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Advanced Synthesis & Catalysis

Tandem C(sp^3)–H Arylation/Oxidation and Arylation/Allylic Substitution of Isoindolinones

Jacqueline Jiménez,[+a,b] Byeong-Seon Kim,[+b] and Patrick J. Walsh[b,*]

[a] Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla 72570, México
[b] Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, Department of Chemistry, University of Pennsylvania, 231 S, 34thSt., Philadelphia, PA 19104-6323, USA
Fax: (+1)-215-573-2112; e-mail: pwalsh@sas.upenn.edu
[+] These authors contributed equally

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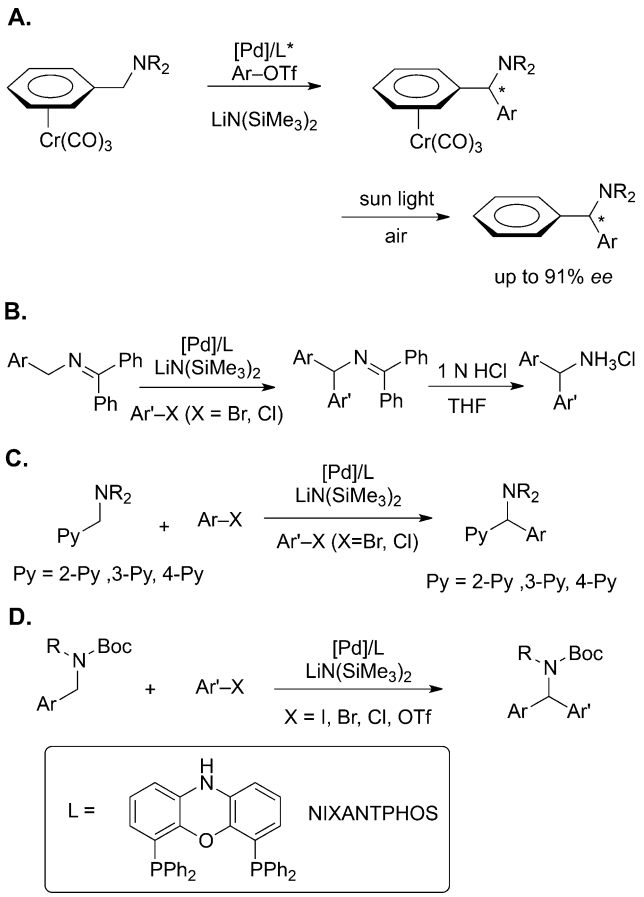
Abstract: Isoindolinones comprise an important class of medicinally active compounds. Herein we report a straightforward functionalization of isoindolinones with aryl bromides (22 examples) using a palladium(II) acetate/NIXANTPHOS-based catalyst system. Additionally 3-aryl-3-hydroxyisoindolinone derivatives, which exhibit anti-tumor activity, can be accessed *via* a tandem reaction. Thus, when the arylation product is exposed to air under basic conditions, *in situ* oxidation takes place to install the 3-hydroxy group. Furthermore, a tandem arylation/allylic substitution reaction is advanced in which both the arylation and allylic substitution are catalyzed by the same palladium catalyst. Finally, a tandem arylation/alkylation procedure is presented. These tandem reactions enable the synthesis of a variety of structurally diverse isoindolinone derivatives from common starting materials.

Keywords: arylation; cross-coupling; isoindolinones; palladium; tandem reactions

Introduction

Chemoselective functionalization of C–H bonds situated adjacent to nitrogen constitutes an attractive strategy to elaborate amine derivatives, which are found in numerous marketed pharmaceuticals.[1] One tactic for this approach involves the direct deprotonation of the amino alkyl moiety's sp^3 C–H followed by functionalization.[2] Because of the low acidity of these C–H bonds,[3] chemists usually resort to a two-step protocol beginning with a low temperature deprotonation of the amine derivative with an organolithium base followed by treatment with an electrophile.[3] The basic nature of the organolithiums and lithiated intermediates, however, can lead to compatibility issues with substrates and transition metal catalysts.[4] To circumvent this problem, researchers often rely on an intermediate transmetallation step, usually to zinc or to copper, allowing the successful C-arylation of amine derivatives.[5]

We envisioned a different strategy to simplify these two-step processes. Our idea involves a reversible deprotonation of amino alkyl C–H's, followed by catalytic *in situ* arylation, akin to enolate arylation reactions.[6] To perform the deprotonation and functionalization in the presence of a catalyst and potentially sensitive functional groups, we surmised that commonly employed strong bases (organolithiums and LDA) that might decompose the catalyst or limit the scope of the reaction, were to be avoided.[4a] At the outset of our work, and other groups[2a,b,g,h] in this area, we hypothesized that an activating group would be necessary to acidify the amino alkyl C–H's to the point where they could be deprotonated under relatively mild conditions. Thus, we initially employed benzylic amines activated by coordination to electron-deficient metal complexes, (η^6-C_6H_5-CH_2NR_2)$Cr(CO)_3$ (Scheme 1A).[2c,d] Using these substrates, enantioselective arylation reactions could be conducted to synthesize diarylmethylamines with high *ee*.[2d] Following the lead of Oshima and co-workers,[2a] we explored organic activating groups, such as ketimines, in the arylation of 2-azaallyl anions (Scheme 1B).[2e,f,k] Heteroaryl benzylic amines also exhibit enhanced acidity, facilitating arylation (Scheme 1C).[2j] We also applied our approach to the arylation of weakly acidic *N*-Boc-benzylic amines and related compounds in the presence of $LiN(SiMe_3)_2$ and a Pd-based catalyst to afford diarylmethylamine derivatives (Scheme 1D).[2i] These

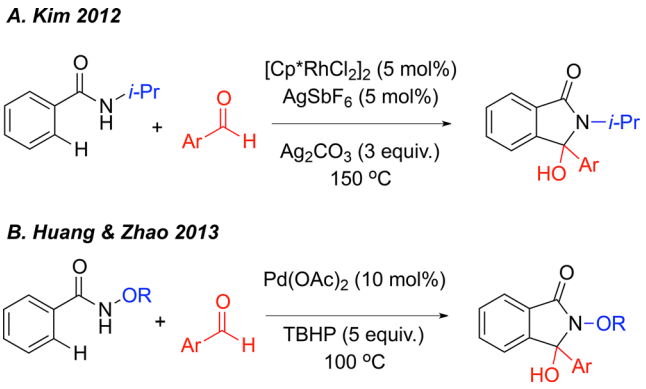


Scheme 1. Prior approaches to arylation adjacent to nitrogen.

methods allow efficient access to pharmaceutically relevant diarylmethylamine core structures. It is noteworthy that the ligand used in Schemes 1B–D is van Leeuwen's NIXANTPHOS,[7] a deprotonatable ligand that forms bimetallic catalysts that exhibit exceptional reactivity.[8]

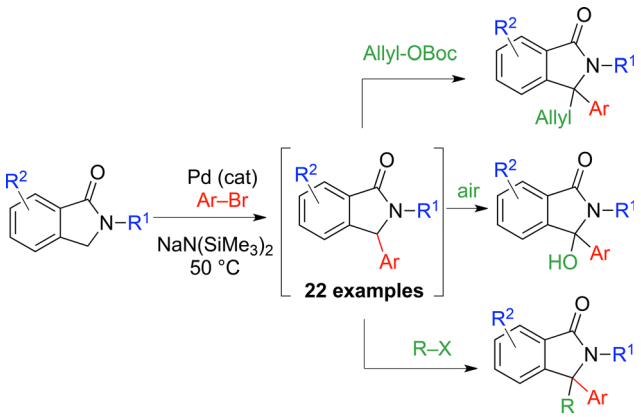
To broaden the scope and synthetic utility of our approach to functionalize amino alkyl C–H's, we envisioned the arylation of isoindolinones. The isoindolinone moiety is found in several natural products such as lennoxamine,[9] stachybotrine C,[10] pestalachloride A,[11] and taliscanine.[12] It is also the core structure of biologically active compounds, including pagoclone,[13] chlorthalidone[14] and NU8165.[15] Isoindolinone derivatives display a wide range of biological activities including antihypertensive,[16] antipsychotic,[17] anxiolytic,[18] antiviral,[19] antileukemic,[20] antitumoral,[19b,21] and anti-inflammatory.[22] They are also vasodilatory agents.[23]

Given the widespread utility of isoindolinones, it is not surprising that a variety of methods have been introduced for their synthesis, including several transition metal-catalyzed reactions.[24] Nonetheless, certain classes of isoindolinones remain difficult to efficiently



Scheme 2. Synthesis of 3-substituted isoindolinones.

access. These include isoindolinones with quaternary centers or oxidation adjacent to nitrogen. Recent advances include C(sp^2)–H functionalization reactions. An elegant approach by Kim and co-workers is acylation of *N*-isopropyl benzamides with a rhodium-based catalyst (Scheme 2A).[24j] More recently Zhao and co-workers circumvented the need for excess silver oxidant using TBHP in a Pd-catalyzed C–H activation/annulation reaction for the preparation of 3-hydroxyisoindolinones (Scheme 2B).[24m] The conceptual significance of these works not withstanding, they both have practical drawbacks, including use of 3 equiv. of silver and the *N*-isopropyl group, and excess TBHP and use of hydroxamides as *N*-protecting groups. Herein, we introduce an *in situ* arylation of isoindolinones adjacent to the nitrogen to provide rapid access to a series of 3-arylisoindolinones (Scheme 3). This class of compounds is found in the core structure of alkaloids **3**.[25] To access more challenging 3-hydroxyisoindolinones, which exhibit antitumor activity, a streamlined tandem arylation/oxidation is advanced (Scheme 3). Finally, arylation/functionalization reactions that enable the rapid one-pot preparation of a wide range of isoindolinones containing quaternary carbons at the C-3 position are presented. Among



Scheme 3. Arylation of isoindolinones and arylation/tandem reactions of this work.

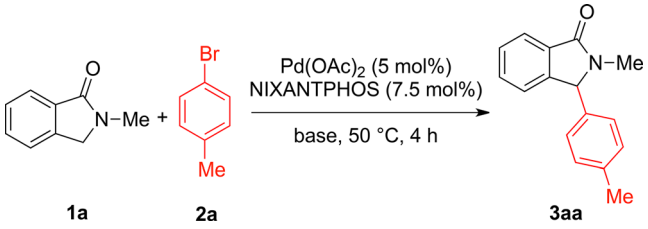
these, a tandem arylation/allylic substitution reaction is developed in which both steps are promoted by the same palladium catalyst.[26]

Results and Discussion

In our experience with deprotonative cross-coupling processes (DCCP) of weakly acidic substrates[2c–f,i–k,8a,27] we have observed that palladium complexes of van Leeuwen's NIXANTPHOS ligand (see Scheme 1 for structure) display outstanding reactivity toward a wide variety of transformations whereas other ligands are much less effective. Based on these studies, we employed $Pd(OAc)_2$ (5 mol%) and NIXANTPHOS (7.5 mol%) as catalyst to examine the arylation of *N*-methylisoindolinone (**1a**) with 4-bromotoluene **2a**. Reactions were conducted in the presence of six bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$], using 1,4-dioxane as solvent at 50 °C for 4 h. As illustrated in Table 1 (entries 1–6) the six bases afforded the desired arylation product **3aa** in 19–98% assay yields (AY, determined by ^{1}H NMR spectroscopy of the crude products). The highest yield was afforded with $NaN(SiMe_3)_2$ (98% AY, entry 5). Decreasing the amount of $NaN(SiMe_3)_2$ from 2 to 1.5 equivalents provided the product without a significant drop in yield (95% AY and 91% isolated yield, entry 7). Reducing the reaction time from 4 to 3 h afforded a lower yield of the arylation product (89% AY, entry 8). When the reaction temperature was reduced from 50 °C to room temperature, no arylated product was obtained (entry 9). Lower catalyst loadings [2.5 mol% $Pd(OAc)_2$ and 3.75 mol% NIXANTPHOS] generally resulted in lower yields.

The optimized conditions (Table 1, entry 7) were carried forward to evaluate the substrate scope of the arylation reaction of 2-methylisoindolinone (**1a**) with various aryl bromides **2** (Table 2). The arylated products were obtained in good yields with bromobenzene and 4-*tert*-butylbromobenzene providing **3ab** and **3ac** both in 90% yield. 3-Bromotoluene was also a good

Table 1. Selected optimization steps for the arylation of *N*-methylisoindolinone **1a** with 4-bromotoluene **2a**.

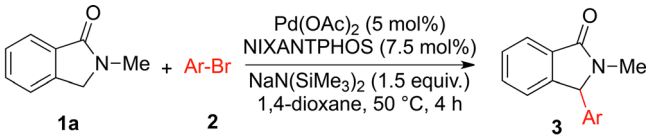


1a 2a 3aa

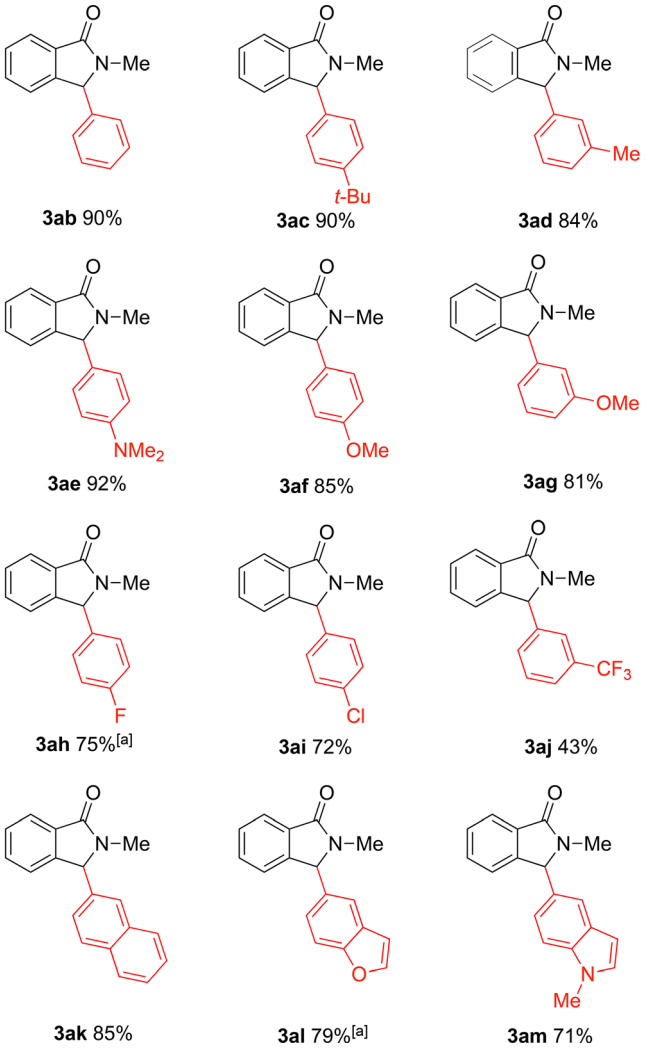
Entry	Base	**1a**:**2a**:base	Solvent	Yield[a] [%]
1	LiO-*t*-Bu	1:1:2	1,4-dioxane	19
2	NaO-*t*-Bu	1:1:2	1,4-dioxane	71
3	KO-*t*-Bu	1:1:2	1,4-dioxane	58
4	$LiN(SiMe_3)_2$	1:1:2	1,4-dioxane	79
5	$NaN(SiMe_3)_2$	1:1:2	1,4-dioxane	98
6	$KN(SiMe_3)_2$	1:1:2	1,4-dioxane	68
7	$NaN(SiMe_3)_2$	1:1:1.5	1,4-dioxane	95 (91)[b]
8	$NaN(SiMe_3)_2$	1:1:1.5	1,4-dioxane	89[c]
9	$NaN(SiMe_3)_2$	1:1:1.5	1,4-dioxane	0[d]

[a] Yields determined by ^{1}H NMR analysis of unpurified reaction mixtures with internal standard CH_2Br_2.
[b] Isolated yield.
[c] Reaction time 3 h.
[d] Reaction at room temperature.

Table 2. DCCP of *N*-methylisoindolinone **1a** with various aryl bromides **2**.



1a 2 3



3ab 90% **3ac** 90% **3ad** 84%
3ae 92% **3af** 85% **3ag** 81%
3ah 75%[a] **3ai** 72% **3aj** 43%
3ak 85% **3al** 79%[a] **3am** 71%

[a] 2 equiv. of $NaN(SiMe_3)_2$ were used.

coupling partner, furnishing **3ad** in 84% yield. Aryl bromides bearing electron-donating groups, such as 4-*N*,*N*-dimethylamino and 4-methoxy resulted in cross-coupling products **3ae** and **3af** in 92–85% yield. 3-Bromoanisole generated the coupling product **3ag** in 81% yield. The cross-coupling reactions with aryl bromides bearing electron-withdrawing 4-fluoro and 4-chloro exhibited good yields of **3ah** (75%) and **3ai** (72%). 3-Bromobenzotrifluoride provided the arylated product **3aj** in 43% yield. Other substrates, such as 2-bromobenzofuran, 2-bromonaphthalene and *N*-methyl-5-bromoindole, also showed good reactivity, furnishing the products **3ak–3am** in 71–85% yield.

We next turned our attention to the substrate scope of isoindolinone derivatives with electron-donating 4-bromoanisole and electron-withdrawing 1-bromo-4-chlorobenzene (Table 3). In general, *N*-ethylisoindolinone (**1b**) exhibited good reactivity, affording the corresponding products **3bf** and **3bi** in 85 and 80% yield, respectively. The *N*-benzylisoindolinone **1c** furnished the products **3cf** and **3ci** in 93 and 91% yield. It is noteworthy that in the arylation of *N*-benzylisoindolinone (**1c**) no arylation of the *N*-benzyl group was observed. The *N*-methyl 6-methyl derivative (**1d**) provided coupling products **3df** and **3di** in 76 and 69% yield, respectively. 6-Chloro-*N*-methylisoindolinone (**1e**) proved to be more challenging, affording the products **3ef** and **3ei** in 57 and 47% yield, respectively. The origin of the reduced yield is most likely due to the proximity of the chloride to the carbonyl group, which will activate the chloride to oxidative addition. We have previously demonstrated that the (NIXANTPHOS)Pd catalyst can activate aryl chlorides, even at room temperature.[8a] Unfortunately, *N*-methyl-5-methoxyisoindolinone (**1f**) resulted in low yields when using $NaN(SiMe_3)_2$ under our standard conditions. It was, therefore, necessary to perform additional optimization, which revealed that use of 2 equiv. of $LiN(SiMe_3)_2$ in 1,4-dioxane at 50 °C with 4-bromotoluene led to the product **3fa** in 70% yield.

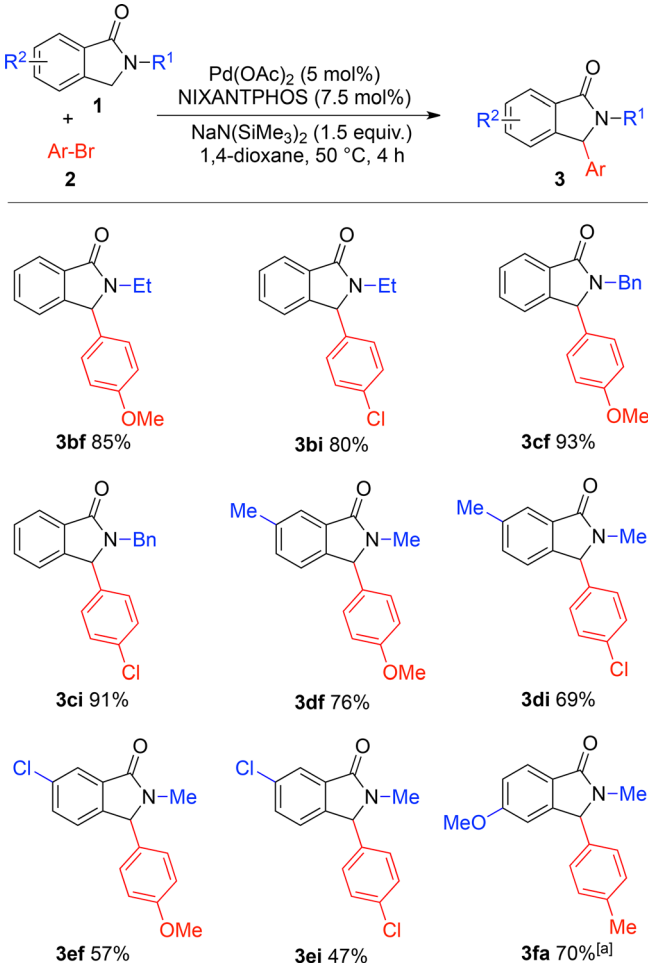
Recently, Hardcastle and co-workers[15] reported that the 3-aryl-3-alkoxyisoindolinone scaffold exhibits promising antitumor activity through interaction with MDM2-p53. We therefore set out to develop a one-pot arylation/oxidation approach to access the core structure of 3-aryl-3-hydroxyisoindolinone. We envisioned that conducting our arylation of isoindolinones in the presence of additional base could be followed by exposure of the resulting 3-arylisoindolinone to air.[27l,28] The excess base was anticipated to deprotonate the isoindolinone product and the resulting anion would react with dioxygen in the air to generate the oxidized core.

When the arylation reaction of *N*-methylisoindolinone (**1a**) with 4-bromotoluene (**2a**) was conducted with 3.0 equiv. of $NaN(SiMe_3)_2$ the arylation proceeded to completion, as determined by TLC. The reaction mixture was then cooled to room temperature and exposed to air for 2 h. Work-up and analysis of the reaction products indicated complete conversion of the arylated intermediate to the oxidation product, 3-aryl-3-hydroxy-*N*-methylisoindolinone.

Next, a series of tandem arylation/oxidation reactions was performed (Table 4). The cross-coupling of *N*-methylisoindolinone (**1a**) with electron neutral aryl bromides **2a–d** followed by air oxidation exhibited good reactivity, generating the products **4aa–4ad** in 77–89% yield. Aryl bromides bearing electron-donating and electron-withdrawing groups such as 4-*N*,*N*-dimethylamino, 4-methoxy, 3-methoxy, 4-fluoro and 4-chloro resulted in the desired products **4ae–4ai** in 61–87% yield. The key core structure in the study by Hardcastle et al.[15] could be accessed by coupling of the *N*-benzylisoindolinone (**1c**) with 4-chlorobromobenzene followed by oxidation. Using the one-pot procedure, *N*-benzyl-3-(4-chlorophenyl)-3-hydroxyisoindolinone (**4ci**) was generated in 71% yield.

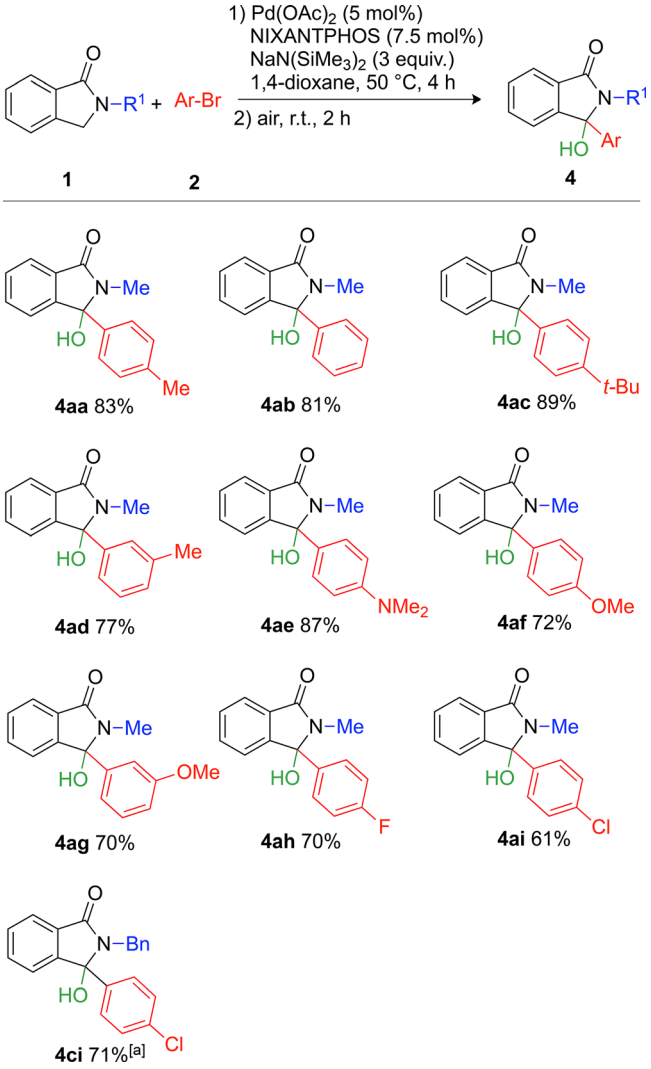
To diversify the isoindolinone core structures accessible *via* one-pot tandem reactions initiated with ary-

Table 3. DCCP of isoindolinones **1** with aryl bromides **2**.



[a] 2 equiv. of $LiN(SiMe_3)_2$ were used.

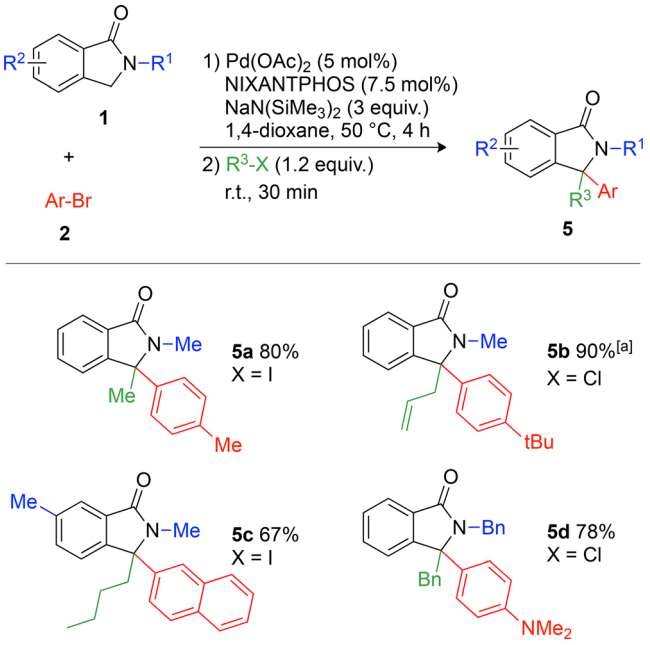
Table 4. DCCP of isoindolinones **1** with various aryl bromides **2** and tandem oxidation with air.



[a] 2.0 equiv. of $LiN(SiMe_3)_2$ were used.

lation, we next explored use of various electrophiles. Thus, following the approach in Table 4, the arylation was performed, but instead of adding oxygen, different alkyl halides were injected into the reaction mixtures under nitrogen at room temperature. To our satisfaction we obtained the arylation/alkylation products **5** in moderate to high yields (67–90%, Table 5). Arylation of *N*-methylisoindolinone (**1a**) with 4-bromotoluene in the presence of 3 equiv. of $NaN(SiMe_3)_2$ was followed by treatment with methyl iodide to generate the methylated adduct containing a quaternary center (**5a**) in 80% yield. Similarly, arylation of **1a** with 4-*tert*-butylbromobenzene using 3 equiv. of $LiN(SiMe_3)_2$ followed by reaction with allyl chloride provided the allylated adduct in 90% yield. Employing the *N*-methyl-6-methylisoindolinone (**1d**) with 2-bromonaphthalene and $NaN(SiMe_3)_2$ followed by *n*-

Table 5. DCCP of isoindolinones with aryl bromides and tandem alkylation.



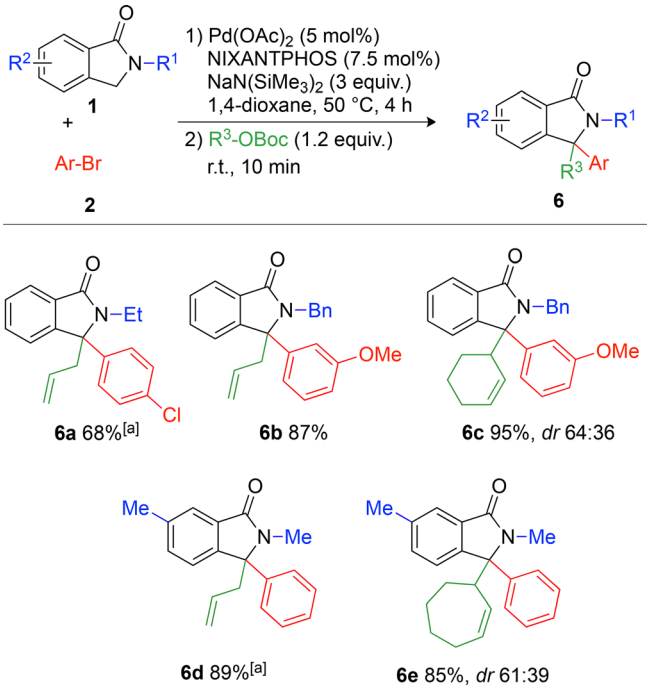
[a] 3.0 equiv. of $LiN(SiMe_3)_2$ were used.

butyl iodide furnished the alkylated product in 67% yield. *N*-Benzylisoindolinone (**1c**) was arylated using $NaN(SiMe_3)_2$ and 4-bromo-*N,N*-dimethylaniline with subsequent treatment with benzyl chloride to give the benzylation product **5d** in 78% yield. The successful generation of these compounds *via* substitution reactions inspired us to consider other methods to functionalize the arylated isoindolinone intermediates, including metal-catalyzed processes.

Given that the Pd-based catalyst promotes deprotonative cross-coupling reactions, we envisioned reusing this catalyst in the second step of the tandem reaction. We therefore focused on the Tsuji–Trost reactions using different allylic electrophiles. As such, once the reactions between isoindolinones **1** and aryl bromide **2** reached completion, as judged by TLC, allylic carbonates were added at room temperature. We were surprised to find that the palladium-catalyzed allylic substitution was completed in 10 min, as judged by TLC (Table 6). The allyl *tert*-butyl carbonate furnished the arylation/allylation products **6a**, **6b** and **6d** in moderate to good yields (68–89%, Table 6). The cyclic allylic alcohol derivatives were also good substrates in the arylation/allylation reaction. The *tert*-butyl cyclohex-2-en-1-yl carbonate provided the product **6c** in 95% yield with a diastereomeric ratio of ~2:1 and *tert*-butyl cyclohept-2-en-1-yl carbonate provided the product **6e** in 85% yield with a similar diastereomeric ratio (Table 6).

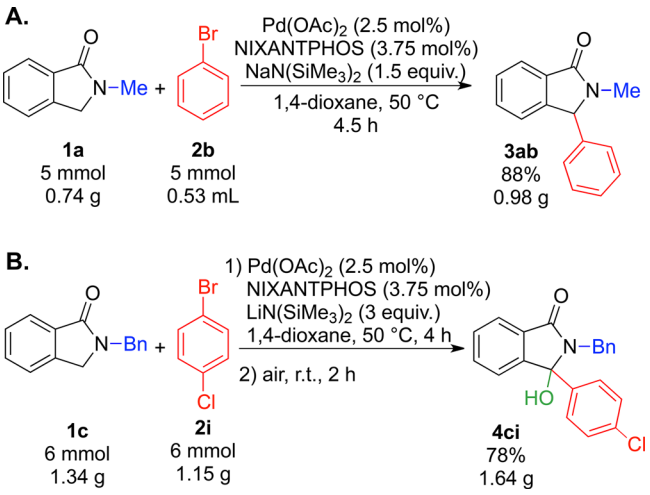
We examined the scalability of our method by performing the arylation reaction of *N*-methylisoindoli-

Table 6. DCCP of isoindolinones with aryl bromides and allylation in a one-pot procedure.



[a] 2.0 equiv. of $LiN(SiMe_3)_2$ were used.

none (**1a**) with bromobezene **2b** on a 5 mmol scale in the presence of 2.5 mol% $Pd(OAc)_2$ and 3.75 mol% of NIXANTPHOS. This procedure afforded the coupling product **3ab** in 88% isolated yield (0.98 g, Scheme 4A). We also performed the arylation reaction of *N*-benzylisoindolinone (**1c**) with 4-chlorobromobenzene **2i** on a 6 mmol scale in the presence of 2.5 mol% $Pd(OAc)_2$ and 3.75 mol% of NIXANTPHOS followed by air oxidation in a one-pot procedure, which furnished the product **4ci** in 78% isolated yield (1.64 g, Scheme 4B). It is noteworthy that both



Scheme 4. Gram scale cross-coupling of isoindolinones.

these reactions were conducted with a 1:1 ratio of the pronucleophiles (isoindolinone) to aryl bromide, demonstrating the high efficiency of these reactions.

Conclusions and Outlook

In summary, we have developed the first direct palladium-catalyzed C(sp^3)–H arylation of substituted isoindolinones with various aryl bromide *via* a deprotonative cross-coupling process (DCCP). In addition, the arylated products can be further transformed into oxidized, alkylated or allylated products in one-pot procedures in good yields. It is noteworthy that our protocol for the tandem arylation/oxidation allows the generation of isoindolinone derivatives that are the key intermediate for the synthesis of promising lead compounds that display interesting antitumor activity.

Experimental Section

General Methods

All reactions were conducted under an inert atmosphere of dry nitrogen. Anhydrous 1,4-dioxane and cyclopentyl methyl ether (CPME) were purchased from Sigma–Aldrich and used without further purification. Dimethoxyethane (DME) dichloromethane, and tetrahydrofuran (THF) were dried through activated alumina columns under nitrogen. Other solvents were commercially available and used as received. Chemicals were purchased from Sigma–Aldrich, Acros, Fisher Scientific or Matrix Scientific and solvents were obtained from Fisher Scientific. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light. Silica gel (Silicaflash, P60, 40–63 μm, Silicycle) was used for air-flashed chromatography. NMR spectra were obtained using a Bruker 500 MHz Fourier-transform NMR spectrometer at the University of Pennsylvania NMR facility. ^1H and ^{13}C NMR chemical shifts in parts per million (δ) were referenced to internal tetramethylsilane (TMS). The infrared spectra were obtained with KBr plates using a Perkin–Elmer Spectrum 1600 Series spectrometer. High-resolution mass spectrometry (HR-MS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

Preparation of $Pd(OAc)_2$/NIXANTPHOS Stock Solution

An oven-dried 20-mL vial with a stir bar under a nitrogen atmosphere was charged with $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), NIXANTPHOS (82.7 mg, 0.15 mmol) and 1,4-dioxane (10 mL). The solution was stirred for 5 min before

use. 1.0 mL of the stock solution was used for 0.2 mmol scale reactions

General Procedure for the Arylation of Isoindolinone

An oven-dried microwave vial equipped with a stir bar was charged with isoindolinone (0.20 mmol) and $NaN(SiMe_3)_2$ (55.0 mg, 0.3 mmol) under a nitrogen atmosphere. The stock solution (1.0 mL) of $Pd(OAc)_2$ (5.0 mol%) and NIXANTPHOS (7.5 mol%) in 1,4-dioxane were added to the reaction vial. The vial was sealed with a cap and the solution was stirred at room temperature for 5 min. Aryl bromide (0.20 mmol) was added to the solution. Note that solid aryl bromides were added to the reaction vial prior to $NaN(SiMe_3)_2$. The vial was removed from the glove box, and heated to 50 °C in an oil bath with stirring for 4 h. The sealed vial was cooled to room temperature and stirred for 5 min. Water (3 drops) was added to the vial. The reaction mixture was then diluted with diethyl ether (2 mL) and filtered over a short pad of Celite. The pad was rinsed with additional diethyl ether (5 mL) and the solvent was removed under reduced pressure to yield a viscous oil. The crude material was purified by flash column chromatography.

General Procedure for the Tandem Arylation/Oxidation

To an oven-dried microwave vial equipped with a stir bar was charged with isoindolinone (0.20 mmol) and $NaN(SiMe_3)_2$ (110.0 mg, 0.6 mmol) under a nitrogen atmosphere. The stock solution (1.0 mL) of $Pd(OAc)_2$ (5.0 mol%) and NIXANTPHOS (7.5 mol%) in 1,4-dioxane were added to the reaction vial. The vial was sealed with a cap and the solution was stirred at room temperature for 5 min. Aryl bromide (0.20 mmol) was added to the solution. Note that solid aryl bromides were added to the reaction vial prior to $NaN(SiMe_3)_2$. The sealed vial was removed from the glove box and heated to 50 °C in an oil bath with stirring for 4 h. The sealed vial was cooled to room temperature and stirred for 5 min. The vial was opened to air and stirred for 2 h. To the vial was added 3 drops of water and the reaction mixture was diluted with diethyl ether (2 mL) and filtered over a short pad of Celite. The pad was rinsed with additional diethyl ether (5 mL) and the solvent was removed under reduced pressure to yield a viscous oil. The crude material was purified by flash column chromatography.

General Procedure for the Tandem Arylation/Alkylation

To an oven-dried microwave vial equipped with a stir bar was charged isoindolinone (0.20 mmol) and $NaN(SiMe_3)_2$ (110.0 mg, 0.6 mmol) under a nitrogen atmosphere. 1.0 mL of the stock solution of $Pd(OAc)_2$ (5.0 mol%) and NIXANTPHOS (7.5 mol%) in 1,4-dioxane were added to the reaction vial. The vial was sealed with a cap and the solution was stirred at room temperature for 5 min. Aryl bromide (0.20 mmol) was added to the solution. Note that solid aryl bromides were added to the reaction vial prior to $NaN(SiMe_3)_2$. The vial was removed from the glove box, and heated to 50 °C in an oil bath with stirring for 4 h. The sealed vial was cooled to room temperature and stirred for 5 min. The alkyl halide (0.24 mmol) was taken up by a syringe and added to the reaction vial through the cap. The reaction mixture was stirred for 30 min at room temperature. Next, water (3 drops) was added to the vial. The reaction mixture was diluted with diethyl ether (2 mL) and filtered over a short pad of Celite. The pad was rinsed with additional diethyl ether (5 mL) and the solvent was removed under reduced pressure to yield a viscous oil. The crude material was purified by flash column chromatography.

General Procedure for the Tandem Arylation/Allylic Substitution

To an oven-dried microwave vial equipped with a stir bar was charged isoindolinone (0.20 mmol) and $LiN(SiMe_3)_2$ (100.4 mg, 0.6 mmol) or $NaN(SiMe_3)_2$ (110.0 mg, 0.6 mmol) under a nitrogen atmosphere. The stock solution (1.0 mL) of $Pd(OAc)_2$ (5.0 mol%) and NIXANTPHOS (7.5 mol%) in 1,4-dioxane were added to the reaction vial. The vial was sealed with a cap and the solution was stirred at room temperature for 5 min. Aryl bromide (0.20 mmol) was added to the solution. Note that if the aryl bromide was a solid, it was added to the reaction vial prior to $NaN(SiMe_3)_2$. The sealed vial was removed from the glove box and heated to 50 °C with stirring in an oil bath for 4 h. The sealed vial was cooled to room temperature and stirred for 5 min. Allyl *tert*-butyl carbonate (0.24 mmol) was taken up by a syringe and added to the reaction vial through the cap. The reaction mixture was stirred for 10 min. Water (3 drops) was added to the vial. The reaction mixture was diluted with diethyl ether (2 mL) and filtered over a short pad of Celite. The pad was rinsed with additional diethyl ether (5 mL) and the solvent was removed under reduced pressure to yield a viscous oil. The crude material was purified by flash column chromatography.

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10 Tandem C(sp^3)–H Arylation/Oxidation and Arylation/Allylic Substitution of Isoindolinones

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