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Novel spiroketal-based diphosphite ligands for hydroformylation of terminal and internal olefins†

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Spiroketal-based diphosphite ligands have been developed for the rhodium-catalyzed hydroformylation reaction. Under the optimized reaction conditions, a turnover number (TON) of up to 2.4 × 10^4 and a linear to branched ratio (l/b) of up to 93 were obtained in the hydroformylation of terminal olefins. The catalysts were also found to be effective in the isomerization–hydroformylation of some internal olefins.

Hydroformylation of alkenes is one of the most important homogeneous catalytic reactions in industry. The products containing an aldehyde group are versatile intermediates and building blocks for various pharmaceuticals, agrochemicals, commodities and fine chemicals.[1] One of the key issues in hydroformylation research is the development of new ligands to obtain highly active and selective catalysts. Over the past several decades, a variety of P-ligands have been successfully developed for Rh-catalyzed hydroformylation of olefins. Some elegant examples include Bisbi,[2] Xantphos,[3] Biphephos,[4] Naphos,[5] calix[4]arene-based bisphosphites,[6] pyrrole-based bisphos-phoramidites,[7] and self-assembled bisphosphanes.[8] Compared with phosphines, the phosphite ligands are generally weak σ-donors but strong π-acceptors, which can facilitate the CO dissociation from the metal centers in the catalytic species. Therefore, the replacement of phosphines by phosphites in the Rh-catalyzed hydroformylation often leads to a substantial enhancement in the reactivity. In addition, the regioselectivity of the phosphate/Rh catalysts can also be modulated by judicious incorporation of appropriate substituents into a ligand backbone.

These salient features, coupled with their ready synthesis and oxidation stability, contributed to a substantial research interest in the development of phosphite ligands for hydroformylation of various olefins.[1d] Recently, we have reported a new class of bidentate spiroketal-based bis(dipyrrolyl)phosphoramidite ligands, which demonstrated high activity and excellent regioselectivity for the linear aldehydes in the rhodium-catalyzed hydroformylation of both terminal and internal olefins.[9] Encouraged by these results, we sought to extend our studies to other spiroketal-based diphosphine ligands for hydroformylation reactions. Herein, we wish to report the synthesis of a new class of spiroketal-based diphosphite ligands, and their application in the Rh-catalyzed hydroformylation of linear olefins. It is noteworthy that since the introduction of the SPANphos by van Leeuwen in 2003,[10] a handful of spiroketal-based ligands have been successfully developed and used in several catalytic reactions.[11] Despite these efforts, however, P-ligands with a spiro backbone have only rarely been explored in hydroformylation reactions.[12]

The spiroketal bisphosphite ligands **3a–h** were easily prepared *via* a four-step reaction sequence (Scheme 1). Aldol condensation of 2,3-dimethoxyarylaldehyde with acetone, cyclopentanone, or cyclohexone afforded the corresponding penta-1,4-dien-3-ones **1**, which upon RANEY®-Ni catalyzed hydrogenation followed by deprotection with BBr_3, led to the formation of the key spiroketal-based intermediate diphenols **2**.[9] Condensation of diphenols **2** with the preformed phosphorochloridites with triethylamine as a HCl scavenger gave the corresponding bisphosphites **3a–h** in good to excellent yields. These ligands are stable in the air, and thus were purified under an ambient atmosphere by column chromatography on silica gel without special precautions.

Hydroformylation of terminal olefins was first investigated with the catalyst generated *in situ* by mixing $Rh(acac)(CO)_2$ and ligand **3a** in toluene, using 1-hexene as the model substrate at a substrate/catalyst (S/C) molar ratio of 10 000, with decane as the internal standard. The effects of ligand to metal molar ratios, reaction temperature, and the ratio of the partial pressures of CO/H_2 on the regioselectivity and the catalytic activity were evaluated, and the results are summarized in Table 1. As expected, the Rh(I)–**3a** ratio has a significant effect on the reaction, as

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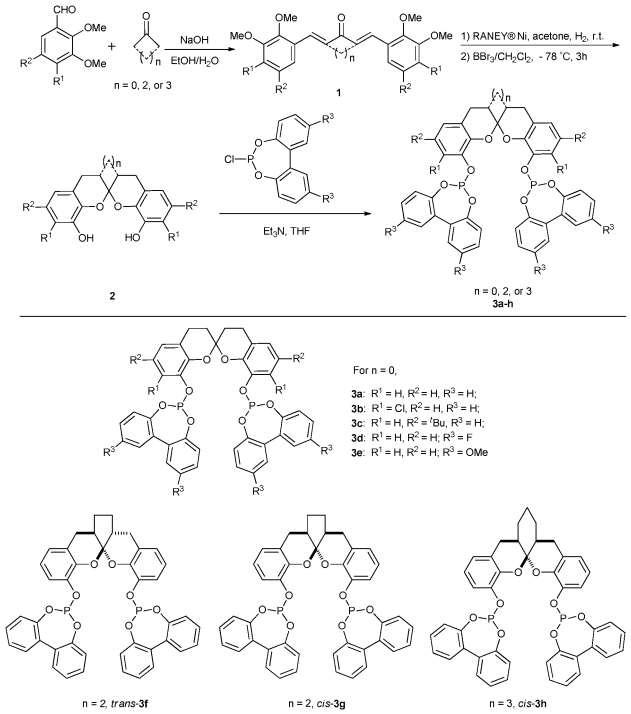
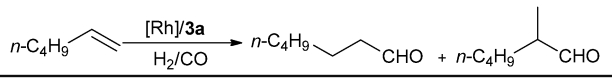


Scheme 1 Synthesis of spiroketal bisphosphite ligands **3a–h**.

Table 1 Optimization of conditions for hydroformylation of 1-hexene catalyzed by $Rh(acac)(CO)_2$/**3a**[a]

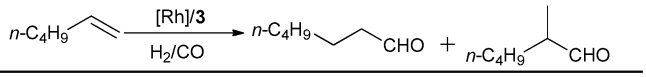


Entry	Rh/L	T (°C)	H_2/CO (bar)	l/b[b]	Linear[c] (%)	Iso.[d] (%)	TON[e]
1	1 : 1	90	10/5	5	84.1	24	7.5×10^3
2	1 : 2	90	10/5	60	98.4	18	8.1×10^3
3	1 : 3	90	10/5	93	98.9	13	7.5×10^3
4	1 : 4	90	10/5	72	98.6	7	6.0×10^3
5	1 : 3	90	10/10	27	96.5	5	5.7×10^3
6	1 : 3	90	5/5	56	98.3	7	6.6×10^3
7	1 : 3	90	20/5	72	98.6	11	8.1×10^3
8	1 : 3	80	10/5	94	99.0	7	4.8×10^3
9	1 : 3	100	10/5	70	98.6	15	8.4×10^3

[a] S/C = 10 000, $Rh(acac)(CO)_2$ (0.001 mmol), toluene (1.0 mL) as the solvent, decane as the internal standard, reaction time = 3 h. [b] Linear/branched ratio, determined by GC analysis. [c] Percentage of linear aldehyde in all aldehydes. [d] Isomerization to 2-hexenes. [e] Determined by GC analysis.

increasing the value from 1 : 1 to 1 : 3 (entries 1–3) resulted in alleviated isomerization (24–13%) and a dramatic enhancement in the regioselectivity for the linear aldehyde (l/b ratio from 5 to 93). Further increment of the metal–ligand ratio to 1 : 4, however, led to a decline in catalytic activity (entries 1–3 *vs.* 4). The ratio of the CO/H_2 partial pressures was also found to have a profound effect on the reaction (entries 5–7). While increasing the partial pressure of CO resulted in a marked depression of alkene isomerization, the TON (turnover number) value and especially the l/b ratio decreased to a considerable extent (entry 5 *vs.* 3). On the other hand, lowering the H_2 partial pressure from 10 to 5 bar also resulted in a somewhat

Table 2 Ligand screening for hydroformylation of 1-hexene[a]



Entry	L	l/b[b]	Linear[c] (%)	Isomerization[d] (%)	TON[e]
1	**3a**	93	98.9	13	7.5×10^3
2	**3b**	69	98.6	3	3.3×10^3
3	**3c**	66	98.5	13	8.4×10^3
4	**3d**	79	98.8	2	3.3×10^3
5	**3e**	64	98.5	5	4.8×10^3
6	**3f**	36	97.3	13	8.7×10^3
7	**3g**	66	98.5	2	2.7×10^3
8	**3h**	11	91.9	2	1.7×10^3

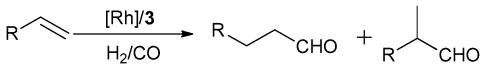
[a] S/C = 10 000, $Rh(acac)(CO)_2$ (0.001 mmol), ligand/Rh ratio = 3 : 1, temperature = 90 °C, CO/H_2 = 5/10 bar, 3 h, toluene (1.0 mL) as solvent, decane as the internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] See Table 1.

deteriorated activity and linear aldehyde regioselectivity (entry 6 *vs.* 3). Raising the H_2 partial pressure from 5 to 20 bar led to a comparable regioselectivity and activity (entry 7 *vs.* 3). Finally, the reaction temperature also displayed a significant effect on the hydroformylation. Decreasing the temperature from 90 to 80 °C resulted in a slight enhancement in the linear aldehyde selectivity, but the catalytic activity was compromised in this case (entry 8). In contrast, elevation of the reaction temperature to 100 °C resulted in an increase of isomerization and a degraded regioselectivity for linear aldehyde (entries 9). Overall, the optimal conditions (toluene, 90 °C, H_2/CO = 10/5 bar, substrate/L/Rh = 10 000/3/1) were chosen for the subsequent ligand screenings.

Subsequently, ligands **3b–h** were examined as ligands in combination with $Rh(acac)(CO)_2$ for the catalysis of hydroformylation of 1-hexene. The reactions were conducted under the reaction conditions optimized as above, and the results are shown in Table 2. In comparison with the prototype ligand **3a**, ligands with electron-withdrawing substituents on either the spiroketal phenyl backbone (**3b**) or the biphenol moieties (**3d**) led to a substantially declined reaction rate (entries 2 and 4 *vs.* 1). Intriguingly, while the use of **3c** with weak electron-donating *t*-Bu groups on the ligand backbone improved the TON value from 7.5×10^3 to 8.4×10^3 (entry 3 *vs.* 1), ligand **3e** with methoxy groups on the diphenyl moiety exhibited lower catalytic activity (entry 5 *vs.* 1). Finally, ligands **3f**, **3g** and **3h** with a tethered spiroketal backbone are somewhat less favorable in controlling the regioselectivity as compared with their conformationally more flexible analogue **3a** (entries 6–8 *vs.* 1). In addition, the *cis*-configured ligands **3g** and **3h** consistently delivered lower catalytic activities (entries 7 and 8). These results suggested that the subtle influences of the ligand backbones and their electronic features are important for Rh/**3**-catalyzed hydroformylation.

Under the optimized reaction conditions, a variety of olefins were investigated as substrates for the Rh-catalyzed hydroformylation using **3a** or **3c** as the ligand. As shown in Table 3, the industrially important short-chain feedstocks propylene and 1-butylene are readily amenable to the hydroformylation procedure, affording the corresponding aldehydes with high l/b ratios (12–55, entries 1–4) and good TON values (1.6×10^4–2.4×10^4, entries 1–4) at a S/C ratio

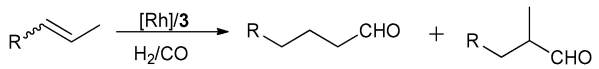
Table 3 Rh/**3** catalyzed hydroformylation of terminal olefins[a]



Entry	Substrate	L	T (°C)	l/b[b]	Linear[c] (%)	Iso.[d] (%)	TON[e]
1[f]	Propylene	**3a**	90	15	93.9	—	1.8×10^4
2[f]	Propylene	**3c**	90	12	92.8	—	1.6×10^4
3[g]	1-Butylene	**3a**	90	55	98.2	—	2.4×10^4
4[g]	1-Butylene	**3c**	90	37	97.4	—	2.3×10^4
5	1-Hexene	**3a**	90	93	98.9	13	7.5×10^3
6	1-Hexene	**3c**	90	66	98.5	13	8.4×10^3
7	1-Octene	**3a**	90	43	97.7	16	6.4×10^3
8	1-Octene	**3c**	90	36	97.4	12	7.8×10^3
9[h]	Styrene	**3a**	100	2.1	68.0	—	7.2×10^3
10[h]	Styrene	**3c**	100	3.6	78.1	—	6.0×10^3

[a] S/C = 10 000, Rh(acac)$(CO)_2$ (0.001 mmol), Rh/ligand ratio = 1 : 3, temperature = 90 °C, CO/H_2 = 5/10 bar, 3 h, toluene (1.0 mL) as solvent, decane as the internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] See Table 1. [f] S/C = 50 000, toluene (2.0 mL) as solvent. [g] S/C = 50 000. [h] Rh/ligand ratio = 1 : 2, CO/H_2 = 5/5 bar.

Table 4 Rh/**3** catalyzed hydroformylation of internal olefins[a]



Entry	Substrate	L	l/b[b]	Linear[c] (%)	TON[d]
1	(*Z*)-2-Butylene	**3a**	3.8	79.3	6.0×10^3
2	(*Z*)-2-Butylene	**3c**	3.2	76.1	5.5×10^3
3	(*E*)-2-Butylene	**3a**	3.5	77.9	5.2×10^3
4	(*E*)-2-Butylene	**3c**	3.2	75.9	4.7×10^3
5[e]	2-Octene	**3a**	3.8	79.3	2.7×10^3
6[e]	2-Octene	**3c**	3.2	76.0	2.9×10^3

[a] S/C = 50 000, Rh(acac)$(CO)_2$ (0.001 mmol), Rh/ligand ratio = 1 : 3, temperature = 110 °C, CO/H_2 = 5/10 bar, 15 h, toluene (1.0 mL) as solvent, decane as the internal standard. [b] See Table 1. [c] See Table 1. [d] See Table 1. [e] S/C = 10 000.

of 50 000. In the cases of the medium-chain olefins 1-hexene and 1-octene, the regioselectivities towards the linear aldehyde products were excellent (l/b = 36–93, entries 5–8), albeit accompanied by some amount of isomerization products. Remarkably, for the hydroformylation of styrene, an olefinic substrate well-known to favor the branched aldehyde in most Rh-catalyzed hydroformylation systems,[7e] both **3a** and **3c** afforded preferentially the linear aldehyde, albeit with a moderate selectivity (2.1–3.6, entries 9 and 10).

Under the optimized reaction conditions, the isomerization–hydroformylation of some more challenging internal olefins was also investigated using **3a**/Rh or **3c**/Rh as the catalyst. At a S/C ratio of 50 000, the industrially important olefins (*Z*)- and (*E*)-2-butylenes, both are major components of the so-called Raffinate II from Crack-C_4 products of naphtha steam cracking,[1d] were transformed to the *n*-valeraldehyde and isovaleraldehyde with similar l/b ratios (3.2–3.8, entries 1–4). The isomerization–hydroformylation reactions involving the isomeric mixture of longer chain substrate 2-octene (*Z*/*E* = 4/1) are somewhat more sluggish, affording an overall similar regioselectivity (l/b = 3.2 or 3.8, entries 5 and 6, Table 4) with a lower TON value.

In conclusion, a new series of spiroketal-based diphosphite ligands have been synthesized and applied in the Rh-catalyzed hydroformylation of unfunctionalized olefins. High catalytic activity and good to excellent regioselectivity for the linear aldehydes were obtained in the Rh-catalyzed hydroformylation of terminal olefins. In the case of the isomerizing hydroformylation of internal olefins, the linear aldehydes were obtained with a moderate linear regioselectivity. Further application of the ligands for related catalytic reactions is underway.

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