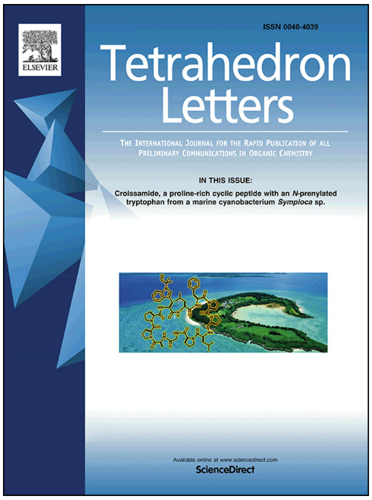

Copper-Promoted Chan−Lam Coupling between Enaminones and Aryl Boronic Acids

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Graphical Abstract

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Copper-Promoted Chan−Lam Coupling between Enaminones and Aryl Boronic Acids

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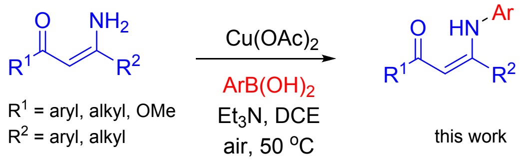
Xiyan Duan,[a] Ning Liu, [a] Kun Liu,[a] Yakun Song,[a] Jia Wang,[a] Xianhua Mao,[a] Weidong Xu,[a] Shijie Yang,[a] Huixian Li,[a] Junying Ma *[a]*



- 24 examples
- up to 98% yield
- effective C-N bond formation
- broad scope

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Copper-Promoted Chan−Lam Coupling between Enaminones and Aryl Boronic Acids

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[a] *School of Chemical Engineering & Pharmaceutics, Henan University of Science and Technology, Luoyang 471003, Henan, China;*

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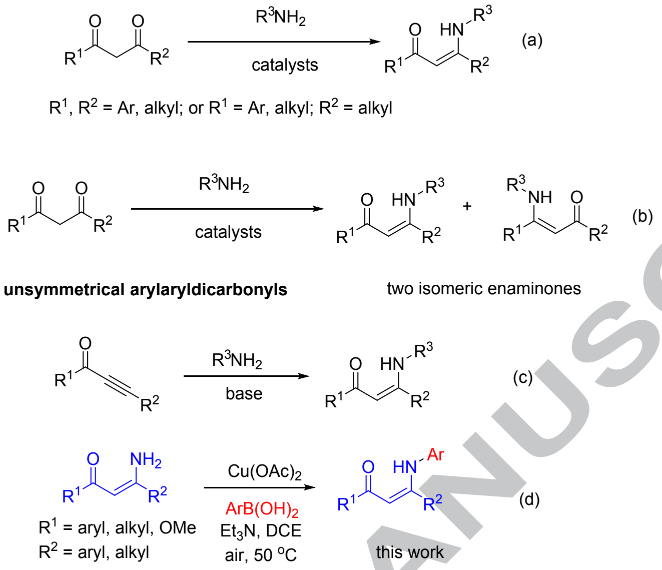
ABSTRACT

A novel copper-promoted *N*-arylation of enaminones with aromatic boronic acids has been developed, which provides an efficient way to synthesize *N*-aryl enaminones with a broad substrate scope and excellent functional group compatibility. The *N*-aryl enaminones could be converted into a series of highly valuable building blocks and bioactive compounds. Notably, in comparison with traditional methods, this alternative approach provides accesses to *N*-aryl enaminones bearing multiple aromatic rings.

N-aryl enaminones have been recognized as important synthetic intermediates and building blocks in organic chemistry because of their versatile chemical reactivities.[1a-1i] For instance, elegant methodologies have been developed for the transformation of *N*-aryl enaminones into various *N*-heterocycles including indole,[1b,1h] 1,2,3-Triazoles,[1f] Benzo[b][1,4]oxazins,[1i] and pyrroles[1c]. In addition, *N*-aryl enaminones derivatives have drawn extensive and enduring attention for their broad range of biological activities and significant pharmaceutical potentials, such as antiviral, anti-bacterial, anticonvulsant, anti-tussive, and anti-inflammatory activities.[2]

The most well-known synthetic methods of *N*-aryl enaminones have utilized the direct condensation of 1,3-dicarbonyl compounds with amines in a refluxing aromatic solvent in the presence of various catalysts (Scheme 1a).[3] Although these methods are in general well suitable for symmetrical β-diketones and several unsymmetrical β-dicarbonyls (arylalkyldicarbonyls), the reaction of unsymmetrical β-diketones bearing substituted aromatic ring with aniline gives two isomeric enaminones (Scheme 1b).[4a] Moreover, most of these procedures suffer from drawbacks which include the need for the excess amount of amine reagents, drastic reaction conditions,[4b,4f] non-reusability of the catalyst,[4c] long reaction times,[4d-f] unsatisfactory yields and low selectivity[4f].

Sonogashira cross-coupling of terminal alkynes with aroyl chlorides, followed by the Michael addition of anilines with the resultant α, β-ynones has been developed as an alternative strategy to build *N*-aryl enaminones (Scheme 1c),[1b,5] especially in the synthesis of *N*-aryl enaminones bearing multiple aromatic rings. [1b,1h,1f] However, this method generally suffers from drawbacks which include the need for expensive transition-metal catalysts, harsh reaction conditions, and multistep operations. Therefore, new synthetic methods for *N*-aryl enaminones synthesis are still under great demand.

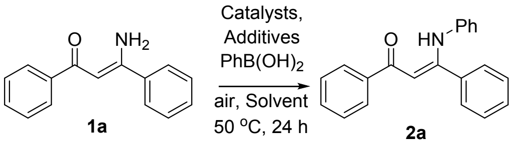


Scheme 1. Synthesis of *N*-aryl enaminones

Copper-promoted Chan-Lam reactions represent one of the most powerful and straightforward tools to construct C-heteroatom bonds via cross-coupling reactions of aryl boronic acids and different nucleophiles that possess significantly synthetic utility in chemical synthesis.[6] A wide range of *N* nucleophiles such as amines, anilines, amides, imides, ureas, carbamates, sulfonamides, cyanate ion, indazole, aqueous ammonia, and azides have been reported to be utilizable in the Chan-Lam reaction with aryl boronic acids.[6a-6o] However, the Chan-Lam reactions have rarely been used in the C-N cross-coupling reactions of enaminones. Herein, we report an easy and highly efficient copper-promoted method for the synthesis of *N*-aryl enaminones in air at low temperature (50 °C) without the addition of a ligand (Scheme 1d).

We commenced our investigation by using (*Z*)-3-amino-1,3-diphenylprop-2-en-1-one **1a** and phenylboronic acid as the model substrates and examined the reaction parameters to identify optimal conditions (Table 1). Firstly, various copper catalysts were investigated in an open flask using 1,2-dichloroethane (DCE) as a solvent at 50 °C. Only CuCl and $Cu(OAc)_2$ worked for this reaction (entry 1 and entry 6). Other copper catalysts including CuBr, CuI, $CuCl_2$, and $CuBr_2$ were also studied, but no desired *N*-arylated product **2a** was observed in any of the cases (entries 2-5). The dosage of $Cu(OAc)_2$ was decreased from 1 to 0.5 equivalents led to no substantial change. Different additives were also screened (Table 1, entries 8-10) and it was found that Et_3N was the most efficient (Table 1, entry 10). Decreasing the amount of $Cu(OAc)_2$ led to a decrease in yield and incomplete conversion was observed. For example, when the amount of $Cu(OAc)_2$ was decreased to 0.1 equiv, the reaction afforded a 45% yield of the product **2a** (Table 1, entry 11). To our disappointment, when the reaction was operated at room temperature, the reaction turned out to be sluggish with lower conversions and yield (Table 1, entry 12).

Table 1. Optimization of Reaction Conditions[a]

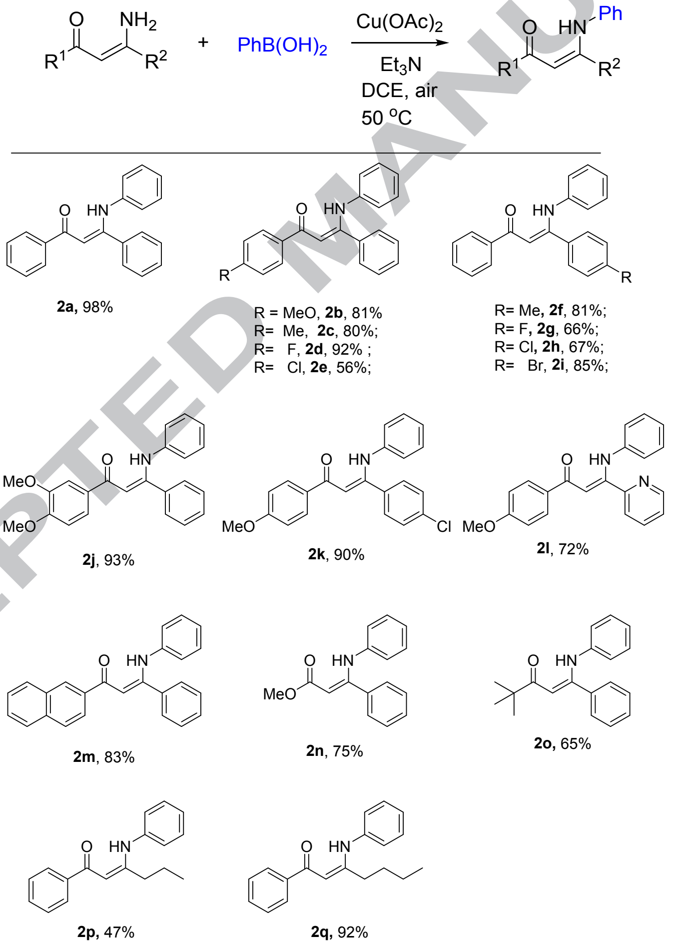


Entry	Catalysts (equiv)	Additives (equiv)	Yield (%)[b]
1	CuCl (1)	-	47
2	CuBr (1)	-	NR
3	CuI (1)	-	NR
4	$CuCl_2$ (1)	-	NR
5	$CuBr_2$ (1)	-	NR
6	$Cu(OAc)_2$ (1)	-	58
7[c]	$Cu(OAc)_2$ (0.5)	-	57
8[c]	$Cu(OAc)_2$ (0.5)	KO^tBu (0.5)	60
9[c]	$Cu(OAc)_2$ (0.5)	Pyridine(0.5)	95
10[c]	$Cu(OAc)_2$ (0.5)	Et_3N (0.5)	98
11	$Cu(OAc)_2$ (0.1)	Et_3N (0.5)	45
12[d]	$Cu(OAc)_2$ (0.5)	Et_3N (0.5)	60

[a] Reaction conditions: catalysts (0.2 mmol), enaminone **1a** (0.2 mmol), phenylboronic acid (0.4 mmol), DCE (5 mL), 50 °C, under air, 24 h. [b] Determined by ^{1}H NMR using 1,3,5-Trimethoxybenzene as an internal standard. [c] Reaction conditions: catalysts (0.1 mmol), additives (0.1 mmol), enaminone **1a** (0.2 mmol), phenylboronic acid (0.4 mmol), DCE (5 mL), 50 °C, under air, 24 h. d. room temperature

With the optimized conditions in hand, we first investigated the scope of the Cu-promoted Chan−Lam coupling with respect to various enaminones. As shown in Table 2, most of enaminones employed under the optimized conditions furnished moderate-to-excellent yields within 24 h at 50 °C. It was found that enaminones bearing either electron-donating or electron-withdrawing groups on the benzene ring **1b-i** could perform the Chan-Lam coupling with phenylboronic acid to give the desired *N*-aryl enaminones **2b-i** in moderate to good yields. The method was shown to be also well applicable to the enaminone substrates with R^1 being 3, 4-dimethoxy phenyl group (**2j**). For the enaminone substrate with two substituted aryl group, the reaction also conveniently afforded the desired product **2k** in excellent yield. For substrates where the phenyl group was replaced by a pyridine group, product **2l** was produced in 72% yield. Replacing the phenyl ring with a naphthyl ring in the substrate does not hamper the reaction, and the desired product **2m** could be obtained in good yield. Moreover, when the benzene ring of the substrates was changed to ester group, the reactions successfully provided the *N*-aryl enaminone product **2n** in moderate yield. For substrate when the benzene group of the substrate (R^1) was changed to a more sterically hindered tert-butyl group, product **2o** was produced in 65% yield. Further experiments showed that this method worked equally well for enaminones when the benzene group of the substrate (R^2) was changed to the alkyl group (**2p-q**).

Table 2. Scope of the enaminones [a, b]



2a, 98%

R = MeO, **2b**, 81%
R= Me, **2c**, 80%;
R= F, **2d**, 92% ;
R= Cl, **2e**, 56%;

R= Me, **2f**, 81%;
R= F, **2g**, 66%;
R= Cl, **2h**, 67%;
R= Br, **2i**, 85%;

2j, 93%

2k, 90%

2l, 72%

2m, 83%

2n, 75%

2o, 65%

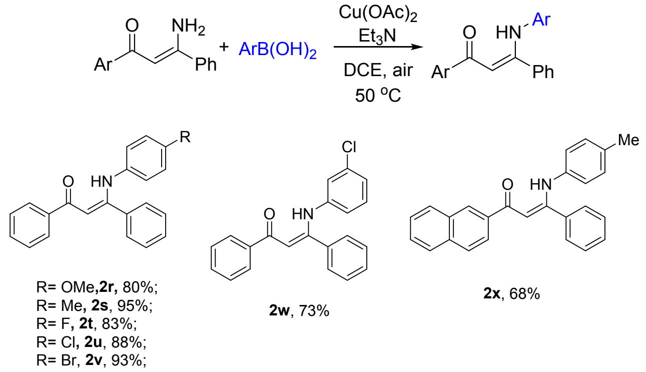
2p, 47%

2q, 92%

[a]Reaction conditions: $Cu(OAc)_2$ (0.5 mmol), Et_3N (0.5 mmol), enaminone **1a** (1 mmol), phenylboronic acid (2 mmol), DCE, 50 °C, under air, 24 h. [b]Isolated yields.

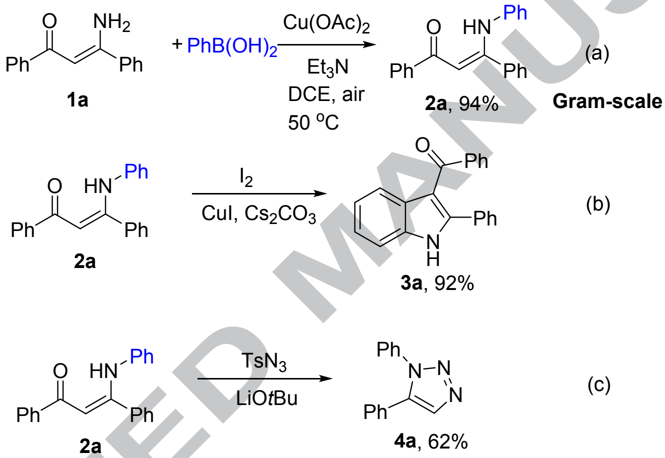
To further explore the scope of the reaction, various aromatic boronic acids were examined under the standard reaction conditions (Table 3). In general, the aromatic boronic acids containing either electron-donating (Me− and MeO−) groups or electron-withdrawing (F−, Cl−, and Br−) groups at the para or meta position gave the corresponding *N*-aryl enaminones product in good to excellent yields (**2r-2w**). Gratifyingly, naphthyl enaminone also efficiently reacted with 4-methylphenylboronic acid, giving product **2x** in 68% yield.

Table 3. Scope of the aryl boronic acids [a, b]



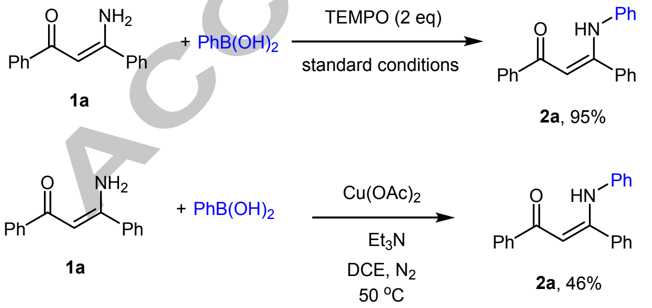
[a] Reaction conditions: $Cu(OAc)_2$ (0.5 mmol), Et_3N (0.5 mmol), enaminone **1a** (1 mmol), aryl boronic acid (2 mmol), DCE, 50 °C, under air[redacted] 24 h. [b] Isolated yields.

The practical utility of this methodology was also investigated, and a gram-scale reaction of **1a** and phenylboronic acid under standard conditions yielded the desired product **2a** in 94% yield (Scheme 2a). The *N*-aryl enaminones products could be easily converted into diverse building blocks for biological interesting molecules.[1] For example, I_2/CuI-mediated intramolecular direct C-H functionalization of *N*-aryl enaminone **2a** gave indole **3a** in excellent yield (Scheme 2b).[1h] Deacylative diazo transfer/cyclization reaction of *N*-aryl enaminone **2a** and sulfonyl azides gave 1,5-disubstituted 1,2,3-triazoles **4a** in moderate yield (Scheme 2c).[1f]



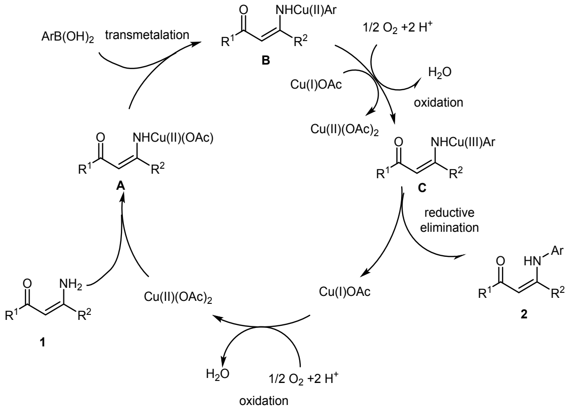
Scheme 2. Gram-scale reaction and synthetic applications

Our control experiment showed that the addition of radical scavenger TEMPO did not retard the reaction, which indicated that this reaction may not involve a radical pathway (Scheme 3). Further experiment was conducted in order to gain insight into the mechanism of the reaction. When the reaction was carried out under N_2 atmosphere, the reaction afforded a 46% yield of the product **2a** with the recovery of substrate **1a** in 35% yield.



Scheme 3. Control experiment.

On the basis of the above results and previous reports, [6n, 6p, 7] we propose a possible mechanism for the coupling reaction between enaminones and aryl boronic acids. Initially, the enaminones can coordinate to the Cu(II) salt forming intermediate **A**, which subsequently undergoes transmetalation with aryl boronic acid to give intermediate **B**. The resulting intermediate **B** is oxidized by one equivalent of Cu(II) or air to yield the corresponding higher oxidation-state Cu(III) intermediate **C**, which can undergo reductive elimination to afford the product **2**.



Scheme 4. Proposed reaction mechanism.

In summary, Cu-promoted Chan-Lam coupling reaction of enaminones with aryl boronic acids has been developed. This novel method provides an efficient access to *N*-aryl enaminones. Various substituted *N*-aryl enaminones were synthesized in moderate to high yields with a good functional group tolerance. This work not only provides an effective approach to access *N*-aryl enaminones, but also contributes new knowledge to Chan-Lam coupling reaction.

Acknowledgments

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Supplementary data

Supplementary data (list of new compounds along with their yield and copies of ^{1}H NMR and ^{13}C NMR spectra are included) associated with this article can be found, in the online version, at http://.

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- Chan−Lam coupling between enaminones and aryl boronic acids.
- Our approach provides accesses to N-aryl enaminones bearing multiple aromatic rings.
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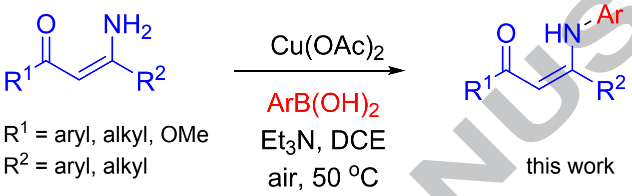

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