Asymmetric Hydroformylation of Vinylfurans Catalyzed by {(11b*S*)-4-{[(1*R*)-2′-Phosphino[1,1′-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1′,2′-*f*]-[1,3,2]dioxaphosphepin}rhodium(I) [Rh^{I}{(*R*,*S*)-binaphos}] Derivatives

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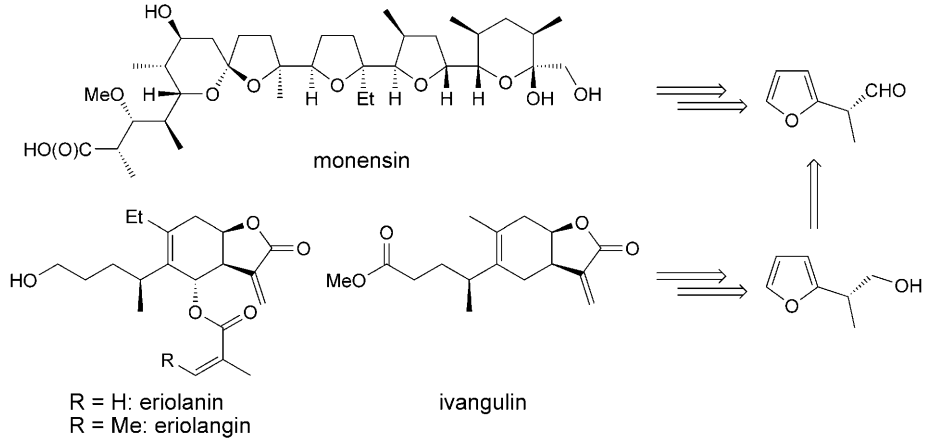
Dedicated to Professor *Giambattista Consiglio* on the occasion of his 65th birthday

The asymmetric hydroformylation of 2- and 3-vinylfurans (**2a** and **2b**, resp.) was investigated by using [Rh{(*R*,*S*)-binaphos}] complexes as catalysts ((*R*,*S*)-binaphos = (11b*S*)-4-{[1*R*)-2′-phosphino[1,1′-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin; **1**). Hydroformylation of **2** gave isoaldehydes **3** in high regio- and enantioselectivities (*Scheme 2* and *Table*). Reduction of the aldehydes **3** with $NaBH_4$ successfully afforded the corresponding alcohols **5** without loss of enantiomeric purity (*Scheme 3*).

Introduction. – Transition-metal-catalyzed hydroformylation is one of the most important reactions that transform a C–C moiety to a formyl group, a versatile functional group. In the last 15 years, many efforts have been devoted to develop new asymmetric-hydroformylation catalysts, since optically active aldehydes are useful intermediates for the synthesis of biologically active compounds as well as new chiral materials [1–4]. We have previously reported the asymmetric hydroformylation of a variety of olefins such as styrene and its substituted analogs, 1,3-dienes, vinyl esters, *N*-vinylphthalimide, and cyclic alkenes such as dihydrofurans and dihydropyrroles by using [Rh^{I}{(*R*,*S*)-binaphos}] complexes ((*R*,*S*)-binaphos = (11b*S*)-4-{[(1*R*)-2′-phosphino[1,1′-binaphthalen]-2-yl]oxy}dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin; **1**) [5–10]. In the field of hydroformylation, olefins with a heteroaryl group such as pyridyl [11–16], pyrrolyl [17–19], furanyl [20], and thienyl [21] groups have been found to be employable to give the corresponding aldehydes. These aldehydes also have a potential utilization as synthetic building blocks: thus, (2*R*)-2-(furan-2-yl)propanal could be a starting material to synthesize monensin (*Scheme 1*) [22]. In addition, (2*S*)-2-(furan-2-yl)propan-1-ol, which should be obtained by reduction of the asymmetric hydroformylation product of 2-vinylfuran, is a key starting material for the 1,10-seco-eudesmanolide synthesis [23][24]. However, asymmetric hydroformylation of vinylheteroarenes is confined to that of vinylthiophene [25].

Herein, we describe the asymmetric hydroformylation of vinylfurans **2** by using [Rh^{I}{(*R*,*S*)-binaphos}] complexes.

Scheme 1. *Synthesis of Biologically Active Compounds from (2*R*)-2-(Furan-2-yl)propanal*



Results and Discussion. – Hydroformylation of vinylfurans **2** was carried out in the presence of [Rh(acac)(CO)$_2$] (acac = pentane-2,4-dionato) and (*R*,*S*)-binaphos (**1**) in benzene under H_2/CO 1:1 pressure (p = 2.0 MPa, *Scheme 2*). The yields and iso/normal ratios of products, *i.e.*, of **3**/**4**, were determined by ^{1}H-NMR spectroscopy of the reaction mixtures by using naphthalene as an internal standard (see *Table*). The enantiomer excess (ee) of the isoaldehydes **3** was determined by HPLC or GC analyses of the reaction mixtures. In all reactions, no hydrogenated products, *i.e.*, ethylfurans, were detected by ^{1}H-NMR spectroscopy. Thus, 2-vinylfuran (**2a**) was hydroformylated in a quantitative conversion within 2 h (TOF = 96 mol aldehyde·mol $Rh^{-1}\cdot h^{-1}$) by using the [Rh(**1a**)] system (*Table*, *Entry 1*). A formyl group was selectively introduced at the α-position of the furan ring to give isoaldehyde **3a** with the iso/normal ratio **3a**/**4a** of 97:3. The ee of **3a** was 79%. The isoaldehyde **3a** was isolated in 92% yield without reduction of the ee. Compared to the [Rh(**1a**)] system, the [Rh(**1b**)] system showed slightly lower catalytic activity (89% conversion; TOF = 89 mol aldehyde·mol $Rh^{-1}\cdot h^{-1}$), 86% yield by ^{1}H-NMR for **3a**) and a lower enantioselectivity (76% ee for **3a**) as demonstrated in our previous report on the asymmetric hydroformylation of styrene (*Table*, *Entry 2*) [26][27].

Hydroformylation of 3-vinylfuran (**2b**) also gave the corresponding isoaldehyde **3b** with high ee (> 98%) in good yields (73–90% by ^{1}H-NMR) (*Table*, *Entries 3* and *4*), although longer reaction times of 6 h were required for high conversion of substrate (TOF = 28–33 mol aldehyde·mol $Rh^{-1}\cdot h^{-1}$). The regioselectivity in the reaction of **2b** (**3b**/**4b** *ca.* 90:10) was lower than in the case of **2a**. The differences in reactivity and regioselectivity between the hydroformylations of **2a** and **2b** could be attributed to a resonance effect: greater conjugation between the furan and vinyl moieties of **2a** than between those of **2b** [28] causes higher reactivity and more-favorable 2,1-insertion to give the isoaldehyde [7].

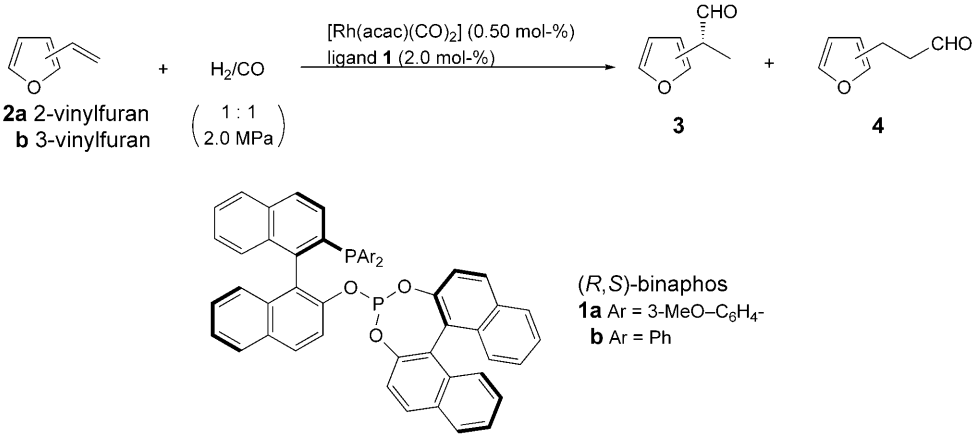
The hydroformylation products **3** of vinylfurans **2** were successfully reduced without loss of ee by $NaBH_4$ to give the corresponding alcohols **5** with high ee (*Scheme 3*). The optical rotation of the obtained 2-furanylpropan-1-ol **5a** (see *Exper. Part*) established

Table. *Results of the Asymmetric Hydroformylation of Vinylfurans by Using [Rh(I){(*R,S*)-binaphos}) Complexes*[a])

Entry	Furan	Ligand	Time [h]	Conversion [%][b])	TOF[b])[c])	**3**/**4**[b])	NMR yield of **3** (%)[b])	ee of **3** [%]
1	**2a**	**1a**	2	100	96	97:3	93 (92)[d])	79[e]) (*R*)
2		**1b**	2	89	89	97:3	86	76[e]) (*R*)
3	**2b**	**1a**	6	100	33	92:8	90 (80)[d])	99[f]) (*R*)
4		**1b**	6	85	28	88:12	73	98[f]) (*R*)

[a]) Reaction conditions: vinylfuran **2** (2.0 mmol), H_2/CO 1:1 (2.0 MPa), [Rh(acac)$(CO)_2$] (0.010 mmol), ligand **1** (0.040 mmol), benzene (1.0 ml), 60°. [b]) Determined by ^{1}H-NMR spectroscopic analyses of the reaction mixtures by using naphthalene as an internal standard. [c]) TOF = turnover frequency in mol aldehyde·mol $Rh^{-1}\cdot h^{-1}$. [d]) Isolated yield in parenthesis. [e]) Determined by GC analyses (*Chrompack Chirasil-DEX-CB* column). [f]) Determined by HPLC analyses (*Daicel-Chiralpak-IA* column).

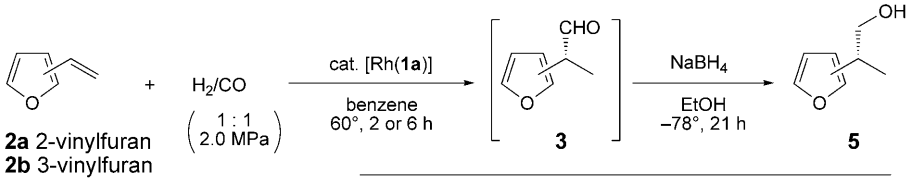
Scheme 2. *Asymmetric Hydroformylation of Vinylfurans* **2**



the absolute configuration of the major enantiomer to be (2*S*) [24]. This demonstrates that asymmetric hydroformylation of 2-vinylfuran (**2a**) by using [Rh^I{(*R*,*S*)-binaphos}] complexes predominantly gave the (2*R*)-aldehyde, and that the sense of enantiofacial selection is the same as that observed for styrene and its substituted analogs [5]. The absolute configuration of 2-furanylpropan-1-ol **5b** was determined to be (2*R*) based on the known optical rotation of (2*S*)-3-hydroxy-2-methylpropanoic acid (**6**) (see *Exper. Part*), which was obtained by oxidation of **5b** with $RuCl_3/NaIO_4$ in 78% yield (*Scheme 4*) [29–31]. Thus, olefin insertion into the Rh–H bond also proceeded through the same enantiofacial selection in this case.

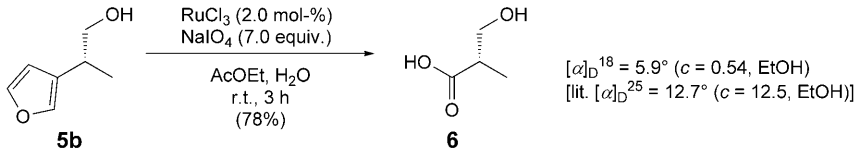
In summary, we have reported the asymmetric hydroformylation of vinylfurans by use of [Rh^I{(*R*,*S*)-binaphos}] complexes. To the best of our knowledge, the present work is the first successful example of asymmetric hydroformylation of vinylfurans. The produced furanylpropanals should have a potential use as synthetic intermediates. Thus, the hydroformylation of vinylfurans should be a new convenient access to such useful compounds.

Scheme 3. *Hydroformylation of Vinylfurans* **2** *and Subsequent Reduction of the Aldehydes* **3**



	NMR yield of **3** [%]	ee of **3** [%]	Isolated yield of **5** [%]	ee of **5** [%]
2a	93	79 (*R*)	86	79 (*S*)
2b	84	99 (*R*)	74	99 (*R*)

Scheme 4. *Determination of the Absolute Configuration of* **5b**



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Experimental Part

General. All the solvents used for reactions were distilled under Ar after drying over an appropriate drying agent, or passed through solvent-purification columns. Most of the agents, were purchased from *Aldrich Chemical Co.*, *Tokyo Kasei Kogyo Co., Ltd.*, or *Kanto Kagaku Co., Ltd.*, and were used without further purification unless otherwise specified. 2-Vinylfuran (**2a**) [32] and 3-vinylfuran (**3a**) [33] were synthesized according to the literature. All manipulations involving air- and/or moisture-sensitive compounds were carried out by using the standard *Schlenk* technique under Ar purified by passing through a hot column packed with *BASF* catalyst *R3-11*. Anal. TLC: glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (*Merck*). Column chromatography (CC): silica gel *60N* (spherical neutral, particle size 63–210 μm, *Kanto Kagaku Co., Ltd.*). HPLC: *Jasco-LC-2000Plus* system (*PU-2080* pump, *LG-2080-02* gradient unit, *DG-2080-53* degasser, *CO-2060* column oven and *MD-2010* UV detector); *Daicel-Chiralpak®-IA* column (4.6 mm × 250 mm). GC: *Shimadzu-GC-2010*; *Chrompack-Chirasil-DEX-CB* column; He as carrier gas. IR Spectra: *Shimadzu-FTIR-8100A* spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Jeol-JNM-ECP500* (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer; $CDCl_3$ solns.; δ in ppm rel. to the internal standard $SiMe_4$ (0 ppm), J in Hz. Elemental analyses were performed by the Microanalytical Laboratory of the Department of Chemistry, Faculty of Science, The University of Tokyo.

Rhodium-Catalyzed Hydroformylation of Vinylfurans: General Procedure (G. P.). A mixture of vinylfuran **2** (2.0 mmol), [Rh(acac)$(CO)_2$] (2.8 mg, 0.010 mmol), and (*R*,*S*)-binaphos **1a** (33 mg, 0.040 mmol) in benzene (1.0 ml) was degassed by three freeze-thaw cycles (*Schlenk* tube). The soln. was transferred into a 50-ml autoclave under Ar, and then H_2/CO was introduced. The mixture was stirred at 60° for the appropriate time and then cooled down to r.t. After the H_2/CO pressure was released, naphthalene was added and the mixture was stirred for a few minutes. An aliquot of the resulting mixture was diluted with $CDCl_3$ and analyzed by ^1H-NMR to determine the conversion and the yields of products **3** and **4**. Another aliquot of the mixture was analyzed by HPLC (*Daicel-Chiralpak® IA*) or by GC (*Chrompack Chirasil-DEX CB*) to determine the ee of aldehyde **3**.

Hydroformylation of 2-Vinylfuran (**2a**). According to the *G. P.*, with **2a** (0.20 ml, 2.0 mmol). GC (70°) of the product: t_R 16.4 min for (*S*)-**3a** and 16.6 min for (*R*)-**3a**; 79% (*R*) ee. The product was purified by CC (hexane/AcOEt (5 : 1; R_f 0.55): *(2*R*)-2-(furan-2-yl)propanal* (**3a**; 228 mg, 92%) [34]. Colorless oil. GC of isolated **3a**: 79% (*R*) ee. $[\alpha]_D^{16} = -27.0$ ($c = 0.90$, $CHCl_3$).

Hydroformylation of 3-Vinylfuran (**2b**). According to the *G. P.*, with **2b** (0.20 ml, 2.0 mmol) (hexane, 1.0 ml·min^{-1}) of the product: t_R 24.5 min for (*S*)-**3b** and 25.3 min for (*S*)-**3b**; 99% (*R*) ee. The product was purified by CC (hexane/AcOEt 10 : 1; R_f 0.40): *(2*R*)-2-(furan-3-yl)propanal* (**3b**; 199 mg, 80%). Colorless oil. HPLC of isolated **3b**: 99% (*R*) ee. $[\alpha]_D^{20} = -57.4$ ($c = 0.85$, $CHCl_3$). IR (neat): 1732. ^{1}H-NMR ($CDCl_3$): 9.63 (*d*, *J* = 1.6, 1 H); 7.44 (*t*, *J* = 1.7, 1 H); 7.37 (*m*, 1 H); 6.33 (*dd*, *J* = 1.7, 0.8, 1 H); 3.54 (*m*, 1 H); 1.40 (*d*, 7.1, 3 H). ^{13}C-NMR ($CDCl_3$): 200.66; 143.69; 139.75; 121.80; 109.84; 43.66; 13.88. Anal. calc. for $C_7H_8O_2$: C 67.73, H 6.50; found: C 67.58, H 6.49.

Hydroformylation of **2a** *and Subsequent Reduction of* **3a**. According to the *G. P.*, **2a** (0.20 ml, 2.0 mmol) was hydroformylated, and the yield (^{1}H-NMR) and ee (GC) of the formed **3a** were determined to be 93% and 79%, resp. Then, the reaction mixture was transferred into a *Schlenk* tube under Ar, and EtOH (4.0 ml) was added. The resulting soln. was cooled to −78°, and powdered $NaBH_4$ (76 mg, 2.0 mmol) was added in small portions over 10 min. After stirring at −78° for 21 h, H_2O was added to quench the reaction. Then the mixture was extracted with CH_2Cl_2 (3 × 5.0 ml), the combined org. layer was dried (Na_2SO_4) and evaporated, and the residue was purified by CC (hexane/AcOEt 3 : 2; R_f 0.42): *(2*S*)-2-(furan-2-yl)propan-1-ol* (**5a**; 218 mg, 86%) [24]. Colorless oil. $[\alpha]_D^{18} = +15.7$ ($c = 0.58$, $CHCl_3$) ([24]: $[\alpha]_D^{25} = +6.5$ ($c = 1.00$, $CHCl_3$) for (*S*)-**5a** (> 95% ee)). The ee of isolated **5a** was determined to be 79% (*S*) by ^{1}H-NMR analysis (C_6D_6) of the corresponding α-methoxy-α-(trifluoromethyl)benzeneacetic acid (MTPA) ester.

Hydroformylation of **2b** *and Subsequent Reduction of* **3b**. According to the *G. P.*, **2b** (0.20 ml, 2.0 mmol) was hydroformylated and the produced aldehyde **3b** (84% yield (^{1}H-NMR), 99% ee (HPLC)) was reduced as described for **3a**. Purification by CC (hexane/AcOEt 3 : 2; R_f 0.37) gave *(2*R*)-2-(furan-3-yl)propan-1-ol* (**5b**) (185 mg, 74%). Colorless oil. GC (95°): t_R 22.7 min for (*R*)-**5b**; 99% (*R*) ee. $[\alpha]_D^{19} = +20.0$ ($c = 0.73$, $CHCl_3$). IR (neat): 3356. ^{1}H-NMR ($CDCl_3$): 7.40 (*t*, *J* = 1.7, 1 H); 7.31 (*m*, 1 H); 6.34 (*dd*, *J* = 1.7, 0.8, 1 H); 3.66 (*ddd*, *J* = 10.7, 7.0, 5.8, 1 H); 3.61 (*ddd*, *J* = 10.7, 7.0, 5.4, 1 H); 2.88 (*m*, 1 H); 1.39 (*dd*, *J* = 7.0, 5.4, 1 H); 1.23 (*d*, *J* = 7.1, 3 H). ^{13}C-NMR ($CDCl_3$): 143.24; 139.10; 127.11; 109.38; 67.92; 33.16; 17.00. Anal. calc. for $C_7H_{10}O_2$: C 66.65, H 7.99; found: C 66.45, H 8.05.

Transformation of **5b** *to (2*S*)-3-Hydroxy-2-methylpropanoic Acid* (**6**). To a mixture of $RuCl_3$ (2.6 mg, 0.013 mmol) and $NaIO_4$ (593 mg, 2.8 mmol) in H_2O (1.6 ml) (*Schlenk* tube), **5b** (53 mg, 0.42 mmol) in AcOEt (2 ml) was added *via* a syringe. The mixture was stirred at r.t. for 3 h, and then the reaction was quenched by adding 1M aq. HCl (5 ml). The resulting mixture was extracted with $CHCl_3$ (5 × 10 ml), the combined org. layer was evaporated, and the crude residue was purified by CC (hexane/acetone 1 : 1; R_f 0.16): **6** (34 mg, 78%). Colorless oil. $[\alpha]_D^{18} = +5.9$ ($c = 0.54$, EtOH) ([30]: $[\alpha]_D^{25} = +12.7$ ($c = 12.5$, EtOH); [31]: $[\alpha]_{578}^{20} = +4.4$ ($c = 11.5$, EtOH)), confirming the absolute configuration (2*R*) of the isolated **5b**.

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