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Synthesis and evaluation of phosphine–N ligands in transition metal-catalysed C–C bond forming reactions

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Abstract

A series of phosphino-imine and the corresponding phosphino-amine P,NR ligands (R = alkyl, aryl) was synthesised from the commercially available starting material 2-(diphenylphosphino)benzaldehyde, including P,N bi-, tri- and tetradentate imine ligands, their secondary amine analogues, and also the methylated tertiary amine equivalents. As an extension, some $P,NPPh_2$ and $P,NPCy_2$ derivatives were also prepared from the same starting material. All of these ligands were successfully applied in catalytic reactions (Heck, cross-coupling and hydroformylation), and benchmarked against traditional ligands with satisfying results. While providing catalyst systems that were stable and generally acceptably active in comparison with the benchmarks, the Pd–ligand catalyst systems of this study were found to be especially active in Stille reactions.

Keywords: Ligands; Catalysis; Palladium; Rhodium

1. Introduction

Much emphasis has been placed on the synthesis of bidentate P–P [1–4], N–N [5,6] Salen O–N–N–O-type [7,8] and bidentate imine ligands [9], which are used for catalytic transformations ranging from asymmetric transformations to epoxidation and hydrogenation reactions. The presence of different heteroatoms in a bidentate ligand (including P–S [10–12], P–O [13], P–N [14–17], S–C–S [18], P–C–P [19], S–N–S, N–S–N and P–N–N ligands [20]) often allows better control over stereoelectronic variables that influence the characteristics of the catalyst, as is amply evidenced by the second generation carbene–O bidentate ligand-containing Ru-based Grubbs-Hoveyda metathesis catalyst [21]. These mixed-donor multidentate ligands possess the ability to co-ordinate in more than one fashion to a metal centre, depending on the hardness or softness of the different heteroatoms. In the case of P,N ligands, the soft phosphorus atom co-ordinates strongly to soft metals, while the hard nitrogen atom is weakly co-ordinated and therefore more easily displaced, allowing hemi-lability [22,23].

Our focus was the synthesis of a wide range of different P,N derived ligands, with the view to expand the current knowledge base of catalysts employing such ligands. These compounds are the subject of continued interest and have previously been applied in selected catalysed transformations. For example, P,N (primarily phosphino-imines) ligands have found application in the alkynylstannylation of alkynes [24], formylation reactions [25], Stille and Suzuki reactions [26], oligomerisation of ethylene [27], arylation of alkynes [28], and in a few allylic amination reactions [29]. Accordingly, in order to provide scope within the series of P,N compounds, we prepared several new iminophosphine ligands, their corresponding aminophosphine analogues, and the *N*-alkylated derivatives thereof, from the commercially available starting material 2-(diphenylphosphino)benzaldehyde. A series of $P,NPPh_2$ and $P,NPCy_2$ PNP-type ligands, derived from some of our amine intermediates, was also synthesised *via* the same protocol. These various ligands were applied in different metal-catalysed reactions, including the Heck reaction, Suzuki- and Stille cross-coupling reactions, and the hydroformylation reaction, to evaluate their catalytic activities.

2. Results and discussion

2.1. Ligand synthesis

2-(Diphenylphosphino)benzaldehyde was condensed with alkyl and aryl amines by heating in toluene [26]. The iminophos-

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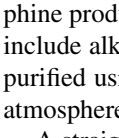
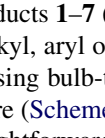
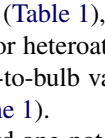
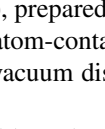
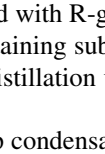
phine products **1–7** (Table 1), prepared with R-group variety to include alkyl, aryl or heteroatom-containing substituents, were purified using bulb-to-bulb vacuum distillation under an argon atmosphere (Scheme 1).

A straightforward one-pot two-step condensation–reduction procedure produced the corresponding aminophosphine analogues, affording the desired products directly from the aldehyde starting material. The first step was carried out in toluene as solvent, whereafter the toluene was removed *in vacuo*, and ether and $LiAlH_4$ were added, affording the anticipated amines **8–14** (Table 1) in good yields.

A series of the methylated analogues was prepared by deprotonation of amines **8–14** with *n*-butyllithium, followed by reaction with iodomethane, affording the products **15–21** (Table 1) in acceptable yields. X-ray single crystal structures were obtained for ligands **11** and **18** [30], which showed an isomorphous packing arrangement, implying that the methyl group does not play a significant role in the crystal packing of the product, presumably as a result of the crystal conformation of the two molecules being insensitive to the additional steric bulk of the methyl group. It is also evident that there is no hydrogen bonding between the N–H and the P-atom in the solid state for **11**.

The introduction of a second phosphorus atom into the backbone of our ligands was achieved by reaction of the secondary aminophosphine ligands **8–14** with Ph_2PCl or PCl_3 then 2CyMgCl (this latter combination may be used to prepare Cy_2PCl [31] *ex situ*) in the presence of a base such as triethylamine or *n*-butyllithium, affording the desired P,NPPh_2-type compounds **22–28** or P,NPCy_2-type ligands **29–33** (Table 1) in moderate to good yields after chromatography (Scheme 1). An X-ray single crystal structure determination of a complex of $PdCl_2$ and P,NP ligand **31** has previously unambiguously demonstrated that these types of ligands act as bidentate chelators [32].

Table 1
P,N ligands synthesised

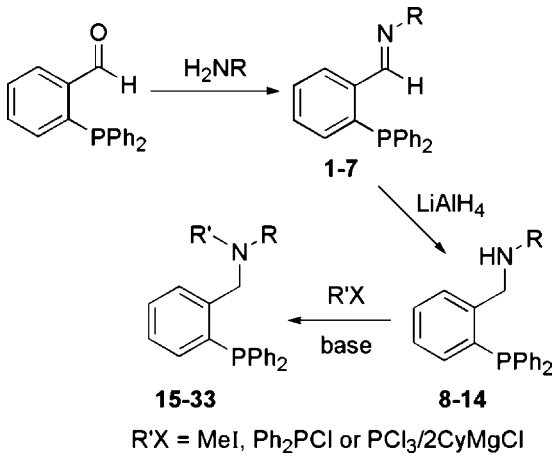
				
1 R = *n*-Bu, 96%	**8** R = *n*-Bu, 65%	**15** R = *n*-Bu, 61%	**22** R = *n*-Bu, 78%	**29** R = *n*-Bu, 55%
2 R = $(CH_2)_2$Ph, 95%	**9** R = $(CH_2)_2$Ph, 65%	**16** R = $(CH_2)_2$Ph, 62%	**23** R = $(CH_2)_2$Ph, 60%	**30** R = $(CH_2)_2$Ph, 60%
3 R = Bn, 94%	**10** R = Bn, 66%	**17** R = Bn, 63%	**24** R = Bn, 61%	**31** R = Bn, 59%
4 R = Ph, 96%	**11** R = Ph, 64%	**18** R = Ph, 59%	**25** R = Ph, 70%	**32** R = Ph, 42%
5 R = $(CH_2)_2$-2-pyridyl, 95%	**12** R = $(CH_2)_2$-2-pyridyl, 63%	**19** R = $(CH_2)_2$-2-pyridyl, 61%	**26** R = $(CH_2)_2$-2-pyridyl, 61%	–
6 R = $(CH_2)_3N(CH_3)_2$, 96%	**13** R = $(CH_2)_3N(CH_3)_2$, 67%	**20** R = $(CH_2)_3N(CH_3)_2$, 62%	**27** R = $(CH_2)_3N(CH_3)_2$, 70%	**33** R = $(CH_2)_3N(CH_3)_2$, 54%
7 R = 2-*N*-(piperazino)ethyl, 91%	**14** R = 2-*N*-(piperazino)ethyl, 59%	**21** R = 2-*N*-(piperazino)ethyl, 60%	**28** R = 2-*N*-(piperazino)ethyl, 36%	–

2.2. Catalysed reactions

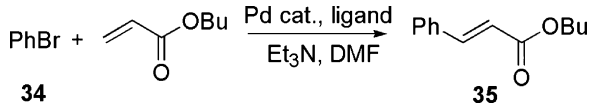
All of the synthesised ligands were applied in certain metal-catalysed C–C bond forming transformations in order to evaluate their suitability to act as ligands in these selected reactions. The transformations in question included the Heck reaction, a modified Heck-type reaction in the presence of carbon monoxide, Suzuki- and Stille coupling reactions. Rhodium-catalysed hydroformylation reactions were also investigated. The efficiency of our ligands was evaluated against the more common monodentate triphenylphosphine and bidentate 1,3-bis(diphenylphosphino)propane (dppp) ligands. The former was incorporated for comparison purposes as this ligand is most frequently used in industrial scenarios.

2.2.1. Heck reactions

The ease of oxidative addition of a C–X bond to palladium(0) follows the order: I > OTf > Br ≫ Cl [33]. We therefore used the less reactive bromobenzene together with butyl acrylate in the palladium-catalysed Heck [34] reaction to evaluate the efficacy of the newly synthesised P,N ligands (Scheme 2). The best results after a 32-h reaction time are summarised in Table 2 (isolated



Scheme 1. Ligand synthesis.



Scheme 2. Heck reaction.

yields of products when using ligands were not shown in the order of 10–65%).

Reactions that were carried out in the presence of 1 mol% palladium afforded acceptable conversions (Table 2). Entries 1–3 in the Table provide benchmark comparisons; several of our new P,N ligands provided much-improved reactions with higher yields. What is interesting to note is that the R-groups of the highest yielding ligands contain an additional nitrogen atom in the molecular structure, which possibly assisted to stabilise the palladium catalyst under the specific conditions employed, to afford a more active catalytic system (possibly *via* temporary weak chelation of that N atom to the Pd to form a 5- or 6-membered ring), which was also found to be the case for the N–PPh_2-functionalised materials. Conversely, the N-methylated or N–PCy_2-functionalised products faired poorly, seemingly as a function of the electron-rich nature of the N or P atoms in these ligands possibly causing a more stable chelation as shown in Fig. 1.

The Heck reaction (Scheme 3) between halo-arenes and acrylates generally proceeds smoothly to give high yields of products [35]. Here, we have found that the intermolecular coupling of aryl halides with acrylates in the presence of carbon monoxide

Table 2
Heck reaction of bromobenzene[a]

Entry	Ligand	Yield (%)
1	No ligand	3
2	2 PPh_3	36
3	dppp	53
4	**12**	80
5	**13**	79
6	**26**	77
7	**27**	85

Bold values are ligand or product numbers as they appear in the schemes.
[a] 1:1 Pd:L, DMF, 1% $Pd(OAc)_2$.

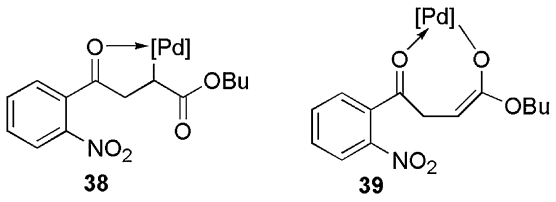
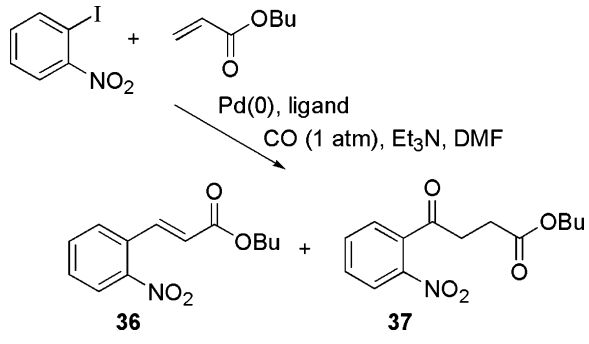


Fig. 1. Possible chelation modes of Pd.

(Scheme 3) is substantially less efficient. Both bromobenzene and *p*-bromobenzonitrile failed altogether to provide products in the presence of CO and precipitation of Pd black was a consistent observation.

When reverting to the more reactive *o*-nitroiodobenzene in the presence of 10 mol% catalyst, a mixture of two products formed in all instances: the Heck product **36** as well as a carbonylated product **37** were produced in differing ratios (Table 3), depending on the ligand employed. Generation of the saturated carbonylated product **37** was not anticipated but interesting, since the double bond was not conserved as is normally anticipated for Heck reactions [34]. The reason for the lack of β-hydride elimination in compound **37** is not fully understood, but it can be rationalised as follows: it is submitted that the intramolecular complexation of the newly introduced carbonyl functionality to the palladium formed a stable chelate intermediate **38** or **39**, which prevented β-hydride elimination. Such chelate structures are proposed in the polyketone (ethylene/CO co-polymerisation) reaction [36]. This intermediate was then subjected to protonation or reductive degradation to afford adduct **37**. The origin of the hydrogen atom in the product is unclear, although it might be derived from the HI (*via* $Et_3N{\cdot}HI$) which is generated in the standard Heck reaction.

Overall yields varied between 26% in the worst case scenario, to an excellent 82% in the best case. The ratio of **36**:**37** varied from 9:1 to 1:3, indicating a dependence on subtle ligand changes. Here, it appeared as if the *N*-alkyl or -alkylaryl functionalised imine and amine ligands favoured the formation of **36**, while the *N*-aryl substituted ligands **4** and **11** favoured the production of the CO-inserted product **37**, indicating a possible electronic effect that influenced the CO incorporation (the more electron-poor ligand facilitated CO incorporation). In all instances, the tertiary amine ligands **15**–**20** faired poorer than their secondary amine counterparts, supporting the idea that electronic considerations play a dominant role here.



Scheme 3. Heck–CO reaction.

Table 3
Pd-catalysed carbonylation in the Heck reaction of *o*-nitroiodobenzene and butyl acrylate: P,N ligands[a]

Phosphine ligand	Yield (%) **36**:**37**	Imine ligand	Yield (%) **36**:**37**	Secondary amine ligand	Yield (%) **36**:**37**	Tertiary amine ligand	Yield (%) **36**:**37**
PPh_3 (20%)	25:33	**1**	60:22	**8**	21:19	**15**	23:11
dppp (10%)	22:29	**2**	28:22	**9**	38:20	**16**	13:13
		3	37:12	**10**	36:19	**17**	16:11
		4	12:37	**11**	28:30	**18**	25:11
		5	34:20	**12**	34:21	**19**	36:11
		6	46:7	**13**	30:22	**20**	47:5

Bold values are ligand or product numbers as they appear in the schemes.
[a] 1:1 Pd:L, DMF, 10% $Pd(OAc)_2$, 1 atm CO.

Table 4
Pd-catalysed carbonylation *o*-nitroiodobenzene and butyl acrylate with PNP-ligands (32 h) in DMF under 1 atm CO

Entry	Ligand	TON/1.0% Pd[a] (Ratio **36**:**37**)	TON/0.1% Pd[b] (Ratio **36**:**37**)	TON/0.01% Pd[c] (Ratio **36**:**37**)
1	**22**	85:14	898:84	9 990 (trace **37**)
2	**23**	84:16	889:98	9 990 (trace **37**)
3	**24**	84:13	902:78	9 951 (trace **37**)
4	**25**	80:14	844:120	9 992 (trace **37**)
5	**26**	84:13	828:111	9 987 (trace **37**)
6	**27**	88:9	845:68	9 990 (trace **37**)
7	**28**	87:6	820:102	9 897 (trace **37**)
8	2 PPh_3	86:9	852:132	9 930 (trace **37**)
9	dppp	88:7	890:57	9 913 (trace **37**)
10	None	93:5	882:(trace **37**)	9 302 (trace **37**)

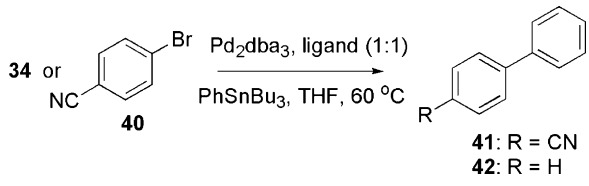
Bold values are ligand or product numbers as they appear in the schemes.
[a] %yield = TON.
[b] % yield = TON / 10.
[c] % yield = TON / 100.

The effect of catalyst concentration on the outcome of the reaction (yield and turnover number [TON]) was investigated using a selection of our P,N ligands at palladium concentrations of 1 mol%, 0.1 mol% and 0.01 mol%, respectively (Table 4).

With 1 mol% Pd catalyst, varying overall yields were obtained that were generally higher than those obtained in the previous case where 10 mol% of palladium was used (*cf.* Table 3). However, the overall insertion of carbon monoxide decreased, resulting in lower production of compound **37**. When using an even lower catalyst loading (0.1 mol% palladium, 0.032 mol substrate scale), yields of the Heck product **36** increased to around 85%, while the portion of the carbonylated compound **37** remained more or less constant. Excellent yields were obtained for the standard Heck reaction (product **36**), but in the cases where 0.01 mol% palladium was used (0.321 mol scale reactions) only traces of the CO-insertion compound were formed, together with essentially quantitative yield of the Heck product, which indicated that this particular reaction required higher palladium concentrations to afford CO-insertion. That there are very limited examples of successful intermolecular Heck-type carbonylation reactions reported in the literature further emphasises the difficulties involved with this type of work [37]. From the table it appears as if the *N*-phenyl ligand **25** and those containing the remote N atom (**26–28**) faired slightly worse than those containing only the *N*-alkyl groups, especially at the lower (0.1%) catalyst loading, again pointing to the possibility of a combination of electronic and co-ordination effects influencing the outcome. What is also clear from the table is that the rate of the reaction is not extremely sensitive to the type of ligand used. Presumably, this is because the iodonitro substrate is very active towards oxidative addition reactions [33], implying that ligand effects on this step of the reaction will be difficult to observe at all (possibly being observable only at extremely low catalyst loadings) and that even ligandless systems, such as that shown in entry 10, also proceed with this step quite smoothly. It is presumably because this set of reactions is operating mainly by the standard Heck pathway and only very slightly by the CO incorporation mechanism that ligand effects here are less pronounced than those noted with the reaction listed in Table 4. Future work in this area will include the use of higher CO pressures in these reactions, which was not investigated here. These ligands may well prove useful in tandem Pd-mediated reactions where one reaction is required to introduce a carbonyl moiety while the other is not.

2.2.2. *Cross-coupling reactions*

In the next set of test reactions, a series of our ligands was applied in the Stille [38] cross-coupling reaction



Scheme 4. Stille cross-coupling.

Table 5
Stille-coupling reaction of phenyltributyltin with bromobenzene[a]

Entry	Ligand	Yield (%)[b]
1	None	14
2	2 PPh_3	22
3	dppp	15
4	**1**	100 (92)[c]
5	**8**	100 (95)
6	**15**	100
7	**22**	100
8	**29**	100

Bold values are ligand or product numbers as they appear in the schemes.
[a] THF, 5% $Pd(OAc)_2$, 60 °C.
[b] Determined by GC analysis.
[c] Yields in parentheses are isolated yields of large-scale reactions.

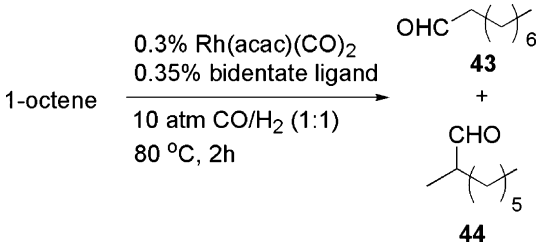
of phenyltributyltin and bromobenzene or *p*-bromobenzonitrile (Scheme 4, Table 5) in the presence of 5 mol% Pd(0) in THF at 60 °C for 24 h.

The reaction of *p*-bromobenzonitrile afforded a 33% yield in the absence of ligands, while with PPh_3 and dppp yields of 76% and 61% were obtained, respectively. Our ligands afforded acceptable yields of **41** in most instances, providing excellent yields for ligands **22** and **29** (83% and 92%, respectively). An exciting development was found when using the less reactive bromobenzene as the substrate. It was found that the absence of ligands allowed a conversion of only 14% to the biphenyl product **42**, a situation that was not improved upon by the addition of PPh_3 or dppp. However, use of our new P,N ligands allowed quantitative conversion to be obtained. This was surprising, since bromobenzene was expected to afford lower and slower conversion to product than the more reactive *p*-bromobenzonitrile.

For comparative purposes, catalysts using tri(2-furyl)phosphine as ligand afforded yields of 95% (2 mol% catalyst loading) with iodobenzene (more reactive than bromobenzene) and vinyltributyltin as substrates [39], while the more recent carbene-based ligands afforded 99% (3 mol% catalyst loading) with the activated *p*-bromoacetophenone and phenyltrimethyltin as substrates [40]. Shirakawa has also observed good activity for a single P,N ligand, but made use of aryl iodides and an activated aryl bromide [26a]. Our new P,N ligands afforded good to very good yields for the Stille cross-coupling reaction of *p*-bromobenzonitrile, and excellent, unprecedented yields for the reaction of the less reactive bromobenzene, in the absence of otherwise-used activators such as fluoride ion. This statement is true for the complete set of P,N ligands tested, irrespective of the oxidation state of the N atom (imine vs. amine), or its substitution patter (secondary amine vs. tertiary amine vs. PPh_2 vs. PCy_2). What apparently is required for a highly successful reaction here is a differentiated ligand in the form of a P,N (**1**, **8**, **15**) or a P,P (**22** or **29**, in which the two P atoms are different: compare dppp) bidentate[32] compound.

2.2.3. Hydroformylation

A selection of our bidentate [32] $P,NPPh_2$ and $P,NPCy_2$ ligands was evaluated in the rhodium-catalysed hydroformylation



Scheme 5. Hydroformylation reaction.

of 1-octene (Scheme 5); the use of heteronuclear bidentate ligands containing P–O, P–S, and P–N atoms has been reported for the hydroformylation reaction [41,42]. Especially mild conditions were selected to highlight ligand influences. Under these conditions the presence of a ligand is essential (*cf.* entry 1, Table 6) and it should be kept in mind that much-improved conversions and yields are readily attainable with more forcing (pressure and temperature) conditions.

The hydroformylation reaction was performed in toluene with 0.3 mol% of $Rh(acac)(CO)_2$ as catalyst and 0.35 mol% of the P,NP ligand. Reactors were pressurised to 10 atm with syngas (1:1 $CO:H_2$)and were placed into pre-heated oil baths at a temperature of 80 °C. The reactions were specifically terminated after only 2 h (time limitation to allow ligand effects to be detectable) and GC analysis was used to analyse reaction mixtures (Table 6, which again shows only the best results for our ligands).

Although a conversion of 60% and turnover frequency (TOF) of 109 was obtained for triphenylphosphine (entry 2), the bidentate ligand dppp did not afford much product at all. In contrast, our P,NP ligands faired much better than dppp in these reactions forming stable catalysts that produced yields of 50–60% (within the 2 h time limitation), linear:branched (*l*:*b*) ratios of about 2.5:1 to 3:1, and selectivities for aldehyde typically around 65–80%. Some reactions were performed at elevated temperature (100 °C) and at a higher ligand/Rh ratio (10:1) for added catalyst stability [43], giving similar *l*:*b* product results but at higher conversions and yields (of >90%) after 2 h, demonstrating the usefulness of these ligands (which provided stable active catalysts even at the low original ligand loading of 1:1) in high-conversion reactions. The more active catalysts were those derived from the P,P chelating ligands rather than from the P,N bidentate analogues. In general, the $N–PCy_2$ derivatives were more active

Table 6
Rh-catalysed hydroformylation of 1-octene[a]

Entry	Ligand	*l*:*b*	Conv (%)	TOF	Selectivity for aldehydes (%)
1	None	2.3:1.0	5	8	21
2	PPh_3	2.7:1.0	60	109	78
3	dppp	2.7:1.0	8	15	26
4	**23**	2.8:1.0	49	90	83
5	**29**	1.4:1.0	55	100	76
6	**31**	1.5:1.0	63	114	76

Bold values are ligand or product numbers as they appear in the schemes.
[a] 0.3 mol% Rh, 0.35 mol% ligand, 10 atm, 1:1 $CO:H_2$, toluene, 80 °C, 2 h.

than the N–PPh_2 analogues, and the N–Ph ligands again faired poorly, indicating a preference for the more electron-rich ligands (of which the N–PPh_2 and N–PCy_2 varieties are also examples [45]).

3. Conclusion

This work shows the facile synthesis of a series of P,N ligands, in which the oxidation state and degree of alkylation at the nitrogen atom have been varied together with the denticity of the ligands, from a common starting material. These ligands were successfully applied in selected catalytic transformations with palladium and rhodium, the results of which showed that our P,N bidentate ligands form stable active catalysts. The ligands gave results that were similar to, and generally better than, those of commercially available ligands, comparing in several instances with the best literature benchmark ligands. In many instances, a curious effect was observed in increasing TONs, TOFs and yields with decreasing catalyst concentration. In at least one type of reaction (Stille), our ligands provided unprecedented results with non-activated bromobenzene, and our ligands allowed the observation of a rare case of CO insertion in a Heck reaction.

4. Experimental

Iminophosphine ligands **1**–**7** were prepared according to reference [26]. Ligands **2** [26a], **3** [44], **4** [26b] and **5** [29] have been previously prepared. Phosphino-imine **1**: (169 mg, 95%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, 1H, J = 4.8 Hz), 7.97 (dd, 1H, J = 7.7 and 3.8 Hz), 7.47–7.21 (m, 12H), 6.85 (dd, 1H, J = 7.3 and 4.8 Hz), 3.46 (t, 2H, J = 6.7 Hz), 1.50–1.41 (m, 2H), 1.17–1.04 (m, 2H), 0.78 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 (d, J = 21.2 Hz), 139.3 (d, J = 17.1 Hz), 136.9 (d, J = 19.2 Hz), 136.2 (d, J = 9.6 Hz), 133.7 (d, J = 19.8 Hz), 132.9, 129.7, 128.6, 128.5, 128.3 (d, J = 7.2 Hz), 127.3, 61.0, 32.5, 20.0, 13.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ −12.81; IR ($CHCl_3$) 2970, 1640; EIMS m/z 345 (M^+, 86), 288 (100); HRMS Calculated for $C_{23}H_{24}NP$ 345.1646; found 345.1648. Ligands **6** and **7** were prepared in a similar fashion (see supporting information).

4.1. General procedure for the synthesis of aminophosphine ligands 8–14: phosphino-amine (8)

117 mg, 65%. The iminophosphine intermediate was prepared according to Ref. [26]. The toluene solvent was removed *in vacuo* and freshly distilled dry ether (5 mL) and $LiAlH_4$ (1.034 mmol, 2.5 equiv.) were added to the imine substrate **1** (crude product from a 0.517 mmol reaction as described above). Formation of the product at room temperature was followed *via* TLC analysis, and typically took about 8–12 h. The reaction was quenched by the addition of ice to the reaction mixture. The volatile component was removed *in vacuo*, followed by extraction with DCM and water. Flash chromatography (6:1 hexanes:EtOAc) afforded amine **8** as an oil. R_f 0.44 (6:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (ddd, 1H, J = 7.3, 4.5 and 1.2 Hz), 7.30–7.22 (m, 11H), 7.09 (td, 1H, J = 7.5 and 1.4 Hz), 6.88 (ddd, 1H, J = 7.6, 3.8 and 1.4 Hz), 3.97 (d, 2H, J = 1.5 Hz), 2.46 (t, 2H, J = 7.1 Hz), 1.58 (br s, 1H), 1.31–1.11 (m, 4H), 0.81 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (d, J = 23.6 Hz), 136.5 (d, J = 9.9 Hz), 135.4 (d, J = 13.7 Hz), 133.6 (d, J = 19.5 Hz), 133.3, 129.1 (d, J = 5.5 Hz), 128.7, 128.4, 128.3 (d, J = 6.8 Hz), 126.9, 52.4 (d, J = 20.5 Hz), 48.8, 31.9, 20.2, 13.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ −15.42; IR ($CHCl_3$) 2970, 1441; EIMS m/z 347 (M^+, 65), 275 (100); HRMS Calculated for $C_{23}H_{26}NP$ 347.1803; found 347.1803. Amines **9**–**14** were prepared using the same method (see supporting information).

4.2. General procedure for the synthesis of ligands 15–21: N-methyl-phosphino-amine (15)

63 mg, 61%. To the secondary aminophosphine ligand **8** (100 mg, 0.288 mmol) was added dry THF and the solution was cooled to −78 °C. *n*-Butyllithium (0.36 mL of a 0.9 M solution in hexanes, 1.1 equiv.) was added and the mixture was left to stir for 30 min. Methyl iodide (0.32 mmol, 1.1 equiv.) was added and the reaction progress was monitored with TLC analysis. The reaction was complete within 2 h, and was quenched using water, after which the THF was removed under reduced pressure. DCM and water were used to extract the product, which was purified using a short (5 cm) flash silica column (6:1 hexanes:EtOAc) yielding **15** as a light yellow oil. R_f 0.46 (6:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd with unresolved fine coupling, 1H, J = 6.9 and 3.9 Hz), 7.32–7.20 (m, 11H), 7.12 (td, 1H, J = 7.5 and 0.9 Hz), 6.86 (ddd, 1H, J = 7.4, 4.2 and 1.2 Hz), 3.67 (d, 2H, J = 1.5 Hz), 2.25 (t, 2H, J = 7.2 Hz), 2.02 (s, 3H), 1.22–1.13 (m, 4H), 0.81 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (d, J = 22.6 Hz), 137.5 (d, J = 10.8 Hz), 136.2 (d, J = 14.7 Hz), 133.7, 133.6 (d, J = 19.5 Hz), 128.9 (d, J = 5.4 Hz), 128.4, 128.2, 128.1 (d, J = 6.9 Hz), 126.7, 60.6 (d, J = 19.2 Hz), 56.9, 41.3, 29.0, 20.6, 14.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ −15.15; IR ($CHCl_3$) 3040, 2970, 1438; EIMS m/z 361 (M^+, 29), 275 (100); HRMS calculated for $C_{24}H_{28}NP$ 361.1959; found 361.1959. Ligands **16**–**21** were prepared using the same techniques (see supplementary information). In the case of the methylation of **13** to form **20**, double amounts of *n*-butyllithium and methyl iodide were employed to form the *N,N′*-dimethyl derivative.

4.3. General procedure for the synthesis of ligands 22–28

In general, two different strategies towards the formation of the desired ligands were used. In the one instance, triethyl amine was used as a base (Section 4.3.1, given here). In the other instance, sec-butyl lithium was used as a base (Method B, see supporting information).

4.3.1. Method A

4.3.1.1. General procedure for the synthesis of P,N-P ligands with triethyl amine as base: N-diphenylphosphino-phosphino-amine (22).

166 mg, 78%. To the secondary amine substrate **8** (140 mg, 0.40 mmol) dissolved in toluene (10 mL) was added an excess of triethyl amine (2.0 mmol, 5 equiv.) at 0 °C, and

1.2 equiv. of chlorodiphenylphosphine (107 mg, 0.48 mmol) were added. The reaction mixture was left to stir for 30 min at 0 °C, whereafter the ice bath was removed and the solution was left to stir overnight. Progress of the reaction was followed by TLC analysis. However, the products were not very stable on the TLC plates, which made identification and isolation of these a difficult process. Work-up of the reaction by phase separation using DCM and water, followed by flash silica chromatography on a short (15 cm) column to prevent degradation of the compound on the silica afforded P,N-P ligand **22** as a clear oil. R_f 0.81 (6:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.15 (m, 22H, aromatic), 7.04 (t, 1H, J = 7.2 Hz), 6.76 (dd with unresolved fine coupling, 1H, J = 6.9 and 4.8 Hz), 4.37 (dd with unresolved fine coupling, 2H, J = 7.1 and 3.2 Hz), 3.00–2.91 (m, 2H), 1.39–1.29 (m, 2H), 1.02 (sextet, 2H, J = 7.2 Hz), 0.71 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4 (dd, J = 20.9 and 3.07 Hz), 139.9 (d, J = 14.4 Hz), 136.1 (d, J = 9.9 Hz), 134.9 (d, J = 13.7 Hz), 133.8 (d, J = 19.8 Hz), 132.6, 132.1 (d, J = 20.1 Hz), 128.6, 128.4 (d, J = 6.9 Hz), 128.4, 128.2, 127.9 (d, J = 5.7 Hz), 127.5 (d, J = 4.8 Hz), 126.5, 52,5 (dd, J = 27.0 and 11.6 Hz), 51.4 (d, J = 15.7 Hz), 31.2 (dd, J = 4.0 and 1.9 Hz), 20.2, 13.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 64.35 (d, 1P, J = 2.1 Hz), −15.16 (d, 1P, J = 2.1 Hz); IR ($CHCl_3$) 3053, 2939, 2844; EIMS m/z 532 ($[M+1]^+$, 15), 346 (100); HRMS Calculated for $C_{35}H_{36}NP_2$ 532.2323; found 532.2323. Ligands **23**–**28** were prepared using either Section 4.3.1 or Method B, depending on the ligand (see supporting information).

4.4. General procedure for the synthesis of ligands *29–33*: N-dicyclohexylphosphino-phosphino-amine (*29*)

302 mg, 55%. The cyclohexyl magnesium chloride Grignard reagent was prepared as follows in a two-necked flask equipped with a dropping funnel: 1 mL of a solution of chlorocyclohexane (480 μL, 4.048 mmol, 4.0 equiv.) in 5 mL of ether was added to a mixture of magnesium turnings (108 mg, 4.452 mmol, 4.4 equiv.) in 5 mL of ether. An iodine crystal was added and the reaction mixture was slowly heated to initiate the reaction. Slow addition of the remaining chlorocyclohexane solution was continued after the reaction proceeded under gentle reflux without external heating. The reaction mixture was stirred under reflux for 4 h after the addition was complete.

In another two-necked flask the secondary aminophosphine ligand **8** (350 mg, 1.01 mmol) was dissolved in dry toluene (10 mL). Triethylamine (306 mg, 3.04 mmol, 3 equiv.) was added and the reaction mixture was cooled to 0 °C. Phosphorus trichloride (166 mg, 1.21 mmol, 1.2 equiv.) was slowly added to the reaction mixture, which was allowed to stir for 2 h while gradually warming to ambient temperature. The milky solution was filtered under argon and washed with ether. All solvents were removed under reduced pressure and the crude mixture was re-dissolved in 5 mL of toluene, and used without further purification.

The prepared Grignard reagent was transferred to a dropping funnel, and was slowly added to the above mentioned crude reaction mixture at −10 °C with vigorous stirring. After 2 h, the reaction mixture was slowly quenched by the addition of ice. DCM and water were used to extract the reaction mixture and the organic solvent was removed *in vacuo*. The product **29** was isolated using flash silica chromatography (6:1 hexanes:EtOAc) as a clear oil. R_f 0.64 (6:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd with unresolved fine coupling, 1H, aromatic, J = 6.9 and 4.5 Hz), 7.30–7.18 (m, 11H, aromatic), 7.04 (t, 1H, J = 7.2 Hz), 6.71 (ddd, 1H, J = 7.6 and 4.9 and 1.2 Hz) 4.06 (broad s, 2H), 2.76–2.66 (m, 2H'), 1.64–0.97 (m, 26H), 0.74 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (d, J = 19.4 Hz), 135.9 (d, J = 9.5 Hz), 134.9 (d, J = 14.0 Hz), 134.1 (d, J = 19.7 Hz), 132.2, 128.8, 128.5 (d, J = 7.5 Hz), 128.2, 127.2 (d, J = 4.8 Hz), 126.2, 53.8 (broad d, J = 20.6 Hz), 53.0 (broad d, J = 23.7 Hz), 36.0 (d, J = 15.1 Hz), 30.0, 29.1 (d, J = 18.0 Hz), 29.0 (d, J = 8.5 Hz), 27.2–26.5 (4C), 26.5, 20.3, 14.0; ^{31}P NMR (121 MHz, $CDCl_3$) δ 77.5, –14.2; IR ($CHCl_3$) 3053, 2918, 2842, 1434; EIMS m/z 544 ($[M+1]^+$, 1), 460 (100); CIMS m/z 543 (M^+, 85); HRMS Calculated for $C_{35}H_{48}NP_2$ (M + 1) 544.3262; found 544.3261. Compounds **30**–**33** were prepared using the same synthetic approach (see supporting information).

4.5. General procedure for the Heck reaction

The desired phosphine ligand (0.05 mmol when bidentate, 0.098 mmol when monodentate) and palladium acetate (11 mg, 0.049 mmol) were dissolved in 3 mL of DMF and allowed to stir for 30 min while heating to 40 °C. To this mixture were added butyl acrylate (63 mg, 0.49 mmol), triethylamine (74 mg, 0.74 mmol) and 0.49 mmol of the aryl halide. Reaction mixtures were heated under reflux at 110 °C and the reaction progress was followed by TLC analysis. Reaction times varied from 4 h to 24 h. The crude reaction mixtures were cooled to room temperature and extracted with DCM and water. The organic layers were dried over $MgSO_4$, and the products were isolated with flash silica chromatography. Larger amounts of the substrates were used for lower catalyst loadings to ensure accuracy.

4.6. General procedure for the Heck-type carbonylation reaction

Generally, the experimental procedures were the same as for the Heck reaction. However, after adding all of the reagents to the reaction flasks, these were flushed with carbon monoxide and further kept under one atmosphere (balloon pressure) of carbon monoxide. Work-up and isolation procedures were as for the Heck reaction. Reactions performed with 0.1% and 0.01% catalyst loadings made use of large-scale reactions (0.0321 mol substrate or 0.321 mol substrate, respectively) to ensure accuracy and repeatability.

4.7. General procedure for the Stille cross-coupling reaction

The desired P,N ligand (0.016 mmol, 5.8 mol%) was dissolved in 10 mL of THF and 6.2 mg of $Pd_2(dba)_3$ (0.0068 mmol, 5.0 mol% Pd) were added. The reaction mixture was allowed to

stir for 20 min. Phenyltributyltin (100 mg, 0.272 mmol, 1 equiv.) and 43 mg of bromobenzene (0.272 mmol, 1 equiv.) were added and the reaction mixture was stirred at 60 °C for 24 h. The crude reaction mixture was filtered through silica and the filtrate was analysed *via* GC chromatography to determine the conversion of reagents to product, which was isolated in a pure form using flash silica chromatography. Larger scale reactions were carried out on 5 mmol scale.

4.8. General procedure for the hydroformylation reaction

The desired P,N ligand (0.042 mmol, 0.35 mol%) and 9 mg of $Rh(acac)(CO)_2$ (0.035 mmol, 0.3 mol%) were added to a small high-pressure reactor containing 2 mL of 1-octene (11.7 mmol) and 2 mL of toluene. The reactor was evacuated, pressurised to 10 atmospheres of pressure with synthesis gas (CO/H_2, 1:1) and heated to 80 °C. The reaction mixture was left to stir at 80 °C for 2 h, after which the reactor was cooled down, depressurised and opened. The reaction mixture was filtered through silica and GC-analysis was used to analyse the reaction mixture.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.molcata.2008.01.007.

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