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Novel monoligated imine-Pd-NHC complexes: extremely active pre-catalysts for Suzuki-Miyaura coupling of aryl chlorides



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ABSTRACT

Novel monoligated imine-Pd-NHC pre-catalysts with extremely high activity for the coupling of aryl chlorides and aryl boronic acids have been well explored. Three diffident catalysts could be obtained through one reaction. Changes in imine ligands would lead to remarkable variation on catalytic activity. Under mild reaction conditions, high reaction yields were achieved. A wide range of biphenyls could be efficiently obtained at ultra low catalyst loadings of 0.005 mol %.

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Since the first report in 1979, the versatility of Suzuki-Miyaura coupling reaction has greatly progressed, especially inspired by 2010 Nobel Prize in chemistry.¹ It has become one of the most powerful and convenient carbon-carbon bond-forming process in agrochemistry, pharmaceutical chemistry, materials and synthetic chemistry.^{2,3} Despite the successful application of aryl iodides and bromides in the reaction, the use of aryl chlorides is more significant and attractive due to their low cost, wide availability, and good stability. However, aryl chlorides are more difficult to be activated because of high C-Cl bond strength. Thus, highly active catalysts are in great demand to improve this transformation. Novel catalysts have been investigated most intensively since 1998 when Fu first demonstrated Pd₂(dba)₃/P^{t-} Bu₃ catalytic system to facilitate the activation of aryl chlorides in Suzuki-Miyaura cross coupling.⁴ Varieties of excellent catalysts including phosphine palladium complexes, palladacycle complexes and N-heterocyclic carbene palladium complexes have been established, while relatively high catalyst loadings were often required to attain satisfactory results.⁵ Very few literatures revealed their achievements in Suzuki-Miyaura coupling of aryl chlorides based on lower catalyst loadings (<0.5 mol %) and milder reaction conditions.^{5f,6}

Recently, a number of monoligated Pd-NHC complexes have been prepared and show high levels of activity including phosphine ligands, allyl-palladium, acac-palladium, and Pd-PEPPSI-NHC complexes (Fig. 1).^{5e-h} Despite stability coming from NHC ligands, it is known that palladacycles would exhibit higher air and thermal stability. For the coupling of aryl halides with organoboronic acids, palladacycle catalysts are adequate catalysts with TONs between 10^2 and $10^{6.7}$ Thus, it would be guite attractive to use both NHC ligands and palladacycles as catalysts for Suzuki-Miyaura coupling of aryl chlorides.

In this context, we set out to develop monoligated imine-Pd-NHC complexes as pre-catalysts with extremely high catalytic activity for Suzuki-Miyaura coupling reaction of aryl chlorides under relatively mild conditions. It is the first time



Figure 1. A selection of monoligated Pd-NHC complexes.

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Scheme 1. Synthesis of Pd-NHC complexes.

to utilize imine-based ligands in Pd–NHC complexes which could be prepared straightforward within only two steps (Scheme 1).

Acetophenone oxime 5a reacted with PdCl₂ at room temperature to give the corresponding palladacycle dimer,^{8a} which was fragmentized by IPr [1,3-bis(2,6-diisopropylphenyl) imidazolium chloride] to form Pd–NHC complex **6** in the presence of KO^tBu in dry THF.^{8b} Compounds **6a** and **6c** could be isolated by column chromatography and recrystallized respectively as a yellow crystals from hexane/ether, whose structures could be determined by X-ray crystallographic study (Figs. 2 and 3). X-ray diffraction analysis reveals that complex 6a crystallizes in triclinic system, space group P-1 and the asymmetrical unit of the unit cell contains two Pd atom (Pd1 and Pd2), two IPr ligands, and two imine ligands. The Pd1 center is in a distorted quadrilateral coordination environment, ligated by one carbon atom (C1) from IPr ligand, one terminal chlorine atom (Cl1) and the other two atoms (C28 and N3) from the same imine ligand. The Pd2 center is also guadrilateral coordinated by two carbon atoms (C37, C64), one nitrogen atom (N6) and one chlorine atom (Cl2), which is very similar to Pd1. Palladium is found to be well coordinated in the X-ray crystal structure. While Pd-NHC complex 6c crystallizes in orthorhombic system, space group P2(1)2(1)2(1) and the asymmetrical unit of the unit cell contains one Pd atom (Pd1), one IPr and one imine ligand. Aza-allyl scaffold coordinated to Pd1 center is similar to the reported structures.^{5f} But in compound 6c, the distances of Pd1-C35 and Pd1-N3 are shorter than the corresponding distances, while the distance of Pd1-C34 is much longer. When acetophenone oxime 5b was employed as substance, only one Pd-NHC complex 6b was obtained as product in 79% yield.



Figure 2. X-ray crystal structure of Pd-NHC complex 6a.



Figure 3. X-ray crystal structure of Pd-NHC complex 6c.

With the catalysts in hand, we set out to test their catalytic activities in Suzuki-Miyaura coupling especially at low catalyst loadings. The coupling of 4-chlorotoluene and phenyl boronic acid in the presence of 0.1 mol % of **6a** was examined as a model system to identify an effective reaction condition (Table 1). It is worthy to note that catalyst loadings in the model system were decreased by one order of magnitude as compared with the normal. Several bases were investigated including K₂CO₃, K₃PO₄, KOH, and KO^tBu. It seems likely that the reaction would perform better with a stronger base as an additive (Table 1, entries 1–3), but with KO^tBu as an exception. Only moderate yield was obtained, and ca. 30% of the chloride was converted to toluene (Table 1, entries 4 and 13). It was also noteworthy that the dechlorination byproduct was detected to be ca. 5% in the case of KOH. Though in the cases of K₂CO₃ and K₃PO₄, dechlorination did not appear, the conversion of chloride was much lower. Screening of several solvents revealed that alcoholic solvents would be beneficial to the reaction with imine-Pd-NHC complexes 6a (Table 1, entries 3 and 5-8). To our delight, ⁱPrOH mixed with 10% water could reduce the amount of dechlorination byproduct effectively to ca. 1-2% and increase the

Table 1

Various reaction parameters for Suzuki-Miyaura coupling^a

Cat.6 (0.1 mol%)/ base	
Solvent, Temp	

Entry	Cat.	Solvent	Base	Time (h)	Temp (°C)	Conv. ^b (%)	Yield ^c (%)
1	6a	ⁱ PrOH	K ₂ CO ₃	2	80	6	6
2	6a	ⁱ PrOH	K ₃ PO ₄	2	80	26	26
3	6a	ⁱ PrOH	KOH	2	80	86	81
4	6a	ⁱ PrOH	KO ^t Bu	2	80	100	66
5	6a	MeOH	КОН	2	80	63	62
6	6a	Toluene	КОН	2	80	27	27
7	6a	DMF	КОН	2	80	4	4
8	6a	Dioxane	КОН	2	80	4	4
9	6a	ⁱ PrOH ^d	КОН	2	80	90	88
10	6a ^e	ⁱ PrOH ^d	КОН	2	80	89	87
11	6a ^e	ⁱ PrOH ^d	КОН	6	50	88	87
12	6a ^e	ⁱ PrOH ^d	КОН	-	rt	-	-
13	6a	ⁱ PrOH	KO ^t Bu	6	50	99	67
14	6b	ⁱ PrOH	КОН	2	80	82	67
15	6b	ⁱ PrOH	KO ^t Bu	5	80	56	18
16	6c ^e	ⁱ PrOH ^d	КОН	2	80	85	85

^a Reaction condition: 4-chlorotoluene (3.0 mmol), PhB(OH)₂ (3.15 mmol, 1.05 equiv), base (4.5 mmol, 1.5 equiv), solvent (5 mL).

^b Determined by GC.

^c GC yield of coupling product.

^d Mixed with water (${}^{i}PrOH/H_{2}O = 10:1$).

^e Catalyst loading = 0.05 mol %.

product yield to 88% at the same time (Table 1, entry 9). Interestingly, the same yield could be obtained when the catalyst loading was decreased to 0.05 mol % (Table 1, entry 10). Moreover, the reaction temperature can be lowered to 50 °C although a prolonged time was needed to achieve a similar yield (Table 1, entry 11). But, when the reaction was carried out under room temperature, the result was not satisfactory (Table 1, entry 12).

As compared with **6a**, pre-catalyst **6b** led to an unsatisfactory result because of the absence of one methyl group (Table 1, entries 3 vs 14 and entries 4 vs 15).⁹ On the other hand, pre-catalyst **6c** could perform as well as **3a**, though the structure of imine ligand was quite different (Table 1, entries 10 vs 16). Thus, we reasoned that using 0.05 mol % **6a** or **6c** as pre-catalyst in combination with ¹PrOH-H₂O as solvent and 1.5 equiv KOH as base might be optimized reaction conditions (Table 1, entries 10 and 16).

With optimized conditions in hand, we set out to explore the scope of the cross coupling of aryl chlorides and aryl boronic acids. As summarized in Table 2, a series of aryl chlorides **7** and aryl boronic acids **8** were investigated in ⁱPrOH/H₂O in the presence of 0.05 mol % pre-catalyst **6** and 1.5 equiv KOH at 80 °C (Table 2).

Gratifyingly, all of the coupling proceeded rapidly and efficiently to afford the desired biphenyls in remarkable yields, whatever catalyst **6a** or **6c** was used. Both electron-donating and withdrawing groups on the phenyl ring of aryl chlorides did not seem to affect the product yields apparently (Table 2, entries 1– 10). It was illustrated that the reaction was quite feasible with single *ortho*-substituted aryl chlorides whatever the aryl boronic acids were used (Table 2, entries 2, 4, 11, 12, and 15). A more sterically hindered double substitution in *ortho* positions of aryl chlorides was used, though a slightly lower yield was observed (Table 2, entries 3, 14, and 16). However, when catalyst **6c** was employed, the reaction of double substitution aryl chlorides proceeded better (Table 2, entries 14 and 16).

The compatibility of heteroaromatic aryl chlorides in this process was also proven to be feasible by employing 3-chloropyridine and 2-chlorothiophene as representative substrates, giving the corresponding products in 93% yields. And the yields could be increased to 99% when catalyst **6c** was used (Table 2, entries 6–7). In addition, even better results could be afforded when aryl boronic acids with 4-^{*t*}Bu and 4-F substituent were used (Table 2, entries 12, 13 and 15, 16). It was also noted that catalysts were quite active that most of the reactions completed in 2 h with 84–97% isolated yields (in the presence of catalyst **6a**), which implies the feasibility of using lower catalyst loadings in this reaction.

Inspired by these results and our continuous interest in exploring the limits of the catalytic activity, the amount of pre-catalyst 6 was reduced one step further to only 0.005 mol %. An ideal catalyst 6d explored by Nolan^{5f} was chosen as a contrast.¹⁰ Some representative substrates presented in Table 3 were investigated under the same condition in the presence of **6a**, **6c**, and **6d**. To our delight, in most cases, the reaction was carried out smoothly and approached to corresponding products in very high yields. Notably, the activity of catalyst 6c was much better than that of catalysts 6a and 6d. The contrast of catalyst 6c and catalyst 6d was quite interesting. For ortho-substituted aryl chlorides, catalyst 6c performed better in all cases (Table 3, entries 1-7). It is implied that catalyst 6d is not effective enough in our milder reaction conditions. While substrates with electron-withdrawing groups were selected, both of the catalysts achieved the same level of activity (Table 3, entries 8-10).

In conclusion, we have developed several novel monoligated imine–Pd–NHC complexes which showed extremely high activity in the coupling of aryl chlorides and aryl boronic acids. Our observation of dramatic methyl group effect implied a crucial factor between catalytic activity and the structure of imine ligand. The use of ⁱPrOH–H₂O as the solvent and KOH as the base at 80 °C proved to be an efficient and mild condition for the synthesis of biphenyls in excellent yields with only 0.05 mol % catalyst loadings. More impressively, almost the same level yields could also be achieved even at the condition of 0.005 mol % catalyst loadings, especially with catalyst **6c**. Further studies Yield^b (%)

66

85

>99

94

94

87

97

99

>99

98

95

99

>99

>99

97

96

99

96

6a

87

(85)

>99

(92)

92

(86)

96

(92)

88

(84)

93

(89)

93

(86)

>99

(96) 95

(91)

95

(88)

96

(90)

>99

(91)

99

(97)

91

(86)

>99

(93)

90

(84)

93

(85)

Product

9a

9b

9c

9d

9e

9f

9g

9h

9i

9j

9k

91

9m

9n

90

9p

9q

Ru

Bυ

Table 2

Entry^a

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

OHC

Aryl chlorides

OMe

CI

Suzuki-Miyaura coupling of various aryl chlorides and aryl boronic acids in the presence of ${\bf 6a}$ and ${\bf 6c}$

			Cat.6 (0.05 mol%)	
A=CI			KOH (1.5 equiv)	A - A -
AIG	т	AI B(UH)2	in autura an 00	Ar-Ar
7		8	PrOH-H ₂ O, 80 °C	9

Boronic acids

(HO)_oB

(HO)₂B

Гa	bl	e	3

Suzuki-Miyaura coupling of aryl chlorides and aryl boronic acids at 0.005 mol % catalyst loading 11





^a Reaction condition: catalyst **6** (0.005 mol %), ArCl **7** (3.0 mmol), ArB(OH)₂ **8** (3.15 mmol, 1.05 equiv), KOH (4.5 mmol, 1.5 equiv), ⁱPrOH/H₂O = 10:1 (5 mL). Reactions were completed in 2 h.

^b GC yield based on ArCl 7.

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Supplementary data

Supplementary data (detailed description of all experimental procedures, spectroscopic data and crystallographic data of CCDC 945633 & CCDC 977586) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04. 044. These data include MOL files and InChiKeys of the most important compounds described in this article.

^a Reaction condition: catalyst 6a (0.05 mol %), ArCl 7 (3.0 mmol), ArB(OH)2 8
3.15 mmol, 1.05 equiv), KOH (4.5 mmol, 1.5 equiv), i PrOH/H ₂ O = 10:1	(5 mL).
Reactions were completed in 2 h.	
^b CC yield based on ArCl 7 (isolated yield)	

B(OH)₂

^D GC yield based on ArCl 7 (isolated yield).

concerning the function of the substitution on imine ligand, the application of the pre-catalyst in other coupling reactions, and some more similar pre-catalysts with better catalytic activity are underway.

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- The reason to account for the dramatic methyl group effect which led to much better results is still unclear. However, the different catalytic activity of catalyst 6a, 6b, and 6c could prove the crucial effect of imine ligand in this reaction. Some further works are in progress to find the activation mechanism of imine ligand in pre-catalyst.
- 10. Catalyst 6d was purchased from J&K (Product of Umicore).
- 11. General procedure: In a Schlenk flask, a magnetic stirring bar was charged with potassium hydroxide (4.5 mmol, 252 mg), arylboronic acid (3.15 mmol), and aryl chlorides (3 mmol) (if liquid, was injected through the septum later). 0.1 mL catalyst **6** (catalyst loading 0.005 mol %, 2 mg catalyst were dissolved in 2 mL 2-propanol) was injected, followed by the addition of 2-propanol (4.5 mL) and H₂O (0.45 mL). The mixture was then stirred at 80 °C and monitored by gas chromatography until the reaction reached completion, or no further conversion was observed. Water was added to the reaction mixture, which was extracted by ethyl acetate, dried over anhydrous Na₂SO₄, and the solvent was evaporated in vacuum. When necessary the product was purified by flash chromatography.