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Wanyun Liu,* Dayan Xiong, Ping Huo,* Xiaohui He, and Guangquan Mei

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Efficient Benzocyclohexan-Ketoamine Ligands for Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction

Wanyun Liu^{*1}, Dayan Xiong¹, Ping Huo^{*1}, Xiaohui He², and Guangquan Mei^{1,3}

¹Key Laboratory of Jiangxi University for Applied Chemistry and Chemical Biology, Yichun University, Yichun 336000, China;

²School of Materials Science and Engineering, Nanchang University, Nanchang 330031, China;

³State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China

E-mail: liuwanyun@ycu.jx.cn (W. Liu); pinghuo@ycu.jx.cn (P. Huo).

In the presence of 0.02 mol% Pd(OAc)₂, a series of benzocyclohexan-ketoamine ligands were demonstrated to form a highly efficient catalyst for the Suzuki-Miyaura cross-coupling of various aryl halides with arylboronic acids in ethanol/aqueous media under ambient atmosphere.

Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl halides with arylboronic acids has become one of the most powerful carbon-carbon bond forming methods with the advantages of high yields, mild reaction conditions, wide functional groups tolerance and commercial availability of the diverse arylboronic acids.¹ It has widely applied in the synthesis of natural products, pharmaceuticals and functional polymer materials.² Generally speaking, the catalytic features of Suzuki-Miyaura cross-coupling reaction rely on the electronic or steric influence of the ligands used.³ Therefore, the design and synthesis of ligands are very important. It is well known that the palladium catalyzed Suzuki-Miyaura cross-coupling reaction can be efficiently proceeded using bulky, electron-rich phosphine ligands. Though these ligands own superior donor capability and stabilization effects, most phosphines suffer the serious drawbacks in highly toxic and air- and moisture-sensitive.⁴ To overcome these disadvantages and get efficient and air- and moisture-stable ligands, the simple and efficient synthesis of phosphine-free ligands remains a scientific challenge.

To our knowledge, phosphine-free ligands, such as heterocyclic carbenes,⁵ α -diimine,⁶ phenolic Schiff base⁷ and β -ketoamine⁸ have also emerged for use in the Suzuki-Miyaura cross-coupling reaction. In particular, β-ketoamine ligands and their palladium complexes have shown excellent catalytic activity because of their strong σ -donating abilities.^{8a} The $Pd(OAc)_2/\beta$ -ketoamine ligands derived from acetylacetone system had been successfully developed by Hong and coworkers,^{8b} which showed moderate catalytic activity for cross-coupling of aryl halides with arylboronic acids. Recently, a series of β-ketoamine ligands with different steric and electronic substituents on the backbone and aniline moieties were used to catalyze Suzuki-Miyaura crosscoupling reaction.8c Among these ligands, it could be found that the ligand with sterically-demanding and electrondonating phenyloxyl group on the ortho aniline moiety exhibited the highest activity.

Inspired by the above results, we herein report a simple and efficient preparation of a series of novel benzocyclohexan-ketoamine ligands which contains benzocyclohexan ring on 2-acetyl-1-tetralone and phenyl ring on aniline, which show a big steric effect and strong electronic effect, the conjugation effect of phenyl and benzocyclohexan rings also enhances the electronic effect. The combination of these β -ketoamine ligands and Pd(OAc)₂ was found to form a highly efficient catalyst for the Suzuki-Miyaura cross-coupling of various aryl bromides and activated aryl chlorides with arylboronic acids. The desired products could be obtained in high yields under aerobic conditions, with a great tolerance of raw material for a broad range of functional groups on the aryl halides.

As shown in Scheme 1, the target β -ketoamine ligands with various substituted aniline moieties, such as phenyl, 2,6-dimethylphenyl, naphthyl and fluoryl, were prepared according to the previously reported method,⁹ with some modifications.



Scheme I The benzocyclonexan-ketoamine ligands

In order to investigate the effect of aryl ring substituents on β -ketoamine ligands (L1-L4) toward Suzuki-Miyaura cross-coupling reaction, 4-bromoacetophenone and phenylboronic acid were selected as coupling partners in the presence of 0.02 mol% ligand and 0.02 mol% Pd(OAc)₂. The experiments were carried out under aerobic conditions at room temperature for 2 h utilizing K₂CO₃ as a base in EtOH/H₂O (v/v, 1:1).

As illustrated in Table 1, the data revealed that these β ketoamine ligands were effective ligands for palladiumcatalyzed Suzuki-Miyaura cross-coupling. For a comparison, in the absence of ligands, only 28 % yield of product was produced in the presence of 0.02 mol% of $Pd(OAc)_2$ (entry 1, Table 1). However, when adding the ligands, the yield of product increased dramatically, to a range of 81-99% (entries 2-5, Table 1), indicating that the catalysts were formed in situ. From the Table 1, it could be found that the steric and electronic substituents of the ligand played an important role in catalytic ability. Among the ligands investigated, L1, with no substituent on aryl ring, showed the lowest efficiency and provided the coupling product in 81% yield (entry 2, Table 1). L2 with methyl group on aryl ring was found to be more efficient ligand and afforded the coupling product in 89% yield (entry 3, Table 1). The results suggested that the increase the electron-donating properties and the steric effect of the ligand would lead to an improvement in the rate of oxidative addition and stablitization of the palladium species. Comparatively, the activities of L3 and L4 with bulky substituent on the aryl ring were higher than that of L1 and L2. Particularly, the L4 with fluoryl on aryl ring exhibited the highest activity up to 99% yield under the same conditions (entry 5, Table 1). The reason was ascribed to the steric and electron-donating properties.⁶

Table 1 Influence of β -ketoamine ligands on the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-bromoacetophenone with phenylboronic acid^a

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Entry	Ligand	Yield(%) ^b
1	No L	28
2	L1	81
3	L2	89
4	L3	92
5	L4	99

^{*a*} Reaction conditions: 1.0 mmol of 4-bromoacetophenone, 1.2 mmol of phenylboronic acid, 2.0 mmol of K₂CO₃, 0.02 mol% Pd(OAc)₂, 0.02 mol% ligand, 4 ml EtOH/H₂O (v/v, 1:1), room temperature, 2 h. ^{*b*} Isolated yields.

In order to determine the most suitable palladiumcatalyzed Suzuki-Miyaura cross-coupling reaction condition, investigations of 4-bromoacetophenone initial with phenylboronic acid catalyzed by L4/Pd(OAc)₂ were conducted with various conditions, such as the amount of the ligand and Pd(OAc)₂, reaction time, and different base. As shown in Table 2, the effect of the amount of the ligand and Pd(OAc)₂ on the coupling reaction was studied. We could found that lowering the amount of ligand and Pd(OAc)₂ from 0.2 mol% to 0.02 mol% did not affect the reaction performance in 0.5 h (entries 1-4, Table 2). The amount of ligand decreased to 0.01 mol%, the reaction yield had shown a sharp decline (entry 5, Table 2). Then the reaction time was also investigated and found that played an important role on the coupling reaction. Increasing the reaction time from 0.5 h to 2.0 h (entries 4, 6-8, Table 2), the yield improved remarkable. The reaction time was prolonged to 2.5 h, the yield hardly went on increasing (entry 9, Table 2). The reason was that the substrate was completely converted to the product over 2 h. Furtherly, an investigation of the influence of the base suggested that the common and inexpensive inorganic bases, such as K₂CO₃ are more effective, while other bases such as Na₂CO₃, KOH, Ca(OH)₂, NaOEt, K₃PO₄, gave slightly lower yields (entries 10-14, Table 2). Therefore, the 0.02 mol % of the ligand, 2 h of reaction time and 2.0 mmol of K₂CO₃ as base would be the most effective condition.

Entry	Catalyst (mol%)	Base	Time (h)	Yield(%) ^b
1	0.2	K ₂ CO ₃	0.5	91
2	0.1	K ₂ CO ₃	0.5	89
3	0.05	K_2CO_3	0.5	88
4	0.02	K ₂ CO ₃	0.5	87
5	0.01	K_2CO_3	0.5	65
6	0.02	K ₂ CO ₃	1	91
7	0.02	K_2CO_3	1.5	95
8	0.02	K ₂ CO ₃	2	99
9	0.02	K_2CO_3	2.5	98
10	0.02	Na ₂ CO ₃	2	95
11	0.02	KOH	2	93
12	0.02	Ca(OH) ₂	2	72
13	0.02	NaOEt	2	93
14	0.02	K_3PO_4	2	94

Table 2 Optimization of reaction conditions at room temperature^a

^{*a*} Reaction conditions: 1.0 mmol of 4-bromoacetophenone, 1.2 mmol of phenylboronic acid, 2.0 mmol of base, $n(Pd(OAc)_2)=n(ligand)$, 4 ml EtOH/H₂O (v/v, 1:1). ^{*b*} Isolated yields.

Based on the above results, L4 was chosen as the most effective ligand in the following Suzuki-Miyaura crosscoupling reactions of different aryl halides with arylboronic acids. With the optimal reaction conditions in hand, we checked the scope of the aryl bromides by conducting a series of experiments (Table 3). Overall, aryl bromides bearing either electron-rich or electron-deficient substituents all led to biaryl compounds in moderate to high yields. Many important functional groups, such as the methyl, methoxy, acetyl, aldehyde, ester, amino, chloro and nitryl, were quite welltolerated (entries 1-8, Table 3). Most remarkably, aryl bromides bearing a naphthalene ring underwent reaction smoothly with yield as high as 96% within 3 hours (entry 9, Table 3). Generally speaking, due to retarding both the oxidative addition and transmetalation processes, the aryl halides with ortho-substituent had less active. But in this study, the sterically hindered ortho-substituent aryl bromides were also a competent coupling partner leading to high product yield (entries 10-13, Table 3). Furthermore, the effect of various para-substituents on the aryl boronic acids toward the cross coupling were investigated (entries 14-16, Table 3). It could be found that no significant difference was obeserved in yield or in the reaction time. When the phenylboronic acid with ortho-substituents reacted with the aryl halides, the catalytic system could also show good activity through prolonged reaction time (entry 17, Table 3). However, rather low activity was observed at 6 h toward the reaction of aryl bromide with ortho-substituents and phenylboronic with ortho-substituents (entry 18, Table 3).

To demonstrate the generality of this catalytic system, the reaction of unactivated aryl chlorides with phenylboronic acid was explored. To our delight, by increasing the amount of ligand and $Pd(OAc)_2$ to 0.2 mol% in conjuction with reaction time (12 hours) and temperature (80 °C), good yields were still obtained (entries 19-20, Table 3). In contrast to the aryl bromides, the elecronic effect of substituents on aryl chlorides was significant difference in yield. The aryl chlorides bearing electron-deficient substituents led to biaryl compounds in higher yields.

 Table 3 Suzuki-Miyaura cross-coupling reaction of aryl halides with phenylboronic acid under aerobic conditions^a

X	B	OH) ₂ Pd(OAc) ₂ , L4		
\mathbf{R}_1 \mathbf{R}_2	R ₂	EtOH/H ₂ O, K ₂ CO ₃ .	R ₁	∠ ∕ _{R2}

Entry	Aryl halide	Aryl boronic	Time (h)	Yield $(\%)^b$
1	Me - Br	B(OH) ₂	2	96
2	MeO-Br	B(OH) ₂	2	97
3	O C H ₃ C	B(OH)2	2	99
4	OHCBr		2	98
5	O C H _b CO Br	B(OH)2	2	98



^{*a*} Reaction conditions: 1.0 mmol of aryl bromide, 1.2 mmol of aryl boronic acid, 2.0 mmol of K_2CO_3 , 0.02 mol % Pd(OAc)₂, 0.02 mol % ligand, 4 ml EtOH/H₂O (v/v, 1:1), room temperature. ^{*b*} Isolated yields.

^c Reaction conditions: 1.0 mmol of aryl chloride, 1.2 mmol of aryl boronic acid, 2.0 mmol of K_2CO_3 , 0.2 mol % Pd(OAc)₂, 0.2 mol % ligand, 4 ml EtOH/H₂O (v/v, 1:1), reaction temperature: 80 °C.

A series of benzocyclohexan-ketoamine ligands were successfully employed in the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. It was shown that the ligand with bulky steric and electron-donating substituent was facilitated for the Suzuki-Miyaura cross-coupling reaction. A significant advance in the efficiency of Suzuki-Miyaura crosscoupling of aryl bromides or aryl chlorides with arylboronic acids to give desired biaryls was demonstrated in ethanol/aqueous media under ambient atmosphere.

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Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/ chem-lett/index.html.

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