

One step entry to P,O- and P,N-type heterocyclic tertiary phosphine ligands and application in Suzuki–Miyaura cross-coupling reactions†

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Received 17th March 2011, Accepted 20th April 2011

DOI: 10.1039/c1ob05426k

A direct synthesis of conformationally mobile P,O- and P,N-type heterocyclic phosphine ligands is described involving radical-mediated addition of diisobutylphosphine to olefinic-heterocycles. Palladium complexes of the P,N-ligand were determined to be highly active in the Suzuki–Miyaura cross-coupling reactions, including deactivated aryl chlorides.

The development of novel phosphine ligands has been of central importance to advances in palladium-mediated cross-coupling reactions (C–C, C–O, C–N *etc.*) over the last few decades.^{1–4} Successful substrate activation and progression through the catalytic cycle is often highly dependent on the nature of the ligand employed.² The general mechanism of palladium catalyzed cross-coupling processes with aryl or vinyl halides (or equivalents) is well understood, however the relative importance of the contributing steps is variable. In addition to the ligand, the nature of the halide (I > Br > Cl), including its steric and electronic environment, is often critical, with electron rich, hindered aryl/vinyl chlorides being the most challenging. Sterically hindered, electron-rich phosphines have proved to be useful in effecting both oxidative addition and reductive elimination processes in these catalytic cycles and many ligands incorporating this feature have been developed.^{5–9} Among these, the Buchwald-type biaryl ligands^{1b,2,5} and di-*tert*-butyl-alkyl phosphine and related ligands introduced by Fu and co-workers^{1c,2e–g} have proven to be of great value in activating difficult substrates and uncovering novel chemoselectivity.

Related to these monodentate ligands are a growing number of monophosphine P,N and P,O- type ligands that incorporate a sterically hindered phosphine in conjunction with a weaker, tunable *n*- or π -Lewis basic donor substituent.^{1d,6,7,8} A few examples are shown in Fig. 1. Kwong and co-workers reported the synthesis and application of indolylphosphines **A** and **B** for Suzuki–Miyaura and other coupling reactions.^{1d,6} Guram and co-workers introduced the ketal-containing P,O-type ligand **C** for Suzuki–Miyaura cross-coupling of aryl chlorides.⁸ P,N-type ligands include the pyridine-phosphine **D** and phosphine-oxazoline ligand **E**

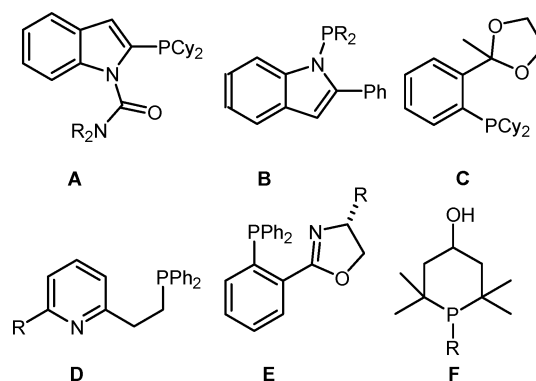


Fig. 1 Examples of P,O and P,N type ligands.

introduced by Kamer^{8c} and Pfaltz^{8f} respectively. Bidentate ligands containing different soft and hard donor substituents (*i.e.* hemilabile ligands) have great potential in homogenous catalysis.^{1d,6,7,8,9} Such ligands possess one weakly coordinating group that can provide unsaturation at the metal center through dissociation during the catalytic cycle.

Our group has been involved in the design and application of new hindered phosphine ligands over the last few years.^{10,11} The synthesis of the P,O-type hemilabile ligand **F**, incorporating a novel conformational feature into the ligand design, was recently reported.¹² A key consideration in the design of ligand **F** was the introduction of dual-functionality through conformational mobility. The ligand is expected to function as an electron-rich monodentate ligand assisting oxidative addition in one conformer (*i.e.* L₂Pd to LPd involves only a conformational change). The hydroxyl appendage would become engaged through a chair–boat conformational flip, converting to a bidentate ligand, assisting ligand exchange/reductive elimination processes. Pd-complexes of ligand **F** proved to be very efficient in effecting Suzuki–Miyaura cross-coupling reactions on challenging, hindered and electron rich aryl chlorides. The success of this ligand prompted us to explore other ligand architectures that might allow synthesis of hemilabile P,O and P,N-type ligands. Herein we report the synthesis of the novel (tetrahydrofuran-3-yl)phosphine ligand **3** and 2-[(diisobutylphosphinyl-ethyl)-pyridine] ligand **4** and their application in challenging Pd-mediated Suzuki–Miyaura reactions.

The design features of these new ligands are outlined in Fig. 2. We were attracted to the incorporation of a tetrahydrofuranyl core given the role played by ethereal solvents such as THF

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† Electronic supplementary information (ESI) available: General experimental details, procedures, NMR and MS data for all new compounds. See DOI: 10.1039/c1ob05426k

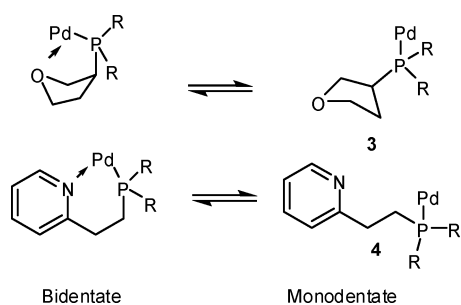
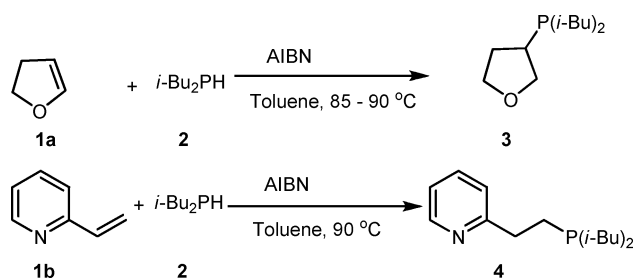


Fig. 2 Bi- and monodentate complexes of ligands **3** and ligand **4** ($R = i\text{Bu}$).

as weakly coordinating ligands in transition metal and *s*-block metal complexation. We envisioned that a bulky electron-rich phosphine ($R = \text{Cy}$, $i\text{Bu}$, $i\text{Bu}$ etc.) could be incorporated onto a tetrahydrofuran core to give **3** or onto a 2-vinylpyridine to give **4**. The hemi-labile nature of the ligands would involve the two contributing envelope-type conformers shown (top) for the furan **3**, and a fused-bicyclo to monodentate exchange in the case of ligand **4**.

The synthesis of ligands **3** and **4** is outlined in Scheme 1. The ligands were synthesized by the addition of diisobutylphosphine to 2-vinylpyridine and dihydrofuran in the presence of AIBN (or VAZO 67) in toluene.^{9,13} Both ligands are reported here for the first time. Derivatives of ligand **4** (**D**, Fig. 1) have been previously reported prepared *via* multi-step routes involving either a hydrophosphination oxidation/reduction sequence,^{8e} or *via* an Arbuzov reaction, phosphine oxide reduction sequence.¹⁴ While the synthesis of ligand **3** proved uneventful, the radical-mediated addition of the secondary phosphine to 2-vinylpyridine was initially problematic due to polymerization. Satisfactory conditions were eventually found, involving the slow addition of both initiator and 2-vinylpyridine to the secondary phosphine at 90 °C in toluene. The desired ligands could be readily accessed on either a laboratory or multi-gram scale (>750g) *via* this simple, single step procedure from commercially available precursors.



Scheme 1 Synthesis of phosphine ligands **3** and **4**.

A catalyst system employing ligand **3** and $\text{Pd}(\text{OAc})_2$ was screened for the Suzuki–Miyaura cross-coupling of phenylboronic acids with a range of aryl halides, the overall results of which are collected in Table 1. The reaction with bromobenzene (entry 1) was attempted with different solvents and bases to optimize the coupling. Pre-complex formation^{6b} using freshly distilled Et_3N and dichloromethane, generated a highly active catalytic system that provided the biphenyl product in 96% isolated yield. This same protocol was successfully applied to a series of Suzuki–Miyaura cross-couplings with both activated and non-activated aryl iodides

Table 1 Suzuki–Miyaura cross coupling reaction of aryl halides with ligand **3**^a

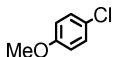
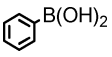
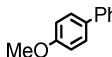
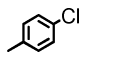
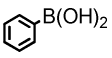
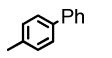
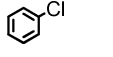
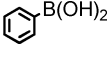
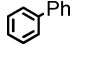
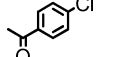
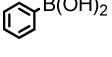
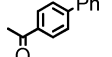
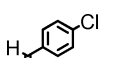
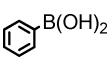
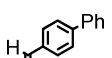
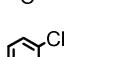
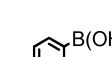
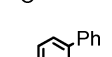


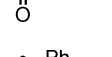
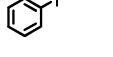
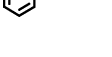
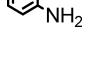
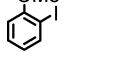
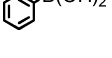
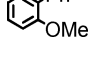
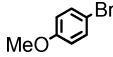
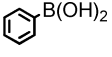
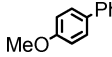
Entry	Ar-X + Ar'B(OH) ₂		Ligand 3 , 3.0 mol-% $\text{Pd}(\text{OAc})_2$, 1.0 mol-% K_3PO_4 , 3.0 equiv. <i>t</i> -BuOH, 110 °C		Ar-Ar'	Isolated yield of 7 (%) ^b
	5	6				
1						96%
2						78%
3						97%
4						85%
5						89%
6						93%
7						75%
8						98%
9						10%
10						95%

^a Reaction conditions. Aryl halide (3.18 mmol), phenylboronic acid (6.36 mmol), ligand **3** (3.00 mol%), $\text{Pd}(\text{OAc})_2$ (1.00 mol%), $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ (9.54 mmol) in *t*-BuOH at 110 °C, 12 h. ^b Isolated yield after column chromatography.

and bromides (Table 1). Aryl chlorides proved very difficult to activate using ligand **3** under these conditions and various modifications. For example, activated 4-chloroacetophenone yielded only 10% of the biaryl adduct under the standard condition.

Ligand **4** was next investigated in the cross-coupling reaction with aryl boronic acids and met with immediate success, the overall results of which are summarized in Table 2. Deactivated 4-methoxychlorobenzene was smoothly coupled using ligand **4** under these conditions in toluene at 110 °C. A wide range of electron deficient, electron rich and hindered *ortho*-substituted chlorobenzene derivatives could readily be activated with the Pd-complex of **4** and coupled with arylboronic acids (entries 1 to

Table 2 Suzuki–Miyaura cross coupling reaction of aryl halides with pyridine ligand **4**^a

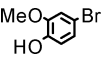
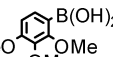

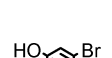
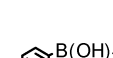
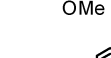
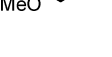
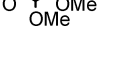
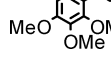
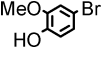
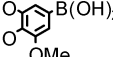
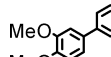
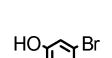
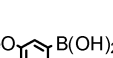
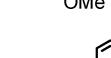
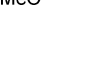
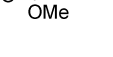
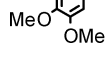
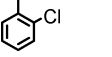
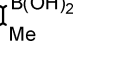
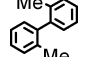
Entry	R-X 5	Boronic acid 6	Product 7	Isolated yield of 7 (%) ^b
1				74%
2				78%
3				70%
4				90%
5				86%
6				72%
7				78%
8				81%
9				80%
10				95%

^a Reaction conditions. Aryl halide (0.70 mmol), phenylboronic acid (1.40 mmol), ligand **4** (3.0 mol%), Pd(OAc)₂ (1.0 mol%), Cs₂CO₃ (2.10 mmol) in toluene at 110 °C, 12 h. ^b Isolated yield after column chromatography.

5). An interesting example was the efficient cross-coupling of the electron poor 4-acetylphenylboronic acid with chlorobenzene (entry 6). Bromo- and iodobenzene derivatives (entries 7–10) provided the corresponding biaryls in high yield as expected.

The most challenging cases in the Suzuki–Miyaura cross-coupling reaction involve the synthesis of hindered biaryls from the reaction of unactivated aryl halides (particularly readily available chlorides) and *ortho*-substituted hindered phenylboronic acids. Pd-complexes of ligand **4** also proved to be highly effective in promoting such cross-coupling reactions, although these reactions were expectedly slower. The standard reaction time was extended to 24 h and catalyst loading increased to 2.0 mol%. Table 3 summarizes selected examples of these challenging cases employing ligand **4**. The results outlined in Tables 2 and 3 represent a snapshot of the possibilities achievable with ligand **4** under one set of prescribed, unoptimized conditions.

Table 3 Suzuki–Miyaura cross coupling reaction of aryl halides with hindered phenyl boronic acids^a

Entry	R-X 5	Boronic acid 6	Product 7	Isolated yield of 7 (%) ^b
1				60%
2				64%
3				57%
4				62%
5				50%
6				55%
7				61%

^a Reaction conditions. Aryl halide (0.70 mmol), phenylboronic acid (1.40 mmol), ligand **4** (6.0 mol%), Pd(OAc)₂ (2.0 mol%), Cs₂CO₃ (2.10 mmol) in toluene at 110 °C, 24 h. ^b Isolated yield after column chromatography.

In conclusion, while the furano-ligand **3** proved unable to activate challenging aryl halides, ligand **4** clearly has much potential in Pd-mediated cross-coupling chemistry. Both ligands share a monodentate diisobutylphosphino appendage, the difference lies in their ability to function as hemi-labile ligands based on the conformational features described. It appears ligand **3** is unable to function as a hemi-labile ligand, perhaps due to steric constraints within the bidentate envelope conformer. The enhanced catalytic activity seen with ligand **4** clearly illustrates the effectiveness of the 2-ethano-pyridyl substituent in its ability to activate challenging aryl halides and assisting progress of the intermediates through the catalytic cycle. Ligand **4** is also very attractive given its one-step synthesis and availability on a multi-gram scale. Further extension of related hemi-labile systems based on this new lead is under active investigation in our laboratories.

Acknowledgements

We thank NSERC, Cytec Canada Inc. and McMaster University for financial support of this work.

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