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Directing Selectivity to Aldehydes, Alcohols, or Esters with Diphobane Ligands in Pd-Catalyzed Alkene Carbonylations

Dillon W. P. Tay, James D. Nobbs, Srinivasulu Aitipamula, George J. P. Britovsek,* and Martin van Meurs*

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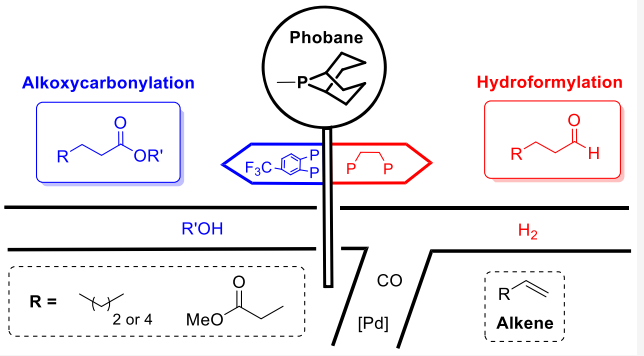
ABSTRACT: Phenylene-bridged diphobane ligands with different substituents (CF_3, H, OMe, $(OMe)_2$, ^tBu) have been synthesized and applied as ligands in palladium-catalyzed carbonylation reactions of various alkenes. The performance of these ligands in terms of selectivity in hydroformylation versus alkoxycarbonylation has been studied using 1-hexene, 1-octene, and methyl pentenoates as substrates, and the results have been compared with the ethylene-bridged diphobane ligand (**BCOPE**). Hydroformylation of 1-octene in the protic solvent 2-ethyl hexanol results in a competition between hydroformylation and alkoxycarbonylation, whereby the phenylene-bridged ligands, in particular, the trifluoromethylphenylene-bridged diphobane **L1** with an electron-withdrawing substituent, lead to ester products via alkoxycarbonylation, whereas **BCOPE** gives predominantly alcohol products (*n*-nonanol and isomers) via reductive hydroformylation. The preference of **BCOPE** for reductive hydroformylation is also seen in the hydroformylation of 1-hexene in diglyme as the solvent, producing heptanol as the major product, whereas phenylene-bridged ligands show much lower activities in this case. The phenylene-bridged ligands show excellent performance in the methoxycarbonylation of 1-octene to methyl nonanoate, significantly better than **BCOPE**, the opposite trend seen in hydroformylation activity with these ligands. Studies on the hydroformylation of functionalized alkenes such as 4-methyl pentenoate with phenylene-bridged ligands versus **BCOPE** showed that also in this case, **BCOPE** directs product selectivity toward alcohols, while phenylene-bridge diphobane **L2** favors aldehyde formation. In addition to ligand effects, product selectivities are also determined by the nature and the amount of the acid cocatalyst used, which can affect substrate and aldehyde hydrogenation as well as double bond isomerization.



INTRODUCTION

Carbonylation of alkenes is an important process to produce bulk and fine chemicals. This is exemplified by olefin hydroformylation, one of the largest applications of homogeneously catalyzed reactions in the chemical industry.[1,2] Examples of hydroformylation products include butyraldehyde (75% of global aldehyde use, plasticizer alcohol precursors), midchain C_6–C_{13} aldehydes (plasticizer alcohol precursors), and C_{12}–C_{18} aldehydes (for detergent alcohols). Due to its scale and commercial importance, hydroformylation has been investigated extensively by industry and academia, in order to improve upon current processes and explore its applications to new products.[3]

Hydroformylation catalysts are generally based on Group 9 metals, with both Co and Rh being employed industrially.[4−6] Other metals, most notably Pd, have also shown some success,[7−12] but Rh-catalyzed hydroformylation is generally regarded as state-of-the-art owing to its high activity and regioselectivity.[13] However, when it comes to higher boiling hydroformylation products, the separation of the expensive Rh catalyst without degradation becomes a significant challenge,[14,15] and less costly Co-based catalysts still tend to dominate production, despite their lower activity.[16]

Hydroformylation and alkoxycarbonylation are mechanistically closely related, with different nucleophiles (H_2 or ROH) attacking a common acyl intermediate to give either aldehydes or esters (see Figure 1).[9,17] Although the latter process is well-established for Pd catalysts,[18−21] Pd-catalyzed hydroformylation is comparatively much rarer.[7]

The direct production of alcohols from olefins, termed reductive hydroformylation, is desirable for certain applications.[22] For example, Co-based catalysts for reductive hydroformylation developed by Shell use 9-phosphabicyclo[3.3.1]-

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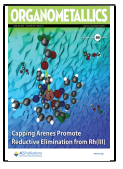

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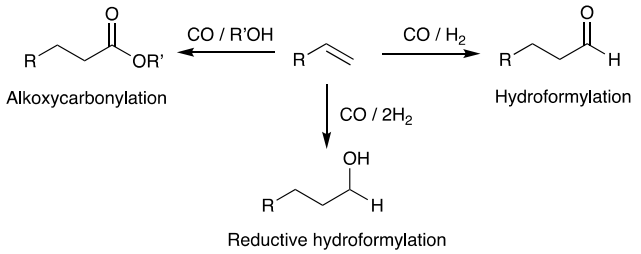


Figure 1. Various carbonylation reactions of olefins.

nonane (PhobPR) ligands for the production of detergent alcohols directly via in situ reduction of the intermediate aldehyde (see Figure 2).[23] A related example is the Co-based catalyst system containing limonene-derived phosphine ligands (LimPR) reported by Sasol and their application in reductive hydroformylation.[24−27]

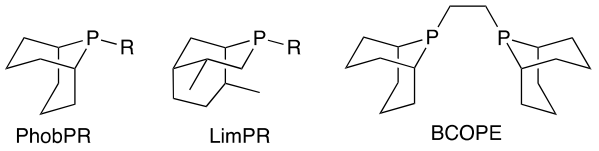


Figure 2. Examples of phobane (PhobPH) and related ligands.

Noteworthy in the context of the present work is the Pd-based catalyst system that uses the bidentate diphobane ligand **BCOPE** to perform tandem isomerizing reductive hydroformylation of internal olefins to linear alcohols (Figure 2).[10]

The strained C−P−C bridgehead in phobane and related ligands affects the p-character of the lone pair orbital, thereby altering the HOMO energy and modulating σ-donor and π-acceptor properties of the P donor atom. As a result, these ligands are generally weaker σ-donors and better π-acceptors.[28] Surprisingly few reports of these ligand systems have been reported,[29,30] perhaps in part due to the nontrivial syntheses of the PhobPH and LimPH precursors, which involve the reaction of pyrophoric PH_3 with 1,5-cyclooctadiene or limonene, respectively, at elevated temperatures.[31,32]

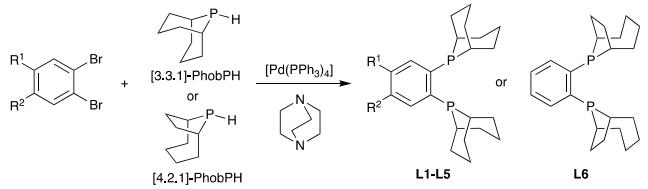
A significant drawback of reductive hydroformylation is the often competing olefin hydrogenation to low-value paraffins.[33,34] This becomes even more problematic for higher-value olefinic substrates with additional functionalities, for example, alkenoate esters.[12,35] Hence, in addition to increasing alcohol yield and minimizing catalyst loss, a significant focus in the commercial development of reductive hydroformylation catalysts has been toward limiting alkene hydrogenation side reactions.[36]

In this work, we describe the synthesis and characterization of a series of phenylene-bridged diphobane ligands with various substituents on the aryl ring. These ligands have been evaluated in the Pd-catalyzed hydroformylation of simple aliphatic as well as functionalized olefins to study the effect of systematic ligand variation on product selectivity. We have found that remote modifications of the C_2 backbone in these diphobane ligands can alter product selectivity in Pd-catalyzed olefin hydroformylation. When conducted in an alcohol solvent such as 2-ethyl hexanol, the solvent is non-innocent, resulting in a competition between olefin hydroformylation and alkoxycarbonylation. Electron-donating substituents favor reductive hydroformylation to alcohols, while electron-withdrawing substituents favor alkoxycarbonylation to give ester products. Furthermore, hydroformylation of the functionalized alkenes methyl 4-pentenoate and methyl 2-pentenoate has been investigated.[35,37,38] These substrates can be prepared from the methoxycarbonylation of C4 feedstocks[39] or from renewable sources such as unsaturated fatty esters or γ-valerolactone (GVL).[40,41] Hydroformylation products such as methyl 5-formylpentanoate and methyl 6-hydroxyhexanoate are of great interest as monomers for the synthesis of polyamides and poly(hydroxyalkanoates) (PHAs), which are important biodegradable polymers.[42,43]

LIGAND SYNTHESIS

The synthesis of phenylene-bridged diphobane **L2** has been previously described by Drent and co-workers.[44] This procedure was adapted to synthesize a series of diphobanes with functionalized aryl bridges with electron-withdrawing (CF_3) or electron-donating (MeO, ^{t}Bu) substituents (Table 1).

Table 1. Synthesis of Substituted Aryl-Bridged Diphobanes[a]



Ligand	R^1	R^2	Yield/%	$^{31}P/\delta$ (ppm)[b]
L1	CF_3	H	47	−15.7, −16.2
L2	H	H	58	−17.3
L3	OMe	H	54	−16.7, −18.7
L4	OMe	OMe	33	−17.7
L5	^{t}Bu	H	32	−16.7, −18.3
L6			37	3.8

[a]Conditions: Substituted dibromobenzene (1 equiv), [3.3.1]- or [4.2.1]-phobane $HP(C_8H_{14})$ (2.1 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), 1,4-diazabicyclo[2.2.2]octane (5 equiv), xylenes, 140 °C, 72 h. [b]$CDCl_3$.

Pd-catalyzed cross-coupling between secondary phobane, $HP(C_8H_{14})$, and the corresponding 1,2-dibromobenzene precursor generated a series of substituted aryl-bridged diphobanes (Table 1). No diphobane product was obtained when a nitro-substituted precursor (R^1 = H, R^2 = NO_2) was used, possibly due to the significant electron-withdrawing effect of the nitro group deactivating the aryl dihalide toward Pd-catalyzed cross-coupling.[45]

^{31}P NMR spectra of **L1**−**L5** revealed chemical shifts between −16 to −18 ppm ($CDCl_3$), a surprisingly narrow range but in line with the range of chemical shifts observed for related 1,2-bis(diphenylphosphino)benzene (−12.7 ppm, $CDCl_3$)[46] and 1,2-bis(diphenylphosphino)-4,5-dimethoxybenzene (−12.9 ppm, $CDCl_3$).[47] The introduction of a single OMe substituent on the aryl-bridge to give **L3** renders the P atoms inequivalent. The electron-withdrawing inductive effect of the OMe substituent in the *meta* position results in a deshielding of the P donor, whereas the positive mesomeric effect of the *para* OMe substituent leads to an overall shielding effect (Figure 3).

For dimethoxylated ligand **L4**, the *meta* electron-withdrawing inductive effect appears to balance out the *para* electron-donating mesomeric effect due to its symmetrical

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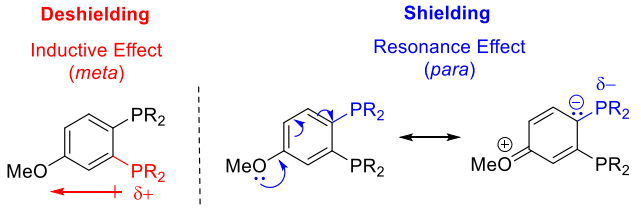

Figure 3. Inductive and resonance effects in **L3**.

substitution, resulting in a chemical shift very similar to that of the unsubstituted ligand **L2**. The electron-withdrawing CF_3 group in **L1** appears to deshield each P atom proportionate to the distance between them, resulting in two chemical shifts both downfield from that of the unsubstituted ligand **L2**. A more significant deshielding effect is observed when changing the [3.3.1]-phobane to [4.2.1]-phobane substituents in **L6**, resulting in a downfield shift of more than 20 ppm.

PALLADIUM DIPHOBANE COMPLEXES

Palladium(II) complexes of **L2**, **L6**, and **BCOPE** have been prepared by reacting equimolar amounts of the corresponding diphobane ligand with $[Pd(COD)Cl_2]$ in CH_2Cl_2 at room temperature to give $[Pd(\mathbf{L2})Cl_2]$, $[Pd(\mathbf{L6})Cl_2]$, and $[Pd(\mathbf{BCOPE})Cl_2]$ in excellent yields (Figure 4). The addition of 1

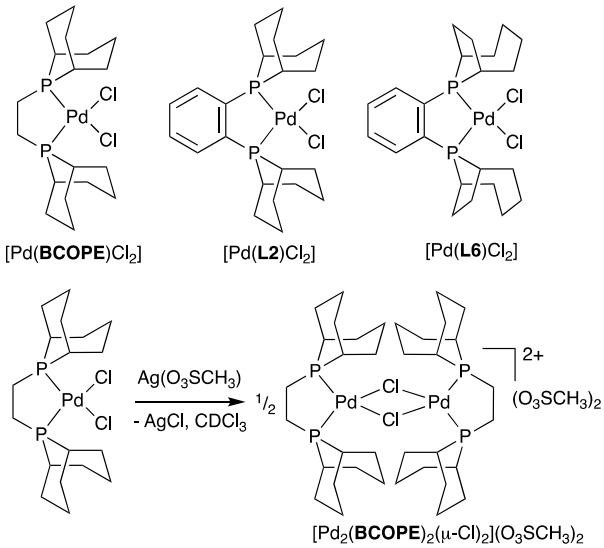

Figure 4. Palladium chloride complexes with diphobane ligands.

equiv of $Ag(O_3SCH_3)$ to $[Pd(\mathbf{BCOPE})Cl_2]$ in $CDCl_3$ removes one of the chloride ligands and results in a chloro-bridged dinuclear complex $[Pd_2(\mathbf{BCOPE})_2(\mu\text{-}Cl)_2](O_3SCH_3)_2$, which was also isolated and crystallographically characterized (see Supporting Information). Their molecular structures, along with selected bond angles and lengths, are shown in Figures 5 and 6 and in the Supporting Information for $[Pd(\mathbf{L6})Cl_2]$ and $[Pd_2(\mathbf{BCOPE})_2(\mu\text{-}Cl)_2](O_3SCH_3)_2$.

All complexes are 4-coordinate in the solid state and adopt square planar geometries characteristic of d^8 metal complexes. $[Pd(\mathbf{BCOPE})Cl_2]$ exhibits C_2 symmetry, whereas $[Pd(\mathbf{L2})Cl_2]$ shows C_s symmetry and the square planar geometries are slightly distorted in different ways. $[Pd(\mathbf{L2})Cl_2]$ tends toward a square pyramidal geometry with Cl1−P1−P2−Cl2 lying within 0.09 Å of the same plane and Pd1 displaced 0.20 Å away from the plane. $[Pd(\mathbf{BCOPE})Cl_2]$ distorts toward a tetrahedral

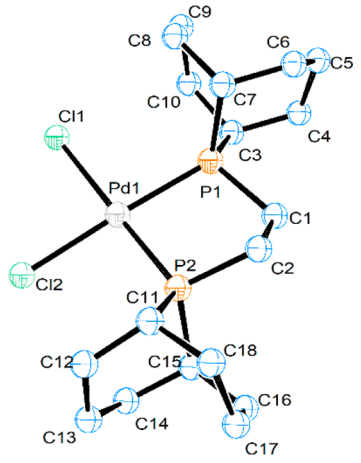

Figure 5. Molecular structure of $[Pd(\mathbf{BCOPE})Cl_2]$. Selected bond angles (deg) and lengths (Å). P1−Pd1−P2, 85.48(5); P2−C2−C1, 108.7(5); C2−C1−P1, 107.4(5); C2−P2−Pd1, 106.1(2); C1−P1−Pd1, 106.0(2); C3−P1−C7, 96.4(3); C11−P2−C15, 96.6(3); P1−Pd1, 2.2840(15); P2−Pd1, 2.2752(15); C1−P1, 1.824(7); C2−P2, 1.834(6); C1−C2, 1.500(9).

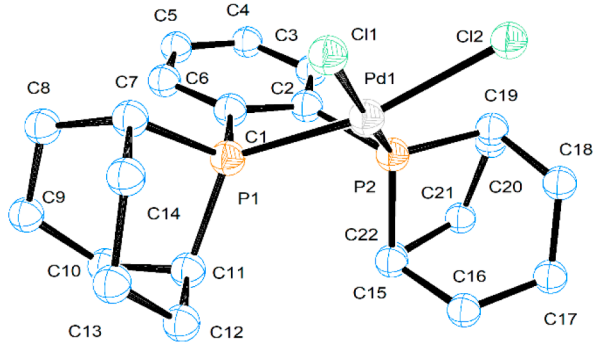

Figure 6. Molecular structure of $[Pd(\mathbf{L2})Cl_2]$ complex. Selected bond angles (deg) and lengths (Å). P1−Pd1−P2, 82.31(3); P2−C2−C1, 115.2(2); C2−C1−P1, 115.5(2); C2−P2−Pd1, 99.93(11); C1−P1−Pd1, 99.59(11); C7−P1−C11, 95.52(15); C19−P2−C22, 95.95(15); P1−Pd1, 2.2817(8); P2−Pd1, 2.2484(8); C1−P1, 1.855(3); C2−P2, 1.823(4); C1−C2, 1.405(5).

arrangement by twisting its Cl atoms, with Cl1 being 0.22 Å and Cl2 being 0.19 Å away from the Pd−P1−P2 plane on opposite sides. The P−Pd−P bite angles in $[Pd(\mathbf{BCOPE})Cl_2]$ of 85.48(5)° and 84.94(2)°/84.31(2)° for the dinuclear complex $[Pd_2(\mathbf{BCOPE})_2(\mu\text{-}Cl)_2](O_3SCH_3)_2$ are comparable to those of 84.20(4)° and 84.36(3)° reported for the related complexes $[Pd(\mathbf{BCOPE})(H_2O)_2](OTf)_2$ and $[Pd(\mathbf{BCOPE})(MeOH)_2](OTf)_2$.[9,48] Differences in ligand bite angles can have implications for catalytic performance. Studies into ligand bite angle effects on catalytic activity and selectivity in carbonylation catalysis have been reported by van Leeuwen and co-workers.[49−51] The P−Pd−P ligand bite angles in the phenylene-bridged complexes $[Pd(\mathbf{L2})Cl_2]$ and $[Pd(\mathbf{L6})Cl_2]$ were determined as 82.31(3)° and 82.18(2)°, considerably smaller than 85.48(5)° for $[Pd(\mathbf{BCOPE})Cl_2]$. The rigid phenylene backbone results in a well-defined "envelope" conformation with C_s symmetry for the 5-membered chelate formed between ligand and metal center, giving a P1−C1−C2−P2 dihedral angle of 5.8° for $[Pd(\mathbf{L2})Cl_2]$ and 4.3° for $[Pd(\mathbf{L6})Cl_2]$. The more flexible ethylene backbone in $[Pd(\mathbf{BCOPE})Cl_2]$ allows twisting into a C_2 symmetric "half-

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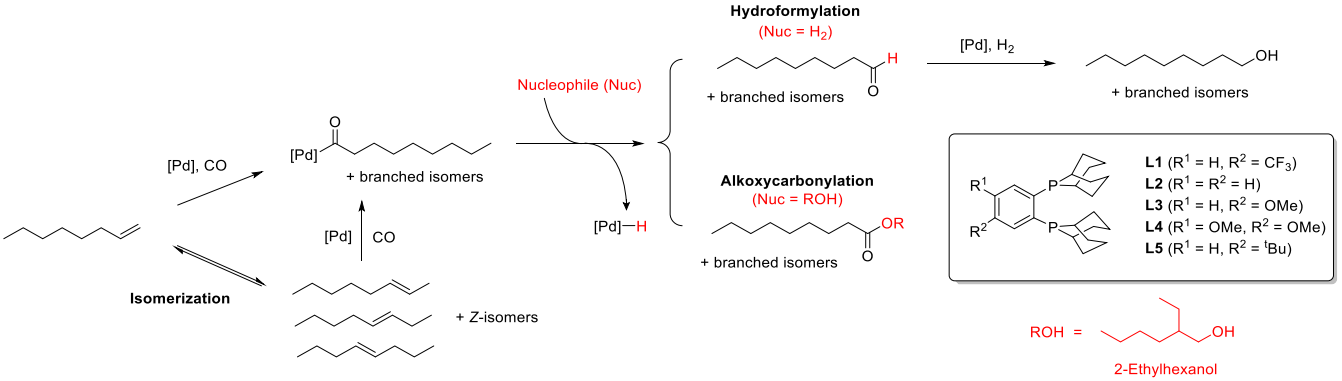
Table 2. Pd-Catalyzed Carbonylation of 1-Octene[a]



		isomerization	hydroformylation		alkoxycarbonylation		
ligand	conv. %	internal[b] octenes sel. %	nonanal[b] sel. % [lin. %]	nonanol[b] sel. % [lin. %]	2-ethylhexyl nonanoate[b] sel. % [lin. %]	chemoselectivity[b]	TON[c]
L1	99	51	9 [68]	4 [79]	35 [82]	27/73	950
L2	99	54	12 [65]	17 [73]	16 [76]	65/35	900
L3	99	55	14 [66]	17 [76]	13 [77]	70/30	900
L4	99	57	5 [69]	20 [72]	17 [78]	60/40	850
L5	99	59	8 [63]	14 [72]	18 [80]	55/45	850
BCOPE	99	35	1 [73]	61 [74]	2 [72]	97/3	1300

[a]Conditions: 1-Octene (80.6 mmol), $Pd(OAc)_2$ (0.04 mmol), Ligand (L/Pd = 1.4), CH_3SO_3H (Acid/Pd = 40), aqueous NaCl solution (NaCl/Pd = 0.4, 1 mL), 60 bar CO/H_2 (1:2), 2-Ethyl hexanol (20 mL), 100 °C, 2 h. Yields were determined via gas chromatography using anisole as an internal standard. Note: Trace amounts nonyl nonanoate and nonanoic acid were detected in all runs. [b]sel.: selectivity = product/all products; lin.: linearity = linear/linear+branched products. chemoselectivity = ratio hydroformylation/alkoxycarbonylation. [c]TON (turnover number) = moles of carbonylation products/moles of catalyst.

chair" conformation, giving a larger P1−C1−C2−P2 dihedral angle of 56.7°. Both complexes exhibit similar phobane geometries, with the quaternary bridgehead atoms held in a strained position to give C−P−C angles of about 96° for [3.3.1]-phobane ligands and 93° for [4.2.1]-phobane ligands. The propylene bridges are folded away from the P atom as observed in [3.3.1]-phobane, $HP(C_8H_{14})$.[28] This restricted geometry has been proposed as one of the reasons for the unique properties of phobane-based ligands.[52,53]

Analysis by ^{31}P NMR spectroscopy in CD_2Cl_2 solution shows a singlet at 51.3 ppm for [Pd(**BCOPE**)Cl_2], at 38.2 ppm for [Pd(**L2**)Cl_2] and 65.1 ppm for [Pd(**L6**)Cl_2]. In d_6-DMSO, a singlet at 70.2 ppm is observed for [Pd(**BCOPE**)Cl_2], most likely due to the exchange of the chloro ligands for DMSO ligands.[54] Similar chemical shifts have been reported for [Pd(**BCOPE**)$(MeOH)_2$]$(OTf)_2$ (74 ppm) and [Pd(**BCOPE**)$(H_2O)_2$]$(OTf)_2$ (73.11 ppm) complexes.[9,48]

The in situ catalyst system was prepared by combining the diphobane ligand, $Pd(OAc)_2$ and CH_3SO_3H. The combination of diphosphine ligands (P−P) and $Pd(OAc)_2$ generally leads initially to the formation of the kinetic product, a bis-chelate complex $[Pd(P-P)_2]^{2+}$, which is catalytically inactive.[55] Upon addition of acid (HX), this bis-chelate complex is slowly converted to the catalytically active monochelate complex $[Pd(P-P)X_2]$, where X can be the anion derived from HX or a solvent ligand.[48] A mixture of **BCOPE** and $Pd(OAc)_2$ (ratio 1:1.4) and an excess of CH_3SO_3H in d_6-DMSO at room temperature showed initially the formation of two species according to ^{31}P NMR analysis: a singlet at 54.5 ppm assigned to the bis-chelate complex $[Pd(\mathbf{BCOPE})_2]^{2+}$ and a singlet at 70.2 ppm assigned to the monochelate complex [Pd(**BCOPE**)$(DMSO)_2$]$^{2+}$ in a ratio of 2:1. This ratio changed after 24 h at room temperature to 1:3, indicating a slow conversion of $[Pd(\mathbf{BCOPE})_2]^{2+}$ to the active species [Pd(**BCOPE**)$(DMSO)_2$]$^{2+}$, as seen previously in studies with related ligand systems.[55]

HYDROFORMYLATION VERSUS ALKOXYCARBONYLATION

The ligands **L1**−**L5** have been evaluated in Pd-catalyzed carbonylation reactions of 1-octene, and the results are summarized in Table 2. Results obtained with **BCOPE** have been included for comparison. The catalysts were formed in situ via the sequential combination of diphobane ligand, $Pd(OAc)_2$, CH_3SO_3H, and aqueous NaCl in 2-ethyl hexanol. 2-Ethyl hexanol, a common industrial solvent,[56] was chosen in order to benchmark previous reports where this solvent was used.[10] As will be shown, the alcohol solvent is non-innocent and can participate in competing alkoxycarbonylation reactions to form ester products.

The addition of substoichiometric amounts of NaCl with respect to Pd has been reported to improve yields and selectivity toward alcohol products in reductive hydroformylation reactions.[10] The reason for this halide effect is believed to involve heterolytic H_2 activation during the hydrogenolysis step of the palladium acyl intermediate. We briefly explored this NaCl effect in the hydroformylation of 1-hexene using **BCOPE**, and we could confirm a promotional effect with respect to heptanol formation (vide infra). In order to promote reductive hydroformylation, we used NaCl as an additive in all our hydroformylation studies.

High conversions were achieved in all runs, but there is a marked difference in the product distribution obtained with **BCOPE**, which predominantly favors alcohols (95% selectivity), and the aryl-bridged diphobanes **L1**−**L5** that give significant amounts of both hydroformylation and alkoxycar-

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bonylation products. The unsubstituted **L2** ligand gave a product distribution consisting of similar amounts of nonanal, nonanol, and 2-ethylhexyl nonanoate esters. With **L1**, there is a change in chemoselectivity in favor of alkoxycarbonylation to give 2-ethylhexyl nonanoate as the major product (73% selectivity). The electron-withdrawing effect conferred by CF_3 appears to bias the mechanism toward alcoholysis, yielding nearly three times more alkoxycarbonylation than hydroformylation products.[17]

According to the mechanism for alcoholysis proposed by van Leeuwen and co-workers, deprotonation of a coordinated alcohol species to form a Pd-alkoxy intermediate is followed by reductive elimination to yield the ester product (Figure 7).[17]

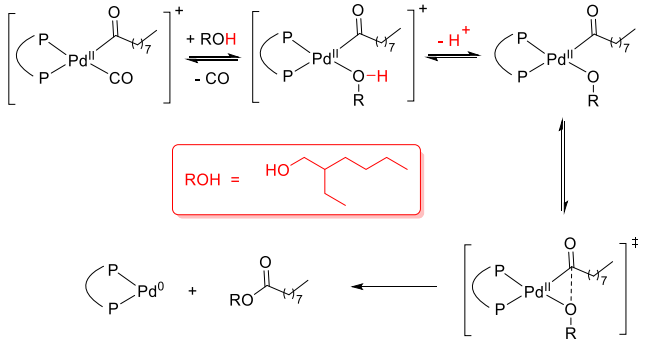

Figure 7. Alcoholysis mechanism adapted from van Leeuwen and co-workers.[17]

The CF_3 group in **L1** draws electron density away from the P donors and consequently results in a more electrophilic Pd center. This in turn should polarize the O−H bond of a coordinated 2-ethyl hexanol ligand, facilitate its deprotonation, and accelerate the alcoholysis of the Pd-acyl species to favor the formation of 2-ethylhexyl esters. When an electron-donating OMe substituent is introduced in **L3**, there is no significant impact upon product selectivity compared to **L2**. It is only upon the introduction of a second OMe group in **L4** that an increase in reductive hydroformylation activity is observed.

Zhou and co-workers have proposed a mechanism for the homogeneous Pd-catalyzed reduction of aldehydes to alcohols (Figure 8).[57] In the proposed mechanism, Pd-hydride attacks the carbonyl group in heptanal to give a Pd-alkoxy species that is protonated by CH_3SO_3H to yield the heptanol product. An increase in electron density at the P donor atoms and, hence, at the Pd center may facilitate this process by increasing the nucleophilicity of the hydride ligand in the Pd-hydride complex. If the nucleophilic attack of Pd-hydride on heptanal is rate-determining, reductive hydroformylation activity would then directly correlate with electron density, and more electron-rich ligands such as **L4** and **BCOPE** should yield more alcohol product, which is indeed observed.

1-HEXENE HYDROFORMYLATION

The series of aryl-bridged diphobane ligands **L1**−**L6** has been evaluated in Pd-catalyzed hydroformylation of 1-hexene in the aprotic solvent diglyme, which avoids competing alkoxycarbonylation, and the results are summarized in Table 3. The catalysts were formed in situ by the sequential combination of diphobane ligand, $Pd(OAc)_2$, CH_3SO_3H, and aqueous NaCl in diglyme. Results obtained with **BCOPE** have been included for

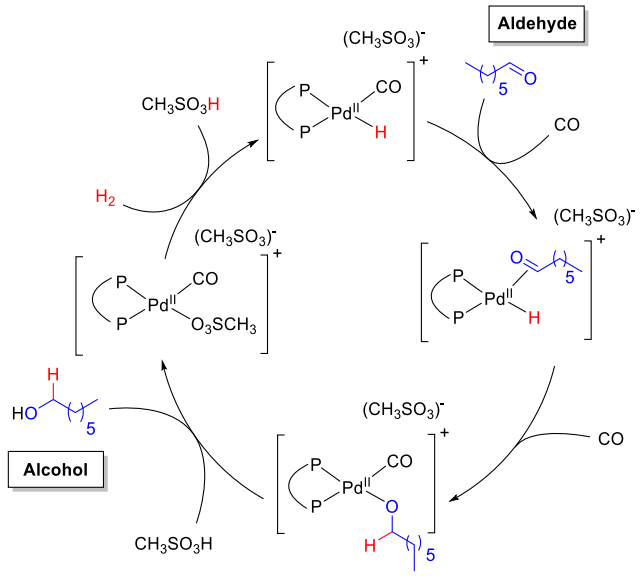

Figure 8. Proposed mechanism for Pd-catalyzed reduction of heptanal to heptanol, adapted from the literature.[57]

comparison, and the promotional effect of the addition of NaCl on conversion and product selectivity is seen in the last two runs in Table 3.

Also in this case, high conversions were achieved in all runs. Pd black formation was not observed in any of the product mixtures, indicating catalyst robustness under these reaction conditions. Hydroformylation activity was in the order **BCOPE** > **L2**−**L5** > **L1**,**L6**. Comparison of the product compositions between the aryl-bridged diphobanes **L1**−**L6** and **BCOPE** show that **L1**−**L6** give more internal hexenes, while **BCOPE** favors reductive hydroformylation to heptanol (89% selectivity). Product linearities were similar (ca. 77%) across the entire series despite the variety of electron-donating and electron-withdrawing substituents, suggesting that regioselectivity is not determined by electronic effects in this case. Drent and Budzelaar reported similar findings, showing instead a direct correlation between Pd-catalyzed hydroformylation product linearity and ligand steric bulk.[58]

The diphobanes **L2**−**L5** yielded similar amounts of hydroformylation products (ca. 60%), while the CF_3-substituted **L1** and the [4.2.1]-diphobane ligand **L6** were markedly less active (35−43% hydroformylation product). **L1** and **L6** also demonstrated poorer reductive hydroformylation ability compared to **L2**−**L5**. The unsubstituted ligand **L2**, OMe-substituted **L3**, and ^{t}Bu-substituted **L5** all showed similar reductive hydroformylation abilities (ca. 30%). However, for **L4** with two OMe substituents, reductive hydroformylation activity increased to favor nonanol as the major product (68% selectivity). These results suggest again that electron-rich donor ligands and hence a more electron-rich Pd center favor reductive hydroformylation of olefins to alcohols.

1-OCTENE METHOXYCARBONYLATION

The series of aryl-bridged diphobane ligands **L1**−**L5** has been evaluated for Pd-catalyzed methoxycarbonylation of 1-octene and the results obtained are summarized in Table 4. Results obtained with **BCOPE** have been included for comparison.

Methoxycarbonylation activity follows the order **L1** > **L2** − **L5** > **BCOPE**. In contrast to the excellent performance in Pd-catalyzed 1-hexene reductive hydroformylation (89% heptanol,

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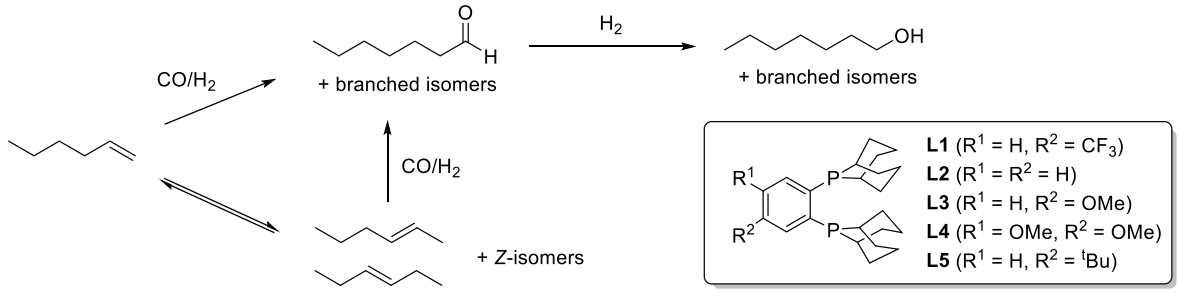
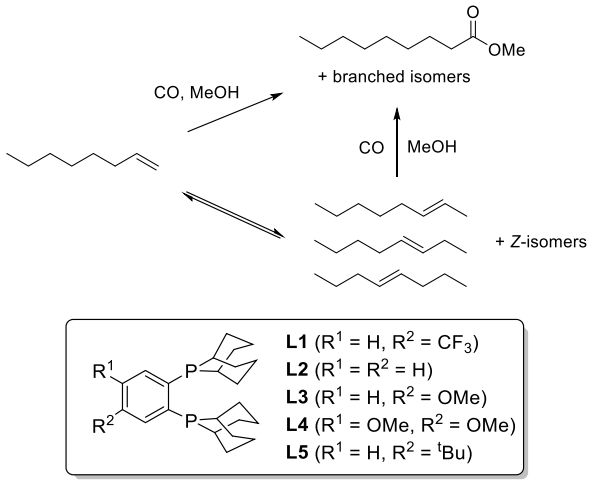
Table 3. Pd-Catalyzed Hydroformylation of 1-Hexene[a]



ligand	conv. %	internal hexenes[b] sel. %	heptanal[b] sel. % [lin. %]	heptanol[b] sel. % [lin. %]	chemosel.[c] al/ol	TON[d]
L1	98	55	38 [77]	5 [82]	88/12	850
L2	100	40	42 [75]	16 [78]	72/28	1150
L3	100	34	45 [75]	19 [79]	70/30	1200
L4	100	38	19 [69]	41 [76]	32/68	1300
L5	100	38	40 [72]	20 [77]	67/33	1200
L6	100	65	34 [69]	1 [71]	97/3	700
BCOPE	100	5	4 [81]	89 [78]	4/96	1850
BCOPE[e]	95	45	3 [84]	52 [68]	5/95	1050

[a]Conditions: 1-Hexene (161 mmol), $Pd(OAc)_2$ (0.05 mol %), Ligand (L/Pd = 1.4), CH_3SO_3H (Acid/Pd = 40), aqueous NaCl solution (NaCl/Pd = 0.4, 1 mL), 60 bar CO/H_2 (1:2), diglyme (60 mL), and 100 °C, 2 h. Yields were determined via gas chromatography using anisole as internal standard. [b]sel.: selectivity = product/all products; lin.: linearity = linear/linear+branched products. [c]chemosel.: chemoselectivity = ratio hydroformylation/reductive hydroformylation = heptanal/heptanol. [d]TON (turnover number) = moles of heptanal and heptanol/moles of catalyst. Note: trace amounts of C_{13} ketones and heptanoic acids were detected in all runs. [e]No NaCl added.

Table 4. Pd-Catalyzed Methoxycarbonylation of 1-Octene[a]



ligand	conv. %	internal octenes sel. %	methyl nonanoate[b] sel. % [lin. %]	TON[c]
L1	98	42	56 [73]	1150
L2	98	82	16 [74]	300
L3	99	87	12 [76]	250
L4	99	84	15 [77]	300
L5	99	84	15 [76]	300
BCOPE	100	96	3 [77]	50
L2[d]	99	62	35 [75]	700
L2[e]	99	35	55 [73]	1100

[a]Conditions: 1-Octene (80.6 mmol), $Pd(OAc)_2$ (0.05 mol%), Ligand (L/Pd = 1.4), CH_3SO_3H (Acid/Pd = 40), 50 bar CO, MeOH (20 mL), 100 °C, 2 h. Yields were determined via gas chromatography using anisole as an internal standard. [b]selectivity = product/all products. lin.: linearity = linear/linear+branched products. [c]TON (turnover number) = moles of methyl nonanoate/moles of catalyst. [d]With addition of aqueous NaCl solution (NaCl/Pd = 0.4, 1 mL). [e]With addition of water (1 mL).

Table 3), **BCOPE** demonstrates poor methoxycarbonylation activity. Olefin isomerization appears to be facile in all cases, with the majority of the starting substrate 1-octene isomerizing to a thermodynamic distribution of internal olefins with a 1:49 ratio of 1-octene:internal octenes.[59] As previously observed in Table 2, **L1** possessing the electron-withdrawing CF_3 substituent exhibits the greatest activity of the diphobane ligand series for Pd-catalyzed olefin alkoxycarbonylation (56% methyl nonanoate).

We also investigated briefly the effect of the addition of aqueous NaCl on the methoxycarbonylation performance of **L2**. As can be seen in Table 4, the addition of aqueous NaCl does lead to fewer internal olefins and an improved yield of methyl nonanoate from 12% to 35%. However, even better results were obtained when only water was added, although the mole balance was incomplete in this case, possibly due to some additional hydroxycarbonylation or hydrogenation activity. Catalytic improvement in methoxycarbonylation reactions upon addition of small amounts of water has been reported previously.[60]

HYDROFORMYLATION OF METHYL PENTENOATE

Reductive hydroformylation of the functionalized alkene methyl 4-pentenoate was investigated next. These studies follow on from previous work by some of us on the Pd-catalyzed hydroxycarbonylation of methyl pentenoic acid mixtures to bioadipic acid.[61] Similar reaction conditions were employed here, using diglyme as the solvent and methane sulfonic acid (MSA) or trifluoroacetic acid (TFA) as the cocatalyst. **L2** and **BCOPE** have been compared using both methyl 4-pentenoate (M4P) and methyl 2-pentenoate (M2P) as the substrate, and the results are summarized in Table 5.

Initial attempts with M4P and excess methanesulfonic acid (MSA/Pd = 40, Table 5) gave near-quantitative conversions with both **BCOPE** and **L2**. When **BCOPE** was employed, 54% of the undesired hydrogenated olefin product (methyl

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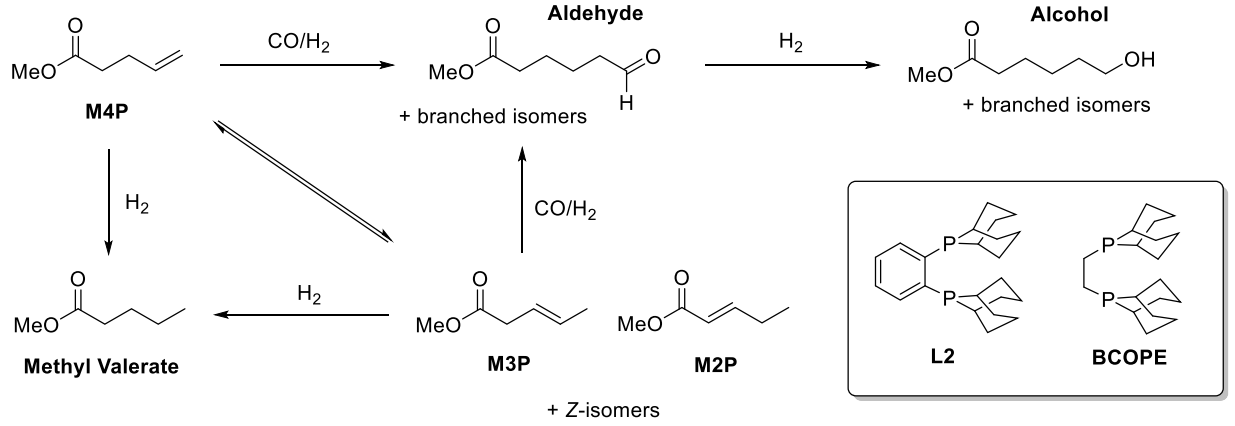
Table 5. Pd-Catalyzed Hydroformylation of Methyl Pentenoate[a]



substrate	ligand	acid (w.r.t. Pd)	conv. %	M2P %	M3P %	M4P %	methyl valerate[b] sel. %	aldehyde[b] sel. % [lin. %]	alcohol[b,c] sel. % [lin. %]	TON[d]
M4P	**BCOPE**	MSA (40 equiv)	100[e]	0	0	0	54	0	32 [71]	650
M4P	**L2**	MSA (40 equiv)	99[f]	4	3	<1	5	3 [79]	75 [74]	1450
M4P	**BCOPE**	MSA (4 equiv)	99	9	3	1	11	8 [76]	68 [63]	1550
M4P	**L2**	MSA (4 equiv)	92	1	16	8	<1	70 [79]	4 [80]	1500
M4P	**BCOPE**	TFA (40 equiv)	99	18	30	1	1	47 [79]	3 [72]	1000
M4P	**L2**	TFA (40 equiv)	60	1	10	40	<1	47 [82]	1 [76]	950
M2P	**BCOPE**	TFA (40 equiv)	48	52	12	1	10	23 [73]	2 [43]	500
M2P	**L2**	TFA (40 equiv)	5	95	2	<1	2	1	0	<10

[a]Conditions: Methyl pentenoate (40.3 mmol), $Pd(OAc)_2$ (0.05 mol %), Ligand (L/Pd = 1.4), 60 bar CO/H_2 (1:2), diglyme, 100 °C, 4 h. Yields were determined via gas chromatography using anisole as internal standard. [b]sel.: selectivity = product/all products; lin.: linearity = linear/branched product. [c]Inclusive of ε-caprolactone. [d]TON (turnover number) = moles of aldehyde and alcohol/moles of catalyst. [e]Suspected ketone or alcohol derivative side-products (14%). [f]Dimethyl adipate (7%) detected. w.r.t. = with respect to. MSA = methanesulfonic acid. TFA = trifluoroacetic acid.

valerate) was obtained together with only 32% of the desired alcohol. In contrast, the run employing **L2** gave significantly less methyl valerate (5%) and a much greater proportion of alcohol (75%). Decreasing the amount of MSA from 40 to 4 equiv with respect to Pd lowered olefin hydrogenation even further to 11% and <1% methyl valerate in the runs using **BCOPE** and **L2**, respectively. These results suggest that MSA plays an active role in the catalytic cycle to influence olefin hydrogenation, instead of simply acting as a spectator counterion. Beller and co-workers demonstrated previously that the identity and concentration of the acid cocatalyst can affect catalytic activity and linear selectivity in Pd-catalyzed olefin hydroformylation.[62] Drent and Budzelaar also demonstrated that varying the acid cocatalyst can affect product selectivity in Pd-catalyzed olefin hydroformylation reactions.[58] At MSA/[Pd] = 4, a remarkable difference in product selectivity is observed. **BCOPE** primarily favors reductive hydroformylation to alcohols (68% selectivity), but **L2** favors aldehyde (70% selectivity) instead. This is in line with our prior observations in the hydroformylation of 1-hexene (Table 3), where **BCOPE** favored reductive hydroformylation of 1-hexene to heptanol.

Changing from MSA (pK_a = −1.86) to the less acidic trifluoroacetic acid (TFA, pK_a = 0.23) as the acid cocatalyst (TFA/[Pd] = 40, Table 5), both **BCOPE** and **L2** yield similar amounts of aldehyde (47%) and minor amounts of methyl valerate or alcohol, although the conversion in the case of **L2** was significantly lower at 60% versus 99% for **BCOPE.** There appears to be a significant role played by the acid cocatalyst in the hydrogenation of both the starting olefin substrate and the in situ generated aldehyde intermediate. Furthermore, the isomerization ability of the two ligands appears to be different. **BCOPE** demonstrated facile isomerization of M4P to its internal isomers, leaving only 1% of the starting M4P in the final product mixture, whereas with **L2**, 40% of the starting M4P was found in the final product mixture. This difference in isomerization ability is also seen when the internal olefin M2P is used as the substrate. **BCOPE** gave 48% conversion in this case (23% aldehyde), whereas **L2** was essentially inactive, leaving most of the starting M2P (95%) unreacted. The poorer isomerizing ability of **L2** to convert M2P to the more reactive substrate M4P is likely responsible for this observed lack of reactivity.

Drent and co-workers noted previously that ligand steric bulk affects catalytic activity in the Pd-catalyzed hydroformylation of internal olefins.[10] Bulkier ligands give a more congested coordination sphere at the metal center, which is expected to hinder the formation of sterically demanding branched Pd-alkyl intermediates from the insertion of internal olefin substrates. We have determined ligand steric bulk by measuring the amount of space occupied by each ligand in a sphere of a given radius around the Pd center (i.e., the "ligand buried volume").[63,64] **BCOPE** shows a smaller ligand buried volume (36.3%) compared to **L2** (37.2%), which may explain its greater isomerization ability (see Supporting Information for details on ligand buried volume calculations).

The distribution of methyl pentenoate isomers in the product mixtures for **L2** (MSA/[Pd] = 4, Table 5) and **BCOPE** (TFA/[Pd] = 40, Table 5) favored M3P, although the conjugated ester M2P is the thermodynamically most stable product.[35] The Pd-alkyl precursors to M3P are likely to be stabilized by 5- or 6-membered chelates as shown in Figure 9, which would result in M3P as the kinetically preferred isomerization product. Such chelates have been proposed

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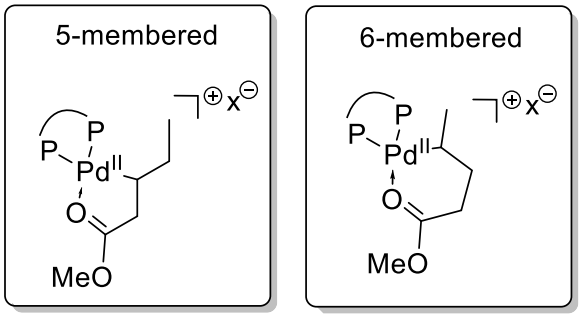

Figure 9. Five- and six-membered Pd-alkyl chelate.

previously in our study on Pd-catalyzed hydroxycarbonylation of pentenoic acids, where a similarly unexpected preference for isomerization to the 3-position was observed.[61]

SIDE PRODUCTS – MECHANISTIC CONSIDERATIONS

The mechanism for Pd-catalyzed alkene carbonylation is assumed to proceed according to the catalytic cycle shown in Figure 10.[58] M4P coordinates to a cationic Pd-hydride complex before undergoing migratory insertion to give a Pd-alkyl intermediate. Subsequent coordination and migratory insertion of CO yields the key Pd-acyl intermediate from which several different products can be derived.

Hydrogenolysis with H_2 results in aldehydes (hydroformylation), whereas alcoholysis with MeOH yields esters (methoxycarbonylation). As a third alternative, a second methyl pentenoate molecule can coordinate and insert into the Pd-acyl species to give a secondary Pd-alkyl intermediate (hydroacylation). This Pd-alkyl intermediate can undergo hydrogenolysis with H_2 to give a saturated ketone or perform β-hydride elimination to yield an unsaturated ketone.[10,58] Indeed, aside from the aldehyde and alcohol products obtained with **BCOPE** (MSA/[Pd] = 40, Table 5), for example, smaller amounts of side products with higher molecular weight were observed by GC analysis. Further analysis by GC/MS indicated the formation of ketone side products, but their exact identity could not be established (see Supporting Information for details). Since M4P can insert in a 1,2- or 2,1-fashion, or isomerize to M2P/M3P prior to insertion, several structural isomeric ketones can be obtained (Figure 11). Formation of ketone side products in Pd-catalyzed hydroformylation has been observed previously using 1-pentene as the substrate.[65] Interestingly, the selectivity of aldehyde versus ketone products was affected by the nature of the acid cocatalyst. When trifluoroacetic acid was replaced with the more acidic trifluoromethanesulfonic acid as the cocatalyst, more ketone side products were observed, which was ascribed to the weakly coordinating ability of trifluoroacetate versus the noncoordinating triflate anion.

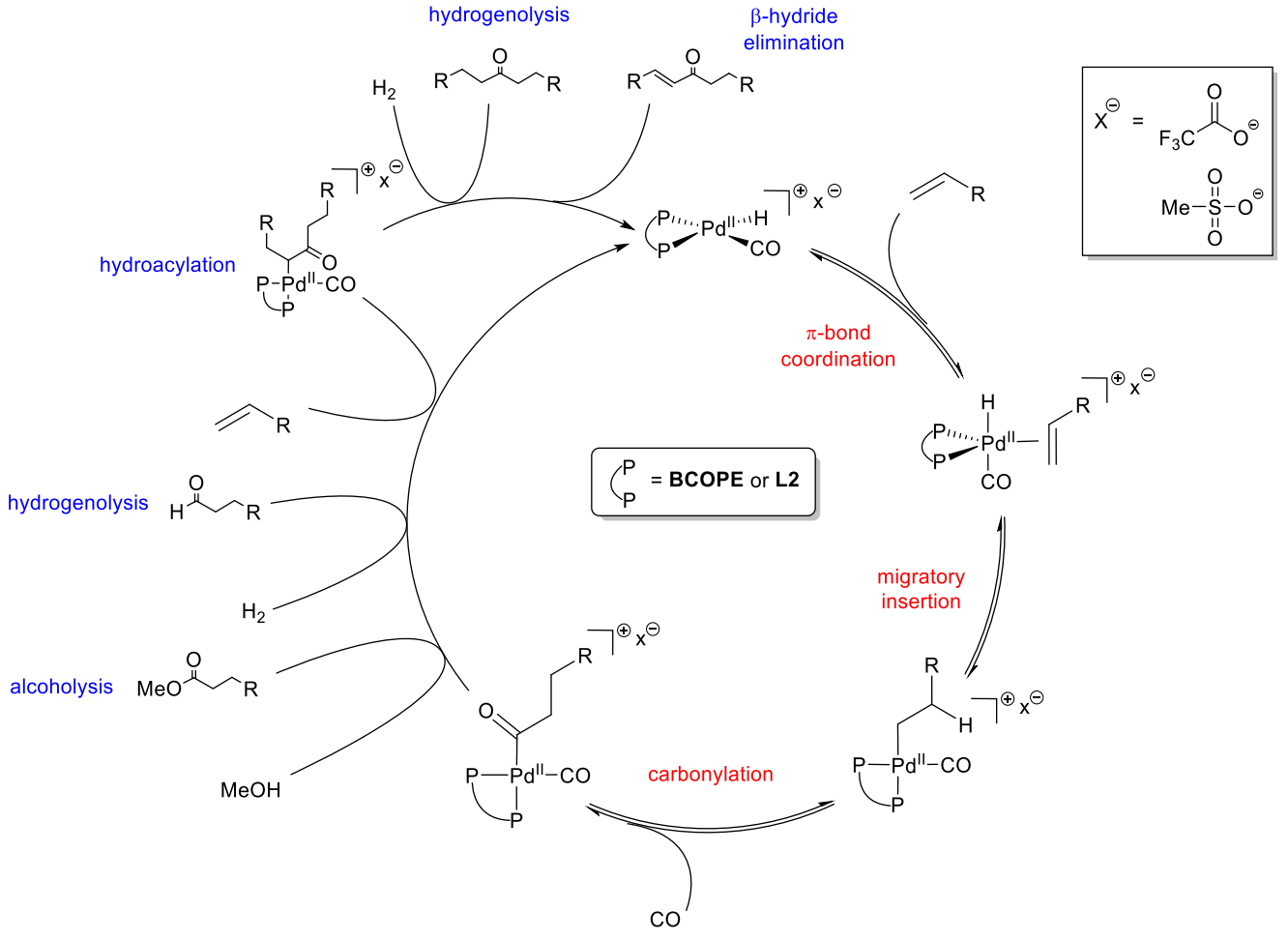

Figure 10. Competing mechanistic pathways in Pd-catalyzed alkene hydroformylation.

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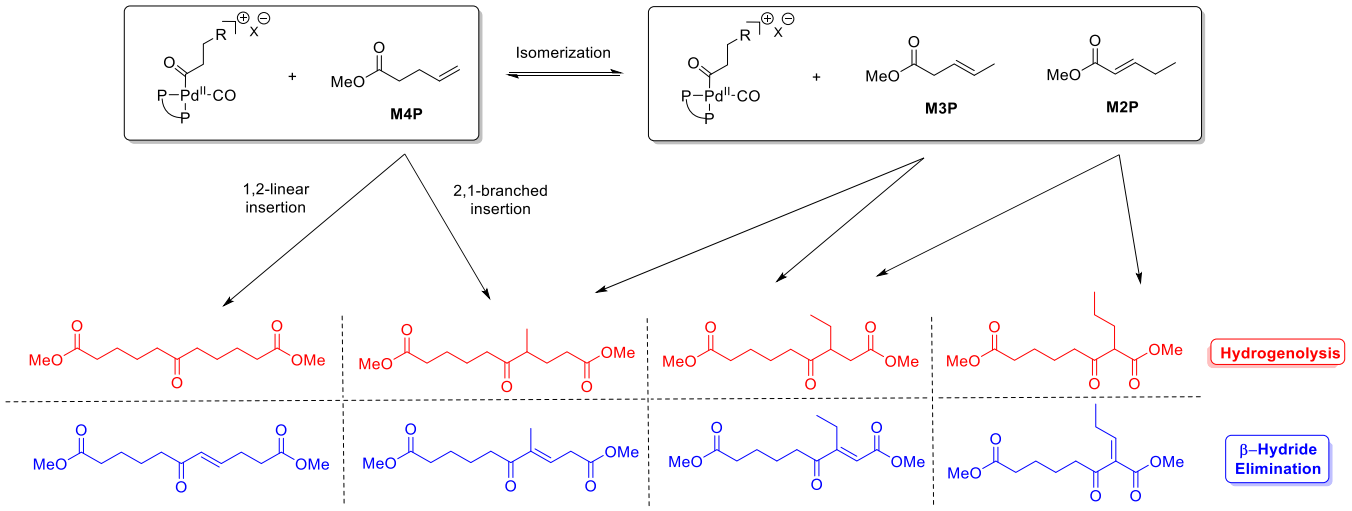

Figure 11. Possible ketone products derived from the linear Pd-acyl intermediate in Pd-catalyzed hydroformylation of methyl 4-pentenoate.

Other side products can arise from the alcohol products produced via reductive hydroformylation of methyl pentenoate. For example, methyl 6-hydroxyhexanoate could react further in four main pathways as shown in Figure 12: (a) as ROH in the alcoholysis of Pd-acyl intermediates, (b) in transesterification with methyl esters to release MeOH, (c) as ROH in hemiacetal formation to release H_2O, and (d) in intramolecular cyclization to form caprolactone.

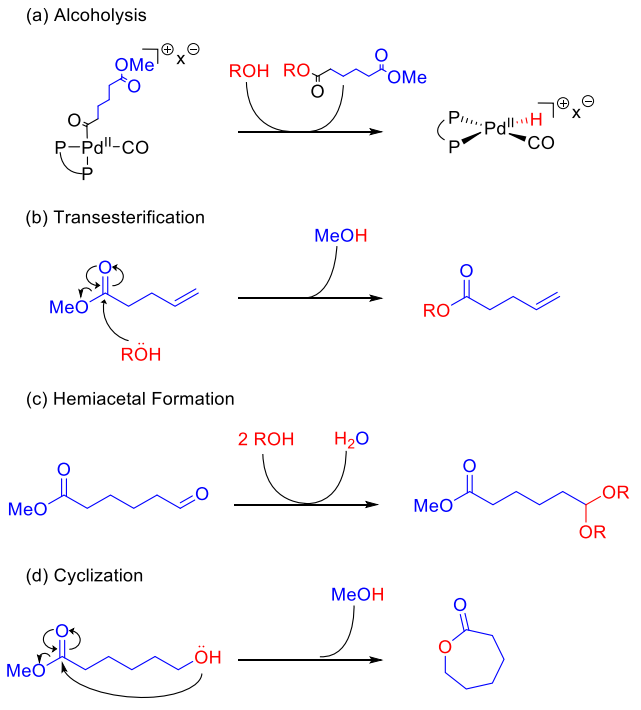

Figure 12. Possible alcohol-derived side reactions: (a) alcoholysis, (b) transesterification, (c) hemiacetal formation, and (d) cyclization.

Quantification of the desired alcohol product, methyl 6-hydroxyhexanoate, is therefore complicated by the various possible side reactions. In Figure 12 reaction (a), the alcohol product can engage in alcoholysis to give an ester. In reaction (b), the alcohol product can attack itself or other methyl esters present such as methyl 4-pentenoate to produce oligomeric esters. In reaction (d), the alcohol product can undergo an intramolecular ring-closing reaction to form caprolactone. MeOH and caprolactone were indeed observed by GC/MS analysis and are most likely formed from such transesterification and cyclization reactions. In order to revert these various derivatives of the alcohol product back to methyl 6-hydroxyhexanoate (and isomers), the product mixtures were refluxed in MeOH overnight before GC analysis. Some of the MeOH produced may also engage in methoxycarbonylation and 7% dimethyl adipate was indeed observed for **L2** (MSA/[Pd] = 4, Table 5). Drent and co-workers were able to circumvent this issue by using MeOH as a cosolvent in order to out-compete the alcohol product in side reactions (b) and (d).[12] This, however, may lead to methoxycarbonylation in addition to hydroformylation. It is clear from the study that these side reactions in Pd-catalyzed hydroformylation result in complications which make comprehensive analysis of the product mixture rather difficult. Further studies are underway to address these challenges.

CONCLUSIONS

A series of substituted aryl-bridged diphobane ligands **L1**–**L5** have been prepared. Crystallographic analyses of the palladium dichloride complexes have shown some differences in their coordination compared to the ethylene-bridged BCOPE ligand. The rigid bridge in [Pd(**L2**)Cl_2] enforces a constrained geometry that results in a smaller P–Pd–P ligand bite angle of 82° compared to 85° found in [Pd(**BCOPE**)Cl_2]. Perhaps more important than the change in bite angle is the change in symmetry, with [Pd(**BCOPE**)Cl_2] showing C_2 symmetry, whereas [Pd(**L2**)Cl_2] has C_s symmetry.

The ligands **L1**–**L5** have been applied in Pd-catalyzed hydroformylation of 1-octene in the presence of 2-ethyl hexanol solvent. The solvent is non-innocent, resulting in a competition between hydroformylation and alkoxycarbonylation. **BCOPE** directs product selectivity to nonanol (97% selectivity), whereas **L1**–**L5** give a mix of nonanal, nonanol, and nonanoate esters. Electron-withdrawing CF_3-substituted **L1** favored alkoxycarbonylation to esters (73% selectivity). The preference for alkoxycarbonylation by electrophilic Pd centers may be related to the deprotonation of a coordinated alcohol species to generate Pd-alkoxy complexes that can reductively eliminate ester products.

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The Pd-catalyzed hydroformylation of 1-hexene in diglyme gave an activity order of **BCOPE** > **L2**−**L5** > **L1**. **BCOPE** predominantly favored reductive hydroformylation to heptanol (89% selectivity), whereas **L1**−**L5** gave mixtures of heptanal and heptanol products, whereby the dimethoxy-substituted **L4** favored reductive hydroformylation activity to heptanol. Electron-donating groups give rise to more electron-rich Pd centers that can facilitate the nucleophilic attack of Pd-hydride on in situ generated aldehydes to yield alcohols. Similar linear selectivity (ca. 77%) across the series, despite the variety of substituents, suggests that regioselectivity is not significantly influenced by electronic effects, but is more likely a result of sterics.

For Pd-catalyzed methoxycarbonylation of 1-octene, the activity observed was in the order **L1** > **L2**−**L5** > **BCOPE**, which was the inverse of that observed for 1-octene hydroformylation.

Comparison of **BCOPE** and **L2** in Pd-catalyzed hydroformylation of the functionalized olefin 4-methyl pentenoate revealed that the nature and the amount of acid cocatalyst play a significant role in olefin and aldehyde hydrogenation activity. The use of **L2** resulted in a decrease in hydrogenation activity, yielding less hydrogenated byproduct (methyl valerate), and the main carbonylation product was the aldehyde (95%) when TFA was used. Increased olefin isomerization was observed for **BCOPE** compared to **L2**, which may be attributed to the less congested coordination sphere that allows for the formation of sterically demanding branched Pd-alkyl intermediates. As a result, **BCOPE** was found to be more active than **L2** in Pd-catalyzed hydroformylation of the internal olefin 2-methyl pentenoate (M2P).

These investigations indicate that remote ligand modifications such as the backbone variation investigated here can have significant implications on product selectivity. The application of such ligand modifications in the lesser established field of Pd-catalyzed hydroformylation can serve to provide insight and inform future efforts in the development of such catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00228.

Materials and methods, synthetic procedures, NMR spectra, computational details, XRD analysis (PDF)

Accession Codes

CCDC 2042303−2042304 and 2076315−2076316 contain 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.

■ AUTHOR INFORMATION

Corresponding Authors

George J. P. Britovsek − *Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, London W12 0BZ, United Kingdom;* orcid.org/0000-0001-9321-4814; Email: g.britovsek@imperial.ac.uk

Martin van Meurs − *Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research, Jurong Island, Singapore 627833;* orcid.org/0000-0002-8816-3458; Email: martin_meurs@ices.a-star.edu.sg

Authors

Dillon W. P. Tay − *Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research, Jurong Island, Singapore 627833*

James D. Nobbs − *Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research, Jurong Island, Singapore 627833;* orcid.org/0000-0002-4237-2772

Srinivasulu Aitipamula − *Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research, Jurong Island, Singapore 627833;* orcid.org/0000-0001-7640-9513

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.1c00228

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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