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Ligand-Controlled Direct Hydroformylation of Trisubstituted Olefins

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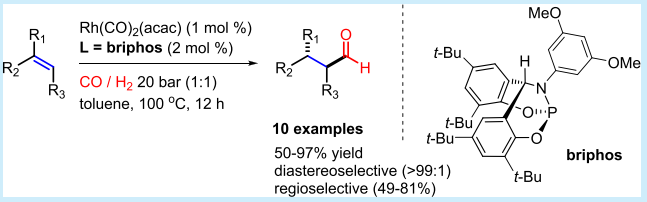
Supporting Information

ABSTRACT: The direct hydroformylation of trisubstituted olefins has been achieved with a combination of a Rh(I) catalyst and a π-acceptor phosphorus (briphos) ligand. A sterically bulky briphos ligand with a large cone angle that forms a 1:1 complex with Rh(I) is found to be reactive for the hydroformylation of trisubstituted olefins. The aldehyde products were obtained with high diastereoselectivity (>99:1) and regioselectivity (49%–81%).

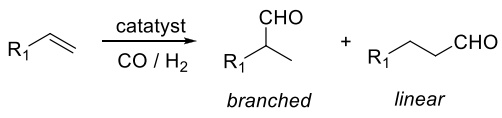


Hydroformylation is a highly atom-economical synthetic reaction to prepare aldehydes by the addition of CO and H_2 to olefins.[1] It is an industrial process that utilizes homogeneous catalytic reaction. The resulting aldehyde products are used to further produce more than 10 million tons of oxo-alcohols annually.[1] Although Co-based catalysts were initially developed for hydroformylation,[2] Rh-based catalysts have been a topic of recent research because the regioselectivity and stereoselectivity of Rh-catalyzed hydroformylation can be controlled by ligand design. Monodentate or bidentate phosphorus ligands such as phosphines, phosphoramidites, phosphinites, and phosphites, as well as their mixed forms, have been used.[3]

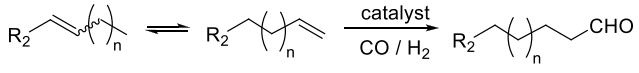
Industrial hydroformylation mainly utilizes substrates of C2 or monosubstituted C3–C8 olefins isolated from petroleum.[1c] Considering industrial applications, research on ligand development has been focused on controlling the branched to linear ratio of monosubstituted olefins (Scheme 1a).[4] In cases of internal olefins, tandem approaches including isomerization to terminal olefins followed by hydroformylation to give linear aldehyde products have been developed with various transition-metal catalysts[5] such as Co, Rh, Ru, Pd, and Pt (Scheme 1b). For the direct hydroformylation of internal olefins without involving the isomerization process, the substrate scope has only been extended to 1,1- or 1,2-disubstituted olefins,[6] whereas more-substituted olefins, such as trisubstituted or tetrasubstituted olefins, have rarely been used.[7] Although regioselective hydroformylation of trisubstituted allyl alcohols or acetates has been reported,[8] it has been a challenge to utilize trisubstituted olefins without any other functional groups. Given the importance of hydroformylation in industry, it is highly desirable to expand the utility of hydroformylation to more-substituted olefins. Here, we report Rh-catalyzed direct hydroformylation of trisubstituted olefins by ligand modification of bicyclic bridgehead phosphoramidite (briphos) ligands (Scheme 1c).

Scheme 1. Regioselective Hydroformylation

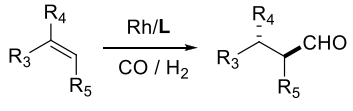
(a) Regioslective hydroformylation



(b) Tandem isomerization-hydroformylation



(c) **This work**: direct hydroformylation of trisubstituted olefins



Since the discovery of ligand effects on Rh-catalyzed hydroformylation, various phosphorus ligands have been creatively developed and applied to hydroformylation to control the regioselectivity and stereoselectivity. Bidentate phosphorus ligands with larger bite angles favor the formation of linear isomers.[9] Phosphorus ligands of π-acceptor properties enhanced the reactivity,[1c,10] and those with sterically bulky groups favored the formation of branched isomers.[11] On the basis of the reported ligand effects, the ligand choice for the hydroformylation of highly substituted olefins can be monodentate, sterically bulky, or π-acceptor phosphorus ligands.

To meet the ligand requirement, we used tunable π-acceptor phosphorus ligands, bicyclic briphos ligands.[12] Because of the geometrical constraints, the briphos ligands exhibit enhanced π-accepting properties, which can be further modulated by substituents.[12g] In order to enhance the steric repulsion, we newly prepared briphos ligands with *tert*-butyl groups at the

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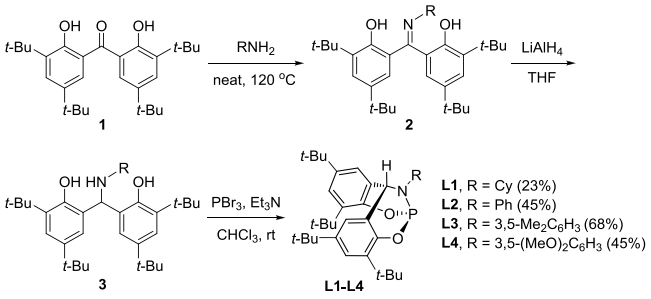
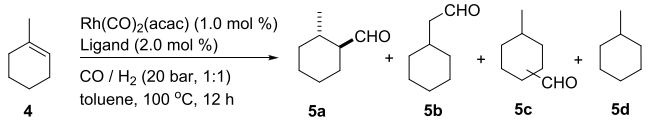
ortho and *para* positions of the phenol rings, as shown in Scheme 2. The three-straightforward-step reactions from compound **1**,[13] imine formation, reduction, and phosphoramidite formation, gave briphos ligands **L1**–**L4** in overall yields of 23%–68%.

Scheme 2. Synthesis of Briphos Ligands L1–L4 Containing *tert*-Butyl Groups



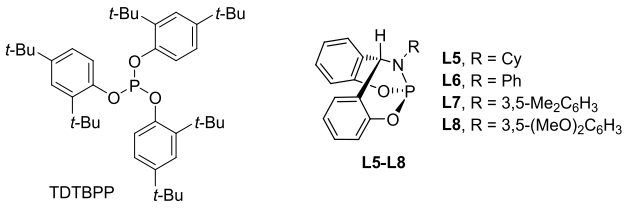
As a model substrate for hydroformylation of trisubstituted olefins, 1-methyl-1-cyclohexene (**4**) was selected (Table 1). When 20 bar syngas (CO and H_2) was applied to a solution of 1-methyl-1-cyclohexene (**4**) in toluene at 100 °C in the presence of $Rh(CO)_2(acac)$ (1 mol %) and phosphorus ligand (2 mol %), two aldehyde products, **5a** and **5b**, were mainly produced, together with other minor aldehydes (**5c**) and reduced methylcyclohexane (**5d**). In the cases of monodentate phosphorus ligands PCy_3, PPh_3, and $P(OPh)_3$, the conversion was determined to be <17% (see Table 1, entries 1–3). When a reported sterically bulky π-accepting phosphorus ligand, tris(2,4-di-*tert*-butylphenyl)phosphite (TDTBPP), was used, an increase of the conversion (65%) and moderate selectivity (**5a**/**5b** = 2.1) were observed, indicating that both the π-accepting property and steric bulkiness are required for the hydroformylation of **4** (see Table 1, entry 4). We next sought to further optimize the reactivity and selectivity by using our briphos ligand platform. To our delight, briphos ligands with *tert*-butyl groups **L1**–**L4** showed remarkable reactivity except **L2**. Both the cyclohexyl group (**L1**) and the 3,5-dimethoxyphenyl group (**L4**) were found to be effective, giving a high conversion of 83%. In particular, **L4** showed the highest selectivity for the formation of aldehydes (**5a**/**5b** = 4.0) without the formation of any side products of **5c** and **5d** (see Table 1, entries 5–8). Moreover, the hydroformylation was highly diastereoselective (>99:1) to provide **5a**. Indeed, the briphos ligands with unsubstituted phenol groups **L5**–**L8** showed poor conversion (<11%), confirming the importance of the sterically bulky functional groups (Table 1, entries 9–12). In addition, bidenate phosphorus ligands (xanphos, DPPE, and BINAP) were all inefficient (Table 1, entries 13–15).

Table 1. Ligand Effect on the Hydroformylation of 1-Methylcyclohexene



			Selectivity (%)[c]			
entry[a]	ligand	conversion (%)[b]	**5a**[c,d]	**5b**	**5c**	**5d**
1	PCy_3	8	71	29	–	–
2	PPh_3	11	64	31	4	1
3	$P(OPh)_3$	17	67	28	1	4
4	TDTBPP	65	64	31	4	1
5	**L1**	83	73	25	2	–
6	**L2**	11	73	27	–	–
7	**L3**	70	73	25	2	–
8	**L4**	83	80	20	–	–
9	**L5**	11	64	25	11	–
10	**L6**	14	73	25	2	–
11	**L7**	4	42	21	37	–
12	**L8**	3	60	33	7	–
13	xantphos	6	46	39	2	13
14	DPPE	NR	–	–	–	–
15	*rac*-BINAP	6	55	34	2	9

[a]Conditions: 1-methyl-1-cyclohexene (1.0 mmol) and [Rh] = 0.5 mM in a stainless-steel pressure reactor without exclusion of air or moisture. [b]Determined by ^{1}H NMR spectra. [c]Determined by GC-MS spectra. [d]**5a** was obtained with >99:1 dr (trans/cis).



In order to understand the origin of reactivity and regioselectivity, we conducted several control experiments. In our previous study, briphos ligand **L6** and Rh(I) was found to form the 2:1 complex, which is an active species for Rh-catalyzed conjugate additions of aryl boronic acids.[12g] We obtained a crystal structure of a dinuclear $[Rh(\mathbf{L6})_2Cl]_2$ complex.[12g] However, *tert*-butyl substituted briphos **L4** was found to form a 1:1 complex with $Rh(CO)_2(acac)$. The crystal structure of Rh(CO)(acac)(**L4**) is shown in Figure 1. When 1 mol % of Rh(CO)(acac)(**L4**) was used for hydroformylation of 1-methyl-1-cyclohexene, the desired aldehyde was produced at 32% with 80% regioselectivity, indicating that Rh(CO)(acac)(**L4**) is an active precatalyst.

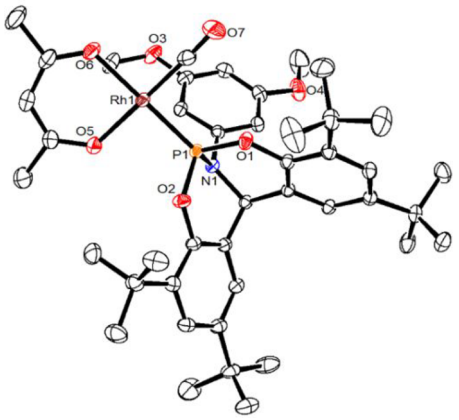


Figure 1. Crystal structure of Rh(CO)(acac)(**L4**) (thermal ellipsoids at 50% probability: all hydrogen atoms are omitted for clarity).

In the solution state, the ligand **L4** forms only the 1:1 complex, Rh(CO)(acac)(**L4**), even when 4 equiv of ligand **L4** was used, as determined by $^{31}P\{^1H\}$ NMR analysis (Figures 2a and 2b). When this complex was applied to 20 bar syngas, a

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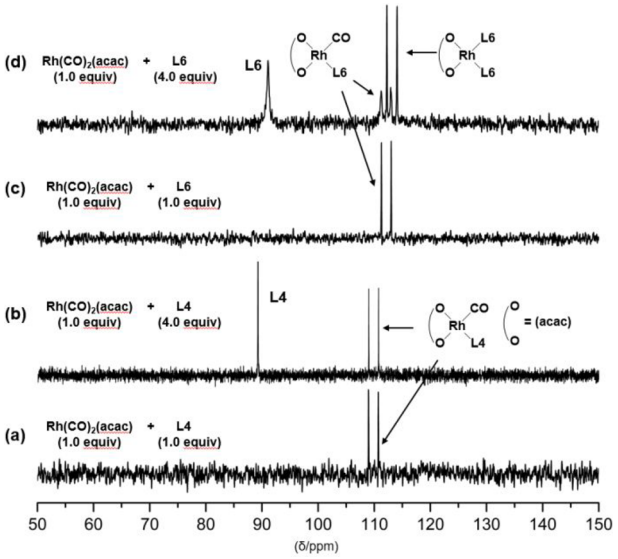


Figure 2. Stacked $^{31}P\{^{1}H\}$ NMR spectra showing ligation of **L4** and **L6** with $Rh(CO)_2(acac)$.

new Rh complex $HRh(CO)_2$(**L4**) was formed. A doublet signal at 121.5 ppm in $^{31}P\{^{1}H\}$ NMR and a triplet signal at −9.29 ppm in ^{1}H NMR spectra support the structure of $HRh(CO)_2$(**L4**) (see the Supporting Information). Even when 1 equiv of substrate, 1 mol % of $Rh(CO)(acac)_2$, and 4 mol % of ligand **L4** were mixed for 1 h in benzene-d_6 under 20 bar syngas at ambient temperature, the $^{31}P\{^{1}H\}$ NMR spectra indicated that Rh(CO)(acac)(**L4**) and $HRh(CO)_2$(**L4**) are the only detectable intermediates (see the Supporting Information). Interestingly, briphos **L6** without *tert*-butyl groups forms 2:1 complexes with Rh(I). Rh(acac)(**L6**)$_2$ and HRh(CO)(**L6**)$_2$ are in the solution state, as determined by $^{31}P\{^{1}H\}$ NMR analysis (Figures 2c and 2d and the Supporting Information). Because briphos **L6** showed only 3% conversion, the formation of a 1:2 complex of Rh and ligand appears to be inactive for hydroformylation of trisubstituted olefins.

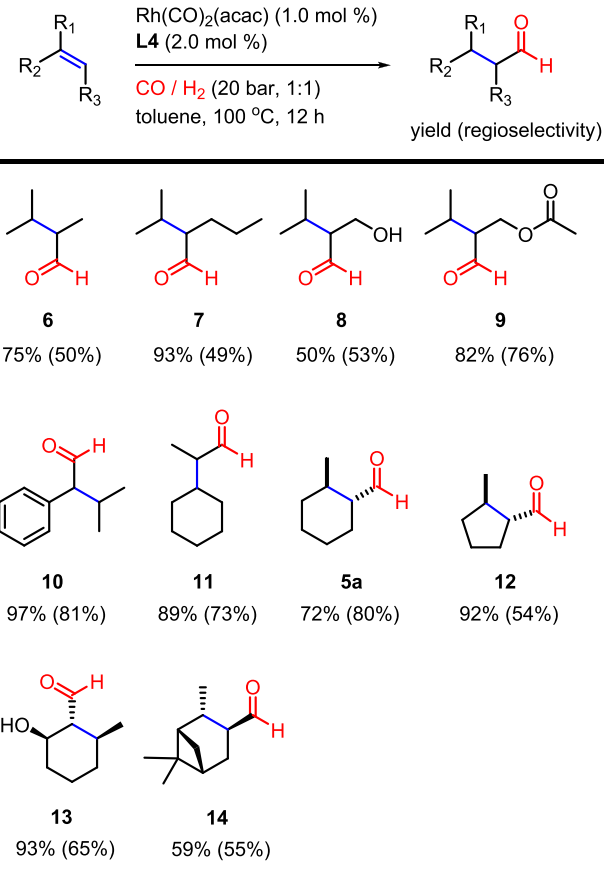
The steric bulkiness of the phosphorus ligands can be evaluated by measuring ligand parameters such as cone angles or buried volumes. Briphos **L4** showed $\%V_{bur}$ and cone angle θ values of 30.8 and 195°, respectively, and Briphos **L6** gave corresponding values of 28.6 and 156°, respectively. (See Table 2.) Because ligands **L4** and **L6** have compatible $\%V_{bur}$ values but different θ values, the angular steric effect expressed by the θ value appears to be crucial to form the 1:1 Rh-ligand complex, which is effective for the direct hydroformylation of trisubsituted olefins.

Table 2. Steric Parameters[14] of L4 and L6

ligand	L4	L6
$\%V_{bur}$	30.8	28.6
cone angle, θ (°)	195	156

With the optimized reaction conditions of using 1 mol % of $Rh(CO)_2(acac)$ and 2 mol % of briphos ligand **L4**, we investigated the substrate scope (Scheme 3). In the case of acyclic trisubstituted olefins, the hydroformylation proceeded with >99% conversion and the regioselectivity of the major aldehyde products **6**–**9** was 49%–76%. An aryl-substituted olefin gave product **10** with 97% yield and 81% regioselectivity.

Scheme 3. Substrate Scope for the Hydroformylation of Trisubstituted Olefins



We then used cyclic trisubstituted olefins. In the case of an exocyclic olefin, the desired aldehyde **11** was produced in 89% yield and 73% regioselectivity. For endocyclic olefins, the desired products **5** and **12**–**14** were obtained in somewhat reduced yields of 59%–72%. Our structural analysis supported *syn*-addition of hydrogen and formyl group to the olefins, thus producing all trans products (see the Supporting Information). The regioselectivity for endocyclic olefins was higher than that for the acyclic olefins, ranging from 60% to 81%. Considering two or three possible isomerizations in acyclic trisubstituted olefins, the observed regioselectivity was quite significant.

In conclusion, we have demonstrated that sterically bulky π-acceptor phosphorus ligands, briphos ligands, can efficiently promote the direct hydroformylation of trisubstituted olefins. Crystallographic and NMR data support that briphos ligand substituted with di-*tert*-butyl groups is found to form a 1:1 complex with Rh catalyst, likely due to the large cone angle. The briphos ligand **L4** was utilized to promote direct hydroformylation of various trisubstituted olefins including acyclic, exocyclic, and endocyclic forms with moderate to good yields (50%–97%) and regioselectivity (49%–81%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01639.

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Experimental procedures; compound characterization data; ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{1H\}$ and 2D NMR spectra; and crystal data of Rh(CO)(acac)(**L4**) (PDF)

Accession Codes

CCDC 1897350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(14) See the Supporting Information for computational details about percent buried volume (%V_{bur}) and cone angle θ (°).

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