EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402003

Copper-Catalyzed C(sp^3)–C(sp^2) Cross-Coupling: Synthesis of 4-Aryl-2-alkylamino-3-nitro-4*H*-chromenes

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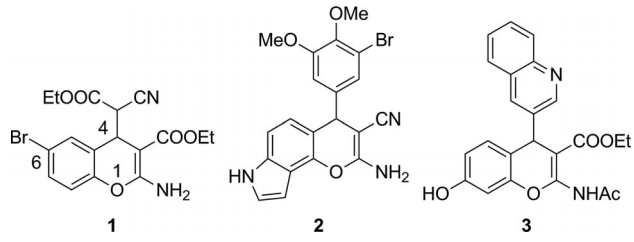
Keywords: C–C coupling / Copper / Cross-coupling / Medicinal chemistry / Drug discovery

Inexpensive copper(II) acetate effectively catalyzes cross-coupling of electron-deficient as well as electron-rich arylboronic acids with 4-methylsulfanyl-2-alkylamino-3-nitro-4*H*-chromenes under near neutral conditions at room temp. to furnish a range of 4-aryl-4*H*-chromenes. This new strategy enabled substitution of the C(4)SMe group present on a sp^3 hybridized carbon of the 4*H*-chromenes with aryl/heteroaryl groups. Mechanistic probing revealed that the Cu^{I}–Cu^{III} cycle is involved in catalysis. One-pot sequential substitution of C(4)SMe followed by C(6)Br with aryl groups has been achieved through Cu(OAc)$_2$ and Pd$_2$(dba)$_3$ (Suzuki coupling) catalysis.

Introduction

Among the fundamental requirements of de novo discovery of lead molecules for medicinal use are the possibilities of (i) quick, high yielding, experimentally facile and environmentally benign combinatorial assembly, (ii) lack or minimal number of stereogenic (chiral) centers, (iii) rigid heterocyclic ring systems, (iv) structural diversity in terms of well-defined functional group disposition that can be finely tuned for target recognition and (v) absence of labile functional groups.[1] The parent molecular entities that can incorporate such guiding concepts are referred to as "privileged medicinal scaffolds".[2] In the quest for the development of lead molecules for specific targets there is a need to unearth high yielding and catalytic methods that are tolerant to a variety of functional groups. These concepts underlie the focal themes of research in modern medicinal chemistry and drug discovery.[3] Reflecting the above concepts, in recent years, 2*H*-chromene (2*H*-1-benzopyran) and its close relative 4*H*-chromene (4*H*-1-benzopyran) have emerged as privileged scaffolds because their derivatives have found applications as drug candidates.[4] Whereas 2*H*-chromene is surprisingly well-represented as a structural element in biologically active and naturally occurring compounds such as tocopherols, flavonoids, anthocyanins and some alkaloids, there are very few natural products with 4*H*-chromene structure.[5] The derivatives of 4*H*-chromene, however, exhibit a plethora of favorable medicinal properties including antifungal, antioxidant, antileishmanial, hypotensive, antiproliferation, local anesthetic, antiallergenic, anticoagulant, antianaphylactic, spasmolytic and diuretic activities.[6] Furthermore, 4*H*-chromene derivatives have been employed for the treatment of Alzheimer's disease and schizophrenia disorder.[7] In cancer chemotherapy, 4*H*-chromene **1** (Figure 1) was marked for drug development because it effectively binds to cancer-implicated Bcl-2 proteins and induced programmed cell death (apoptosis) in selected cancer cell lines.[8] The 4-aryl-4*H*-chromenes, the target structures of the present study, represented by **2** (Figure 1), exhibit highly useful proapoptotic properties for the treatment of a wide range of cancer ailments including breast, lung and colo-rectal cancers.[9] In certain cases these compounds act on cancer cells that are resistant to common anticancer drugs such as paclitaxel and vinblastine. Apart from applications in cancer chemotherapy, 4-aryl-4*H*-chromenes for example **3** have found application in the enhancement of cognitive functions such as memory, and are thus useful in the treatment of dementia.[10] Overall, synthesis and biological evaluation of structurally diverse 4-aryl-4*H*-chromenes is of high importance. For diversity oriented synthesis, 4-aryl-4*H*-chromenes of type **2** provide opportunities in three regions of the molecule, namely, the aromatic ring of the benzopyran, substitution at the C2-amine, and the aryl group at the C4 position.



1 **2** **3**

Figure 1. Structure of anticancer agents **1** and **2**, and an agent for the treatment of cognitive dysfunction **3**.

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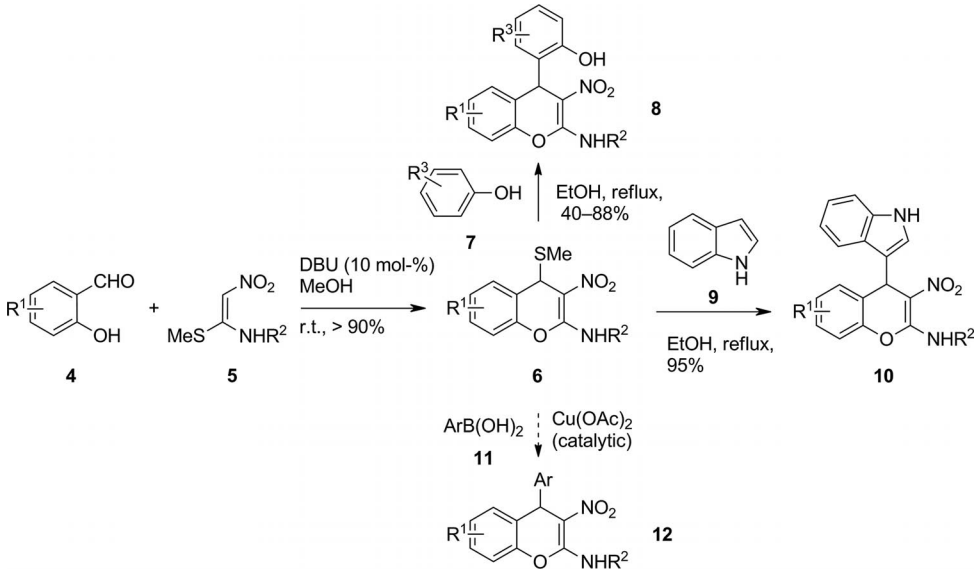
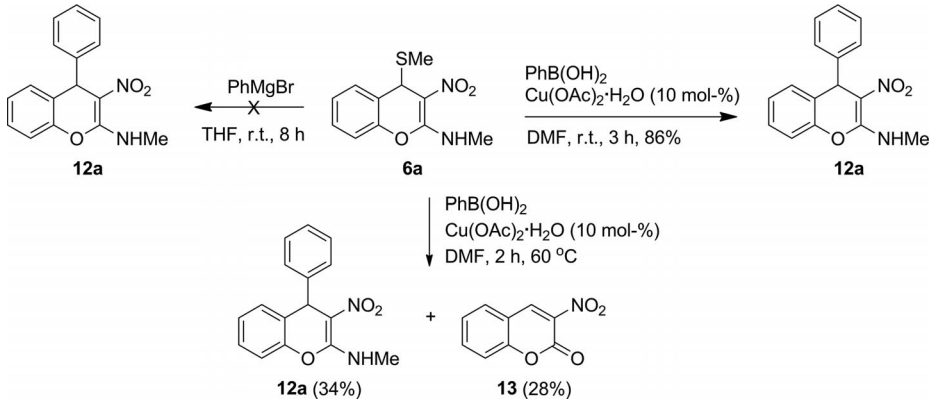
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402003.

We have recently described a facile, high yielding, atom-economic synthesis of 4-methylsulfanyl-4*H*-chromenes **6** from readily available 2-hydroxybenzaldehydes (salicylaldehydes) **4** and nitroketene-*N*,*S*-acetals **5** (Scheme 1).[11] The 4*H*-chromenes **6** have a highly labile C(4)SMe group that is open for substitution with nucleophiles through the intermediary of benzopyrylium cations. As an example, the reactions of **6** with phenols **7**, lead to exclusive substitution at the *ortho* position in phenols to provide 4-aryl-4*H*-chromenes **8** (Scheme 1).[12] Whereas this aromatic electrophilic substitution in phenols is high yielding and regiochemically defined, the reaction is, however, limited to phenols. In addition, the reaction is also limited to products formed from the reaction of phenols at their *ortho* position. The C(4)SMe group in **6a**, however, can be replaced with highly electron-rich aromatic compounds such as indole **9** to generate 4-aryl-4*H*-chromenes of type **10**.[13] Once again, the substitution is limited to electron-rich aromatic compounds. In our quest to develop a generic method for substitution of C(4)SMe with a range of aromatic rings to produce 4-aryl-4*H*-chromenes **12**, initially, we attempted the reaction of **6** with phenylmagnesium bromide, but the reaction did not provide any tangible product (Scheme 2). By screening various options, we found that the substitution of C(4)SMe in **6** with an aryl group could be achieved through its cross-coupling with arylboronic acids **11** under copper(II) acetate catalysis (Scheme 2), details of which are presented here. Although there have been several reports on copper-catalyzed substitution of the SMe group present on sp^2 carbon atoms, particularly under aerobic conditions (Chan–Lam reaction),[14] to the best of our knowledge, the present reaction constitutes the first report on cross-coupling involving an SMe group present on a sp^3 hybridized carbon.

Despite the fact that copper-mediated coupling reactions as a means of carbon–carbon bond formation were discovered several decades earlier than the palladium-catalyzed reactions,[15] due to the requirement for harsh reaction conditions and high catalytic loading, they have been largely excluded from synthetic planning. Nevertheless, in recent years there has been a huge resurgence of cross-coupling reactions involving organocopper intermediates due to the



Scheme 1. Synthesis of 4-methylsulfanyl-4*H*-chromene **6** and its further transformations into 4-aryl-4*H*-chromenes **8**, **10**, and **12**.



Scheme 2. Reactions of 4*H*-chromene **6a** with different reagent systems.

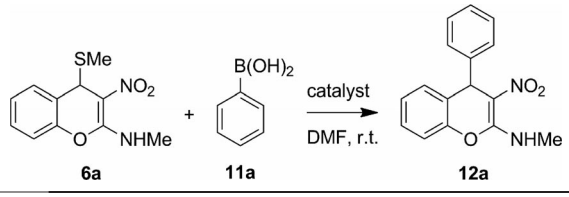
discovery of milder reaction conditions and because of the advantages of copper catalysts over the use of more expensive and toxic palladium catalysts.[16] As a result, there is now a paradigm shift in the conduct of cross-coupling reactions with palladium catalysis to copper catalysis. Like the Pd^0–Pd^{II} redox cycle in palladium-mediated cross-coupling reactions, copper exhibits facile Cu^I–Cu^{III} or occasionally Cu^0–Cu^{II} redox cycles, and involves oxidative addition, transmetallation, and reductive disintegration steps to facilitate cross-coupling.[17] One additional advantage of employing copper reagents in cross-coupling is that, unlike those of its close neighbors palladium and nickel, the copper salts or complexes tolerate functional groups with sulfur, a facet that we demonstrate in the present work.

Results and Discussion

For screening of catalysts and development of optimal reaction conditions, the cross-coupling reaction of 4*H*-chromene **6a** with phenylboronic acid **11a** to form the parent 4-phenyl-4*H*-chromene **12a** was selected (Scheme 2, Table 1). The reactions were conducted at room temp. on a 0.4 mmol scale with catalyst and in solvents that have been extensively employed previously for promoting Cu or Pd mediated cross-coupling reactions.[18] Among the copper(II) catalysts screened [$Cu(OAc)_2$, $Cu(OCOCF_3)_2$, $Cu(OTf)_2$, $CuSO_4$, $CuCl_2$, $CuBr_2$, CuO, $Cu(acac)_2$] it was found that 10 mol-% $Cu(OAc)_2$ provided 4*H*-chromene **12a** in the best yield (Table 1, entry 2). Although the difference in yield of **12a** was not high, the rate of the reaction was at least half when 5 mol-% $Cu(OAc)_2$ was used (entry 1). On the other hand, the addition of larger quantities of $Cu(OAc)_2$ did not improve either the rate or the yield (entries 3 and 4). Copper(I) catalysts such as CuBr, CuI, CuCl, and Cu_2O were not as efficient as $Cu(OAc)_2$ (Table 1, entries 12–15). Surprisingly, coupling was not observed when organic solvent soluble but air-sensitive copper(I) catalysts such as Cu^IBrSMe_2 (entry 15) or $Cu(PPh_3)_3Br$ (entry 16) were employed. Similarly, there was no reaction with air-stable copper(I) complexes such as copper(I)-thiophene-2-carboxylate (CuTC)[19] (entry 18) or Cu^I-3-methylsalicylate (CuMeSal)[20] (entry 19). Notably, there was no reaction when well-known palladium(II) catalyst $Pd(OAc)_2$ (entry 20) or palladium(0) catalyst $Pd_2(dba)_3$ (entry 21) were employed. However, when two equivalents of the base Na_2CO_3[21] was present in the reaction medium, $Pd(OAc)_2$ or $Pd_2(dba)_3$ catalyzed the reaction to provide the target cross-coupled product in moderate yield (entries 22 and 23). No reaction was observed when common nickel(0) catalysts such as $Ni(cod)_2$ (entry 24) or $Ni[P(OEt)_3]_4$ (entry 25) were employed, possibly due to the presence of the sulfur functional group. Based on the above experiments, we concluded that 10 mol-% $Cu(OAc)_2$ is the best catalyst for the preparation of a series of 4-aryl-4*H*-chromenes **12**.

We then screened solvents for optimization of the reaction conditions (Table 2). Of the solvents investigated such as dimethyl sulfoxide (DMSO; polar aprotic, entry 1), *N*,*N*-dimethylformamide (DMF; polar aprotic, entry 2), acetonitrile (polar aprotic, entry 6), EtOH (polar protic, entry 7), and dioxane (nonpolar, entry 8), DMF worked well when

Table 1. Optimization of reaction conditions for cross-coupling using different catalysts.

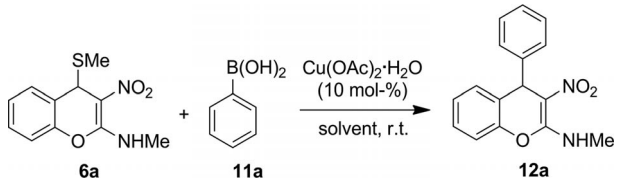


6a **11a** **12a**

Entry	Catalyst	Time [h]	mol-%	Yield [%][a]
1	$Cu(OAc)_2·H_2O$	6	5	82
2	$Cu(OAc)_2·H_2O$	3	10	86
3	$Cu(OAc)_2·H_2O$	3	20	85
4	$Cu(OAc)_2·H_2O$	3	30	81
5	$Cu(CF_3COO)_2·H_2O$	6	5	61
6	$Cu(OTf)_2$	6	5	n.r.
7	$CuSO_4·5H_2O$	4	10	51
8	$CuCl_2·2H_2O$	4	10	n.r.
9	$CuBr_2$	4	10	25
10	$Cu(acac)_2$	4	10	67
11	CuO	4	10	51
12	CuBr	5	10	57
13	CuI	5	10	35
14	CuCl	6	10	72
15	Cu_2O	4	10	n.r.
16	Cu^IBrSMe_2	6	10	n.r.
17	$Cu(PPh_3)_3Br$	6	10	n.r.
18	CuTC	4	10	n.r.
19	CuMeSal	5	10	n.r.
20	$Pd(OAc)_2$	6	5	n.r.
21	$Pd_2(dba)_3$	12	5	n.r.
22	$Pd(OAc)_2$, Na_2CO_3 (2 equiv.)	6	5	48
23	$Pd_2(dba)_3$, Na_2CO_3 (2 equiv.)	14	5	38
24	$Ni(cod)_2$	1	10	n.r.
25	$Ni[P(OEt)_3]_4$	1	10	n.r.

[a] n.r.: no reaction.

Table 2. Optimization of reaction conditions for cross-coupling using different solvents.



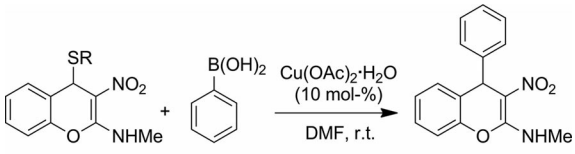
6a **11a** **12a**

Entry	Solvent	Ligand/Base	Atmosphere	Time [h]	Yield [%]
1	DMSO	–	N_2	4	26
2	DMF	–	N_2	3	86
3	DMF	–	Air	4	62
4	DMF	–	O_2	4	24
5	NMP	–	N_2	6	15
6	MeCN	–	N_2	4	nr
7	EtOH	–	N_2	4	nr
8	dioxane	–	N_2	4	16
9	DMF	PPh_3	N_2	4	34
10	DMF	phenanthroline	N_2	4	46
11	DMF	Na_2CO_3	N_2	4	72
12	DMF	K_2CO_3	N_2	3	78

conducted under an atmosphere of nitrogen.[22] Reaction under aerobic conditions (entry 3) or in an oxygen atmosphere (entry 4) provided lower yields, indicating that the reaction does not go through oxygen-mediated oxidation for catalyst regeneration. The use of ligands such as PPh_3 (entry 9) or phenanthroline (entry 10), which could complex with reactive copper species, in fact led to a decrease in yield. The inclusion of acid-scavenging bases such as Na_2CO_3 (entry 11) or K_2CO_3 (entry 12) did not improve the yield of the product. The reaction with $Cu(OAc)_2$ in DMF worked well at room temp. (25–30 °C); although it was faster at elevated temperature (60 °C), the reaction provided a mixture of the cross-coupled product **12a** (34%) and the hydrolysis product **13** (28%) (Scheme 2).

The nature of leaving group in 4*H*-chromene **6** was evaluated for its influence in the cross-coupling reaction (Table 3). Of the three substrates **6a** (R = Me, entry 1), **6b** (R = *n*Bu, entry 2), and **6c** (R = Ph, entry 3) studied, the reaction worked best with C(4)SMe (**6a**), indicating that a smaller (Me vs. *n*Bu) electron-donating (Me vs. Ph) group is better suited for the cross-coupling.

Table 3. Effect of different thio-ether leaving groups in cross-coupling.



6a–c **11a** **12a**

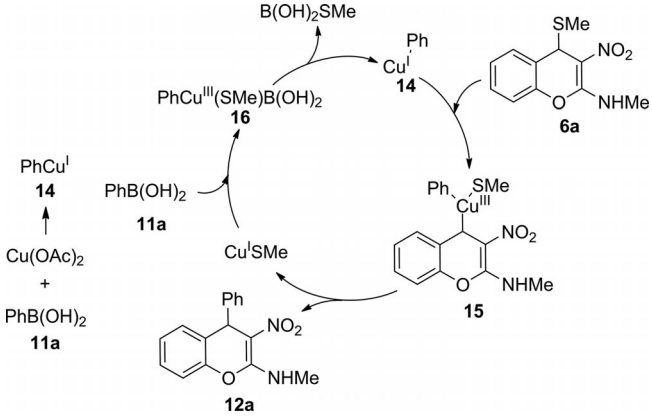
Entry	Substrate	Time [h]	Yield [%]
1	**6a**: R = Me	3	86
2	**6b**: R = *n*Bu	4	76
3	**6c**: R = Ph	14	41

Two experiments were conducted to evaluate the effect of the sequence of addition of the two reactants, namely, phenylboronic acid (**11a**) and 4*H*-chromene **6a**. The yield of the product **12a** was higher in the former experiment (86%) in which **11a** was stirred with $Cu(OAc)_2$ before the addition of **6a**. In an analogous experiment in which **6a** was stirred with $Cu(OAc)_2$ before the addition of **11a**, the yield was less than half (37%). In the absence of $Cu(OAc)_2$, formation of **12a** was not observed, even when the reaction was conducted at elevated temperatures. These experiments showed that the first step in the catalytic cycle is the reaction of $Cu(OAc)_2$ with **11a**. To evaluate whether the transformation of **6a** into **12a** proceeded through an S_N1 or S_N2 pathway, instead of going through cross-coupling, **6a** was treated with phenylmagnesium bromide in the presence of a catalytic amount of CuI (Scheme 3) under classical Cu^I-mediated substitution reaction conditions.[23] This reaction provided **12a** in only 8% yield, indicating that simple nucleophilic substitution was not the major route for the transformation.

Although several reliable copper-mediated coupling reactions have been well-documented, a mechanistic understanding of the reaction is sketchy owing to the occurrence of multiple oxidation states of copper (0, +1, +2, +3) in the reaction medium and weak C–Cu bond energy (200 ± 30 kJ mol^{-1}).[24] Additionally, reactive copper species could occur in clusters with Cu–Cu bonds. Based on the experimental results discussed above, a possible mechanism of $Cu(OAc)_2$-mediated cross-coupling of 4*H*-chromene **6a** with phenylboronic acid (**11a**) is depicted in Scheme 4. In the first cycle, phenylboronic acid reacts with $Cu(OAc)_2$ to form a Cu^IPh species.[25] Newly generated Cu^IPh **14** reacts with **6a** to form transmetallated Cu^{III} species **15**. Cross-coupling leads to generation of the product **12a** and Cu^ISMe. Newly formed Cu^ISMe reacts with **11a** to generate PhCu^{III}(SMe)B(OH)$_2$ **16**. Decomposition of this Cu^{III} intermediate furnishes stable $B(OH)_2$SMe and reactive Cu^IPh **14**, which enters into the catalytic cycle again. Although the Cu^0–Cu^{II} redox cycle could be invoked as the driving force for the coupling process, we believe that in view of the high standard reduction potential[26] (+0.34 volts for Cu^{2+} to Cu^0) this is unlikely. To rule out involvement of Cu^0 as the active catalyst for the transformation, a Hg^0-poisoning experiment was carried out. As shown in Scheme 5, the inclusion of a 30-fold excess of Hg^0 did not exhibit any effect on the reaction.[27] If Cu^0 was generated in the reaction, it was expected to become rapidly poisoned by Hg^0 by amalgamation, thereby suppressing the catalytic cycle.[28]

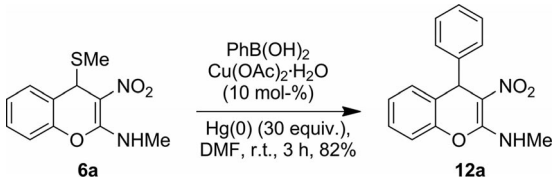
6a **12a**

Scheme 3. Reaction of 4*H*-chromene **6a** with PhMgBr under reaction conditions for substitution.



Scheme 4. A plausible mechanism for $Cu(OAc)_2$-catalyzed cross-coupling of arylboronic acids with 4*H*-chromenes **6a**.

The 4-phenyl-4*H*-chromene **12a** was characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR and DEPT-135) and analytical data. A singlet for C(4)H at δ = 5.3 ppm in the ^{1}H NMR spectrum is a diagnostic signal for 4-phenyl-4*H*-chromene **12a**. To demonstrate the scope of the cross-coupling reaction, a range of arylboronic acids **11b–o** were



Scheme 5. Cu-catalyzed cross-coupling in the presence of Hg^0.

treated with 4*H*-chromene **6a** under the optimized reaction conditions to realize fourteen 4-aryl-4*H*-chromenes **12b–o** (Table 4). These arylboronic acids were selected with a view to their structural diversity and their potential binding to biological targets and thus for their potential as medicinally important compounds. High efficiency of cross-coupling was observed regardless of the presence of strongly electron-withdrawing [C(4)CF_3 **11b**, C(3) and C(5)CF_3 **11c**, C(3) and C(5)F **11d**], mildly electron-withdrawing [C(4)F **11e**, C(4)Cl **11f**, C(4)Br **11g**, C(3)Cl **11h** and C(3)OMe **11i**], strongly electron-donating [C(4)OMe **11j**, C(4)OEt **11k** and C(4)OBn **11l**] or mildly electron-donating [C(4)Et **11m**] nature of the substituents in arylboronic acids employed. Notably, the cross-coupling reaction worked well even with *ortho*-substituted boronic acids [C(2) and C(3)-OMe **11n** and C(2) and C(5)OMe **11o**], indicating that the cross-coupling is not highly sensitive to steric bulk on the aryl ring.

To demonstrate the possibilities of diversity in the aryl ring of the 4*H*-chromene moiety, three C(4)-methanesulfanyl 4*H*-chromenes **6d–f** were subjected to $Cu(OAc)_2$-catalyzed cross-coupling with **11a** to realize 4-phenyl-4*H*-chromenes **12p–r** (Table 5). Similarly, possibilities of diversity in nitrogen substitution was demonstrated by subjecting 4*H*-chromene with *N*-butyl substitution **6g** to coupling with **11a** to furnish the corresponding cross-coupled product **12s**.

We then targeted cross-coupling of **6a** with heteroarylboronic acids because several such heterocyclic motifs are important structural elements within bioactive molecules. The $Cu(OAc)_2$-mediated reaction of **6a** with furan-2-boronic acid smoothly provided **12t** (Scheme 6). However, no reaction was observed with pyridine-2-boronic acid at room temp. On mild heating, the reaction provided dimeric product **17** (24%) together with hydrolysis product **13** (31%) instead of the anticipated cross-coupled product (Scheme 6). Likely, radical intermediates that are generated from **6a** dimerize to form **17**. The reaction with thiophene-2-boronic acid also did not yield the desired cross-coupled product when the reaction was conducted at room temp. At higher temperature (45 °C) both dimeric product **17** (15%) and hydrolysis product **13** (37%) were isolated. Although it is not clear, we presume that both pyridine-2-boronic acid and thiophene-2-boronic acid are less reactive in copper-

Table 4. Scope of Cu-catalyzed cross-coupling of arylboronic acids with 4*H*-chromene **6a**.

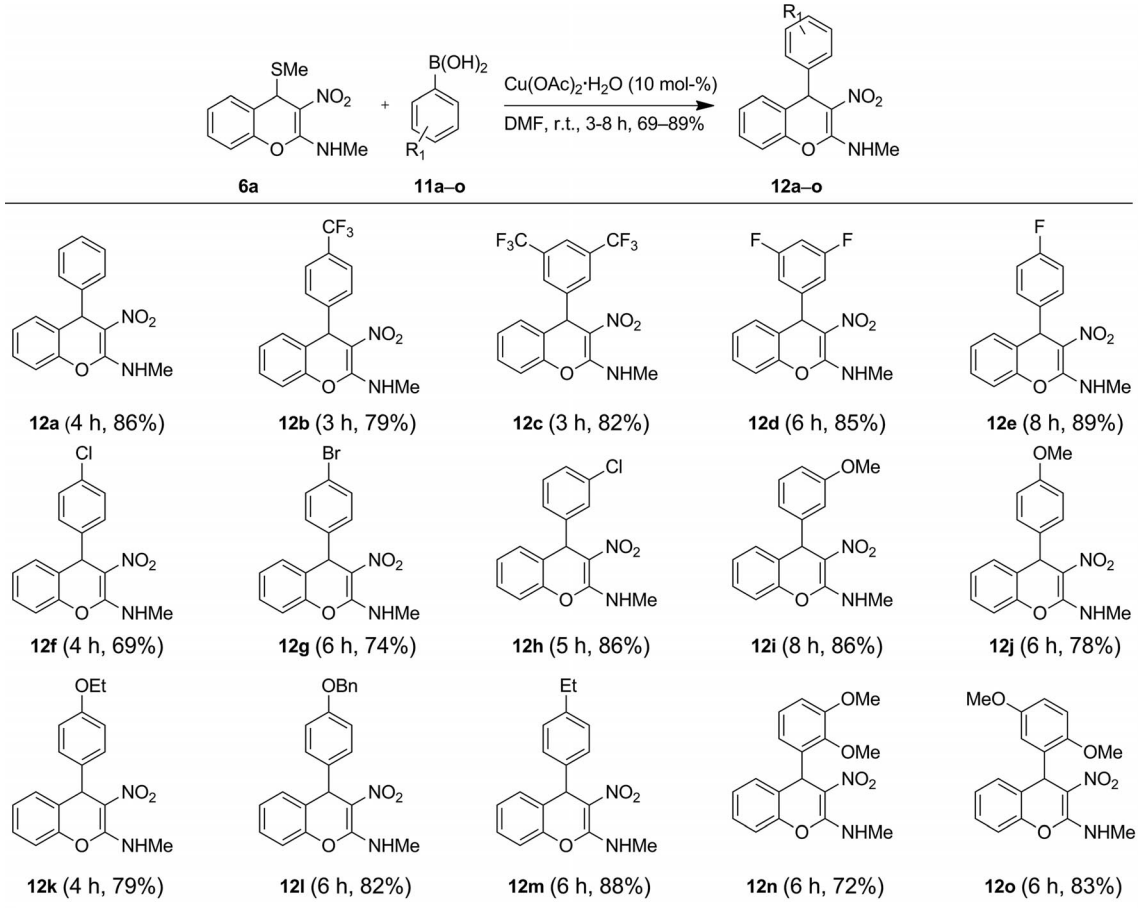
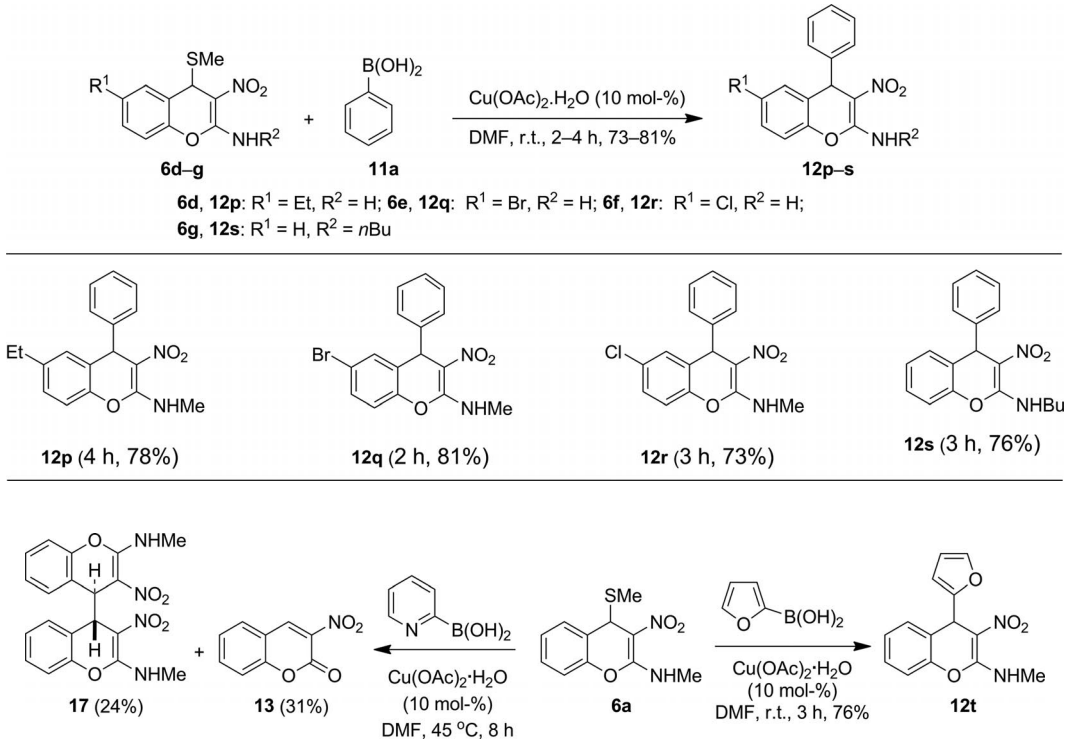


Table 5. Exploring the scope of diversity in 4*H*-chromenes for coupling with **11a**.



Scheme 6. $Cu(OAc)_2$-catalyzed cross-coupling reactions of **6a** with heteroarylboronic acids.

mediated cross-coupling reactions owing to their ability to act as Cu coordinating ligands and in the process do not allow efficient copper insertion into the aryl–boron bond.

Among four 4-methylsulfanyl-4*H*-chromenes **6d**–**g** that were subjected to cross-coupling with arylboronic acids, 4*H*-chromene **6e** is the most interesting because of the presence of C(6)Br. The molecule is open for sequential coupling reactions with arylboronic acids first under $Cu(OAc)_2$ catalysis to substitute C(4)SMe, followed by Pd^0 catalysis to substitute C(6)Br. The one-pot sequential substitution was demonstrated on **6e** by initial coupling with phenylboronic acid under $Cu(OAc)_2$ catalysis, followed by coupling with 4-methoxyphenylboronic acid under $[Pd_2(dba)_3]$ catalysis to provide bis-aryl-4*H*-chromene **18** in good yield (Scheme 7). Heating the reaction mixture to at least 60 °C was required to induce the second step to take place. 4-Methoxyphenylboronic acid was employed in the second step to follow the reaction by using ^1H NMR spectroscopy. The $[Pd_2(dba)_3]$ appeared to be a more suitable

Scheme 7. Sequential $Cu(OAc)_2$- and Pd-catalyzed cross-coupling reactions of **6c** with arylboronic acids.

catalyst for the second Suzuki coupling step because when $Pd(OAc)_2$ or $PdCl_2$ were employed 4*H*-chromene **18** was isolated in low yield of 11 or 13%, respectively.

Conclusion

We have shown that $Cu(OAc)_2$ efficiently catalyzes cross-coupling of *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amines **6** with arylboronic acids **11** in DMF under anaerobic conditions to provide *N*-methyl-3-nitro-4-aryl-4*H*-chromen-2-amines **12**. A combinatorial library of 4-aryl-4*H*-chromenes could be synthesized by varying the substitution in the arylboronic acid, aryl ring of the chromone, and C(2)-amino group. The cross coupling works well with furan-2-boronic acid but not with less reactive thiophene-2-boronic acid or pyridine-2-boronic acid. Sequential one-pot $Cu(OAc)_2$ coupling followed by Suzuki coupling could be achieved on 4*H*-chromene **6e**. Thus, we have demonstrated the first example of a copper-catalyzed coupling reaction on a substrate having a SMe functional group on a carbon with sp^3 hybridization.

Experimental Section

General Experimental Methods: Progress of all the reactions was monitored by TLC using hexanes (60–80 °C boiling mixture)/ethyl acetate mixture as eluent. Column chromatography was performed on silica gel (100–200 mesh SRL Chemicals) using increasing per-

centage of ethyl acetate in hexanes. ^{1}H NMR spectra (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for $CDCl_3$ or [D_6]DMSO solutions with a Bruker Avance 400 spectrometer with TMS as internal standard. Coupling constants *J* are given in Hz. IR spectra were recorded as KBr pellets with a Nicolet-6700 FTIR spectrometer. Melting points were recorded using open-ended capillary tubes with a VEEGO VMP-DS instrument and are uncorrected. High-resolution mass spectra were recorded with a Micromass Q-TOF micro mass spectrometer using electrospray ionization mode. X-ray diffraction measurements were carried out at 298 K with an Oxford CrysAlis CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å). Organic solvents were dried by standard methods. Commercially obtained reagents were used after purification. Arylboronic acid were purchased from Sigma-Aldrich and copper salts from MERCK and were used as received. The catalyst [$Pd_2(dba)_3$] and the starting compounds *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amines were prepared according to reported procedures.[29]

Synthesis of 4-Aryl-2-alkylamino-3-nitro-4*H*-chromenes. General Procedure: A solution of arylboronic acid **11** (0.48 mmol, 1.2 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 equiv.) in anhydrous DMF (0.3 mL) in an atmosphere of nitrogen was stirred for 10 min, by which time copper salt dissolved and the reaction mixture became light-green. To this, 4*H*-chromen **6** (0.4 mmol, 1 equiv.) in anhydrous DMF (0.2 mL) was added and the mixture was stirred at room temp. until TLC showed the disappearance of 4*H*-chromene. The reaction mixture was then diluted with ice-cold water (10 mL) and the organic layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water (2 × 20 mL), brine (1 × 10 mL) and CH_2Cl_2 was removed under reduced pressure. The crude product was subjected to column chromatography (silica gel; gradient elution with increasing volume of EtOAc in hexanes) to give 4-aryl-2-alkylamino-3-nitro-4*H*-chromenes **12**. An analytical sample was obtained by recrystallization from a 9:1 mixture of hexanes and EtOAc.

***N*-Methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (12a):** Yield 96 mg (86%); white solid; m.p. 183 °C. IR (KBr): $\tilde{\nu}$ = 1642, 1607, 1467, 1401, 1369, 1209, 1168, 1065, 754, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.33 (br. s, 1 H), 7.14–6.98 (m, 9 H), 5.31 (s, 1 H), 3.11 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C), 147.6 (C), 143.7 (C), 129.7 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 126.9 (CH), 125.9 (CH), 125.0 (C), 116.1 (CH), 109.0 (C), 41.8 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{14}N_2O_3Na$ [M + Na] 305.0902; found 305.0900.

***N*-Methyl-3-nitro-4-[4-(trifluoromethyl)phenyl]-4*H*-chromen-2-amine (12b):** Yield 101 mg (79%); white solid; m.p. 219 °C. IR (KBr): $\tilde{\nu}$ = 3202, 1644, 1470, 1363, 1248, 1213, 1163, 1117, 1062, 826, 757, 416 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.34 (br. s, 1 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.20–7.16 (m, 1 H), 7.10 (d, *J* = 8.1 Hz, 1 H), 7.04–7.03 (m, 2 H), 5.38 (s, 1 H), 3.16 (d, *J* = 5.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C), 147.6 (C), 129.7 (CH), 129.3 (C), 129.0 (C), 128.7 (CH), 128.2 (CH), 126.2 (CH), 125.6 (q, *J* = 7.3 Hz, CH), 124.0 (C), 122.8 (C), 116.4 (CH), 108.4 (C), 41.8 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{13}N_2O_3F_3Na$ [M + Na] 373.0776; found 373.0779.

4-[3,5-Bis(trifluoromethyl)phenyl]-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12c): Yield 136 mg (82%); white solid; m.p. 191 °C. IR (KBr): $\tilde{\nu}$ = 1645, 1613, 1476, 1404, 1370, 1279, 1213, 1168, 1132, 1069, 761cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.32 (br. s, 1 H), 7.59 (s, 3 H), 7.24–7.20 (m, 1 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 7.6 Hz, 1 H), 5.46 (s, 1 H), 3.20 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C), 147.6 (C), 146.2 (C), 131.8 (q, *J* = 66.1 Hz, C), 129.8 (CH), 129.2 (CH), 128.2 (CH), 126.5 (CH), 124.6 (C), 123.0 (C), 121.9 (C), 121.2 (t, *J* = 3.7 Hz, CH), 116.7 (CH), 107.9 (C), 41.9 (CH), 28.1 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{12}F_6N_2O_3Na$ [M + Na] 441.0650; found 441.0655.

4-(3,5-Difluorophenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12d): Yield 108 mg (85%); light-yellow crystals; m.p. 228 °C. IR (KBr): $\tilde{\nu}$ = 3174, 3092, 2925, 2859, 1642, 1463, 1363, 1216, 1160, 1114, 1058, 992, 908, 848, 774, 696, 660 cm^{-1}. ^{1}H NMR (400 MHz, [D_6]-DMSO): δ = 10.34 (br. s, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.21–7.19 (m, 1 H), 7.13–7.09 (m, 1 H), 6.89–6.85 (m, 2 H), 6.76–6.71 (m, 1 H), 5.40 (s, 1 H), 3.22 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 163.7 (d, *J* = 12 Hz, C), 161.2 (d, *J* = 13 Hz, C), 158.5 (C), 148.6 (t, *J* = 8 Hz, C), 147.1 (C), 129.2 (CH), 128.4 (CH), 125.5 (CH), 123.5 (C), 116.2 (CH), 110.2 (q, *J* = 18 Hz, CH), 106.7 (C), 101.9 (t, *J* = 25 Hz, CH), 41.0 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{12}F_2N_2O_3Na$ [M + Na] 341.0714; found 341.0717.

4-(4-Fluorophenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12e): Yield 106 mg (89%); white plates; m.p. 169 °C. IR (KBr): $\tilde{\nu}$ = 1642, 1609, 1506, 1473, 1401, 1367, 1215, 1170, 1065, 828, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.35 (br. s, 1 H), 7.18–7.04 (m, 6 H), 6.86–6.81 (m, 2 H), 5.33 (s, 1 H), 3.17 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (C), 160.4 (C), 159.3 (C), 147.9 (C), 139.4 (C), 129.6 (CH), 129.3 (d, *J* = 8 Hz, CH), 128.3 (CH), 126.0 (CH), 124.8 (C), 116.1 (CH), 115.3 (d, *J* = 21 Hz, CH), 108.9 (C), 41.0 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{13}FN_2O_3Na$ [M + Na] 323.0808; found 323.0809.

4-(4-Chlorophenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12f): Yield 67.7 mg (69%); white solid; m.p. 162 °C. IR (KBr): $\tilde{\nu}$ = 3174, 2925, 1650, 1605, 1462, 1372, 1213, 1172, 1066, 816, 763, 706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.42 (br. s, 1 H), 7.27–7.09 (m, 8 H), 5.39 (s, 1 H), 3.25 (d, *J* = 5.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C), 147.6 (C), 142.2 (C), 132.7 (C), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 126.1 (CH), 124.5 (C), 116.3 (CH), 108.7 (C), 41.3 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{13}ClN_2O_3Na$ [M + Na] 339.0512; found 339.0514.

4-(4-Bromophenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12g): Yield 107 mg (74%); white solid; m.p. 209 °C. IR (KBr): $\tilde{\nu}$ = 1644, 1612, 1487, 1474, 1459, 1435, 1403, 1367, 1253, 1238, 1211, 1170, 1066, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.32 (br. s, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.17–7.15 (m, 1 H), 7.09–7.03 (m, 5 H), 5.29 (s, 1 H), 3.16 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C), 147.6 (C), 142.8 (C), 131.6 (CH), 129.7 (CH), 129.6 (CH), 128.5 (CH), 126.1 (CH), 124.4 (C), 120.9 (C), 116.3 (CH), 108.7 (C), 41.4 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{13}BrN_2O_3Na$ [M + Na] 383.0007; found 383.0010.

4-(3-Chlorophenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12h): Yield 108 mg (86%); white solid; m.p. 194 °C. IR (KBr): $\tilde{\nu}$ = 1639, 1608, 1472, 1429, 1403, 1354, 1211, 1235, 1168, 1112, 1036, 769, 723, 690, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.34 (br. s, 1 H), 7.20–7.02 (m, 8 H), 5.31 (s, 1 H), 3.18 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (C), 147.6 (C), 145.6 (C), 134.4 (C), 129.8 (CH), 129.7 (CH), 128.6 (CH), 127.8 (CH), 127.2 (CH), 126.2 (CH), 126.1 (CH), 124.3 (C), 116.3 (CH), 108.5 (C), 41.7 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{13}ClN_2O_3Na$ [M + Na] 339.0512; found 339.0512.

4-(3-Methoxyphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12i): Yield 106 mg (86%); white solid; m.p. 177 °C. IR (KBr): $\tilde{\nu}$ = 3176, 2944, 1645, 1609, 1489, 1457, 1403, 1364, 1277, 1255, 1209, 1144, 1067, 1047, 778, 754, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.43 (br. s, 1 H), 7.26–7.07 (m, 5 H), 6.84–6.81 (m, 2 H), 6.71–6.68 (m, 1 H), 5.39 (s, 1 H), 3.74 (s, 3 H), 3.22 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C), 159.5 (C), 147.6 (C), 145.3 (C), 129.6 (CH), 129.5 (CH), 128.2 (CH), 125.9 (CH), 124.9 (C), 120.1 (CH), 116.1 (CH), 114.1 (CH), 111.7 (CH), 108.9 (C), 55.2 (CH_3), 41.8 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{16}N_2O_4Na$ [M + Na] 335.1008; found 335.1009.

4-(4-Methoxyphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12j): Yield 96 mg (78%); white solid; m.p. 146 °C. IR (KBr): $\tilde{\nu}$ = 1645, 1509, 1466, 1367, 1249, 1170, 1066, 823, 757 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.37 (br. s, 1 H), 7.18–7.03 (m, 6 H), 6.70–6.68 (m, 2 H), 5.30 (s, 1 H), 3.65 (s, 3 H), 3.16 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (C), 158.5 (C), 147.7 (C), 136.0 (C), 129.8 (CH), 128.8 (CH), 128.1 (CH), 126.0 (CH), 125.5 (C), 116.1 (CH), 113.9 (CH), 109.3 (C), 55.3 (CH_3), 41.0 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{16}N_2O_4Na$ [M + Na] 335.1008; found 335.1017.

4-(4-Ethoxyphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12k): Yield 103 mg (79%); white solid; m.p. 174 °C. IR (KBr): $\tilde{\nu}$ = 1639, 1610, 1513, 1477, 1456, 1436, 1398, 1357, 1245, 1208, 1173, 1116, 1061, 827, 800, 753 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.36 (br. s, 1 H), 7.18–7.13 (m, 1 H), 7.10–7.02 (m, 5 H), 6.68 (d, J = 6.8 Hz, 2 H), 5.29 (s, 1 H), 3.89–3.84 (m, 2 H), 3.15 (d, J = 5.2 Hz, 3 H), 1.27 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (C), 157.9 (C), 147.7 (C), 135.8 (C), 129.8 (CH), 128.8 (CH), 128.1 (CH), 126.0 (CH), 125.5 (C), 116.1 (CH), 114.5 (CH), 109.4 (C), 63.4 (CH_2), 41.0 (CH), 28.0 (CH_3), 14.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_4Na$ [M + Na] 349.1164; found 349.1161.

4-[4-(Benzyloxy)phenyl]-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12l): Yield 126 mg (82%); white solid; m.p. 214 °C. IR (KBr): $\tilde{\nu}$ = 3446, 1759, 1642, 1608, 1508, 1474, 1457, 1401, 1358, 1237, 1214, 1168, 1135, 1112, 1056, 767, 743, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.36 (br. s, 1 H), 7.29–7.21 (m, 4 H), 7.17–7.13 (m, 1 H), 7.10–7.09 (m, 1 H), 7.08–7.03 (m, 5 H), 6.76 (d, J = 6.8 Hz, 2 H), 5.30 (s, 1 H), 4.90 (s, 2 H), 3.15 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (C), 157.8 (C), 147.7 (C), 137.1 (C), 136.2 (C), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.5 (CH), 126.1 (CH), 125.5 (C), 116.1 (CH), 114.9 (CH), 109.4 (C), 70.1 (CH_2), 41.0 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{23}H_{20}N_2O_4Na$ [M + Na] 411.1324; found 411.1315.

4-(4-Ethylphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12m): Yield 109 mg (88%); white solid; m.p. 169 °C. IR (KBr): $\tilde{\nu}$ = 1646, 1610, 1463, 1401, 1372, 1212, 1169, 1067, 828, 753, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.31 (br. s, 1 H), 7.14–7.04 (m, 5 H), 6.97–6.95 (m, 3 H), 5.29 (s, 1 H), 3.07 (d, J = 5.2 Hz, 3 H), 2.48–2.42 (m, 2 H), 1.06 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C), 147.6 (C), 142.7 (C), 140.9 (C), 129.6 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 125.9 (CH), 125.3 (C), 116.0 (CH), 109.1 (C), 41.4 (CH), 28.3 (CH_2), 27.8 (CH_3), 15.4 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_3Na$ [M + Na] 333.1215; found 333.1218.

4-(2,5-Dimethoxyphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12n): Yield 113 mg (83%); white solid; m.p. 222 °C. IR (KBr): $\tilde{\nu}$ = 3202, 2934, 2831, 1639, 1609, 1475, 1394, 1357, 1250, 1215, 1177, 1062, 1004, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (br. s, 1 H), 7.31 (d, J = 7.8 Hz, 1 H), 7.29 (d, J = 6.9 Hz, 1 H), 7.10 (d, J = 8.1 Hz, 1 H), 7.05 (td, J = 7.5, 1.2 Hz, 1 H), 6.93 (t, J = 7.8 Hz, 1 H), 6.86 (dd, J = 7.8, 1.6 Hz, 1 H), 6.74 (dd, J = 8.0, 1.6 Hz, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 3.25 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (C), 153.0 (C), 147.4 (C), 146.5 (C), 137.2 (C), 129.8 (CH), 127.9 (CH), 125.7 (CH), 124.8 (C), 123.8 (CH), 121.3 (CH), 115.8 (CH), 111.3 (CH), 108.4 (C), 60.2 (CH_3), 55.7 (CH_3), 37.7 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_5Na$ [M + Na] 365.1113; found 365.1110.

4-(2,3-Dimethoxyphenyl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12o): Yield 98 mg (72%); white solid; m.p. 206 °C. IR (KBr): $\tilde{\nu}$ = 1648, 1608, 1500, 1457, 1402, 1374, 1245, 1220, 1175, 1057, 1025, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.55 (br. s, 1 H), 7.18–7.17 (m, 1 H), 7.10–7.08 (m, 1 H), 7.02–6.95 (m, 2 H), 6.80 (d, J = 3.0 Hz, 1 H), 6.64 (d, J = 8.8 Hz, 1 H), 6.61–6.58 (m, 1 H), 5.51 (s, 1 H), 3.66 (s, 3 H), 3.58 (s, 3 H), 3.17 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C), 153.7 (C), 151.4 (C), 147.8 (C), 133.0 (C), 129.4 (CH), 127.9 (CH), 125.5 (CH), 124.5 (C), 116.3 (CH), 115.6 (CH), 113.0 (CH), 112.2 (CH), 108.1 (C), 56.5 (CH_3), 55.7 (CH_3), 38.0 (CH), 27.9 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_5Na$ [M + Na] 365.1113; found 365.1111.

6-Ethyl-*N*-methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (12p): Yield 96 mg (78%); light-yellow solid; m.p. 198 °C. IR (KBr): $\tilde{\nu}$ = 3176, 3047, 2954, 1640, 1474, 1399, 1353, 1211, 1169, 1061, 827, 776, 702, 634 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.36 (br. s, 1 H), 7.18–6.89 (m, 8 H), 5.31 (s, 1 H), 3.12 (d, J = 5.2 Hz, 3 H), 2.45 (m, 2 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C), 145.8 (C), 143.7 (C), 142.0 (C), 128.6 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 126.8 (CH), 124.7 (C), 115.9 (CH), 109.2 (C), 41.9 (CH), 28.1 (CH_2), 27.8 (CH_3), 15.4 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{18}H_{18}N_2O_3Na$ [M + Na] 333.1215; found 333.1210.

6-Bromo-*N*-methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (12q): Yield 116 mg (81%); white solid; m.p. 232 °C. IR (KBr): $\tilde{\nu}$ = 3054, 3025, 2879, 1637, 1602, 1461, 1399, 1360, 1252, 1212, 1161, 1063, 1017, 920, 824, 740, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.35 (br. s, 1 H), 7.36–7.33 (m, 1 H), 7.29–7.18 (m, 6 H), 7.05 (d, J = 8.4 Hz, 1 H), 5.36 (s, 1 H), 3.23 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C), 146.8 (C), 143.0 (C), 132.5 (CH), 131.4 (CH), 128.8 (CH), 127.8 (CH), 127.4 (CH), 127.3 (C), 118.6 (CH), 118.0 (C), 108.6 (C), 41.8 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{14}BrN_2O_3Na$ [M + Na] 383.0007; found 383.0006.

6-Chloro-*N*-methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (12r): Yield 93 mg (73%); white solid; m.p. 218 °C. IR (KBr): $\tilde{\nu}$ = 2945, 2193, 1641, 1606, 1471, 1362, 1254, 1219, 1169, 1061, 1018, 916, 816, 768, 741, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.39 (br. s, 1 H), 7.27–7.10 (m, 8 H), 5.37 (s, 1 H), 3.25 (d, J = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C), 146.2 (C), 143.0 (C), 131.1 (C), 129.5 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 127.4 (CH), 126.9 (C), 117.7 (CH), 108.6 (C), 41.9 (CH), 28.1 (CH_3) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{14}ClN_2O_3$ [M + H] 317.0693; found 317.0688.

***N*-Butyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (12s):** Yield 98 mg (76%); white solid; m.p. 137 °C. IR (KBr): $\tilde{\nu}$ = 3047, 2963, 2933, 1638, 1604, 1445, 1360, 1310, 1259, 1236, 1174, 1065, 778, 752, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.54 (br. s, 1 H), 7.25–7.21 (m, 5 H), 7.18–7.10 (m, 4 H), 5.43 (s, 1 H), 3.67–3.60 (m, 2 H), 1.76–1.67 (m, 2 H), 1.52–143 (m, 2 H), 1.0 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1 (C), 147.7 (C), 143.7 (C), 129.8 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.0 (CH), 126.0 (CH), 125.3 (C), 116.1 (CH), 108.9 (C), 41.9 (CH),

41.3 (CH_2), 31.8 (CH_2), 20.0 (CH_2), 13.7 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{19}H_{21}N_2O_3$ [M + H] 325.1552; found 325.1548.

4-(Furan-2-yl)-*N*-methyl-3-nitro-4*H*-chromen-2-amine (12t): Yield 82 mg (76%); m.p. 162 °C. IR (KBr): $\tilde{\nu}$ = 3200, 2946, 1734, 1643, 1609, 1475, 1403, 1365, 1246, 1215, 1175, 1144, 1067, 929, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.41 (br. s, 1 H), 7–32–7.25 (m, 2 H), 7.20–7.13 (m, 3 H), 6.22–6.21 (m, 1 H), 6.18 (d, *J* = 3.2 Hz, 1 H), 5.60 (s, 1 H), 3.24 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C), 154.1 (C), 148.1 (C), 141.9 (CH), 129.5 (CH), 128.7 (CH), 125.9 (CH), 122.4 (C), 116.2 (CH), 110.4 (CH), 106.2 (C), 106.0 (CH), 35.7 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{14}H_{12}N_2O_4Na$ [M + Na] 295.0695; found 295.0697.

Experimental Procedure for Hg^0 Poisoning Experiment: A solution of phenylboronic acid **11b** (0.48 mmol, 1.2 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 equiv.) in anhydrous DMF (0.3 mL) under an atmosphere of nitrogen was stirred for 10 min, by which time copper salt dissolved and the reaction mixture became light-green. To this solution *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine **6a** (0.4 mmol, 1 equiv.) in anhydrous DMF (0.2 mL) and Hg^0 (12 mmol, 30 equiv.) was added and the mixture was stirred at room temp. until TLC showed the consumption of 4*H*-chromene (3 h). The reaction mixture was then diluted with ice-cold water (10 mL) and the organic layer was extracted with CH_2Cl_2 (2× 20 mL). The organic layer was washed with water (2× 20 mL) and brine (10 mL) and CH_2Cl_2 was removed under reduced pressure. The crude product was subjected to column chromatography (silica gel; gradient elution with increasing volume of EtOAc in hexanes) to yield *N*-methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (**12a**) (101 mg, 82%) as a white solid.

3-Nitro-2*H*-chromen-2-one (13): A stirred solution of phenylboronic acid (0.48 mmol, 1.2 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 equiv.) in anhydrous DMF (0.3 mL) was stirred under an atmosphere of nitrogen for 10 min, by which time copper salt dissolved and reaction mixture became light-green. To this solution, *N*-methyl-4-(methylthio)-3-nitro-4*H*-chromen-2-amine (0.4 mmol, 1 equiv.) in anhydrous DMF (0.2 mL) was added and the reaction mixture was heated at 60 °C until TLC showed the consumption of 4*H*-chromene (2 h). The reaction mixture was then diluted with ice-cold water (10 mL) and the organic layer extracted with CH_2Cl_2 (2× 20 mL). The organic layer was washed with water (2× 20 mL) and brine (10 mL), and CH_2Cl_2 was removed under reduced pressure. The crude product was subjected to column chromatography (silica gel; gradient elution with increasing volume of EtOAc in hexanes) to yield **13** (21 mg, 28%).

6-(4-Methoxyphenyl)-*N*-methyl-3-nitro-4-phenyl-4*H*-chromen-2-amine (18): A solution of phenylboronic acid **11** (0.48 mmol 1.2 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 equiv.) in anhydrous DMF (0.3 mL) was stirred under an atmosphere of nitrogen for 10 min by which time copper salt dissolved and reaction mixture became light-green. To this solution, 4*H*-chromen **6c** (0.4 mmol, 1 equiv.) in anhydrous DMF (0.2 mL) was added and the mixture was stirred at room temp. until TLC showed the consumption of 4*H*-chromene. To the mixture, $[Pd_2(dba)_3]$ (2 mol-%), $NaHCO_3$ (0.8 mmol, 2 equiv.), and 4-methoxyphenylboronic acid (0.4 mmol, 1 equiv.) were added and the mixture was heated at 60 °C for 3 h. The reaction mixture was then diluted with ice-cold water (10 mL) and the organic layer was extracted with CH_2Cl_2 (2× 20 mL). The organic layer was washed with water (2× 20 mL) and brine (10 mL) and CH_2Cl_2 was removed under reduced pressure. The crude product was subjected column chromatography (silica gel; gradient elution with increasing volume of EtOAc in hexanes) to give 4*H*-chromenes **18**. An analytical sample was obtained by recrystallization from 9:1 mixture of hexanes and CH_2Cl_2 to give a white solid, yield 124 mg (78%); m.p. 197 °C. IR (KBr): $\tilde{\nu}$ = 3059, 3029, 2938, 2836, 1640, 1604, 1472, 1402, 1367, 1244, 1174, 1119, 1067, 821, 755, 725, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.44 (br. s, 1 H), 7.42–7.37 (m, 3 H), 7.31–7.15 (m, 7 H), 6.92 (d, *J* = 8.2 Hz, 2 H), 5.48 (s, 1 H), 3.82 (s, 3 H), 3.27 (d, *J* = 5.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C), 159.5 (C), 146.9 (C), 143.7 (C), 139.0 (C), 132.2 (C), 128.7 (CH), 128.1 (CH), 127.87 (CH), 127.83 (CH), 127.1 (CH), 126.6 (CH), 125.5 (C), 116.5 (CH), 114.4 (CH), 109.2 (C), 55.5 (CH_3), 42.1 (CH), 28.0 (CH_3) ppm. HRMS (ESI): *m/z* calcd. for $C_{23}H_{20}N_2O_4Na$ [M + Na] 411.1321; found 411.1320.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra, HRMS data for the compounds **12a**–**t** and **18**, and the ORTEP plot of the X-ray structure of **12d** along with crystal data.

Acknowledgments

H. S. P. R thanks the University Grants Commission (UGC), New Delhi, the University Grants Commission – Special Assistance Program (UGC-SAP), the Council of Scientific and Industrial Research (CSIR), New Delhi and the Department of Science and Technology – Fund for Improvement of Science and Technology Infrastructure (DST-FIST) for financial assistance. A. V. R thanks CSIR for a fellowship. The authors thank the Central Instrumentation Facility (CIF), Pondicherry University, and the Indian Institute of Science (IISc), Banglore for recording spectra.

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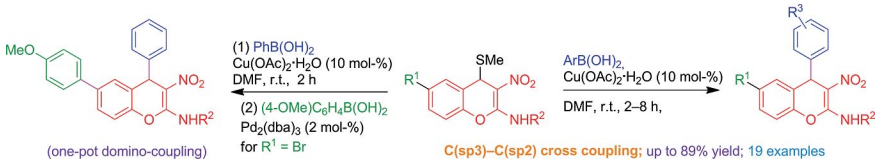
Received: February 3, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry

Cross-Coupling with Copper



Copper(II) acetate efficiently catalyzes C–C bond formation between 4-methylsulfanyl-2-alkylamino-3-nitro-4*H*-chromenes and arylboronic acids to provide a library of 4-aryl/heteroaryl-4*H*-chromenes via sp^3–sp^2 cross-coupling. The reaction also allows one-pot sequential substitution of C(4)SMe and C(6)Br with aryl groups through $Cu(OAc)_2$ and $Pd_2(dba)_3$ (Suzuki coupling) catalysis.

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Copper-Catalyzed C(sp^3)–C(sp^2) Cross-Coupling: Synthesis of 4-Aryl-2-alkylamino-3-nitro-4*H*-chromenes

Keywords: C–C coupling / Copper / Cross-coupling / Medicinal chemistry / Drug discovery

