Synthesis of Indoles by Copper-Catalyzed Heteroannulation of *o*-Aminophenylboronic Acid Pinacol Esters with β-Keto Esters

Ala Bunescu, Qian Wang, Jieping Zhu*

Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland
Fax +41(21)6939740; E-mail: jieping.zhu@epfl.ch

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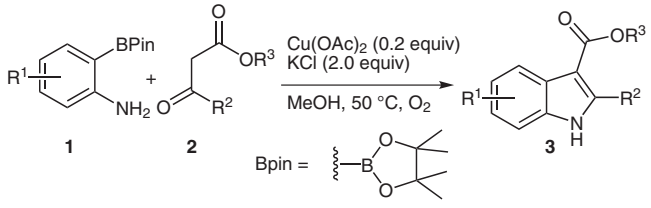
Abstract: Copper-catalyzed coupling of *o*-aminophenylboronic acid pinacol esters with β-keto esters afforded, under mild base-free oxidative conditions, 2,3-disubstituted indoles featuring a key Chan–Lam-type carbon–carbon bond-forming reaction.

Key words: indole, copper catalysis, Chan–Lam reaction, *o*-aminophenylboronic ester, β-keto ester

The indole scaffold is found in many natural products and pharmacologically active compounds.[1] Given the omnipresent character of this heterocyclic motif, numerous synthetic methodologies have been developed.[2] Among them, metal-catalyzed cyclization of enamines has proved to be of great utility. Since the first report of Kibayashi on the palladium-catalyzed cyclization of *N*-(2-halophenyl)enaminone,[3] this method has been largely explored for the synthesis of diversely functionalized indoles.[4] Based on this strategy, a one-pot synthesis of 3-substituted indoles, including functionalized tryptophanes, using aldehydes as coupling partners with *o*-haloanilines has subsequently been developed[5–7] and conditions allowing the direct cyclization of *N*-phenylenaminone have been uncovered.[8] Similar cyclization has been realized using a copper salt as the catalyst.[9] All of these methods required the use of a base and high reaction temperature, which could be problematic in the case of base-sensitive substrates.[10] Herein we report a copper-catalyzed indole synthesis from *o*-aminophenylboronic esters and β-keto esters under mild, base-free oxidative conditions (Scheme 1).



Scheme 1 Copper(II) acetate catalyzed synthesis of indoles

Copper-mediated N- and O-arylation using arylboronic acids as coupling partners was reported independently, in 1998, by Chan, Lam, and Evans.[11] Subsequently, the substrate scope has been extended to other heteroatom nucleophiles[12] and to other boronic acids such as vinyl[13] and cyclopropyl.[14] However, the Chan–Lam reaction has been rarely explored for C–C cross coupling,[15] in sharp contrast to the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction. To investigate this under-explored research field with the aim of developing a base-free indole synthesis, copper-catalyzed heteroannulation was examined using *o*-aminophenylboronic acid pinacol ester (**1a**) and methyl acetoacetate (**2a**) as test substrates. A large number of solvents, copper catalysts, ligands, temperature ranges, and oxidants were screened. Some representative conditions using copper(II) acetate as catalyst and oxygen as terminal oxidant are shown in Table 1.

Table 1 Optimization of the Reaction Conditions

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

Entry	Additive	Molar ratio **1a**/**2a**	Yield[a] (%) of **3a**
1[b]	–	1:1.2	33
2[b]	3 Å MS	1:1.2	27
3[b]	CsF (1.5 equiv)	1:1.2	22
4[b]	NaI	1:1.2	–
5[b]	L-proline	1:1.2	21
6[b]	TMEDA	1:1.2	–
7[b]	–	2:1	traces
8[b]	–	1:2	40
9[c]	–	1:2	48
10[c,d]	LiCl (2 equiv)	1:2	55
11[c,d]	KCl (2 equiv)	1:2	68

[a] Isolated yield.
[b] $Cu(OAc)_2$ (0.2 equiv), MeOH (0.23 M), r.t.
[c] $Cu(OAc)_2$ (0.2 equiv), MeOH (0.06 M), r.t.
[d] 50 °C.

The stoichiometry between **1a** and **2a** was found to be important and excess β-keto ester **2a** (2.0 equiv) relative to *o*-aminophenylboronate **1a** should be used in order to ob-

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tain reasonable yields of the indole **3a** (Table 1, entry 8 vs. 7). Indeed, β-keto esters are known to be good ligands for copper.[16] In our case, it was possible that methyl acetoacetate (**2a**) formed a chelate with the metal, reducing, therefore, the rate of protodeboronation. The following control experiments supported this hypothesis. When copper(II) acetate was added to a methanol solution of **1a**, the formation of aniline was observed instantaneously. However, when copper(II) acetate was added to a solution of **1a** and **2a**, the process of protodeboronation was almost negligible even after five days at room temperature. In addition, the reaction of **1a** and **2a** in the presence of presynthesized bis(ethyl acetoacetato)copper complex [$Cu(etac)_2$] (Figure 1)[17] afforded indole **3a** in a similar yield. Reducing the concentration of the reaction mixture from 0.23 M to 0.06 M increased the yield of the annulated product (entry 9 vs. 8). Finally, addition of lithium chloride or, in particular, potassium chloride significantly increased the yield of **3a** under otherwise identical conditions (entries 10 and 11). Although the exact role of lithium or potassium chloride is unclear,[18,19] they may help the dissociation of the copper acetate dimer to its more soluble monomer via a chloride ion complex of type $Cu(II)Cl_x(OAc)_y$.[20] Overall, the optimum conditions consisted of performing the heteroannulation in MeOH (0.06 M) in the presence of copper(II) acetate (0.2 equiv) and potassium chloride (2.0 equiv) at 50 °C under an oxygen atmosphere.

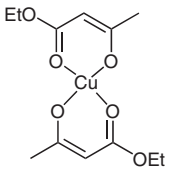


Figure 1 Bis(ethyl acetoacetato)copper(II) [$Cu(etac)_2$]

The scope of this transformation was investigated using the optimized reaction conditions. As shown in Figure 2, the reaction was sensitive to steric hindrance. Thus, ethyl acetoacetate gave higher yields of indole than *tert*-butyl acetoacetate (**3b** vs. **3e**) A variety of β-keto esters including branched (*i*-Pr) and functionalized esters (C=C, 2-furyl) and substituted anilines participated in this annulation reaction to afford the corresponding indoles in moderate to good yields. In most cases, both the ^{1}H NMR spectrum and TLC of the crude reaction mixture were quite clean and no distinct side products could be identified. Therefore, we assumed that the moderate yields obtained were due to the occurrence of decomposition pathways.

Two pathways could account for the present heteroannulation process (Scheme 2). Condensation of the aniline with the β-keto ester would produce an enaminone intermediate **A**. Ligand exchange with the copper(II) salt followed by oxidation would afford **B**, which upon reductive elimination provided the indole **3** (pathway *a*).[21,22] Alternatively, the β-keto ester could undergo the copper-catalyzed α-arylation to provide **C**, which then underwent

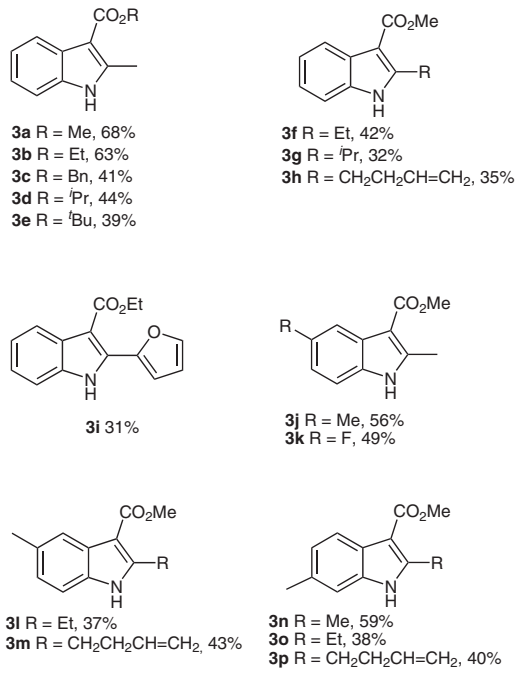
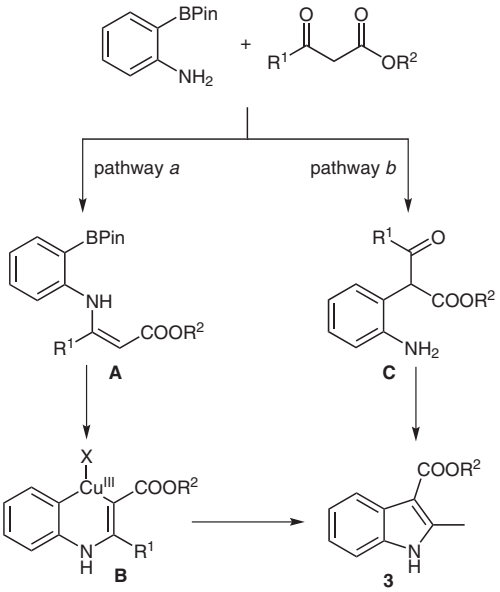


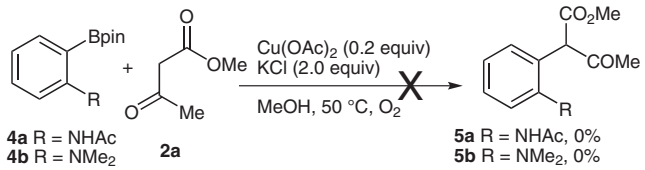
Figure 2 Substrate scope



Scheme 2 Plausible reaction pathways

intramolecular condensation to produce the indole **3** (pathway *b*).[9]

To distinguish these two pathways, 2-acetamidophenylboronate **4a** and 2-(dimethylamino)phenylboronate **4b** were submitted to our standard oxidative conditions. The reaction of **4a** or **4b** with methyl acetoacetate failed to give the corresponding 2-aryl-3-oxobutanoate **5a** or **5b** (Scheme 3) as would be expected from pathway *b*.[23] From these control experiments, we assumed that pathway *a* might be responsible for the present heteroannulation process.



Scheme 3 Control experiments

In summary, we have developed a novel base-free copper catalyzed synthesis of 2,3-disubstituted indoles from readily available *o*-aminophenylboronic esters and β-keto esters. The work represents a rare example in which the Chan–Lam reaction is used for the formation of a carbon–carbon bond.

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI + and –) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters. NMR spectra were recorded on a Bruker Avance III-400, Bruker Avance-400 or Bruker DPX-400 spectrometer at r.t., ^{1}H (400.13 MHz), ^{13}C (100.62 MHz) in $CDCl_3$. IR spectra were recorded in a Jasco FT/IR-4100 spectrophotometer outfitted with a PIKE technology. Melting points were determined using a Stuart SMP30 and were uncorrected. Flash column chromatography was performed using Silicycle silica gel: 230–400 mesh (40–63 μm) silica. Reactions were monitored using Merck Kieselgel 60 F254 aluminum. TLC was visualized by UV fluorescence (254 nm) then one of the following: $KMnO_4$, ninhydrin, pancaldi, *p*-anisaldehyde, or vanillin. All reagents were obtained from commercial suppliers unless otherwise stated.

1*H*-Indole-3-carboxylates 3a–p; General Procedure

To a suspension of *o*-aminophenylboronic acid pinacol ester **1** (0.114 mmol, 1.0 equiv), β-keto ester **2** (0.228 mmol, 2.0 equiv), and KCl (0.228 mmol, 2.0 equiv) in MeOH (0.06 M) was added $Cu(OAc)_2$ (0.023 mmol, 0.2 equiv). The mixture was stirred at 50 °C under O_2 until total consumption of **1** (12–24 h) (TLC monitoring). After completion of the reaction, MeOH was evaporated under reduced pressure. To the resulting residue was added EtOAc (5.0 mL) and 10% aq NH_3 soln (5.0 mL). The aqueous phase was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, petroleum ether–EtOAc) to give the desired indole **3**.

Compounds **3a**,**b**,**e**,**f**,**j**,**k**,**n**,[8a] **3g**,[9c] **3h**,[24] **3i**[25] were described previously.

Benzyl 2-Methyl-1*H*-indole-3-carboxylate (3c)

Yellow solid; yield: 12.4 mg (41%); mp 140–143 °C.

IR (neat): 2931, 2857, 2359, 1748, 1631, 1472, 1428, 1214, 1113, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.09–8.11 (m, 1 H), 7.48–7.51 (m, 2 H), 7.41–7.39 (m, 2 H), 7.36–7.28 (m, 2 H), 7.23–7.15 (m, 2 H), 5.42 (s, 2 H), 2.75 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 144.4, 137.0, 134.6, 128.7, 128.2, 128.1, 127.3, 122.6, 122.0, 121.5, 110.6, 104.5, 65.5, 14.5.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{17}H_{16}NO_2$: 266.1181; found: 266.1183.

Isopropyl 2-Methyl-1*H*-indole-3-carboxylate (3d)

Yellow solid; yield: 10.8 mg (44%); mp 96–100 °C.

IR (neat): 3285, 2979, 2923, 2360, 1658, 1454, 1271, 1202, 1085, 747, 671 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.19–8.05 (m, 1 H), 7.29–7.31 (m, 1 H), 7.24–7.15 (m, 2 H), 5.33–5.27 (m, 1 H), 2.74 (s, 3 H), 1.42 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8, 143.9, 134.6, 127.4, 122.4, 121.8, 121.5, 110.6, 105.1, 66.9, 22.5, 14.4.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{13}H_{16}NO_2$: 218.1181; found: 218.1183.

Methyl 2-Ethyl-5-methyl-1*H*-indole-3-carboxylate (3l)

Yellow solid; yield: 9.1 mg (37%); mp 109–113 °C.

IR (neat): 3232, 2922, 2360, 1651, 1463, 1207, 1100, 1060, 808, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 7.87 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 1 H), 7.02 (d, *J* = 8.2, 1 H), 3.93 (s, 3 H), 3.16 (q, *J* = 7.6 Hz, 2 H), 2.47 (s, 3 H), 1.35 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 149.1, 134.9, 132.4, 125.1, 123.5, 121.2, 110.7, 103.6, 50.9, 21.7, 21.4, 13.3.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{13}H_{16}NO_2$: 218.1181; found: 218.1176.

Methyl 2-(But-3-enyl)-5-methyl-1*H*-indole-3-carboxylate (3m)

Yellow solid; yield: 12.0 mg (43%); mp 87–90 °C.

IR (neat): 3284, 2919, 2852, 1669, 1473, 1218, 1158, 1083, 906, 797, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.90–7.89 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 7.03 (dd, *J* = 8.2, 1.7 Hz, 1 H), 5.90 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1 H), 5.11 (dq, *J* = 17.1, 1.4 Hz, 1 H), 5.05 (dq, *J* = 10.2, 1.4 Hz, 1 H), 3.93 (s, 3 H), 3.27 (t, *J* = 7.4 Hz, 2 H), 2.56–2.48 (m, 2 H), 2.47 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 147.7, 137.6, 132.8, 131.4, 127.4, 124.1, 121.4, 116.2, 110.4, 103.8, 50.9, 33.1, 27.5, 21.7.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{15}H_{18}NO_2$: 244.1338; found: 244.1335.

Methyl 2-Ethyl-6-methyl-1*H*-indole-3-carboxylate (3o)

Yellow solid; yield: 9.5 mg (38%); mp 119–120 °C.

IR (neat): 3295, 2967, 2922, 1662, 1448, 1207, 1162, 1053, 788, 714, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H), 7.96 (d, *J* = 8.2 Hz, 1 H), 7.11 (s, 1 H), 7.05 (d, *J* = 8.2 Hz, 1 H), 3.92 (s, 3 H), 3.19 (q, *J* = 7.5 Hz, 2 H), 2.45 (s, 3 H), 1.34 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5, 149.7, 132.8, 131.4, 127.6, 123.9, 121.3, 110.3, 103.3, 50.9, 21.8, 21.5, 13.3.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{13}H_{16}NO_2$: 218.1181; found: 218.1176.

Methyl 2-(But-3-enyl)-6-methyl-1*H*-indole-3-carboxylate (3p)

Yellow solid; yield: 11.2 mg (40%); mp 91–94 °C.

IR (neat): 3228, 2976, 2922, 1645, 1462, 1361, 1207, 1080, 907, 806 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.96 (d, *J* = 8.1 Hz, 1 H), 7.11 (s, 1 H), 7.05 (d, *J* = 8.1 Hz, 1 H), 5.90 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1 H), 5.11 (dq, *J* = 16.9, 1.6 Hz, 1 H), 5.04 (dq, *J* = 10.1, 1.6 Hz, 1 H), 3.92 (s, 3 H), 3.26 (t, *J* = 7.4 Hz, 2 H), 2.54–2.47 (m, 2 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 147.1, 137.6, 135.0, 132.5, 124.9, 123.5, 121.3, 116.2, 110.8, 104.2, 50.9, 33.1, 27.4, 21.7.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{15}H_{18}NO_2$: 244.1338; found: 244.1335.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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