Transition Met Chem (2012) 37:331–335
DOI 10.1007/s11243-012-9593-4

A highly active and stable imidazolidine-bridged N,O-donor ligand for efficient palladium catalyzed Suzuki–Miyaura reactions in water

Jun Xue · Zhonggao Zhou · Yulan Liu ·
Li Huang · Hongwei Yu · Yongrong Xie ·
Chen Lai

Received: 21 January 2012 / Accepted: 22 February 2012 / Published online: 23 March 2012

Abstract We have used the sterically hindered N,O-donor ligand 1,4-bis(2-hydroxy-3,5-di-tert-butyl-benzyl)-imidazolidine with various Pd salts as a catalyst for the Suzuki reaction. This system exhibited excellent catalytic activity in Suzuki reactions of arylboronic acids with aryl halides, including aryl iodides, aryl bromides and activated aryl chlorides, using aqueous methanol as solvent under mild conditions. The catalytic system can be reused once without significant loss of activity.

Introduction

The discovery of the Suzuki reaction is one of the most important landmarks of modern day organic chemistry, as recognized by the award of a Nobel Prize to Akira Suzuki in 2010 [1–3]. The Suzuki reaction has been used in numerous syntheses, in the areas of materials science and medicinal chemistry [4–6]. The reaction is generally catalyzed by palladium complexes with or without supporting ligands in organic solvents and, more recently, in aqueous media [7–11]. Mixed donor ligands are very common in such applications and can be linear, branched or cyclic, with at least two different donor groups capable of chelation to metal atoms [12–14]. The development of new ligands bearing mixed donor atoms other than phosphorus has been arousing more and more interest in the field of organic chemistry, especially, in transition metal-catalyzed coupling reactions [15–18].

Previously, Mohanty et al. used piperazine-bridged phenol ligands (ligands **2**, **3** and **4** in Scheme 1) for Pd-catalyzed Heck and Suzuki reactions. The presence of the nitrogen atom in the piperazine ring seems to have a significant effect on the catalytic activity in Pd-catalyzed C–C bond-forming reactions [19, 20]. Our previous studies have also revealed that ligands **2**, **5** and **6** give high catalytic activities for Suzuki reactions under mild conditions [21, 22]. Since imidazolidine-bridged bis-phenols can act as anionic bifunctional ligands, rigid backbones that can actually enforce a constrained geometry and, thereby, a certain coordination mode can influence one or more reaction steps of a catalytic cycle in several ways, for example, stabilization or destabilization of the initial, transition or final states [23]. Current technologies demand new catalysts, which are inexpensive, readily accessible, moisture- and air-stable and most importantly, highly effective. In recent years, amine bis(phenolate) ligands have received considerable attention in organometallic chemistry [24]. It is expected that such ligands may have high catalytic activity for C–C bond-forming reactions.

As a part of our interest in studying Pd-catalyzed cross-coupling reactions and the use of mixed donor N,O-ligands in catalytic applications [21, 22, 25], we report herein on

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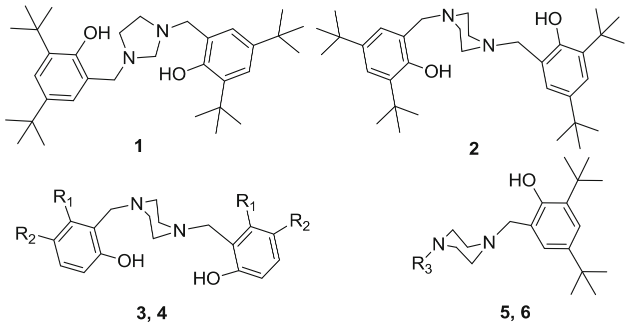
Electronic supplementary material The online version of this article (doi:10.1007/s11243-012-9593-4) contains supplementary material, which is available to authorized users.

J. Xue · Z. Zhou (✉) · L. Huang · Y. Xie (✉) · C. Lai
College of Chemistry and Chemical Engineering,
Gannan Normal University, Ganzhou 341000,
People's Republic of China
e-mail: zhgzhou@foxmail.com

Y. Xie
e-mail: yongrongxie@foxmail.com

Y. Liu
College of Architecture and Environment, Sichuan University,
Chengdu 610207, People's Republic of China

H. Yu
School of Chemical Engineering, Shijiazhuang University,
Shijiazhang 050035, People's Republic of China



Scheme 1 Structures of selected ligands. 3, R_1–R_2 = –(CH)$_4$–; 4, R_1 = H, R_2 = *t*Bu; 5, R_3 = Me; 6, R_3 = Ph

air- and moisture-stable palladium complexes of the imidazolidine-bridged phenol ligand **1** in Suzuki–Miyaura reactions of aryl iodides, aryl bromides, and activated aryl chlorides in aqueous media under mild conditions.

Experimental

All starting materials and reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received. Solvents were dried with standard methods and freshly distilled prior to use. 1,4-bis(2-hydroxy-3,5-di-tert-butyl-benzyl)-imidazolidine (**1**) was prepared by a modification of the literature method (see below) [24]. NMR spectra were recorded on a Bruker Avance III 400 MHz (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer. The NMR studies were carried out using $CDCl_3$ as solvent, and signals are quoted in ppm as δ downfield from TMS as internal standard.

GC–MS analyses were carried out on an Agilent 6,890 GC with 5,973 mass spectrometer, using an AT.SE-30 column of 50 m length, 0.32 mm diameter and 0.5 μm film thicknesses. GC parameters for Suzuki reactions were as follows: injector temperature, 280 °C; detector temperature, 280 °C; initial temperature, 60 °C; initial time, 5 min; temperature ramp 1, 30 °C min^{-1}; final temperature, 200 °C; ramp 2, 20 °C min^{-1}; final temperature, 250 °C; run time, 25 min; inject, 1.0 μL; helium carrier gas; system pressure, 3.5 bar.

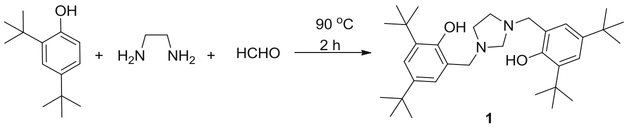
A mixture of ethylenediamine (1.34 mL, 0.020 mol) and 40% aqueous formaldehyde solution (6.57 mL, 0.080 mol) was stirred at room temperature for 0.5 h, and then 2,4-di-tert-butylphenol (8.25 g, 0.040 mol) was added and the mixture was stirred for 2.0 h at 90 °C oil bath. The resulting solid was washed with hot methanol (100 mL), and the white solid precipitate was collected by vacuum filtration; yield, 9.26 g (91%). Mp: 183.9–184.2 °C (184.1–184.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.76 (br, 2H, OH), 7.29 (s, 2H, Ph), 6.90 (s, 2H, Ph), 3.95 (s, 4H, CH_2), 3.59 (s, 2H, imidazolidine ring), 3.06 (br, 4H, imidazolidine ring), 1.49 (s, 18H, ^{t}Bu), 1.34 (s, 18H, ^{t}Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.16, 140.75, 135.75, 123.35, 123.12, 120.88, 74.40, 59.27, 51.80, 34.94, 31.73, 29.68 ppm. The ^{1}H NMR spectrum of **1** shows a broad singlet at 10.76 ppm for the phenolic OH protons, similar to ligand **2**. The presence of OH proton was confirmed by a D_2O exchange experiment.

General procedure for the Suzuki reaction

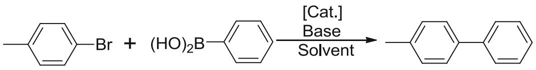
The appropriate amounts of ligand and metal precursor were added to the required solvent (3.0 mL). The mixture was stirred for 5 min, and then the aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol), and base (1.0 mmol) were added and the mixture was stirred and reacted under an inert atmosphere. The course of the reaction was monitored by GC–MS analysis, and yields were calculated against the aryl halides. On completion of the reaction, the solvent was removed under reduced pressure. The residue was diluted with H_2O (3.0 mL) and Et_2O (3.0 mL), followed by extraction with Et_2O (2 × 3.0 mL). The organic fraction was dried over anhydrous $MgSO_4$ and then filtered, and the solvent was evaporated under reduced pressure. The crude product that was purified by column chromatography using 100–200 mesh silica gel and the purified products were characterized by comparing their ^{1}H NMR spectra with those found in the literature; 4-methoxybiphenyl (Table 6, entries 1, 5 and 14) [26]; 4-methylbiphenyl (Table 6, entries 2, 3, and 12) [19]; 2-methylbiphenyl (Table 6, entries 4 and 13) [26]; 4-acetylbiphenyl (Table 6, entries 6 and 15) [19]; biphenyl (Table 6, entries 7 and 11) [27]; 4-trifluoromethylbiphenyl (Table 6, entries 8, 9 and 10) [21]; 4,4′-dimethylbiphenyl (Table 6, entries 16 and 18) [28]; 4-methoxyl-4′-methyl-1,1′-biphenyl (Table 6, entries 17 and 19) [29].

Results and discussion

The Mannich reaction is a convenient method to synthesize amine bridged bis(phenol)s. Shen and co-workers have reported the synthesis of ligand **1** in methanol at 60 °C oil bath in 65% yield [24]. We have developed an alternative atom-economic synthesis of ligand **1**, giving a yield of 91% within 2.5 h (Scheme 2).



Scheme 2 Modified experimental procedure for the preparation of ligand **1**



Scheme 3 Pd-catalyzed Suzuki reaction of 4-bromotoluene with phenylboronic acid

Table 1 Effect of different bases on the Suzuki reaction

Entry	Base	Yield (%)[a]
1	Cs_2CO_3	96
2	K_2CO_3	97
3	K_3PO_4	98
4	KOH	92
5	Na_2CO_3	91
6	*t*-BuONa	96
7	NaOH	85
8	LiCl	65
9	Et_3N	90

Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst 1.0 mol %, $Pd(COD)Cl_2$:**1** = 1:1, base (2.0 equiv), methanol (3.0 mL), room temperature, 3 h

[a] Average of two runs, measured by GC

For our initial experiments, we chose 4-bromotoluene and phenylboronic acid as standard substrates to optimize the conditions for the Suzuki–Miyaura reaction in methanol. Ligand **1** was combined with $Pd(COD)Cl_2$ in situ to give the catalyst (Scheme 3, Tables 1, 2). The inorganic bases Cs_2CO_3, K_2CO_3, K_3PO_4, KOH and Na_2CO_3 and organic bases *t*-BuONa and Et_3N were investigated for the coupling reaction. Most of these bases gave good to excellent conversions (Table 1). The best yields were obtained using K_3PO_4 or K_2CO_3 as base, and we chose K_2CO_3 in the following Suzuki reactions.

Solvents have a key influence on the environmental impact of chemical processes and also affect cost, safety and health issues [8]. According to the green solvent selection guide [30], water, acetone, ethanol and methanol can be considered environmentally friendly, whereas the use of dioxane, acetonitrile, acids, formaldehyde, toluene and tetrahydrofuran is not recommended. To examine the effects of solvent on the present system, a set of reactions between 4-bromotoluene and phenylboronic acid catalyzed by the catalyst [$Pd(COD)Cl_2$:**1** = 1:1] with a range of solvents (Table 2) was carried out. Polar solvent such as methanol proved to be more productive (entry 2). This may be due to better catalyst solubility. Ligand **1** is insoluble in cold water, and when the water content was increased from 5 to 60%, we found the optimum water content (entry 11). Although non-polar solvents like toluene also gave good conversions, these reactions required more time (entry 5). Therefore, the subsequent Suzuki reactions were performed using this solvent/base combination.

Table 2 Effect of solvents on the Suzuki reaction

Entry	Solvent	Time (h)	Yield (%)[a]
1	Ethanol	3	85
2	Methanol	3	97
3	Water	12	75
4	Acetone	3	82
5	Toluene	24	85
6	Chloroform	12	70
7	Ethanol + water (5%)	3	90
8	Methanol + water (5%)	3	95
9	Acetone + water (5%)	12	85
10	Ethanol + water (50%)	3	91
11	Methanol + water (50%)	3	99
12	Methanol + water (60%)	3	83

Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (1.0 mol%,), K_2CO_3 (2.0 equiv), solvent (3.0 mL), room temperature

[a] Average of two runs, measured by GC

The palladium–ligand mole ratio and the palladium source used frequently have a dramatic influence on Pd-catalyzed Suzuki chemistry also [31–33]; thus, the best palladium source and amount of ligand **1** added to the Suzuki reaction were also studied. Several palladium compounds were tested, and the best result were obtained for $Pd(COD)Cl_2$/**1**, giving 98% conversion with a 1:1.3 Pd–ligand ratio (Table 3, entry 7). The yield decreased rapidly when the Pd–L ratio was increased further (entries 9 and 10). Similar effects have been observed for other Pd-catalyzed cross-coupling reactions [34]. We also confirmed that the ligand-free catalytic system gave poor results (ca. 36% GC yield, entry 14). Next, the effect of concentration of palladium was examined. The same experiment was repeated using 0.5 mol% of palladium loading under identical reaction conditions as above, where complete consumption of the 4-bromotoluene was observed after 3 h with 97% conversion (entry 11). However, 0.1 mol% palladium loading gave only 40% conversion (entry 12), and raising the temperature to 100 °C only improved this to 82% (entry 13). Therefore, in all of the subsequent experiments, a loading of 0.5 mol% of palladium and 1:1.3 mol ratio of $Pd(COD)Cl_2$/**1** was employed.

To test the reusability of the catalyst system, we chose the reaction of 4-bromotoluene with phenylboronic acid as a model (Table 4), using methanol–water (1:1) as solvent, After completion of each reaction without separation of the products, the same amount of fresh substrate and reagent was added and the reaction was completed within 3 h with 95% conversion (entry 2). Hence, the catalytic system can

Table 3 Effect of palladium source and Pd:**1** ratio on the Suzuki reaction

Entry	Pd source	Pd:**1** ratio	Yield (%)[a]
1	$Pd(COD)Cl_2$	1:1	96
2	$Pd(CF_3COO)_2$	1:1	86
3	$PdCl_2$	1:1	43
4	$Pd_2(dba)_3$	1:1	85
5	$Pd(OAc)_2$	1:1	81
6	$Pd(COD)Cl_2$	1:0.9	78
7	$Pd(COD)Cl_2$	1:1.3	98
8	$Pd(COD)Cl_2$	1:1.5	85
9	$Pd(COD)Cl_2$	1:2.0	56
10	$Pd(COD)Cl_2$	1:3.0	37
11	$Pd(COD)Cl_2$	1:1.3	97[b]
12	$Pd(COD)Cl_2$	1:1.3	40[c]
13	$Pd(COD)Cl_2$	1:1.3	82[d]
14	$Pd(COD)Cl_2$	1:0	36
15	$Pd(COD)Cl_2$	0:1	Trace

Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (Pd/**1**, 1.0 mol%), K_2CO_3 (2.0 equiv), methanol–water (1:1, 3.0 mL), room temperature

[a] Average of two runs, measured by GC

[b] Catalyst 0.5 mol%

[c] Catalyst 0.1 mol%

[d] Catalyst 0.1 mol%, 100 °C

Table 4 Reusability of the catalyst in the Suzuki reaction

Entry	Run	Time (h)	Yield (%)[a]
1	1	3	97
2	2	3	95
3	3	12	76
4	4	12	55
5	5	12	Trace

Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst ($Pd(COD)Cl_2$:**1** = 1:1.3, 0.5 mol %), methanol–water (1:1, 3.0 mL), room temperature

[a] Average of two runs, measured by GC

Table 5 Suzuki reactions of aryl halides with arylboronic acids

Entry	Aryl halide	Arylboronic acid	Time (h)	Yield (%)[a]
1	$4\text{-}MeOC_6H_4I$	$C_6H_5B(OH)_2$	0.5	100 (98)
2	$4\text{-}MeC_6H_4I$	$C_6H_5B(OH)_2$	0.5	100 (99)
3	$4\text{-}MeC_6H_4Br$	$C_6H_5B(OH)_2$	3	97 (96)
4	$2\text{-}MeC_6H_4Br$	$C_6H_5B(OH)_2$	3	95 (95)
5	$4\text{-}MeOC_6H_4Br$	$C_6H_5B(OH)_2$	3	98 (97)
6	$4\text{-}MeCOC_6H_4Br$	$C_6H_5B(OH)_2$	3	99 (98)
7	C_6H_5Br	$C_6H_5B(OH)_2$	3	100 (100)
8	$4\text{-}CF_3C_6H_4Cl$	$C_6H_5B(OH)_2$	6	75 (73)
9	$4\text{-}CF_3C_6H_4Cl$	$C_6H_5B(OH)_2$	6	81 (80)[b]
10	$4\text{-}CF_3C_6H_4Cl$	$C_6H_5B(OH)_2$	6	97 (94)[c]
11	C_6H_5Cl	$C_6H_5B(OH)_2$	24	83 (81)[c]
12	$4\text{-}MeC_6H_4Cl$	$C_6H_5B(OH)_2$	24	70 (70)[c]
13	$2\text{-}MeC_6H_4Cl$	$C_6H_5B(OH)_2$	24	68 (65)[c]
14	$4\text{-}MeOC_6H_4Cl$	$C_6H_5B(OH)_2$	24	67 (65)[c]
15	$4\text{-}MeCOC_6H_4Cl$	$C_6H_5B(OH)_2$	24	75 (72)[c]
16	$4\text{-}MeC_6H_4Br$	$4\text{-}MeC_6H_4B(OH)_2$	3	100 (99)
17	$4\text{-}MeC_6H_4Br$	$4\text{-}MeOC_6H_4B(OH)_2$	3	97 (96)
18	$4\text{-}MeC_6H_4Cl$	$4\text{-}MeC_6H_4B(OH)_2$	24	86 (85)[c]
19	$4\text{-}MeC_6H_4Cl$	$4\text{-}MeOC_6H_4B(OH)_2$	24	69 (68)[c]

Reaction conditions: aryl halide (0.5 mmol), arylboronic acid (0.75 mmol), K_2CO_3 (2.0 equiv), catalyst (0.5 mol %), methanol–water (1:1, 3.0 mL), room temperature

[a] Average of two runs, isolated yields given in parentheses

[b] Catalyst 1.0 mol%, 100 °C

[c] Catalyst 2.0 mol%, 100 °C

be reused once without significant loss of activity. However, the yield deceased in subsequent experiments.

Finally, the scope of the reaction was explored with a range of aryl iodides, aryl bromides and aryl chlorides under the optimized conditions (Table 5). Generally, aryl iodides and bromides were converted to the corresponding biaryl derivatives quantitatively, even at room temperature. The reactions of aryl chlorides with arylboronic acids in the presence of higher loadings of catalyst were carried out at 100 °C. A good yield was obtained with an activated aryl chloride, namely 4-(trifluoromethyl) chlorobenzene (entry 10), when the reaction was performed at 100 °C in the presence of 2.0 mol% of catalyst. Chlorobenzene yields biphenyl in 83% GC yield under the same conditions (entry 11); however, other aryl chlorides only gave moderate yields.

Conclusion

In summary, we have developed a new synthesis of ligand **1** and investigated the $Pd(COD)Cl_2$/**1** system for Suzuki reactions. This bulky imidazolidine-bridged mixed N,O-ligand proved to be an efficient catalyst for Suzuki chemistry, and the stability toward oxygen and moisture explained by the bulky tert-butyl substituents. Applications of this catalyst for other C–C bond-forming reactions are currently being investigated.

Acknowledgments Financial support for this work was provided by the National Natural Science Foundation of China (Contract No. 20861001 and 21061001), the Key Laboratory of Jiangxi University for Functional Materials Chemistry and Gannan Normal University.

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