The Synthesis and Application of 2-acetyl-6-(1-naphthyl)-pyridine Oxime as a New Ligand for Palladium Precatalyst in Suzuki Coupling Reaction

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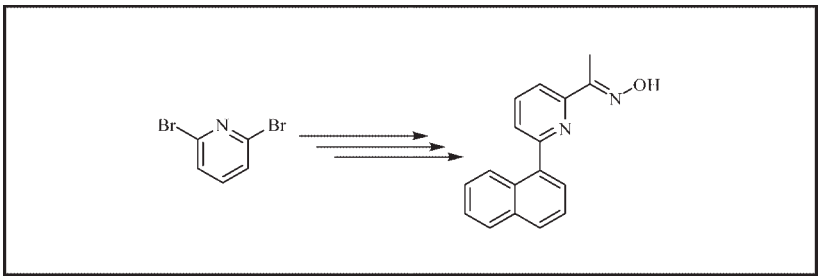

The synthesis of 2-acetyl-6-(1-naphthyl)-pyridine oxime ligand from 2,6-dibromopyridine and 1-bromo-naphthalene is described, and the new palladium(II) complex used as a Pd(0) precatalyst in the Suzuki cross-coupling reaction was studied. The results showed that the novel naphthalene pyridine oxime complex could serve as an efficient precatalyst.

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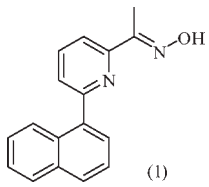
INTRODUCTION

It is widely accepted that palladium-catalyzed cross-coupling reaction are one of the most important processes in synthesis chemistry, of which Suzuki–Miyaura cross-coupling reaction of aryl halides with organoboron reagents has become one of the most efficient and widely utilized methods for the formation of sp^2-sp^2 carbon-carbon bonds [1–4]. Traditional phosphane containing palladium catalysts have many disadvantages such as high cost, air- and thermo-sensitivity, low activity towards deactivated substrates, contamination of the products with the phosphane-based byproducts [5,6]. Therefore, many efforts have been made to find more active and stable palladium catalysts. In our lab, oxime containing molecule [7] was synthesized and its catalyst activity in cross-coupling reaction was examined. Poor enantioselectivity was observed. So, we want to improve the activity by substitution of naphthalene group to pyridine.

Some common conclusions concerning the influence of the electronic and steric properties of the ligands on the efficiency of the catalysts in Suzuki-Miyaura reaction were made based on the structure-activity analysis of these catalysts. Increasing the electronic density on palladium could enhance the catalytic activity particularly by promoting the aryl halide oxidative addition; while the bulkness of the ligand presumably could facilitate the reductive elimination step [6]. We introduced the 1-naphthalene group to the pyridine oxime to obtain more active catalyst, and here, we reported the synthesis and application of a novel naphthalene pyridine oxime ligand on the Suzuki reaction (1).



(1)

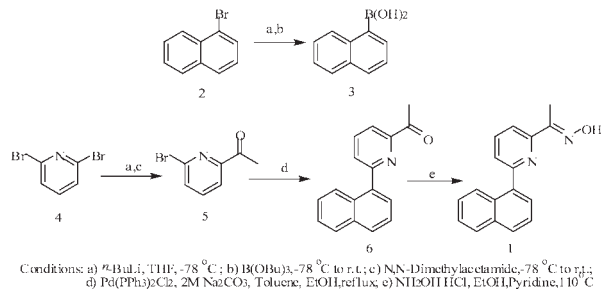
RESULTS AND DISCUSSION

Scheme 1 outlined the synthetic route employed in our lab for preparation of the substrate 1-[6-(1-naphthyl)-2-pyridyl]-1-ethanone oxime 1.

Our strategy for the synthesis of **6** was first based on the selective lithiation of 2,6-dibromopyridine [8–11] and then Suzuki cross coupling reaction [7]. After the synthesis of substrate of oxime, the precatalyst **7** was prepared by Scheme 2.

After the synthesis of (**7**), the application of naphthlene oxime ligand on Suzuki-cross coupling reaction was studied. At first, the optimal reaction time was investigated. The reaction was preceded very quickly at the first 60 min. Higher yield was not observed when the reaction time was longer as shown in Figure 1. So the optimal value for reaction time was 60 min.

Scheme 1



Conditions: a) *n*-BuLi, THF, -78 °C ; b) B(OBu)3, -78 °C to r.t.; c) N,N-Dimethylacetamide, -78 °C to r.t.; d) Pd(PPh3)2Cl2, 2M Na2CO3, Toluene, EtOH,reflux; e) NH2OH HCl, EtOH,Pyridine,110 °C

The activity of the ligand was examined as shown in Table 1. The results demonstrated that the yield was influenced by the substitution of the aryl halides. The yield of bromo-benzene was the highest; the yield of *p*-bromo toluene was higher than that of *o*- and *m*-bromo toluene. 1-Methyl-4-nitrobenzene showed the lowest yield among all the reactions. This may be the reason that the substituents had the effect on reactivity of aryl halides. The nitro group was one of electron-withdrawing substituents decreasing the reactivity of the aryl halides, leading to the low yield in reaction. In addition, the effect of substituents on orientation was shown in Table 1. The methyl group was the weak electron-donating substituent. Therefore, the *ortho*/*para* bromo toluene was more active than the *meta* one because of a steric effect of the *ortho* methyl group behind the electron effection, the yield of *para* one was higher than that of *ortho* one. When water was added during the reaction, the yields become lower. When the 1-bromo-4-nitrobenzene was used as aryl halide in toluene with base of $CsCO_3$ for reflux 60 min, the yield was decreased to 33% (Run 8).

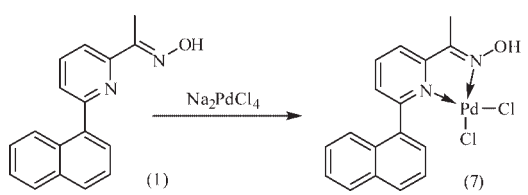
When the reaction of 1-(6-bromopyridin-2-yl)ethanone with naphthalen-1-ylboronic acid was carried out in toluene as solvent and Na_2CO_3 as base for refluxing 60 min and the yield was up to 85%, (Run 11), higher than the former reaction (Run 10).

Further research related to higher activity based on the date is also underway.

EXPERIMENTAL

Deuterium NMR and CMR spectra were measured with a JNM-ECS400 NMR spectrometer at 400 MHz. Mass spectra (MS) were recorded on a JOEL JMS-AX505HA. The melting point was determined by MFB-595-030G digital thermometer apparatus.

Scheme 2



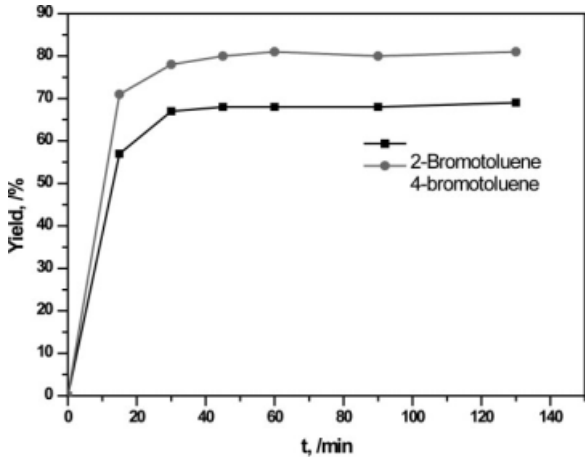


Figure 1. The yield-time relationship.

1-Naphthylboronic acid(3). Dropwise addition of 7.95 mL (13.5 mmol) of a 1.7*M* solution of *t*-BuLi in pentane to a stirred solution of 1-bromonaphthaline (**2**) (2.67 g, 12.9 mmol) in 50 mL of THF at –78°C led to the formation of a white precipitate. After 45 min, 1.40 g (1.5 mL, 13.5 mmol) of $B(OMe)_3$ was added, and the resulting clear solution was maintained at –78°C for 1 h. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 h. A 10% solution of HCl (25 mL) and ethyl acetate (50 mL) were added. The aqueous layer was extracted with 4 × 20 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The off-white solid residue was suspended

Table 1

Suzuki cross-coupling reaction.

Run	Ar-boronic acid	Br-Ar	Base	Water/ Toluene	Yield
1			Na_2CO_3	0:20	90
2			Na_2CO_3	0:20	73
3			Na_2CO_3	10:20	60
4			Na_2CO_3	0:20	60
5			Na_2CO_3	0:20	82
6			Na_2CO_3	10:20	55
7			Na_2CO_3	0:20	79
8			Ca_2CO_3	10:20	33
9			Na_2CO_3	0:20	94[a]
10			Na_2CO_3	10:20	80[b]
11			Na_2CO_3	10:20	85

Reagents and conditions: (2 mol%) Pd-catalyst, toluence, base, reflux, 60 min.

[a] Reactions time is 360 min.

[b] Catalyst is $Pd(PPh_3)_4$, reaction time is 12 h.

in 50 mL of petroleum ether and filtered to give **3** (2.13 g, yield 96%).

Mp 202–203°C; MS: *m/z* 172[M^+]; ^{1}H NMR (400 MHz, DMSO, δ, ppm); 7.50–8.10(*m*, 6H, Hnaph), 8.38(*s*, 2H, H_{OH}), 8.53(*d*, 1H, Hnaph, J = 13.5 Hz); IR(cm^{-1}) 3310 (—OH).

1-(6-Bromopyridin-2-yl)ethanone (5). A solution of 7.08 g (30 mmol) of 2,6-dibromopyridine (**4**) dissolved in 42 mL of dry THF was cooled to −78°C. The 2,6-dibromopyridine was lithiated by slowly adding 12 mL of a 2.6*M* solution of *n*-butyllithium in hexane. After the addition, the resulting dark yellow solution was stirred at −78° for 30 min. Then neat *N*,*N*-dimethylacetamide (4.2 mL, 54.3 mmol) was added over a period of 30 s. The reaction solution was stirred at −78 °C for 15 min, and then the solution was allowed to warm to room temperature. The resulting yellow solution was hydrolyzed with saturated NH_4Cl (40 mL). The mixture was stirred for additional 60 min, and the aqueous layer was separated and extracted with diethyl ether twice (100 mL and 60 mL, respectively). The combined organic layer was washed with brine 60 mL, dried (sodium sulfate) and evaporated to *ca*. 10 mL in volume and cooled to 0°C. After a few hours, a brown solid was isolated by filtration. The crude product was purified by chromatography on silica eluting with hexane/ethyl acetate (95:5) to afford white crystals, 5.1g (85%).

Mp 54–55°C; MS: *m/z* 199[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) 2.69(*s*, 3H, CH_3),7.65–7.71(*m*, 2H, H_{Ar}), 7.97–7.99 (dd, J = 7.25, 1.36, 1H, CH_{Ar}); IR(KBr, cm^{-1}) 1696 (C=O); 593 (C—Br).

1-(6-Naphalen-1-yl)pyridin-2-yl]ethanone(6). To a solution of 3 (0.72 g, 3.60 mmol) and $Pd(OAc)_2$ (0.13 g) in 10 mL of deaerated toluene, 4 mL of a 4.4*M* aqueous solution of Na_2CO_3 were added, followed by a solution of 0.79 g (4.58 mmol) of 1-naphthylboronic acid in 10 mL of MeOH. The mixture was heated to 80–85°C under stirring for 30 h. The resulting solution was allowed to cool to room temperature and a solution of 8 mL of concentrated aqueous NH_3 in 20 mL of saturated aqueous Na_2CO_3 was added. The mixture was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were washed with 50 mL of water and 100 mL of brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 1.15 g of the crude product which was purified by flash chromatography [CC, SiO_2, i) petroleum ether/CH_2Cl_2 (4:1), R_f = 0.1, ii) CH_2Cl_2]. The desired product was obtained as an off-white solid in 80% yield (0.71 g).

MS: *m/z* 246[M − 1], 247 [M^+], 248[M + 1]; IR(cm^{-1}) 1698(C=O); ^{1}H NMR (400MHz, $CDCl_3$, δ, ppm) 2.76 (*s*, 3H, CH_3), 7.47–7.55 (*m*, 2H, H_{Ar}), 7.56–7.60 (*t*, J = 7.30, 7.70, 7.25, 1H, H_{Ar}), 7.64–7.66 (dd, J = 7.02, 0.91, 1.36, 1H, H_{Ar}), 7.76–7.78 (dd, J = 7.70, 0.91, 1H, H_{Ar}), 7.92–7.98(*m*, 3H, H_{Ar}),8.16-8.18(*d*, J = 8.15, 1H, H_{Ar})

1-(6-(Naphtgalene-1-yl)pyridin-2-yl)ethanone oxime (1). To a solution of $NH_2OH{\cdot}HCl$ (0.75 g, 10.8 mmol) in 10 mL of pyridine was added **6** (1.00 g, 5.22 mmol) and the mixture was stirred at 80°C for 4 h. After cooling to room temperature, the reaction mixture was poured into cold water and allowed to stay for 24 h. Precipitate thus formed was then collected by filtration, washed with water and dried in air to give 1.05 g (91%) of 3,5-diacetyl-2,6-dimethyl-pyridine dioxime.

Mp: 150–151°C; MS: *m/z* 262 [M^+]; ^{1}H NMR (400 MHz, DMSO, δ,ppm) 2.19(*s*, 3H, CH_3), 7.47–7.55(*m*, 2H, H_{Ar}), 7.57–7.61(*t*, J = 7.25, 1H, H_{Ar}), 7.61–7.63(dd, J = 4.76, 1.81, 1.36, 1H, H_{Ar}), 7.87–7.92(*t*, J = 8.83, 8.15, 9.51, 1H, H_{Ar}), 7.92–7.96(*t*, J = 7.70, 7.25, 8.15, 1H, H_{Ar}), 7.98–8.01(dd, J = 7.16, 1.36, 2H, H_{Ar}), 8.09–8.11(d, J = 8.15, 1H, H_{Ar}), 11.53(*s*, 1H, N-OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm) 10.87, 118.67, 124.97, 125.90, 125.99, 126.53, 127.07, 128.06, 128.88, 129.33, 131.10, 134.06, 137.91, 138.39, 154.57, 157.96, 159.48. IR (KBr, cm^{-1}) 3300 (—OH).

Oxime-derived palladacycle (7) (preparation of precatalyst). To a stirred solution of sodium tetrachloropalladate(II) (147 mg, 0.5 mmol), which was obtained as well-formed crystals by treating $PdCl_2$ solutions with stoichiometric quantities of sodium chlorides and slowly evaporating the solutions in MeOH (2 mL), 2-acetyl-6-(1-naphthyl)-pyridine oxime (131 mg, 0.5 mmol) in MeOH (1 mL) was added dropwise. The precipitate was collected by filtration after stirring for 2 h and washed with MeOH and H_2O, then dried in vacuum over P_2O_5. Precatalyst **7** was obtained as a yellow-brownish powder (400 mg, 80%).

Mp > 300°C; IR(cm^{-1}): 1755, 1730, 1705 (C—O); MS: *m/z* 440[M + 1],880[M + M]; ^{1}H NMR (400 MHz, DMSO, δ, ppm) 2.19(*s*, 3H, CH_3), 7.47–7.64 (*m*, 5H, H_{Ar}), 7.87–8.00 (*m*, 4H, H_{Ar}), 11.53(*s*, 1H, N—OH); ^{13}C NMR (400 MHz, DMSO, δ, ppm) 10.87, 118.67, 124.96, 125.89, 125.98, 126.51, 127.06, 128.05, 128.87, 129.33, 131.09, 134.05, 137.91, 138.39, 154.57, 155.05, 157.96.

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