

Cascade Reactions

Palladium-Catalyzed Cascade Reaction for the Synthesis of Substituted Isoindolines**

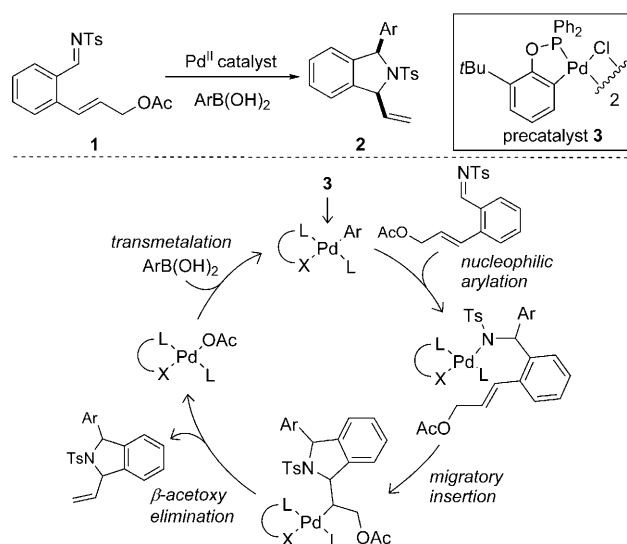
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Isoindoline heterocycles have demonstrated potential in medicinal chemistry as they exhibit activity across diverse biological targets. They are present in molecules which act as bronchodilators, *N*-methyl-D-aspartate agonists, multidrug resistance reversal agents, and fibrinogen receptor antagonists.^[1] While several approaches to the synthesis of unsubstituted or monosubstituted isoindolines have been reported,^[2] few methods exist to produce disubstituted isoindolines with high diastereoselectivity.^[3] In addition, there are no diastereoselective methods for the synthesis of 1,3-disubstituted isoindolines that allow for incorporation of readily available boronic acids, which are practical building blocks in medicinal chemistry. Synthetic methods for isoindoline synthesis that provide straightforward introduction of substituents on the heterocycle would enable preparation of families of biologically significant compounds.

We designed a cascade sequence for isoindoline synthesis that we anticipated could be catalyzed by a palladium(II) complex and would utilize boronic acids as a starting material (Scheme 1). The cascade reaction would initiate with arylation of imine **1**.^[4] The resultant sulfonamide would engage the pendant allylic acetate by aminopalladation; β -acetoxy elimination would release the isoindoline product.^[5,6]

A major challenge was identification of a catalyst with the appropriate electronic balance to facilitate all steps in the catalytic cycle. While nucleophilic arylation of imines requires electron-donating ligands,^[4] migratory insertion is generally promoted by palladium(II) catalysts with electrophilic character.^[7] We selected phosphinite palladacycle **3**, which is a catalyst with demonstrated activity for arylation of imines,^[4b] with the thought that the π -accepting phosphonite would balance σ donation from the aryl group.^[8] In practice, we have found this complex to be an effective catalyst for our cascade sequence (see below).

We began our investigation with reaction conditions similar to those employed for imine arylation.^[4b] At room



Scheme 1. Proposed synthesis of isoindoline derivatives. L = ligand, Ts = 4-toluenesulfonyl.

temperature, in the presence of catalyst **3**, effective arylation of **1** with phenyl boronic acid occurs (Table 1, entry 1). Elevated reaction temperatures promote the cyclization reaction (Table 1, entry 2; Method A). Notably, isoindoline **2** is generated as a single diastereomer under these reaction conditions.

Table 1: Optimization of reaction conditions for cascade cyclizations.

Entry	ArBX ₂ (equiv)	T [°C]	Method	t [h]	Yield [%] ^[a]		
					2	4	5
1 ^[b]	PhB(OH) ₂ (1)	23	–	48	< 5	85	< 5
2	PhB(OH) ₂ (1)	80	A	24	93	< 5	7
3	(PhBO) ₃ (0.5)	80	–	24	43	23	> 5
4	(PhBO) ₃ (0.5)	110	B	10	90	< 5	< 5
5	2-naphthyl-B(OH) ₂ (1)	80	A	19	35	10	30
6	2-naphthyl-B(OH) ₂ (1)	80	A	7	57	12	22
7	(2-naphthyl-BO) ₃ (0.5)	110	B	10	79	< 5	16
8	(<i>m</i> -BnOC ₆ H ₄ BO) ₃ (0.5)	110	B	10	23	< 5	7
9 ^[c]	(<i>m</i> -BnOC ₆ H ₄ BO) ₃ (0.5)	110	C	2	67	< 5	5

[a] Determined by ¹H NMR spectroscopy of aliquots taken from the reaction mixture utilizing Ph₂SiMe₂ as an internal standard. [b] Relative ratio of products to starting material reported. [c] 2 equiv of CsF added. Bn = benzyl.

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To develop robust conditions for the cascade reaction, we optimized the reaction conditions for two additional boronic acid partners.^[9] We found that the initial conditions (Method A) worked well for electron-rich aryl boronic acids. However, reactions of electron-neutral and electron-poor aryl boronic acids suffered from competitive hydrolysis of the imine. We utilized aryl boroxines, the anhydrous trimer of boronic acids, to minimize competitive hydrolysis (Table 1, entry 7; Method B). Despite reduced hydrolysis, certain electron-poor aryl boroxines still provided slow reaction rates and, under prolonged reaction times, decomposition of the isoindoline occurred (Table 1, entry 8). We examined a series of additives thought to accelerate transmetalation events and found that CsF accelerated reactions of particularly sluggish boroxines and avoided the formation of decomposition products (Table 1, entry 9; Method C).

Good yields of isoindoline compounds incorporating a variety of substituted boronic acid derivatives were obtained with excellent diastereoselectivity (Table 2). For electron-rich aryl boronic acids as well as certain electron-neutral aryl boronic acids, our original conditions at 80 °C were quite successful (Method A; Table 2, entries 1–3). For example, ether-substituted boronic acids reacted smoothly under these conditions. When hydrolysis was a problem with an electron-neutral aryl boronic acid, the corresponding boroxine was used, and the reaction was run at an elevated temperature (Method B; Table 2, entries 4, 5, and 7). Finally, if an electron-poor aryl boron partner was needed, the corresponding boroxine was used with added cesium fluoride to increase the reaction rate (Method C; Table 2, entries 6, 8, and 9). Halide- and trifluoromethyl-substituted boroxines afforded good yields of product under these reaction conditions.

All of the isoindoline products shown in Table 2 were formed with high diastereoselectivity for the *cis* isomer. We hypothesized that the *cis* isoindoline was lower in energy than the *trans* isoindoline as that isomer minimized steric interactions between the sulfonamide group and isoindoline substituents.^[10] To determine the relative stabilities of the diastereomers we performed DFT calculations using B3LYP/6-311G(d) to identify an energy difference between the lowest energy *cis* product conformer and the lowest energy *trans* product conformer.^[11] The *cis*-**2a** product was calculated to be 3 kcal mol^{−1} lower in energy than the *trans*-**2a**. Therefore, the major product formed is indeed the more stable diastereomer. Resubjection of the *trans* diastereomer of **2h** to the reaction conditions resulted in partial isomerization back to the *cis* diastereomer. These results indicate thermodynamic control of product distribution.^[12]

We sought to determine whether or not this reaction would be capable of preparing tetrahydroisoquinoline compounds. Imine **6** was designed to undergo cascade cyclization to provide 1-aryl-3-vinyl-tetrahydroisoquinoline **7**. Under our standard reaction conditions, arylation of the imine preceded smoothly, however, the reaction stalled and cyclization was not observed. We hypothesized that while the palladacycle may be capable of catalyzing migratory insertion to form a five-membered ring, formation of a six-membered ring would be more challenging and could require a more electrophilic catalyst. We examined alternative catalysts for the cyclization

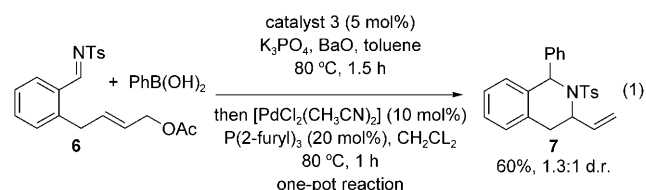
Table 2: Scope of isoindoline synthesis.

Reaction scheme showing the synthesis of **(±)-2** from **1** and ArBX_2 using catalyst **3** (5 mol%), K_3PO_4 (1 equiv), BaO (2 equiv), toluene, Method A, B or C.

Entry	Ar	Method ^[a]	<i>t</i> [h]	2	Yield [%] ^[b]	d.r. ^[c]
1	R = OMe	A	24	2a	74	> 20:1
2	R = OBn	A	11	2b	73	> 20:1
3	R = CH ₂ OtBu	A	12	2c	66	> 20:1
4	R = H	B	6	2d	82	20:1
5	R = Ph	B	6	2e	60	> 20:1
6	R = CF ₃	C	1	2f	54	18:1
7		B	10	2g	83	> 20:1
8		C	2	2h	72	11:1
9		C	2	2i	64	14:1

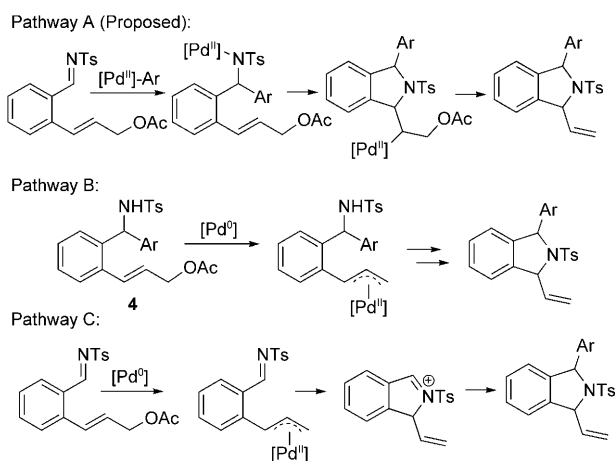
[a] All reactions were performed in sealed vials with [1] = 66 mm. Method A: 1 equiv of ArB(OH)₂, 80 °C; Method B: 0.5 equiv of (ArBO)₃, 110 °C; Method C: 0.5 equiv of (ArBO)₃, 2 equiv of CsF, 110 °C. [b] Yield of isolated product after column chromatography on silica gel. [c] Determined by ¹H NMR spectroscopy.

and β-acetoxy elimination steps. We found that addition of [PdCl₂(CH₃CN)₂] and P(2-furyl)₃ resulted in good yields of the desired tetrahydroisoquinoline **7** [Eq. (1)].^[13] The reaction



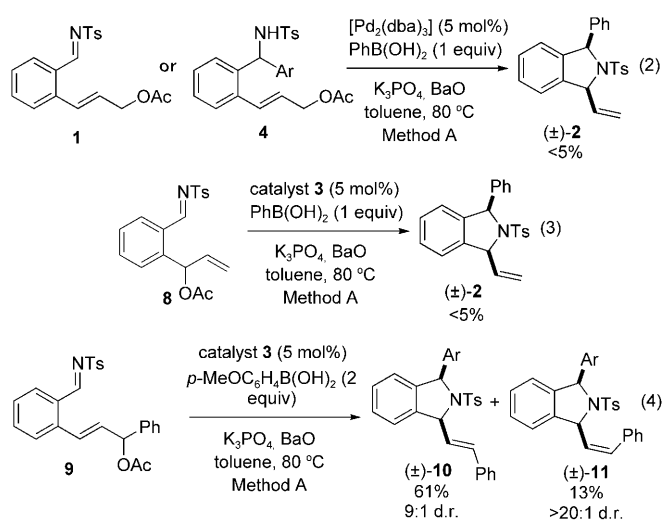
could be performed in one reaction flask by simply adding the second catalyst directly to the reaction after the arylation step was complete. While the diastereoselectivity of this reaction is modest, formation of the more challenging six-membered ring heterocycle is noteworthy.

Our development of the isoindoline-forming reaction was influenced by our mechanistic rationale (Scheme 1), however, we recognized that alternative mechanisms could also be viable. In the proposed mechanism, the catalyst remains in the palladium(II) oxidation state throughout the transformation (Scheme 2, Pathway A). However, alternative mechanisms involving oxidative addition of a palladium(0) catalyst with the allylic acetate could also lead to product formation. Two likely alternative mechanisms are outlined (Pathway B and C).^[14] In Pathway B, palladium-catalyzed imine arylation provides sulfonamide **4**. Subsequent formation of a π-allylpalladium(II) intermediate and intramolecular attack by the sulfonamide generates the heterocycle. Pathway C involves formation of a π-allylpalladium(II) intermediate, attack of the imine nitrogen to form an iminium ion, and capture by a nucleophilic aryl species.



Scheme 2. Possible mechanism for annulation.

To distinguish between the proposed mechanism of the cascade sequence (Pathway A) and alternative mechanisms involving oxidative addition into the allylic acetate (Pathway B and C), we designed a series of experiments (Scheme 3). While no one experiment conclusively rules out



Scheme 3. Mechanistic experiments. dba = *trans,trans*-dibenzylideneacetone.

alternative Pathways B or C, taken as a whole, the experiments in Scheme 3 are most consistent with Pathway A and make mechanisms involving π -allylpalladium intermediates unlikely. First, we performed a series of reactions using a palladium(0) catalyst and either imine **1** or sulfonamide **4** as starting materials [Scheme 3, Eq. (2)].^[15] All reactions were run under our standard reaction conditions. In contrast to reactions using catalyst **3**, when $[\text{Pd}_2(\text{dba})_3]$ was employed as the catalyst no discernable isindoline **2** was generated. These results are consistent with mechanisms that do not involve oxidative addition by a palladium(0) catalyst.

For further information concerning the viability of π -allylpalladium intermediates in the reaction, we synthesized

branched allylic acetate **8** [Scheme 3, Eq. (3)]. If Pathway B or C is operative, and the reaction proceeds through a π -allylpalladium intermediate, both **1** and **8** should provide similar yields of the desired isindoline **2**. However, isindoline **2** cannot be formed from **8** according to Pathway A. Upon subjecting branched allylic acetate **8** to our standard reaction conditions employing catalyst **3**, less than 5% isindoline **2** was formed [Scheme 3, Eq. (3)]. This data is inconsistent with Pathways B and C and supports reaction via Pathway A.

To obtain additional evidence to distinguish between alternative mechanisms we designed a positive control where reaction according to Pathway A would provide a different product than reaction along Pathway B or C [Scheme 3, Eq. (4)]. Imine **9** would undergo cascade cyclization according to Pathway A to provide a mixture of *E*- and *Z*-olefin isomers (**10** and **11**) because both aminopalladation and β -acetoxy elimination proceed stereospecifically.^[5,6] However, if Pathway B or C is operative, attack on the π -allylpalladium(II) intermediate would result in exclusive formation of the thermodynamically favored olefin isomer, **10**.^[13] Under the standard reaction conditions, imine **9** afforded a 4.7:1 mixture of *E*- and *Z*-olefin isomers.^[16] Although the *Z* isomer was formed as the minor product, its appearance provides evidence that Pathway A is operative. In addition to providing insight into the proposed mechanism, this reaction demonstrates that substitution on the allylic acetate is tolerated in the reaction.

In conclusion, we report a palladium-catalyzed cascade reaction that affords *cis*-1,3-disubstituted isindolines. A range of electron-rich and electron-poor aryl boronic acid derivatives participate. In addition, isindoline products contain a new terminal olefin, thus providing a functional handle for future derivatization. The method is also amenable to reactions of substituted allylic acetates and the synthesis of tetrahydroisoquinoline compounds. Mechanistic experiments are consistent with palladium(II) catalysis where the key C–N bond-forming event occurs by aminopalladation of a pendant olefin.

Experimental Section

Standard procedure for Method A: In a glove box, a vial equipped with a stir bar and septum was charged with **1** (36 mg, 0.10 mmol, 1.0 equiv), catalyst **3** (4.4 mg, 0.0046 mmol, 0.046 equiv), K_3PO_4 (21 mg, 0.10 mmol, 1.0 equiv), and BaO (30 mg, 0.20 mmol, 2.0 equiv). Outside of the glove box aryl boronic acid (0.20 mmol, 2.0 equiv) was added to the vial, followed by an inlet for positive pressure of N_2 . Toluene (1.5 mL) was added, the N_2 inlet was removed and the vial was placed in an 80 °C bath. Once the reaction was complete (as evident by TLC), the reaction mixture was directly purified by column chromatography on silica gel (0–15% EtOAc/hexanes).

Standard procedure for Method B: In a glove box, a vial equipped with a stir bar and septum was charged with **1** (36 mg, 0.10 mmol, 1.0 equiv), catalyst **3** (4.4 mg, 0.0046 mmol, 0.046 equiv), boroxine (0.050 mmol, 0.50 equiv), K_3PO_4 (21 mg, 0.10 mmol, 1.0 equiv), and BaO (30 mg, 0.20 mmol, 2.0 equiv). The vial was brought out of the glove box, and toluene (1.5 mL) was added under positive pressure of N_2 . The N_2 inlet was removed and the vial was set to stir in a 110 °C bath and monitored by TLC. Once the reaction was

complete (as evident by TLC), the reaction mixture was directly purified by column chromatography on silica gel (0–15 % EtOAc/hexanes).

Standard procedure for Method C: In a glove box, a vial equipped with a stir bar and septa cap was charged with **1** (36 mg, 0.10 mmol, 1.0 equiv), catalyst **3** (4.4 mg, 0.0046 mmol, 0.046 equiv), boroxine (0.050 mmol, 0.50 equiv), K₃PO₄ (21 mg, 0.10 mmol, 1.0 equiv), BaO (30 mg, 0.20 mmol, 2.0 equiv), and CsF (30 mg, 0.20 mmol, 2.0 equiv). The vial was brought out of the glove box, and toluene (1.5 mL) was added under positive pressure of N₂. The N₂ inlet was removed and the vial was set to stir in a 110 °C bath and monitored by TLC. Once the reaction was complete (as evident by TLC), the reaction mixture was directly purified by column chromatography on silica gel (0–15 % EtOAc/hexanes).

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- [15] In the presence or absence of phosphonite ligand, isoindoline **2** was formed in lower yields when using a palladium(0) catalyst than when using catalyst **3**. Representative experiments are shown in Scheme 3, see the Supporting Information for more detail.
- [16] The major diastereomers of **10** and **11** were assumed to be *cis* in analogy to isoindolines **2**.