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A novel P,O-type phosphorinane ligand for the Suzuki–Miyaura cross-coupling of aryl chlorides

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ABSTRACT

The Pd-mediated Suzuki–Miyaura cross-coupling of substituted and unsubstituted aryl chlorides with phosphorinane ligands was investigated uncovering an interesting ligand effect. The scope of the most effective 4-hydroxyl-substituted phosphorinane ligand in Suzuki cross-coupling with challenging aryl chlorides is described.

1. Introduction

Palladium-catalyzed C–X (X = C, N, O, S) bond forming reactions have been extensively investigated over the last few decades. Many of these processes have become standard reactions in effecting these important bond connections.[1] A wide range of applications on both laboratory and industrial scales have been developed.[2,3] New and emerging ligands have expanded the scope of substrates that enter such catalytic cycles to include less reactive aryl chlorides and chemoselectivity to include substrates susceptible to β-hydride elimination. The dialkylbiarylphosphines (Fig. 1, **A**) introduced by Buchwald and co-workers have allowed for some remarkable advances in catalyst stability and general reactivity. The ligand structural features required have been extensively investigated in this series.[1b] In general, incorporation of an electron-rich phosphine increases the rate of oxidative addition while steric bulk at phosphorus increases the rate of reductive elimination. In addition, the lower aryl ring of these ligands is generally electron rich which provides additional π-type Pd-arene stabilizing interactions in the active L_1-Pd^0 catalyst.[4]

Other interesting examples of such hemilabile ligands include the P,O-type indolylphosphines **B** introduced by Kwong and co-workers for Suzuki–Miyaura and other coupling,[1d,5] the BIPI P,N-type ligands **C** introduced by Busacca et al. for Pd-mediated Heck coupling and asymmetric hydrogenation,[6] the pyrrole- and imidazole- based systems **D** introduced by Beller,[7] and the ketal-containing P,O-type ligands **E** introduced by Guram and co-workers for the Suzuki cross-coupling of aryl chlorides.[8c] The desire to activate inexpensive, readily available aryl chlorides has been a driving force behind the development and application of many of these ligands.[8] The general structural feature incorporated into the design of all these ligands is the presence of a bulky, electron-rich phosphine donor in addition to a weaker, tunable *n*- or π- Lewis basic hemilabile donor. Monodentate complexes of type L_1-Pd^0 are implicated[1p] as the key species involved in the initiating oxidative addition step in these catalytic cycles. The additional weak Pd-ligand interaction provides a stabilizing and tunable appendage to the unsaturated catalyst.

2. Results and discussion

We recently reported on the use of a series of a P-substituted phorone-derived tertiary phosphines, analogs of ligand **3c** (Fig. 2), as part of our ongoing research with new ligand scaffolds.[9]

The phosphorinane ligands incorporate a variably substituted phosphine within a rigid, bulky di-*tert*butyl-like framework. Many structurally interesting P,O-type ligands have now been reported in the Suzuki and other cross-coupling reactions.[1d] It occurred to us that the monodentate ligand scaffold **3c** could possibly be further

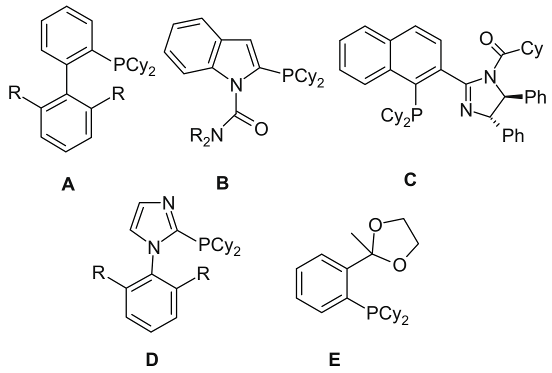

Figure 1. Selected examples of hemilabile phosphine ligands.

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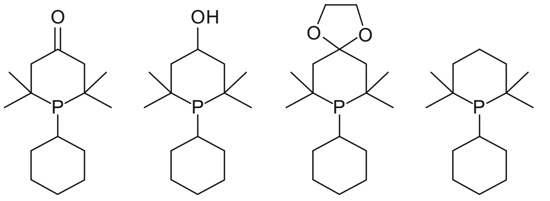


2 **3a** **3b** **3c**

Figure 2. P-Cyclohexylphosphorinone **2** and 4-substituted analogs **3a**, **3b**, and **3c**.

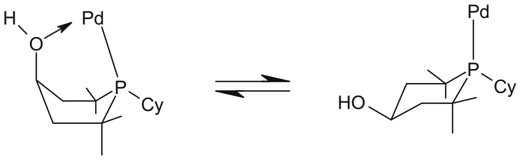
tuned to function as a hemilabile-bidentate ligand **3a** of the type described above through the incorporation of a novel design feature involving a *chair–boat* conformational change. This design feature is outlined in Figure 3 in which it is postulated that a remote 4-hydroxyl substituent could function to stabilize the catalyst in a *boat* conformer, but generate the reactive monodentate L_1-Pd^0 species through a ring flip to the *chair* conformer of **3a** as shown.

In order to probe this possibility, the series of phosphorinane derivatives shown in Figure 2 were prepared. In this Letter we report on the synthesis of these phosphorinane ligands (Fig. 2) and their application in the Suzuki–Miyaura cross-coupling reaction, including the successful activation of challenging aryl chlorides.

The required parent P-cyclohexylphosphorinone **2** (Scheme 1) was readily obtained through the double Michael addition of mono-cyclohexylphosphine **1** to phorone.[10] Attempts to prepare the 4-hydroxylphosphorinone **3a** using $NaBH_4$-mediated reduction of the ketone **2** yielded the phosphine-borane adduct of **3a** which proved difficult to deprotect.[9a] The desired product **3a** was readily made via $LiAlH_4$-mediated reduction of **2** however. The 4-substituted ketal **3b**, analogous to the Guram ligand **E** (Fig. 1) and the unsubstituted derivative **3c** were prepared via standard ketalization and Wolf-Kishner reduction, respectively, of the parent ketone.[11]

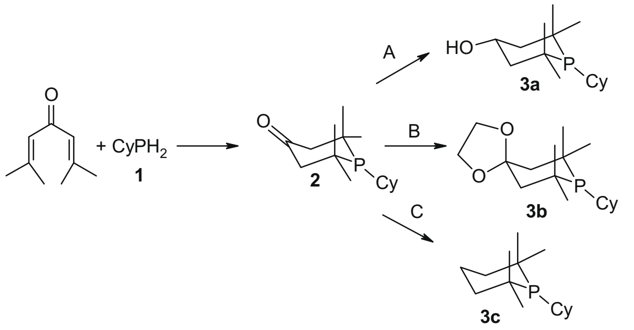
Many catalyst systems are now known for Suzuki–Miyaura cross-couplings of aryl bromides and iodides. We opted to focus on the activation of challenging aryl chlorides, in particular electron-rich and *ortho*-substituted derivatives, in order to realize the true potential of these new ligands. The Suzuki cross-coupling of 4-chloroacetophenone (1.0 equiv) with phenyl boronic acid (2.0 equiv) was first investigated. A catalyst system comprising palladium (II) acetate (1.0 mol %), ligand **2**, **3a**, **3b**, or **3c** (3.0 mol %) and cesium carbonate was investigated in toluene. The cross-coupling was followed through monitoring the disappearance of the aryl chloride and appearance of the biaryl using GC. While all the ligands proved partly successful, ligands **3a** and **3c** gave a complete conversion of the aryl chloride in 1.5 and 2 h, respectively. The ketal-containing ligand **3b** was least successful, requiring 24 h to give 80% conversion of the aryl chloride. The activation of electron-rich aryl chlorides is among the more challenging issues in Pd-mediated cross-coupling. Ligands **3a** and **3c** also proved effective in the activation of 4-chloroanisole under the same conditions, although as expected the reactions were slower. Nonetheless, full conversion of 4-chloroanisole was realized within 16 hours using ligand **3a**. Under these conditions, ligand **3c** gave around 69% conversion, comparable to other P-substituted phosphorinanes previously investigated,[7b] and required up to 48 h to achieve full conversion.

The scope of the Suzuki–Miyaura cross-couplings employing ligand **3a** with a range of activated and non activated aryl chlorides was investigated and results are collected in Table 1. All reactions



3a Bidentate *boat* **3a** Monodentate *chair*

Figure 3. Bi- and monodentate complexes of ligand **3a**.

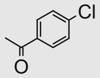
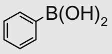
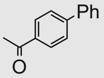
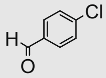
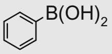
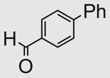
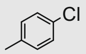
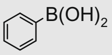
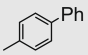
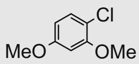
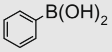
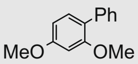
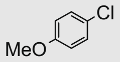
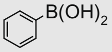
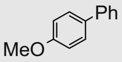
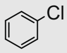
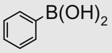
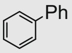
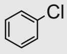
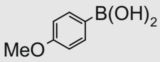
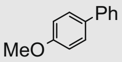
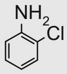
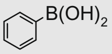
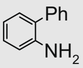
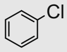
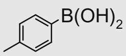
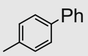
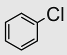
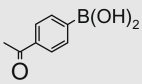
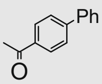


Scheme 1. Reagents: (A) $LiAlH_4$, THF; (B) ethylene glycol, PTSA; (C) hydrazine, KOH.

Table 1

Suzuki cross-coupling reaction of various aryl chlorides and phenylboronic acids with Pd-complex of **3a**[12]

$$\underset{\mathbf{4}}{\text{Ar-Cl}} + \underset{\mathbf{5}}{\text{PhB(OH)}_2} \xrightarrow[\text{Cs}_2\text{CO}_3\text{, 3.0 eq; toluene, 110 °C, 16h}]{\mathbf{3a}\text{, Pd(OAc)}_2\text{, 1.0 mol\%}} \underset{\mathbf{6}}{\text{Ar-Ph}}$$

Entry	R-Cl	Boronic acid	Product **6**	Isolated yield of **6** (%)
1				93
2				85
3				78
4				60
5				80
6				70
7				62
8				82
9				74
10				85

were performed under the conditions described above and, in order to allow direct comparison, the reactions in the Table were terminated after 16 h and isolated yields of the biaryl adducts are shown. The Pd-complex of ligand **3a** proved to be highly effective in activating a wide range of substrates including most notably chloroanisole (entry 5) and the more difficult 2,4-dimethoxychlorobenzene (entry 4), which gave a respective 60% isolated yield. By direct comparison, the use of a Pd-DABCO-based catalyst in DMF, at 110 °C for 19 h provided 63% yield of the same product from 2,4-dimethoxychlorobenzene,[13a] while a solvent-free Pd-Cy_3P catalyst system was reported to give 78% yield of this product.[13b] The present results therefore place the 4-hydroxyl-substituted phorone **3a** among only a handful of systems that allow activation of these most challenging electron-rich and *ortho*-substituted aryl chlorides.

That the 4-hydroxyl substituted phosphorinane **3a** proved to be the ligand of choice in this reaction is interesting given the remote nature of this hydroxyl group from the strongly co-ordinating phosphorus donor. It is difficult to consider an explanation other than the hypothesis that this ligand functions as a hemilabile P,O-bidentate ligand in accord with the models shown in Figure 3. Ligand **3a** may thus be considered a member of the expanding class of useful hemilabile-bidentate ligands collected in Figure 1. The incorporation of a strongly co-ordinating, sterically hindered soft phosphine donor and a second, weaker co-ordinating atom into a bidentate ligand core may thus be a useful general feature allowing participation of 14- and 16-electron palladium species at various points in the catalytic cycle.

3. Conclusion

In conclusion, a series of 4-substituted phosphorinane ligands were prepared. The ligand P-cyclohexyl-4-hydroxy-2,2,6,6-tetramethylphosphorinane **3a** proved most effective in the Suzuki–Miyaura cross-coupling of challenging aryl chlorides disclosing an interesting ligand substituent effect. This ligand is among a handful that are currently available that allow activation of these substrates. The use of such hemilabile ligands in cross-coupling processes appears to be a general structural feature, we are currently exploring other structural types that incorporate this feature. Ligand **3a** is easily prepared in two steps from commercial materials. Further modification of ligand **3a**, including immobilization onto a solid support[14,15] and its application to other cross-coupling processes is under investigation.

Acknowledgments

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12. General procedure for reactions reported in Table 1. Into an oven dried Schlenk flask equipped with a magnetic stirring stir bar were added under argon the aryl halide (0.20 g, 1.30 mmol), boronic acid (0.31 g, 2.58 mmol), $Pd(OAc)_2$ (0.003 g, 0.013 mmol), ligand (0.009 g, 0.039 mmol), and Cs_2CO_3 (1.27 g, 3.9 mmol, Aldrich, ReagentPlus, 99%). The flask was capped, evacuated, and flushed with argon three times. Toluene (10.0 ml) was introduced and the reaction mixture was immersed in a pre-heated oil bath at the indicated temperature until the reaction was complete (Table 1, 16 h at 110 °C). The reaction mixture was then diluted with ethyl acetate, filtered through silica and the solvent was removed at reduced pressure. The crude product was then purified by column chromatography on silica gel. The physical and spectral data of all biphenyl compounds were identical to those previously described.
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