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Highly Regioselective Hydroformylation of Styrene and Its Derivatives Catalyzed by Rh Complex with Tetraphosphorus Ligands

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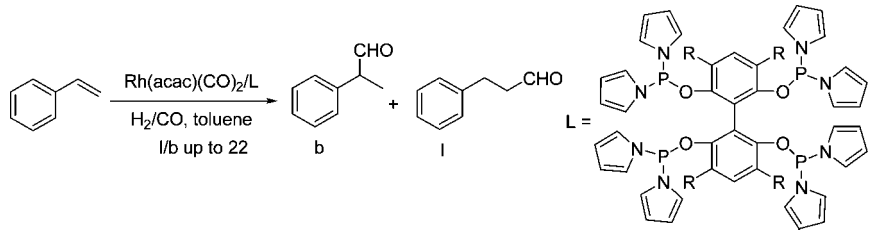
ABSTRACT



Styrene has been hydroformylated to the linear aldehyde with surprisingly high regioselectivity (l/b up to 22 for styrene) by using Rh complex with tetraphosphorus ligand. To the best of our knowledge, this is the highest linear regioselectivity reported for the hydroformylation of styrene and its derivatives. This protocol is in sharp contrast to other processes that favor producing branched aldehyde (typically >95% branched for most bidentate systems).

Hydroformylation of olefins represents one of the most important reactions in homogeneous catalysis and leads to products containing an aldehyde group, which are versatile intermediates and building blocks for various pharmaceuticals, agrochemicals, and other fine chemicals.[1] Most commercial hydroformylation processes use rhodium catalysts modified with monophosphorus ligands or bisphosphorus ligands to address the issue of regioselectivity and stereoselectivity. Styrene is an interesting class of substrates that favor producing branched aldehyde. It was suggested that the formation of a stable benzylic Rh-species induced by the $\eta 2$ electron donation from the benzene ring might contribute to this regioselectivity (Scheme 1).[2] Thus, most previous studies have been focused on the development of chiral ligands or processes to efficiently produce the desired branched enantioisomer in high optical purity.[3]

However, recent progress on the Rh-catalyzed hydroformylation of styrene has revealed that contrary selectivity for linear aldehyde may also be possible through the choice of solvent,[4] biphasic system,[5] another catalytic system (for $PtCl_2/SnCl_2$, l/b = 3.35,[6] for Co−W bimetallic catalyst l/b = 1.30[7]), or fine-tuned ligands (xanphosphite afforded l/b up to 2.3,[8] calixarenes diphosphane led to a l/b = 77/23,[9] and so far, the bulky phosphite ligands of UCC gave the highest linear regioselectivity, a value of l/b = 14[10]). Both the linear and branched aldehydes are very important, as the

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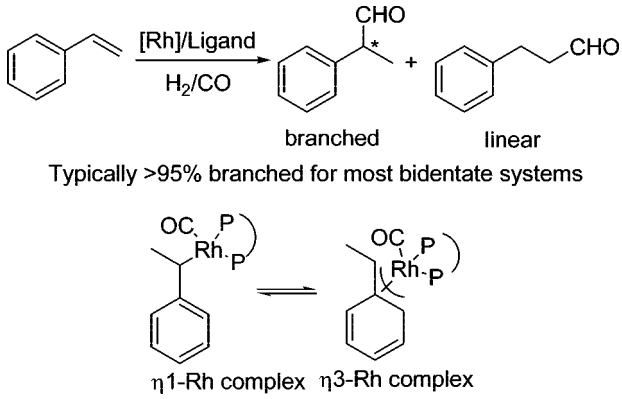
Scheme 1



latter constitute an important class of anti-inflammatory drugs and the linear aldehyde is widely used for the production of detergents and plasticizers and in organic synthesis as an important intermediate[11] (for example, it can be used as key starting material for the synthesis of enalapril, marketed by Merck & Co. as a drug for lowering blood pressure[12]). In the literature, 3-arylpropanal is usually obtained indirectly by rather sophisticated and tedious procedures (e.g., by the reduction of *trans*-cinnamaldehyde[13] or 3-phenylpropionyl chloride or its derivatives[14] or by the oxidation of 3-arylpropanol[15]), which inhibits its wide applications. Therefore, it is highly desirable to develop new, economic, and efficient methodologies[16] for the synthesis of 3-arylpropanal.

Recently, we reported the synthesis and application of a class of new tetraphosphorus ligands (biphenyl-2,2′,6,6′-tetrakis(dipyrrolylphosphoramidite)) (Figure 1), which shows high regioselectivity for the homogeneous isomerization−hydroformylation of internal olefins.[17] The high regioselectivity prompted us to assess our ligands further in the hydroformylation of styrene and its derivatives. Herein, we disclose our recent studies on the hydroformylation of styrene and its derivatives with unprecedented high linear selectivity.

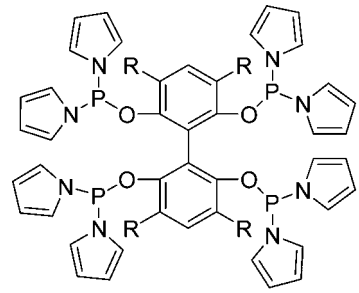


Figure 1. Ligands used in this study.

Initially, we set out to identify the optimal conditions for our ligands system. Some representative results are given in Table 1. An increase in the temperature from 40 to 80 °C led to improved activity and regioselectivity (Table 1, entries 1, 2, and 7). Further increase in the temperature from 80 to 100 °C gave lower regioselectivity, albeit the conversion increased somewhat (Table 1, entry 8). The pressure dependency of the catalytic system is also pronounced, as the activity and selectivity decreased sharply with the increased pressure (Table 1, entries 2−4). A lower ligand

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Table 1. Hydroformylation of Styrene Using Ligand L1 under Different Reaction Conditions[a]

						linear selectivity	
entry	T (°C)	L/Rh	H_2/CO (atm)	convn[b] (%)	ald sel[c] (%)	l/b[d]	linear[e] (%)
1	40	3	5/5	7	99	2.9	74
2	60	3	5/5	43	97	6.7	87
3	60	3	10/10	44	98	3.2	76
4	60	3	20/20	29	98	1.9	66
5	60	2	5/5	46	98	5.2	84
6	60	1	5/5	53	98	4.9	83
7	80	3	5/5	80	97	6.8	87
8	100	3	5/5	99	93	5.9	86

[a] S/C = 1,000, [Rh] = 1.0 mM, t = 1 h, toluene as solvent, decane as internal standard. [b] Conversion of the styrenes, determined on the basis of GC. [c] The hydrogenated product accounts for the product balance. [d] Linear/branched ratio, determined on the basis of GC analysis. The reaction was repeated twice, error is estimated <0.3. [e] Percentage of linear aldehyde in all aldehydes.

loading was also investigated, and it was found that although there is not much effect on catalytic activity, the regioselectivity is somewhat lowered (Table 1, entries 5 and 6). Thus, the preliminary optimal conditions (toluene, 80 °C, 5 atm H_2/CO, substrate/L/Rh = 1000/3/1) were chosen for the ligand screening.

Based on the best reaction conditions for ligand L1, ligands L2−L7 were tested. It was found that the introduction of substituents on the 3,3′,5,5′-position of the biphenyl moiety greatly increased the regioselectivity for the linear aldehyde as shown in Table 2. The use of ligand L2 bearing a chlorine

Table 2. Hydroformylation of Styrene Using Ligand L2−L7 under Optimized Pressure and Temperature

				linear selectivity	
entry	ligand	convn(%)[b]	ald sel (%)[c]	l/b[d]	linear (%)[e]
1	L2	98	93	12.9	92.8
2	L3	71	93	15.9	94.1
3	L4	54	94	17.2	94.5
4	L5	99	92	19.3	95.1
5	L6	99	92	20.2	95.3
6	L7	95	97	22.4	95.7

[a] S/C = 1,000, [Rh] = 1.0 mM, 80 °C, H_2/CO = 5/5 atm, t = 1 h, toluene as solvent, decane as internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] See Table 1.

substituent increased the linear to branch ratio to 12.9:1 (Table 2, entry 1). Alkyl-substituted ligands L3 and L4 gave a higher regioselectivity affording linear to branch ratios of 15.9:1 and 17.2:1, respectively; however, the conversion was dropped somewhat (Table 2, entries 2 and 3). This phenomenon indicates that the electronic property of ligand has some effect on the catalytic activity. Aryl substituents showed comparable regioselectivity, of which ligand L7 afforded the best result (Table 2, entries 4−7). The overall results clearly demonstrated that the steric property of the substituents determined the regioselectivity of the hydroformylation process.

A series of styrene derivatives were then hydroformylated using the Rh/L7 catalyst. The substrate to catalyst ratio was 10000, and the catalyst concentration was 0.17 mM. The reaction was terminated after 12 h (Table 3). It was found

Table 3. Hydroformylation of Styrene and Its Derivatives with Rh-L7 Catalyst[a]

				linear selectivity		
entry	substrate	convn[b] (%)	ald sel[c] (%)	l/b[d]	linear[e] (%)	TOF[f]
1	styrene	98	91	21.2	95.5	1.1×10^3
2	4-F-styrene	99	89	14.2	93.4	1.3×10^3
3	4-Me-styrene	83	95	19.4	95.0	9.7×10^2
4	4-MeO-styrene	80	96	26.0	96.3	7.4×10^2
5	2-Me-styrene	99	90	144.7	99.3	1.8×10^3
6[g]	2,4,6-trimethylstyrene	16	94	>99	>99	7.0×10

[a] S/C = 10,000, [Rh] = 0 0.17 mM, temperature = 80 °C, CO/H_2 = 5/5 atm, t = 12 h, toluene as solvent, decane as internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] See Table 1. [f] Average turnover frequency after reaction for 1 h: mole of aldehyde formed per mole of catalyst per hour, determined based on GC. [g] L1 was used as ligand.

that styrene substituted with electron-withdrawing group gave a lower linear to branch ratio than that of styrene with electron-donating groups (entries 2−4). The steric hindrance of the substrates on the regioselectivity of the hydroformylation is also remarkable. When one methyl group was introduced to the *ortho* position of the styrene, the reactivity and the regioselectivity were improved greatly (entry 5). This can be explained by the inhibition of the formation of the benzylic Rh-species that would favor producing branched aldehyde due to the presence of *ortho* substituent and fast reduction elimination stemming from the steric interactions.[18] However, when one more *ortho* methyl group was introduced, the reactivity of this substrate was greatly decreased which might be the hindrance blocking the coordination of the substrate to the metal center.

Although further studies are required to reconcile these results, the present observation may be rationalized as follows. The high regioselectivity for the hydroformylation of styrene to linear aldehyde might be accounted for by the steric interactions between the ligands and the substrate. It was previously proposed for the reaction of vinylidene-type olefins catalyzed by Rh complex that the significant difference in the steric environment between the two ends of the olefinic bond gave excellent regioselectivity for the linear aldehyde.[19] In the present system, the dependency of the selectivity on the steric nature of the ligand was similar, as observed when higher linear to branch ratio was obtained with the more hindric ligand. It is very likely that the hindrance of the ligand creates an obstacle for the formation of $\eta 3$ Rh-complex that would favor the formation of branched aldehyde. UCC's bulky phosphite ligands for hydroformylation of styrene afforded a linear to branch ratio of 14 is another example of this steric effect.[10]

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In summary, we have shown that the hydroformylation of styrene and its derivatives can be achieved with high regioselectivity for linear aldehyde (l/b up to 22 for styrene) using Rh complex with 3,3′,5,5′-substituted tetraphosphorus ligands. To the best of our knowledge, this is the highest linear regioselectivity reported for the hydroformylation of styrene and its derivatives. The high regioselectivity was accounted for by the steric interactions between the ligands and the substrate. This protocol is in sharp contrast to other processes that favor producing branched aldehyde (typically >95% branched for most bidentate systems). Further mechanistic study is under investigation and will be disclosed in due course.

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Supporting Information Available: General procedure for hydroformylation. This material is available free of charge via the Internet at http://pubs.acs.org.

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