Hydroformylation of Vinyl Sulfones and Sulfoxides Catalyzed by a Zwitterionic Rhodium Complex. A Diastereoselective Process

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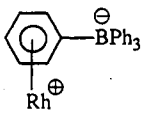
The hydroformylation of unsaturated sulfones and sulfoxides catalyzed by η^6-$C_6H_5B^-Ph_3Rh^+$ (1,5-COD) (1) was achieved in excellent yield and regiocontrol, with exclusive formation of branched-chain aldehydes. In the case of phenyl vinyl sulfoxide, evidence is presented for stereoselectivity in the reaction.

Introduction

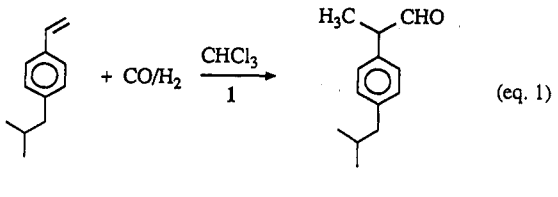
It has recently been reported that the zwitterionic rhodium η^6-tetraphenyl borate complex 1 is a most efficient catalyst for the hydroformylation of alkenes.[1]



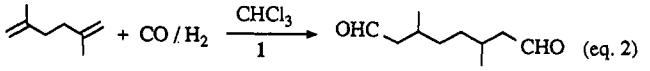
(COD)

1

The reaction is highly regioselective in most cases, resulting in the formation of mainly branched or linear aldehydes depending on the nature of the reactant. For example, styrenes (eq 1) or α,β-unsaturated esters[2] afford the branched-chain aldehyde as the predominant or exclusive product, while the straight-chain aldehyde is obtained from 1,1-disubstituted alkenes (eq 2).



(eq. 1)



(eq. 2)

Pyrrolidines or pyrrolidinones were formed using allylic amines as substrates for the hydroformylation process.[3]

Application of the hydroformylation reaction to organic sulfur compounds, particularly sulfones and sulfoxides, is very important from a synthetic standpoint. Molecules containing a sulfone moiety are useful for chain-extension reactions due to the good leaving group ability of the RSO_2 unit. Sulfoxides are often used in aldol-type condensations to make chain extensions on route to the synthesis of natural products. For example, Corey's total synthesis of (−)-maytansine, a potent antileukemic agent,[4] exploits such a method. In addition, the asymmetric nature of sulfoxides can be used in catalytic transformations.[5a,b] Stereoselectivity of the new carbon–carbon bond formed may also be enhanced by coordination of the sulfoxide group of the substrate to the metal center through the oxygen or sulfur atoms.[6,7]

Catalytic transformations of sulfur-containing substrates has proven to be a challenging problem as the usual result is poisoning of the catalyst itself. It is also well-known that organosulfur compounds form stable complexes with transition metals.[8]

We now describe the efficient catalytic hydroformylation of a series of vinyl sulfones and sulfoxides, resulting in the generation of new bifunctional compounds. In addition, the diastereoselective hydroformylation of phenyl vinyl sulfoxide is examined.

Experimental Section

General. Methylene chloride was freshly distilled from CaH_2 under nitrogen. Methyl, ethyl, and phenyl vinyl sulfones (3, R = CH_3, C_2H_5, Ph, respectively) and phenyl vinyl sulfoxide (5, R = Ph) were purchased from Aldrich Chemical Co. and were used as received. Naphthyl vinyl sulfone (2, R = 2-$C_{10}H_7$) was synthesized using a modified procedure of Foa et al.[9] (see below). The zwitterionic rhodium complex 1 was prepared following a literature procedure.[10] Proton and carbon NMR spectra were recorded on a Varian Gemini 200-MHz or Varian 300-MHz spectrometer using $CDCl_3$ as the solvent. Melting point determinations were made using a Fisher-Johns apparatus, and uncorrected values are reported. Elemental analyses were carried out by MHW Laboratories, Phoenix, AZ.

Yields given in Figures 1 and 2 were calculated by ^1H NMR using ferrocene as the internal standard.

2-Naphthyl Vinyl Sulfide. A solution of 2-naphthalenethiol (3.84 g, 24 mmol) in NaOH (25 mL, 30%) was gradually added at room temperature to a solution of vinyl bromide (2.57 g, 24 mmol), $C_{10}H_7Ni[P(C_6H_5)_3]_2Cl$ (1.0 g, 1.3 mmol),[11] hexadecyltri-*n*-butylphosphonium bromide (507 mg, 1 mmol), and $P(C_6H_5)_3$ (0.35 g, 1.3 mmol) in toluene (20.0 mL). Due to the volatility of vinyl bromide (bp 16 °C) it was pipetted into the reaction vessel periodically to compensate for losses due to evaporation. After 24 h, the phases were separated, extracted with ether, purified on a small column containing neutral alumina, and eluted with pentane to yield 65% of 2-naphthyl vinyl sulfide. ^1H NMR ($CDCl_3$): δ 5.38 (d, 1H, J = 17 Hz, CH), 5.39 (d, 1H, J = 9 Hz, CH), 6.61 (dd, 1H, J = 17, 9 Hz, CH), 7.00–8.00 (m, 7H, aromatic).

2-Naphthyl Vinyl Sulfone. 2-Naphthyl vinyl sulfide (0.93 g, 5 mmol) was oxidized according to the literature[12] in the absence

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of diisopropyltartrate. The mixture was separated using preparative thin-layer chromatography (SiO_2), using 30% ethyl acetate in hexane as eluant, to yield naphthyl vinyl sulfone (162 mg, 0.74 mmol). ^1H NMR ($CDCl_3$) δ 6.03 (dd, 1H, J = 1, 10 Hz, CH), 6.48 (dd, 1H, J = 1, 16 Hz, CH), 6.70 (dd, 1H, J = 10, 16 Hz, CH), 7.58–8.47 (m, aromatic protons).

General Procedure for the Hydroformylation Reactions. To a 46-mL Parr autoclave fitted with a glass liner and magnetic stirring bar was added dry CH_2Cl_2 (10 mL), substrate (2.0 mmol), (1,5-COD)$RhBPh_4$ (0.02 mmol), and 1,4-bis(diphenylphosphino)-butane (dppb) (0.04 mmol). Note that the amount of dppb was increased to 0.08 mmol when phenyl vinyl sulfoxide (**5**) was used as the substrate. The system was purged three times with CO to displace the air and subsequently pressurized to 600 psi with a 1/1 mixture of CO and H_2. The vessel was heated with stirring at 75 °C. The reaction mixture was filtered through Celite, and the filtrate was concentrated by rotary evaporation. The aldehydic sulfone **3**, R = $C_{10}H_7$, was isolated by crystallization. When R = Ph, an enamine derivative was made by reaction with 1 equiv of α-methylbenzylamine stirred with calcinated molecular sieves in dry methylene chloride. For R = CH_3 and C_2H_5, the aldehydes were distilled under reduced pressure using a Kugelrohr apparatus. The aldehydic sulfoxide **5**, R = Ph, was isolated as its enamine derivative.

2-(2-Naphthylsulfonyl)propanal (3, R = $C_{10}H_7$). Mp: 96–98 °C. ^1H NMR ($CDCl_3$): δ 1.44 (d, 3H, J = 7 Hz, CH_3), 4.07 (dq, 1H, J = 7, 1.6 Hz, CH), 7.5–8.5 (m, 7H, $C_{10}H_7$), 9.91 (d, 1H, J = 1.6 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 8.7 (CH_3), 70.2 (CH), 122.8, 128.0, 129.2, 129.4, 129.6, 129.8, 131.0, 132.0, 133.5, 135.6 (aromatic carbons C_1–C_{10}), 193.0 (CHO). Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.90; H, 4.89; S, 12.93. Found: C, 62.87; H, 5.04; S, 13.20.

2-(Phenylsulfonyl)propanal, Enamine Derivative (3, R = Ph), $(C_6H_5)S(O)_2C(CH_3)$=$CHNHCH(CH_3)(C_6H_5)$. Mp: 159–161 °C. ^1H NMR ($CDCl_3$): δ 1.46 (d, 3H, J = 7 Hz, CH_3), 1.61 (s, 3H, CH_3), 4.40 (m, 1H, CH), 4.73 (m, 1H, NH), 7.16–7.48 (m, 10H, aromatic), 7.69 (d, 1H, J = 8 Hz, =CH). ^{13}C NMR ($CDCl_3$): δ 9.5 (CH_3), 23.4 (CH_3), 57.1 (CH), 100.5 (—C=), 126.0, 126.9, 127.6, 128.8, 131.8, 142.2 143.6 (aromatic carbons), 144.0 (=CH). Anal. Calcd for $C_{17}H_{19}NSO_2$: C, 67.73; H, 6.37; N, 4.65; S, 10.64. Found: C, 67.81; H, 6.08; N, 4.81; S, 10.54.

2-(Methylsulfonyl)propanal (3, R = CH_3), $(CH_3)S(O)_2$-$CH(CH_3)(CHO)$. ^1H NMR ($CDCl_3$): δ 1.57 (d, 3 H, J = 7 Hz, CH_3), 2.87 (s, 3H, CH_3), 3.89 (dq, 1H, J = 7, 2 Hz, CH), 9.74 (d, 1H, J = 2 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 8.1 (CH_3), 39.2 (CH_3), 68.4 (CH), 194.1 (CHO). Anal. Calcd for $C_4H_8SO_3$: C, 35.27; H, 5.93; S, 23.55. Found: C, 35.62; H, 6.11; S, 23.47.

2-(Ethylsulfonyl)propanal (3, R = C_2H_5), $(C_2H_5)S(O)_2CH$-$(CH_3)(CHO)$. ^1H NMR ($CDCl_3$): δ 1.37 (t, 3H, J = 7 Hz, CH_3), 1.59 (d, 3H, J = 7 Hz, CH_3), 3.00 (m, 2H, CH_2), 3.83 (dq, 1H, J = 7, 2 Hz, CH), 9.72 (d, 1H, J = 2 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 5.8 (CH_3), 7.7 (CH_3), 46.5 (CH_2), 66.3 (CH), 194.2 (CHO). Anal. Calcd for $C_5H_{10}SO_3$: C, 39.97; H, 6.72; S, 21.35. Found: C, 39.65; H, 6.66; S, 20.99.

2-(Phenylsulfinyl)propanal, Enamine Derivative (6, R = Ph), $(C_6H_5)S(O)C(CH_3)$=$CHNHCH(CH_3)(C_6H_5)$. Mp: 127–129 °C. ^1H NMR ($CDCl_3$): δ 1.43 (d, 3H, J = 1 Hz, CH_3), 1.51 (d, 3H, J = 7 Hz, CH_3), 4.11 (m, 1H, NH), 4.42 (m, 1H, CH), 6.85 (dd, 1H, J = 13, 1 Hz, =CH), 7.23–7.54 (m, 10H, aromatic). ^{13}C NMR ($CDCl_3$): δ 6.0 (CH_3), 23.6 (CH_3), 56.4 (CH), 107.5 (—C=), 124.9, 126.1, 127.7, 128.6, 128.8, 128.9, 129.5, 143.5, 144.1 (aromatic carbons), 142.4 (=CH—). Anal. Calcd for $C_{17}H_{19}NSO$: C, 71.53; H, 6.72; N, 4.91; S, 11.24. Found: C, 71.57; H, 6.38; N, 4.91, S, 11.24.

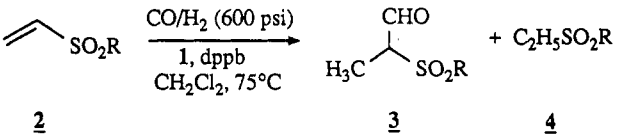
Results and Discussion

(a) Vinyl Sulfones. A series of vinyl sulfones (**2**) were subjected to hydroformylation in the presence of **1** to give only branched-chain aldehydes **3** in high yields (Table I). The original hydroformylation conditions[1] using the rhodium zwitterionic complex (100:1 ratio of substrate/catalyst precursor) were significantly improved by the addition of 2 mol equiv (relative to the rhodium catalyst) of 1,4-bis(diphenylphosphino)butane (dppb). The presence of the latter resulted in a notable increase in the conversion of starting material as well as in the chemo- and regioselectivities. In the absence of dppb, the results were much less satisfactory; i.e., the conversions were low and the products were a mixture of branched aldehyde **3** and hydrogenated olefin **4**. For example, in the case of ethyl vinyl sulfone (**2**, R = C_2H_5) a conversion of 53% was achieved with 29% branched aldehyde **3**, 24% hydrogenated olefin **4**, and the remaining 47% being starting material.

Table I. Hydroformylation of Unsaturated Sulfones Catalyzed by 1 and dppb

substrate	yield[a,b]/% 3	4	2
ethyl vinyl sulfone	98 (29)	0 (24)	0 (47)
methyl vinyl sulfone	98 (21)	0 (27)	0 (52)
2-naphthyl vinyl sulfone	83 (–)	17 (–)	0 (–)
phenyl vinyl sulfone	83 (5)	17 (13)	0 (82)

[a] NMR yields based on ferrocene as internal standard. [b] Value in brackets for reaction in absence of dppb.



2 **3** **4**

In all cases, the hydroformylation of vinyl sulfones, in the presence of 2 equiv of dppb relative to **1**, resulted in complete conversion of the starting material predominantly to the branched aldehyde (Table I). The branched chain aldehydic sulfone **3** was formed in nearly quantitative yield for ethyl or methyl vinyl sulfone. High yields of aromatic sulfones (**3**, R = Ph, $C_{10}H_7$) also resulted using **2**, R = Ph, $C_{10}H_7$, as the reactant, with the saturated sulfone **4** obtained as a byproduct.

Naphthyl vinyl sulfone (**2**, R = $C_{10}H_7$) was synthesized by oxidation of the parent sulfide which itself was prepared using a phase-transfer technique. The synthesis of vinyl sulfides[13] by the reaction of the thiol with acetylene at high pressures and temperatures was found to be unsuitable. In addition, vinyl halides are not reactive toward nucleophiles; therefore, aryl vinyl sulfides could not be synthesized by traditional nucleophilic substitution. A procedure employing phase-transfer catalysis was developed by Foa et al.[9] to prepare aryl and alkenyl sulfides. The original procedure did not include any unsubstituted vinyl sulfides. Our modification of this procedure employs the direct addition of vinyl bromide to naphthalenethiol for the synthesis of naphthyl vinyl sulfones (see Experimental Section). The sulfide was then oxidized to the sulfone.

To our knowledge, this is the first synthesis of branched-chain aldehydes containing the sulfone functionality attached to the carbon atom bearing the aldehyde unit.

(b) Vinyl Sulfoxide. Although the hydroformylation of phenyl vinyl sulfoxide was not as facile as the vinyl sulfones, the corresponding aldehyde was obtained in as much as 50% yield. The reaction conditions, however, were much more sensitive, particularly to time and temperature. Figure 1 shows that at room temperature

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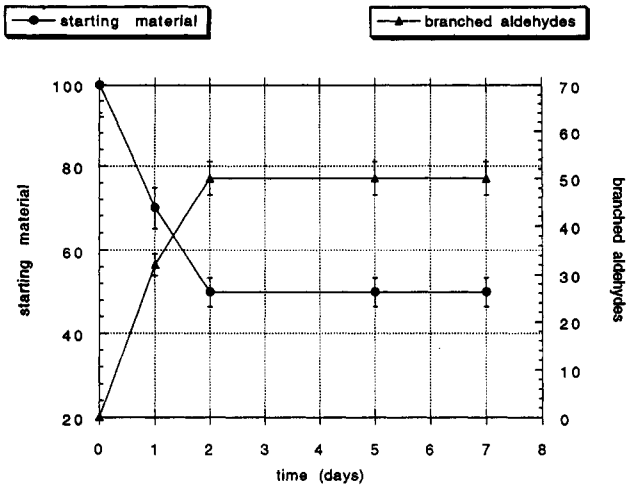

Figure 1. Hydroformylation of phenyl vinyl sulfoxide at room temperature.

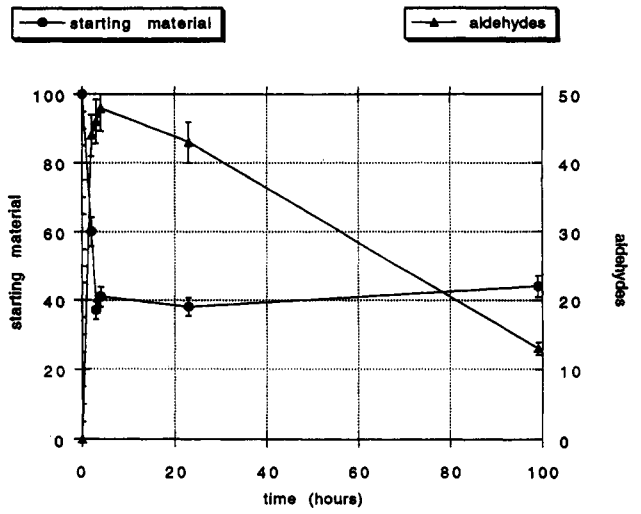

Figure 2. Hydroformylation of phenyl vinyl sulfoxide at 75 °C.

(20 °C) the conversion of starting material (phenyl vinyl sulfoxide, **5**) proceeds slowly (50% after 2 days) but is very specific affording only the branched-chain aldehyde. The reaction then stops, possibly due to the poisoning of the catalyst. In contrast to the hydroformylation of vinyl sulfones, phenyl vinyl sulfoxide is much more sensitive to the amount of added phosphine ligand. To achieve 50% conversion, 4 equiv of dppb (relative to **1**) was used, with complete conversion realized using 10 equiv of the bidentate phosphine. At 75 °C (Figure 2, using 4 equiv of dppb), the rate of conversion is much higher with 50% conversion of starting material resulting in 2 h. The feature to note, however, is that the concentration of aldehyde decreases if the reaction is maintained at 75 °C for more that 2 h. Also, only **6** was present in the first 2 h of reaction, while traces of linear aldehyde were detected on extended reaction. Under such conditions, an undesirable side reaction occurs to convert the branched aldehyde **6** to diphenyl disulfide **7**, which was isolated and identified by comparison with an authentic sample. A plausible route is outlined in Scheme I.

From this study, the optimum conditions for the hydroformylation of phenyl vinyl sulfoxide was found to be 75 °C for 2 h using 4 equiv of dppb.

(c) Diastereoselective Hydroformylation. Since the olefins under investigation, when hydroformylated, exhibit

Scheme I

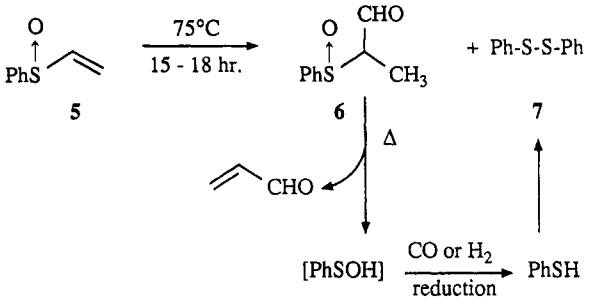

Table II. Hydroformylation of Phenyl Vinyl Sulfoxide with 1 and BINAP

entry	L*	% yield	% de[a]	% ee[c]
1	(*R*)-(+)-BINAP	27	40	18
2	(*S*)-(−)-BINAP	22	50	21
3	(*S*/*R*)-(±)-BINAP[b]	43	46	0
4	DPPB	50	0	0

[a] Measured directly from ^{1}H NMR spectra. [b] Racemic BINAP. [c] Resolved using Eu(hfc)$_3$.

such high regioselectivity with our catalyst system, we chose to replace the dppb ligand with one that is chiral. This allows exploration of the ability of the catalytic system to effect asymmetric induction. The achiral phosphine, dppb, was substituted by optically pure 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). The results for the hydroformylation of phenyl vinyl sulfoxide in the presence of (*R*)-, (*S*)-, or (*RS*)-BINAP are presented in Table II.

An interesting feature of these reactions can be seen in the comparison of entries 1–3 of Table II. In all cases it appears that the same diastereomer is in excess regardless of which antipode of optically pure BINAP is used. In contrast, however, when the enantiomers are resolved, (*R*)-BINAP causes one isomer to predominate while (*S*)-BINAP causes the opposite isomer to predominate. This is what one would expect, along with the observation that racemic BINAP does not effect induction. The following rationale accounts for these observations.

Hydroformylation of racemic phenyl vinyl sulfoxide, as described above, afforded diastereomeric branched aldehydes. The different chemical shifts of the diastereomers were well resolved in the NMR. Consideration of the hydroformylation products of racemic phenyl vinyl sulfoxide yields two possible sets of diastereomers, *RS*/*SR* and *RR*/*SS*. By definition, different pairs of diastereomers are chemically different, having different physical properties, and can therefore have different chemical shifts in an NMR spectrum. However, the diastereomeric pairs *RR*/*SS* and *RS*/*SR* are nonsuperimposible mirror images (enantiomers) differing only in their "handedness". As a consequence, they have identical chemical and physical properties.

The simplest result to explain is entry 4 in Table II. The ligand DPPB is achiral and consequently cannot induce any optical activity in the new product. Additionally, the intermediate must be enantiomeric in nature, thereby yielding no diastereomeric excess. This is confirmed by the generation of equal quantities of the four stereoisomers.

The result of entry 1 can best be interpreted by consideration of the following scheme.

For each of the four possible stereoisomers, the first letter represents the configuration at the sulfur atom and

	(R)-BINAP	x	x	(1 - x)	(1 - x)
R/S	→	RR	SR	RS	SS
racemic		(1 - n)	n	n	(1 - n)
starting material					

the second letter designates the configuration of the newly formed carbon center. If one assumes that the (*R*)-BINAP catalyst complex prefers to generate the new chiral center in the *R* configuration, then the isomers *RR* and *SR* will be equal and present in the amount denoted by *x*. The remainder, *RS* and *SS*, would have the amount (1 - *x*). The second factor which must also be considered is the interaction between the chiral starting material and the active catalyst to form the diastereomeric intermediates. If *R* starting material forms a complex to yield the *RS* product in amount *n*, then *S* starting material would form a complex to yield the *SR* product also in amount *n*. The remaining combinations, *SS* and *RR*, would be formed in the amount (1 - *n*).

From this, one can determine the relative quantities of each stereoisomer [$RR = x(1-n)$; $SS(1-x)(1-n)$; $RS = n(1-x)$; $SR = xn$]. Since the isomers *RR* and *SS* are enantiomers, they occur at the same chemical shift and would correspond to the amount (1 - *n*). By using the same assumptions with the (*S*)-(−)-BINAP (prefers in this case to produce the *S* product) and again with the racemic BINAP ligand, the end result is the same. That is, in each case, the *SS*/*RR* pair will be formed in the amount (1 - *n*) and the *RS*/*SR* pair will be present in the amount *n*. This analysis is in excellent agreement with the observation that each diastereomer is formed in the same excess irrespective of the antipode of ligand used. Using the same analysis, the enantiomers are predicted to occur with an excess, but in addition, the opposite isomer will exist if the opposite antipode of BINAP is used. In addition, when racemic BINAP is applied to the catalyst, there will be no enantiomeric excess. Again, this prediction is borne out by the experimental results presented in Table II.

In conclusion, **1** together with dppb is an excellent catalytic system for the production of branched-chain aldehydic sulfones and sulfoxides from the corresponding vinyl sulfones and sulfoxides. Moderate diastereoselectivity and enantioselectivity resulted in the hydroformylation of racemic phenyl vinyl sulfoxide using **1** and BINAP.

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