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Copper-Catalyzed Imino C–N Bond Formation with Aryl Boronic Acids under Aerobic Conditions

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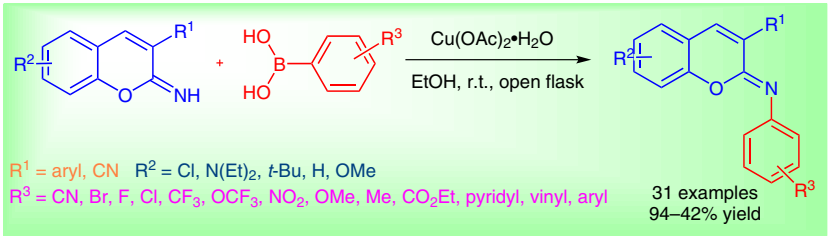

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Abstract A copper-catalyzed, ligand- and base-free C–N cross-coupling reaction of iminochromenes with arylboronic acids in a nontoxic ethanol solvent at room temperature under air is developed. The product yields are found to be good to moderate. The conservation of the sensitive imine functional group implies the mildness of this protocol

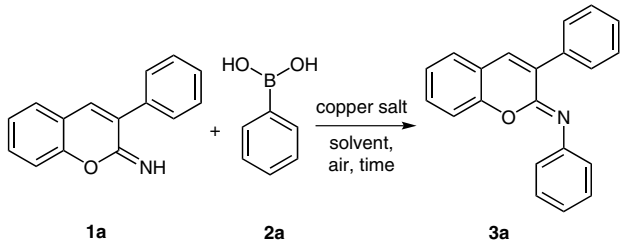
Key words iminochromenes, copper, arylboronic acid, cross-coupling, aerobic conditions

Iminochromenes[1] are a class of chroman-based heterocyclic motifs that show promising biological activities such as antitumor,[2] antimicrobial,[3] anti-inflammatory,[3c] antifungal,[4] mitogen-activated protein kinase inhibition (MK-2),[5] dynamins I and II GT Pase,[6a] HIV-1 integrase inhibition,[6b] and cell imaging.[7] Further they are also useful as fluorescent dyes,[8] laser dyes,[9] sensing thiols[10] and sensing H_2S.[11] Knoevenagel reaction[12] and multicomponent reactions[13] are the existing methods for synthesizing iminochromenes. However, the major drawbacks of these procedures are limited substrate scope, cumbersome purifications steps, and low product yields especially for electron-deficient aromatic groups, because the transamination is hampered by the low nucleophilicity of the electron-deficient anilines.[12a] In addition, the synthesis of iminocoumarins is not completely exploited, especially the *N*-arylation of the imine functional group owing to sensitivity of the imine bond, which is not tolerated under the harsh conditions. Hence, alternative methods for the *N*-arylated iminochromenes are highly desirable. Over past years, the Chan–Lam–Evans reaction[14] has emerged as a versatile tool for C–C and C–heteroatom bond formation. The reaction is highly advantageous, as it can be accomplished with relatively inexpensive copper salts and milder conditions. In continuation to our novel methodologies development program,[15] we herein present for the first time a copper-catalyzed cross-coupling of iminochromenes with arylboronic acids under aerobic conditions.

Initially, we tried the reaction of 3-phenyliminochromene (**1a**) and phenylboronic acid (**2a**) with $Cu(OAc)_2{\cdot}H_2O$ as the catalyst in methanol at room temperature to afford product **3a** in 85% yield (Table 1, entry 8). The yield was further improved through optimization of various solvents and copper salts. The product yields were superior with $Cu(OAc)_2{\cdot}H_2O$ when compared with other copper salts such as $CuBr_2$, $CuSO_4{\cdot}5H_2O$, $CuCl_2{\cdot}2H_2O$, and anhydrous $Cu(OAc)_2$. The reaction was examined with different solvents such as chloroform, acetonitrile, dichloromethane, dichloroethane, DMSO, and DMF (Table 1). Among them, ethanol was superior for the reaction. No significant improvement of product yields was observed with various bases and ligands. The products yields were found to be the same under oxygen and air atmospheres. Therefore, with these optimized conditions,[16] namely $Cu(OAc)_2$/ethanol/air, we tested various substituted arylboronic acids for their reactivity with 3-phenyliminochromene (**1a**).

The scope of *N*-arylation reaction was examined with various aromatic boronic acids. The best yields were obtained with 4-Br- (**3b**, 85%), 4-Cl- (**3c**, 82%), 4-F- (**3d**, 79%), 3-Me- (**3e**, 82%), 2-naphthyl- (**3f**, 83%), 1-naphthyl- (**3g**, 79%), 3,4-methylenedioxy- (**3h**, 76%), and 4-vinyl-substituted (**3i**, 78%) boronic acids. The yields in the case of boronic acids with electron-donating groups such as 3-MeO (**3k**, 68% yield and the electron-withdrawing groups such as 4-F_3CO (**3j**, 73%), 3- F_3CO (**3l**, 63%), 4-EtO_2C (**3m**, 71%), 4-F_3C (**3n**, 64%), 2-F_3C (**3o**, 55%), 4-O_2N (**3p**, 42%) were moderate. The yield in the case of 4-cyano phenylboronic acid (**3q**, 74%) was slightly higher than the other electron-withdrawing groups, this was an exception. Other aromatic boronic

Table 1 Evaluation of Optimal Reaction Conditions of *N*-Arylation of Iminochromene with Phenylboronic Acid[a]



1a **2a** **3a**

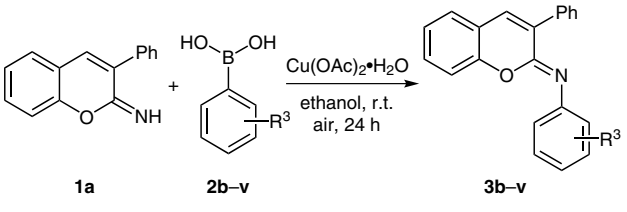
Entry	Copper	Solvent	Yield (%)[b]
1	$CuBr_2$	EtOH	75
2	$CuCl_2·2H_2O$	EtOH	60
3	$CuSO_4·5H_2O$	EtOH	91
4	$Cu(OAc)·H_2O$	EtOH	93
5	$Cu(OAc)_2·H_2O$	EtOH	78[c]
6	$Cu(OAc)_2·H_2O$	EtOH	55[d]
7	$Cu(OAc)_2$	EtOH	80
8	$Cu(OAc)_2·H_2O$	MeOH	85
9	$Cu(OAc)_2·H_2O$	CH_2Cl_2	87
10	$Cu(OAc)_2·H_2O$	$CHCl_3$	80
11	$Cu(OAc)_2·H_2O$	MeCN	62
12	$Cu(OAc)_2·H_2O$	DCE	74
13	$Cu(OAc)_2·H_2O$	DMF	80
14	$Cu(OAc)_2·H_2O$	DMSO	55
15	–	EtOH	–

[a] Reaction conditions: **1a** (0.9 mmol), **2a** (2.3 mmol), Cu salt (20 mol%), solvent (5 mL), 24 h at room temperature.
[b] isolated yield.
[c] $Cu(OAc)_2.H_2O$ (10 mol%).
[d] $Cu(OAc)_2.H_2O$ (5 mol%).

acids, such as 4-biphenyl (**3r**, 73%), 1-pyrene (**3s**, 73%), 3-pyridyl (**3t**, 73%), and non-arylboronic acids, such as *trans*-2-(4-fluorophenyl)vinyl (**3u**, 76%) and *trans*-2-phenylvinyl (**3v**, 72%), afforded the products in moderate yields. Altogether a wide variety of substrates were successfully synthesized by the reaction of various arylboronic acids with 3-phenyliminochromene (**1a**, Scheme 1).

We further extended the study by subjecting different iminochromenes with substituents at different positions on the chromene ring for *N*-arylation. The reaction of iminochromenes bearing substituents at 3-, 6-, and 7-positions was carried out with simple unsubstituted phenylboronic acid (**2a**). The reactions proceeded smoothly and afforded the corresponding products in high yields. The yields in the case of 3-phenyl-substituted chromenes bearing electron-withdrawing groups such as 3-F_3C (**3w**, 94%) and 4-NO_2 (**3x**, 82%) on the phenyl ring were the highest, followed by 4-Cl (**3y**, 81%) and 2-F (**3z**, 77%). Similarly, the 3-cyano iminochromenes (**1f**–**j**) with *tert*-butyl, diethylamino, methoxy, and chloro substituents on the chromene ring proceeded to react with phenylboronic acid to afford the products in good yields. The yields are as follows: 3-cyanochromene (**3aa**, 91%), 6,8-di-*t*-Bu (**3ab**, 79%), 7-(diethylamino) (**3ac**, 86%), 7-MeO (**3ad**, 81%), and 6-Cl (**3ae**, 80%). The reaction of 7-(diethylamino)-3-(4-nitrophenyl) iminochromene (**1k**) also proceeded smoothly to afford the product **3ac** in 84% yield (Scheme 2). Studying a variety of substrates showed that the reaction scope is not only limited to simple phenyl-substituted chromene but also could be extended to substituted iminochromenes. In addition the single-crystal analysis of the compound chromene **3l** was obtained, and confirmed that the arylation of iminochromenes occurs at the N atom (Figure 1).

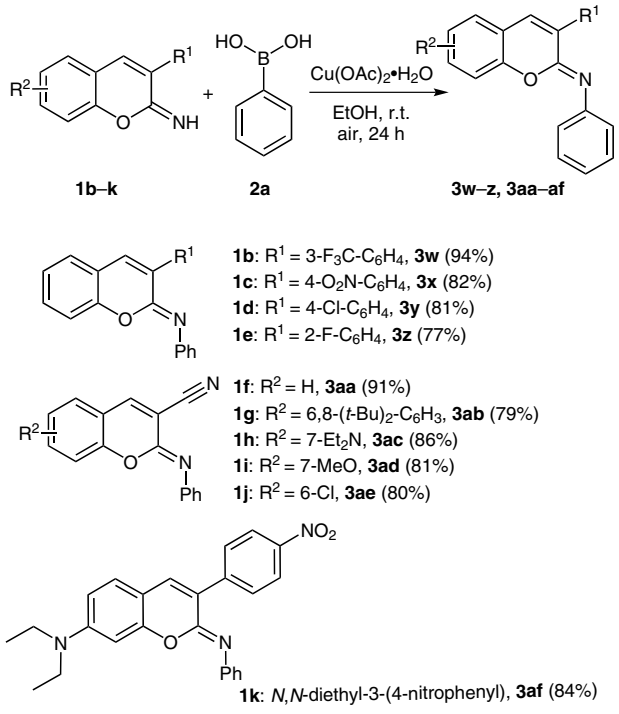
Having studied the substrate scope, we further examined the one-pot synthesis of *N*-arylated iminochromene, in which the imine formation and *N*-arylation are done sequentially in a one-pot fashion. At first the imine was prepared by Knoevenagel reaction of salicylaldehyde and malononitrile in the presence of piperidine as reported previously.[12d] This was followed by addition of $Cu(OAc)_2·H_2O$ and phenylboronic acid to the same flask. Unfortunately,



1a **2b–v** **3b–v**

2b: R^3 = 4-Br-C_6H_4, **3b** (85%)
2c: R^3 = 4-Cl-C_6H_4, **3c** (82%)
2d: R^3 = 4-F-C_6H_4, **3d** (79%)
2e: R^3 = 3-Me-C_6H_4, **3e** (82%)
2f: R^3 = 2-naphthyl, **3f** (83%)
2g: R^3 = 1-naphthyl, **3g**(79%)
2h: R^3 = 3,4-$(OCH_2O)C_6H_3$, **3h** (76%)
2i: R^3 = 4-vinylphenyl, **3i** (78%)
2j: R^3 = 4-F_3CO-C_6H_4, **3j** (73%)
2k: R^3 = 3-MeO-C_6H_4, **3k** (68%)
2l: R^3 = 3-F_3CO-C_6H_4, **3l** (63%)
2m: R^3 = 4-ethoxycarbonyl-C_6H_4, **3m** (71%)
2n: R^3 = 4-F_3C-C_6H_4, **3n** (64%)
2o: R^3 = 2-F_3C-C_6H_4, **3o** (55%)
2p: R^3 = 4-O_2N-C_6H_4, **3p** (42%)
2q: R^3 = 4-NC-C_6H_4, **3q** (74%)
2r: R^3 = 4-biphenyl, **3r** (73%)
2s: R^3 = 1-pyrene, **3s** (73%)
2t: R^3 = 3-pyridine, **3t** (73%)
2u: R^3 = *trans*-2-(4-fluorophenyl)vinyl, **3u** (76%)
2v: R^3 = *trans*-2-phenylvinyl, **3v** (72%)

Scheme 1 Study of substrate scope in the *N*-arylation of 3-phenyliminochromene with arylboronic acids. *Reagents and conditions*: 3-phenyliminochromene (**1a**, 0.9 mmol), arylboronic acid **2b**–**v** (2.3 mmol), $Cu(OAc)_2·H_2O$ (0.18 mmol), EtOH (5 mL), 24 h at r.t.; yields in parentheses are isolated yields.



Scheme 2 Study of substrate scope in the *N*-arylation of iminochromenes with phenylboronic acid. *Reagents and conditions*: iminochromene **1b–k** (0.9 mmol), phenylboronic acid (**2a**, 2.3 mmol), $Cu(OAc)_2·H_2O$ (0.18 mmol), EtOH (5 mL), 24 h at r.t., yields in parenthesis are isolated yields.

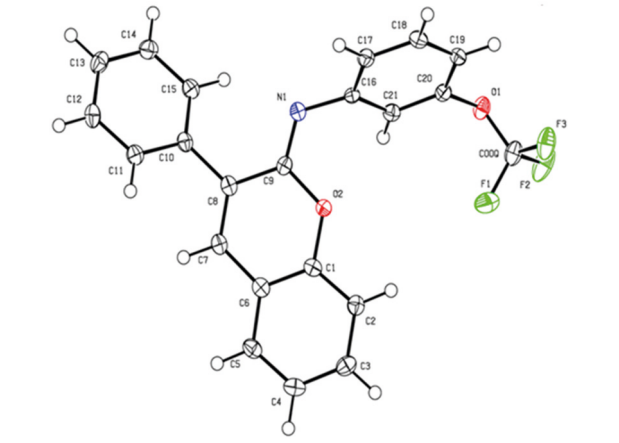
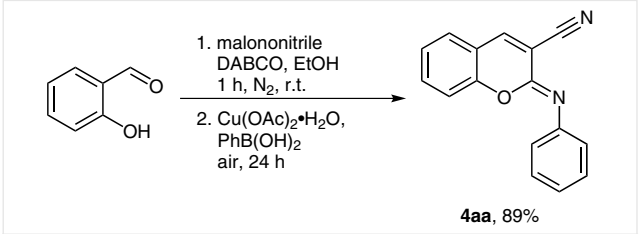


Figure 1 Crystal structure of (*Z*)-3-phenyl-*N*-[3-(trifluoromethoxy)phenyl]-2*H*-chromen-2-imine

piperidine was less effective in the reaction affording only 49% of **4aa**. The yield was further improved to 89% by replacing piperidine with DABCO (Scheme 3).



Scheme 3 One-pot procedure: iminochromene synthesis followed by *N*-arylation

Thus, the telescopic procedure could be advantageously utilized for the *N*-arylation of iminochromenes precluding the isolation of iminochromene.

Finally, we propose a plausible mechanism for the *N*-arylation of iminochromenes based on a preliminary study to understand the catalytic pathway. Substrates are known to bind to copper metal in Chan–Lam–Evans cross-coupling reactions. We envisaged a similar type of association of copper and iminochromene in the present system. So we performed a control experiment in which $Cu(OAc)_2·H_2O$ and 3-phenyliminochromene (1:1 ratio) were stirred together at room temperature in ethanol for 24 hours. The solution was analyzed by MALDI-ESI mass spectrometry. Dimeric and monomeric copper–iminochromene complexes could be seen in the spectra.[17] This evidence indicated the formation of iminochromene–copper complex during the reaction. We hypothesize that this association of the substrate with copper metal enables a more facile reaction (Scheme 4).

In conclusion, we have developed a mild protocol for the synthesis of *N*-arylated iminochromenes under Chan–Lam–Evans conditions for the first time. The sensitive imine functional group which is prone to hydrolysis is sustained, and the yields of the products are good to moderate. We have also demonstrated a one-pot procedure in which the *N*-arylated iminochromenes can be synthesized. The mechanistic investigation revealed evidence for the copper–iminochromene complex formation during the reaction. Further efforts to study the detailed mechanism and synthetic applications of this methodology are in progress in our group.

Acknowledgment

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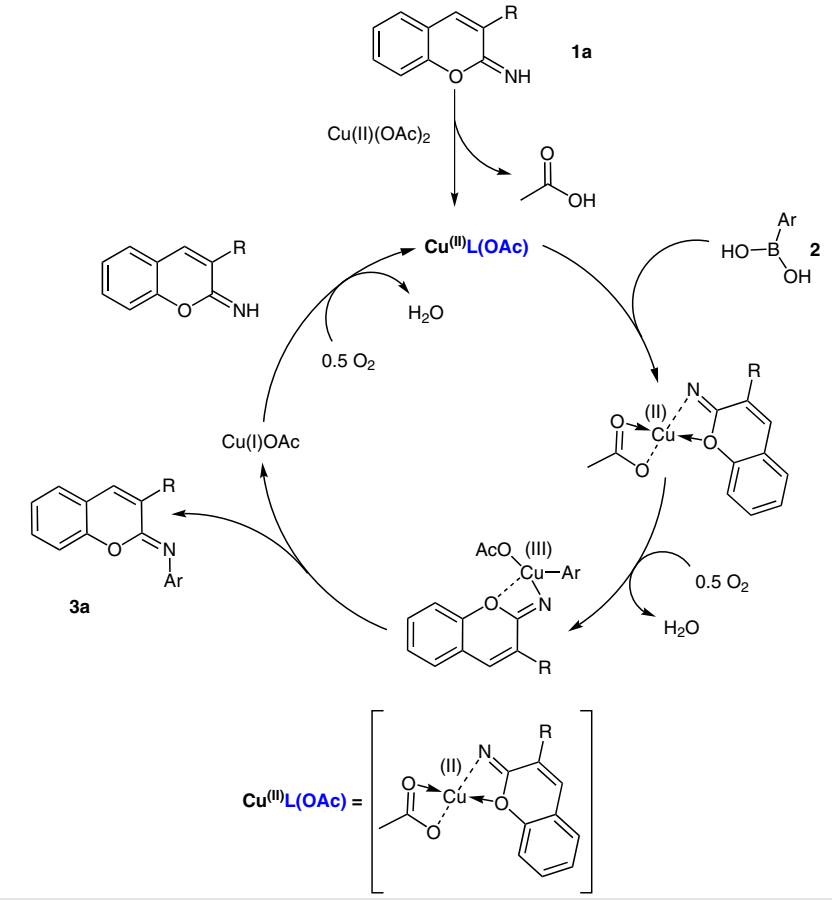

Scheme 4 Plausible mechanistic pathway of copper-catalyzed *N*-arylation of iminochromene

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561382.

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(16) **General Procedure for the Copper-Catalyzed Coupling of Iminochromene with Arylboronic Acids**

To a round-bottomed flask equipped with a stir bar, the iminochromene (1 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol%), and arylboronic acid (2.3 mmol) were added. EtOH (5 mL) was added, and the reaction mixture was stirred for 24 h at r.t. After completion of the reaction as monitored by TLC, the organic phase was concentrated under reduced pressure, and the solid residue was fractioned in EtOAc (20 mL) and H_2O (10 mL) thrice. The organic phase was separated and dried on anhydrous Na_2SO_4. The solvent was removed in vacuum, and the crude residue was purified by column chromatography with EtOAc–PE to afford the respective *N*-arylated chromene.

Physical and spectroscopic data given below are for compound **3a** and may be taken as representative. For further details, see the Supporting Information.

(*Z*)-*N*-3-Diphenyl-2*H*-chromen-2-imine (3a)

Yellow solid (249 mg, 93% yield); mp 112–113 °C. IR (KBr): ν = 1737, 1643, 1587, 1485, 1365, 1230, 1116 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.72 (m, 2 H), 7.46–7.30 (m, 7 H), 7.29 (s, 1 H), 7.20–7.13 (m, 2 H), 7.13–7.05 (m, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 148.9, 146.6, 136.7, 133.6, 133.3, 132.1, 130.1, 129.1, 128.7, 128.4, 128.3, 128.0, 127.2, 123.9, 123.4, 122.8, 122.5, 120.4, 115.6, 115.3. ESI-HRMS: *m/z* calcd for $C_{21}H_{16}NO$ $[M + H]^+$: 298.1226; found: 298.1277.

(17) See the Supporting Information.