



Benzaldimines as ligands for palladium in Suzuki–Miyaura reactions

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ARTICLE INFO

Article history:

Received 30 June 2008

Revised 11 August 2008

Accepted 15 August 2008

Available online 22 August 2008

ABSTRACT

Schiff bases derived from substituted benzaldehydes are effective ligands for palladium(0) in the Suzuki–Miyaura coupling of phenylboronic acid with aryl, benzyl and allyl bromides under mild conditions.

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The biaryl linkage is an important structural motif in several natural products and bioactive compounds.¹ It is also a critical structural component of axially dissymmetric ligands that are used extensively with various metals in homogeneous enantioselective catalysis. The Suzuki–Miyaura coupling reaction is a powerful and widely used method for the synthesis of biaryls.² Allyl and vinyl halides, similarly, can be coupled with boronic acids to afford allyl- and vinylarenes, respectively. Such a reaction is usually catalyzed by a palladium(0) complex featuring a suitable ligand that controls the selectivity and efficiency. While phosphines are used extensively as ligands,³ their sensitivity to air and moisture is known to limit their stability and shelf-life. The search for effective non-phosphine ligands has yielded viable alternatives such as N-heterocyclic carbenes (NHC),⁴ imine,⁵ amine⁵ and oxime⁶ palladacycles, diazabutadienes,⁷ oxazolines,⁸ amines⁹ and hydrazones¹⁰ for use in this reaction. Examples of Schiff base ligands, however, remain scarce to date.¹¹ We recently reported the use of pyrazole-tethered aryl phosphines and aryl Schiff bases as effective ligands for palladium in Suzuki reactions.¹² Simplifying the design further, we now report that simple Schiff bases themselves serve as extremely useful ligands in Suzuki coupling reactions.

The Schiff base ligands **1a–h**, prepared by standard procedures from the corresponding aldehydes and amines, were screened for the Suzuki–Miyaura coupling reaction of *p*-bromoanisole with phenylboronic acid. Coupling reactions were examined using two procedures that differed slightly in detail. According to the first protocol, 1 mmol of substrate, 1.5 mmol of boronic acid and 3 mmol of KF were stirred with 2 mol % of Pd(OAc)₂ and 5 mol % of ligand in THF at 35 °C. In the second method, the reagents were first stirred at 0 °C for 15 min and then the temperature was gradually increased to 35 °C. The latter method afforded a better yield of the coupling product and hence it was adopted for the examples described below (Scheme of Table 1). The structures of the Schiff

bases used are displayed in Table 1 along with the yields of the coupling products.

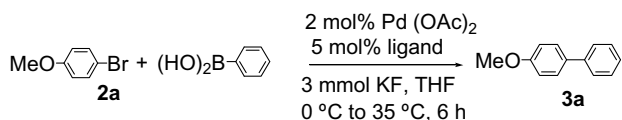
The molar ratio of metal:ligand was maintained at 1:2.5 throughout the present set of experiments since a lower proportion of ligand decreased the yield. As seen from Table 1, the Schiff base **1c** derived from *o*-anisaldehyde and α -methylbenzylamine provided the highest yield of coupled product (92%, entry 3). The absence of an *o*-OMe group (entry 1) or the presence of an *o*-OH group (entry 2) led to a reduction in the yield. Increasing the steric bulk using an *o*-O^{*i*}Pr group did not improve the yield. Yields were low to moderate using Schiff bases derived from cyclohexylamine or *tert*-butylamine (entries 6 and 7). The Schiff base derived from 2,6-diisopropylaniline (entry 8) afforded the coupling product in a slightly higher yield. We observed that for an activated aryl bromide, such as 4-bromoacetophenone, the ligands were of comparable activity. For a deactivated aryl bromide, ligand **1c** was more active than ligand **1a** or **1b**. An investigation on the influence of base indicated that KF was more effective than Na₂CO₃, K₂CO₃ and ^{*t*}BuOK. Both THF and DMF gave comparable yields with KF as base, but the yields were lower when toluene, benzene or acetonitrile was used.

While salen-type complexes with imine donors were investigated earlier for developing catalysts immobilized on a solid support,^{11a} other report on Schiff base ligands for palladium catalysis describes imines derived from aromatic ketones^{11c} or di-imines affording a six-membered chelate.^{11d} The ligands discussed in the present Letter, on the other hand, are monodentate imines derived from an aromatic aldehyde and an aliphatic or aromatic amine.

A significant advantage of using such ligands is that the reaction can be performed at a much lower temperature and with a shorter reaction time than required by other ligands without jeopardizing the yield. That the coordination to palladium is primarily through the imine nitrogen is borne out by the requirement of over two equivalents of imine per equivalent of palladium during catalysis. The usefulness of an *o*-OMe group on the aldehyde part suggests a hemilabile participation of the methoxy group which adds to the stability of the catalyst and its efficiency. The superior

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Table 1
Schiff base ligands used and the yields of product from the coupling reaction^a



Entry	Ligand	% Yield
1		55
2		60
3		92
4		80
5		90
6		70
7		72
8		80

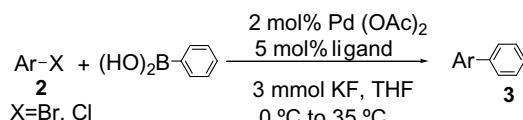
^a Reaction conditions: aryl bromide (1 mmol), phenyl boronic acid (1.5 mmol), Pd(OAc)₂: 2 mol %, ligand: 5 mol %, base: KF: 3 mmol, THF: 4 mL, temp: 0 °C for 15 min, then 35 °C. Yields are based on isolated pure product and reflect an average of two runs.

performance of the ligand **1c** with respect to ligands **1a**, **1b** and **1d** perhaps reflects a better balance of steric bulk and donor ability. These data do not indicate, whether a benzylic amine is necessary for superior activity.

The reaction was extended to variously substituted aromatic and heteroaromatic bromides and with different ligands on palladium (Table 2). For aryl groups with electron-withdrawing groups, the yields were excellent irrespective of the ligand selected. In general, ligand **1c** was found to be the most effective. High yields of products prompted an examination of the influence of a low catalyst loading on the coupling reaction. The quantity of the catalyst was decreased to 0.002 mol %, giving the product in high yield (90%) after 20 h stirring at 35 °C. This indicated that the catalyst not only has high efficiency, but also has stability under the reaction conditions. The results are summarized in Table 3.

Encouraged by these results, we proceeded to exploit this method to synthesize diarylmethanes via a similar Pd-catalyzed reaction¹³ (Table 4). Diarylmethane derivatives are important structural constituents of pharmacologically important com-


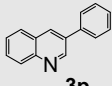

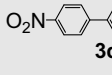

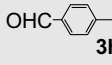
Table 2
Pd(OAc)₂/ligand **1** catalyzed coupling of aryl halides with phenyl boronic acid^a



Entry	Ligand	Ar	Product	Time (h)	% Yield
1	1a			3	98
2	1b	2b	3b	3	90
3	1c	2b	3b	1.5	99
4	1d	2b	3b	3	99
5	1f	2b	3b	3	95
6	1g	2b	3b	3	95
7	1h	2b	3b	3	98
8	1c			2.5	99
9	1c			3.5	98
10	1c			2.5	95
11	1c			2.5	98
12	1c			3	88
13	1c			2.5	95
14	1c			2.5	96
15	1c			3	95
16	1a			4	75
17	1b	2k	3k	4	75
18	1c	2k	3k	4	92
19	1d	2k	3k	4	80
20	1e	2k	3k	4	90
21	1h	2k	3k	4	84
22	1c			4.5	82
23	1c			2.5	95
24	1c			5	98
25	1c			5	90

(continued on next page)

Table 2 (continued)




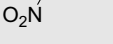
Entry	Ligand	Ar	Product	Time (h)	% Yield
26	1c			5	88
27	1h	2p	3p	5	82
28	1c			7	82 ^b
29	1c			7	40 ^b

^a Reaction conditions: as described in Table 1.

^b For chloro substrate, 20 mol % TBAB (tetrabutylammonium bromide) was added, reaction at 65 °C.

Table 3

Influence of low catalyst loading on the coupling reaction^a

Substrate	Product	Pd (mol %)	Time (h)	% Yield
		2.0	2.5	99
		0.20	3	98
		0.02	15	95
		0.002	20	90

^a Reaction conditions: as described in Table 1.


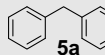
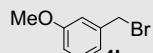
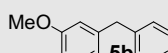
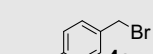
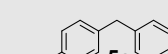

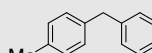
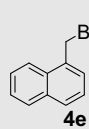
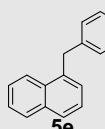
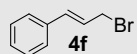
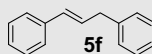
pounds¹⁴ as well as useful subunits of a wide range of macrocycles, catenanes and rotaxanes.¹⁵

Coupling of electrophiles containing sp³C–X bonds with arylboronic acids utilizes benzyl bromide, chloride, carbonate or phosphate as the X-group.^{13,16} We applied the optimized reaction conditions described above for the coupling reaction of different benzyl and allyl bromides with phenylboronic acid. All the substrates furnished the expected coupling products in high yield (Table 4). The tolerance of functional groups is well known for such coupling reactions.¹⁷ The reactivity of benzyl and allyl bromides thus enhances the scope of this reaction significantly for complex synthetic targets.

A change in colour of the solution from yellow to dark brown during the Suzuki reaction indicated the possibility of nanoparticle formation during the reaction. From the reaction between phenylboronic acid and 4-bromoacetophenone in THF, an aliquot was withdrawn and submitted to transmission electron microscopy (TEM) which established that palladium nanoparticles with a diameter of ~6 nm were formed in the reaction mixture (Fig. 1). The spectral change in the UV region during incremental addition

Table 4

Pd(OAc)₂/ligand **1** catalyzed coupling of benzyl and allyl halides with phenylboronic acid^a

Entry	Substrate	Product	Time (h)	% Yield
1			2.5	95
2			2.5	98
3			2.5	96
4			2.5	98
5			3.5	98
6			3.5	98

^a Reaction conditions: as described in Table 1.

of the ligand to a solution of Pd(OAc)₂ in THF was consistent with Pd(II) gradually being transformed to Pd(0) nanoparticles (Fig. 1).

However, it is not possible to conclude solely on this basis whether nanoclusters or palladium complexes are responsible for the catalysis. Despite extensive and rigorous experiments to settle the issue,¹⁸ it is still unclear in most instances whether the reaction takes place on the surface of the solid Pd nanocluster or whether the active catalyst is a solvated Pd molecule leached from the cluster that simply acts as a Pd reservoir. There are recent reports that suggest Suzuki–Miyaura couplings to be actually catalyzed by palladium nanoparticles produced by palladacycles originally added to the reaction.¹⁹ Poisoning experiments are often used to distinguish between ‘homogeneous’ and ‘heterogeneous’ catalysis.¹⁸ Following the procedure developed by Widergren and Finke,¹⁸ we observed that at least 0.8 equiv of CS₂ was required to poison our reaction effectively. This is substantially higher than the amount that would have been required to poison active metals on the surface of the nanocluster. Addition of even 300 M equiv of mercury failed to contain the catalytic turnover indicating, once again, that nanoparticles are perhaps not the catalytic agents in this reaction.

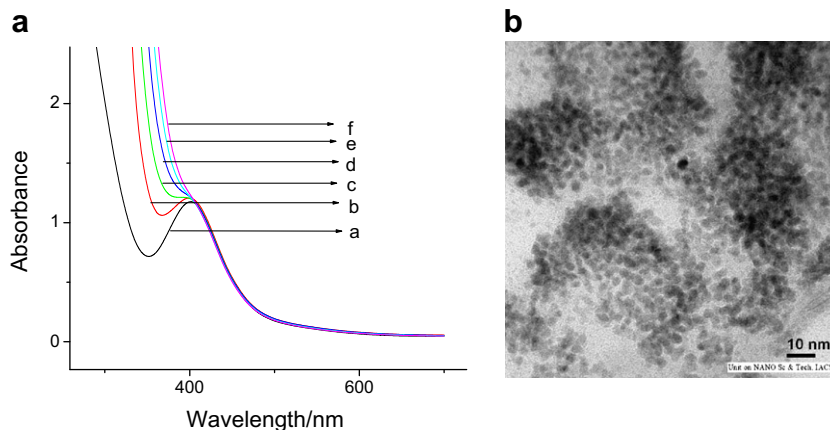


Figure 1. (a) UV–vis spectral changes during the addition of ligand **1c** in THF solution to Pd(OAc)₂ in THF Pd: ligand **1c** molar ratio (a) 1:0, (b) 1:0.5, (c) 1:1.0, (d) 1:1.5, (e) 1:2 and (f) 1:2.5, respectively. (b) TEM micrograph of palladium nanoparticles generated from the coupling reaction catalyzed by **1c**.

In summary, an inexpensive and highly efficient method²⁰ was developed for the Suzuki–Miyaura coupling that can be performed under phosphine free conditions and at near ambient temperature. Various aryl bromides, benzyl bromides and heteroaryl bromides were converted to the coupled products in excellent yields when Pd(0) was used in combination with ligand **1c**. The challenge of chloride activation, however, still persists. Further studies on the applicability of these ligands on other synthetic transformations are currently under investigation in our laboratory.

Acknowledgements

We thank CSIR, India, and Syngene International, Bangalore, India, for financial support. D.S is thankful to CSIR, India, for a Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.08.056](https://doi.org/10.1016/j.tetlet.2008.08.056).

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- General procedure for Suzuki–Miyaura coupling*: An oven-dried 10 mL round-bottomed flask was cooled under argon and charged with aryl halide (1 mmol), phenyl boronic acid (1.5 mmol), Pd(OAc)₂ (2 mol %), ligand (5 mol %), and base (3 mmol). The flask was evacuated and flushed with argon once again, and THF (4 mL) was added to the reaction mixture by a syringe. The reaction mixture was primarily stirred at 0 °C for 15 min and then stirring was continued at 35 °C for the specified time. The reaction mixture was then cooled to room temperature, filtered through Celite and washed with dichloromethane. The crude material was purified by flash chromatography using petroleum ether or a mixture of 2–5% acetone in petroleum ether as eluent. Yields reported herein are based on isolated, purified products (purity was ascertained from the absence of extra signal in 300 MHz proton NMR spectrum).