REGULAR ARTICLE

Special Section on Transition Metal Catalyzed Synthesis of Medicinally Relevant Molecules

Copper (cat) and phenylboronic acid mediated deformylative C-N coupling of isoindolinone-3-ols with formamides provide C(3) aminoisoindolinones

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Abstract. Copper(I) iodide efficiently catalyzes deformylative C-N coupling of formamides and isoindolinone-3-ols to provide C(3) primary/secondary amine substituted isoindolinones. The transformation requires a stoichiometric amount of phenylboronic acid as a co-reactant. In the reaction, formamides act as the synthetic equivalent of primary/secondary amines. The method is amenable for the synthesis of a combinatorial library of medicinally relevant C(3) amino substituted isoindolinones.

Keywords. Isoindolinones; copper catalysis; deformylative C-N coupling; phenylboronic acid.

1. Introduction

Isoindole is not as ubiquitous as indole, it is, however, represented as a part-structure in many bio-active alkaloids.¹ Isoindolinones (1,3-dihydro-2*H*-isoindole-1-one; phthalimidines; the highlighted portion in stachybotrysam A **1**, Figure 1) form a distinctive sub-group among isoindoles. Significantly, several alkaloids isolated from marine fungi (e.g., **1**) imbibe isoindole core.² Alkaloids with this heterocyclic core exhibit potent and varied biological activities and thus isoindole is considered as a medicinally privileged structure.³ For example, the potent antifungal agent pestalachloride A **2** (Figure 1), isolated from the fungus *Pestalotiopsis adusta* has an isoindolinone core.⁴ Over the past few years, medicinal chemists have been engaged in the synthesis and biological evaluation of a variety heterocyclic compounds with this core; with an aim to unearth pharmaceutical compounds.⁵ Such efforts yielded development of anticancer compound lenalidomide **3**, used for treating multiple myeloma,⁶ and (*S*)-pazinaclone **4** and its siblings used for sedative and anxiolytic effects.⁷ Among the family of isoindolinone heterocyclic compounds, synthesis of those which have a substitution on

N(2) and C(3) have attracted greater attention (highlighted portion in pazinaclone **4**, Figure 1).⁸ Several efforts were directed towards the synthesis of this core structure, most of which go through cyclization to form an isoindolinone nucleus in the final step.⁹

For the past few years, we have been engaged in the copper-mediated synthesis of a variety of heterocyclic compounds via C(sp³)-C(sp²) coupling reactions.¹⁰ In the context of the synthesis of C(3) substituted isoindolinones, we have reported a facile copper-mediated coupling of 3-hydroxyisoindolinones **5** and aryl-, heteroaryl- and alkenylboronic acids with concomitant removal of boric acid to provide C(3) aryl/heteroaryl/alkenyl substituted isoindolinones **6** (Equation 1, Scheme 1).¹¹ Among the various copper catalysts, tried copper(II) trifluoromethanesulfonate (Cu(OTf)₂) worked well in dichloroethane (DCE) reflux. Both inter- and intra-molecular versions of the reaction were facile. When we conducted the reaction of **5** in *N,N*-dimethylformamide (DMF) medium, unexpectedly, it provided C-N coupled product **7** instead of anticipated C-C coupled product **6** (Equation 2, Scheme 1). The product **7**, obviously did not have the component of phenylboronic acid, but the reaction did

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Figure 1. Representative examples of natural products (**1** and **2**) and synthetic drugs (**3** and **4**) with isoindolinone core.

Our previous work

Present work

Scheme 1. Our previous and present work on the synthesis of C(3) substituted isoindolinones **6** and **7**.

not take place in the absence of this reagent as well as in the absence of copper catalyst. The product formation of **7** was evidently going through deformylation of DMF. Since the reaction was going to completion only in the presence of one equivalent of phenylboronic acid, we concluded that it was a co-reactant. Overall, the intriguing and surprising result prompted us to explore the reaction in greater detail and the results are reported herein. Of late, copper-catalyzed transformations are gaining more popularity over palladium catalyzed reactions as the copper catalysts are less expensive, less toxic and biocompatible.¹² Recently, Palombi and coworkers reported access to isoindolinones of the type **7** (*N*-Mannich bases of 1-isoindolinones) by the reaction of 2-formylbenzonitriles with primary or secondary amines under chemical or electrochemical activation.¹³ In our reaction, DMF (Equation 2, Scheme 1) is a surrogate and convenient source of dimethyl amine which is a toxic gas at rt (B.p. = 7 °C). Previously, DMF and similar formamides have been used as a source of (i) *N*-acylamines, (ii) amines, (iii) alkyl groups to effect

a variety of coupling reactions conducted under copper catalysis under aerobic/oxidative conditions.¹⁴ In our reaction, deformylative C-N coupled product **7** formed exclusively. The reaction did not provide even traces of dehydrative C-C coupled product **8**, dehydrogenative C-O coupled product **9** or methylated product **10** (Scheme 1). To the best of our knowledge, copper and phenylboronic acid-mediated deformylative and dehydroxylative C-N coupling as seen in the conversion of 3-hydroxyisoindolinone **5** to C(3) *N,N*-dimethylamino isoindolinone **7** is not known and is being reported for the first time.

2. Experimental

2.1 General Experimental Methods

The progress of all the reactions was monitored by TLC using a suitable mixture of hexanes (a mixture of aliphatic hydrocarbons that boil between 60–80 °C) and ethyl acetate as an

eluent. Column chromatography was performed on silica gel (100–200 mesh) using increasing percentages of ethyl acetate in hexanes. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded for CDCl_3 or $\text{CDCl}_3/\text{CCl}_4$ (1/1) solutions with a 400 MHz NMR spectrometer with TMS as the internal standard. Chemical shifts (in ppm) and coupling constants (J in Hz) are given here. IR spectra were recorded as KBr pellets with a Nicolet-6700 FT-IR spectrometer. The melting points were recorded with open-ended capillary tubes with a VEEGO VMP-DS instrument and are uncorrected. High-resolution mass spectra were recorded on a quadrupole time-of-flight (QTOF) mass spectrometer using electro-spray ionization mode (ESIMS). X-Ray diffraction measurements were carried out at 298 K on a diffractometer equipped with a graphite monochromator and a Mo-K α fine focus sealed tube ($\lambda = 0.71073 \text{ \AA}$). Organic solvents were dried by standard methods.¹⁵ Commercially obtained reagents were used after purification. Arylboronic acids were purchased from Sigma-Aldrich and copper salts were purchased from Avra Chemicals.

2.2 General Procedure for synthesis of *N*(2) substituted *C*(3) aminoisoindolin-1-ones Synthesis of 2-benzyl-3-(dimethylamino)isoindolin-1-one **7a**

To an oven-dried test tube charged with a mixture of 2-benzyl-3-hydroxyisoindolin-1-one **5a** (100 mg, 1 mmol), *N,N*-dimethylformamide (DMF, 30 mg, 1 mmol), copper iodide (7.9 mg, 0.1 mmol), phenylboronic acid (50 mg, 1 mmol), *N*-methylpyrrolidinone (1 mL) were added. The test tube with the resulting inhomogeneous solution was kept in a pre-heated (100 °C) oil-bath and the contents were stirred. The progress of the reaction was periodically checked by TLC for its completion. After the disappearance of the reactants the reaction mixture was cooled to rt and then diluted with dichloromethane (DCM, 20 mL) and water (20 mL). The aqueous layer was extracted with (DCM, 20 mL). The organic layers were mixed and washed with water (2 × 20 mL) and brine (1 × 10 mL) sequentially. The organic layer was dried over Na_2SO_4 . Removal of DCM by under reduced pressure resulted in a crude product which was purified by column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes) to yield pure 2-benzyl-3-(dimethylamino)isoindolin-1-one as yellow solid.

2.2a 2-Benzyl-3-(dimethylamino)isoindolin-1-one (**7a**):

Yellow solid (92 mg, 80% yield); M.p. 105 °C; IR (KBr, cm^{-1}) 3343, 3035, 2926, 2846, 2787, 1690, 1425, 1358, 1279, 1210, 1124, 1059, 976, 936, 796, 747, 700, 600, 523; ^1H NMR

(400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.86–7.81 (m, 1H), 7.44 (dd, $J = 5.7, 2.5 \text{ Hz}$, 2H), 7.40 (d, $J = 6.4 \text{ Hz}$, 1H), 7.27 (d, $J = 6.0 \text{ Hz}$, 2H), 7.26–7.22 (m, 2H), 7.19 (dd, $J = 5.8, 2.7 \text{ Hz}$, 1H), 5.21 (d, $J = 14.7 \text{ Hz}$, 1H), 4.98 (s, 1H), 4.21 (d, $J = 14.6 \text{ Hz}$, 1H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 142.2 (C), 137.5 (C), 133.0 (C), 131.3 (CH), 129.1 (CH), 128.7 (CH), 128.5 (CH), 127.5 (CH), 124.0 (CH), 123.5 (CH), 77.3 (CH), 43.6 (CH_2), 39.1 (2 × CH_3); HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}$ ($M + \text{H}$) 267.1497, found 267.1511.

2.2b 2-Benzyl-3-(phenylamino)isoindolin-1-one (**7b**):

White solid (103 mg, 78% yield); M.p. 163 °C; IR (KBr, cm^{-1}) 3349, 3033, 2924, 2859, 1683, 1600, 1499, 1261, 1077, 1024, 805, 746, 698; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.80 (dd, $J = 6.6, 1.4 \text{ Hz}$, 1H), 7.50–7.44 (m, 2H), 7.44–7.41 (m, 1H), 7.25 (d, $J = 1.7 \text{ Hz}$, 1H), 7.24 (d, $J = 0.7 \text{ Hz}$, 1H), 7.22 (d, $J = 3.7 \text{ Hz}$, 1H), 7.16–7.13 (m, 2H), 7.11 (d, $J = 1.1 \text{ Hz}$, 1H), 7.11–7.08 (m, 1H), 6.77 (t, $J = 7.4 \text{ Hz}$, 1H), 6.55 (dd, $J = 8.5, 0.9 \text{ Hz}$, 2H), 5.81 (s, 1H), 5.11 (d, $J = 15.1 \text{ Hz}$, 1H), 4.13 (d, $J = 15.1 \text{ Hz}$, 1H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 145.6 (C), 144.0 (C), 137.4 (C), 132.19 (C), 132.12 (CH), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 123.8 (CH), 123.2 (CH), 119.5 (CH), 114.4 (CH), 68.8 (CH), 43.2 (CH_2); HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}$ ($M + \text{H}$) 315.1497, found 315.1494.

2.2c 2-Benzyl-3-(cyclohexylamino)isoindolin-1-one (**7c**):

White solid (103 mg, 77% yield); M.p. 104 °C; IR (KBr, cm^{-1}) 3347, 2928, 2845, 1670, 1510, 1467, 1391, 1354, 1306, 1235, 1176, 1121, 1090, 1035, 964, 842, 746, 694, 624, 520; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.84–7.82 (m, 1H), 7.49–7.47 (m, 2H), 7.44 (dd, $J = 8.8, 2.1 \text{ Hz}$, 1H), 7.28 (s, 2H), 7.27 (s, 2H), 7.20 (dd, $J = 8.6, 4.5 \text{ Hz}$, 1H), 5.22 (d, $J = 15.0 \text{ Hz}$, 1H), 5.16 (s, 1H), 4.29 (d, $J = 15.0 \text{ Hz}$, 1H), 2.43 (dd, $J = 8.6, 4.7 \text{ Hz}$, 1H), 1.68–1.63 (m, 2H), 1.60–1.56 (m, 1H), 1.50 (d, $J = 4.4 \text{ Hz}$, 1H), 1.48–1.43 (m, 1H), 1.12 (d, $J = 8.0 \text{ Hz}$, 2H), 1.09–1.02 (m, 2H), 1.00–0.92

(m, 1H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.4 (C), 145.1 (C), 137.7 (C), 132.4 (C), 131.6 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 123.6 (CH), 123.3 (CH), 71.2 (CH), 51.9 (CH), 43.0 (CH_2), 35.3 (CH_2), 35.0 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 24.93 (CH_2); HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}$ (M + H) 321.1967, found 321.1968.

2.2d 2-Benzyl-3-(benzylamino)isoindolin-1-one (7d):

Yellow liquid (110 mg, 80% yield); IR (KBr, cm^{-1}); 3331, 3032, 2914, 1762, 1689, 1461, 1404, 1361, 1300, 1210, 1139, 1078, 966, 794, 741, 701, 519; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 7.3$ Hz, 1H), 7.50 (d, $J = 0.9$ Hz, 1H), 7.49 (s, 1H), 7.46–7.41 (m, 1H), 7.32 (dd, $J = 8.0$, 1.2 Hz, 2H), 7.28 (d, $J = 1.6$ Hz, 1H), 7.27–7.24 (m, 2H), 7.23 (s, 1H), 7.21 (d, $J = 0.7$ Hz, 1H), 7.18 (d, $J = 7.0$ Hz, 1H), 7.15–7.10 (m, 2H), 5.29 (s, 1H), 5.11 (d, $J = 15.0$ Hz, 1H), 4.35 (d, $J = 15.0$ Hz, 1H), 3.31 (d, $J = 13.1$ Hz, 1H), 3.21 (d, $J = 13.1$ Hz, 1H), 2.28 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7 (C), 143.4 (C), 139.7 (C), 137.5 (C), 132.8 (C), 131.9 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 123.4 (CH), 123.3 (CH), 72.4 (CH), 45.5 (CH_2), 43.2 (CH_2); HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}$ (M + H) 329.1654, found 329.1648.

2.2e 2-Benzyl-3-(phenethylamino)isoindolin-1-one (7e):

White solid (108 mg, 75% yield); M.p. 105 °C; IR (KBr, cm^{-1}) 3335, 3029, 2924, 2856, 1762, 1685, 1459, 1407, 1360, 1141, 1080, 1020, 745, 700, 557; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.71 (d, $J = 7.2$ Hz, 1H), 7.34 (dd, $J = 7.4$, 1.3 Hz, 1H), 7.31 (dd, $J = 7.3$, 1.3 Hz, 1H), 7.25 (d, $J = 7.1$ Hz, 1H), 7.15 (dd, $J = 11.9$, 4.5 Hz, 2H), 7.09 (d, $J = 6.7$ Hz, 4H), 6.97 (d, $J = 7.0$ Hz, 4H), 5.00 (s, 1H), 4.95 (d, $J = 14.9$ Hz, 1H), 3.76 (d, $J = 14.9$ Hz, 1H), 2.57–2.48 (m, 1H), 2.45–2.36 (m, 1H), 2.35–2.27 (m, 1H), 2.17 (dt, $J = 11.8$, 6.1 Hz, 1H), 2.02–1.86 (m, 1H); ^{13}C

NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 143.2 (C), 139.5 (C), 137.1 (C), 132.7 (C), 131.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.3 (CH), 126.3 (CH), 123.3 (CH), 123.0 (CH), 71.8 (CH), 42.6 (CH_2), 41.7 (CH_2), 36.0 (CH_2); HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}$ (M + H) 343.1810, found 343.1847.

2.2f 3-(Benzo[d]thiazol-2-ylamino)-2-benzylisoindolin-1-one (7f):

White solid (125 mg, 80% yield); M.p. 170 °C; IR (KBr, cm^{-1}) 3256, 3037, 2926, 1754, 1693, 1603, 1538, 1443, 1261, 1208, 1127, 1065, 804, 749, 700; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.77 (dd, $J = 6.7$, 1.0 Hz, 1H), 7.61–7.55 (m, 2H), 7.54–7.45 (m, 3H), 7.35–7.26 (m, 3H), 7.24–7.19 (m, 3H), 7.17–7.11 (m, 1H), 6.48 (s, 1H), 4.92 (d, $J = 14.9$ Hz, 1H), 4.28 (d, $J = 14.9$ Hz, 1H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.6 (C), 165.3 (C), 151.6 (C), 142.6 (C), 137.1 (C), 132.5 (C), 132.1 (C), 131.1 (CH), 130.0 (CH), 128.7 (CH), 128.7 (CH), 127.8 (CH), 126.3 (CH), 123.8 (CH), 123.6 (CH), 122.6 (CH), 121.0 (CH), 119.7 (CH), 68.4 (CH), 43.8 (CH_2); HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{OS}$ (M + H) 372.1171, found 372.1162.

2.2g 2-Benzyl-3-(piperidin-1-yl)isoindolin-1-one (7g):

Yellow solid (104 mg, 81% yield); M.p. 115 °C; IR (KBr, cm^{-1}) 3422, 2934, 2803, 1677, 1623, 1594, 1399, 1354, 1121, 1081, 986, 862, 750, 698, 631, 511; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.85–7.79 (m, 1H), 7.48–7.34 (m, 3H), 7.29 (t, $J = 5.5$ Hz, 3H), 7.25–7.10 (m, 2H), 5.17 (d, $J = 14.4$ Hz, 1H), 4.90 (s, 1H), 4.25 (d, $J = 13.6$ Hz, 1H), 2.54 (s, 2H), 2.37 (s, 2H), 1.52 (s, 4H), 1.44 (s, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.2 (C), 142.8 (C), 137.8 (C), 133.1 (C), 131.1 (CH), 128.7 (CH), 128.7 (CH), 127.4 (CH), 124.0 (CH), 123.4 (CH), 115.6 (CH), 77.9 (CH), 48.6 (CH_2), 43.2 (CH_2), 26.5 (CH_2), 24.6 (CH_2); HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}$ (M + H) 307.1810, found 307.1823.

2.2h 2-Benzyl-3-morpholinoisoindolin-1-one (**7h**):

White solid (94 mg, 73% yield); M.p. 129 °C; IR (KBr, cm^{-1}) 3217, 2924, 2703, 1670, 1438, 1306, 1211, 1115, 1057, 969, 919, 743, 698, 633, 600, 519; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.80 (dd, $J = 5.8, 2.3$ Hz, 1H), 7.46–7.39 (m, 2H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.25–7.22 (m, 3H), 7.22–7.13 (m, 2H), 5.14 (d, $J = 14.5$ Hz, 1H), 4.87 (s, 1H), 4.24 (d, $J = 14.5$ Hz, 1H), 3.56 (t, $J = 4.5$ Hz, 4H), 2.63–2.49 (m, 2H), 2.43–2.29 (m, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.2 (C), 141.7 (C), 137.3 (C), 132.8 (CH), 131.3 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 123.9 (CH), 123.4 (CH), 77.2 (CH), 67.2 (CH_2), 47.6 (CH_2), 43.5 (CH_2); HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2$ (M + H) 309.1603, found 309.1594.

2.2i 2-Benzyl-3-(S)-1-phenylethylamino)isoindolin-1-one (**7i**):

Yellow liquid (95 mg, 66% yield); IR (KBr, cm^{-1}) 3493, 3335, 3032, 2968, 2923, 1764, 1688, 1460, 1409, 1360, 1276, 1212, 1081, 975, 747, 700; ^1H NMR (400 MHz, CDCl_3) δ 7.82–7.75 (m, 2H), 7.51–7.47 (m, 1H), 7.46–7.40 (m, 2H), 7.34–7.30 (m, 2H), 7.28 (t, $J = 4.1$ Hz, 2H), 7.24 (s, 1H), 7.22 (d, $J = 1.8$ Hz, 2H), 7.21–7.20 (m, 2H), 7.19 (d, $J = 1.4$ Hz, 2H), 7.18 (s, 3H), 7.16 (d, $J = 2.8$ Hz, 2H), 7.14 (t, $J = 2.7$ Hz, 2H), 7.13–7.11 (m, 5H), 5.16 (d, $J = 14.9$ Hz, 1H), 5.09 (s, 1H), 5.05 (s, 1H), 4.91 (d, $J = 15.3$ Hz, 1H), 4.34 (d, $J = 15.0$ Hz, 1H), 3.98 (d, $J = 15.4$ Hz, 1H), 3.83 (q, $J = 6.6$ Hz, 1H), 3.70 (t, $J = 6.6$ Hz, 1H), 2.08 (s, 2H), 1.24 (d, $J = 6.6$ Hz, 3H), 1.18 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6 (C), 167.4 (C), 145.7 (C), 145.4 (C), 144.49 (C), 144.40 (C), 137.56 (C), 137.53 (C), 132.3 (C), 131.9 (C), 131.7 (CH), 131.2 (CH), 129.0 (CH), 128.7 (CH), 128.67 (CH), 128.62 (CH), 128.60 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.35 (CH), 127.30 (CH), 126.9 (CH), 126.7 (CH), 126.4 (CH), 123.4 (CH), 123.3 (CH), 123.28 (CH), 123.24 (CH), 71.5 (CH), 71.0 (CH), 53.8 (CH), 52.8 (CH), 42.9 (CH_2), 42.8 (CH_2),

25.0 (CH), 24.7 (CH); HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}$ (M + H) 343.1810, found 343.1817.

2.2j 2-Benzyl-3-(R)-1-phenylethylamino)isoindolin-1-one (**7j**):

Yellow liquid (90 mg, 62% yield); IR (KBr, cm^{-1}) 3452, 3335, 3028, 2970, 2924, 1758, 1690, 1459, 1407, 1359, 1280, 1211, 1078, 839, 746, 700; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.75 (d, $J = 7.5$ Hz, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 7.3$ Hz, 1H), 7.41–7.39 (m, 1H), 7.37 (d, $J = 6.7$ Hz, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 7.22 (s, 2H), 7.19 (d, $J = 5.4$ Hz, 3H), 7.17 (d, $J = 3.4$ Hz, 3H), 7.14 (d, $J = 4.7$ Hz, 2H), 7.11 (s, 3H), 7.10 (s, 2H), 7.08 (s, 2H), 7.06 (s, 2H), 7.05 (s, 2H), 5.10 (d, $J = 14.9$ Hz, 1H), 5.02 (s, 1H), 4.99 (s, 1H), 4.85 (d, $J = 15.3$ Hz, 1H), 4.27 (d, $J = 14.9$ Hz, 1H), 3.89 (d, $J = 15.3$ Hz, 1H), 3.78 (q, $J = 6.6$ Hz, 1H), 3.63 (q, $J = 6.6$ Hz, 1H), 1.89 (s, 2H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.5 (C), 167.3 (C), 145.9 (C), 145.5 (C), 144.6 (C), 144.5 (C), 137.78 (C), 137.71 (C), 132.5 (C), 132.2 (C), 131.7 (CH), 131.2 (CH), 130.0 (CH), 129.1 (CH), 128.82 (CH), 128.80 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.5 (CH), 126.0 (CH), 123.58 (CH), 123.56 (CH), 123.54 (CH), 123.3 (CH), 122.1 (CH), 71.6 (CH), 71.0 (CH), 54.0 (CH), 53.0 (CH), 43.2 (CH_2), 43.0 (CH_2), 25.3 (CH), 24.9 (CH); HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}$ (M + H) 343.1810, found 343.1801.

2.2k 3-(Dimethylamino)-2-(4-methoxybenzyl)isoindolin-1-one (**7k**):

White solid (102 mg, 92% yield); M.p. 115 °C; IR (KBr, cm^{-1}) 3480, 2939, 2836, 2791, 1763, 1691, 1614, 1512, 1464, 1411, 1361, 1248, 1180, 1100, 1038, 836, 746, 692, 595, 534; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.82 (dd, $J = 5.8, 2.7$ Hz, 1H), 7.47–7.40 (m, 2H), 7.38 (d, $J = 1.9$ Hz, 1H), 7.21 (d, $J = 8.6$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 5.15 (d, $J = 14.5$ Hz, 1H), 4.95 (s, 1H), 4.13 (d, $J = 14.5$ Hz, 1H),

Table 1. Crystallographic data and structure refinement for **7k**.

Empirical Formula	C ₁₈ H ₂₀ N ₂ O ₂
Formula Weight	296.37
Bond precision	C-C 0.0026 Å
Wavelength	0.71073
a, Å	11.8224(9)
b, Å	6.2257(5)
c, Å	21.7641(17)
α, °	90
β, °	90.456(7)
γ, °	90
Temperature	295 K
Volume	1601.9 (2)
Space group	P 21/c
Hall group	-P 2ybc
Mr	296.36
Dx, g cm ⁻³	1.229
Z	4
Mu (mm ⁻¹)	0.081
F000	632.0
F000'	632.26
h,k,lmax	16,8,29
Nref	4287
Tmin,Tmax	0.975, 0.992
Tmin'	0.941
Correction method:	
TminTmax	0.707, 0.922
Data completeness	0.774
Theta(max)	29.060
R(reflections)	0.0466 (2295)
wR2(reflections)	0.1332 (3320)
S	1.086
Npar	201

3.73 (s, 3H), 2.25 (s, 6H); ¹³C NMR (100 MHz, CDCl₃/CCl₄, 1/1) δ 167.1 (C), 158.9 (C), 142.2 (C), 132.9 (C), 131.1 (CH), 129.7 (CH), 129.5 (C), 128.9 (CH), 123.7 (CH), 123.3 (CH), 113.9 (CH), 77.1 (CH), 55.0 (CH), 42.7 (CH₂), 38.9 (CH); HRMS (ESI) calcd. for C₁₈H₂₁N₂O₂ (M + H) 297.1603, found 297.1600 (Table 1).

2.2l 2-(4-Methoxybenzyl)-3-(phenylamino)isoindolin-1-one (7l):

White solid (108 mg, 85% yield); M.p. 150 °C; IR (KBr, cm⁻¹): 3315, 2924, 2839, 1689, 1604, 1512, 1407, 1301, 1249, 1173, 1098, 1030, 972, 902, 824, 749, 694, 546; ¹H NMR (400 MHz, CDCl₃/CCl₄, 1/1) δ 7.81–7.76 (m, 1H),

7.50–7.44 (m, 2H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.14 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.84–6.78 (m, 1H), 6.78–6.75 (m, 2H), 6.61 (d, *J* = 1.0 Hz, 1H), 6.59 (d, *J* = 0.9 Hz, 1H), 5.80 (s, 1H), 5.05 (d, *J* = 14.9 Hz, 1H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 3H); ¹³C NMR (100 MHz, CDCl₃/CCl₄, 1/1) δ 167.1 (C), 159.1 (C), 145.7 (C), 144.1 (C), 132.1 (C), 132.0 (CH), 129.7 (C), 129.6 (CH), 129.49 (CH), 129.46 (CH), 123.7 (CH), 123.2 (CH), 119.5 (CH), 114.5 (CH), 114.1 (CH), 68.64 (CH), 55.24 (CH), 42.58 (CH₂); HRMS (ESI) calcd. for C₂₂H₂₁N₂O₂ (M + H) 345.1603, found 345.1610.

2.2m 3-(Cyclohexylamino)-2-(4-methoxybenzyl)isoindolin-1-one (7m):

White solid (113 mg, 86% yield); M.p. 113 °C; IR (KBr, cm⁻¹) 3337, 2928, 2847, 1679, 1510, 1467, 1391, 1352, 1306, 1236, 1176, 1121, 1090, 1032, 964, 842, 746, 694, 620, 520; ¹H NMR (400 MHz, CDCl₃/CCl₄, 1/1) δ 7.82 (d, *J* = 6.9 Hz, 1H), 7.46 (dt, *J* = 8.8, 3.5 Hz, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.18 (d, *J* = 14.8 Hz, 1H), 5.14 (s, 1H), 4.20 (d, *J* = 14.8 Hz, 1H), 3.76 (s, 3H), 2.48–2.40 (m, 1H), 1.75–1.71 (m, 1H), 1.70–1.63 (m, 2H), 1.62–1.57 (m, 1H), 1.54–1.45 (m, 2H), 1.15 (d, *J* = 7.4 Hz, 2H), 1.12–1.06 (m, 2H), 1.00 (dd, *J* = 11.1, 8.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃/CCl₄, 1/1) δ 167.3 (C), 159.1 (C), 145.2 (C), 132.6 (C), 131.6 (CH), 129.8 (C), 129.5 (CH), 129.0 (CH), 123.6 (CH), 123.3 (CH), 114.2 (CH), 71.1 (CH), 55.2 (CH), 51.8 (CH), 42.4 (CH₂), 35.4 (CH₂), 35.1 (CH₂), 25.9 (CH₂), 25.1 (CH₂), 24.9 (CH₂); HRMS (ESI) calcd. for C₂₂H₂₇N₂O₂ (M + H) 351.2073, found 351.2099.

2.2n 3-(Benzylamino)-2-(4-methoxybenzyl)isoindolin-1-one (7n):

Colorless liquid (119 mg, 89% yield); IR (KBr, cm⁻¹) 3333, 2915, 2841, 1690, 1611, 1510, 1458, 1401, 1356, 1245, 1176, 1086, 1033, 967, 903, 836, 746, 699, 587; ¹H NMR (400 MHz, CDCl₃/CCl₄, 1/1) δ 7.86 (d, *J* = 7.3 Hz, 1H), 7.51 (s, 2H), 7.47 (dd, *J* = 7.9, 5.1 Hz, 1H), 7.28 (s, 1H), 7.24 (s, 2H),

7.21 (d, $J = 7.0$ Hz, 2H), 7.15 (d, $J = 6.9$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 5.31 (s, 1H), 5.10 (d, $J = 14.8$ Hz, 1H), 4.27 (d, $J = 14.8$ Hz, 1H), 3.75 (s, 3H), 3.35 (d, $J = 13.0$ Hz, 1H), 3.24 (d, $J = 13.0$ Hz, 1H), 2.14 (s, 1H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.7 (C), 159.1 (C), 143.3 (C), 139.7 (C), 132.9 (C), 131.8 (CH), 129.6 (C), 129.5 (CH), 129.2 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 123.5 (CH), 123.2 (CH), 114.2 (CH), 72.2 (CH), 55.3 (CH), 45.6 (CH_2), 42.7 (CH_2); HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2$ (M + H) 359.1760, found 359.1747.

2.2o 2-(4-Methoxybenzyl)-3-(phenethylamino)isoindolin-1-one (7o):

Viscous solid (116 mg, 84% yield); IR (KBr, cm^{-1}) 3446, 2923, 2837, 1685, 1610, 1463, 1406, 1247, 1177, 1089, 1031, 808, 750, 696, 464; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.75 (dd, $J = 6.5$, 1.1 Hz, 1H), 7.43–7.35 (m, 2H), 7.32–7.28 (m, 1H), 7.23 (dd, $J = 6.1$, 1.3 Hz, 1H), 7.18 (d, $J = 6.5$ Hz, 2H), 7.08–7.03 (m, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.68 (d, $J = 8.7$ Hz, 2H), 5.02 (s, 1H), 4.95 (d, $J = 14.8$ Hz, 1H), 3.70 (d, $J = 16$ Hz, 1H), 3.68 (s, 3H), 2.65–2.56 (m, 1H), 2.53–2.43 (m, 1H), 2.38 (ddd, $J = 11.1$, 8.4, 5.8 Hz, 1H), 2.27–2.20 (m, 1H), 1.72 (s, 1H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.5 (C), 159.2 (C), 143.3 (C), 139.7 (C), 133.1 (C), 131.7 (CH), 129.6 (C), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 126.6 (CH), 123.6 (CH), 123.2 (CH), 114.2 (CH), 71.9 (CH), 55.3 (CH), 42.4 (CH_2), 41.8 (CH_2), 36.2 (CH_2); HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2$ (M + H) 373.1916, found 373.1904.

2.2p 2-(4-Methoxybenzyl)-3-(piperidin-1-yl)isoindolin-1-one (7p):

Yellow solid (102 mg, 82% yield); M.p. 120 °C; IR (KBr, cm^{-1}) 3451, 2933, 2845, 1767, 1693, 1612, 1511, 1459, 1408, 1246, 1172, 1095, 1038, 1003, 835, 744, 695, 520, 449; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.84 (dd, $J = 5.8$, 2.6 Hz, 1H), 7.45 (t, $J = 2.8$ Hz, 2H), 7.39 (d,

$J = 7.9$ Hz, 1H), 7.26 (d, $J = 1.5$ Hz, 1H), 7.24 (s, 1H), 6.82 (d, $J = 2.0$ Hz, 1H), 6.81 (d, $J = 2.1$ Hz, 1H), 5.15 (d, $J = 14.3$ Hz, 1H), 4.90 (s, 1H), 4.19 (d, $J = 14.3$ Hz, 1H), 3.77 (s, 3H), 2.62–2.51 (m, 2H), 2.39 (d, $J = 5.0$ Hz, 2H), 1.54 (d, $J = 5.0$ Hz, 4H), 1.46 (d, $J = 4.2$ Hz, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.2 (C), 159.0 (C), 142.9 (C), 133.2 (C), 131.1 (CH), 130.0 (CH), 129.9 (CH), 128.9 (CH), 123.9 (CH), 123.5 (CH), 114.0 (CH), 77.8 (CH), 55.3 (CH), 48.6 (CH_2), 42.8 (CH_2), 26.6 (CH_2), 25.0 (CH_2); HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$ (M + H) 337.1916, found 337.1921.

2.2q 2-(4-Methoxybenzyl)-3-morpholinoisoindolin-1-one (7q):

White solid (99 mg, 79% yield); M.p. 130 °C; IR (KBr, cm^{-1}) 3240, 2923, 2703, 1670, 1440, 1307, 1211, 1118, 1058, 960, 919, 791, 742, 698, 633, 600, 520; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.88–7.83 (m, 1H), 7.51–7.45 (m, 2H), 7.42 (dd, $J = 5.9$, 2.5 Hz, 1H), 7.26 (s, 1H), 7.24 (d, $J = 1.9$ Hz, 1H), 6.84–6.82 (m, 1H), 6.82–6.79 (m, 1H), 5.17 (d, $J = 14.4$ Hz, 1H), 4.92 (s, 1H), 4.23 (d, $J = 14.4$ Hz, 1H), 3.78 (s, 3H), 3.66 (t, $J = 4.6$ Hz, 4H), 2.71–2.60 (m, 2H), 2.49–2.41 (m, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 159.2 (C), 142.0 (C), 133.1 (C), 131.4 (C), 130.0 (CH), 129.6 (CH), 129.3 (CH), 124.1 (CH), 123.5 (CH), 114.1 (CH), 77.3 (CH), 67.4 (CH_2), 55.3 (CH), 47.8 (CH_2), 43.1 (CH_2); HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3$ (M + H) 339.1709, found 339.1709.

2.2r 2-(4-Methoxybenzyl)-3-(4-phenylpiperazin-1-yl)isoindolin-1-one (7r):

Viscous solid (120 mg, 78% yield); IR (KBr, cm^{-1}) 2933, 2833, 1701, 1603, 1507, 1452, 1394, 1344, 1302, 1244, 1152, 1095, 1018, 967, 836, 752, 527, 479; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.89–7.87 (m, 1H), 7.50–7.47 (m, 2H), 7.44 (dd, $J = 5.8$, 2.8 Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H),

7.27 (s, 1H), 7.22 (d, $J = 7.4$ Hz, 2H), 6.88 (d, $J = 7.8$ Hz, 2H), 6.84–6.81 (m, 3H), 5.21 (d, $J = 14.4$ Hz, 1H), 5.02 (s, 1H), 4.24 (d, $J = 14.4$ Hz, 1H), 3.78 (s, 3H), 3.15 (t, $J = 4.8$ Hz, 4H), 2.80 (dd, $J = 10.4, 5.1$ Hz, 2H), 2.64–2.60 (m, 2H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 159.2 (C), 151.5 (C), 142.2 (C), 133.9 (C), 133.1 (CH), 131.4 (CH), 130.0 (CH), 129.7 (C), 129.3 (CH), 124.1 (CH), 123.6 (CH), 120.3 (CH), 116.6 (CH), 114.2 (CH), 77.0 (CH), 55.3 (CH), 50.1 (CH_2), 47.4 (CH_2), 41.2 (CH_2); HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_2$ ($M + H$) 414.2182, found 414.2213.

2.2s 3-(Dimethylamino)-2-(2-nitrobenzyl)isoindolin-1-one (7s):

White solid (59 mg, 54% yield); M.p. 105 °C; IR (KBr, cm^{-1}) 2937, 2867, 2784, 1701, 1611, 1528, 1461, 1410, 1352, 1290, 1036, 979, 856, 791, 743, 568; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.99–7.95 (m, 1H), 7.87 (dd, $J = 6.3, 1.5$ Hz, 1H), 7.56–7.52 (m, 1H), 7.51 (dd, $J = 2.9, 1.8$ Hz, 2H), 7.50–7.46 (m, 1H), 7.46–7.42 (m, 1H), 7.40 (dd, $J = 8.3, 2.2$ Hz, 1H), 5.26 (d, $J = 16.4$ Hz, 1H), 5.10 (s, 1H), 4.95 (d, $J = 16.4$ Hz, 1H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.8 (C), 148.9 (C), 142.1 (C), 133.23 (C), 133.21 (CH), 132.3 (C), 131.5 (CH), 130.3 (CH), 129.1 (CH), 127.9 (CH), 124.6 (CH), 123.9 (CH), 123.3 (CH), 78.9 (CH), 40.2 (CH_2), 38.7 (CH); HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_3$ ($M + H$) 312.1348, found 312.1345.

2.2t 2-Allyl-3-(dimethylamino)isoindolin-1-one (7t):

Yellow solid (83 mg, 72% yield); M.p. 55 °C; IR (KBr, cm^{-1}) 3032, 2933, 2790, 1695, 1610, 1463, 1409, 1363, 1283, 1205, 1143, 1037, 977, 794, 743, 700, 609, 526; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 7.83 (d, $J = 6.8$ Hz, 1H), 7.46 (dd, $J = 10.3, 3.8$ Hz, 3H), 5.94–5.76 (m, 1H), 5.20 (t, $J = 11.2$ Hz, 3H), 4.57 (dd, $J = 15.3, 4.4$ Hz, 1H), 3.77 (dd, $J = 15.3, 7.4$ Hz, 1H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CCl}_4$, 1/1) δ 167.3 (C), 142.6 (C), 133.6 (C), 133.2 (CH), 131.3 (CH), 129.1 (CH), 123.9 (CH), 123.5 (CH), 117.7 (CH_2), 77.9 (CH), 42.7 (CH_2), 39.2 (CH); HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}$ ($M + H$) 217.1341, found 217.1329.

3. Results and Discussion

As a first attempt, we conducted the reaction of C(3)-hydroxy isoindolinone **5a** with phenylboronic acid under $\text{Cu}(\text{OTf})_2$ catalysis in DMF medium under the optimized conditions worked out for the conversion of **5a** to **6a** (Previous work, Scheme 1). The reaction, however, provided C-N coupled product **7a** exclusively in 56% yield (Present work, Scheme 1). Structure of **7a** was confirmed on the basis of spectroscopic (IR, ^1H NMR, ^{13}C NMR, DEPT-135, HSQC and HMBC 2D NMR) and analytical (ESIMS HRMS) data. Particularly, the ^1H NMR spectrum of **7a** displayed the characteristic singlet for C(3)H at δ 4.98 ppm, which was located between two doublets for diastereomeric benzylic hydrogens (δ 5.21 and 4.21 ppm). As anticipated from the structure, the signal for C(3)H of **7a** moved to up-field by about δ 0.54 ppm when compared to its location (δ 5.52 ppm) in the parent isoindolinone **5a**.¹⁶ A signal for C(3) located at δ 77.3 ppm (CH type in DEPT-135) and HMBC 2D NMR correlation between C(3)H and NMe supported the assigned structure.

Next, we have taken up optimization of reaction conditions to increase the yield of **7a**. We conducted a series of reactions by changing the Cu catalysts. We tried Cu(II) catalysts like $\text{Cu}(\text{OOCF}_3)_2$ (27%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (47%) and CuBr_2 (41%) followed by Cu(I) catalysts like CuI (Scheme 2 and Figure 2, 80%), CuBr (64%), CuCl (61%) and copper(I) thiophene-2-carboxylate (CuTc; 43%). These set of experiments clearly showed that CuI is the best catalyst for the transformation. We found that the reaction works in open air and does not proceed under a blanket of dry N_2 indicating oxygen is involved in the regeneration of the catalyst. Alternate oxidizing agents like *t*-butyl hydroperoxide (TBHP, 12%) or 30% hydrogen peroxide (8%) did not promote the reaction which showed their lower efficiency. By varying mol% of CuI from 0.1 mol% to 1 equivalent, we found that the transformation is best achieved with 10 mol% of CuI. The reaction did not take place in the presence of radical initiators like azobisisobutyronitrile (AIBN) or stable radical like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) which indicate that radical chain reactions may not be driving the reaction. Reaction worked less efficiently in presence of one equivalent of 4- $\text{ClC}_6\text{H}_4\text{B}(\text{OH})_2$ (50%) or 4- $\text{MeC}_6\text{H}_4\text{B}(\text{OH})_2$ (48%) compared to $\text{C}_6\text{H}_5\text{B}(\text{OH})_2$ (80%). Unlike the transformation of isoindolinol **5** to C-C coupled product **6** (Scheme 1, Equation 1) which required Na_2CO_3 , the reaction of **5** with DMF did not require any base.

To be a successful synthetic scheme for the development of medicinal drugs, products should be derived

Scheme 2. Copper and phenylboronic acid mediated deformylative amination of isoindolinols **5** with *N*-formyl amines **8** to form C(3)amino isoindolinins **7**.

from the reactants which have readily variable domains. In the reactants of the present scheme (Scheme 2), namely isoindolinone **5** and amines **8**, we envisage possibilities of changes in three domains, that is, substituents on (i) amines **8**, (ii) N(2) and (iii) aromatic ring of **5**. For the present work, we varied substituents in two domains, namely amines **8** and N(2) of isoindolinones **5** to generate a combinatorial library of twenty isoindolinones **7** (Scheme 2 and Figure 2). In the first instance, we employed formamides derived from primary (**8b–f**) and secondary amines (**8g–h**) and reacted each of them with **5a**, in *N*-methylpyrrolidone (NMP) medium in the presence of CuI (cat) and phenylboronic acid (stoichiometric). The reactions provided a very good yield of the isoindolinones **7b–f**. The products **7e** and **7f** are noteworthy as they respectively have medically privileged phenylethylamino and benzo[d]thiazol-2-ylamino moieties. Next, we employed formamides derived from secondary amines like *N*-formylpiperidine **8g** and *N*-formylmorpholine **8h**. The reactions provided corresponding isoindolinones **7g–h** in good yield. We reasoned that the reaction with optically active [*S*] or [*R*] 1-phenylethylamine could provide one of the two possible diastereomers in excess. Regrettably, however, the reactions conducted with [*S*] **8i** and [*R*] **8j** *N*-formyl-1-phenylethylamines provided diastereomeric mixtures **7i–j** in which the diastereomers were present in 1:1 ratio; as evidenced by ¹³C NMR spectra. Next, we changed benzyl group on N(2) to 4-methoxybenzyl (PMB) to evaluate the influence of electron donating OMe in the outcome of the deformylative amination.

Furthermore, PMB group is amenable for removal under oxidative conditions. The series of reactions of **5b** conducted with *N*-formylamides **8a–h** consistently provided a better yield of the products **7k–q** indicating that electron donating substituents on the benzyl ring promote substitution at C(3). Finally, in the series we reacted **5b** with N(4)phenyl N(1)formylpiperazine **8k** under optimized reaction conditions to get isoindolinone **7r** which has many structural similarities of the developmental drug, a dopamine D4 antagonist (S)-PD172938.¹⁷ Next, we sought to evaluate if an electron-withdrawing group (e.g., NO₂) in the N(2) benzyl substituent would reduce the reactivity of isoindolinone **5** with DMF. Accordingly, we reacted **5c** with DMF **8a** under optimized reaction conditions and realized **7s**, albeit, in lower yield. The N(2) 2-nitrobenzyl group on isoindolinone **5c** was selected because of photo-labile nature of 2-nitrobenzyl substitution. Thus, the set of reactions of DMF with **5a–c** showed that electron-donating groups on N(2) benzyl promote deformylative amino-substitution whereas electron-withdrawing groups impede. Finally, in the present series, we conducted the reaction of isoindolinone with *N*-allyl substitution **5d** with DMF and realized **7t** without any difficulty. Structures of the isoindolinones **7b–t** were confirmed by spectroscopic (IR, NMR) and analytical (ESIMS HRMS) data. In the case of **7k**, we recorded single crystal X-ray structure data and the out-put confirmed the assigned structure (see experimental section and supplementary information) (Figure 3).

Figure 2. Structures of N(2) and C(3) substituted isoindolinones **7a–t** with time taken for the reaction and yield.

Figure 3. ORTEP diagram for 3-(dimethylamino)-2-(4-methoxybenzyl)isoindolin-1-one **7k**.

Based on the above results we propose a speculative mechanism as given in Scheme 3. We believe that in the first step Cu(I) reacts with phenylboronic acid to form Cu(III) transmetallated product **9**. Highly reactive Cu(III) intermediate **9** then reacts with isoindolinone **5** to form stable boric acid and organo-copper(III) intermediate **10**. Reaction of **10** with formamides **8** leads to benzene and **11**. Loss of carbon-monoxide generates **12**. Final step in the sequence is the generation of C-N coupled product **7** and Cu(I) species. The intermediate **10** or even **9** can generate biphenyl as the side product. Indeed, we have isolated biphenyl as a minor side product (about 20%) in each of the reactions given in Scheme 2. In the presence of copper-chelating formamides, the reaction does not follow the path where C-C bond formation (Equation 1, Scheme 1) takes

Scheme 3. Proposed mechanism for the copper and phenylboronic acid mediated deformylative amination of isoindolinones.

place; instead it goes through C-N bond formation (Scheme 3).

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4. Conclusions

In conclusion, we have demonstrated an unprecedented Cu(I) catalyzed and phenylboronic acid-mediated transformation of isoindolinone-3-ols into C(3) substituted amino isoindolinones. The reaction goes through a deformylative C-N coupling. We have demonstrated that DMF is a synthetic equivalent of foul smelling, toxic and gaseous *N,N*-dimethylamine. The transformation has wide scope and can be applied for the synthesis of a combinatorial library of medicinally relevant molecules.

Supplementary Information (SI)

Characterization data, details of the NMR structural determination of all new compounds and copies of ^1H , ^{13}C NMR, DEPT-135 and HRMS spectra for all the compounds are given in the supplementary information. Supplementary information is available at www.ias.ac.in/chemsci.

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