Tetrahedron Letters 55 (2014) 3038–3040

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

O-Aryloxime ether analogues as novel and efficient ligands for palladium-catalyzed Suzuki–Miyaura coupling in water

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ARTICLE INFO

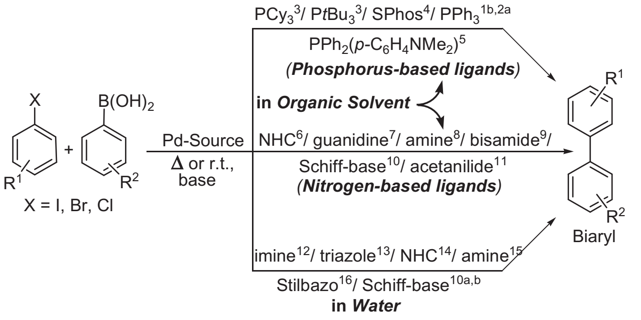
Article history:
Received 2 January 2014
Revised 24 March 2014
Accepted 25 March 2014
Available online 2 April 2014

Keywords:
Suzuki–Miyaura
Cross-coupling
O-Aryloxime ether
Water
Palladium chloride

ABSTRACT

O-Aryloxime ether analogues **L1**–**L3** were studied as ligands in palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl bromides and aryl boronic acids in water at room temperature. Reaction conditions for the cross-coupling were optimized using $PdCl_2$ and $Pd(OAc)_2$ under aerobic condition. From the three electronically diverse *O*-aryloxime ether ligands studied herein, the use of 1-*phenyl-ethanone O*-(4-*chloro-phenyl*)-*oxime* **L2** exhibits the best catalytic system in the presence of K_2CO_3 as the base and TBAB as the promoter.

The palladium-catalyzed Suzuki–Miyaura cross-coupling of organic halides with boronic acids is one of the most widely used methods for the synthesis of biaryls[1] and alkene derivatives, that are structural components of numerous agrochemicals, natural products, pharmaceuticals, and polymers.[2] Conventionally, the reactions have been carried out with numerous phosphorus and nitrogen based ligands, as they are known to increase the electron density over palladium, which can accelerate the oxidative addition step (Scheme 1).[3–16] Usually, these reactions are performed in organic solvents. However from the viewpoint of green chemistry, the use of water as an economical and environmentally benign alternative to organic solvent has received tremendous interest.[17] Water, compared to common organic solvent is most abundant, non-toxic, non-corrosive, as well as non-flammable.[18] In addition, water shows excellent chemical reactivity, and in many cases facilitates the solubility of base, salts, and polar compounds, thus enhancing the rate of reaction.[19] Moreover, studies of various natural processes occurring in aqueous environment reveal that water could be an effective media for almost every organic reaction.[20] Accordingly, numerous catalytic protocols have been developed for the Suzuki–Miyaura cross-coupling in water.[21] However in majority of cases either an elevated reaction temperature or the use of co-solvent is required to maximize catalytic performances.[22]



Scheme 1.

Based on the previous literature reports of N-containing ligands,[6–15] we expect that the *O*-aryloxime ether bearing nitrogen and oxygen atoms (Fig. 1) will be an interesting class of ligand in the Suzuki–Miyaura reaction. However, to the best of our knowledge the potential of oxime ether as ligand has never been investigated in the Suzuki–Miyaura reaction. Through this communication, we wish to report the use of simple catalytic system, composed of palladium chloride and *O*-aryloxime ether as ligands, which promotes Suzuki–Miyaura cross-coupling reactions of aryl halides and arylboronic acids at room temperature in water.

Initially, we synthesized a series of the analogous aryloxime ethers **L1–L3**,[23] (Fig. 1) to study their efficiency as ligands in

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http://dx.doi.org/10.1016/j.tetlet.2014.03.113
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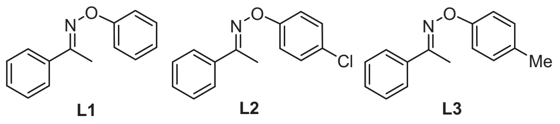
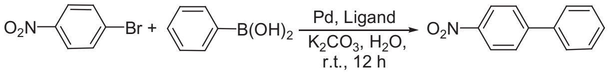


Figure 1. Ligands screened for Suzuki–Miyaura reaction.

palladium-catalyzed Suzuki–Miyaura cross-coupling reaction in water. The reaction of 4-bromonitrobenzene (0.5 mmol) and phenylboronic acid (0.55 mmol) was chosen as the prototype, and carried out in the presence of 1 mol % of palladium salt, K_2CO_3 (2 equiv), and ligands **L1**–**L3** (2 mol %) at room temperature.[24] It could be seen from Table 1 that the reaction proceeds more efficiently with the ligand **L2** compared to **L1** and **L3**, in the presence of $PdCl_2$ and TBAB (*tert*-butyl ammonium bromide) (Table 1, entry 4).

This is a significant result, as most of the reported ligand-based palladium-catalyzed Suzuki–Miyaura reactions require high temperature, long reaction time, and organic or biphasic media. Encouraged by the highest yield in the presence of ligand **L2**, we further optimized $PdCl_2$/**L2** (Table 2). As shown in entries 1 and 2 (Table 2), it was found that the time required for the formation of 4-nitro-biphenyl increases to 5 h from 2.5 h when 1 mol % of **L2** was used, while less amount of $PdCl_2$ (0.5 mol %) led to slightly lower yield with increase in reaction time (Table 2, entry 3). Generally, presence of water increases solubility of the bases, which are responsible for the activation of boronic acid resulting in enhancing the rate of the reaction in an aqueous medium. This may be the reason for low yield in isopropanol (Table 2, entry 4). To further optimize the reaction conditions, different bases were screened in the presence of 2 mol % of **L2** and 1 mol % of $PdCl_2$ (Table 2, entries 5–10). As previous work has revealed that phosphate base was able to perform as highly efficient base in Pd-catalyzed Suzuki–Miyaura reaction,[25] we employed $Na_3PO_4{\cdot}12H_2O$ as the base to study if the rate of reaction could get enhanced, but it turned out to be poorer base as compared to K_2CO_3 (Table 2, entries 1 and 5). Similarly, Na_2CO_3 and Cs_2CO_3 also gave lower yields of product (Table 2, entries 6 and 7). We further examined the effect of metal hydroxides in our reaction conditions. KOH and NaOH have provided 73% and 78% isolated yield after 24 h, respectively, (Table 2, entries 8 and 9). Organic base such as triethyl-amine (Et_3N) gave only a trace amount of product after 24 h (Table 1, entry 10). However, no cross-coupling product was observed in the absence of base (Table 2, entry 11). Usually a strong base stimulates side reactions lowering the yield, and a weak base remains unable to activate boronic acids. Metal carbonates as compared to other bases offer clean and mild reaction condition, high yield, and reaction rate, and simple work-up procedure. As recognized from the literature, the presence of electron-rich and bulky ligands in palladium-catalyzed reaction provides extra stabilization to the rate determining transition state.[26] Similar to the ligands like aryl oximes[27] and arylamines,[28] the aryl ring of the aryloxime ether is expected to undergo ortho-metalation through CH activation to form highly active palladacycle.

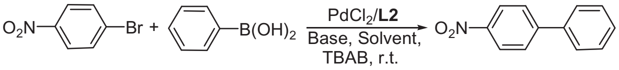
Table 1
Effect of the *O*-aryloxime ether ligand (**L1**–**L3**) on palladium-catalyzed Suzuki–Miyaura reaction[a]



Entry	Ligand	[Pd]-source	Additive	Yield[b] (%)
1	–	$PdCl_2$	–	10
2	**L1**	$PdCl_2$	–	23
3	**L1**	$PdCl_2$	TBAB	91
4	**L2**	$PdCl_2$	TBAB	99
5	**L3**	$PdCl_2$	TBAB	87
6	–	$Pd(OAc)_2$	–	9
7	**L1**	$Pd(OAc)_2$	TBAB	87
8	**L2**	$Pd(OAc)_2$	TBAB	94
9	**L3**	$Pd(OAc)_2$	TBAB	81

[a] Reaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), K_2CO_3 (1 mmol), Pd-source (1 mol %), ligand (2 mol %), water (4 mL), TBAB (0.5 mmol), 12 h, ca. 27 °C in air unless otherwise noted.
[b] Isolated yield.

Table 2
Optimization of the Suzuki–Miyaura reaction of 4-bromonitrobenzene with phenylboronic acid in the presence of **L2**[a]



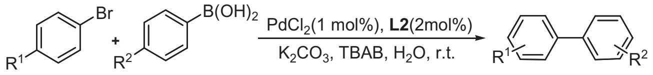
Entry	Solvent	Base	$PdCl_2$/**L2** (mol %)	Time (h)	Yield[b] (%)
1	H_2O	K_2CO_3	1/2	2.5	99
2	H_2O	K_2CO_3	1/1	5	96
3	H_2O	K_2CO_3	0.5/1	6.5	96
4	*i*-PrOH	K_2CO_3	1/2	4	94[c]
5	H_2O	$Na_3PO_4{\cdot}12H_2O$	1/2	6	92
6	H_2O	Na_2CO_3	1/2	6	85
7	H_2O	Cs_2CO_3	1/2	12	75
8	H_2O	KOH	1/2	24	73
9	H_2O	NaOH	1/2	24	78
10	H_2O	Et_3N	1/2	24	Trace
11	H_2O	–	1/2	24	no reaction

[a] Reaction conditions: 4-bromonitrobenzene (0.5 mmol), phenylboronic acid (0.55 mmol), base (1 mmol), TBAB (0.5 mmol), solvent (4 mL), ca. 27 °C in air unless otherwise noted.
[b] Isolated yield.
[c] Without TBAB.

After attaining the optimal reaction conditions, we then examined the applicability of the present catalytic system to the cross-coupling of various electronically diverse aryl bromides and aryl boronic acids. Generally, aryl bromides with electron-donating groups at the *para* position are significantly less reactive than aryl bromides bearing electron-withdrawing groups. However, as shown in Table 3, most of the aryl bromides were found equally reactive toward electronically different aryl boronic acids, yielding corresponding biphenyl derivatives in good to excellent yields (90–100%, Table 3). Similarly, 4-bromonitrobenzene reacts with electronically diverse arylboronic acids with almost comparable reactivity (Table 3, entries 1–3). When 4-bromoanisole was used as substrate, slight decrease in yield was observed with all types of arylboronic acids (Table 3, entries 4–6). However, in case of 4-bromotoluene, higher yield was observed (Table 3, entry 7 and 8). Conversely, for other aryl bromides, having electron-withdrawing substituent at *para* position, such as for 4-bromobenzaldehyde and 4-bromoacetophenone, the amount of biaryl products remains relatively similar to that with 4-bromonitrobenzene (Table 3, entries 1–3 and 9–14). In another case, bromobenzene was found to react efficiently with all three types of aryl boronic acids yielding biaryl products in excellent yields (Table 3, entries 15–17). These results are quite significant as the desired biaryls could be efficiently achieved at room temperature using water as a solvent and with relatively lower palladium loading (1 mol %) in the presence of *O*-aryloxime ether (2 mol %).

In conclusion, we have developed a simple and convenient methodology based on $PdCl_2$ and *O*-aryloxime ether analogous for Suzuki–Miyaura coupling of aryl bromides and aryl boronic acids. From the three electronically diverse ligands studied herein, the use of 1-*phenyl-ethanone O*-(4-*chloro-phenyl*)-*oxime* **L2** resulted

Table 3
Suzuki–Miyaura reaction of arylbromides with different arylboronic acids[a]



Entry	R^1	R^2	Time (h)	Yield[b] (%)
1	NO_2	H	2.5	99
2	NO_2	Cl	4.5	95
3	NO_2	OCH_3	6	94
4	OCH_3	H	2.5	94
5	OCH_3	Cl	4	90
6	OCH_3	OCH_3	4.5	92
7	CH_3	H	1.5	98
8	CH_3	OCH_3	2	99
9	CHO	H	5	98
10	CHO	OCH_3	4	97
11	CHO	Cl	6	95
12	$COCH_3$	H	4	95
13	$COCH_3$	OCH_3	5.5	93
14	$COCH_3$	Cl	6	90
15	H	H	1	100
16	H	OCH_3	3	95
17	H	Cl	4.5	96

[a] Reaction conditions: aryl bromide (0.5 mmol), arylboronic acid (0.55 mmol), K_2CO_3 (1 mmol), $PdCl_2$ (1 mol %), **L2** (2 mol %), water (4 mL), TBAB (0.5 mmol), ca. 27 °C in air unless otherwise noted.
[b] Isolated yield.

in most efficient conversion in pure water at room temperature. The present method, involving aerobic condition, is in accordance with the concept of green chemistry, and offers mild and effective alternative to the existing protocols. Further effort to identify the exact role of the ligands in the catalytic system and more application of this system are currently under investigation in our laboratory.

Acknowledgements

We gratefully thank UGC, New Delhi (India) for support (No. 41-254/2012 (SR). M.M. thanks UGC, New Delhi for UGC-BSR (RFSMS) fellowship.

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23. Preparation of ligands **L1**–**L3**[29a]
Acetophenone oxime (1 mmol) and corresponding aryl boronic acids (2 mmol) were stirred in a round bottom flask with $Cu(OAc)_2$ (0.5 mmol), Cs_2CO_3 (1 mmol), and 4 mL of DMSO under open atmosphere. The progress of the reaction was monitored by TLC (Merck silica gel $60F_{254}$ plates). After completion, the reaction mixture was quenched with dil. $NH_4Cl–H_2O$ solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined extract was washed with brine (2 × 20 ml) and dried over anhydrous Na_2SO_4. After evaporation of ethyl acetate under reduced pressure, the residue was chromatographed {silica gel (60–120 mesh) ethyl acetate-hexane; 1.5:8.5} to obtain the desired products. The analytically pure product was obtained in 82% (**L1**), 80% (**L2**), and 79% (**L3**).
Ligand **L1**: Colorless oil.[29]
^{1}H NMR: ($CDCl_3$, 300 MHz, ppm) δ: 7.63–7.60 (m, 2H), 7.39–7.37 (m, 3H), 7.22–7.20 (m, 2H), 6.91 (s, 1H), 6.82–6.79 (m, 2H), 2.31 (s, 3H, $–CH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 156.2, 155.6, 136.4, 129.6, 129.3, 128.6, 126.1, 120.5, 115.4, 12.5.
24. Typical experimental procedure for Suzuki–Miyaura reaction of aryl bromides with aryl boronic acids.
All the reactions were carried out in open atmosphere. A mixture of aryl bromide (0.5 mmol), aryl boronic acid (0.55 mmol), K_2CO_3 (1 mmol), $PdCl_2$ (1 mol %), ligand (2 mol %), TBAB (0.5 mmol), and water (4 mL) was stirred at room temperature for the indicated time in a 25 mL round bottom flask. The progress of the reaction was monitored using TLC (Merck silica gel $60F_{254}$ plates) under UV light. After completion, the reaction mixture was diluted with brine (10 mL) and extracted with ether (3 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4. After evaporation of ether under vacuum, the product was isolated by short-chromatography {silica gel (60–120 mesh), ethyl acetate-hexane; 0.5:9.5}. The isolated products were confirmed by comparing their ^{1}H and ^{13}C NMR and mass spectral data with reported samples.
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