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A Study of the Heck Reaction in Non-Polar Hydrocarbon Solvents and in Supercritical Carbon Dioxide

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The effects of electronic and steric properties of phosphorus ligands on Heck reactions in supercritical CO_2 and non-polar hydrocarbon solvents were studied. In Heck reactions between iodobenzene and butyl acrylate, higher yields were obtained with less electron-rich phosphine ligands. This trend was also observed with the electron-poor triphenyl phosphite. A range of sterically demanding phosphites were then investigated. Biphenyl-containing phosphites **8** and **13** were found to be highly effective. In the Heck reaction between the less-reactive bromobenzene and butyl acrylate, the bulky, electron-rich tri*-tert*-butylphosphine ligand produced the best yield. These results emphasize the importance of both electronic and steric properties of phosphorus ligands in the Heck reaction in non-polar solvents.

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Introduction

Organic solvents constitute the major proportion of the chemicals required in chemical processes, particularly in the production of fine chemicals and pharmaceuticals.^[1] These solvents are toxic, flammable, environmentally damaging, and difficult to recycle.^[2] To address this issue, research has been pursued in two directions: the development of solvent-free processes,^[3,4] and replacement of hazardous solvents with environmentally benign alternatives, such as water, ionic liquids, and supercritical carbon dioxide (scCO₂).^[2,5,6] Solvent replacement is the preferred option because of the important role solvents play, e.g., improving mass and heat transfer during reaction and dissolving unwanted substances in purification stages.

Supercritical carbon dioxide is defined as the state of CO₂ above its critical pressure (P_c 7.38 MPa) and temperature (T_c 31.1°C).^[7] The non-toxic and non-flammable characteristics of scCO₂ along with its ready availability and inexpensive price make it a strong alternative to conventional organic solvents. Like a liquid, scCO₂ displays substantial dissolution power that can be manipulated for specific requirements, for example, extraction or chromatography.^[8] Like a gas, it has very low viscosity and high diffusivity, which enable effective mass and heat transfer.^[8,9]

The palladium-mediated alkenylation reaction has received much attention since its discovery by Heck in the late 1960s.^[10] As one of the most convenient methods to prepare substituted olefins, the Heck reaction has been extensively studied in industry as well as in academia.^[11–14] More efficient reaction conditions are continually being developed. These have been

accompanied by ongoing research into the complicated reaction mechanism. $^{\left[12,15,16\right] }$

Most studies of the Heck reaction in scCO₂ have focused on adapting catalyst systems already established in polar organic solvents, for example, by modifying the structure of phosphine ligands and Pd precursors to increase their solubility in nonpolar scCO₂. It was demonstrated that the Heck reaction could be accomplished in scCO₂ by appending perfluoroalkyl or short poly(dimethylsiloxane) chains to the phosphine ligands.^[17–19] Alkylphosphines and phosphites that improve the solubility of Pd complexes in scCO₂ have also been reported to catalyze the Heck reaction.^[20,21] In addition to ligand modification, it was shown that the solubility of Pd–phosphine complexes could be enhanced by exploiting perfluoroalkyl-containing Pd precursors.^[22]

Although solubility of the Pd catalyst in $scCO_2$ is important, the electronic and steric properties of the ligand also have an impact on the Heck reaction and these have received less attention to date. In polar aprotic solvents the Pd catalyst can be stabilized by solvent molecules; however, in $scCO_2$ or nonpolar hydrocarbon solvents, the reaction is dependent on the ligand for stabilization and activation of the catalyst. This means the properties of the ligand required in Heck reactions in nonpolar solvents are different from those required in polar organic solvents.

Herein we describe studies into the impact of electronic properties of phosphine ligands on a Heck reaction carried out in non-polar hydrocarbon solvents and in $scCO_2$. These studies are then followed by an investigation into steric effects.



Fig. 1. Influence of the 4-substituent on χ_i values in selected triphenylphosphines.



Scheme 1. (a) 2.45 mmol 5, 2.94 mmol 6, 2.70 mmol Et₃N, 0.0245 mmol Pd(OAc)₂, 0.0490 mmol phosphine ligand, $scCO_2$ (~21 MPa) or heptane (in a sealed tube), 110°C, 16 h, 10 cm³ reaction vessel.

 Table 1. Summary of Heck reactions in the presence of phosphine ligands 1-4 (Scheme 1)

Entry	Solvent	Ligand	Yield (GC) ^A [%]
1	Heptane	_	16
2	Heptane	1	15
3	Heptane	2	35
4	Heptane	3	42
5	Heptane	4	54
6	scCO ₂	-	21
7	scCO ₂	1	44
8	scCO ₂	2	27
9	scCO ₂	3	34
10	scCO ₂	4	54

^AYields were calculated from the peak area of **7** on a GC chromatogram by comparing it with an internal standard (mesitylene).

Results and Discussion

To examine the contribution of the electronic properties of the phosphine ligands to the outcome of the Heck reaction in nonpolar solvents, triphenylphosphine **2**, and three derivatives **1**, **3**, and **4** were chosen as model ligands (Fig. 1).^[23] Phosphines **1**–**4** have comparable steric bulk about the phosphorus nuclei (cone angle 145°),^[24,25] but contain different substituents at the *para*-position to the phosphorus atom. The phosphorus atom of phosphine **4** has the lowest electron density based on the highest χ_i value of Ar–CF₃,^[24] whereas that of phosphine **1** has the highest electron density (Fig. 1).

The Heck coupling between iodobenzene and butyl acrylate in heptane and $scCO_2$ was selected as a suitable test reaction, and was examined in the presence of 1 mol-% Pd(OAc)₂ and 2 mol-% phosphine ligand (Scheme 1). The results of the test reactions, with and without ligand, are summarized in Table 1.

 Table 2. Results of the Heck reaction using (PhO)₃P, the bulky phosphites 8 and 9, bulky phosphines, and phosphoramidite 10 (Scheme 1)

Entry ^A	Solvent ^B	Ligand	Yield (GC) [%]
1	Heptane	(PhO) ₃ P	76
2	Heptane	8	82
3	Heptane	9	<1
4	Heptane	Cy ₃ P	7
5	Heptane	$(Bu^t)_3P$	36
6	Heptane	10	<1
7	scCO ₂	(PhO) ₃ P	50
8	scCO ₂	8	87
9	scCO ₂	9	9
10	scCO ₂	Cy ₃ P	45
11	scCO ₂	$(\mathrm{Bu}^t)_3\mathrm{P}$	72
14	scCO ₂	10	3

^AReaction conditions as in Scheme 1.

^BIn both scCO₂ and heptane the reaction mixture was initially homogeneous. After a short time a solid (presumably triethylamine hydrochloride) precipitated from the solution; at the end of the reaction in scCO₂ a separate liquid phase mixed with solid was observed. This was presumed to be butyl cinnamate and triethylamine hydrochloride.

Comparing the results obtained in heptane, it was observed that the yield increased as a function of the increasing electronwithdrawing power of the aromatic substituent. The CF₃substituted phosphine **4** exhibited the highest yield, while methoxy-substituted **1** afforded the lowest. A similar trend was observed in reactions performed in scCO₂ with the least electronrich phosphine **4**, which gave the highest yield. An exception was the most electron-rich ligand **1**, which gave a higher yield than the phosphine **3** in scCO₂. Although the mechanism is not identical, a similar observation was reported in a study of hydroformylation reactions carried out in scCO₂.^[26] The activity of Rh–ligand complexes increases as the electron density of the phosphorus nuclei of the phosphine ligands decreases.

We were interested in investigating if the trend observed in Table 1 was applicable to the electron-poor triphenyl phosphite ligand [(PhO)₃P], where χ_i of OPh = 9.7 and the cone angle = 128° ,^[24] which has been used in previous studies of the Heck reaction.^[21,27] In heptane, the use of (PhO)₃P gave a 76% yield, considerably higher than the 54% yield obtained with phosphine **4** (Table 2). The performance of (PhO)₃P in scCO₂ was comparable to that of the phosphine ligand **4**.

Attention was then directed to studying the steric properties of triaryl phosphites. Triphenyl phosphite has a relatively small steric bulk.^[24,28] It was decided to investigate the relationship between increasing structural bulk and reaction yields in a range of phosphites. Phosphite ligands $\mathbf{8}^{[28]}$ and $\mathbf{9}^{[29]}$ were synthesized (Fig. 2). Phosphite **8** is bulkier than (PhO)₃P but is less bulky than compound **9**, which has a cone angle of 175° .^[24]

The incorporation of the bulky, biphenyl-containing phosphite **8** significantly improved the yields of the Heck reaction both in $scCO_2$ and heptane (Table 2). This is believed to be a result of the combination of the steric bulk and electron-poor properties of the ligand. Interestingly, the bulkiest phosphite ligand **9** did not catalyze the reaction effectively. In this case, in heptane (and in toluene) there appeared to be no visible change in the appearance of the reaction solution, and the precipitation of black Pd particles was not observed. In $scCO_2$ only a very low yield was observed (9%). Presumably, Pd⁰ was excessively stabilized by the bulkiest phosphite **9** and thus did not participate



Fig. 2. Structures of sterically bulky phosphites 8, 9, and phosphoramidite 10.



Scheme 2. Reagents and conditions: (a) 1.68 mmol 2,4-di-*tert*-butylphenol, 1.68 mmol 11, 1.68 mmol BuⁿLi, THF, -78° C to room temp., 1 h; (b) 4.21 mmol hexan-1-ol, 4.21 mmol 11, 4.63 mmol BuⁿLi, Et₂O, -78° C to room temp., 1 h; (c) 2.53 mmol cyclohexanol, 2.53 mmol 11, 0.253 mmol 12-crown-4, 2.53 mmol BuⁿLi, THF, -78° C to room temp., 1 h; (d) 2.53 mmol 11, 2.53 mmol KO(Bu^t), 0.253 mmol 18-crown-6, THF, -78° C to room temp., 1 h.

 Table 3. Results of Heck reactions using structurally modified phosphites 12–15 (Scheme 1)

Entry ^A	Solvent	Ligand	Yield (GC) [%]
1	Heptane	12	<1
2	Heptane	13	90
3	Heptane	14	81
4	Heptane	15	68
5	scCO ₂	12	37
6	scCO ₂	13	70
7	scCO ₂	14	39
8	scCO ₂	15	17

^AReaction conditions as in Scheme 1.

in the catalytic cycle. An alternative explanation is the formation of an *ortho*-palladated triarylphosphite species; this is known to be stable up to 140°C in *N*,*N*-dimethylformamide (DMF).^[30]

The performance of the electron-poor, bulky phosphite ligand **8** in the Heck reaction was compared to that of the highly electron-rich bulky phosphines, Cy₃P (χ_i of Cy = 0.1 and cone angle = 170°) and (Bu^t)₃P (χ_i of Bu^t = 0 and cone angle = 182°).^[24] These phosphines did not exhibit good activity in heptane (entries 4 and 5 in Table 2). Only (Bu^t)₃P performed well in scCO₂, as was previously reported by Early et al.^[20] It is

 Table 4. Results of Heck reactions between bromobenzene and butyl acrylate in octane and scCO2

Br	+ >	(a)	OOBu	
	OBu			
16	6	7		
Entry ^A	Solvent	Ligand	Yield (GC) [%]	
1	Octane	_	8	
2	Octane	8	7	
3	Octane	13	28	
4	Octane	$(\mathbf{B}\mathbf{u}^t)_{3}\mathbf{P}$	80	
5	scCO ₂	_	2	
6	scCO ₂	13	12	
7	scCO ₂	$(\mathrm{Bu}^t)_3\mathrm{P}$	24	

^AReagents and conditions: 2.45 mmol **16**, 2.94 mmol **6**, 2.70 mmol Et₃N, 0.0245 mmol Pd(OAc)₂, 0.0490 mmol phosphine or phosphite ligand, octane (in a sealed tube) or scCO₂ (\sim 21 MPa), 130°C, 16 h, 10 cm³ vessel.

interesting that highly electron-rich phosphines, which include the arylphosphine 1 (entry 7 in Table 1), showed better yields in $scCO_2$ than in heptane. A more detailed study is needed to elucidate this phenomenon. The performance of the phosphoramidite 10, a close analogue of which has been reported to be highly active in polar aprotic solvent conditions,^[28] was also compared with that of phosphite **8**. However, the phosphoramidite **10** showed poor performance in both solvents: heptane and $scCO_2$.

The effect of modifying the phosphite **8** was then examined (Table 3). By incorporating an *ortho* Bu^t group into **8**, the more sterically congested phosphite **12** was prepared (Scheme 2). Alkyl–aryl mixed phosphites **13–15** were also synthesized. Evaluation reactions were then carried out under identical conditions to those in Scheme 1.

The Heck reaction using the phosphite ligand 12 showed a 37% yield in scCO₂, but the reaction did not proceed at all in heptane (or in toluene). The alkyl–aryl phosphite 13 showed good to high activities in both scCO₂ and in heptane and was found to be as active as the phosphite ligand 8. This result is useful because alkyl chains may be exploited in immobilizing phosphite ligands onto a solid support. As the steric bulk of the substituents increased from *n*-hexyl to cyclohexyl and again to *tert*-butyl, the yield of the Heck reaction decreased.

Having successfully developed ligands 8 and 13 for the Heck reaction between iodobenzene and butyl acrylate, we were then interested in applying the same catalyst system to reactions involving a less reactive substrate, such as bromobenzene. The Heck reaction between bromobenzene and butyl acrylate was examined in both octane and scCO₂ (Table 4). Reactions were carried out at 130°C with phosphites 8, 13, and (Bu^t)₃P. The higher boiling solvent octane was selected for these studies owing to the higher reaction temperatures required.

The phosphites 8 and 13 were not effective ligands for bromobenzene Heck couplings (Table 4). Although phosphite 13 performed better than 8, the yield observed was 28%. A synthetically useful yield (80%) was obtained with the bulky electron-rich (Bu¹)₃P. It is presumed that the higher yield using the solvent octane (Table 4, entry 4) compared with heptane (Table 2, entry 5) is a consequence of the higher reaction temperature employed. Phosphite 13 and (Bu¹)₃P were then examined under the same conditions in scCO₂ and gave yields of 12 and 24%, respectively. It is believed that, in scCO₂, the catalytic species was insufficiently soluble owing to the lower density of CO₂ at the higher operating temperatures. It is noted that the higher temperature used here does not alter the phase behaviour.

Conclusions

In the Heck reaction between iodobenzene and butyl acrylate in scCO₂ and in heptane, less electron-rich phosphines resulted in higher yields. This general result was then extended further to the electron-poor ligand, (PhO)₃P. The impact of steric bulk of phosphite ligands was then investigated. Biphenyl-containing phosphite ligands **8** and **13** resulted in high-yielding Heck reactions. In the Heck reaction between the less-reactive bromobenzene and butyl acrylate, the bulky, highly electron-rich (Bu^t)₃P gave the best yield, whereas the bulky phosphites **8** and **13** were less effective. These results indicate the importance of both electronic and steric properties of the phosphorus ligand in Heck reactions in scCO₂ and non-polar hydrocarbon solvents.

Experimental

General

Caution! All high-pressure scCO₂ reactions should be carried out with adequate containment and with extreme caution.

¹H NMR spectra were recorded on a Bruker DPX-400 (400 MHz) or DRX-500 (500 MHz) spectrometer, using the

chemical shift of a residual protic solvent (CHCl₃ at δ 7.28 or dimethyl sulfoxide (DMSO) at δ 2.50) as an internal reference. All shifts are quoted in parts per million (ppm) relative to CHCl3 or DMSO and coupling constants J are measured in Hz. ¹³C NMR spectra were recorded on a Bruker DPX-400 (101 MHz) spectrometer using the central resonance of the triplet of CDCl₃ at δ 77.0 as an internal reference. ³¹P NMR (162 MHz) spectra were recorded on a Bruker DPX-400 spectrometer with a QNP probe using the chemical shift of H_3PO_4 at $\delta 0.0$ as an internal reference. Microanalyses were carried out by the Department of Chemistry (University of Cambridge, UK). Mass spectra were recorded by the EPSRC National Mass Spectrometry Service Centre (Swansea, UK). All chemical ionization (CI) measurements were performed with NH₃ as the carrier gas. In cases where reaction yields were estimated by gas chromatography, the sample was injected with a known amount of internal standard (mesitylene). From the peak areas of the sample and internal standard in the chromatogram, the yield was calculated using a calibration curve.

All scCO₂ reactions were carried out in a 10 cm^3 Hastelloy reaction vessel equipped with a thermocouple, pressure transducer, sapphire window, and bursting disc. CO₂ was passed through an Oxisorb catalyst to remove traces of oxygen and was delivered to the reaction vessel in a safety-glass cabinet, using a Pickel PM101 N₂-driven CO₂ pump.^[31]

Carbon dioxide (purity, 99.999% min.) was purchased from Messer. Heptane (HPLC grade, Aldrich), octane (anhydrous, Aldrich), and Pd(OAc)₂ (Strem) were used as received. Triphenylphosphine was used after recrystallization from EtOH. Triphenylphosphine derivatives $1,^{[32]},^{[32]}$ and $4^{[33]}$ were prepared according to the literature procedures and recrystallized from EtOH. Tris(2-*tert*-butylphenyl) phosphite **9** was prepared according to the literature procedure,^[29] and recrystallized from hexane.

Representative Procedure for the Heck Reaction in scCO₂

To a $scCO_2$ reaction vessel were added $Pd(OAc)_2$ (0.0055 g, 0.0245 mmol), a phosphine or phosphite ligand (0.0490 mmol), iodobenzene (0.500 g, 2.45 mmol), butyl acrylate (0.377 g, 2.94 mmol), and Et₃N (0.273 g, 2.70 mmol). After purging with N₂, the reactor was sealed and filled to approximately half the volume of the vessel with liquid CO₂. The reaction mixture was magnetically stirred and heated to 110°C. At this temperature the internal pressure was around 21 MPa. After 16 h the mixture was allowed to cool to ambient temperature and the CO2 vapour was released by bubbling into a bottle that contained CH₂Cl₂ $(40 \,\mathrm{cm}^3)$. The reactor was then rinsed with another portion of CH_2Cl_2 (20 cm³) and the wash solution was combined with the vented solution. After mixing with a known amount of mesitylene (~ 0.058 g), an aliquot (0.2 μ L) of the CH₂Cl₂ solution was injected into the gas chromatograph. The yield was calculated using a calibration curve. The chemical identity of butyl cinnamate 7, isolated by preparative TLC, was confirmed by IR spectroscopy through comparison with the authentic material, $R_{\rm F}$ 0.35 (1/5, EtOAc/hexane). ν_{max} (film)/cm⁻¹ 3058, 3027, 2958, 2870, 1709, 1637, 1454, 1309, 1274, 1166, 980, 766, 709, 684.

3,3',5,5'-Tetra(tert-butyl)-2,2'-bisphenol Phosphorochloridite **11**

To a magnetically stirred solution of 3,3',5,5'-tetra(*tert*-butyl)-2,2'-bisphenol^[34] (10.2 g, 24.8 mmol) and PCl₃ (6.82 g,

49.7 mmol) in toluene (150 cm³) was added a catalytic amount of 4-dimethylaminopyridine (0.152 g, 1.24 mmol) at ambient temperature under a N2 atmosphere. After the solution was heated to reflux, N₂ was bubbled into the solution to expel the HCl gas generated from the reaction. After 2 h, the mixture was cooled to ambient temperature while maintaining the N₂ bubbling and then concentrated under reduced pressure. The resulting yellow coloured solid was purified by recrystallization from 1,2-dichloroethane/MeCN (1/2, 105 cm³) to give the phosphorochloridite 11 as colourless crystals (10.1 g, 86%), mp 184–186°C (lit.^[35] 183–186°C). ν_{max} (solid)/cm⁻¹ 2958, 2905, 2870, 1468, 1436, 1397, 1363, 1295, 1223, 1203, 1168, 1117, 1084, 1019, 978, 929, 877, 854, 781, 704. δ_H (400 MHz, CDCl₃) 7.50 (2H, d, J 2.5, ArH), 7.21 (2H, d, J 2.5, ArH), 1.51 (18H, s, C(CH₃)₃), 1.39 (18H, s, C(CH₃)₃). δ_C (101 MHz, CDCl₃) 147.6, 145.5 (d, J_{CP} 6), 140.4, 132.6 (d, J_{CP} 4), 126.7, 124.9, 35.5, 34.7, 31.5, 30.9. δ_P (162 MHz, CDCl₃) 172.2. The δ_H and δ_P data are in agreement with literature values.[36]

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl 4-(tert-Butyl)phenyl Phosphite **8**

To a magnetically stirred solution of **11** (2.00 g, 4.21 mmol) in Et₂O (20 cm³) was added a solution of 4-tert-butylphenol (0.664 g, 4.42 mmol) and Et₃N (0.490 g, 4.84 mmol) in Et₂O (20 cm^3) dropwise at ambient temperature under a N₂ atmosphere. The solution was then stirred for 1 h at ambient temperature and concentrated under reduced pressure. The crude product containing Et₃N·HCl was purified by flash column chromatography (1/20, EtOAc/hexane), where the adsorbent (silica gel) was first treated by flushing successively with Et₂O and petroleum spirits (40– 60° C). The resulting viscous liquid crystallized from MeCN to give phosphite 8 as colourless crystals (1.82 g, 73%), mp 168–169°C. $R_{\rm F}$ 0.74 (1/10, EtOAc/hexane). (Found: C 77.55, H 9.2. C₃₈H₅₃O₃P requires C 77.5, H 9.1%.) $\nu_{\rm max}$ (solid)/cm⁻¹ 2960, 2906, 2869, 1502, 1462, 1435, 1396, 1361, 1231, 1201, 1166, 1122, 1088, 870, 844, 782, 756, 705. δ_H (500 MHz, CDCl₃) 7.48 (2H, d, J 2.5, ArH), 7.31 (2H, d, J 8.5, ArH), 7.22 (2H, d, J 2.5, ArH), 7.02 (2H, d, J 8.5, ArH), 1.54 (18H, s, C(CH₃)₃), 1.39 (18H, s, C(CH₃)₃), 1.32 (9H, s, C(CH₃)₃). δ_{C} (101 MHz, CDCl₃) 150.2 (d, J_{CP} 7), 146.9 (d, *J*_{CP} 2.5), 145.7 (d, *J*_{CP} 6), 140.4 (d, *J*_{CP} 1.5), 133.1 (d, *J*_{CP} 3.5), 126.9, 126.7, 124.6, 120.1 (d, J_{CP} 8), 35.7, 34.9, 34.6, 31.8, 31.7, 31.6, 31.5. δ_P (162 MHz, CDCl₃) 139.7. m/z (ES⁺) 589.3805 $[(M + H)^+, C_{38}H_{54}O_3P$ requires 589.3805], 589 [CI, $(M + H)^+$, 100%], 471 (18), 456 (29), 441 (50), 428 (26), 412 (13), 135 (23).

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl N,N-Diisopropylphosphoramidite **10**

To a magnetically stirred solution of diisopropylamine (0.234, 2.31 mmol) in tetrahydrofuran (THF, 5 cm³) was added BuⁿLi (1.6 M solution in hexane, 1.64 cm³, 2.63 mmol) at ambient temperature under a N₂ atmosphere. The solution was stirred for 10 min and cooled to -78° C. A solution of **11** (1.00 g, 2.10 mmol) in THF (10 cm³) was subsequently added and the resulting mixture was allowed to warm to ambient temperature. After the solution was stirred overnight, it was concentrated under reduced pressure. The crude product was purified by flash column chromatography [petroleum spirits (40–60°C)] and crystallized from CH₂Cl₂/MeCN to give the phosphoramidite **10** as colourless crystals (0.224 g, 20%), mp 184–185°C. R_F 0.23 [petroleum spirits (40–60°C)] (Found: C 75.7, H 10.1, N 2.6. C₃₄H₅₄NO₂P requires C 75.65, H 10.1, N 2.6%). ν_{max}

(solid)/cm⁻¹ 2958, 2870, 1459, 1436, 1396, 1361, 1279, 1231, 1197, 1168, 1118, 1091, 1020, 971, 857, 842, 774, 761, 687. $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.42 (2H, d, *J* 2.5, ArH), 7.16 (2H, d, *J* 2.5, ArH), 3.45–3.36 (2H, m, NCH), 1.52 (18H, s, C(CH₃)₃), 1.37 (18H, s, C(CH₃)₃), 1.2–0.7 (12H, br s, NCH(CH₃)₂). $\delta_{\rm C}$ (101 MHz, CDCl₃) 148.0 (d, *J*_{CP} 6.5), 145.2, 139.7, 132.4 (d, *J*_{CP} 3), 126.3, 123.8, 47.3–43.9 (br s), 35.3, 34.5, 31.5, 31.4, 27.6–25.3 (br s), 23.6–21.2 (br s). $\delta_{\rm P}$ (162 MHz, CDCl₃) 154.2. *m/z* (ES⁺) 540.3962 [(M + H)⁺, C₃₄H₅₅NO₂P requires 540.3965], 539 (EI, M⁺, 12%), 524 (12), 496 (16), 482 (10), 439 (36), 377 (8), 132 (13).

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl 2,4-Di(tert-butyl)phenyl Phosphite **12**

The crude product was purified by flash column chromatography [petroleum spirits (40-60°C)] and crystallized from THF/MeCN to give the phosphite 12 as colourless crystals (0.455 g, 42%), mp 202–205°C. R_F 0.33 [petroleum spirits (40–60°C)] (Found: C 77.9, H 9.6. C₄₂H₆₁O₃P requires C 78.2, H 9.5%). v_{max} (solid)/cm⁻¹ 2958, 2906, 2869, 1464, 1396, 1361, 1198, 1169, 1122, 1086, 913, 851, 783, 693. δ_H (500 MHz, CDCl₃) 7.44 (2H, d, J 2.5, ArH), 7.33 (1H, d, J 2.5, ArH), 7.25 (2H, d, J 2.5, ArH), 7.07 (1H, dd, J 2.5 and 8.5, ArH), 7.02 (1H, dd, J 2.5 and 8.5, ArH), 1.42 (18H, s, C(CH₃)₃), 1.39 (18H, s, C(CH₃)₃), 1.31 (9H, s, C(CH₃)₃), 1.24 (9H, s, C(CH₃)₃). δ_C (101 MHz, CDCl₃) 148.9 (d, *J*_{CP} 6), 146.5, 146.0 (d, *J*_{CP} 6), 145.1, 140.1 (d, *J*_{CP} 1.5), 138.9, 132.8 (d, J_{CP} 4), 126.5, 124.2, 123.1, 119.3, 119.1, 35.4, 34.8, 34.7, 34.4, 31.5, 31.1, 31.0, 30.0. δ_P (162 MHz, CDCl₃) 142.6. m/z (ES⁺) 645.4432 [(M+H)⁺, C₄₂H₆₂O₃P requires 645.4431], 646 [CI, (M+H)⁺, 100%], 457 (31), 441 (91), 429 (32), 413 (31), 226 (19), 206 (48), 191 (67).

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl Hexyl Phosphite **13**

The crude product was purified by flash column chromatography [petroleum spirits (40-60°C)] in which the adsorbent (silica gel) was first treated by flushing with Et₂O. The purified product crystallized from CH₂Cl₂/MeCN to give the phosphite 13 as colourless crystals (1.05 g, 46%), mp 121-123°C. $R_{\rm F}$ 0.25 [petroleum spirits (40–60°C)] (Found: C 75.4, H 9.9. C₃₄H₅₃O₃P requires C 75.5, H 9.9%). v_{max} (solid)/cm⁻¹ 2954, 2868, 1469, 1437, 1394, 1361, 1229, 1201, 1123, 1090, 992, 864, 848, 781, 765, 694. δ_H (400 MHz, CDCl₃) 7.45 (2H, d, J 2.5, ArH), 7.19 (2H, d, J 2.5, ArH), 3.79 (2H, q, J 7.0, OCH₂), 1.60-1.54 (2H, m, CH₂), 1.52 (18H, s, C(CH₃)₃), 1.38 (18H, s, C(CH₃)₃), 1.32–1.22 (6H, m, CH₂), 0.88 (3H, t, J7.0, CH₂CH₃). δ_C (101 MHz, CDCl₃) 146.3 (d, J_{CP} 6), 146.2, 139.8, 132.7 (d, J_{CP} 3.5), 126.5, 124.1, 65.0 (d, J_{CP} 4), 35.3, 34.6, 31.5, 31.4 (d, *J*_{CP} 5.5), 31.1 (d, *J*_{CP} 2.5), 30.9, 25.3, 22.5, 14.0. δ_P (162 MHz, CDCl₃) 137.9. m/z (ES⁺) 541.3804 [(M + H)⁺, C₃₄H₅₄O₃P requires 541.3805], 542 [ES, $(M + H)^+$, 46%], 524 (24), 502 (16), 475 (53), 457 (13), 314 (48), 292 (47), 273 (42), 268 (38), 251 (100), 208 (23), 167 (22).

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl Cyclohexyl Phosphite **14**

The crude product was purified by flash column chromatography [petroleum spirits (40–60°C)], where the adsorbent (silica gel) was first treated by flushing with Et₂O. The purified product crystallized from CH₂Cl₂/MeCN to give the phosphite **14** as colourless crystals (0.450 g, 33%), mp 182–183°C. R_F 0.74 (1/10, EtOAc/hexane) (Found: C 75.7, H 9.4. C₃₄H₅₁O₃P requires C 75.8, H 9.5%). ν_{max} (solid)/cm⁻¹ 2960, 2930, 2865, 1442, 1396, 1361, 1283, 1226, 1202, 1122, 1089, 955, 875, 839, 778, 759, 700. $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.43 (2H, d, *J* 2.5, ArH), 7.18 (2H, d, *J* 2.5, ArH), 4.29–4.20 (1H, m, OCH), 1.91–1.87 (2H, m, CH₂), 1.74–1.71 (2H, m, CH₂), 1.55–1.48 (21H, s, C(CH₃)₃ and CH₂), 1.37 (18H, s, C(CH₃)₃), 1.24–1.18 (3H, m, CH₂). $\delta_{\rm C}$ (101 MHz, CDCl₃) 146.1, 146.0 (d, *J* 6.5), 140.0 (d, *J*_{CP} 1.5), 132.8 (d, *J*_{CP} 4), 126.5, 124.0, 75.3 (d, *J*_{CP} 12), 35.3, 34.6, 34.5 (d, *J*_{CP} 4), 31.5, 31.2, 25.2, 24.2. $\delta_{\rm P}$ (162 MHz, CDCl₃) 145.9. *m/z* (ES⁺) 539.3649 [(M + H)⁺, C₃₄H₅₂O₃P requires 539.3649], 539 (EI, M⁺, 12%), 524 (12), 496 (16), 482 (10), 439 (36), 377 (8), 132 (13).

3,3',5,5'-Tetra(tert-butyl)-1,1'-biphenyl-2,2'-diyl tert-Butyl Phosphite **15**

The crude product was purified by flash column chromatography [petroleum spirits (40-60°C)], where the adsorbent (silica gel) was first treated by flushing with Et₂O. The purified product crystallized from CH2Cl2/MeCN to give the phosphite **15** as colourless crystals (0.224 g, 17%), mp 151–153°C. $R_{\rm F}$ 0.70 (1/10, EtOAc/hexane) (Found: C 74.9, H 9.7. C₃₂H₄₉O₃P requires C 75.0, H 9.6%). v_{max} (solid)/cm⁻¹ 2960, 2869, 1464, 1434, 1394, 1363, 1230, 1168, 1125, 1090, 951, 940, 874, 848, 819, 780, 694. δ_H (400 MHz, CDCl₃) 7.43 (2H, d, J 2.5, ArH), 7.17 (2H, d, J 2.5, ArH), 1.56 (9H, s, C(CH₃)₃), 1.52 (18H, s, C(CH₃)₃), 1.36 (18H, s, C(CH₃)₃). δ_C (101 MHz, CDCl₃) 145.9, 145.8, 140.0 (d, *J*_{CP} 1.5), 133.0 (d, *J*_{CP} 3.5), 126.5, 124.0, 79.1 (d, J_{CP} 10), 35.3, 34.6, 31.5, 31.2 (d, J_{CP} 3), 31.1. δ_P (162 MHz, CDCl₃) 147.1. *m/z* (ES⁺) 530.3750 [(M + NH₄)⁺, C₃₂H₅₃NO₃P requires 530.3758], 456 (EI, 20%), 441 (30), 423 (4), 385 (5), 367 (4).

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