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Palladacycle-catalyzed Suzuki-Miyaura reaction of aryl/heteroaryl halides with MIDA boronates in EtOH/H_2O or H_2O

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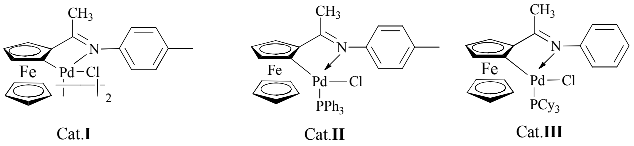
Abstract

With good to excellent yields, a series of mono- or diheteroaryl compounds were synthesized *via* the palladacycle-catalyzed Suzuki-Miyaura reaction of various *N*-methyliminodiacetic acid (MIDA) boronates with aryl/heteroaryl halides in EtOH/H_2O or H_2O.

Introduction

Mono- and diheteroaryl compounds as one of the most prevalent and important motifs are ubiquitous in a wide range of pharmaceutical building blocks, natural products, unnatural nucleotides, molecule probes, advanced materials, and metal-complexing ligands.[1] Although these compounds are generally synthesized *via* the typical cross-coupling reactions,[2] there are still some limitations for the synthesis of 2-heteroaryls such as the unstability of the building blocks,[3] use of toxic metals,[4] and inefficient couplings with aryl chlorides.[5] Recently, the low toxicity and high tolerance of organoboronic acids are widely used as one of the coupling partners in Suzuki reaction. Many progresses have been achieved in this field, the reaction conditions in most cases could not be well suited for the reaction with inherently unstable 2-heteroaryl boronic acids.[6] To solve this problem, professor Martin Burke and Gillis[6b, 7] found that the easily handled and stable MIDA-protected boronates could slowly hydrolyze and release the active boronic acids under mild aqueous basic conditions to take part in Suzuki reaction.[8] To improve the existing technology, more recently, Lipshutz and co-workers reported a catalytic system for the reaction of aryl/heteroaryl MIDA boronates with aryl halides in water.[9] Their reaction protocol realized the value of environmental conservation, however, unusual polymer phase transfer catalyst TPGS-750-M and high catalytic loading ($PdCl_2$(dtbpf)) were employed. Therefore, the development of effective and environmentally friendly protocols for Suzuki-Miyaura coupling reaction of heteroaryl MIDA boronates with heteroaryl halides is still needed. In the course of our investigation on the catalytic activity of cyclopalladated ferrocenylimines (Scheme 1),[10] herein, we report the palladacycle-catalyzed Suzuki-Miyaura coupling reaction involving various MIDA boronates with aryl/heteroaryl halides in EtOH/H_2O or H_2O.



Scheme 1. Palladacycle precatalysts used in this study.

Results and discussion

Our initial experiments were focused on identifying reaction conditions with 4-bromoanisole (**1a**) and phenylboronic acid MIDA ester (**2a**). Palladacycle catalysts Cat.**I**-Cat.**III** (Scheme 1) were selected for the reaction, Cat.**II** could provide superior yield 76% of **3a** (Table 1, entries 1-3). It was found that large amounts of water were necessary to promote hydrolysis of MIDA boronates (Table 1, entries 2 and 4). Some bases (e.g., Cs_2CO_3, K_2CO_3, and KOH) were evaluated, and the best choice was K_3PO_4 (84%; Table 1, entries 4-7). Surprisingly, the discovered reaction was carried out in H_2O (with 20% TBAB) or EtOH/H_2O (6:1) to give the excellent yields (Figure 1). Other factors such as reaction temperature, reaction time, and catalyst loading were respectively investigated in two different solvents EtOH/H_2O (6:1) or H_2O (with 20% TBAB) (Figure2). It was found that the coupling reaction could smoothly proceed at 90 ^oC to give excellent yield. Although the conversion yield was reduced with decreasing the catalyst loading, it was worth noting that the yield could be given in 71-80% with 0.1 mol% catalyst. In addition, a lower yield was obtained when the reaction was carried out under air atmosphere (Table 1, entry 10-11).

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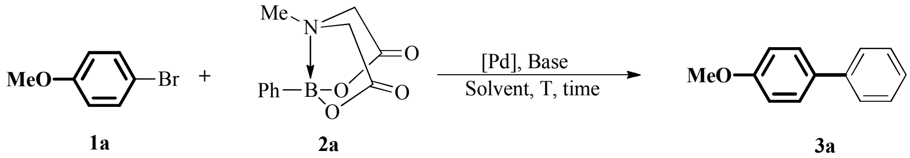
Table 1. Optimization of the reaction conditions[a]



entry	Cat. (mol%)	base	solvent (mL)	T (°C)	time (h)	Yield [b](%)
1	**I** (1)	K_3PO_4	$DMF:H_2O = 9:1$ (2)	100	12	38
2	**II** (1)	K_3PO_4	$DMF:H_2O = 9:1$ (2)	100	12	76
3	**III** (1)	K_3PO_4	$DMF:H_2O = 9:1$ (2)	100	12	70
4	**II** (1)	K_3PO_4	$DMF:H_2O = 9:1$ (3)	100	12	84
5	**II** (1)	Cs_2CO_3	$DMF:H_2O = 9:1$ (3)	100	12	trace
6	**II** (1)	K_2CO_3	$DMF:H_2O = 9:1$ (3)	100	12	trace
7	**II** (1)	KOH	$DMF:H_2O=9:1$(3)	100	12	40
8	**II** (1)	**K_3PO_4**	**$EtOH:H_2O = 6:1$ (2.1)**	**90**	**4**	**94**
9	**II** (1)	**K_3PO_4**	**H_2O (20% TBAB) (2.5)**	**90**	**4**	**95**
10[c]	**II** (1)	K_3PO_4	$EtOH:H_2O = 6:1$ (2.1)	90	4	90
11[c]	**II** (1)	K_3PO_4	H_2O (20%TBAB) (2.5)	90	4	87

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid MIDA ester (0.52 mmol), base (2 mmol), solvent (2-3 mL), under a nitrogen atmosphere. [b] Isolated yield. [c] Under an air atmosphere.

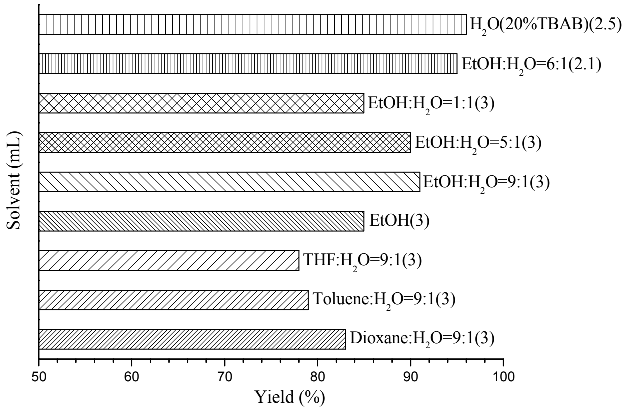


Figure 1. Influence of solvents. Reaction conditions: 4-bromoanisole (0.5 mmol), phenyl boronic acid MIDA ester (0.52 mmol), K_3PO_4 (2 mmol), Cat.II (1 mol%), solvent (2-3 mL) under nitrogen at 100 °C in 12 h.

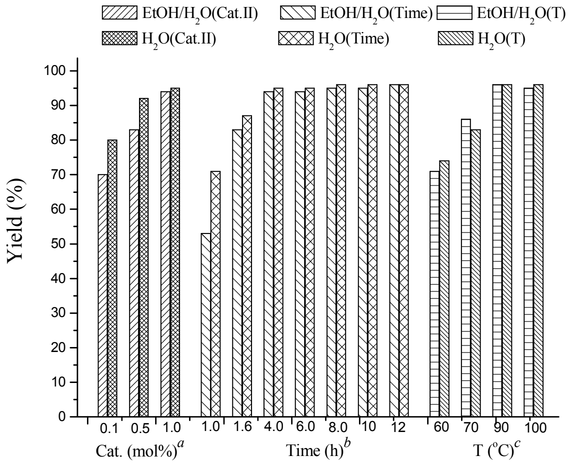


Figure 2. Influence of catalyst loading, reaction time and temperature. [a] The catalyst loading of Cat.**II** was optimized at 90 °C in 4 h. [b] Reaction time was optimized with 1 mol% Cat.**II** at 90 °C. [c] The reaction temperature was optimized with 1 mol% Cat.**II** in 12 h.

With the optimized reaction conditions, the substrate scope of both catalytic systems ($EtOH/H_2O$ or H_2O with 20% TBAB) was investigated with a series of aryl/heteroaryl MIDA boronates and aryl/heteroaryl bromides (Table 2). The desired products **3a** and **3b** were obtained in excellent yields regardless of the electronic effect of functional groupson aryl bromides. Sterically hindered *ortho*-substituted aryl bromides could be also transformed into target products in good yields (Table 2, **3c** and **3d**). When the reaction of methyl 2-bromobenzoate with **2a** was carried out in $EtOH/H_2O$, an ester-exchange reaction product of ethyl 2-biphenylcarboxylate was found in 20% yield by NMR spectroscopy (Table 2, **3c**, Supporting Information, NMR spectra). 3-Bromopyridine, 3-bromoquinoline,

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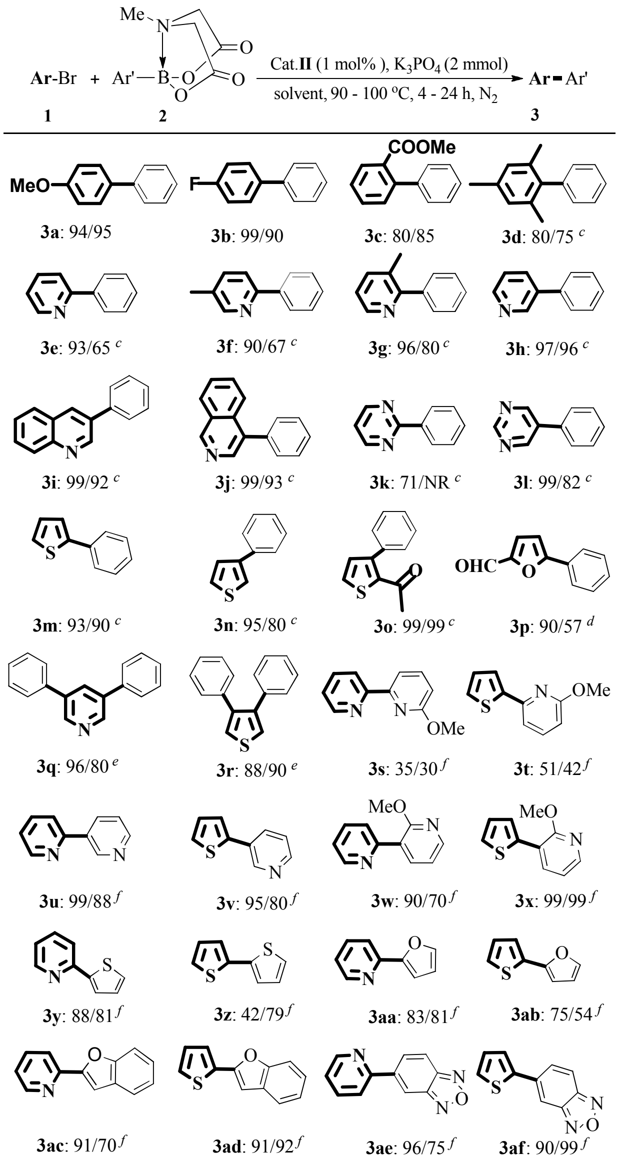
Table 2. Suzuki-Miyaura cross-coupling of aryl/heteroaryl bromides[a,b]



3a: 94/95 **3b**: 99/90 **3c**: 80/85 **3d**: 80/75 [c]

3e: 93/65 [c] **3f**: 90/67 [c] **3g**: 96/80 [c] **3h**: 97/96 [c]

3i: 99/92 [c] **3j**: 99/93 [c] **3k**: 71/NR [c] **3l**: 99/82 [c]

3m: 93/90 [c] **3n**: 95/80 [c] **3o**: 99/99 [c] **3p**: 90/57 [d]

3q: 96/80 [e] **3r**: 88/90 [e] **3s**: 35/30 [f] **3t**: 51/42 [f]

3u: 99/88 [f] **3v**: 95/80 [f] **3w**: 90/70 [f] **3x**: 99/99 [f]

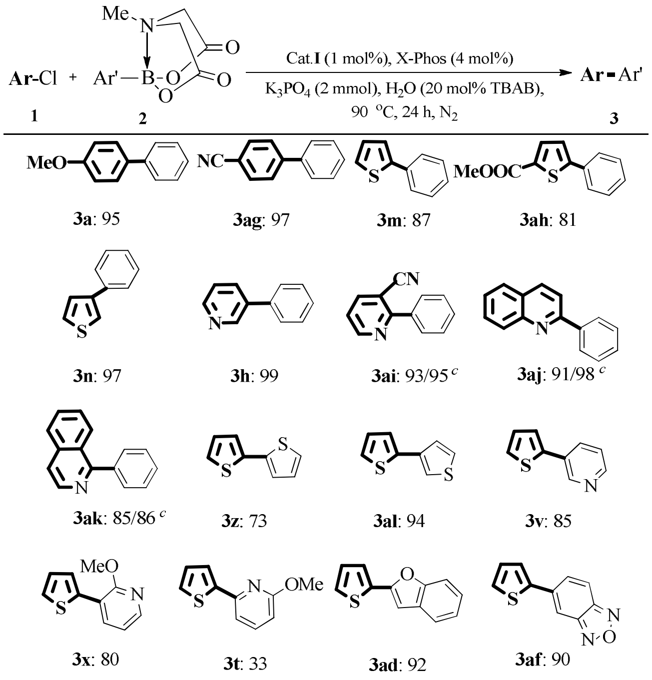
3y: 88/81 [f] **3z**: 42/79 [f] **3aa**: 83/81 [f] **3ab**: 75/54 [f]

3ac: 91/70 [f] **3ad**: 91/92 [f] **3ae**: 96/75 [f] **3af**: 90/99 [f]

[a] Reaction conditions: aryl or heteroaryl bromide (0.5 mmol), boronic acid MIDA ester (0.52 mmol), base (2 mmol), Cat.**II** (1 mol%), EtOH/H_2O (6:1, 2.1 mL) or H_2O (2.5 mL) with TBAB (20 mol%), under nitrogen at 90 °C in 4 h. [b] Isolated yield for EtOH/H_2O and H_2O. [c] reaction time 12 h. [d] 20 h. [e] Heteroaryl bromide (0.5 mmol), boronic acid MIDA ester (1.1 mmol), base (4 mmol), Cat.**II** (2 mol%), EtOH/H_2O (6:1, 4.2 mL) or H_2O (3 mL), TBAB (40 mol%). [f] 100 °C in 24 h.

4-bromoisoquinoline, 2-bromothiophene, and 2-acetyl-3-bromothiophene could be converted to the desired products in excellent yields in EtOH/H_2O and neat water (Table 2, **3h-3j**, **3m**, and **3o**). 2-Phenylpyridinederivatives (**3e**, **3f**, and **3g**) were obtained in excellent yields (93%, 90%, and 96%) in EtOH/H_2O and moderate yields in H_2O (65%, 67%, and 80%). This analogous phenomenon also occurred in the synthesis of **3k**, **3l**, **3n**, and **3p**. Heteroaryl dibromides gave triaryl products **3q** and **3r** in good to excellent yields in both solvents. Subsequently, 2-bromopyridine and 2-bromothiophene were chosen to evaluate the reactivity of various heteroaryl substituted MIDA boronates. The reaction of 3-pyridyl, 2-thiophenyl-, 2-furanyl-, 2-benzofuranyl-, or 5-bebzofurazanboronic acid MIDA esters with 2-bromoheteroaryls afforded **3u-3af** in good to excellent yields in both green solvents, except the coupling of 2-thiophenylboronic acid MIDA ester with 2-bromothiopene in EtOH/H_2O (**3z**). However, the reaction of 2-pyridyl MIDA boronate with 2-bromopyridine gave only a trace amount of product 2,2'-bipyridine by GC analysis. But changing 2-pyridine MIDA boronate to 6-methoxy-2-pyridylboronic acid MIDA ester, surprisingly, heterobiaryls **3s** and **3t** were isolated in 30-51% yields in EtOH/H_2O and H_2O.The structure of **3af** was determined by X-ray diffraction (Supporting Information, Figure S1).

Table 3. Suzuki-Miyaura cross-coupling of aryl/heteroaryl chlorides[a,b]



3a: 95 **3ag**: 97 **3m**: 87 **3ah**: 81

3n: 97 **3h**: 99 **3ai**: 93/95 [c] **3aj**: 91/98 [c]

3ak: 85/86 [c] **3z**: 73 **3al**: 94 **3v**: 85

3x: 80 **3t**: 33 **3ad**: 92 **3af**: 90

[a] Reaction conditions: aryl or heteroaryl chloride (0.5 mmol), boronic acid MIDA ester (0.52 mmol), base (2 mmol), Cat.**I** (1 mol %), X-Phos (4 mol %), H_2O (2.5 mL), TBAB (20 mol%), under nitrogen at 90 °C in 24 h. [b] Isolated yield. [c] EtOH/H_2O (6:1, 2.1 mL) at 90 °C in 24 h.

Encouraged by the above results, aryl/heteroaryl chlorides were then investigated with Cat.**I** (1 mol%) and 4 mol% X-Phos in H_2O at 90 °C (Table 3). It was found that the yields of **3ai**, **3ak**, and **3aj** in EtOH/H_2O were similar with their reaction in H_2O. Thus, considering the economic factor, our subsequent research was carried out in water. The modified catalytic system was suitable for aryl/heteroaryl chlorides substituted with electron-rich, electron-deficient or sterically hindered groups to afford the desired products **3a-3ak** in good to excellent yields. Under the standard reaction conditions, 2-chlorothiophene could also react with a series of heteroaryl MIDA boronates to form the disired products **3z-3af** (Table 3) in moderate to excellent yields except **3t**.

Conclusion

In conclusion, mono- and diheteroaryls were synthesized *via* the palladacycle-catalyzed Suzuki-Miyaura reaction of various MIDA boronates with aryl/heteroaryl halides in EtOH/H_2O or H_2O. The desired cross-coupling products were obtained in good to excellent yields. This modified catalytic system was suitable not only for aryl or heteroaryl halides substituted with electron-rich, electron-deficient or sterically hindered groups, but also for aryl/heteroaryl MIDA boronates.

Experimental section

General

All reactions were run under nitrogen in Schlenk tubes using vacuum lines. Palladacycle precatalysts,[10] phenyl, 2-thiophene and 3-pyridine boronic acid MIDA ester [11] were prepared according to the literature procedures. Unless otherwise noted, chemical reagents used in experiments were purchased from commercial suppliers without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 and 100 MHz instrument using $CDCl_3$ as the solvent at room temperature. High resolution mass spectrometry data of the products were collected on an LC/MS instrument. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. Thin-layer chromatography was visualized with UV light (254 and 365 nm). Flash chromatography was performed on silica gel (200-300 mesh).

General procedures of Suzuki-Miyaura reaction with aryl/heteroaryl bromides

In a typical experiment, Cat.**II** (3.7 mg, 1 mol%), aryl/heteroaryl MIDA boronate (0.52 mmol), aryl/heteroaryl bromide (0.5 mmol) and K_3PO_4 (425 mg, 2 mmol) were dissolved in EtOH/H_2O (6:1, 2.1 mL) or H_2O (2.5 mL with 20 mol% TBAB, 32 mg) under nitrogen atmosphere. Unless otherwise noted, the reaction mixture was stirred at 90 °C for 24 hours. Then, the suspension was cooled to room temperature and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with Na_2SO_4. After evaporation of the solvents, the residue was purified by silica gel column chromatography affording the desired product.

General procedures of Suzuki-Miyaura reaction with aryl/heteroaryl chlorides

In a typical experiment, Cat.**I** (4.6 mg, 1 mol%), X-Phos (9.5 mg, 4 mol%), aryl/heteroaryl MIDA boronate (0.52 mmol), aryl/heteroaryl chloride (0.5 mmol) and K_3PO_4 (425 mg, 2 mmol) were dissolved in H_2O (20 mol% TBAB, 32 mg, 2.5mL) under nitrogen atmosphere. Unless otherwise noted, the reaction mixture was stirred at 90 °C. Then, the suspension was cooled to room temperature and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried with Na_2SO_4. After evaporation of the solvents the residue was purified by silica gel column chromatography affording the desired product.

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