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Copper catalyzed C(sp^3)-OH cleavage with concomitant C-C coupling: Synthesis of 3-substituted isoindolinones

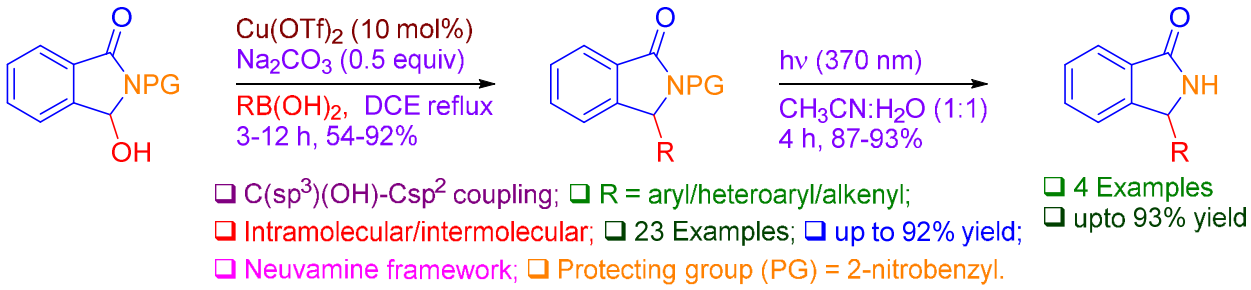
H. Surya Prakash Rao,* A. Veera Bhadra Rao

Department of Chemistry, Pondicherry University, Pondicherry – 605 014. India

E.mail: hspr.che@pondiuni.edu.in; Telephone: +914132654411; Fax: +914132656230

http://www.pondiuni.edu.in/

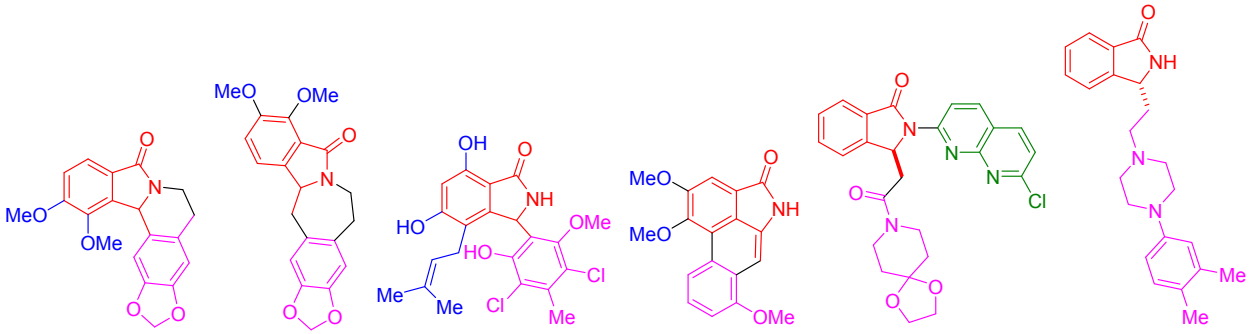
Graphical Abstract



Abstract: Copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) efficiently catalyzes C-C coupling of 3-hydoxyisoindolinones with a variety of aryl/heteroaryl/alkenyl boronic acids to furnish C(3) aryl/heteroaryl/alkenyl substituted isoindolinones. The coupling reactions work smoothly in 1,2-dicholoroethane (DCE) reflux, to effect both inter- and intra-molecular versions. This is the first report on C(sp^3)-OH cleavage with concomitant C-C coupling. Photolabile 2-nitrobenzyl protecting group is most appropriate to promote the coupling reaction and for the deprotection. Tetracyclic ring motif of the alkaloid neuvamine was prepared by applying newly developed copper catalyzed C-C coupling.

Introduction

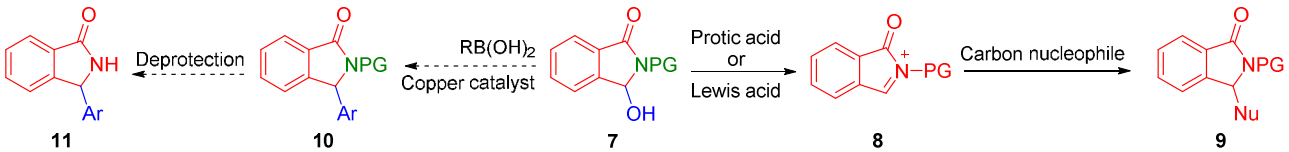
Unlike indole, its isomer, isoindole (2*H*-isoindole) is not a common structural element in natural products.[1] However, bioactive molecules built around isoindole structure are considered privileged due their multifarious medicinal properties.[2] Amongst isoindoles, the C(3) substituted isoindolinones occur as a part structure in a few alkaloids. Representative examples of such isoindole alkaloids are nuevamine **1**, the first known isoindoloisoquinoline alkaloid and lennoxamine **2**, an isoindolobenzazepine alkaloid, both of which have been isolated from *Berberis darwinii* (Figure 1).[3] Pestalachloride A **3**, an antifungal alkaloid isolated from an endophytic fungus *Pestalotiopsis adust*[4] and taliscanine **4**, an antiparkinson alkaloid isolated from the rhizomes of *Aristolochia taliscana*,[5] are other examples of alkaloids with C(3) substituted isoindole structure (Figure 1). Besides medicinally important alkaloids listed above, some central nervous system (CNS) active drug candidates like (*S*)-pazinaclone **5** and (*R*)-PD 172939 **6**[6] possess C(3) substituted isoindole structure (Figure 1). Apart from these two drug candidates, the C(3)-substituted isoindolinones exhibit varied biological activities that include antipsychotic,[7] antihypertensive,[8] antiulcer[9] and anxiolytic[10] properties. In view of importance of isoindolinones, there have been hectic synthetic efforts towards these coveted structures.[11]



1 (Nuevamine) **2** (Lennoxamine) **3** (Pestalachloride A) **4** (Taliscanine) **5** ((*S*)-Pazinaclone) **6** ((*R*)-PD 172939)

Figure 1. Examples of naturally occurring (**1** - **4**) and biologically active (**5** and **6**) C(3) substituted isoindolinones

The C(3) substituted isoindolinones **9** can be viewed as derivatives of phthalimide. Generally they have been synthesized from their hydroxy counterparts **7** by S_N1 substitution at hydroxy carbon with electron rich aromatic compounds (carbon nucleophiles; Scheme 1). Due to poor leaving ability of the hydroxy group, strong protic acids like triflic acid,[12] trifluoroacetic acid,[13] conc. H_2SO_4, [14] conc. HCl[15] or Lewis acids like $Bi(OTf)_3$,[16] $Sn(NTf_2)_4$,[17] Ir-Sn_3 bimetallic complexes, [18] gold catalysts[19] have been employed to generate iminium ion **8**, for quenching with electron-rich aromatic compounds or nucleophiles. Such reactions are generally conducted on **7** having a nitrogen protecting group (PG). Indeed, most of the researchers till date took recourse to robust benzyl as nitrogen PG, but benzyl group is difficult to remove without destroying the isoindolinone ring. Overall, existing methods are beleaguered with several drawbacks like requirement of (i) concentrated protic acids or Lewis acids, (ii) electron rich aromatic compounds to quench acyl iminium ion and (iii) protecting group that cannot be removed without affecting the isoindolinone ring. Thus, there is a need to discover conditions for facile replacement of the hydroxyl group in **7** with electron deficient aromatic, heteroaromatic, or alkenyl groups through C-C coupling without going through acyl iminium ion **8**. Furthermore, there is a need for a PG on nitrogen of the isoindolinone ring, which can be removed under non-hydrogenating, neutral and milder reaction conditions. Towards this goal, we resolved to develop suitable copper-catalyzed C-C coupling reactions and suitable PG for synthesis of C(3) substituted isoindolinones.



11 **10** **7** **8** **9**

Scheme 1. The existing method for substitution of the OH group in **7** to form **9** and the proposed method for replacement of the OH group in **7** with aryl groups through C-C coupling

In recent years, organic synthesis involving transition metal catalyzed C-C coupling, *via* substitution of halides or its congeners involving organometallic intermediates is responsible for paradigm shift in synthetic planning from classical acid-base to coupling pathways.[20] Although palladium catalysts have been in forefront of the emergence of C-C bond coupling reactions, high cost and extreme toxicity of the metals even in trace quantities, forced researchers to look for alternatives.[21] In this quest, copper catalysts have emerged as viable alternatives. Advantages of copper catalyst include (i) variable oxidation states of copper (+1, +2 and +3), (ii) solubility of many copper salts in organic solvents, (iii) low cost, bench-top availability and air- stability, (iv) environmental and biocompatibility.[22] Of late, copper catalyzed cross coupling reactions have become practicable choice for building C-O, C-S and C-N bonds (for example Chan-Lam-Evans Coupling).[23] The Cu catalyzed C-C coupling reactions, however, are yet to become well established for C-C coupling, possibly due to low yields and harsh reaction conditions (e.g. Ulmann coupling).[24] With the advent of organoboron reagents, copper catalyzed C-C coupling reactions are becoming feasible on a variety of substrates.[25] Organoboranes are stable, exhibit higher functional-group tolerance and commercially available or easy to prepare.[26] We have recently demonstrated facile copper catalyzed Csp^3-Csp^2 cross coupling reactions of organoboron reagents with 4*H*-chromenes having C(4) SMe group to furnish a variety of 4–aryl-4*H*-chromenes.[27] In continuation of this study, we present herein the copper catalyzed intermolecular/intramolecular coupling reaction of isoindolinol **7** with aryl/heteroaryl/alkenyl boronic acids for facile synthesis of C(3) substituted isoindolinones (Scheme 1). Although some

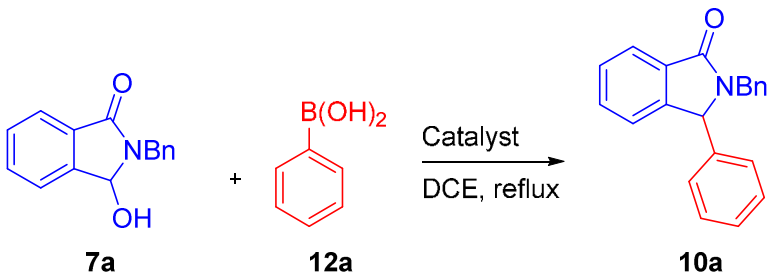
examples of Pd(II) or Ni(0) catalyzed cross coupling of organoboron reagents with activated benzylic hydroxyl are known,[28] ours is the first report on such cross coupling involving free benzylic hydroxyl group, arylboronic acid and a copper catalyst.

Results and discussion

Our initial efforts were directed towards unearthing a suitable copper catalyst and reaction conditions for coupling of *N*-benzyl protected 3-hydroxyisoindolin-1-one **7a** and phenylboronic acid **12a** to furnish 2-benzyl-3-phenylisoindolin-1-one **10a** (Table 1). Following our experience,[27] as a first attempt, we employed $Cu(OAc)_2.H_2O$ in 10 mol% in dichloromethane (DCM) reflux but the reaction provided **10a** in less than 5% yield. The yield rose to 45% when the reaction was conducted in higher boiling dichloroethane (DCE) reflux (entry 1). The yield gradually rose to a plateau of about 85% with increased catalytic loading (entries 2 and 3). Alternate Cu(II) catalysts like $Cu(CF_3COO)_2.H_2O$, $Cu(acac)_2$, $CuCl_2.2H_2O$, $CuBr_2$, $CuSO_4.5H_2O$ and CuO (entries 4-9) did not provide desired **10a** in better yield. However, in the genre of Cu(II) catalysts, 10 mol% of copper(II) trifluoromethane sulfonate ($Cu(OTf)_2$) provided the best yield (86%) after chromatographic purification of the product (entry 10). Lesser amounts of catalytic loading (5 mol%) was not sufficient to complete the transformation in reasonable time (entry 12) and higher amount of catalytic loading (20 mol%) did not improve the yield further. Moreover, we made certain that $Cu(OTf)_2$ catalysis was not due to minor triflic acid impurity, by conducting the reaction in the presence of sodium carbonate as the buffering agent (entry 11). In reality, the yield perceptibly rose to 92% in the presence of 0.5 equivalents of Na_2CO_3 indicating that minor amount of TfOH, which is inevitable in commercial $Cu(OTf)_2$ may actually impede the reaction. Furthermore, a run with 10 mol% of TfOH alone was conducted to convincingly rule out the possibility of TfOH being responsible for the reaction as a Brønsted acid. As

anticipated, the reaction did not proceed to provide **10a** (entry 13). The copper(I) salts like CuCl, CuBr, CuI, Cu_2O or stable copper(I) complexes like $CuBrSMe_2$, $Cu(PPh_3)_3Br$, copper(I)-thiophene-2-carboxylate (CuTC) or Cu(I)-3-methylsalicylate (CuMeSal) did not promote the coupling (entries 14-21) indicating that copper(I) species may not be involved in the reaction. Low yield obtained in the cases of CuCl, CuBr, CuTC, CuMeSal can be attributed to Cu(II) impurities or facile switch of Cu(I) to Cu(II). Notably, there was no reaction when palladium(II) catalyst ($Pd(OAc)_2$, entry 22) or palladium(0) catalyst ($Pd_2(dba)_3$, entry 23) was employed in presence or absence of a base. To evaluate if $Cu(OTf)_2$ catalysis is due to its Lewis acidic nature, we conducted the reaction in presence of catalytic amounts of similar borderline Lewis acids[29] such as $Sc(OTf)_3$, $Fe(OTf)_3$, $Zn(OTf)_2$ and $Yb(OTf)_3$ but the reactions did not work (entries 24-27).

Table 1. Optimization conditions of coupling reactions conducted in DCE reflux in presence of different catalysts



7a **12a** **10a**

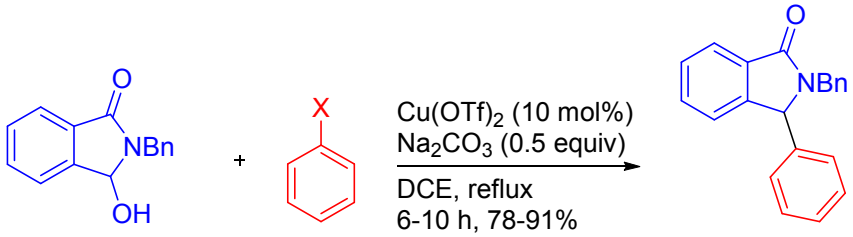
Entry	Catalyst	Time (h)	mol (%)	Yield (%)
1	$Cu(OAc)_2.H_2O$	16	10	45
2	$Cu(OAc)_2.H_2O$	16	20	62
3	$Cu(OAc)_2.H_2O$	14	30	85
4	$Cu(CF_3COO)_2.H_2O$	12	10	72

5	$Cu(acac)_2$	14	10	48
6	$CuCl_2.2H_2O$	14	10	16
7	$CuBr_2$	14	10	25
8	$CuSO_4.5H_2O$	12	10	nr
9	CuO	13	10	nr
10	$Cu(OTf)_2$	4	10	86
11	**$Cu(OTf)_2$, Na_2CO_3 (0.5 equiv)**	**4**	**10**	**92**
12	$Cu(OTf)_2$	14	5	64
13	TfOH	8	10	nr
14	CuCl	14	10	26
15	CuBr	16	10	32
16	CuI	12	10	nr
17	Cu_2O	12	10	nr
18	$Cu(I)BrSMe_2$	12	10	nr
19	$Cu(PPh_3)_3Br$	12	10	nr
20	CuTC	12	10	34
21	CuMeSal	12	10	38
22	$Pd(OAc)_2$, Na_2CO_3 (1 equiv)	6	5	nr
23	$Pd_2(dba)_3$ Na_2CO_3 (1 equiv)	8	5	nr
24	$Sc(OTf)_3$	12	10	nr
25	$Fe(OTf)_3$	12	10	nr
26	$Zn(OTf)_2$	12	10	nr
27	$Yb(OTf)_3$	12	10	nr

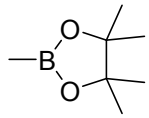
nr = no reaction

As an alternative to DCE we screened some common solvents and changed reaction parameters to decipher best conditions. Of the alternate solvents investigated such as toluene (42%), tetrachloroethane (TCE; 76%), acetonitrile (28%) and dioxane (48%), none of them worked as good as DCE (92%). The transformation worked best under an atmosphere of nitrogen. Under oxygen atmosphere the yield of **10a** was only 16% indicating that the reaction does not go through oxygen mediated catalyst regeneration. Surprisingly, metal complexing and organic solvent solubilising ligands like PPh_3 (34%) or phenanthroline (42%) actually decreased the yield of **10a**.

Next, we looked into the reactivity of two derivatives of phenylboronic acids, namely, phenylboronic acid pinacol ester **12b** and potassium phenyltrifluoroborate **12c** towards the coupling reaction, since both of the reagents have been employed previously in place of phenylboronic acid with concomitant advantages (Scheme 2).[30] We, however, found that in such runs there is not much difference in the yield of **10a** over the reaction when phenylboronic acid was employed. As a result, because of easy availability, we chose to go ahead with phenyl boronic acids for further studies.

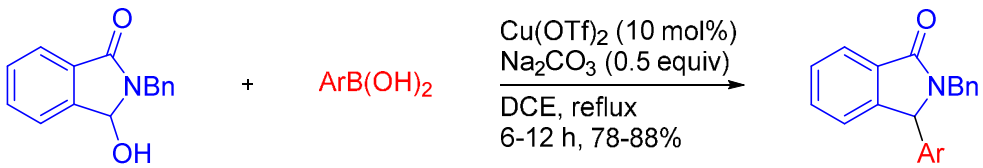


7a **12b-c** **10a**

12b: X =  (91%, 6 h); **12c**: X = BF_3K (78%, 10 h).

Scheme 2. Scope of Cu-catalyzed cross coupling of aryl boronic acid derivatives with 2-benzyl-3-hydroxyisoindolinone **7a**.

With the optimized conditions in hand, we evaluated generality of 3-arylisoindolinone synthesis and outcome of the reaction as a consequence of electron density of the aromatic ring (Scheme 3). We conducted coupling between 2-benzyl-3-hydroxyisoindolinone **7a** and three more aryl boronic acids, namely 4-trifluoromethylphenylboronic acid **12d** having highly electron-withdrawing C4-CF_3 group, 4-methoxyphenylboronic acid **12e** having highly electron-donating C4-OMe group and furan-2-boronic acid **12f** in which boronic acid is on an electron rich heteroaromatic ring. Each reaction provided corresponding 3-arylisoindolinones **10b-d** in good to excellent yield. Among the three boronic acids **12d-f**, the reaction with furan-2-boronic acid **12f** provided lowest yield (78%) and the reaction took longer time (12 h) reflecting sluggish nature of the reactant in coupling reactions.[31] The isoindolinone **10a** was characterized by spectral (IR, ^{1}H NMR, ^{13}C NMR and DEPT-135) and analytical data. A singlet at about δ 5.0 ppm assignable to C(3)H in the ^{1}H NMR spectrum of 2-benzyl-3-phenylisoindolin-1-ones **10**a is the diagnostic signal. Spectral and analytical data of **10b-d** compared well with those of **10a**.



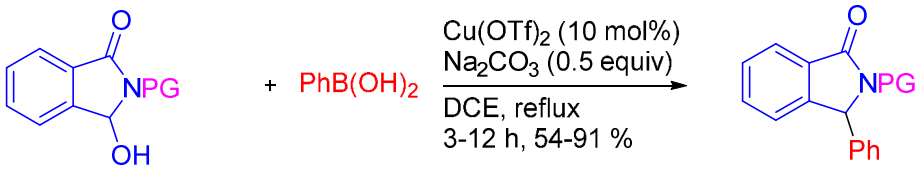
7a **12d-f** **10b-d**

12d: Ar = 4-$CF_3C_6H_4$;
12e: Ar = 4-$OMeC_6H_4$;
12f: Ar = 2-furyl.

10b: Ar = 4-$CF_3C_6H_4$ (88%, 6 h);
10c: Ar = 4-$OMeC_6H_4$ (83%, 10 h);
10d: Ar = 2-furyl (78%, 12 h).

Scheme 3. Scope of Cu-catalyzed cross coupling of different arylboronic acids with 2-benzyl-3-hydroxyisoindolinone **7a**.

Having stabilized reaction conditions for the copper catalyzed cross coupling of **7a** and aryl boronic acids **12**, it was our next endeavor to remove the benzyl PG in **10a** so that the isoindolinone motif gets exposed. As anticipated, selective reductive removal of the PG proved to be difficult as there are two benzylic positions in **10a**, both of which were getting reductively cleaved under hydrogenation conditions resulting in destruction of isoindolinone motif. As an alternative, we placed 4-methoxybenzyl group (PMB) on nitrogen **7b** with an intention of selectively removing under oxidative conditions (Scheme 4).[32] Regrettably, coupling reaction between **7b** and phenylboronic acid **12a** was not efficient. Surprisingly, when palladium sensitive allyl **7c** or propargyl **7d**[33] were placed on nitrogen there was no reaction to provide anticipated **10f-g** respectively. It is possible that **7c-d** and $Cu(OTf)_2$ combine to provide stable complexes. Gratifyingly, when we employed photolabile 2-nitrobenzyl (NB) PG[34] on isoindolinone motif (**7e**) the coupling worked best to provide product **10h** in excellent yield within 3 h.



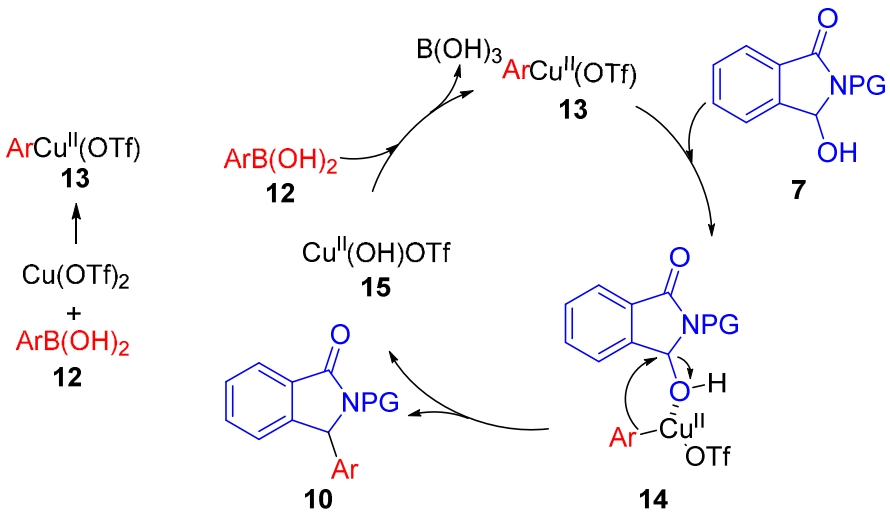
7b-e **12a** **10e-h**

7b: PG = 4-$MeOC_6H_4CH_2$;
7c: PG = $CH_2CH{=}CH_2$;
7d: PG = CH_2CCH;
7e: PG = 2-$NO_2C_6H_4$ (NB).

10e: PG = 4-$MeOC_6H_4CH_2$ (54%, 12 h);
10f: PG = $CH_2CH{=}CH_2$ (nr);
10g: PG = CH_2CCH (nr);
10h: PG = 2-$NO_2C_6H_4$ (91%, 3 h).

Scheme 4. Scope of Cu-catalyzed cross coupling in presence of different protecting groups (PGs).

To understand the reaction mechanism of Csp^3-Csp^2 coupling and to rule out the possibilities of nucleophilic substitution, we conducted two reactions on 3-hydroxyisoindolinone **7a** in THF; one with PhMgBr, a hard nucleophile and the other with 2(PhMgBr)CuI,[35] a soft nucleophile. Both the reactions did not provide the substitution product **10a** ruling out possibilities of a nucleophilic substitution. As noted in Table 1 (entries 10 and 11) TfOH impurity in $Cu(OTf)_2$ or TfOH (entry 13) impede the reaction by engineering towards generation of *N*-acyl iminium ion intermediates, instead of channeling the reactant **7** towards coupling pathways. Based on the evidences so far accumulated, possible mechanism was depicted and shown in Scheme 5. First and important step is the insertion of copper into fragile carbon-boron bond to provide reactive intermediate PhCu(OTf) **13**.[36] The intermediate **13** then enters into the catalytic cycle to react with 3-hydroxyisoindolinone **7** to provide the intermediate **14**. Crucial C-C coupling with concomitant C-O bond cleavage then takes place on **14** to provide the product **10** and copper(II) species **15**. The reaction of **15** with arylboronic acid **12** regenerates **13** and stable boric acid. Throughout the catalytic cycle copper remains in the oxidation state of +2. Interaction of copper(II) species with the C(3) hydroxy group in the intermediate **14** could reflect its Lewis acid characteristics. Driving force for coupling reaction is the formation of stable C-C bond in **10** and Cu-O bond in **15**, at the cost of Ar-Cu and C-OH bonds. Although metal salt solubilizing ligands like PPh_3 and phenanthroline helped dissolution of $Cu(OTf)_2$ in DCE, decreased yield of the desired product **10** (vide supra) indicates that ligand bound copper catalyst is sterially hindered to allow formation of **14**.

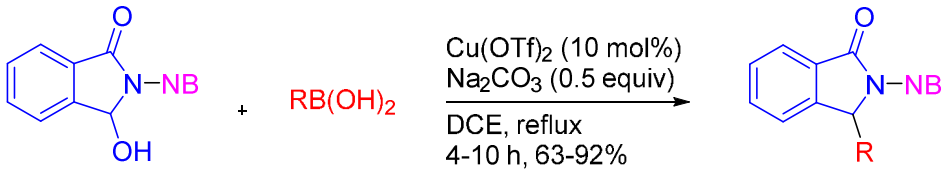


Scheme 5. Plausible mechanism for copper mediated formation of 3-substituted isoindolinones **10**.

To demonstrate scope of the coupling reaction, a range of arylboronic acids **12d-p** were reacted with 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **7e** under optimized conditions to realize fourteen 2-(2-nitrobenzyl)-3-arylisoindolin-1-ones **10i-u** (Table 2). The arylboronic acids **12d-p** were selected with a view of their structural diversity and potential binding to biological targets. High efficiency of cross-coupling was observed regardless of the presence of strongly electron-withdrawing (**12d**, **12g-h** to **10i**, **10l-m**), mildly electron withdrawing (**12i-k** to **10n-p**), strongly electron donating (**12e** to **10j**) or mildly electron donating (**12l-m** to **10q-r**) nature of the substitution in the aryl ring. Notably, the cross-coupling reaction worked well even with *ortho*-substituted boronic acids (**12n-p** to **10s-u**) indicating that the cross coupling is not highly sensitive to the steric bulk on the aryl ring. Boronic acid on an electron-rich heterocyclic ring, namely, furan-2-boronic acid **12f** participated in the coupling with **7e** to furnish isoindolinone **10k**. However, the coupling did not work with thiophene-2-boronic acid, pyridine-3-boronic acid and quinolone-3-boronic acid indicating that the reaction is sensitive to boronic acids that contain coordinating sites. The copper mediated cross coupling between 3-hydroxyisoindolin-1-

one **7e** and alkenyl boronic acids **12q-r** to furnish alkenyl substituted isoindolinones **10v-w** took place without any difficulty.

Table 2. Scope of Cu-catalyzed cross coupling of 2-nitrobenzyl protected 3-hydroxyisoindolinone **7e** with different aryl/heteroaryl/alkenyl boronic acids.

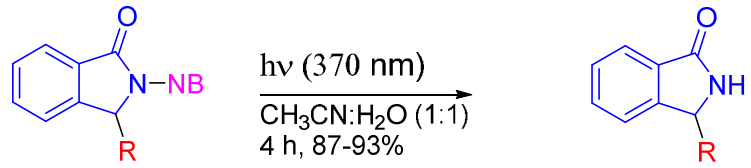


7e **12d-r** **10i-w**

Entry	R	Substrate	Product	Time (h)	Yield (%)
1	4-$CF_3C_6H_4$	**12d**	**10i**	4	92
2	4-$MeOC_6H_4$	**12e**	**10j**	10	77
3	2-Furyl	**12f**	**10k**	6	79
4	4-FC_6H_4	**12g**	**10l**	4	91
5	3,5-$F_2C_6H_3$	**12h**	**10m**	5	81
6	4-ClC_6H_4	**12i**	**10n**	6	81
7	3-ClC_6H_4	**12j**	**10o**	6	88
8	4-BrC_6H_4	**12k**	**10p**	8	85
9	4-MeC_6H_4	**12l**	**10q**	8	89
10	3-MeC_6H_4	**12m**	**10r**	10	86
11	2,3-$(OMe)_2C_6H_3$	**12n**	**10s**	6	79
12	2,5-$(OMe)_2C_6H_3$	**12o**	**10t**	6	81
13	2,6-$(OMe)_2C_6H_3$	**12p**	**10u**	10	74

14	*n*-Hex-1-enyl	**12q**	**10v**	4	63
15	Styreneyl	**12r**	**10w**	6	84

After demonstrating feasibility of synthesis of different C(3)substituted isoindolinones **10h-w** with NB as *N*-protecting group, our next task was to cleave photo-labile NB, so that free isoindole moiety gets exposed. We irradiated dilute (10^{-2} M) CH_3CN:H_2O (1:1) solutions of four selected isoindolinones namely, **10h, 10j, 10l and 10o,** with 4 × 3 μW LED lamps emitting at 370 nm (see supplementary information for an image of the in-house built reactor).[37] The photochemical cleavage reaction was clean and took place within 4 h to provide deprotected products **11a-d** in excellent yield (Scheme 6). The photo cleavage was facile on substrates having aryl ring with electron-donating (**10j**) or electron-withdrawing (**10l, 10o**) substituent's. We found that the LED lamps as a source of 370 nm light for NB deprotection is far superior compared to conventional high pressure mercury vapor lamps as LED lamps do not generate heat and filter to cut-off unwanted light is not required.[38]



10h, 10j, 10l, 10o

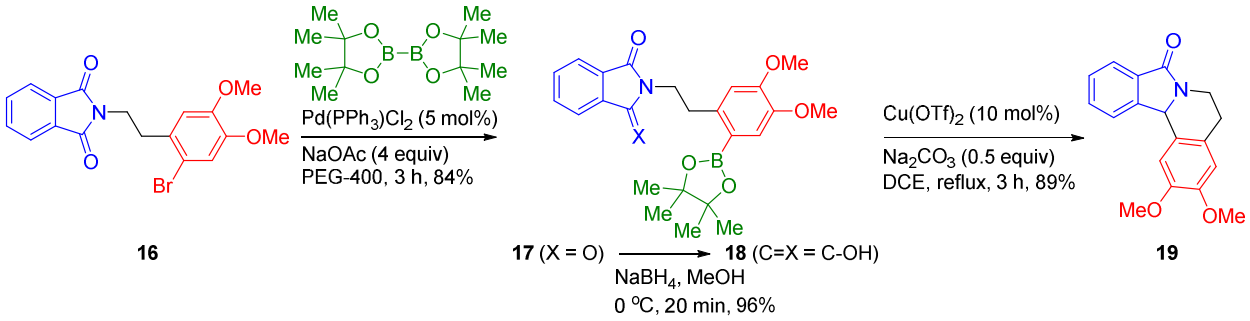
11a-d

10h: R = C_6H_5;
10j: R = 4-$OMeC_6H_4$;
10l: R = 4-FC_6H_4;
10o: R = 3-ClC_6H_4.
NB: 2-Nitrobenzyl

11a: R = C_6H_5 (93%);
11b: R = 4-$OMeC_6H_4$ (88%);
11c: R = 4-FC_6H_4 (87%);
11d: R = 3-ClC_6H_4 (88%).

Scheme 6. The cleavage of NB in the presence of UV light (370 nm).

Finally, we attempted synthesis of tetracyclic lactam system **19** of neuvamine **1** from arylboronic acid **17** to demonstrate intramolecular version of our newly developed $Cu(OTf)_2$ catalyzed C-C coupling reaction (Scheme 7). Starting phthalimide derivative[39] **16** was prepared from corresponding amine[40] and phthalic anhydride in toluene reflux. The aryl bromide **16** was converted into the boronic acid derivative **17** by palladium-catalyzed reaction with bis(pinacolato)diboron.[41] Controlled reduction of one of the carbonyl groups in **17** with sodium borohydride provided isoindolin-3-ol **18** which on treatment with $Cu(OTf)_2$ under our optimized reaction conditions provided neuvamine framework **19** in excellent yield.



Scheme 7. Synthesis of neuvamine like molecule **19** via Cu-catalyzed intramoleculer coupling reaction.

Conclusion

In summary, we described facile $Cu(OTf)_2$ catalyzed Csp3-Csp2 coupling involving 3-hydoxyisoindolinones and a variety of aryl/heteroaryl/alkenyl boronic acids to efficiently furnish C(3) aryl/heteroaryl/alkenyl substituted isoindolinones. This is the first report on copper catalyzed $C(sp^3)$-OH cleavage with concomitant C-C coupling. In this way, we demonstrated facile substitution of OH group in 3-hydoxyisoindolinones with electron rich, electron deficient aryl and alkenyl groups with equal facility. We have shown that photolabile 2-nitrobenzyl is the best *N*-protecting group and DCE reflux is the best medium for the transformation. We

demonstrated both inter- and intra-molecular versions through synthesis of twenty four C(3) substituted isoindolinones and tetracyclic ring motif of the alkaloid neuvamine.

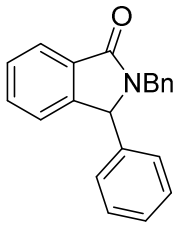
Experimental section

General experimental methods

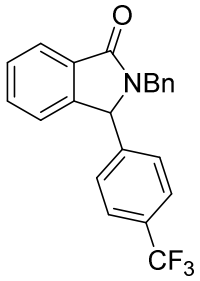
Progression of all the reactions was monitored by TLC using hexanes (60-80 °C boiling mixture) / ethyl acetate mixture as eluent. Column chromatography was performed on silica gel (100-200 mesh) using increasing percentage of ethyl acetate in hexanes. ^{1}H-NMR spectra (400 MHz), ^{13}C NMR (100MHz) and DEPT–135 spectra were recorded for ($CDCl_3$, $CDCl_3$ + CCl_4 (1:1) or DMSO-d_6) solutions on 400 MHz spectrometer with TMS as internal standard. Coupling constants *J* are given in Hz. IR spectra were recorded as KBr pellets on a FT-IR spectrometer. High resolution mass spectra were recorded on quadrupole-time-of-flight (QTOF) mass spectrometer using electrospray ionization mode. The X- ray diffraction measurements were carried out at 298 K on equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). Organic solvents were dried by standard methods. The catalyst $Pd_2(dba)_3$ and the alkenyl boronic acids were prepared according to literature procedures.[41] Light mediated deprotection of NB group to generate isoindolinones was carried out using home-built reactor having four UV-LED (3μW) lamps with emission maximum at 370 nm (see supplementary information for the photograph). Maximum intensity of the LED bulbs as determined using a intensity and wave-length characterization possible UV-visible spectrometer having resolution of 0.23 nm in the range 200-1100 (see Figure 3 in the supplementary information).

General procedure for synthesis of 2-benzyl-3-arylisoindolin-1-one 10a-e.

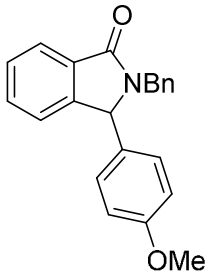
Synthesis of 2-benzyl-3-phenylisoindolinone 10a: An oven-dried 25 mL two-neck round-bottom flask connected to Shlenk line through a condenser was charged with phenylboronic acid **12a** (60 mg, 0.5 mmol), $Cu(OTf)_2$ (18 mg, 0.05 mmol) and Na_2CO_3 (27 mg, 0.25 mmol). The flask was sealed with a rubber septum, evacuated under vacuum and purged nitrogen gas three times. Anhydrous dichloroethane (DCE, 2 mL) was added through a syringe and the contents were stirred for 10 min. 2-Benzyl-3-hydroxyisoindolin-1-one **7a** (120 mg, 0.5 mmol) in DCE (4 mL) was next added at rt (30 °C) over 5 min. The resulting reaction mixture was refluxed for 4 h while periodically checking by TLC for completion of reaction. The reaction mixture was then extracted with dichloromethane (DCM, 2 × 20 mL). The organic layer was washed with water (2 × 20 mL), brine (1 × 10 mL) followed by removal of DCM under reduced pressure. The crude product was subjected to column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes) to yield 2-benzyl-3-phenyl-isoindolinone **10a**.



2-Benzyl-3-phenylisoindolin-1-one 10a: Colourless solid (143 mg, 92% yield) Mp: 135 °C (reported 136 °C); IR (KBr, cm^{-1}) 3030, 2920, 1695, 1613, 1494, 1464, 1399, 1291, 1075, 1026, 978, 761, 738, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 6.6 Hz, 11H), 7.50-7.39 (m, 2H), 7.39-7.02 (m, 1H), 5.40 (d, J = 14.8 Hz, 1H), 5.24 (s, 1H), 3.73 (d, J = 14.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (C), 146.4 (C), 137.1 (C), 136.8 (C), 131.9 (CH), 131.4 (C), 129.2 (CH), 128.8 (2 X CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 123.8 (CH), 123.2 (CH), 63.6 (CH), 43.9 (CH_2); HRMS (ESI) calcd for $C_{21}H_{17}NO$ (M + H) 300.1382, found 300.1382.

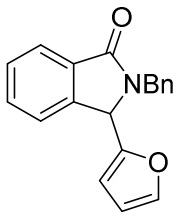


2-Benzyl-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one10b: Colourless solid (167 mg, 88% yield) Mp: 115 °C; IR (KBr, cm^{-1}) 3064, 3033, 2926, 2861, 1702, 1618, 1494, 1467, 1398, 1327, 1119, 1068, 891, 848, 795, 737, 700, 609; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.95 (d, *J* = 7.1 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.52-7.37 (m, 2H), 7.28-7.06 (m, 8H), 5.40 (d, *J* = 14.9 Hz, 1H), 5.27 (s, 1H), 3.72 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) 168.4 (C), 145.6 (C), 141.3 (C), 136.8 (C), 132.2 (CH), 131.4 (C), 131.2 (q, *J* = 32 Hz, C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 126.3 (q, *J* = 4 Hz, CH), 125.3 (C), 124.2 (CH), 123.1 (CH), 63.0 (CH), 44.1 (CH_2); HRMS (ESI) calcd for $C_{22}H_{16}F_3NONa$ (M + Na) 390.1082, found 390.1085.

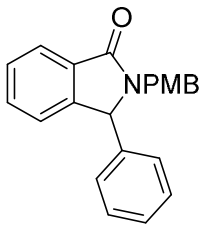


2-Benzyl-3-(4-methoxyphenyl)isoindolin-1-one10c: Colourless solid (136 mg, 83% yield) Mp: 124 °C; (reported 124 °C)IR (KBr, cm^{-1}) 3062, 2927, 2872, 1694, 1611, 1527, 1468, 1400, 1344, 1305, 1142, 1094, 858, 790, 738, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.77 (m, 1H), 7.35-7.24 (m, 2H), 7.16-7.11 (m, 3H), 7.06 (d, *J* = 6.6 Hz, 2H), 6.98-6.92 (m, 1H), 6.88-6.69 (m, 4H), 5.25 (d, *J* = 14.8 Hz, 1H), 5.08 (s, 1H), 3.66 (d, *J* = 3.8 Hz, 3H), 3.61 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C), 159.8(C), 146.6 (C), 137.1 (C), 131.8 (CH), 131.3 (C),

129.0 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 123.5 (CH), 123.1 (CH), 114.4 (CH), 63.0 (CH), 55.2 (CH_3), 43.6 (CH_2); HRMS (ESI) calcd for $C_{22}H_{20}NO_2$ (M + H) 330.1488, found 330.1486.

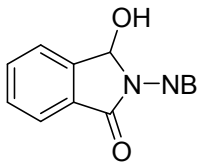


2-Benzyl-3-(furan-2-yl)isoindolin-1-one10d: Colourless solid (106 mg, 78% yield) Mp: 108 °C; IR (KBr, cm^{-1}) 1693, 1592, 1567, 1529, 1305, 1195, 1072, 743, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.86 (m, 1H), 7.54-7.45 (m, 2H), 7.30-7.19 (m, 6H), 6.29-6.36 (m, 2H), 5.40 (s, 1H), 5.32 (d, *J* = 14.9 Hz, 1H), 3.94 (d, *J* = 14.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (C), 149.1 (C), 143.5 (CH), 143.0 (C), 137.0 (C), 131.8 (CH), 128.79 (CH), 128.72 (CH), 128.3 (CH), 127.5 (CH), 123.8 (CH), 123.0 (CH), 110.5 (CH), 110.0 (CH), 57.0 (CH), 44.2 (CH_2); HRMS (ESI) calcd for $C_{19}H_{15}NO_2$ (M + H) 290.1175, found 290.1776.



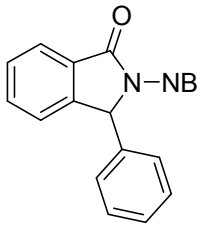
2-(4-Methoxybenzyl)-3-phenylisoindolin-1-one 10e: Colourless solid (88 mg, 54% yield) Mp:132 °C; IR (KBr, cm^{-1}) 3033, 2929, 2835, 1691, 1612, 1512, 1464, 1399, 1246, 1176, 1033, 817, 737, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 6.0, 2.2 Hz, 1H), 7.51-7.30 (m, 5H), 7.17-7.00 (m, 5H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.34 (d, *J* = 14.7 Hz, 1H), 5.22 (s, 1H), 3.77 (s, 3H), 3.68 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (C), 159.1 (C), 146.4, 136.9 (C), 131.8 (CH), 131.5, 129.8 (CH), 129.27 (C), 129.21 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH),

123.7 (CH), 123.2 (CH), 114.1 (CH), 63.5 (CH), 55.3 (CH_3), 43.2 (CH_2); HRMS (ESI) calcd for $C_{22}H_{20}NO_2$ (M + H) 330.1488, found 330.1487.

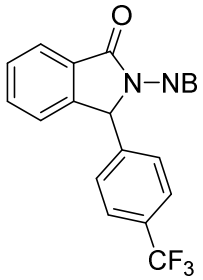


Synthesis of 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one 7e: To a stirred solution of 2-(2-nitrobenzyl)isoindoline-1,3-dione[43] (500 mg, 1.77 mmol) in a mixture of tetrahedrofuran and methanol (5:0.5 mL) sodium borohydride (114 mg, 2.65 mmol) was added during 10 min at -10 ^{o}C.. Resulting mixture was stirred at -10 °C for 2 h. Subsequently, excess sodium borohydride was quenched with aqueous 3 *N* HCl (0.5 mL). Evaporation of solvents on rotary evaporator resulted in colourless solid which washed with water to provide 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one **7e** in 88% yield (443 mg). Mp: 98 °C; IR (KBr, cm^{-1}) 3340, 2865, 1681, 1609, 1577, 1525, 1469, 1431, 1344, 1305, 1207, 1060, 961, 925, 858, 788, 748, 728; ^{1}H NMR (400 MHz, DMSO-d_6 + CCl_4; 1:1) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.73-7.52 (m, 6H), 7.40 (d, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.06 (d, *J* = 17.3 Hz, 1H), 4.88 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + CCl_4; 1:1) δ 166.6 (C), 147.8 (C), 144.8 (C), 133.5 (CH), 132.9 (C), 132.0 (CH), 131.0 (C), 129.2 (CH), 128.8 (CH), 128.0 (CH), 124.5 (CH), 123.6 (CH), 122.4 (CH), 81.1 (CH), 39.8 (CH_2); HRMS (ESI) calcd for $C_{15}H_{12}N_2O_4Na$ (M + Na) 307.0695, found 307.0698.

Synthesis of 2-(2-nitrobenzyl)-3-phenylisoindolin-1-ones 10h-w: The general procedure described for synthesis of 2-benzyl-3-arylisoindolin-1-one **10a-e** was followed for synthesis of 2-(2-nitrobenzyl)-3-phenylisoindolin-1-one **10h-w**.

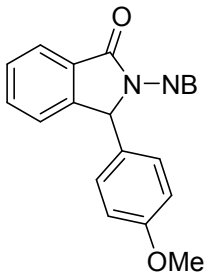


2-(2-Nitrobenzyl)-3-phenylisoindolin-1-one10h: Colourless solid (109 mg, 91% yield), Mp: 116 °C; IR (KBr, cm^{-1}) 3062, 2927, 2872, 1694, 1611, 1527, 1468, 1400, 1344, 1305, 1142, 1094, 858, 790, 738, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 6.9 Hz, 2H), 7.54-7.48 (m, 3H), 7.40-7.36(m, 2H), 7.30-7.28 (m, 3H), 7.19-7.17 (m, 1H), 7.01 (d, *J* = 4.8 Hz, 2H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.40 (s, 1H), 4.50 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C), 148.4 (C), 146.4 (C), 136.3 (C), 133.6 (C), 132.7 (CH), 132.4 (CH), 130.8 (C), 130.0 (CH), 129.3 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 125.5 (CH), 123.9 (CH), 123.4 (CH), 65.0 (CH), 41.2 (CH_2); HRMS (ESI) calcd for $C_{21}H_{16}N_2O_3Na$ (M + Na) 367.1059, found 367.1058.

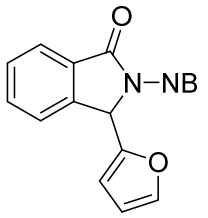


2-(2-Nitrobenzyl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one 10i: Colourless solid (134 mg, 92% yield), Mp: 141 °C; IR (KBr, cm^{-1}) 3070, 2935, 2860, 1699, 1617, 1528, 1395, 1326, 1166, 1125, 1067, 854, 790, 734; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.94-7.89 (m, 2H), 7.56-7.48 (m, 6H), 7.40-7.38 (m, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.15-7.11 (m, 1H), 5.49 (s, 1H), 5.33 (d, *J* = 16.0 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.1 (C), 148.7 (C), 145.8 (C), 140.9 (C), 133.67 (CH), 132.64 (CH), 132.5 (C), 131.5 (C), 131.0 (CH), 130.8 (C), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.3 (m, CH), 124.9 (CH), 124.3

(CH), 123.3 (CH), 64.6 (CH), 41.3 (CH_2); HRMS (ESI) calcd for $C_{22}H_{15}F_3N_2O_3Na$ (M + Na) 435.0932, found 435.0932.

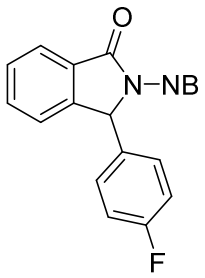


3-(4-Methoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10j: Light yellow solid (93 mg, 77% yield), Mp: 115 °C; IR (KBr, cm^{-1}) 3071, 2935, 2840, 1695, 1609, 1525, 1466, 1400, 1344, 1304, 1248, 1176, 1107, 1027, 787, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H), 7.54-7.48 (m, 3H), 7.40-7.36 (m, 2H), 7.18-7.16 (m, 1H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 5.39-5.35 (m, 2H), 4.48 (d, *J* = 16.8 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 160.0 (C), 148.4 (C), 146.7 (C), 133.7 (CH), 132.9 (C), 132.3 (CH), 130.9 (C), 129.9 (CH), 129.0 (CH), 128.6 (CH), 128.2 (CH), 127.9 (C), 125.0 (CH), 123.9 (CH), 123.4 (CH), 114.6 (CH), 64.5 (CH), 55.4 (CH_3), 41.1 (CH_2); HRMS (ESI) calcd for $C_{22}H_{18}N_2O_4$ Na (M + Na) 397.1164, found 397.1168.

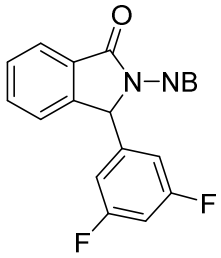


3-(Furan-2-yl)-2-(2-nitrobenzyl)isoindolin-1-one 10k: Colourless solid (93 mg, 79% yield) Mp: 140 °C; IR (KBr, cm^{-1}) 1697, 1596, 1577, 1470, 1395, 1343, 1305, 1190, 1080, 858, 786, 750, 702; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.97-7.93 (m, 2H), 7.61-7.43 (m, 3H), 7.38-7.32 (m, 3H), 7.22 (s, 1H), 6.24 (s, 2H), 5.55 (s, 1H), 5.25 (d, *J* = 16.9 Hz, 1H), 4.83 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 168.4 (C), 148.6 (C), 148.2 (C), 143.5

(CH), 142.8 (C), 133.3 (CH), 132.7 (C), 132.1 (CH), 131.4 (C), 129.5 (CH), 128.9 (CH), 127.9 (CH), 124.7 (CH), 123.9 (CH), 123.2 (CH), 110.5 (CH), 110.2 (CH), 58.3 (CH), 41.5 (CH_2); HRMS (ESI) calcd for $C_{19}H_{14}N_2O_4Na$ (M + Na) 357.0851, found 357.0851.

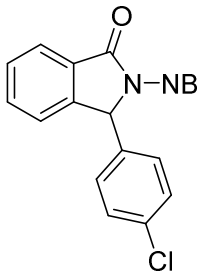


3-(4-Fluorophenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10l: Light yellow solid (116 mg, 91% yield), Mp: 157 °C; IR (KBr, cm^{-1}) 3071, 2930, 1695, 1607, 1527, 1469, 1397, 1342, 1226, 1158, 1097, 856, 788, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.53-7.48 (m, 3H), 7.40-7.35 (m, 2H), 7.16-7.13 (m, 1H), 7.01-6.93 (m, 4H), 5.40 (s, 1H), 5.35 (d, J = 16.4 Hz, 1H), 4.50 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (C), 162.8 (d, J = 241 Hz, C), 148.3 (C), 146.2 (C), 133.6 (CH), 132.5 (C), 132.4 (CH), 132.1 (d, J = 3 Hz, C), 130.7 (C), 130.1 (CH), 129.4 (d, J = 9 Hz, CH), 128.7 (CH), 128.4 (CH), 124.9 (CH), 123.9 (CH), 123.3 (CH), 116.2 (d, J = 22 Hz, CH), 64.2 (CH), 41.0 (CH_2); HRMS (ESI) calcd for $C_{21}H_{15}FN_2O_3Na$ (M + Na) 385.0964, found 385.0964.

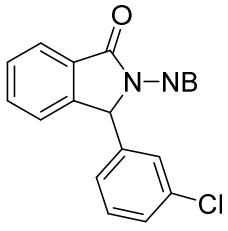


3-(3,5-Difluorophenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10m: Light yellow solid (108 mg, 81% yield), Mp: 167 °C; IR (KBr, cm^{-1}) 1713, 1650, 1574, 1530, 1464, 1409, 1333, 1116, 855, 790, 729; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.8 Hz, 2H), 7.56-7.51 (m, 3H), 7.45-7.39

(m, 2H), 7.18 (d, J = 4.8 Hz, 1H), 6.74 (t, J = 8.5 Hz, 1H), 6.61 (d, J = 5.6 Hz, 2H), 5.41-5.37 (m, 2H), 4.57 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 16.3.5 (d, J = 249 Hz, C) 163.4 (d, J = 250 Hz, C), 148.5 (C), 145.3 (C), 140.8 (C), 133.8 (CH), 132.7 (CH), 132.2 (C), 130.54 (C), 130.48 (CH), 129.1 (CH), 128.7 (CH), 125.1 (CH), 124.3 (CH), 123.2 (CH), 110.4 (t, J = 18 Hz, CH), 104.5 (t, J = 25 Hz, CH) 64.2 (CH), 41.3 (CH_2); HRMS (ESI) calcd for $C_{21}H_{14}F_2N_2O_3Na$ (M + Na) 403.0870, found 403.0871.

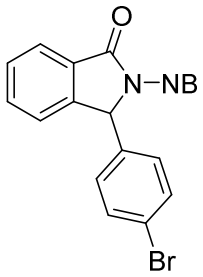


3-(4-Chlorophenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10n: Colourless solid (109 mg, 81% yield), Mp: 151 °C; IR (KBr, cm^{-1}) 1698, 1612, 1526, 1490, 1468, 1395, 1345, 1307, 1088, 789, 748, 719; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.92 (d, J = 7.2 Hz, 2H), 7.52-7.39 (m, 5H), 7.27-7.24 (m, 2H), 7.14-7.12 (m, 1H), 6.98 (d, J = 8.4 Hz, 2H), 5.39 (s, 1H), 5.33 (d, J = 16.4 Hz, 1H), 4.51 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.0 (C), 148.5 (C), 146.0 (C), 135.0 (C), 134.9 (C), 133.5 (C), 132.5 (CH), 132.4 (CH), 130.8 (C), 130.6 (CH), 129.5 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 124.9 (CH), 124.1 (CH), 123.3 (CH), 64.3 (CH), 41.1 (CH_2); HRMS (ESI) calcd for $C_{21}H_{15}ClN_2O_3Na$ (M + Na) 401.0669, found 401.0673.

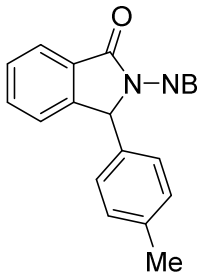


3-(3-Chlorophenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10o: Colourless solid (118 mg, 88% yield), Mp: 165 °C; IR (KBr, cm^{-1}) 3063, 2918, 2859, 1697, 1526, 1470, 1396, 1344, 1305,

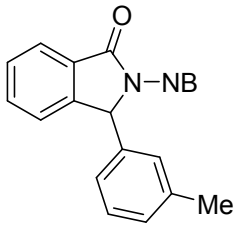
1191, 787, 703; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.94-7.91 (m, 2H), 7.53-7.49 (m, 3H), 7.44-7.38 (m, 2H), 7.25-7.15 (m, 3H), 6.98-6.96 (m, 2H), 5.39 (s, 1H), 5.35 (d, *J* = 16.8 Hz, 1H),(d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.1 (C), 148.5 (C), 145.8 (C), 138.6 (C), 135.2 (C), 133.6 (CH), 132.5 (CH), 132.4 (C), 130.7 (C), 130.5 (CH), 130.4 (CH), 129.2 (CH), 128.9 (CH), 128.4 (CH), 127.6 (CH), 125.8 (CH), 124.9 (CH), 124.1 (CH), 123.3 (CH), 64.5 (CH), 41.2 (CH_2); HRMS (ESI) calcd for $C_{21}H_{15}ClN_2O_3Na$ (M + Na) 401.0669, found 401.0664.



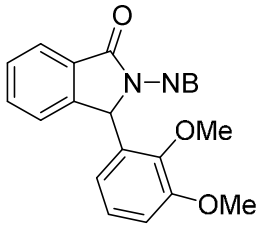
3-(4-Bromophenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10p: Colourless solid (126 mg, 85% yield), Mp: 114 °C; IR (KBr, cm^{-1}) 1697, 1613, 1526, 1469, 1396, 1344, 1306, 1072, 1011, 788, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.54-7.49 (m, 3H), 7.42-7.37 (m, 4H), 7.15-7.13 (m, 1H), 6.91 (d, *J* = 7.0 Hz, 2H), 5.38-5.34 (m, 2H), 4.51 (d, *J* = 16.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (C), 148.5 (C), 145.9 (C), 135.5 (C), 133.7 (CH), 132.5 (CH), 132.4 (2C, C,CH), 130.7 (C), 130.3 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 125.0 (CH), 124.1 (CH), 123.3 (CH), 123.0 (C), 64.4 (CH), 41.2 (CH_2); HRMS (ESI) calcd for $C_{21}H_{15}BrN_2O_3Na$ (M + Na) 445.0164, found 445.0162.



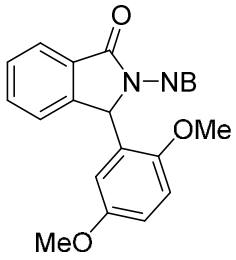
2-(2-Nitrobenzyl)-3-(*p*-tolyl)isoindolin-1-one 10q: Colourless solid (113 mg, 89% yield), Mp: 135 °C; IR (KBr, cm^{-1}) 1696, 1609, 1527, 1468, 1400, 1345, 1305, 1200, 1158, 1095, 858, 787, 734, 706; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.92 (d, *J* = 6.9 Hz, 2H), 7.59-7.30 (m, 5H), 7.20-7.03 (m, 3H), 6.89 (d, *J* = 7.7 Hz, 2H), 5.38-5.33 (m, 2H), 4.45 (d, *J* = 16.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.0 (C), 148.5 (C), 146.6 (C), 138.7 (C), 133.5 (CH), 133.2 (C), 132.9 (C), 132.2 (CH), 131.0 (C), 130.1 (CH), 129.9 (CH), 128.5 (CH), 128.1 (CH), 127.6 (CH), 124.9 (CH), 123.9 (CH), 123.4 (CH), 64.7 (CH), 41.0 (CH_2), 21.3 (CH_3); HRMS (ESI) calcd for $C_{22}H_{18}N_2O_3Na$ (M + Na) 381.1215, found 381.1215.



2-(2-Nitrobenzyl)-3-(*m*-tolyl)isoindolin-1-one 10r: Colourless solid (109 mg, 86% yield), Mp: 129 °C; IR (KBr, cm^{-1}), 3049, 2922, 1694, 1609, 1578, 1526, 1469, 1397, 1342, 1304, 1200, 1095, 857, 787, 770, 730, 706; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.93-7.91 (m, 2H), 7.53-7.47 (m, 3H), 7.40-7.35 (m, 2H), 7.18-7.13 (m, 2H), 7.08-7.06 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 5.38 (d, *J* = 16.8 Hz, 1H), 5.35 (s, 1H), 5.49 (d, *J* = 16.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.2 (C), 148.4 (C), 146.4 (C), 139.0 (C), 136.1 (C), 133.5 (CH), 132.8 (C), 132.3 (CH), 130.9 (C), 130.0 (CH), 129.7 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 124.9 (CH), 124.8 (CH), 123.9 (CH), 123.4 (CH), 65.0 (CH), 41.1 (CH_2), 21.4 (CH_3); HRMS (ESI) calcd for $C_{22}H_{18}N_2O_3Na$ (M + Na) 381.1215, found 381.1214.

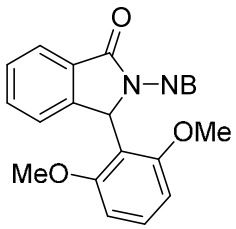


3-(2,3-Dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10s: Light yellow colour solid (113 mg, 79% yield), Mp: 122; °C. IR (KBr, cm^{-1}) 3066, 2937, 2837, 1697, 1605, 1522, 1465, 1399, 1263, 1141, 1027, 858, 788, 730; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.84-7.80 (m, 2H), 7.42-7.36 (m, 4H), 7.30-7.26 (m, 1H), 7.10-7.08 (m, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.27 (s, 1H), 5.25-5.21 (m, 2H), 4.47 (d, *J* = 17.6 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 168.7 (C), 149.6 (C), 149.5 (C), 148.5 (C), 146.4 (C), 133.2 (CH), 132.7 (C), 132.1 (CH), 130.8 (C), 130.2 (CH), 128.4 (CH), 128.3 (C), 128.0 (CH), 124.6 (CH), 123.7 (CH), 123.2 (CH), 120.5 (CH), 111.4 (CH), 109.9 (CH), 64.8 (CH), 55.75 (CH_3), 55.71 (CH_3), 40.8 (CH_2); HRMS (ESI) calcd for $C_{23}H_{20}N_2O_5Na$ (M + Na) 427.1270, found 427.1269.

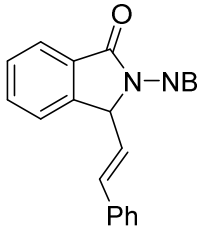


3-(2,5-Dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10t: Colourless solid (116 mg, 81% yield), Mp: 130 °C; IR (KBr, cm^{-1}) 3002, 2936, 2836, 1694, 1526, 1468, 1340, 1280, 1218, 1047, 856, 789, 748; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.93 (d, *J* = 6.8 Hz, 2H), 7.50-7.46 (m, 3H), 7.36-7.28 (m, 3H), 6.78-6.72 (m, 2H), 6.17 (s, 1H), 6.03 (s, 1H), 5.38 (d, *J* = 16.8 Hz, 1H), 5.57 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 169.3 (C), 153.9 (C), 151.9 (C), 148.4 (C), 146.4 (C), 133.4 (CH), 133.3 (C), 132.1

(CH), 131.4 (C), 129.7 (CH), 128.3 (CH), 127.9 (CH), 125.3 (C), 124.7 (CH), 123.9 (CH), 123.4 (CH), 114.4 (CH), 112.8 (CH), 111.9 (CH), 57.4 (CH), 55.8 (CH_3), 55.5 (CH_3), 41.2 (CH_2); HRMS (ESI) calcd for $C_{23}H_{20}N_2O_5Na$ (M + Na) 427.1270, found 427.1273.

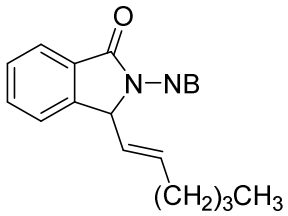


3-(2,6-Dimethoxyphenyl)-2-(2-nitrobenzyl)isoindolin-1-one 10u: Colourless solid (93 mg, 74% yield), Mp: 154 °C; IR (KBr, cm^{-1}) 2933, 2831, 1693, 1528, 1462, 1392, 1284, 1217, 1032, 853, 783, 747; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.51-7.47 (m, 3H), 7.41-7.22 (m, 3H), 6.53 (s, 1H), 6.47-6.26 (m, 2H), 5.98 (s, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 4.54 (d, *J* = 17.1 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C), 161.1 (C), 158.9 (C), 148.3 (C), 146.8 (C), 133.5 (C), 133.5 (CH), 132.1 (CH), 131.5 (C), 129.3 (CH), 128.2 (CH), 127.8 (CH), 124.7 (CH), 123.7 (CH), 123.4 (CH), 116.4 (C), 105.3 (CH), 98.4 (2 × CH), 57.1 (CH), 55.4 (CH_3), 55.3 (CH_3), 41.2 (CH_2); HRMS (ESI) calcd for $C_{23}H_{20}N_2O_5Na$ (M + Na) 427.1270, found 427.1275.

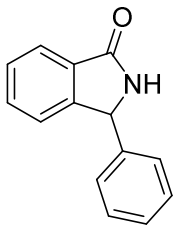


(*E*)-2-(2-Nitrobenzyl)-3-styrylisoindolin-1-one 10v: Viscous solid (82 mg, 63% yield). IR (KBr, cm^{-1}) 3058, 3028, 2960, 2927, 2869, 1696, 1609, 1527, 1469, 1402, 1345, 1305, 1149, 1084, 970, 857, 751, 698; ^1H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.95 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.90 (dd, *J* = 6.7, 1.0 Hz, 2H), 7.59-7.49 (m, 6H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.37 (t, *J* = 7.5

Hz, 4H), 7.28-7.26 (m, 2H), 7.26-7.23 (m, 3H), 6.75 (d, J = 15.7 Hz, 1H), 5.71 (dd, J = 15.7, 9.2 Hz, 1H), 5.31 (d, J = 16.8 Hz, 1H), 4.99 (d, J = 9.2 Hz, 1H), 4.91 (d, J = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 168.7 (C), 148.7 (C), 144.8 (C), 136.6 (C), 135.6 (CH), 133.6 (CH), 133.3 (C), 132.2 (CH), 131.5 (C), 130.2 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 126.9 (CH), 125.1 (CH), 125.0 (CH), 124.2 (CH), 123.5 (CH), 64.2 (CH), 41.3 (CH_2); HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Na$ (M + Na) 393.1215, found 393.1215.

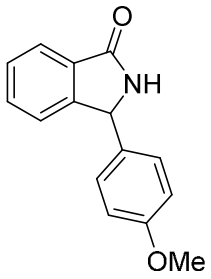


(*E*)-3-(Hex-1-en-1-yl)-2-(2-nitrobenzyl)isoindolin-1-one 10w: Viscous solid (103 mg 84%). IR (KBr, cm^{-1}) 2958, 2928, 2864, 1767, 1696, 1613, 1467, 1401, 1343, 1304, 1223, 1148, 1099, 1049, 974, 857, 789, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.59-7.47 (m, 3H), 7.43-7.32 (m, 3H), 5.95-5.82 (m, 1H), 5.28 (d, J = 17.0 Hz, 1H), 5.05-4.99 (m, 1H), 4.90 (d, J = 17.0 Hz, 1H), 4.79 (d, J = 9.2 Hz, 1H), 2.06-2.00 (m, 2H), 1.30-1.25 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (C), 148.5 (C), 145.2 (C), 139.2 (CH), 133.6 (CH), 133.3 (C), 132.1 (CH), 131.3 (C), 129.7 (CH), 128.6 (CH), 128.1 (CH), 125.6 (CH), 124.9 (CH), 123.9 (CH), 123.3 (CH), 64.2 (CH), 41.0, 31.9 (CH_2), 30.9 (CH_2), 22.1 (CH_2), 13.9 (CH_3); HRMS (ESI) calcd for $C_{21}H_{22}N_2O_3Na$ (M + Na) 373.1528, found 373.1528.

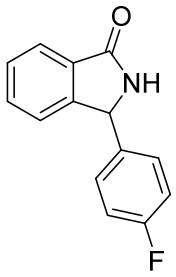


General procedure for deprotection of 2-nitrobenzyl group for synthesis of C(3) substituted isoindolin-1-ones 11a-d.

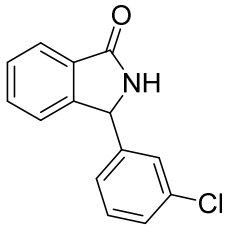
Synthsis of 3-phenylisoindolin-1-one 11a: The stirred solution of 2-(2-nitrobenzyl)-3-phenylisoindolin-1-one **10h** (50 mg, mmol) in CH_3CN:H_2O (1:1; 10 mL) in a Pyrex test tube of 20 mL capacity was exposed to light irradiation with emission maximum at 370 nm emitted by UV-LEDs (4 × 3μW) lamps (see supplementary information for an image of the in-house built reactor). After completion of deprotection (4 h) solvents was removed under reduced pressure, and the resulting white faintly colored solid was subjected to column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes) to separate 3-phenylisoindolin-1-one **11a** from nitroso benzaldehyde. The isoindolin-1-one **11a** was obtained as colourless solid (28 mg, 93% yield). Mp: 219 °C (repoted 219 °C). Spectral data (IR, ^{1}H NMR and ^{13}C NMR and DEPT) of **11a** matched with those reported by Slavov and coworkers.[44]



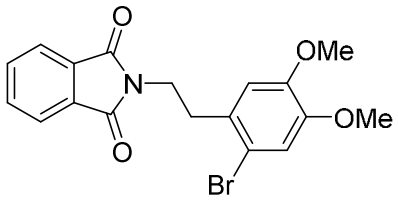
3-(4-Methoxyphenyl)isoindolin-1-one 11b: Colourless solid (28 mg, 88% yield), Mp: 155 °C; IR (KBr, cm^{-1}) 3200, 3074, 2955, 1732, 1697, 1589, 1514, 1346, 1246, 732; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.92-7.86 (m, 1H), 7.53-7.43 (m, 2H), 7.21 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.63 (s, 1H), 5.58 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 171.0 (C), 159.9 (C), 148.3 (C), 132.4 (CH), 130.9 (C), 130.3 (C), 128.4 (CH), 128.2 (CH), 123.9 (CH), 123.4 (CH), 114.5 (CH), 60.4 (CH_3), 55.4 (CH); HRMS (ESI) calcd for $C_{14}H_{11}FNO$ (M + H) 240.1019, found 240.1019.



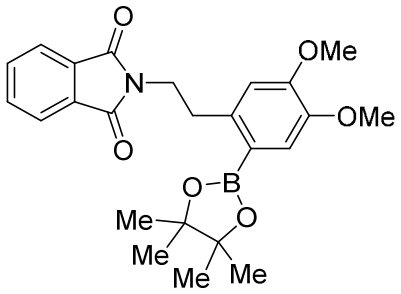
3-(4-Fluorophenyl)isoindolin-1-one 11c: Colourless solid (27 mg, 87% yield), Mp: 179 °C; IR (KBr, cm^{-1}) 3194, 3068, 2837, 1685, 1610, 1512, 1465, 1358, 1247, 1178, 1033, 731; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) 7.83 (m, 1H), 7.63 (bs, 1H), 7.50-7.49 (m, 2H), 7.25-7.18 (m, 3H), 7.01 (t, *J* = 8.8 Hz, 2H), 5.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) 171.3 (C), 162.9 (d, *J* = 247 Hz, C), 148.0 (C), 134.4 (d, *J* = 3 Hz, C), 132.4 (CH), 131.1 (C), 128.7 (CH), 128.6 (d, *J* = 6 Hz, CH), 124.1 (CH), 123.3 (CH), 116.2 (d, *J* = 21 Hz, CH), 60.4 (CH); HRMS (ESI) calcd for $C_{14}H_{11}FNO$ (M + H) 228.0819, found 228.0813.



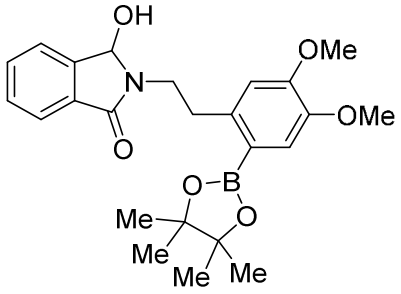
3-(3-Chlorophenyl)isoindolin-1-one 11d: Colourless solid (28 mg, 88% yield), Mp: 157 °C; IR (KBr, cm^{-1}) 3191, 3071, 2924, 1690, 1552, 1469, 1352, 1191, 1139, 1088, 784, 749, 705; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) 7.51-7.48 (m, 1H), 7.29-7.27 (m, 2H), 7.25-7.15 (m, 6H), 6.97 (bs, 1H), 5.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) 171.6 (C), 147.5 (C), 140.7 (C), 135.2 (C), 132.6 (CH), 131.0 (C), 130.5 (CH), 128.9 (CH), 128.8 (CH), 127.1 (CH), 125.0 (CH), 124.2 (CH), 123.3 (CH), 60.5 (CH); HRMS (ESI) calcd for $C_{14}H_{11}ClNO$ (M + H) 244.0529, found 244.0524.



Preparation of 2-(2-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione 16: A suspension of phthalic anhydride (600 mg, 4 mmol), 2-(2-bromo-4,5-dimethoxyphenyl)ethan-1-amine (1.036 g, 4 mmol) in 15 mL toluene in an oven dried 25 mL round bottom flask fitted with Dean-Stark apparatus was heated to reflux until clear solution of the product was obtained (6 h). The condensation worked better in toluene relux with Dean-Stark apparatus compared to the condensation with phthaloyl dichloride in acetonitrile in presence of Hunig's base as described by DiMagno and coworkers.[39] After completion the reaction mixture was concentrated under reduced pressure to give a residue which was subjected to column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes) to furnish **16** as a colourless solid (1.31 g, 82% yield). Mp = 143 ^{o}C. IR (KBr, cm^{-1}) 1713, 1583, 1467, 1386, 1121, 1084, 883, 768, 712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 5.5, 3.0 Hz, 2H), 7.69 (dd, J = 5.4, 3.1 Hz, 2H), 6.98 (s, 1H), 6.66 (s, 1H), 3.94 (t, J = 8.0 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 3.06 (t, J = 8 0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C), 148.48 (C), 148.44 (C), 134.0 (CH), 132.1(C), 129.4 (C), 123.3 (CH), 115.69 (CH), 114.5 (C), 113.3 (CH), 56.1 (CH_3), 56.0 (CH_3), 37.7 (CH_2), 34.4 (CH_2).[43]

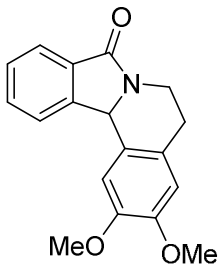


2-(4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)isoindoline-1,3-dione 17: A viscous solution of 2-(2-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione **16** (300 mg 0.75 mmol), bis(pinacolato)diboron (222 mg, 0.90 mmol), NaOAc (242 mg, 3 mmol) and $Pd(PPh_3)_2Cl_2$ (26 mg, 0.08 mmol) in PEG 400 (3 mL) was stirred in an oil bath at 80 °C for an 3 h time under an atmosphere of nitrogen. After completion (TLC, 20% EtOAc in hexanes, Rf = 0.5), cooled reaction mixture was extracted with methyl *tert*-butyl ether (MTBE, 2 ×10 mL). The ether layer was washed with brine and dried over anhydrous sodium sulfate. Crude product obtained after removal of MTBE was purified by column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes) resulted **17** as colourless solid (269 mg, 84% yield) Mp: 124 °C; IR (KBr, cm^{-1}) 3005, 2941, 1712, 1500, 1394, 1361, 1255, 1213, 1163, 1097, 999, 869, 800, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 5.4, 3.0 Hz, 2H), 7.67 (dd, J = 5.4, 3.0 Hz, 2H), 7.28 (s, 1H), 6.65 (s, 1H), 4.00-3.92 (m, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.30-3.22 (m, 2H), 1.37 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C), 150.9 (C), 146.8 (C), 139.1 (C), 133.8 (CH), 132.2 (C), 123.1 (CH), 118.3 (CH), 113.1 (CH), 83.6 (C), 55.9 (CH_3), 55.7 (CH_3), 40.1 (CH_2), 33.9 (CH_2), 24.9 (CH_3); HRMS (ESI) calcd for $C_{24}H_{28}NO_6BNa$ (M + Na) 460.1908, found 460.1906.



2-(4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-3-hydroxyisoindolin-1-one 18: To a stirred solution of 2-(4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)isoindoline-1,3-dione **17** (200 mg, 0.46 mmol) in

Mixture of tetrahydrofuran (3 mL) and methanol (0.3 mL) kept in an ice-water bath sodium borohydride (34 mg, 0.92 mmol) was added in three portions during 10 min. The reaction mixture was then stirred at 0-5 °C for 20 min by which time reduction was complete (TLC). Excess sodium borohydride was quenched with water (1 mL). Removal of THF and MeOH under reduced pressure in a rotary evaporator resulted in a suspension of white solid in residual water. Filtration of solid followed by washing with water (5 mL) provided **18** as a colourless solid in 96% yield (192 mg). Mp 138 °C; IR (KBr, cm^{-1}) 3171, 2943, 1660, 1589, 1516, 1440, 1263, 1143, 1024, 819, 744, 698; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.57-7.43 (m, 3H), 7.36-7.26 (m, 1H), 7.25 (d, *J* = 1.1 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 5.56 (d, *J* = 2.3 Hz, 1H), 3.87 (d, *J* = 1.0 Hz, 3H), 3.73 (d, *J* = 1.8 Hz, 3H), 3.65-3.56 (m, 1H), 3.53-3.43 (m, 1H), 3.21-3.11 (m, 1H), 3.06-2.96 (m, 1H), 1.33 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4; 1:1) δ 167.3 (C), 151.4 (C), 146.9 (C), 144.0 (C), 139.9 (C), 132.0 (C), 131.9 (CH), 129.5 (CH), 123.3 (CH), 123.2 (CH), 118.8 (CH), 113.1 (CH), 83.7 (C), 82.1 (CH), 55.9 (CH_3), 55.7 (CH_3), 42.0 (CH_2), 34.2 (CH_2), 24.9 (CH_3), 24.8 (CH_3); HRMS (ESI) calcd for $C_{24}H_{30}NO_6BNa$ (M + Na) 462.2064, found 462.2064.



2,3-Dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6*H*)-one 19: By following the general procdure described for the copper mediated coupling reactions described earlier, the intramolecular coupling in 2-(4,5-dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)-3-hydroxyisoindolin-1-one **18** (100 mg, 0.23 mmol) in presence of $Cu(OTf)_2$ (8

mg, 0.023 mmol) and Na_2CO_3 (12 mg, 0.11 mmol) in DCE (2 mL) furnished 2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6*H*)-one **19** as a colourless solid in 89% yield (59 mg). Mp 60 °C; IR (KBr, cm^{-1}) 2912, 1678, 1518, 1417, 1253, 1228, 1205, 1093, 724; ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4; 1:1) δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.79 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 6.62 (s, 1H), 5.58 (s, 1H), 4.51-4.45 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.41 - 3.38 (m, 1H), 3.02-2.94 (m, 1H), 2.74 (dt, *J* = 15.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+ CCl_4; 1:1) δ 167.9 (C), 148.6 (C), 148.1 (C), 144.8 (C), 132.9 (C), 131.6 (CH), 128.6 (CH), 127.1 (C), 126.2 (C), 124.2 (CH), 123.1 (CH), 112.2 (CH), 109.0 (CH), 59.1 (CH), 56.3 (CH_3), 56.0 (CH_3), 38.3 (CH_2), 29.2 (CH_2)); HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ (M + H) 296.1287, found 296.1276.

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Associated content

Supporting information

Copies of ^{1}H, ^{13}C NMR and DEPT-135 spectra for all compounds prepared, ORTEP plot of the X-ray structure of **10h** along with crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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