longer reaction times caused a decrease in the *ee*, probably due to the racemization of the product (runs 5,6). In this reaction, a notable pressure effect was observed on the enantioselectivity (runs 2 and 6–10). The enantiomeric excess decreased at both higher and lower total pressure of H_2 and CO. This is in sharp contrast to the fact that the enantioselectivity was observed to be independent of H_2/CO pressure in the hydroformylation of styrene and 1-hexene using the same catalyst system in the pressure range of 10–100 atm.[9]



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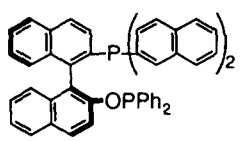

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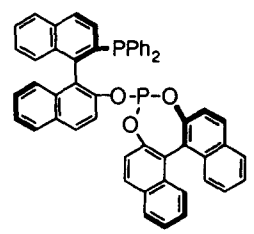

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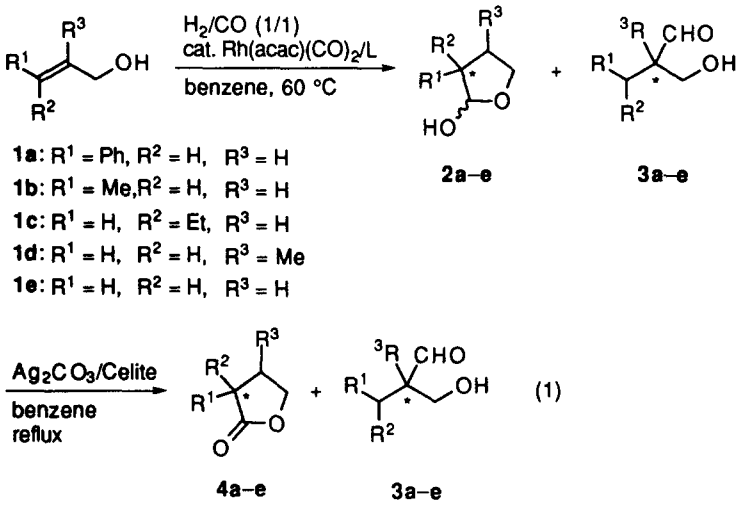


Table 1. Asymmetric Hydroformylation of Cinnamyl Alcohol (**1a**)[a]

Run	Ligand	H_2/CO (atm/atm)	Time (h)	Conv. to **2a**[b] (%)	Yield of **4a** (%)[c]	%*ee* of **4a**[d,e]
1	PPh_3	50/50	72	>99	86	—
2	(*R*,*S*)-BINAPHOS	15/15	30	>99	87	88 (+)
3	(*S*)-BINAP	15/15	30	0	—	—
4	(*R*)-2-Nap-BIPNITE	15/15	30	>99	86	5(+)
5	(*R*,*S*)-BINAPHOS	50/50	57	>99	85	6 (+)
6	(*R*,*S*)-BINAPHOS	50/50	20	53	45	12 (+)
7	(*R*,*S*)-BINAPHOS	25/25	30	65	54	15 (+)
8	(*R*,*S*)-BINAPHOS	20/20	30	73	60	40 (+)
9	(*R*,*S*)-BINAPHOS	5/5	30	64	57	75 (+)
10	(*R*,*S*)-BINAPHOS	0.5/0.5	30	22	n.d.[f]	70 (+)

[a] A degassed solution of **1a** (2.9 mmol), $Rh(acac)(CO)_2$ (0.014 mmol), and a ligand (4 equiv. to Rh) in benzene (1.0 mL) was placed in a 50-mL autoclave under argon and then the system was pressurized with H_2/CO (=1/1). After stirring at 60 °C, the crude lactol **2a** was oxidized with 3.75 g (2.5 equiv.) of Ag_2CO_3/Celite (1.75 mmol/g) in refluxing benzene (100 mL) for 8 h. The resulting lactone **4a** was isolated by column chromatography on silica gel (hexane/EtOAc = 7/3). [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture without evaporation of the solvent. The lactol was obtained in almost 1:1 mitures. [c] Isolated yield. [d] Determined by HPLC analysis (Daicel CHIRALCEL OJ, hexane/2-propanol = 97/3, 1.0 mL·min^{-1}, UV detector, 254 nm). [e] The sign of the optical rotation is shown in parentheses. [f] Not determined.

A series of allylic alcohols were then subjected to asymmetric hydroformylation and representative results are shown in Table 2. For alkyl-substituted allylic alcohols **1b–c**, the product distribution is highly dependent on the reaction conditions. Particularly, the reaction of **1c** afforded a straight-chain aldehyde, 6-hydroxyhexanal as a by-product. The latter likely arises *via* isomerization of **1c** to 4-penten-1-ol prior to

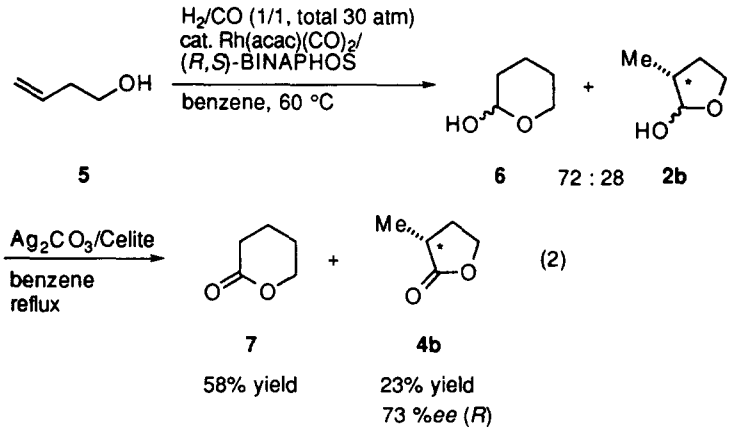
the hydroformylation reaction (run 2).[10] In contrast, no isomerization occured during to the hydroformylation of (*Z*)-2-butene and (*Z*)-3-hexene with the same catalyst.[5b] The *ee*'s of **4b–c** are much lower than that of **4a** and rather lower than our previous results of the hydroformylation of internal aliphatic olefins with the same catalyst system (48% *ee* for (*E*)-2-butene, 79% *ee* for (*Z*)-3-hexene).[5b] Intramolecular coordination of the hydroxyl group to the rhodium center in the transition state may be concernable, but detailed evidence has not been obtained for such a possibility. An allylic alcohol with a substituent at the β-position, **1d**, afforded the lactol **2d** as a single product but the *ee* was low (run 3). The high regioselectivity can be explained by steric hinderance at the C2-position. Hydroformylation of allyl alcohol (**1e**) showed the regioselectivity of **2e/3e** = 90/10. This **2e/3e** ratio corresponds to the *normal/iso* selectivity of terminal olefins and is higher than that observed for 1-hexene (*normal/iso* = 76/24, 75% *ee* for the *iso*-aldehyde).[5a] Thus in this case, contribution of the hydroxyl group to the regioselectivity has again been observed. When the hydroxyl group of **1e** is protected with an acetyl group, the hydroformylation afforded a complex mixture of aldehydes, probably due to the isomerization of the double bond before hydroformylation.[11]

Table 2. Asymmetric Hydroformylation of Allylic Alcohols **1b–e** Catalyzed by Rh(acac)$(CO)_2$–(*R,S*)-BINAPHOS[a]

Run	Substrate	H_2/CO (atm/atm)	Conv[b] (%)	2/3/others[c]	Yield of 4 (%)[d]	%*ee* of 4	%*ee* of 3
1	**1b**	15/15	51	26/74/0	n.d[f]	27 (*R*)[e]	n.d[f]
2	**1c**	15/15	> 99	56/18/12[g]	13	11 (–)[h]	n.d[f]
3	**1d**	15/15	54	>99/<1/0	37	12 (*S*)[i]	—
4	**1e**	15/15	> 99	90/10/0	—	—	16[j]

[a] The reaction and the analyses of the product were carried out in the same way as described in footnote a of Table 1 unless otherwise stated. The reaction was stopped after 30 h. Oxidation of **2** was carried out with 4 equiv. of $AgCO_3$/Celite. [b] Conversion of the olefins into aldehydes. [c] Determined by ^1H NMR of the crude mixture. [d] Isolated yield of the lactone **4** by column chromatography and distillation. [e] Determined by HPLC analysis (CHIRALCEL OD, hexane/2-propanol = 99/1, 0.5 mL·min^{-1}, UV detector, 230 nm). For absolute config., see ref 2a. [f] Not determined. [g] **2c/3c**/6-Hydroxyhexanal = 56/18/12. [h] Determined by HPLC analysis (Daicel CHIRALCEL OD, hexane/2-propanol = 994/6, 1.0 mL·min^{-1}, UV detector, 230 nm). The sign of the optical rotation is minus. [i] Optical purity. Determined by comparison with data in ref. 12. [j] Determined by ^1H NMR of the crude reaction mixture using Eu(hfc)$_3$ as a chiral shift reagent. The aldehyde could not be isolated in pure form and the absolute configuration was not determined.

A homoallylic alcohol, **5**, was also subjected to the asymmetric hydroformylation.[13] The regioselectivity of **6/2b** (72/38 = *normal/iso*) and the *ee* of **2b** (73%) are similar to that of 1-hexene. This result suggests that the hydroxyl group has no effect on the reaction rate and selectivity in this substrate.



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