JOC The Journal of Organic Chemistry

Article

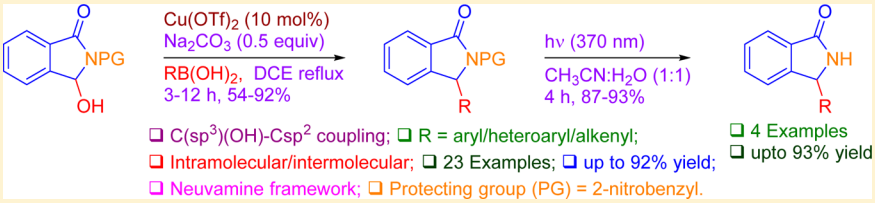
pubs.acs.org/joc

Copper-Catalyzed C(sp^3)−OH Cleavage with Concomitant C−C Coupling: Synthesis of 3-Substituted Isoindolinones

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

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

Supporting Information



ABSTRACT: Copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) efficiently catalyzes the C−C coupling of 3-hydoxyisoindolinones with a variety of aryl-, heteroaryl-, and alkenylboronic acids to furnish C(3) aryl-, heteroaryl-, and alkenyl-substituted isoindolinones. The coupling reactions work smoothly in 1,2-dicholoroethane (DCE) reflux, to effect both inter- and intramolecular versions. This is the first report on C(sp^3)−OH cleavage with concomitant C−C coupling. The photolabile 2-nitrobenzyl protecting group is most appropriate for promotion of the coupling reaction and for deprotection. The tetracyclic ring motif of the alkaloid neuvamine was prepared by applying the 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 the isoindole structure are considered privileged due to their multifarious medicinal properties.[2] Among isoindoles, the C(3)-substituted isoindolinones occur as a partial 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 the endophytic fungus *Pestalotiopsis adust*,[4] and taliscanine (**4**), an anti-Parkinson alkaloid isolated from the rhizomes of *Aristolochia taliscana*,[5] are other examples of alkaloids with a C(3)-substituted isoindole structure (Figure 1). In addition to the medicinally important alkaloids listed above, some central nervous system (CNS) active drug candidates such as (*S*)-pazinaclone (**5**) and (*R*)-PD 172939 (**6**)[6] possess a 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 the importance of isoindolinones, there have been great synthetic efforts toward these coveted structures.[11]

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 the hydroxy carbon with electron-rich aromatic compounds (carbon nucleophiles; Scheme 1). Due to the poor leaving ability of the hydroxy group, strong protic acids such as triflic acid,[12] trifluoroacetic acid,[13] concentrated H_2SO_4,[14] and concentrated HCl[15] or Lewis acids such as $Bi(OTf)_3$,[16] $Sn(NTf_2)_4$,[17] Ir−Sn_3 bimetallic complexes,[18] and 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 to date have taken recourse to robust benzyl as the nitrogen PG, but the benzyl group is difficult to remove without destroying the isoindolinone ring. Overall, existing methods are beleaguered with several drawbacks such as the requirement of (i) concentrated protic acids or Lewis acids, (ii) electron-rich aromatic compounds to quench the acyl minium ion, and (iii) a 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 acyliminium 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. Toward this goal, we resolved to develop suitable copper-catalyzed C−C coupling reactions and suitable PGs for the synthesis of C(3)-substituted isoindolinones.

In recent years, organic synthesis involving transition-metal-catalyzed C−C coupling, via substitution of halides or its congeners involving organometallic intermediates, has been responsible for a paradigm shift in synthetic planning from classical acid−base to coupling pathways.[20] Although palladium catalysts have been in the forefront of the emergence of C−C

Received: October 26, 2014
Published: January 8, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506−1516

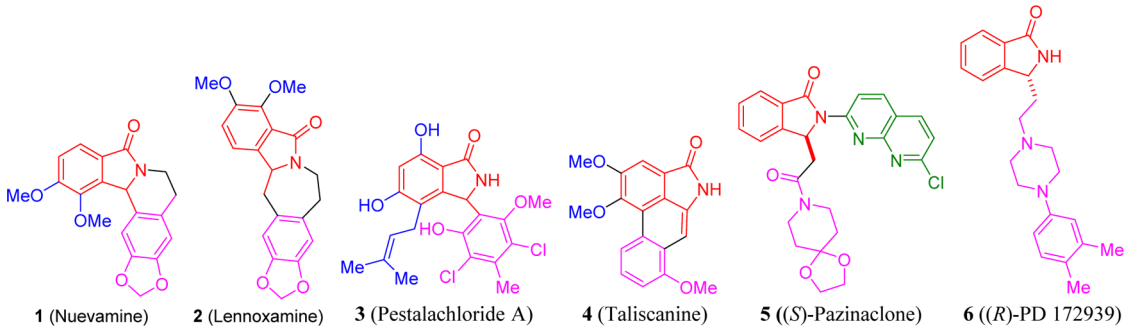
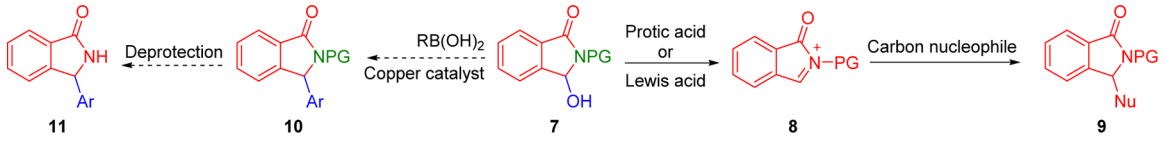


Figure 1. Examples of naturally occurring (**1**–**4**) and biologically active (**5** and **6**) C(3)-substituted isoindolinones.

Scheme 1. 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



bond coupling reactions, the 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 catalysts include (i) variable oxidation states of copper (+1, +2, and +3), (ii) solubility of many copper salts in organic solvents, (iii) low cost, benchtop availability and air stability, and (iv) environmental and biological compatibility.[22] Of late, copper-catalyzed cross-coupling reactions have become a practical 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, have 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 are commercially available or easy to prepare.[26] We have recently demonstrated facile copper-catalyzed $C(sp^3)$–$C(sp^2)$ cross-coupling reactions of organoboron reagents with 4*H*-chromenes having a C(4) SMe group to furnish a variety of 4-aryl-4*H*-chromenes.[27] In a continuation of this study, we present herein the copper-catalyzed intermolecular/intramolecular coupling reaction of isoindolinol **7** with aryl-, heteroaryl-, and alkenylboronic acids for the 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 a free benzylic hydroxyl group, an arylboronic acid, and a copper catalyst.

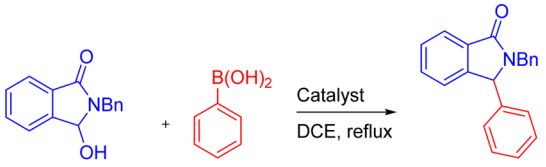
RESULTS AND DISCUSSION

Our initial efforts were directed toward 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 reflux of 10 mol % of $Cu(OAc)_2·H_2O$ in dichloromethane (DCM), 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 such as $Cu(CF_3COO)_2·H_2O$, $Cu(acac)_2$, $CuCl_2·2H_2O$, $CuBr_2$, $CuSO_4·5H_2O$, and CuO (entries 4–9) did not provide the desired **10a** in better yield. However, in the genre of Cu(II) catalysts, 10 mol % of copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) provided the best yield (86%) after chromatographic purification of the product (entry 10). A smaller amount of catalytic loading (5 mol %) was not sufficient to complete the transformation in a reasonable time (entry 12), and a 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 a 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 equiv of Na_2CO_3, indicating that a 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). Copper(I) salts such as CuCl, CuBr, CuI, and Cu_2O or stable copper(I) complexes such as $CuBrSMe_2$, $Cu(PPh_3)_3Br$, copper(I) thiophene-2-carboxylate (CuTC), and 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. The low yield obtained in the cases of CuCl, CuBr, CuTC, and CuMeSal can be attributed to Cu(II) impurities or a facile switch of Cu(I) to Cu(II). Notably, there was no reaction when a palladium(II) catalyst ($Pd(OAc)_2$, entry 22) or palladium(0) catalyst ($Pd_2(dba)_3$, entry 23) was employed in the 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 the 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).

As an alternative to DCE, we screened some common solvents and changed the reaction parameters to decipher the best conditions. Of the alternate solvents investigated such as toluene (42%), tetrachloroethane (TCE; 76%), acetonitrile (28%), and

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

Table 1. Optimization Conditions of Coupling Reactions Conducted in DCE Reflux in the Presence of Different Catalysts



7a 12a 10a

entry	catalyst	time (h)	amt of catalyst (mol %)	yield (%)[a]
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

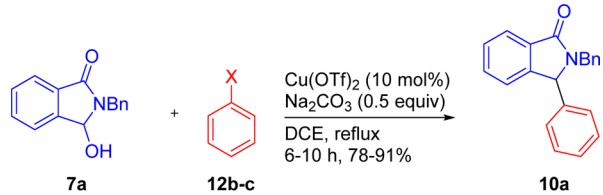
[a]nr = no reaction.

dioxane (48%), none of them worked as well as DCE (92%). The transformation worked best under an atmosphere of nitrogen. Under an 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 solubilizing ligands such as PPh_3 (34%) and phenanthroline (42%) actually decreased the yield of **10a**.

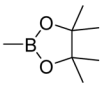
Next, we looked into the reactivity of two derivatives of phenylboronic acids, namely phenylboronic acid pinacol ester (**12b**) and potassium phenyltrifluoroborate (**12c**), toward the coupling reaction, since both of the reagents have been employed previously in place of phenylboronic acid with concomitant advantages (Scheme 2).[30] However, we 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 their easy availability, we chose to go ahead with phenylboronic acids for further studies.

With the optimized conditions in hand, we evaluated the generality of 3-arylisoindolinone synthesis and outcome of the reaction as a consequence of the electron density of the aromatic ring (Scheme 3). We conducted coupling between 2-benzyl-3-hydroxyisoindolinone (**7a**) and three more arylboronic acids:

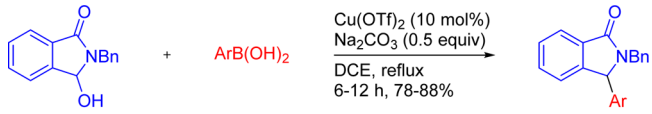
Scheme 2. Scope of Cu-Catalyzed Cross-Coupling of Arylboronic Acid Derivatives with 2-Benzyl-3-hydroxyisoindolinone (7a)



7a 12b-c 10a

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

Scheme 3. Scope of Cu-Catalyzed Cross-Coupling of Different Arylboronic Acids with 2-Benzyl-3-hydroxyisoindolinone (7a)



7a 12d-f 10b-d

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

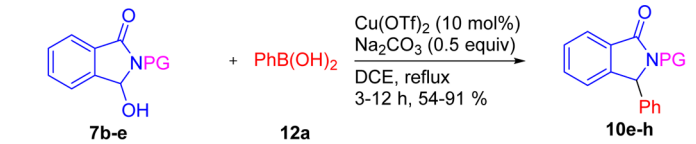
10b: Ar = 4-$CF_3C_6H_4$ (88%, 6 h); **10c**: Ar = 4-$OMeC_6H_4$ (83%, 10 h); **10d**: Ar = 2-furyl (78%, 12 h).

namely, 4-trifluoromethylphenylboronic acid (**12d**), having a highly electron withdrawing C4-CF_3 group, 4-methoxyphenylboronic acid (**12e**), having a highly electron donating C4-OMe group, and furyl-2-boronic acid (**12f**), in which the boronic acid is on an electron-rich heteroaromatic ring. Each reaction provided the corresponding 3-arylisoindolinones **10b–d** in good to excellent yield. Among the three boronic acids **12d–f**, the reaction with furyl-2-boronic acid (**12f**) provided the lowest yield (78%) and the reaction took a longer time (12 h), reflecting the sluggish nature of the reactant in coupling reactions.[31] The isoindolinone **10a** was characterized by spectral (IR, ^1H 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 ^1H NMR spectrum of 2-benzyl-3-phenylisoindolin-1-one (**10a**) is the diagnostic signal. Spectral and analytical data of **10b–d** compared well with those of **10a**.

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 would be 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 becoming reductively cleaved under hydrogenation conditions, resulting in destruction of the isoindolinone motif. As an alternative, we placed a 4-methoxybenzyl group (PMB) on the nitrogen in **7b** with the intent of selectively removing it under oxidative conditions (Scheme 4).[32] Regrettably, the coupling reaction between **7b** and phenylboronic acid (**12a**) was not efficient. Surprisingly, when palladium-sensitive allyl species **7c** and propargyl species **7d**[33] were placed on nitrogen, there was no reaction to provide the anticipated **10f,g** respectively. It is possible that **7c,d** and $Cu(OTf)_2$ combine to provide stable complexes. Gratifyingly, when we employed the photolabile 2-nitrobenzyl (NB) PG[34] on the isoindolinone motif (**7e**), the coupling worked best to provide product **10h** in excellent yield within 3 h.

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

Scheme 4. Scope of Cu-Catalyzed Cross-Coupling in the Presence of Different Protecting Groups (PGs)



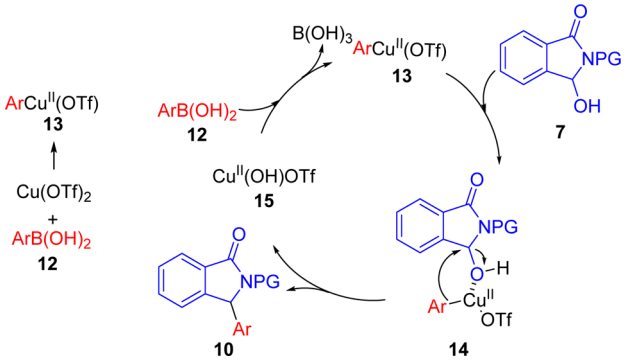
7b-e **12a** **10e-h**

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).

To understand the reaction mechanism of $C(sp^3)-C(sp^2)$ 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. Neither reaction provided the substitution product **10a**, ruling out the possibility of a nucleophilic substitution. As noted in Table 1 (entries 10 and 11), a TfOH impurity in $Cu(OTf)_2$ or TfOH (entry 13) impedes the reaction by engineering toward the generation of *N*-acyliminium ion intermediates, instead of channeling the reactant **7** toward coupling pathways. On the basis of the evidence accumulated so far, a possible mechanism could be depicted as shown in Scheme 5. The first and

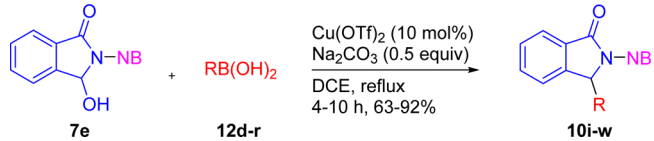
Scheme 5. Plausible Mechanism for Copper-Mediated Formation of 3-Substituted Isoindolinones 10



important step is the insertion of copper into a fragile carbon–boron bond to provide the 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. The driving force for the coupling reaction is the formation of a stable C–C bond in **10** and a Cu–O bond in **15**, at the cost of Ar–Cu and C–OH bonds. Although metal salt solubilizing ligands such as PPh_3 and phenanthroline helped the dissolution of $Cu(OTf)_2$ in DCE, the decreased yield of the desired product **10** (vide supra) indicates that ligand-bound copper catalyst is sterically hindered to allow the formation of **14**.

To demonstrate the scope of the coupling reaction, the arylboronic acids **12d–p** were reacted with 3-hydroxy-2-(2-nitrobenzyl)isoindolin-1-one (**7e**) under the optimized conditions to give the 15 2-(2-nitrobenzyl)-3-arylisoindolin-1-ones

Table 2. Scope of Cu-Catalyzed Cross-Coupling of 2-Nitrobenzyl-Protected 3-Hydroxyisoindolinone 7e with Different Aryl/Heteroaryl/Alkenylboronic 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	styryl	**12r**	**10w**	6	84

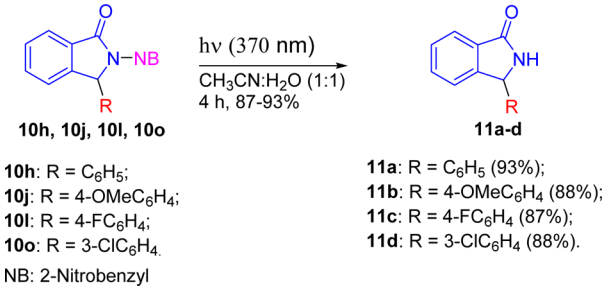
10i–u (Table 2). The arylboronic acids **12d–p** were selected with a view toward their structural diversity and potential binding to biological targets. High efficiency of cross-coupling was observed regardless of the presence of strongly electron withdrawing (**12d,g,h** to **10i,l,m**), mildly electron 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. A boronic acid on an electron-rich heterocyclic ring, namely, furyl-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, pyridene-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 alkenylboronic acids **12q,r** to furnish alkenyl substituted isoindolinones **10v,w** took place without any difficulty.

After we demonstrated the feasibility of synthesizing different C(3)-substituted isoindolinones **10h–w** with NB as the N-protecting group, our next task was to cleave photolabile NB, so that the free isoindole moiety becomes exposed. We irradiated dilute (10^{-2} M) CH_3CN/H_2O (1/1) solutions of four selected isoindolinones, namely **10h,j,l,o**, with 4 × 3 μW

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

LED lamps emitting at 370 nm (see the Supporting Information for an image of the reactor built in-house).[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 photocleavage was facile on substrates having an aryl ring with electron-donating (**10j**) or electron-withdrawing (**10l,o**) substituents. We found that the LED lamps as a source of 370 nm light for NB deprotection is far superior in comparison to conventional high-pressure mercury vapor lamps, as LED lamps do not generate heat and a filter to cut off unwanted light is not required.[38]

Scheme 6. Cleavage of NB in the Presence of UV Light (370 nm)



10h, 10j, 10l, 10o

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-d

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%).

Finally, we attempted the synthesis of the tetracyclic lactam system **19** of neuvamine (**1**) from arylboronic acid **17** to demonstrate an intramolecular version of our newly developed $Cu(OTf)_2$-catalyzed C–C coupling reaction (Scheme 7). The starting phthalimide derivative[39] **16** was prepared from the corresponding amine[40] and phthalic anhydride in refluxing toluene. The aryl bromide **16** was converted into the boronic acid derivative **17** by a 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 the neuvamine framework **19** in excellent yield.

CONCLUSION

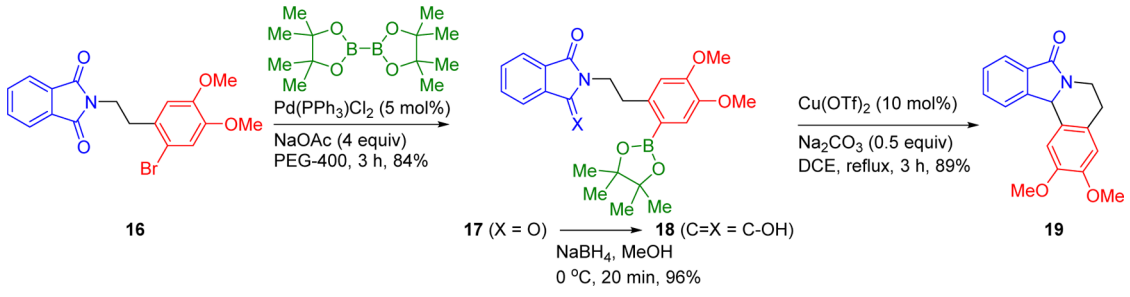
In summary, we have described facile $Cu(OTf)_2$-catalyzed $C(sp^3)$–$C(sp^2)$ coupling involving 3-hydoxyisoindolinones and a variety of aryl-, heteroaryl-, and alkenylboronic acids to efficiently furnish C(3) aryl-, heteroaryl-, and alkenyl-substituted isoindolinones. This is the first report on copper-catalyzed $C(sp^3)$–OH cleavage with concomitant C–C coupling. In this way, we demonstrated facile substitution of the OH group in 3-hydoxyisoindolinones with electron-rich and 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 intramolecular versions through the synthesis of 23 C(3)-substituted isoindolinones and the tetracyclic ring motif of the alkaloid neuvamine.

EXPERIMENTAL SECTION

General Experimental Methods. The progress of all reactions was monitored by TLC using a hexanes (60–80 °C boiling mixture)/ethyl acetate mixture as 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 $CDCl_3$, $CDCl_3/CCl_4$ (1/1), or DMSO-d_6 solutions on a 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 a quadrupole time of flight (QTOF) mass spectrometer using the electrospray ionization mode. The X-ray diffraction measurements were carried out at 298 K on a diffractometer 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 alkenylboronic acids were prepared according to literature procedures.[41] Light-mediated deprotection of the NB group to generate isoindolinones was carried out using a home-built reactor having four UV-LED (3 μW) lamps with an emission maximum at 370 nm (see the Supporting Information for the photograph). The maximum intensity of the LED bulbs was determined using a UV–visible spectrometer capable of intensity and wavelength characterization having a resolution of 0.23 nm in the range 200–1100 nm (see Figure 3 in the Supporting Information).

General Procedure for Synthesis of 2-Benzyl-3-arylisoindolin-1-ones 10a–e: Synthesis of 2-Benzyl-3-phenylisoindolinone (10a). An oven-dried 25 mL two-neck round-bottom flask connected to a Schlenk 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 three times with nitrogen gas. 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 room temperature (30 °C) over 5 min. The resulting reaction mixture was refluxed for 4 h while it was periodically checked by TLC for completion of the reaction. The reaction mixture was then extracted with dichloromethane (DCM, 2 × 20 mL). The organic layer was washed with water (2 × 20 mL) and 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**).

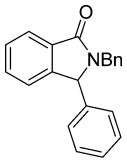
Scheme 7. Synthesis of Neuvamine-like Molecule 19 via a Cu-Catalyzed Intramolecular Coupling Reaction



16 **17** (X = O) → **18** (C=X = C-OH) **19**

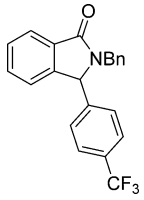
DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

*2-Benzyl-3-phenylisoindolin-1-one (**10a**):*



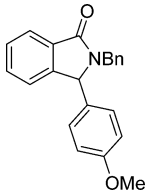
colorless solid (143 mg, 92% yield); mp 135 °C (reported 136 °C); IR (KBr, cm^{-1}) 3030, 2920, 1695, 1613, 1494, 1464, 1399, 1291, 1075, 1026, 978, 761, 738, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 6.6 Hz, 11H), 7.50−7.39 (m, 2H), 7.39−7.02 (m, 1H), 5.40 (d, J = 14.8 Hz, 1H), 5.24 (s, 1H), 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 × 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-one (**10b**):*



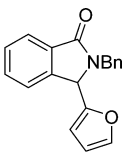
colorless solid (167 mg, 88% yield); mp 115 °C; IR (KBr, cm^{-1}) 3064, 3033, 2926, 2861, 1702, 1618, 1494, 1467, 1398, 1327, 1119, 1068, 891, 848, 795, 737, 700, 609; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4, 1/1) δ 7.95 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.52−7.37 (m, 2H), 7.28−7.06 (m, 8H), 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-one (**10c**):*



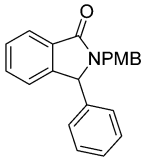
colorless solid (136 mg, 83% yield); mp 124 °C (reported 124 °C); IR (KBr, cm^{-1}) 3062, 2927, 2872, 1694, 1611, 1527, 1468, 1400, 1344, 1305, 1142, 1094, 858, 790, 738, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.77 (m, 1H), 7.35−7.24 (m, 2H), 7.16−7.11 (m, 3H), 7.06 (d, J = 6.6 Hz, 2H), 6.98−6.92 (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-one (**10d**):*



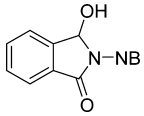
colorless solid (106 mg, 78% yield); mp 108 °C; IR (KBr, cm^{-1}) 1693, 1592, 1567, 1529, 1305, 1195, 1072, 743, 708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.86 (m, 1H), 7.54−7.45 (m, 2H), 7.30−7.19 (m, 6H), 6.29−6.36 (m, 2H), 5.40 (s, 1H), 5.32 (d, J = 14.9 Hz, 1H), 3.94 (d, J = 14.9 Hz, 1H); ^{13}C 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**):*



colorless 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.

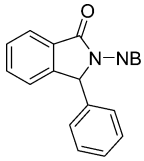
Synthesis of 3-Hydroxy-2-(2-nitrobenzyl)isoindolin-1-one (7e).



To a stirred solution of 2-(2-nitrobenzyl)isoindoline-1,3-dione[43] (500 mg, 1.77 mmol) in a mixture of tetrahydrofuran and methanol (5 mL/0.5 mL) was added sodium borohydride (114 mg, 2.65 mmol) over 10 min at −10 °C. The 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 a rotary evaporator resulted in a colorless solid which was 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-ones **10a−e** was followed for the synthesis of 2-(2-nitrobenzyl)-3-phenylisoindolin-1-ones **10h−w**.

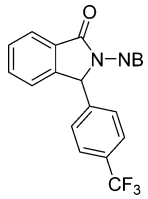
*2-(2-Nitrobenzyl)-3-phenylisoindolin-1-one (**10h**):*



colorless 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.

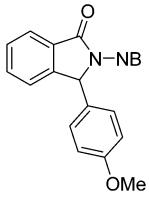
DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506−1516

*2-(2-Nitrobenzyl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (**10i**):*



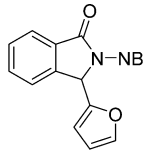
colorless solid (134 mg, 92% yield); mp 141 °C; IR (KBr, cm^{-1}) 3070, 2935, 2860, 1699, 1617, 1528, 1395, 1326, 1166, 1125, 1067, 854, 790, 734; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.94–7.89 (m, 2H), 7.56–7.48 (m, 6H), 7.40–7.38 (m, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.15–7.11 (m, 1H), 5.49 (s, 1H), 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**):*



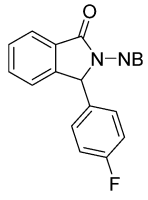
Light yellow solid (93 mg, 77% yield); mp 115 °C; IR (KBr, cm^{-1}) 3071, 2935, 2840, 1695, 1609, 1525, 1466, 1400, 1344, 1304, 1248, 1176, 1107, 1027, 787, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2H), 7.54–7.48 (m, 3H), 7.40–7.36 (m, 2H), 7.18–7.16 (m, 1H), 6.92 (d, J = 8.3 Hz, 2H), 6.80 (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**):*



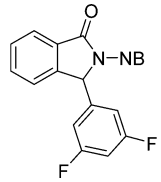
colorless solid (93 mg, 79% yield); mp 140 °C; IR (KBr, cm^{-1}) 1697, 1596, 1577, 1470, 1395, 1343, 1305, 1190, 1080, 858, 786, 750, 702; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.97–7.93 (m, 2H), 7.61–7.43 (m, 3H), 7.38–7.32 (m, 3H), 7.22 (s, 1H), 6.24 (s, 2H), 5.55 (s, 1H), 5.25 (d, J = 16.9 Hz, 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**):*



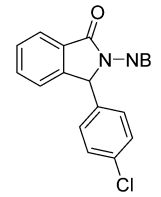
Light yellow solid (116 mg, 91% yield); mp 157 °C; IR (KBr, cm^{-1}) 3071, 2930, 1695, 1607, 1527, 1469, 1397, 1342, 1226, 1158, 1097, 856, 788, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.91 (m, 2H), 7.53–7.48 (m, 3H), 7.40–7.35 (m, 2H), 7.16–7.13 (m, 1H), 7.01–6.93 (m, 4H), 5.40 (s, 1H), 5.35 (d, J = 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**):*



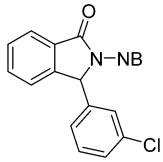
light yellow solid (108 mg, 81% yield); mp 167 °C; IR (KBr, cm^{-1}) 1713, 1650, 1574, 1530, 1464, 1409, 1333, 1116, 855, 790, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.8 Hz, 2H), 7.56–7.51 (m, 3H), 7.45–7.39 (m, 2H), 7.18 (d, J = 4.8 Hz, 1H), 6.74 (t, J = 8.5 Hz, 1H), 6.61 (d, J = 5.6 Hz, 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**):*



colorless 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.

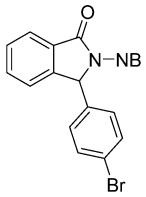
*3-(3-Chlorophenyl)-2-(2-nitrobenzyl)isoindolin-1-one (**10o**):*



colorless 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.

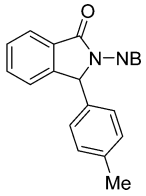
DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

*3-(4-Bromophenyl)-2-(2-nitrobenzyl)isoindolin-1-one (**10p**):*



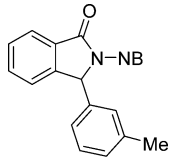
colorless solid (126 mg, 85% yield); mp 114 °C; IR (KBr, cm^{-1}) 1697, 1613, 1526, 1469, 1396, 1344, 1306, 1072, 1011, 788, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 2H), 7.54−7.49 (m, 3H), 7.42−7.37 (m, 4H), 7.15−7.13 (m, 1H), 6.91 (d, J = 7.0 Hz, 2H), 5.38−5.34 (m, 2H), 4.51 (d, J = 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**):*



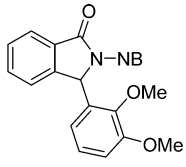
colorless solid (113 mg, 89% yield); mp 135 °C; IR (KBr, cm^{-1}) 1696, 1609, 1527, 1468, 1400, 1345, 1305, 1200, 1158, 1095, 858, 787, 734, 706; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.92 (d, J = 6.9 Hz, 2H), 7.59−7.30 (m, 5H), 7.20−7.03 (m, 3H), 6.89 (d, J = 7.7 Hz, 2H), 5.38−5.33 (m, 2H), 4.45 (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**):*



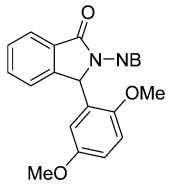
colorless solid (109 mg, 86% yield); mp 129 °C; IR (KBr, cm^{-1}), 3049, 2922, 1694, 1609, 1578, 1526, 1469, 1397, 1342, 1304, 1200, 1095, 857, 787, 770, 730, 706; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.93−7.91 (m, 2H), 7.53−7.47 (m, 3H), 7.40−7.35 (m, 2H), 7.18−7.13 (m, 2H), 7.08−7.06 (m, 1H), 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**):*



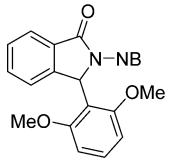
light yellow solid (113 mg, 79% yield); mp 122 °C; IR (KBr, cm^{-1}) 3066, 2937, 2837, 1697, 1605, 1522, 1465, 1399, 1263, 1141, 1027, 858, 788, 730; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.84−7.80 (m, 2H), 7.42−7.36 (m, 4H), 7.30−7.26 (m, 1H), 7.10−7.08 (m, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.56 (d, 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**):*



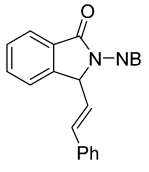
colorless solid (116 mg, 81% yield); mp 130 °C; IR (KBr, cm^{-1}) 3002, 2936, 2836, 1694, 1526, 1468, 1340, 1280, 1218, 1047, 856, 789, 748; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.93 (d, J = 6.8 Hz, 2H), 7.50−7.46 (m, 3H), 7.36−7.28 (m, 3H), 6.78−6.72 (m, 2H), 6.17 (s, 1H), 6.03 (s, 1H), 5.38 (d, 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**):*



colorless solid (93 mg, 74% yield); mp 154 °C; IR (KBr, cm^{-1}) 2933, 2831, 1693, 1528, 1462, 1392, 1284, 1217, 1032, 853, 783, 747; ^{1}H 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**):*

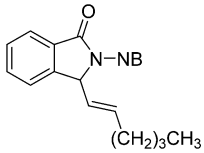


viscous solid (82 mg, 63% yield); IR (KBr, cm^{-1}) 3058, 3028, 2960, 2927, 2869, 1696, 1609, 1527, 1469, 1402, 1345, 1305, 1149, 1084, 970, 857, 751, 698; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.95 (dd, J = 8.2, 1.2 Hz, 2H), 7.90 (dd, J = 6.7, 1.0 Hz, 2H), 7.59−7.49 (m, 6H), 7.44 (d, J = 6.8 Hz, 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),

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506−1516

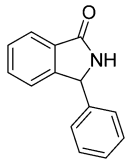
124.2 (CH), 123.5 (CH), 64.2 (CH), 41.3 (CH_2); HRMS (ESI) calcd for $C_{23}H_{18}N_2O_3Na$ (M + Na) 393.1215, found 393.1215.

*(E)-3-(Hex-1-en-1-yl)-2-(2-nitrobenzyl)isoindolin-1-one (**10w**):*



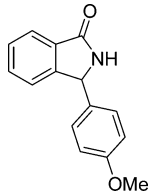
viscous solid (103 mg 84%); IR (KBr, cm^{-1}) 2958, 2928, 2864, 1767, 1696, 1613, 1467, 1401, 1343, 1304, 1223, 1148, 1099, 1049, 974, 857, 789, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 7.4 Hz, 1H), 7.59–7.47 (m, 3H), 7.43–7.32 (m, 3H), 5.95–5.82 (m, 1H), 5.28 (d, J = 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 the 2-Nitrobenzyl Group for Synthesis of C(3)-Substituted Isoindolin-1-ones 11a–d: Synthesis of 3-Phenylisoindolin-1-one (11a).



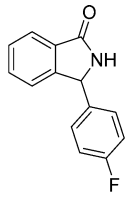
A stirred solution of 2-(2-nitrobenzyl)-3-phenylisoindolin-1-one (**10h**; 50 mg, mmol) in CH_3CN/H_2O (1/1; 10 mL) in a Pyrex test tube of 20 mL capacity was exposed to light irradiation with emission maximum at 370 nm emitted by UV-LED (4 × 3 μW) lamps (see the Supporting Information for an image of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

*3-(4-Methoxyphenyl)isoindolin-1-one (**11b**):*



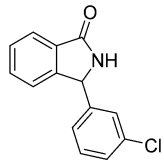
colorless solid (28 mg, 88% yield); mp 155 °C; IR (KBr, cm^{-1}) 3200, 3074, 2955, 1732, 1697, 1589, 1514, 1346, 1246, 732; ^1H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) δ 7.92–7.86 (m, 1H), 7.53–7.43 (m, 2H), 7.21 (dd, J = 7.5, 0.9 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.63 (s, 1H), 5.58 (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**):*



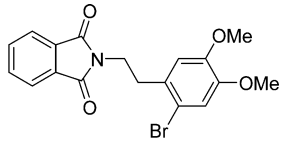
colorless solid (27 mg, 87% yield); mp 179 °C; IR (KBr, cm^{-1}) 3194, 3068, 2837, 1685, 1610, 1512, 1465, 1358, 1247, 1178, 1033, 731; ^1H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) 7.83 (m, 1H), 7.63 (bs, 1H), 7.50–7.49 (m, 2H), 7.25–7.18 (m, 3H), 7.01 (t, J = 8.8 Hz, 2H), 5.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$ 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**):*



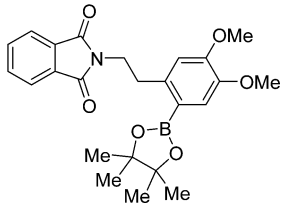
colorless solid (28 mg, 88% yield); mp 157 °C; IR (KBr, cm^{-1}) 3191, 3071, 2924, 1690, 1552, 1469, 1352, 1191, 1139, 1088, 784, 749, 705; ^1H NMR (400 MHz, $CDCl_3/CCl_4$ 1/1) 7.51–7.48 (m, 1H), 7.29–7.27 (m, 2H), 7.25–7.15 (m, 6H), 6.97 (bs, 1H), 5.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$ 1/1) 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) and 2-(2-bromo-4,5-dimethoxyphenyl)ethan-1-amine (1.036 g, 4 mmol) in 15 mL of toluene in an oven-dried 25 mL round-bottom flask fitted with a Dean–Stark apparatus was heated to reflux until a clear solution of the product was obtained (6 h). The condensation worked better in toluene reflux with a Dean–Stark apparatus in comparison to the condensation with phthaloyl dichloride in acetonitrile in the presence of Hunig's base as described by DiMagno and co-workers.[39] After completion of the reaction the 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 colorless solid (1.31 g, 82% yield): mp = 143 °C; IR (KBr, cm^{-1}) 1713, 1583, 1467, 1386, 1121, 1084, 883, 768, 712; ^1H 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]

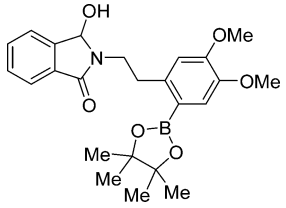
2-(4,5-Dimethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)isoindoline-1,3-dione (17).



DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506–1516

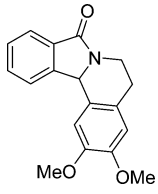
A viscous solution of 2-(2-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione (**16**; 300 mg, 0.75 mmol), bis(pinacolato)diboron (222 mg, 0.90 mmol), NaOAc (242 mg, 3 mmol), and $Pd(PPh_3)_2Cl_2$ (26 mg, 0.08 mmol) in PEG 400 (3 mL) was stirred in an oil bath at 80 °C for 3 h under an atmosphere of nitrogen. After completion of the reaction (TLC, 20% EtOAc in hexanes, R_f = 0.5), the cooled 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. The crude product obtained after removal of MTBE was purified by column chromatography (silica gel, gradient elution with increasing volume of EtOAc in hexanes), resulting in **17** as a colorless 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; ^1H 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 a mixture of tetrahydrofuran (3 mL) and methanol (0.3 mL) kept in an ice−water bath was added sodium borohydride (34 mg, 0.92 mmol) in three portions over 10 min. The reaction mixture was then stirred at 0−5 °C for 20 min, by which time the 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 a white solid in residual water. Filtration of the solid followed by washing with water (5 mL) provided **18** as a colorless 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; ^1H 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, 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 the 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 colorless solid in 89% yield (59 mg): mp 60 °C; IR (KBr, cm^{-1}) 2912, 1678, 1518, 1417, 1253, 1228, 1205, 1093, 724; ^1H 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.

■ ASSOCIATED CONTENT

Supporting Information

Figures and a CIF file giving ^1H and ^{13}C NMR and DEPT-135 spectra for all compounds prepared, an ORTEP plot of the X-ray structure of **10h**, a picture of the home-built UV reactor, and crystal data for **10h**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*H.S.P.R.: e-mail, hspr.che@pondiuni.edu.in; tel, +914132654411; fax, +914132656230; web, http://www.pondiuni.edu.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

H.S.P.R. thanks the UGC, UGC-SAP, CSIR and DST-FIST for financial assistance. A.V.B.R. thanks the CSIR for a fellowship. We thank the CIF, Pondicherry University, and IISC, Bangalore, India, for recording spectra.

■ REFERENCES

(1) (a) Speck, K.; Magauer, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2048−2078. (b) Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Chem. Soc. Rev.* **2012**, *41*, 5626−5640. (c) Subbarayappa, A.; Patoliya, P. U. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48*, 545−552. (d) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *J. Indian Chem. Soc.* **2001**, *78*, 671−688.

(2) (a) Meng, Z.-H.; Liao, L.-H.; Pommier, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 305−320. (b) Garcia-Carbonero, R.; Supko, J. G. *Clin. Cancer Res.* **2002**, *8*, 641−661. (c) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623−2625. (d) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry. Pyrroles and Their Benzo Derivatives: (iii) Synthesis and Application*; Bird, C. W., Cheeseman, G. W. H., Eds.; Elsevier: Amsterdam, 1984; Vol 4, pp 313−376.

(3) Bentley, K. W. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic: Amsterdam, 1998; pp 361−375.

(4) Tejesvi, M. V.; Pirttilä, A. M. In *Endophytes of Forest Trees: Biology and Applications. Forestry Sciences*; Pirttilä, A. M., Frank, A. C., Eds.; Springer: Berlin, 2011; Vol. *80*, pp 302.

(5) Chen, Z.-L.; Zhu, D.-Y. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1987, Vol. *31*, pp 29−62.

(6) (a) Oak, J. N.; Oldenhof, J.; Van Tol, H. H. M. *Eur. J. Pharmacol.* **2000**, *405*, 303−327. (b) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499−1502.

(7) (a) Zhuang, Z.; Kung, M.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157−166. (b) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 149−157.

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506−1516

(8) Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361−365.
(9) Lippmann, W. U.S. Patent 4,267,189, 1981. *Chem. Abstr.* **1981**, *95*, 61988m.
(10) (a) Wada, T.; Fukuda, N. *Pharmacol., Biochem. Behav.* **1992**, *41*, 573−579. (b) Wada, T.; Fukuda, N. *Psychopharmacology* **1991**, *103*, 314−322.
(11) (a) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367. (b) Fujioka, M.; Morimoto, T.; Tsumagari, T.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K. *J. Org. Chem.* **2012**, *77*, 2911−2923. (c) Augner, D.; Gerbino, D. C.; Slavov, N. *Org. Lett.* **2011**, *13*, 1629−1631. (d) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490−3493. (e) Slavov, N.; Cvengroš, J.; Neudörfl, J.-M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 7588−7591.
(12) Zhang, Y.; DeSchepper, D. J.; Gilbert, T. M.; Sai, K. K. S.; Klumpp, D. A. *Chem. Commun.* **2007**, 4032−4034.
(13) Klumpp, D. A.; Zhang, Y.; Connor, M. J. O.; Esteves, P. M.; De Almeida, L. S. *Org. Lett.* **2007**, *9*, 3085−3088.
(14) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905−4908.
(15) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron* **1982**, *38*, 3255−3266.
(16) Pin, F.; Comesse, S.; Garrigues, B.; Marchalín, S.; Daïch, A. *J. Org. Chem.* **2007**, *72*, 1181−1191.
(17) Ben Othman, R.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776−780.
(18) (a) Maity, A. K.; Roy, S. *Adv. Synth. Catal.* **2014**, *356*, 2627−2642. (b) Maity, A. K.; Roy, S. *J. Org. Chem.* **2012**, *77*, 2935−41.
(19) Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem. Eur. J.* **2012**, *18*, 14192−14200.
(20) (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*; Meijere, A. D., Diederich, F., Eds.; Wiley: Weinheim, Germany, 2004; pp 41−123. Reviews: (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177−2250. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447−2464. (d) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027−3043. (e) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288−325. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (g) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283−2321. (h) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *2004*, 2419−2440. (i) Hassan, J.; Se, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (j) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(21) (a) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem.* **2014**, *126*, 3543−3547. (b) Chen, L.; Lang, H.; Fang, L.; Zhu, M.; Liu, J.; Yu, J.; Wang, L. *Eur. J. Org. Chem.* **2014**, *2014*, 4953−4957. (c) Ke, H.; Chen, X.; Zou, G. *J. Org. Chem.* **2014**, *79*, 7132−7140. (d) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270−5298.
(22) (a) Yamamoto,Y. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; Wiley: Hoboken, NJ, 2013; pp 335−399. (b) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829−856. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054−3131. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (e) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (f) Erdik, E. *Tetrahedron* **1984**, *40*, 641. (g) Posner, G. H. *Org. React.* **1975**, *22*, 253.
(23) (a) Flores-Rizo, J. O.; Esnal, I.; Osorio-Martínez, C. A.; Gómez-Durán, C. F. A.; Bañuelos, J.; López Arbeloa, I.; Pannell, K. H.; Metta-Magaña, A. J.; Peña-Cabrera. *Eur. J. Org. Chem.* **2013**, *78*, 5867−5877. (b) Qiao, J. X.; Lam, P. Y. S. In *Boronic Acids: Recent Advances in the Chan-Lam Coupling Reaction*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 315−361. (c) Niu, J.; Zhou, H.; Li, Z.; Xu, J. *J. Org. Chem.* **2008**, *73*, 7814−7817.
(24) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174−2185.
(25) (a) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904−3907. (b) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053−2057. (c) Li, J.-H.; Wang, D.-P. *Eur. J. Org. Chem.* **2006**, 2063−2066. (d) Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 11858−11859.
(26) Hall, D. G. In *Boronic Acids: Structure, Properties, and Preparation of Boronic Acid Derivatives*, 2nd ed.; Hall, D. G., Ed.; Wiley: Weinheim, Germany, 2011; pp 1−133.
(27) Rao, H. S. P.; Rao, A. V. B. *Eur. J. Org. Chem.* **2014**, 3646−3655.
(28) (a) Harris, M. R.; Hanna, L. E.; Greene, M. G.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303−3306. (b) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307−3310. (c) Yu, J-Yi.; Kuwano, R. *Org. Lett.* **2008**, *10*, 973−976.
(29) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.
(30) (a) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412−443. (b) Zhang, N.; Ho, D. J.; Gutsche, N.; Gupta, J.; Percec, V. *J. Org. Chem.* **2012**, *77*, 5956−5964.
(31) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358−3366.
(32) (a) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033−4036. (b) Cappa, A.; Marcantoni, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1999**, *64*, 5696−5699.
(33) (a) Lemaire-Audoire, S.; Savignac, M.; Pierre, J.; Paris, C.; Bernard, J. *Tetrahedron Lett.* **1995**, *36*, 1267−1270. (b) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929−6930.
(34) (a) Givens, R. S.; Conrad, P. G., II; Yousef, A. L.; Lee, J.-I. Photoremovable protecting groups. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004, Chapter 69, pp 1−46. (b) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441−458.
(35) Rahman, M. T.; Nahar, S. K. *J. Organomet. Chem.* **1987**, *329*, 133−138.
(36) Itoh, T.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 2736−2739.
(37) (a) Herrmann, A. *Photochem. Photobiol. Sci.* **2012**, *11*, 446−459. (b) Johnson, E. C. B.; Kent, S. B. H. *Chem. Commun.* **2006**, 1557−1559. (c) Kim, M. S.; Diamond, S. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4007−4010.
(38) Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. *Tetrahedron* **2009**, *65*, 1593−1598.
(39) Wang, B.; Qin, L.; Neumann, K. D.; Uppaluri, S.; Cerny, R. L.; Dimagno, S. G. *Org. Lett.* **2010**, *12*, 3352−3355.
(40) Ito, K.; Tanaka, H.; Kayama, M. *Chem. Pharm. Bull.* **1977**, *25*, 1249−1255.
(41) Lu, J.; Guan, Z.-Z.; Gao, J.-W.; Zhang, Z.-H. *Appl. Organomet. Chem.* **2011**, *25*, 537−541.
(42) Chalker, J. M.; Wood, C. S. C.; Davis, B. G. *J. Am. Chem. Soc.* **2009**, *131*, 16346−16347.
(43) Ong-Lee, A.; Sylvester, L.; Wasley, J. W. F. *J. Heterocycl. Chem.* **1983**, *20*, 1565−1569.
(44) Augner, D.; Gerbino, D. C.; Slavov, N. *Org. Lett.* **2011**, *13*, 1629−1631.

DOI: 10.1021/jo502446k
J. Org. Chem. 2015, 80, 1506−1516