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Synthesis of 2-Substituted Indoles and Indolines via Suzuki−Miyaura Coupling/5-*endo-trig* Cyclization Strategies

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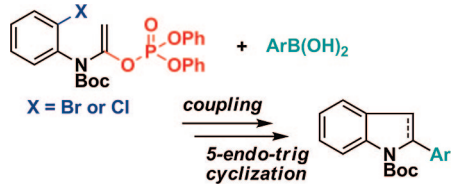

New strategies for the synthesis of 2-substituted indoles and indolines using acyclic, imide-derived enol phosphates, which were readily prepared from *o*-haloanilides, have been developed based on Suzuki−Miyaura coupling−cyclization sequences. A highly chemoselective cross-coupling of imide-derived enol phosphates with boron nucleophiles under Suzuki−Miyaura conditions allowed for the efficient preparation of various *N*-(*o*-halophenyl)enecarbamates that served as useful precursors for subsequent 5-*endo-trig* Heck or 5-*endo-trig* aryl radical cyclizations to furnish 2-substituted indoles or indolines, respectively. Furthermore, a one-pot Suzuki−Miyaura coupling−cyclization cascade starting from enol phosphates has been developed, which was successfully applied to the efficient synthesis of an indol-2-yl-1*H*-quinolin-2-one KDR inhibitor.

Introduction

Over the past two decades, palladium-catalyzed reactions have played a significant role in organic synthesis because of their tolerance of virtually all functional groups, the mild reaction conditions, and their anomalous ability to build up complex molecular architectures.[1] Enol triflates are widely used as substrates for palladium-catalyzed reactions because of their high reactivity as well as their availability from the corresponding carbonyl precursors. However, two major drawbacks of enol triflates are the need for expensive triflating reagents such as Tf_2O and $PhNTf_2$ for their preparation and the inherent instability problems. In this regard, enol phosphates are an attractive alternative to the corresponding triflates due to their sufficient stability and their low cost of preparation. Nonetheless, utilization of enol phosphates as electrophilic components in palladium chemistry has been less explored, and little is known about their reactivity profile and applicability in palladium-catalyzed reactions. Pioneering reports by Oshima and co-workers in the 1980s focused on the palladium-catalyzed cross-coupling of enol phosphates with trialkylaluminums as nucleophiles.[2] In addition, Kumada and his colleagues reported a palladium-catalyzed cross-coupling of enol phosphates with Me_3SiCH_2MgCl.[3] Later, the synthesis of functionalized, medium-sized heterocycles from lactone- or lactam-derived enol phosphates, which are known to readily participate in an oxidative addition to a triarylphosphane-ligated Pd(0) complex, was reported by the Nicolaou group.[4] Thereafter, a number of reports regarding the use of lactone- or lactam-derived enol phosphates in palladium-catalyzed reactions appeared.[5] Meanwhile, recent advances in this area have made it possible to employ ketone-derived, nonactivated enol phosphates in palladium-catalyzed reactions such as Heck, Suzuki−Miyaura, and Negishi. Begtrup

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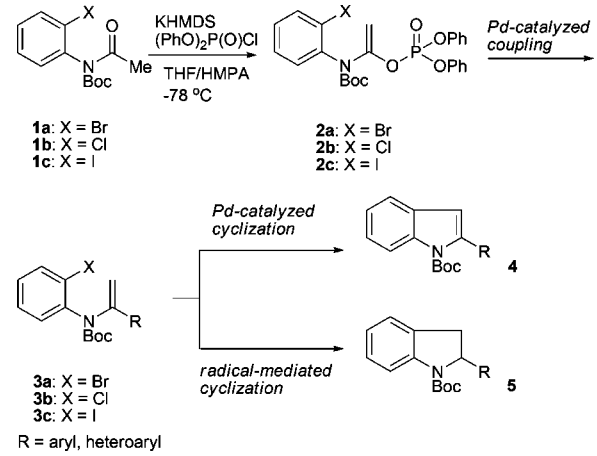
and co-workers have reported a palladium-catalyzed Suzuki−Miyaura coupling of an enol phosphate derived from *N*-(*tert*-butoxycarbonyl)-4-piperidone with arylboronic acids.[6] Very recently, Skrydstrup et al. described palladium-catalyzed Heck and Negishi couplings of nonactivated enol phosphates.[7,8]

We have independently reported the use of Suzuki−Miyaura coupling of lactone-derived enol phosphates for convergent synthesis of marine polycyclic ether natural products.[9,10] Our continuous efforts toward expanding the scope of palladium-catalyzed reactions of α-heteroatom-substituted enol phosphates have culminated in the development of some novel strategies for the synthesis of important heterocycles such as dihydropyrans and indoles.[11,12] We now report in detail our recently developed strategies for the synthesis of 2-substituted indoles and indolines starting from imide-derived enol phosphates, exploiting their unique reactivity profile in palladium-catalyzed reactions.[13,14] The most salient features of our strategies include (1) a highly chemoselective cross-coupling of imide-derived enol phosphates, readily prepared from *o*-haloanilides, with boron nucleophiles, and (2) generally disfavored 5-*endo-trig* Heck and 5-*endo-trig* aryl radical cyclizations. In addition, an efficient synthesis of an indol-2-yl-1*H*-quinolin-2-one KDR inhibitor based on our developed strategy is described.

Results and Discussion

Synthetic Strategies toward 2-Substituted Indoles and Indolines. Indole is a privileged structural motif that is widely found in biologically active natural products and pharmaceuticals.[15] 2-Substituted indoles, especially 2-aryl and 2-heteroaryl indoles, have frequently been utilized as a potential scaffold in the search for novel, biologically active small molecules.[16] Classical methods such as Fischer,[17] Reissert,[18] Madelung,[19] and Bischler−Möhlau[20] indole syntheses have commonly been adopted for the synthesis of 2-substituted indole derivatives. However, these synthetic methods often suffer from harsh reaction conditions and are of limited scope with regard to functional group compatibility. In contrast, palladium-catalyzed reactions have recently gained much attention due to their powerful ability to form C−C and C−N bonds as well as their mild reaction conditions that tolerate a wide range of functional groups.[21,22]

SCHEME 1. Strategies for the Synthesis of 2-Substituted Indoles 4 and Indolines 5



Our strategies for the synthesis of 2-substituted indoles and indolines starting from imide-derived enol phosphates are depicted in Scheme 1. Thus, a highly chemoselective cross-coupling of enol phosphates **2a**−**c**, which are readily derived from the corresponding imides **1a**−**c** by treatment with KHMDS and $(PhO)_2P(O)Cl$, would give enecarbamates **3a**−**c**. The palladium-catalyzed cyclization of **3a**−**c** would afford 2-substituted indole derivatives **4**. In contrast, 5-*endo-trig* aryl radical cyclization of **3a**−**c** would furnish 2-substituted indolines **5**, although this type of cyclization is generally disfavored according to Baldwin's rules.[23]

Synthesis of Imide-Derived Enol Phosphates. Imide-derived enol phosphates were synthesized starting from commercially available *o*-haloanilides (Scheme 2). Thus, anilides **6a**−**c** were reacted with Boc_2O/DMAP in THF at rt to deliver imides **1a**−**c**.[24] Treatment of **1a**−**c** with KHMDS in the presence of $(PhO)_2P(O)Cl$ afforded enol phosphates **2a**−**c**. These phosphates were stable enough to be isolated and purified by rapid flash

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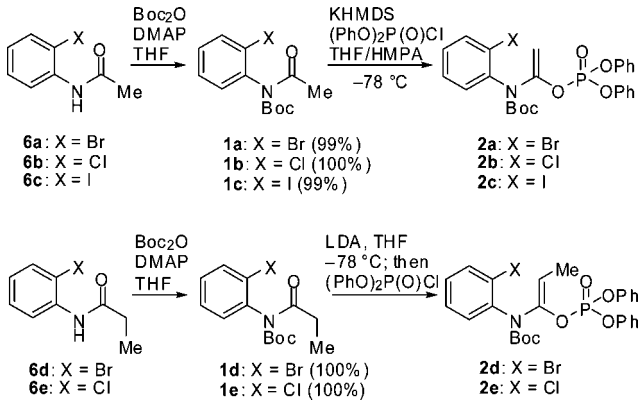
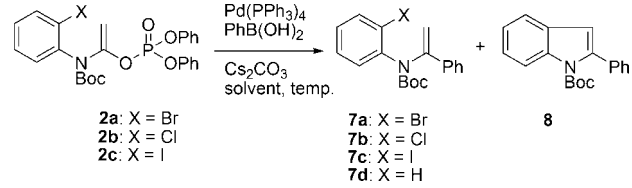
SCHEME 2. Preparation of Enol Phosphates 2a−e



chromatography on silica gel. However, in practice, the following Suzuki−Miyaura coupling reaction was performed without chromatographic purification of these phosphates. The enol phosphates **2d**,**e** were prepared from commercially available *o*-haloanilides **6d**,**e**. Thus, Boc protection of the amide moieties of **6d**,**e** gave the respective imides **1d**,**e**, which, upon treatment with LDA, followed by quenching with $(PhO)_2P(O)Cl$ in the presence of HMPA, afforded **2d**,**e**. The geometry of the double bond of **2d**,**e** was assumed to be *Z* since it is known that lithium enolates generated from acyclic amides by treatment with LDA generally exist as (*Z*)-enolates.[25]

Highly Chemoselective Cross-Coupling of Imide-Derived Enol Phosphates with Boron Nucleophiles. We first examined a chemoselective Suzuki−Miyaura coupling[26] of enol phosphates **2a**−**c** with 1.1 equiv of phenylboronic acid under various conditions (Table 1). When the reaction was performed using **2a**, $PhB(OH)_2$, 10 mol % of $Pd(PPh_3)_4$, and Cs_2CO_3 in 1,4-dioxane at 60 °C, the desired enecarbamate **7a** was isolated in 47% yield from **1a**, along with a considerable amount of indole

TABLE 1. Screening of Reaction Conditions[a]



				% yield	
entry	substrate	solvent	temp (°C)	**7**	**8**
1	**2a**	1,4-dioxane	60	**7a**: 47	24
2	**2a**	1,4-dioxane/H_2O	50	**7a**: 72	0
3	**2a**	THF/H_2O	50	**7a**: 85	0
4	**2a**	DMF/H_2O	50	**7a**: 90	0
5[b]	**2a**	DMF/H_2O	rt	**7a**: 52	0
6	**2b**	DMF/H_2O	50	**7b**: 100	0
7	**2c**	DMF/H_2O	50	**7c**: 0	0

[a] All reactions were performed using 10 mol % of $Pd(PPh_3)_4$, 1.1 equiv of $PhB(OH)_2$, and 3 equiv of Cs_2CO_3 for 1−7 h. Yields are overall from **1a**,**b**. [b] Na_2CO_3 was used as base.

8 (entry 1). To suppress the formation of **8**, we surveyed a series of reaction conditions and found that the addition of H_2O as a co-solvent dramatically increased the yield of **7a**. Thus, when we employed $Pd(PPh_3)_4$ as a catalyst and Cs_2CO_3 as a base in 1,4-dioxane/H_2O at 50 °C, the cross-coupling proceeded smoothly, giving **7a** in 72% overall yield from **1a** (entry 2). The yield of **7a** was improved when the reaction was carried out in THF/H_2O (entry 3). Further examination revealed that DMF/H_2O is the solvent of choice for the cross-coupling; a remarkable chemoselectivity was attained under these conditions, giving **7a** in 90% yield (entry 4). When the reaction was performed at rt, the yield of **7a** was moderate, indicating the necessity of mild heating (entry 5). In each case, a trace amount (<5%) of debrominated byproduct **7d** was also detected in the reaction mixture (entries 1−5). The aryl chloride **2b** was also successfully cross-coupled with phenylboronic acid under the optimized conditions, giving **7b** in quantitative yield (entry 6). The possible aryl−aryl, Suzuki−Miyaura coupling product was not observed in all the above cases.[27] On the other hand, the aryl iodide **2c** failed to undergo cross-coupling; it was observed that the $Pd(PPh_3)_4$ catalyst began to decompose within 30 min, and the desired product was not observed even after prolonged reaction times, giving instead a complex mixture of unidentified products (entry 7). Running the reaction at rt or at 80 °C did not lead to any improvement.

Palladium-Catalyzed Cyclization of *o*-Haloanilide-Derived Enecarbamates. We then investigated the palladium-catalyzed cyclization of **7a**, as summarized in Table 2. Although there are many examples of palladium-catalyzed cyclization of related enamines and enaminones,[28,29] the synthesis of 2-aryl and 2-heteroaryl indoles based on this strategy have been explored less thoroughly, and, to the best of our knowledge, the use of *N*-alkoxycarbonyl derivatives has not been reported. We initially performed the cyclization of **7a** using 10 mol % of $Pd(PPh_3)_4$

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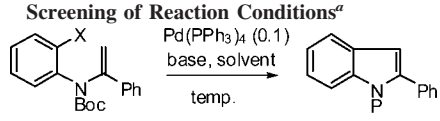
TABLE 2. Screening of Reaction Conditions[a]



7a: X = Br
7d: X = H

8: P = Boc

entry	base (equiv)	solvent	temp (°C)	yield (%)
1	K_2CO_3 (3)	DMF	100	48
2[b,c]	K_2CO_3 (3)	CH_3CN	80	71
3[b,c]	Et_3N (10)	DMF	100	76
4[b]	Et_3N (10)	DMF	100	94
5[b]	*i*-Pr_2NEt (10)	DMF	100	38
6	PMP (5)	DMF	100	18

[a] All reactions were carried out for 20−24 h, unless otherwise noted. [b] Reactions performed in a sealed tube. [c] *n*-Bu_4NCl (1 equiv) was used as an additive.

and K_2CO_3 as a base in DMF at 100 °C (Table 2, entry 1). The desired *N*-Boc-2-phenylindole **8**[21b] was isolated in 48% yield, and the major byproduct was the dehalogenated **7d** (22%). In contrast, under the Jeffery conditions using *n*-Bu_4NCl,[30] the desired product **8** was cleanly obtained in an improved 71% yield, and the formation of **7d** was completely suppressed (entry 2). When employing Et_3N instead of K_2CO_3 as a base, further improvement of the yield was attained (entries 3 and 4). Thus, exposure of **7a** to 10 mol % of $Pd(PPh_3)_4$ and Et_3N in DMF at 100 °C afforded **8** in 94% yield, with no detectable amount of **7d**. Changing the base to diisopropylethylamine (*i*-Pr_2NEt) or 1,2,2,6,6-pentamethylpiperidine (PMP) was found to be detrimental due to the significant dehalogenation (entries 5 and 6).

Utilization of aryl chloride **7b** in the palladium-catalyzed cyclization was next explored (Table 3). Recent reports have described the use of a Pd_2dba_3/X-Phos[31] (X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) catalyst system for the related cyclizations of *o*-chloroaniline-derived enamines.[29a,c] We, therefore, decided to employ a Pd_2dba_3/X-Phos catalyst system and screened bases and solvents. Upon treatment of **7b** with NaO*t*-Bu or KO*t*-Bu in toluene at 110 °C, the cyclization took place smoothly, but with complete loss of the Boc group, affording 2-phenylindole **9** (entries 1 and 2). Although the use of polar solvents such as DMF or DMA at an elevated temperature (>110 °C) gave unsatisfactory results, when the reaction was carried out using a Pd_2dba_3/X-Phos or $Pd(OAc)_2$/X-Phos catalyst system and K_2CO_3 as a base in 1,4-dioxane at 100 °C, the cyclization proceeded cleanly to give only the desired **8** in good yields (entries 3 and 4). However, high catalyst loading (30 mol % of Pd) and a prolonged reaction time (72 h) were necessary under these conditions. Although a combination of Pd_2dba_3/X-Phos and Cs_2CO_3 did not lead to any improvement (entry 5), the use of $Pd(OAc)_2$/X-Phos coupled with Cs_2CO_3 greatly enhanced the efficiency of the cyclization, giving **8** in nearly quantitative yield in a reasonable reaction time (24 h) with a practical level of catalyst loading (10 mol % of Pd) (entry 6). The results of entries 3−6 suggested the possibility that in situ formed CsOAc might accelerate the cyclization. However, a control experiment using a Pd_2dba_3/X-Phos catalyst system (10 mol % of Pd), Cs_2CO_3 (3 equiv) as a base, and CsOAc (80 mol %) as an additive in 1,4-dioxane at 100 °C resulted in only ca. 62% conversion after 24 h, indicating that CsOAc has no significant effect on the reaction rate. We also found that the reaction rate of the cyclization of **7b** using $Pd(OAc)_2$/X-Phos and Cs_2CO_3 in 1,4-dioxane could be significantly enhanced under microwave heating conditions (160 °C for 30 min), affording **8** in 87% yield (entry 7). Overall, the cyclization of aryl chloride **7b** was found to be best carried out using $Pd(OAc)_2$/X-Phos as a catalyst system and Cs_2CO_3 as a base in 1,4-dioxane at 100 °C (thermal heating) for 24 h or at 160 °C (microwave heating) for 30 min.[32]

Having secured reliable conditions for the cross-coupling and cyclization processes, the present strategy was applied to a variety of substrates, and the results are summarized in Table 4 and Scheme 3. Suzuki−Miyaura coupling of **2a**−**d** with a range of aryl and heteroaryl boronic acids proceeded without incident to give enecarbamates **10**−**18**. Compounds **17** and **18** existed as a complex mixture of isomers in C_6D_6 solution at rt (600 MHz ^1H NMR) due to the presence of the sterically restricted rotations around the nitrogen atom. Under the established conditions [$Pd(PPh_3)_4$, Et_3N, and DMF at 100 °C], cyclization reactions of aryl bromides **10a**, **11**, **12a**, **13**, and **14** were efficiently achieved, affording 2-aryl and 2-heteroaryl indoles **19**−**23** in good to excellent yields (entries 1−5). Aryl chlorides **10b**, **12b**, **15**, and **16** were also cleanly cyclized under the optimized conditions [$Pd(OAc)_2$/X-Phos (Pd/L = 1/2) and Cs_2CO_3 in 1,4-dioxane at 100 °C (thermal heating) or at 160 °C (microwave heating)] to provide 2-aryl indoles **19**, **21**, **24**, and **25**, respectively (entries 6−9). Thus, our strategy should be generally applicable to the synthesis of 2-aryl and 2-heteroaryl indole derivatives.

In contrast, our efforts to extend the strategy to the synthesis of 2,3-disubstituted indoles met with limited success. Upon exposure of aryl bromide **17** to $Pd(PPh_3)_4$ and Et_3N in DMF at 100 °C, the desired 2,3-disubstituted indole **26** was isolated in only 7% yield, along with several unidentified byproducts (Scheme 3). Interestingly, cyclization of **17** under the Jeffery conditions [$Pd(PPh_3)_4$, K_2CO_3, and *n*Bu_4NCl in CH_3CN at 80 °C] delivered dihydroquinoline **27** in high yield as the sole isolable product. Using a $Pd(OAc)_2$/X-Phos (10 mol %, Pd/L = 1/2) catalyst system and Cs_2CO_3 in 1,4-dioxane at 100 °C, indole **26** was obtained in only 5% yield, with dihydroquinoline **27** again being the major product (84% yield). A similar result was obtained for aryl chloride **18**. Thus, upon treatment of **18** with $Pd(OAc)_2$/X-Phos (30 mol %, Pd/L = 1/2) and Cs_2CO_3 in 1,4-dioxane at 100 °C for 96 h, indole **28** was not obtained at all, and dihydroquinoline **29** was instead isolated in 52% yield.

Development of a One-Pot Suzuki−Miyaura Coupling−Cyclization Cascade. We next investigated a one-pot Suzuki−Miyaura coupling−cyclization cascade starting from enol phosphate **2a**, exploiting its unique reactivity profile. In the previous experiment, we unexpectedly isolated indole **8** as a byproduct in 24%

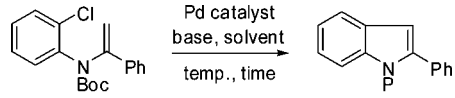
(29) For recent examples: (a) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2008**, *64*, 769. (b) Barluenga, J.; Fernandez, M. A.; Aznar, F.; Valdes, C. *Chem.—Eur. J.* **2005**, *11*, 2276. (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678. (d) Jia, J.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826. (e) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526. (f) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011. (g) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2002**, *4*, 191. (h) Edmonson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109. (i) Chen, C. Y.; Liberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676, and references cited therein.

(30) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(31) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(32) We have found that the use of 10 mol % of $Pd(OAc)_2/Cy_3P$ catalyst (Pd/L = 1/2) in the presence of Cs_2CO_3 (3 equiv) in 1,4-dioxane at 100 °C also gave indole **8** in 89% yield. In contrast, the use of Pd_2dba_3/Davephos, Pd_2dba_3/S-Phos, $Pd_2dba_3/Cy_3P\cdot HBF_4$, or Pd_2dba_3/t-$Bu_3P\cdot HBF_4$ catalyst was less effective for the present reaction.

TABLE 3. Screening of Reaction Conditions[a]



7b

8: P = Boc
9: P = H

entry	catalyst (equiv)	base (equiv)	solvent	temp (°C)	time (h)	yield (%) **8**	yield (%) **9**
1	Pd_2dba_3/X-Phos (0.05/0.20)	NaO*t*Bu (3)	toluene	110	48	0	61
2	Pd_2dba_3/X-Phos (0.05/0.20)	KO*t*Bu (3)	toluene	110	48	0	85
3	Pd_2dba_3/X-Phos (0.15/0.60)	K_2CO_3 (3)	1,4-dioxane	100	72	86	0
4	$Pd(OAc)_2$/X-Phos (0.30/0.60)	K_2CO_3 (3)	1,4-dioxane	100	96	70 (9)	0
5	Pd_2dba_3/X-Phos (0.15/0.60)	Cs_2CO_3 (3)	1,4-dioxane	100	72	84	0
6	$Pd(OAc)_2$/X-Phos (0.10/0.20)	Cs_2CO_3 (3)	1,4-dioxane	100	24	96	0
7[b]	$Pd(OAc)_2$/X-Phos (0.10/0.20)	Cs_2CO_3 (3)	1,4-dioxane	160	0.5	87	0

[a] Yields are from **7b**. Yield in parentheses is recovered **7b**. [b] Microwave heating was applied.

yield when the cross-coupling of **2a** with phenylboronic acid was performed in 1,4-dioxane at 60 °C (see Table 1, entry 1). Under these conditions, however, further conversion of enecarbamate **2a** to indole **8** stalled after ca. 24 h. Elevated temperature (100 °C) and/or prolonged reaction time proved to be ineffective. We, therefore, examined several reaction conditions, and the results are summarized in Table 5. Upon exposure of **2a** to 1.1 equiv of phenylboronic acid, Et_3N, and $Pd(PPh_3)_4$ catalyst in DMF directly afforded **8** in moderate yield (entry 1). Utilization of Cs_2CO_3 as a base in combination with *n*-Bu_4NCl (1 equiv) in DMF/H_2O at 50−100 °C gave a comparable result (entry 2). Finally, we found that the cross-coupling−cyclization cascade could be best realized using 10 mol % of $Pd(PPh_3)_4$, Cs_2CO_3 (3 equiv), arylboronic acid (1.1 equiv), and *n*-Bu_4NBr (1 equiv)[29] in DMF/H_2O at 50−70 °C. Under these conditions, we isolated *N*-Boc-2-substituted indole derivatives **8**, **19**, and **20** in moderate to good yields (entries 3−5). Thus, fine-tuning of the reaction conditions realized a highly efficient synthesis of 2-substituted indole derivatives from imide-derived enol phosphates in a one-pot manner.

Mechanistic Consideration of the Palladium-Catalyzed Cyclization of *o*-Haloaniline-Derived Enecarbamates. Several plausible mechanisms have been discussed for the palladium-catalyzed cyclization of *o*-haloaniline-derived enamines. This cyclization is often classified as an intramolecular Heck reaction,[11b,c,33] although a pathway that involves a six-membered palladacycle intermediate has also been proposed[34,35] (Scheme 4). The catalytic cycle is composed of (i) oxidative addition to a palladium(0) complex (**30** → **31**), (ii) migratory insertion into the enamine double bond (**31** → **32**), and (iii) *syn*-specific β-hydride elimination (**32** → **33**). Although it is widely accepted that 5-*endo* cyclization is generally disfavored due to geometric constraints according to Baldwin's rules,[23] an intramolecular Heck reaction pathway well accounts for the smooth cyclization of enecarbamates represented by **30** and the difficulties in the cyclization of enecarbamates **17** and **18** since *anti*-β-hydride elimination is required for the latter substrates (i.e., **34** → **26** and **35** → **28**). Moreover, the formation of dihydroquinolines **27** and **29** from **17** and **18**, respectively, could be rationally explained by an intramolecular C−H activation of the intermediates **34** and **35**, which is followed by reductive elimination (**36** → **38** and **37** → **39**) and subsequent ring expansion (**38** → **27** and **39** → **29**).[36] Additionally, our observation that enecarbamates **7a**, **10a**, **11**, **12a**, and **13** undergo smooth 5-*endo-trig* aryl radical cyclization to yield *N*-Boc-2-arylindolines (vide infra) suggests that 5-*endo-trig* Heck cyclization may also be feasible for these enecarbamates.

Synthesis of an Indol-2-yl-1*H*-quinolin-2-one KDR Inhibitor Based on the Suzuki−Miyaura Coupling−Cyclization Strategy. Protein tyrosine kinases are involved in cellular signal transduction pathways and many other important biological functions. Impairment of tyrosine kinases is responsible for diseases such as angiogenesis, cancer, and tumor growth.[37] Kinase insert domain receptor (KDR), one of the human tyrosine kinases, is expressed on activated endothelial cells and exhibits a high affinity for vascular endothelial growth factor (VEGF). Since VEGF is believed to be one of the prime mediators of tumor-induced angiogenesis, the inhibition or modulation of KDR by small organic molecules is predicted to be effective for its prevention and treatment.[38,39] Recently, researchers from Merck have reported the synthesis of a series of 5-substituted 1*H*-indol-2-yl-1*H*-quinolin-2-ones (**40**−**43**), a novel class of potent and selective KDR inhibitors (Figure 1).[40] Lautens and co-workers have reported an efficient synthesis of these inhibitors by means of their palladium(0)-catalyzed tandem C−N/Suzuki−Miyaura coupling methodology.[41] Another report on the synthesis of KDR inhibitor **41** utilizing a Sonogashira coupling−cyclization strategy has also appeared in the literature.[42] We envisioned that KDR inhibitor **40** could be derived from enol phosphate **44** and the known boronic acid **45**,[41] based on our strategy.

The synthesis started with alkylation of the known phenol **46**, prepared from 3-bromophenol by nitration under standard conditions (H_2SO_4, $NaNO_3$, and H_2O, 32% yield),[43] by treatment with 2-bromoethyl methyl ether/K_2CO_3, to give compound **47** in 100% yield (Scheme 5). Reduction of the nitro group of **47** with tin(II) chloride gave aromatic amine **48** (90% yield).

(33) For recent examples of 5-*endo* Heck cyclizations excluding enamine-type compounds, see: (a) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684. (b) Ichikawa, J.; Sakoda, K.; Mihara, J.; Ito, N. *J. Fluorine Chem.* **2006**, *127*, 489. (c) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425.

(34) Latham, E. J.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2059.

(35) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873.

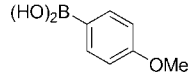
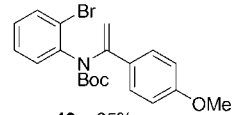
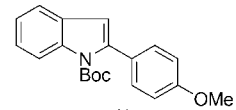
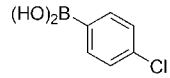
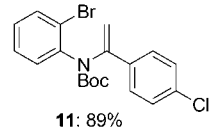
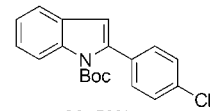
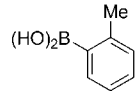
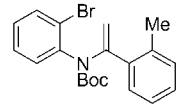
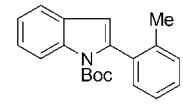
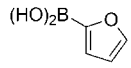
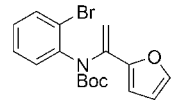
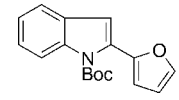
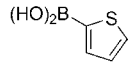
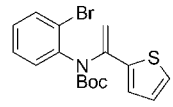
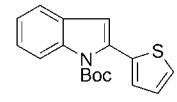
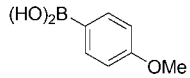
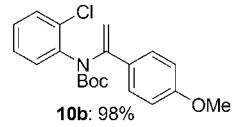
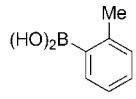
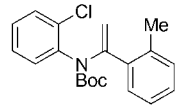
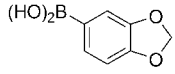
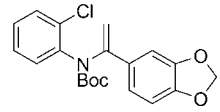
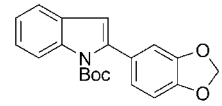
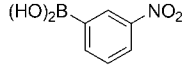
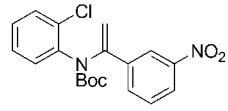
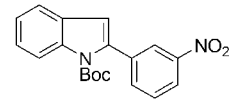
(36) For a related process, see: (a) Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943.

(37) Carmeliet, P.; Jain, R. K. *Nature* **2000**, *407*, 249.

(38) Morin, M. J. *Oncogene* **2000**, *19*, 6574.

(39) Veikkola, T.; Karkkainen, M.; Claesson-Welsh, L.; Alitalo, K. *Cancer Res.* **2000**, *60*, 203.

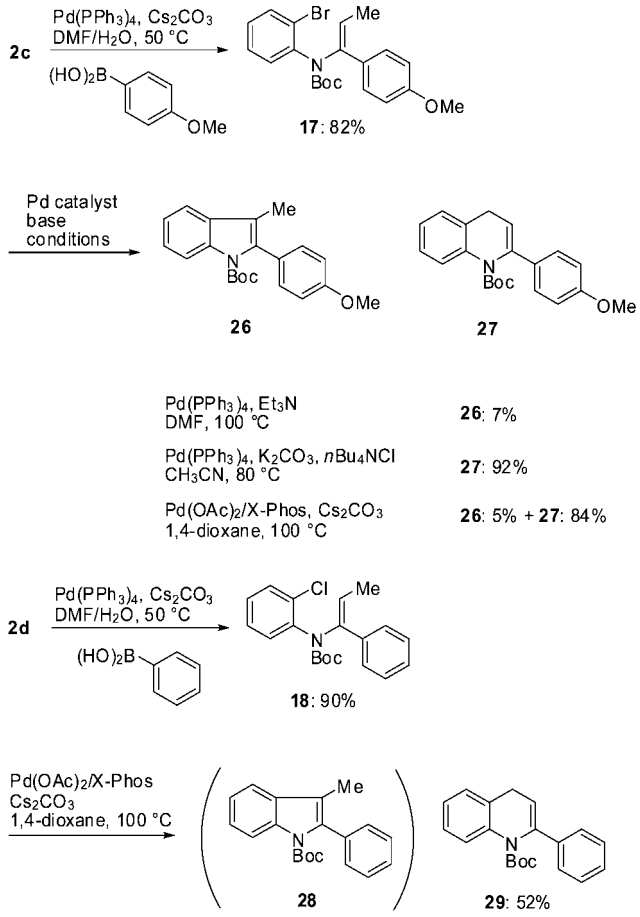
TABLE 4. Synthesis of 2-Substituted Indoles[a]

entry	phosphate	boronic acid	enecarbamate	cyclization conditions[b]	product
1	**2a**		 **10a**: 95%	A	 **19**: 71%
2	**2a**		 **11**: 89%	A	 **20**: 59%
3	**2a**		 **12a**: 86%	A	 **21**: 91%
4	**2a**		 **13**: 100%	A	 **22**: 54% (44%)[c]
5	**2a**		 **14**: 97%	A	 **23**: 63% (31%)[c]
6	**2b**		 **10b**: 98%	B	**19**: 100%
7	**2b**		 **12b**: 89%	B C	**21**: 100% **21**: 86%
8	**2b**		 **15**: 99%	C	 **24**: 91%
9	**2b**		 **16**: 95%	B	 **25**: 81%

[a] All cross-coupling reactions were carried out using $Pd(PPh_3)_4$ (0.1 equiv), Cs_2CO_3 (3 equiv), and boron nucleophile (1.1−1.5 equiv) in DMF/H_2O at 50 °C for 1−2 h. [b] Cyclization conditions A: $Pd(PPh_3)_4$ (0.1 equiv) and Et_3N (10 equiv) in DMF at 100 °C for 20−24 h. Cyclization conditions B: $Pd(OAc)_2$ (0.1 equiv), X-Phos (0.2 equiv), and Cs_2CO_3 (3 equiv) in 1,4-dioxane at 100 °C for 12−24 h. Cyclization conditions C: $Pd(OAc)_2$ (0.1 equiv), X-Phos (0.2 equiv), and Cs_2CO_3 (3 equiv) in 1,4-dioxane at 160 °C for 30 min under microwave heating. [c] Yields in parentheses are the corresponding N-deprotected indole.

Acylation of **48** with acetic anhydride and subsequent protection of the resultant anilide with Boc_2O afforded imide **49** in 68% yield for the two steps. Enolization of **49** with KHMDS in the presence of $(PhO)_2P(O)Cl$ gave enol phosphate **44** that, without purification, was reacted with the known boronic acid **45**[41] (1.1 equiv) in the presence of 10 mol % of $Pd(PPh_3)_4$ and 3 equiv of Cs_2CO_3 as a base in DMF/H_2O at 50 °C, giving rise to enecarbamate **50** in 96% yield from **49**. The subsequent palladium-catalyzed cyclization using 10 mol % of $Pd(PPh_3)_4$ and excess Et_3N in DMF at 100 °C afforded indole **51** in 90% yield. As noted above, the transformation of **44** to **51** could also be achieved in a one-pot process. Thus, treatment of **44** with 1.1 equiv of **45**, 10 mol % of $Pd(PPh_3)_4$, 3 equiv of Cs_2CO_3, and 1 equiv of *n*-Bu_4NBr in DMF/H_2O at 50−70 °C directly afforded indole **51** in 81% overall yield from **49**. Finally, hydrolysis under acidic conditions delivered Merck KDR inhibitor **40** in 79% yield, with spectroscopic data matching those reported previously.[40] The present synthesis clearly

SCHEME 3. Synthesis and Cyclization of Enecarbamates 17 and 18



demonstrates the feasibility of our strategy for the synthesis of structurally complex 2-aryl indole derivatives.

5-*endo-trig* Aryl Radical Cyclization of *o*-Bromoaniline-Derived Enecarbamates Leading to 2-Substituted Indolines. It is well-known that 5-*exo-trig* radical cyclization is a powerful strategy for the construction of 3-substitued indoline derivatives.[44] To the best of our knowledge, however, application of 5-*endo-trig* radical cyclization for the synthesis of an indoline system has not been reported.[45−47] Nonetheless, we examined the 5-*endo-trig* aryl radical cyclization of enecarbamates **7a**, **10a**, **11**, **12a**, and **13**. To our delight, treatment of **7a**, **10a**, **11**, **12a**, and **13** with *n*-Bu_3SnH in the presence of catalytic AIBN in toluene at 100 °C (method A) gave a series of 2-substituted indolines **52**[48] and **53**−**56** in moderate to good yields (Table 6). Furthermore, we found that radical cyclization could also be performed under mild conditions using SmI_2 in the presence of *t*-BuOH in THF/HMPA[49] at rt (method B). The latter method afforded 2-substituted indolines in somewhat better yields and eliminated the need for tedious chromatographic separation of tin byproducts.

Conclusion

The present study demonstrates the synthetic utility of acyclic imide-derived enol phosphates as novel versatile precursors for the synthesis of 2-substituted indoles and indolines by means of palladium chemistry. Noteworthy is the remarkable chemoselectivity of Suzuki−Miyaura coupling; Suzuki−Miyaura coupling using $Pd(PPh_3)_4$ catalyst and Cs_2CO_3 in aqueous DMF allowed for a highly chemoselective cross-coupling of imide-derived enol phosphates with aryl and heteroarylboronic acids, leading to *N*-(*o*-halophenyl)enecarbamates in excellent yields. Cyclization of the enecarbamates derived from *o*-bromoaniline was efficiently performed using $Pd(PPh_3)_4$ catalyst and Et_3N in DMF at 100 °C, while that of *o*-chloroaniline-derived enecarbamates was best accomplished under the influence of a $Pd(OAc)_2$/X-Phos (Pd/L = 1/2) catalyst system and Cs_2CO_3 in 1,4-dioxane at 100 °C (thermal heating) or at 160 °C (microwave heating). Application of microwave heating to the palladium cyclization significantly enhanced the reaction rate. Furthermore, a one-pot Suzuki−Miyaura coupling−cyclization cascade has been developed, and it was applied to an efficient synthesis of an indol-2-yl-1*H*-quinolin-2-one KDR inhibitor. On the basis of experimental evidence, we propose that the palladium-catalyzed cyclization of *o*-haloaniline-derived enecarbamates proceeds via a generally disfavored 5-*endo-trig* Heck cyclization pathway. We have also succeeded in carrying out the 5-*endo-trig* aryl radical cyclization of *o*-bromoaniline-derived enecarbamates, which constitutes an unprecedented example of a successful application of a generally disfavored 5-*endo-trig* cyclization for the synthesis of indoline derivatives. We believe that our chemistry, described herein, significantly broadens the scope and utility of enol phosphates in palladium-catalyzed synthesis of nitrogen heterocycles. Further studies on the development of new synthetic methodologies utilizing enol phosphates and their application in the synthesis of complex biologically active substances are currently underway and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Imides 1a,b,d,e. The synthesis of **1a** is representative. To a solution of *N*-(2-bromophenyl)acetanilide (1.01 g, 4.72 mmol) in THF (30 mL) were added DMAP (0.75 g, 6.14 mmol) and Boc_2O (1.41 mL, 6.14 mmol). After being stirred at rt for 50 min, the reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% EtOAc/hexanes) gave **1a** (1.47 g, 99%).

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(46) For a theoretical study: Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765.

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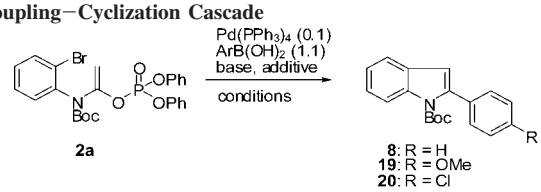
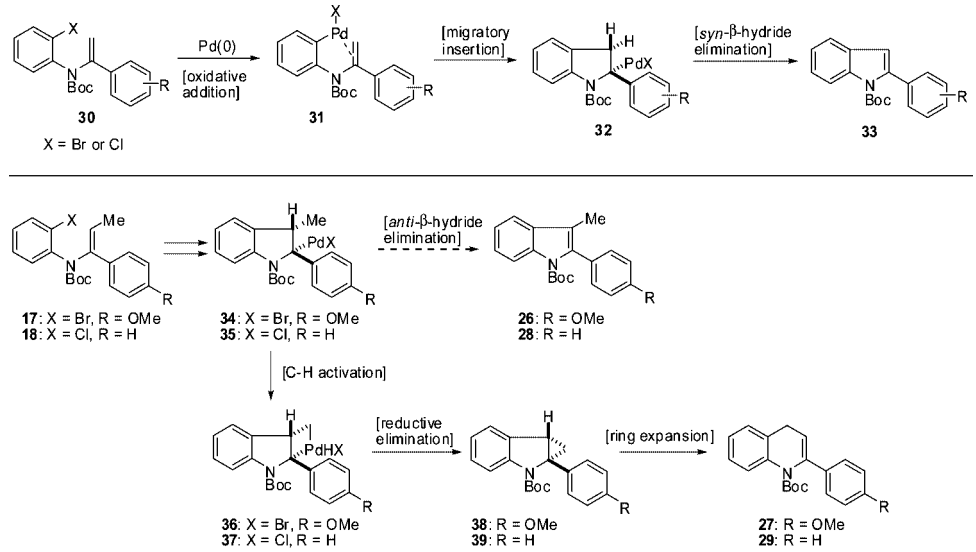
TABLE 5. One-Pot Suzuki−Miyaura Coupling−Cyclization Cascade



entry	Ar	base (equiv)	additive (equiv)	conditions	yield (%)
1	Ph	Et_3N (10)	none	DMF, 100 °C	**8**: 50
2	Ph	Cs_2CO_3 (3)	*n*-Bu_4NCl (1)	DMF/H_2O, 50−100 °C	**8**: 50
3	Ph	Cs_2CO_3 (3)	*n*-Bu_4NBr (1)	DMF/H_2O, 50−70 °C	**8**: 74
4	4-$MeOC_6H_4$	Cs_2CO_3 (3)	*n*-Bu_4NBr (1)	DMF/H_2O, 50−70 °C	**19**: 77
5	4-ClC_6H_4	Cs_2CO_3 (3)	*n*-Bu_4NBr (1)	DMF/H_2O, 50−70 °C	**20**: 55

SCHEME 4. Intramolecular Heck Cyclization Pathway



1a: Colorless crystals; mp 81−82 °C; IR (neat) ν_{max}/cm^{-1} 2979, 1742, 1712, 1474, 1370, 1279, 1157, 1104, 759; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.6, 1.2 Hz, 1H), 7.33 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.19 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.15 (dd, J = 7.6, 1.2 Hz, 1H), 2.61 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 151.6, 138.1, 132.9, 129.9, 129.4, 128.1, 123.0, 83.3, 27.7 (×3), 26.3; HRMS (FAB) calcd for $C_{13}H_{17}{}^{79}BrNO_3$ [(M + H)$^+$] 314.0392, found 314.0388.

General Procedure for the Suzuki−Miyaura Cross-Coupling of 1a,b,d,e. The synthesis of enecarbamate **7a** is representative.

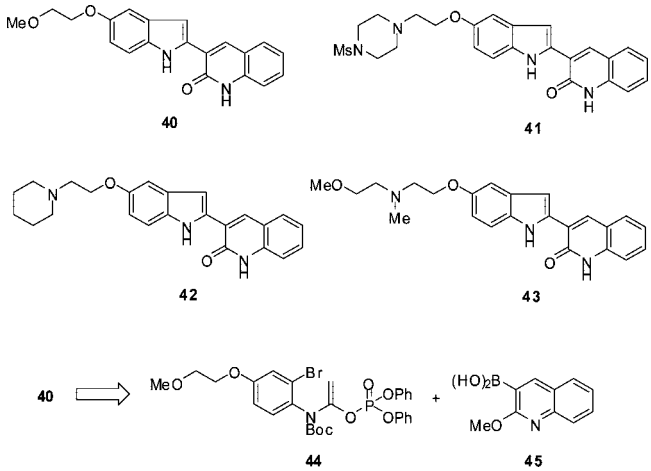


FIGURE 1. Structures of the Merck KDR inhibitors (**40**−**43**) and our synthetic strategy toward **40**.

To a solution of imide **1a** (131.9 mg, 0.4201 mmol) in THF (6 mL) were added HMPA (0.220 mL, 1.26 mmol) and diphenylphosphoryl chloride (0.105 mL, 0.507 mmol). The mixture was cooled to −78 °C and treated with potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 1.0 mL, 0.5 mmol). After being stirred at −78 °C for 30 min, the reaction mixture was treated with 3% ammonium hydroxide and diluted with diethyl ether. The resultant mixture was allowed to warm to rt over 20 min. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude enol phosphate **2a** thus prepared was used immediately without further purification.

To a solution of the above material in DMF (5 mL) were added cesium carbonate (3 M aqueous solution, 0.420 mL, 1.26 mmol), phenylboronic acid (56.4 mg, 0.463 mmol), and $Pd(PPh_3)_4$ (48.5 mg, 0.0420 mmol). The resultant mixture was heated at 50 °C for 7 h. After cooling, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% diethyl ether/hexanes) gave enecarbamate **7a** (140.9 mg, 90%).

7a: Colorless oil; IR (neat) ν_{max}/cm^{-1} 2977, 1715, 1622, 1475, 1299, 1164, 1088, 768, 696; ^1H NMR (500 MHz, C_6D_6) δ 7.59 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.15−7.12 (m, 2H), 7.08 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (dd, J = 8.5, 8.0 Hz, 1H), 6.58 (dd, J = 7.5, 7.5 Hz, 1H), 4.97 (s, 1H), 4.83 (s, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.4,

(48) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653.
(49) (a) Inanaga, J.; Ishkawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (b) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.

SCHEME 5. Synthesis of the Merck KDR Inhibitor 40

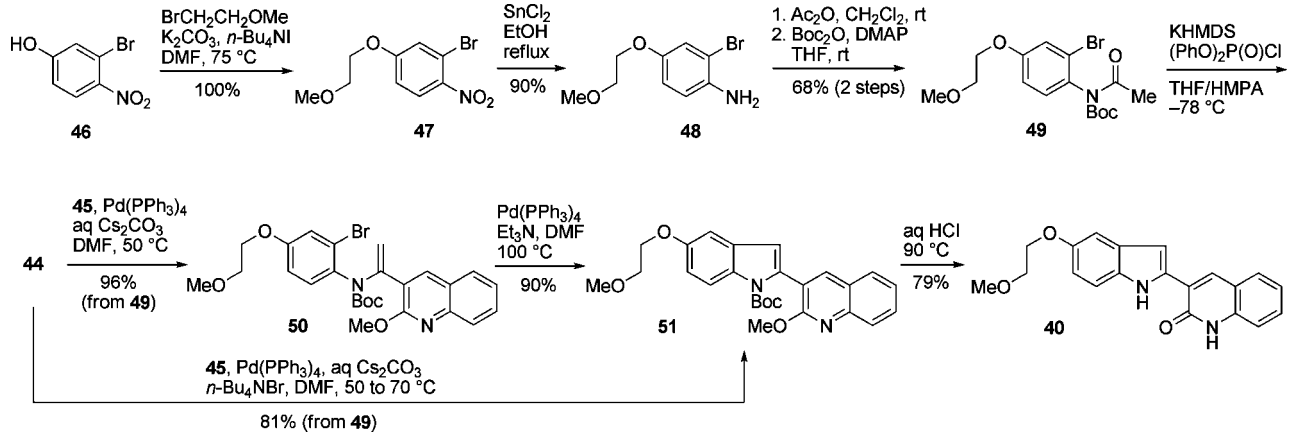
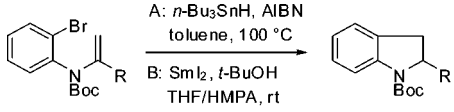
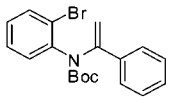
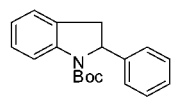
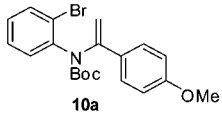
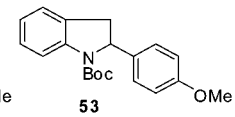
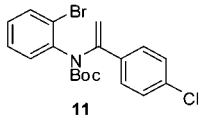
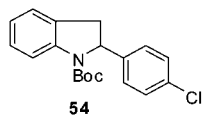
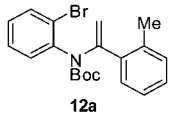
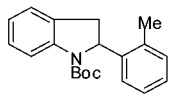
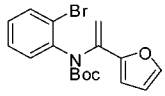
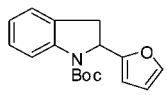


TABLE 6. 5-*endo-trig* Aryl Radical Cyclization of Enecarbamates



entry	enecarbamate	indoline	yield (%) A[a]	yield (%) B[a]
1	 **7a**	 **52**	82	65[b] 90
2	 **10a**	 **53**	85	86
3	 **11**	 **54**	62	80
4	 **12a**	 **55**	72	63
5	 **13**	 **56**	51	54

[a] Method A: *n*-Bu_3SnH, AIBN, toluene, 100 °C. Method B: SmI_2, *t*-BuOH, THF/HMPA, rt. [b] Reaction performed in the absence of *t*-BuOH.

149.3, 143.4, 133.6, 129.8, 129.0, 128.5, 128.4 (×2), 128.3, 128.2, 126.5 (×2), 124.2, 108.1, 80.8, 27.8 (×3); HRMS (FAB) calcd for $C_{19}H_{21}NO_2{}^{79}Br$ [(M + H)$^+$] 374.0756, found 374.0756.

General Procedure for the Heck-Type Cyclization of 7a, 10a, 11, 12a, 13, and 14. The synthesis of compound **19** is representative. In a heavy-walled Pyrex bottle was placed a solution of **10a** (122.2 mg, 0.3032 mmol) in DMF (5 mL). To this solution were added Et_3N (0.420 mL, 3.01 mmol) and $Pd(PPh_3)_4$ (35.0 mg, 0.0303 mmol). The Pyrex bottle was purged with argon, capped, and put into a preheated oil bath (100 °C) for 20 h. After cooling to rt, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% diethyl ether/hexanes) gave indole **19** (69.5 mg, 71%).

19: Colorless oil; IR (neat) ν_{max}/cm^{-1} 2978, 1730, 1504, 1453, 1328, 1247, 1161, 1038, 811, 747; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 9.0 Hz, 2H), 7.31 (dd, J = 8.0, 7.5 Hz, 1H), 7.24 (m, 1H), 6.95 (d, J = 9.0 Hz, 2H), 6.51 (s, 1H), 3.85 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 150.3, 140.4, 137.3, 129.9 (×2), 129.2, 127.4, 124.0, 122.8, 120.2, 115.2, 113.2 (×2), 109.4, 83.3, 55.3, 27.6 (×3); HRMS (EI) calcd for $C_{20}H_{21}NO_3$ (M$^+$) 323.1521, found 323.1529.

General Procedure for the Heck-Type Cyclization of 7b, 10b, 12b, and 16 (Thermal Heating). The synthesis of *N*-Boc-2-phenylindole **8** is representative. To a solution of **7b** (78.4 mg, 0.238 mmol) in 1,4-dioxane (2.5 mL) were added Cs_2CO_3 (232.9 mg, 0.7148 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), and X-Phos (22.7 mg, 0.0476 mmol). The resultant mixture was put into a preheated oil bath (100 °C) for 24 h. After cooling to rt, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% diethyl ether/hexanes) gave indole **8**[21b] (67.0 mg, 96%).

General Procedure for the Heck-Type Cyclization of 7b, 10b, 12b, and 15 (Microwave Heating). The synthesis of *N*-Boc-2-phenylindole **8** is representative. A 5 mL vial was charged with **7b** (47.6 mg, 0.145 mmol), Cs_2CO_3 (141.4 mg, 0.434 mmol), $Pd(OAc)_2$ (3.2 mg, 0.014 mmol), X-Phos (13.8 mg, 0.0289 mmol), and 1,4-dioxane (1.5 mL). The vial was flushed with argon, sealed, and heated at 160 °C for 30 min under microwave irradiation. After cooling to rt, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% diethyl ether/hexanes) gave indole **8**[21b] (36.9 mg, 87%).

General Procedure for the Suzuki−Miyaura Coupling−Cyclization Cascade. The synthesis of **8** is representative. To a solution of **2a**, prepared from **1a** (131.5 mg, 0.4188 mmol) as desribed above, in DMF (6 mL) were added cesium carbonate (3 M solution in H_2O, 0.420 mL, 1.26 mmol), phenylboronic acid (56.2 mg, 0.461 mmol), and $Pd(PPh_3)_4$ (48.4 mg, 0.0419 mmol). After being stirred at 50 °C for 1 h, tetra-*n*-butylammonium bromide (135.0 mg, 0.4188 mmol) was added to the reaction mixture, which was further heated at 70 °C for 20 h. After cooling to rt, the reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% diethyl ether/hexanes) gave **8**[21b] (91.4 mg, 74%).

General Procedure for 5-*endo-trig* Aryl Radical Cyclization (Method A). The synthesis of **53** is representative. To a solution of **10a** (119.9 mg, 0.2975 mmol) in toluene (4 mL) were added

n-Bu_3SnH (0.096 mL, 0.36 mmol) and AIBN (9.8 mg, 0.060 mmol). The reaction mixture was heated at 100 °C for 1 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 10% diethyl ether/hexanes) gave indoline **53** (82.1 mg, 85%).

General Procedure for 5-*endo-trig* Aryl Radical Cyclization (Method B). The synthesis of **53** is representative. To a solution of SmI_2 (0.1 M solution in THF, 15.5 mL, 1.55 mmol) and HMPA (1.08 mL) at rt was added a solution of **10a** (104.4 mg, 0.2591 mmol) and *t*-BuOH (0.150 mL) in THF (3 mL + 1 mL rinse). After being stirred at rt for 6 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The resultant mixture was extracted with EtOAc. The organic layer was washed with H_2O, saturated aqueous Na_2SO_3, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 5% EtOAc/hexanes) gave indoline **53** (72.5 mg, 86%).

53: Colorless oil; IR (neat) ν_{max}/cm^{-1} 2975, 1702, 1608, 1483, 1388, 1248, 1171, 1036, 831, 752; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (br, 1H), 7.20 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.11−7.09 (m, 3H), 6.96 (dd, $J = 7.5$, 7.0 Hz, 1H), 6.80−6.77 (m, 2H), 5.30 (br, 1H), 3.76 (s, 3H), 3.63 (dd, $J = 16.0$, 11.0 Hz, 1H), 2.93 (dd, $J = 16.0$, 3.0 Hz, 1H), 1.34 (br, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 152.4, 143.0, 137.0, 129.4, 127.5, 126.5 (×2), 124.8, 122.5 (×2), 114.7, 113.7, 80.6, 62.0, 55.2, 37.8, 28.2 (×3); HRMS (EI) calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1675, found 325.1680.

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Supporting Information Available: Detailed experimental procedures and characterization data not included in the Experimental Section. Copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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