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Ferrocenyl iminophosphine ligands in Pd-catalysed Suzuki couplings

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ABSTRACT

A mixture of $Pd_2(dba)_3/\{\eta\text{-}C_5H_4CH{=}N[CH(CH_3)(Nap)]\}Fe[\eta\text{-}C_5H_4P(^tBu)_2]$ efficiently catalyzes the Suzuki reactions of a variety of bulky aryl halides and aryl- and alkyl-boronic acids, affording the desired cross-coupling biaryl products in quantitative isolated yields under mild conditions and at low (1×10^{-6} –1 mol%) Pd loadings. Spectroscopic (NMR & ESI) analysis of the mixture of $Pd_2(dba)_3$, the hybrid [P,N] ligands, and aryl halides revealed different structural forms of oxidative addition products that are dependent on the substituent on the imino nitrogen.

1. Introduction

Palladium-catalyzed Suzuki-Miyaura cross-coupling between organoboranes and organo-electrophiles has become one of the most important C–C bond formation methodologies [1]. It enables facile syntheses of biaryls and alkylaromatics that are intermediates of pharmaceuticals, natural products, and stereoselective reactions [2]. For example, tetra-ortho-substituted biaryls can be prepared from this method with the use of bulky monophosphines [3], hybrid ligands [4] and carbene complexes [5] *etc*. There are however some drawbacks, such as high cost of boron reagents, use of high temperatures and high Pd loadings (2–12 mol%) *etc*. These have restricted the use of asymmetric Suzuki cross-coupling reactions in producing biologically active biaryls [6] and prompted the development of more efficient catalytic systems especially on ligand innovations. An example of such is the combinative use of ligand hemilability and metal unsaturation in enhancing the coupling efficiency [7]. By using ferrocenyl iminophosphine as a model for hemilabile ligand, we herein show that the coupling efficiency can be tuned by adjusting the substituent, and hence the donicity, of the labile end of the ligand. This facilitates sp^2-sp^2 and sp^2-sp^3 cross-couplings of sterically encumbered and challenging substrates to proceed under mild conditions and low metal loadings.

2. Results and discussion

The ligand system $R_2PFcC{=}NCH(CH_3)R'$ (Fc = ferrocenyl $(C_5H_4)_2Fe$) is chosen as a model for this study because it contains both strong (phosphine) and weak (imine) donor sites separated by a conformationally flexible ferrocenyl skeleton. Such motif would enable the weak donor to undergo facile reversible coordination. It is also important that both donor sites contain a variable substituent group. This allows the introduction of substituents (R or R′) to systematically and independently alter the electronic and steric properties of both sites.

Within this ligand system, there are two types, *viz.* **1** and **2** (Fig. 1). The former has a fixed phenyl on the imine but the R on the phosphine varies, whereas the latter has a variable group on the imine with a constant ^{t}Bu on the phosphine. Ligands **1** are known to support Pd-catalysed Suzuki coupling of aryl chlorides and aryl boronic acids and Ni catalyzed ethylene oligomerization [8]. We present herein the advantages of **2** towards coupling of highly hindered substrates in 1-bromo-2-methylnaphthalene and 2-methylnaphthyl-1-boronic acid under standard conditions in which ligands **1** are ineffective (Table 1, Entry 1–3). Change of -Ph to $-CH(CH_3)(Ph)$ could be manifested in chelate dissociation and halide-bridge formation (discussed below) [9] thus reducing the metal sphere congestion promoting metal–substrate interaction. Indeed, a significant increase in the cross-coupling product is observed when **1a** is replaced by **2a** (Table 1, Entry 1 and 4). It is evident that the product yields are sensitively dependent on R′ of **2** (Table 1, Entry 4–8). One possible explanation is the different

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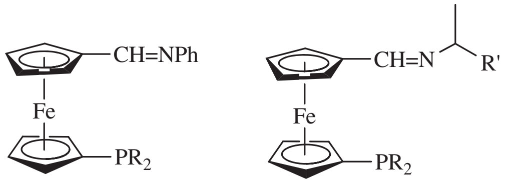


1a, R = ^{t}Bu
1b, R = Cy
1c, R = Ph

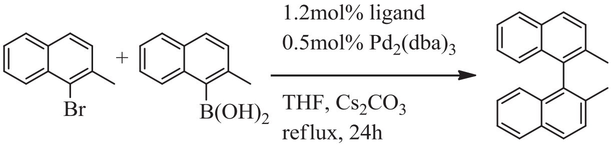
2a, R = ^{t}Bu, R' = Ph
2b, R = ^{t}Bu, R' = *p*-tolyl
2c, R = ^{t}Bu, R' = *p*-fluorophenyl
2d, R = ^{t}Bu, R' = *m*-methoxyphenyl
2e, R = ^{t}Bu, R' = naphthyl

Fig. 1. Ferrocenyl iminophosphine hybrid ligands.

oxidative addition products that are formed as a result of the hemilability of the ligands.

Since **2e** gives the highest yield in the preliminary screen (Table 1), it is used as a model to examine the efficiency of a range of sp^2-sp^2 Ar–Ar′ couplings (Table 2). The yields are satisfactory with many near-quantitative conversions. Consistent with published results [10], sterically demanding substrates require higher catalytic loads to achieve satisfactory yields (Table 2, entries 4, 7–9). Cross-coupling of sterically bulky aryl halides with aryl boronic acids to form tetra-*ortho*-substituted products results in remarkably high isolated yields at 1.0 mol% Pd (Table 2, Entries 7–9 and 16), which are comparable or lower than many reported catalyst systems [4–6]. For example, only 0.1 mol% of Pd (with 0.12 mol% of **2a**) is sufficient to promote quantitative coupling of 1-bromonaphthalene and naphthyl-1-boronic acid at r.t. (Table 2, Entry 5). This is more favorable than the coupling of 1-bromonaphthalene and naphthyl-1-boronic acid at 1 mol% of Pd(dba)$_2$ and 2 mol% of Q-phos at r.t. over 2 days [3d]. Although electron-rich aryl halides tend to be more sluggish in Suzuki couplings [10], electron-rich 1-bromo-2-methoxynaphthalene (Entries 6 & 8) performs better than the electron-poor 1-bromonaphthyl-2-aldehyde (Entry 9) in this system. This could be attributed to a more facile reductive elimination in this system as a result of the large chelate bite angle of the iminophosphine [11], or a more stable oxidative addition intermediate [12] as a result of the strong σ-donating aryl ligand.

Table 1
Ligand effect on the Suzuki cross-coupling reactions of 1-bromo-2-methylnaphthalene and 2-methylnaphthyl-1-boronic acid.[a]



Entry	Ligand	Isolated Yield[b]
1	**1a**	0
2	**1b**	0
3	**1c**	0
4	**2a**	90[c]
5	**2b**	65
6	**2c**	78
7	**2d**	50
8[c]	**2e**	98

[a] 3 equiv. base.
[b] Not optimized.
[c] Isolated yield is 100% when CsF is used.

This system is also effective towards a range of aryl chlorides at low Pd loadings of 0.05–1.0 mol%(Entries 10–16). The coupling of activated *para*-substituted aryl chlorides and phenylboronic acids can be effectively carried out under ambient conditions (Table 2, Entry 10–11), which is comparable to many efficient systems using bulky phosphines [13] and N-heterocyclic carbenes (NHC) [14]. The more sterically hindered substrates can also be effectively consumed under THF reflux (Table 2, Entry 13–16).

Sp^2-sp^3 couplings using *n*-hexylboronic acid could be achieved with good yields (Table 3) that are comparable with the few known systems [13b]. This type of coupling is useful for synthesis of anti-inflammatory and analgesic drugs, synthetic amino acid synthons for protein engineering, biocatalysts and bio-inhibitors [15]. It avoids the normal use of Tl(I) or Ag(I) bases or air-sensitive trialkylboranes such as 9-BBN derivatives, trifluoroalkylborates and dialkylpinacolborates [16]. It is however ineffective towards sp^3-sp^3 couplings.

Oxidative addition is a key step in Suzuki couplings. Ample studies have been conducted on aryl and alkenyl electrophiles with Pd(0) involving hindered monophosphine or diphosphine ligands [such as P(Cy)$_3$, dppf, BINAP] [17]. In systems with hemilabile ligands such as [P, N] donors, it is possible for the reaction intermediates to take several structural forms. For example, imidazol-2-ylphosphine gives two oxidative addition products *viz.* *trans*-PdRX[η^1-PR$_2$(imidazol)]$_2$ and the P,N chelating complex PdRX[η^2-PR$_2$(imidazol)] whose ratio is dependent on the bulk of the ligands and nature of haloarenes [18]. The reactions of **2e** with Pd$_2$(dba)$_3$ and aryl halides, ArX such as pentafluoroiodobenzene, 1-iodonaphthalene or 1-bromonaphthalene have been examined.(Fig. 2) Reaction of **2e** with Pd$_2$(dba)$_3$ gives the dba complex **3** [8d], which undergoes oxidative addition with pentafluoroiodobenzene or 1-iodonaphthalene to give the d^8 Pd(II) **4a** and **4b** with the aryl ligand *trans* to imine nitrogen, similar to the related compounds [8d]. The thermal instability of **4a** (ESI *m/z* 784; δP 75.2 ppm) is exemplified in its decomposition to **3** (major, ESI *m/z* 633) and other unidentified species when heated in THF at 60 °C for 1 h (Fig. 3). The ability of dba to keep the metal (in form of **3**) in solution is apparent [19]. Upon prolonged stirring, **4a** converts to **5a** (major species, δP 80.6 ppm). At 60 °C, **4b** also converts to **5b** (major) over a period of 24 h. The formation of **5** from **4** illustrates the ability of the hemilabile iminophosphine to function in conjunction with the basic iodide to support dinuclear formation. The stability of the chelate is strongly influenced by the substituent effect on the imino nitrogen thereby dictating the structures of the catalytic intermediates formed [20].

Reaction of 1-bromonaphthalene with **2e**/Pd$_2$(dba)$_3$ or **3** gives **6**, which is mononuclear with two unidentate iminophosphine with dangling imines (Fig. 2). The difference between **6** and **5** suggests the influence of the aryl halide on the oxidative addition product, as reported [17a,18]. NMR analysis of **6** suggests that it exists as a mixture of *cis*- (δP = 60.7) and *trans*- (δP = 60.0) isomers. Attempts to separate *cis*-and *trans*-**6** were not successful. Complex **6** decomposes to Pd black and **2e** under elevated temperatures.

3. Conclusion

Hybrid ligands of phosphine-imines Fc(P^{t}Bu$_2$)(CNCH(CH$_3$)(CR′) are suitable ligands to support Suzuki coupling of an array of sterically demanding aryl halides and aryl boronic acids and hexylboronic acid. The R′ = phenyl (**2a**) and naphthyl (**2e**) derivatives are particularly promising. The hemilability of these ligands enables them to switch between the unidentate and chelate mode. Acting in concert with the halo ligand which can also switch between terminal and bridging mode, they create a few structural possibilities for the oxidative addition complexes, which are key intermediate in the Suzuki process. These structural alternatives