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Electronic Effects in Asymmetric Catalysis: Hydroformylation of Olefins

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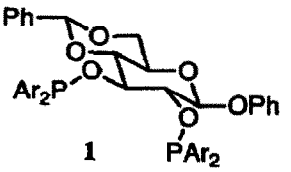
Abstract: Highly tunable carbohydrate vicinal diphosphinites are viable ligands for the Rh-catalyzed hydroformylation of olefins. Substitution of electron-withdrawing aryl groups at phosphorus in these diphosphinites increases the enantioselectivity of the hydroformylation process. Very high branched to linear ratios of product aldehydes (>94%) were obtained. Thus far only moderate enantioselectivity (up to 72%) has been achieved

The development of better asymmetric hydroformylation catalysts continues to be a challenging problem, because the chemoselectivity (eg. hydroformylation products versus hydrogenation products), the regioselectivity (branched versus linear aldehyde formation), and the enantioselectivity must all be excellent in order to have a viable commercial process.[1] The pioneering work in the asymmetric hydroformylation of olefins involved the use of platinum calatlysts in the presence of Lewis acids,[2] but the overall selectivity using these platinum systems still remains modest. Rhodium systems have since been demonstrated to provide excellent chemoselectivity and regioselectivity in the hydroformylation reaction,[3,4] and most recently, high enantioselectivities have been reported with bidentate phosphite[5] and mixed bidentate phosphine/phosphite[6] ligands. Previously, we reported the application of carbohydrate diphosphinites such as **1**[7] in the Ni(0)-catalyzed hydrocyanation of vinylarenes[8] and discovered that electron-deficient aryl groups at phosphorus such as **1b** and **1c** provided higher enantioselectivities. Only a few other examples of the enhancement of selectivity in asymmetric catalysis by electronic tuning of ligands have been reported.[9,10] Herein, we describe the utilization of easily modified ligands **1** in the asymmetric hydroformylation of olefins and the effect of changing the aryl groups at phosphorus.

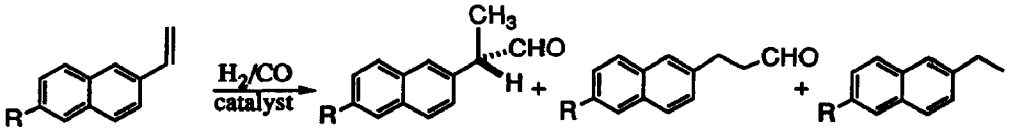


1

a. Ar = C_6H_5
b. Ar = 3,5-$(CF_3)_2C_6H_3$
c. Ar = 3,5-$F_2C_6H_3$
d. Ar = 3,5-$(CH_3)_2C_6H_3$

Initially, the use of Pt-catalysts was explored, but the chemo-, regio-, and enantioselectivity of the hydroformylation reaction was quickly found to be poor in accord with many of the previously used Pt systems.[1,2] For example, the hydroformylation of 6-methoxy-2-vinylnapthalene (**2a**) using complex [**1a**]$PtCl_2$[11] with 1.5 eq of $SnCl_2$ in benzene at 60 °C under 2400 psi of H_2/CO provided a 51:39:10 mixture of branched aldehyde **3a**, linear aldehyde **4a**, and hydrogenated product **5a** in 100% conversion.[12] In this case less than 5% ee was observed for **3a**. Unfortunately, the more electron-deficient diphosphinite **1b** provided a 49:18:33 mixture of **3b** (<5% ee), **4b**, and **5b** when 2-vinylnapthalene (**2b**) was hydroformylated under the above conditions.

These poor results with the Pt catalysts prompted us to investigate the corresponding cationic rhodium systems [1]Rh(COD)BF_4 (see Table).[13] Encouragingly, the rhodium catalysts provided good yields of the desired branched aldehydes under very mild conditions (see Table). Using the rhodium catalysts, we clearly saw an increase in the enantioselectivity of the hydroformylation reaction when the aryl group at phosphorus was changed from the simple phenyl derivitive **1a** to the more electron-deficient 3,5-bis(trifluoromethyl)phenyl **1b**. For example, in benzene **3b** was obtained in 10% ee when **1a** (entry 1) was the ligand in the hydroformylation of **2b**, whereas a 38% ee for **3b** (entry 2) was obtained when **1b** was employed. Thus, the enantioselectivity of the rhodium-catalyzed hydroformylation reaction is sensitive to the electronic nature of the phosphinite ligand in a fashion similar to the Ni(0)-catalyzed hydrocyanation reaction.[8,14]



2a. R = CH_3O
b. R = H

3 **4** **5**

Next, optimization of the reaction conditions using the electron-deficient ligand **1b** was undertaken. Solvent effects were found to be very important in the *enantioselectivity* of the hydroformylation reaction, although the solvent had little effect on the *regioselectivity* of the reaction. Typically >94% of the product was the branched aldehyde **3b**. For example, under identical conditions (1600 psi H_2/CO, room temperature, 18h), in the hydroformylation of **2b** using ligand **1b**, the ee of **3b** increased from 12% in THF (entry 6), to 38% in benzene (entry 2), to 51% in hexane (entry 3). These results are similar to the hydrocyanation reaction,[9] where nonpolar solvents provide higher ee's. The H_2/CO pressure was also found to change the enantioselectivity of the hydroformylation of **2b**. Using the best solvent, hexane, the ee of **3b** was approximately the same at 500 and 1600 psi (49 and 51% ee, respectively), but dropped off to 31% at 2400 psi. Racemization of the product aldehyde has been reported to be a major problem,[1,2] so the reaction was performed in hexane and $CH(OEt)_3$ (10 eq) to trap aldehyde **3b** as the corresponding acetal; however, only a 17% ee was obtained.[15] Thus, the presence of triethyl orthoacetate appears to be detrimental in this case. Attempting to reduce the aldehyde products to the corresponding primary alcohols in situ by using Et_3SiH as the solvent (a presumably nonpolar solvent) provided the most remarkable result. In this case, no reduction to the alcohol was observed, but the enantioselectivity of the reaction increased to 72% ee.[16]

In the present study, it became clear that it was impossible to gauge the electronic effect on the multitude of individual steps (viz. CO insertion, alkyl migration, reductive elimination, etc.) in the hydroformylation reaction. Nonetheless, from a practical standpoint it is useful to estimate the overall effect, so a series of ligands **1** with electron-withdrawing and electron-donating aryl groups were investigated in the Rh-catalyzed hydroformylation of **2a** (see Table, entries 9-20). These reactions were performed in hexane and the pressure of H_2/CO was varied. We confirmed that the ee was not only dependent on the ligand, but that the H_2/CO pressure also had a major impact on the observed ee. However, an overall trend can be established since at any given pressure of H_2/CO, the more electron-deficient phosphinites bis(trifluromethyl) derivative **1b** and difluoro derivative **1c** typically provided higher ee's than the corresponding ligands with simple phenyl **1a** or with the dimethyl derivative **1d**. For example, at 1600 psi the ee of **3a** increases from practically 0 to 10 to 25

to 39%, when using **1d**, **1a**, **1c** and **1b**, respectively. A most curious result is that each ligand appears to have a maximum effect on the enantioselectivity occurring at 1600 psi of H_2/CO with a somewhat sharp apex, except for the difluoro derivative **1c**, which provides similar ee's over a broader pressure range. Because low conversions were obtained in hexane, most likely arising from catalyst solubility problems, we performed the reactions in THF and found a similar trend for the electronic effect.

Table: Asymmetric Hydroformylation of **2** using [1]Rh(COD)BF_4

Entry	Substrate	Ligand	solvent	pressure (psi)	conversion (%).	3a:4a[a]	%ee[a,b]
1	**2b**	**1a**	Benzene	1600	20	95:5	10
2	**2b**	**1b**	Benzene	1600	43	97:3	38
3	**2b**	**1b**	Hexane	1600	53	96:4	51
4	**2b**	**1b**	Hexane	500	100	95:5	49
5	**2b**	**1b**	Hexane	2400	80	96:4	31
6	**2b**	**1b**	THF	1600	71	97:3	12
7	**2b**	**1b**	Hexane + $CH(OEt)_3$	1600	85	95:5	17[c]
8	**2b**	**1b**	Et_3SiH	1600	20	95:5	72
9	**2a**	**1d**	Hexane	500	<5	n.d.	<1
10	**2a**	**1a**	Hexane	500	<5	n.d.	n.d.
11	**2a**	**1c**	Hexane	500	<5	n.d.	24
12	**2a**	**1b**	Hexane	500	73	90:10	12
13	**2a**	**1d**	Hexane	1600	<5	n.d.	<2
14	**2a**	**1a**	Hexane	1600	<5	n.d.	10
15	**2a**	**1c**	Hexane	1600	<5	n.d.	25
16	**2a**	**1b**	Hexane	1600	73	94:6	39
17	**2a**	**1d**	Hexane	2400	<5	n.d.	<1
18	**2a**	**1a**	Hexane	2400	<5	n.d.	7
19	**2a**	**1c**	Hexane	2400	<5	n.d.	16
20	**2a**	**1b**	Hexane	2400	31	95:5	12
21	**2a**	**1d**	THF	500	<5	n.d.	<3
22	**2a**	**1a**	THF	500	18	94:6	8
23	**2a**	**1c**	THF	500	38	95:5	<1
24	**2a**	**1b**	THF	500	35	95:5	24

[a] n.d. (not determined). [b] Determined by HPLC (see reference 12). [c] Determined by ^1H NMR using $Eu(hfc)_3$.

Finally, the hydroformation of other olefins was explored briefly (hexane, 1600 psi) using [1b]Rh(COD)BF_4 as the catalyst: olefin (branched:linear, ee), styrene (96:4, 24%), 4-methylstyrene (94:6, 30%), vinyl acetate (92:8, 14%).

In conclusion, we have shown that diphosphinites **1** are good ligands in the rhodium-catalyzed hydroformylation of olefins providing high regio- and chemoselectivity for branched aldehyde products **3**, although the enantioselectivity remains moderate. We have also demonstrated that the enantioselectivity can indeed be influenced by the electronic nature of the metal catalyst. Further studies are in progress.

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11. Platinum complexes were prepared by reaction of **1b** (1.1 eq) with commercially available $(PhCN)_2PtCl_2$ in benzene: [1b]$PtCl_2$ showed: ^{31}P NMR δ 95.1 (d, 1, J_{pp} = 11 Hz), 94.4 (d, 1, J_{pp} = 11 Hz).

12. Typical procedure for hydroformylation reactions: In the dry box a 140 mL glass liner was charged with 2.0 mmol of vinyl compound, 0.003 mmol of catalyst/cocatalyst, and 10 mL of solvent. This liner was placed in a shaker tube and pressurized with a 1:1 mixture of hydrogen and carbon monoxide. After venting, the mixture was pressurized with the hydrogen, carbon monoxide mixture and shaken at the indicated temperature (Higher reaction temperatures provided lower ee's and more of the undesired linear aldehyde **4**). Upon completion, the mixture was vented and the glass liner was removed from the shaker tube. The solution was filtered through celite and concentrated. Percent conversions were determined by ^1H NMR integration of the resonances corresponding to the starting vinyl compound and product aldehydes. The branched aldehyde to linear aldehyde ratio (b/l) was determined by ^1H NMR integration of the resonances corresponding to the aldehyde protons or by GC. The crude product mixture was treated with $LiAlH_4$ to reduce **3** to the correponding primary alcohol. After flash chromatography, the ee's of these alcohols were determined by analysis on either an OB or OJ chiralcel HPLC column. The products were shown to be enriched with the S-isomer by synthesis of an authentic enriched sample from the correponding nitrile[9] by reduction with DIBAL-H followed by $LiAlH_4$ reduction.

13. Rhodium complexes were prepared by reaction of **1** with $Rh(COD)_2BF_4$ in CH_2Cl_2. Other counterions such as triflate and SbF_6 typically provided lower ee's. Schrock, R. R.; Osborn, J. A. *J. Am. Chem Soc.* **1971**, *93*, 2397.

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15. Lower enantioselectivities using (BPPM)$PtCl_2$•$SnCl_2$ as the hydrofomylation catalyst[2b] with trapping of the aldehyde as the diethyl acetal were obtained in our hands. See also reference 2a.

16. Little hydrosilation product was observed (ca. 5%) in the ^1H NMR of the crude product when the reaction was run at room temperature; however at 50 °C, mostly hydrosilation product was observed.

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