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Highly regioselective hydroformylation of enamides with phosphite ligands

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Abstract

The regioselective hydroformylation of enamides with a catalyst derived from monodentate phosphites and $Rh(acac)(CO)_2$ was studied. In the hydroformylation of *N*-vinylphthalimide, all the biphenol-based ligands led to the branched aldehyde; the fastest reaction was observed when using a sterically bulky phosphite. The olefins (*E*)-*N*-propenylphthalimide, vinylpyrrolidone, vinylcaprolactam and vinylcarbazole were also investigated.

In hydroformylation, which is considered one of the most important processes in catalysis,[1–4] enamides as substrates provide access to important amine derivatives, such as amino acids,[5] amino alcohols, lactones and β lactams,[6–8] which show a wide range of biological properties.[9,10] Despite its potential importance in pharmaceutical synthesis, however, the hydroformylation of enamides has hardly been explored, with only a few reports available in the literature.[11–13] The reaction suffers from low regioselectivity as measured by the branched to linear aldehyde (B/L) ratios and a slow reaction rate. For instance, the asymmetric hydroformylation of *N*-vinylphthalimide, which was first reported by Stille, proceeded at a very low rate (~50% conversion in 5 days) in the presence of a Rh(I)-DIOP type catalyst, providing the branched aldehyde with a low ee of 38%.[12] A major breakthrough was achieved with the use of (*R*,*S*)-Binaphos discovered by Takaya.[13] When combined with rhodium, use of this ligand gave a B/L ratio of 89/11 and a high ee of 85% in 90 h. However, attempts to achieve better regioselectivities and faster reaction rates encountered difficulties. These problems make this reaction difficult to use in synthesis.

Encouraged by the success of phosphite ligands in the asymmetric hydrogenation and hydroformylation and the simplicity of their synthesis,[14–16] we prepared a series of phosphite ligands based on the biphenol backbone using reported procedures.[17–19] Herein, we report the first use of some of these phosphites, which exhibit various electronic and steric properties, in the rhodium-catalyzed hydroformylation of enamides (Scheme 1).

We first investigated the hydroformylation of *N*-vinylphthalimide **1** using ligands **L1**–**L6**.[20,21] For comparison, some common ligands were also tested. The catalyst was prepared in situ by combining the ligand with $Rh(acac)(CO)_2$ at a ligand/Rh (L/Rh) ratio of 3. The results are summarized in Table 1. As can be seen, excellent regioselectivity towards the branched aldehyde was obtained with all the phosphites presented in Scheme 1. No reaction was observed when using bidentate ligands (entries 10–13). Lower B/L ratios were obtained with both PPh_3 and $P(OPh)_3$; the former was less effective than the latter in terms of both regioselectivity and conversion.

Amongst the phosphites **L1** and **L4**, a notable influence from the ligand electronic properties on the rate was observed. The more electron-withdrawing the substituent R, the faster the hydroformylation reaction is (entries 1–4). With three methyl substituents attached, **L5** is thus expected to give a slow reaction. This was indeed the case

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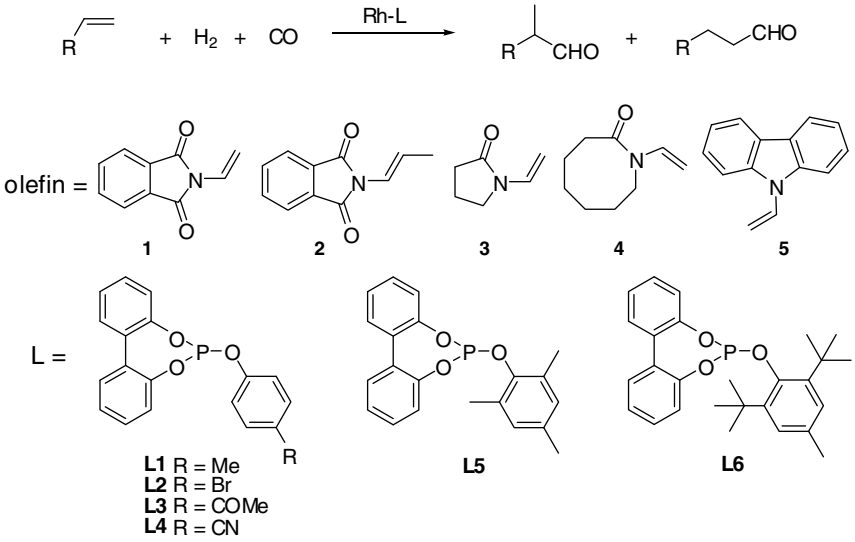


Scheme 1. Hydroformylation reactions examined in this study.

Table 1
Effect of ligands on the hydroformylation of **1**[a]

Entry	Ligand	B/L[b]	Conversion[c] (%)	TOF[d] (h^{-1})
1	**L1**	>99:1	7	11
2	**L2**	>99:1	14	21
3	**L3**	>99:1	65	98
4	**L4**	>99:1	86	129
5	**L5**	>99:1	3	14[e]
6	**L6**	>99:1	78	354[e]
7	**L6**	>99:1	100	225[f]
8	$P(OPh)_3$	93:7	96	134
9	PPh_3	88:12	62	82
10	BINAP	—	0	—
11	Dppf	—	0	—
12	Dppb	—	0	—
13	Xantphos	—	0	—

[a] [Olefin] = 0.20 M, olefin/Rh = 150 (mol/mol), ligand/Rh = 3 (mol/mol), toluene (3 mL), 80 °C, 20 bar syngas pressure, 1 h.
[b] Branched to linear aldehyde ratio, determined by ^{1}H NMR; when the linear product was not detected, a ratio of >99:1 was assigned.
[c] Total conversion, determined by ^{1}H NMR.
[d] Turnover frequency to the branched aldehyde, based on 1 h conversion.
[e] Based on 20 min conversion.
[f] Based on 40 min conversion.

(entry 5). Commonly cited by many groups, the introduction of an electron-withdrawing group on a ligand is expected to accelerate the rate of hydroformylation.[22–24] This might be partly due to a decrease in the electron density of rhodium, which weakens the π back donation from the rhodium to CO, thus inducing faster CO dissociation, which could otherwise inhibit the hydroformylation.

However, ligand **L6**, which is expected to be more basic, affords the highest catalytic activity within the **L1**–**L6** series. It led exclusively to the branched aldehyde with a turnover frequency (TOF) reaching more than 350 h^{-1} (entries 6 and 7). The high rate observed can be attributed to the bulky *ortho* *t*-butyl groups. Evidence of this strong domination of the steric effects on the rate is clearly noted when comparing with ligand **L5** (entry 5). After 20 min reaction time, Rh–**L5** afforded only a 3% conversion, whereas Rh–**L6** was much more active, affording a 78% conversion (entry 6). The high activity observed with **L6** appears to contradict the results obtained with **L1**–**L5** and particularly those from **L5**. However, similar results were reported earlier by Van Leeuwen and coworkers in the hydroformylation of substituted olefins such as 2,2-dialkylalkenes when using the bulky $P(O\text{-}o\text{-}^tBuC_6H_4)_3$ as a ligand. The high activity was ascribed to the exclusive formation of monoligated Rh–phosphite complexes.[25,26] The same explanation may well apply to the hydroformylation of **1** with Rh–**L6**, and appears to be in line with the reasoning presented for **L1**–**L4**, since decreasing the number of coordinated phosphites would make the rhodium electron-deficient.

Bearing in mind that the active catalyst may be the monoligated Rh–phosphite species, we next examined the effect of varying the **L6** loading on the hydroformylation of **1**. The results are summarized in Table 2. As can be seen, an increase in the **L6**/Rh ratio from 1 to 3 accelerates the rate of the reaction moderately. A higher **L6**/Rh ratio was expected to enhance the concentration of the active

Table 2
Effect of ligand/Rh ratio on the hydroformylation of **1**[a]

Entry	**L6**/Rh	B/L[b]	Conversion[c] (%)	TOF[d] (h^{-1})
1	1	>99:1	60	267
2	2	>99:1	75	337
3	3	>99:1	78	354
4	6	>99:1	44	198

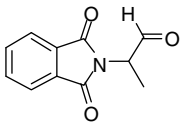
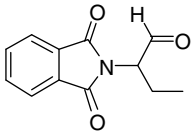
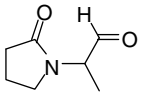
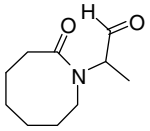
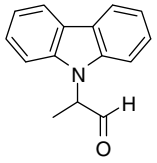
[a] The conditions were the same as in Table 1 (entry 6), 20 min.
[b] When the linear product was not detected by ^{1}H NMR, a ratio of >99:1 was assigned.
[c] Total conversion, determined by ^{1}H NMR.
[d] TOF to branched aldehyde, based on a 20 min conversion.

catalyst species. However, further increase led to a slower reaction (entry 4). On the other hand, in all the cases, the B/L selectivity remained unchanged.

Encouraged by the results obtained with **L6**, we decided to extend the method to other related olefins (Scheme 1). The results are presented in Table 3 using the optimized conditions (Table 2, entry 3). As can be seen, all the substrates underwent full conversions in a few hours, and the regioselectivity of the reactions favoured the branched aldehyde, as in the case of *N*-vinylphthalimide **1**.

However, the reaction no longer favoured the branched products exclusively; the addition of the formyl group at the β positions was observed in all the cases. Furthermore, the reaction became slower, with full conversions requiring longer times. For instance, compared with **1**, which was fully hydroformylated in 40 min (entry 1), the (*E*)-*N*-propenylphthalimide **2** required 6 h for full conversion (entry 2). Apparently, the presence of the methyl group on the position β to the nitrogen makes **2** less reactive. With substrates **3**–**5**, the reaction was also slower. However, we note that the results compare favourably with those available in the literature. In fact, the hydroformylation rate of vinylidic alkenes is extremely slow when more substituents are present on the double bond.[27] Previously, **3** was reported to undergo hydroformylation under severe conditions (100 °C, 80 bar), furnishing a mixture of products.[28] Since then, no further study has been published.

Table 3
Hydroformylation with **L6**[a]

Entry	Olefin	Time (h)	Branched product	B/L	Conversion (%)
1	**1**	0.7		>99:1	100
2	**2**	6		91:9	100
3	**3**	3		67:33	100
4	**4**	3		76:24	100
5	**5**	3		92:8	100

[a] The conditions were the same as in Table 2 (entry 3).

In summary, biphenol-based phosphites have been shown to be effective ligands for the rhodium-catalyzed hydroformylation of enamides for the first time. Whilst all the phosphites led preferentially to the branched aldehyde in the hydroformylation of **1**, the sterically bulky ligand **L6** displayed the highest activity in combination with rhodium. When the steric effects remain the same, however, electron-deficient ligands afford higher rates. Rh–**L6** was also shown to catalyze the regioselective hydroformylation of related olefins, such as vinylcarbazole and vinylcaprolactam, which are important precursors for biologically active compounds.[29]

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20. The phosphite ligands **L1**–**L6** were prepared according to the Ref. 16–18 and were purified by flash chromatography or crystallization to give the products as white solids.
Ligand **L1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.22 (t, $J = 8.0$ Hz, 2H), 7.26–7.32 (m, 4H), 7.33–7.40 (m, 2H), 7.49 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 115.5, 122.2, 122.6, 125.8, 129.6, 130.5, 131.6, 134.2, 149.4,

151.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.3; HRMS calcd for $C_{19}H_{16}O_3P$ $(M+H)^+$: 323.0837. Found: 323.0841; Anal. Calcd for $C_{19}H_{15}O_3P$: C, 70.81; H, 4.69. Found: C, 70.73; H, 4.75.

Ligand **L2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, $J = 7.5$ Hz, 2H), 7.19 (t, $J = 7.5$ Hz, 2H), 7.30–7.40 (m, 6H), 7.50 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.5, 122.5, 122.7, 126.0, 129.7, 130.5, 131.5, 133.1, 149.3, 151.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.0; HRMS calcd for $C_{18}H_{13}BrO_3P$ $(M+H)^+$: 386.9786. Found: 386.9782; Anal. Calcd for $C_{18}H_{12}BrO_3P$: C, 55.84; H, 3.12. Found: C, 55.74; H, 3.01.

Ligand **L3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.21–7.40 (m, 8H), 7.50 (d, $J = 7.6$ Hz, 2H), 7.96 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 120.6, 120.7, 122.4, 126.1, 129.7, 130.5, 130.7, 130.9, 131.4, 149.2, 156.3, 197.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 143.5; HRMS calcd for $C_{20}H_{16}O_4P$ $(M+H)^+$: 351.0786. Found: 351.0777; Anal. Calcd for $C_{20}H_{15}O_4P$: C, 68.57; H, 4.32. Found: C, 68.33; H, 4.41.

Ligand **L4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, $J = 8.0$ Hz, 2H), 7.32 (t, $J = 7.4$ Hz, 2H), 7.37 (d, $J = 7.5$ Hz, 2H), 7.39–7.45 (m, 4H), 7.49 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.1, 122.5, 124.5, 125.8, 126.2, 128.3, 129.7, 130.6, 131.1, 149.1, 152.5; ^{31}P NMR (162 MHz $CDCl_3$) δ 142.3; HRMS calcd for $C_{19}H_{13}NO_3P$ $(M+H)^+$: 334.0633. Found: 334.0628; Anal. Calcd for $C_{19}H_{12}NO_3P$: C, 68.47; H, 3.63; N, 4.20. Found: C, 68.44; H, 3.72; N, 4.24.

Ligand **L5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 6.86–6.99 (m, 2H), 7.24–7.35 (m, 4H), 7.35–7.40 (m, 2H), 7.53 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 20.4, 122.6, 125.7, 126.4, 128.4, 129.5, 130.4, 131.6, 136.3, 149.4, 149.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 148.7; HRMS calcd for $C_{21}H_{20}O_3P$ $(M+H)^+$: 351.1150. Found: 351.1143; Anal. Calcd for $C_{21}H_{19}O_3P$: C, 71.99; H, 5.47. Found: C, 71.63; H, 5.53.

Ligand **L6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 18H), 2.31 (s, 3H), 7.14 (s, 2H), 7.24–7.40 (m, 6H), 7.52 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 30.8, 34.6, 122.5, 125.5, 125.9, 127.8, 128.7, 129.5, 131.5, 136.2, 143.6, 151.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 148.0; HRMS calcd for $C_{27}H_{31}NaO_3P$ $(M+Na)^+$: 457.1909. Found: 457.1925; Anal. Calcd for $C_{27}H_{31}O_3P$: C, 74.63; H, 7.19. Found: C, 74.38; H, 7.25.

21. *General hydroformylation procedure*: All hydroformylation reactions were carried out in a 30 mL stainless-steel autoclave. An example is given for *N*-vinylphthalimide **1**. A glass liner containing a stirrer bar was charged with **1** (0.6 mmol), the catalyst precursor $Rh(acac)(CO)_2$ (3.87×10^{-3} mmol) and a ligand (0.012 mmol) in toluene (3 mL). Next, the vessel was sealed, and 20 bar of a mixture of hydrogen and carbon monoxide (1:1) was introduced and the autoclave was then placed in an oil bath preheated to 80 °C for a period of time given. After cooling with an ice bath for ca 15 min, the syngas was carefully released and the resulting mixture was then passed through a small column of silica. Conversion and selectivity were determined by NMR. Only the branched product 2-*N*-phthalimidopropanal was detected. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, $J = 7.2$ Hz, 3H), 4.75 (q, $J = 7.2$ Hz, 1H), 7.75–7.79 (m, 2H), 7.86–7.90 (m, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 54.5, 124.0, 132.2, 134.8, 168.0, 197.1; Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.72; H, 4.40; N, 6.45.

Other branched products: 2-*N*-phthalimidobutanal from **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, $J = 7.4$ Hz, 3H), 2.06–2.31 (m, 2H), 4.58–4.64 (m, 1H), 7.74–7.80 (m, 2H), 7.86–7.91 (m, 2H), 9.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 21.0, 60.8, 124.0, 132.1, 134.7, 168.3, 196.9; Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.25; H, 5.10; N, 6.42.

2-(2-Oxopyrrolidin-1-yl)propanal from **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, $J = 7.4$ Hz, 3H), 2.09–2.17 (m, 2H), 2.36 (t, $J = 8.1$ Hz, 2H), 3.30 (t, $J = 7.0$ Hz, 2H), 4.68 (q, $J = 7.4$ Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 18.6, 31.0, 43.6, 56.5, 176.1, 199.5; Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.45; H, 7.90; N, 9.83.

2-(2-Oxoazocan-1-yl)propanal from **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, $J = 7.5$ Hz, 3H), 1.60–1.84 (m, 6H), 2.60–2.65 (m, 2H), 3.35–3.43 (m, 2H), 3.57 (t, $J = 6.5$ Hz, 2H), 4.44 (q, $J = 7.5$ Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 23.7, 27.6, 29.7, 30.2, 37.6, 44.5, 62.5, 176.4, 199.1; Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.49; H, 9.28; N,7.62.

2-(9H-Carbazol-9-yl)propanal from **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (d, $J = 7.0$ Hz, 3H), 5.18 (q, $J = 7.0$ Hz, 1H), 7.23–7.33 (m, 4H), 7.41–7.49 (m, 2H), 8.14 (d, $J = 7.4$ Hz, 2H), 9.94 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 59.1, 109.1, 120.3, 121.1, 124.1, 126.5, 140.0, 200.7; Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.60; H, 5.84; N, 6.30.

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