Organic LETTERS

Letter

pubs.acs.org/OrgLett

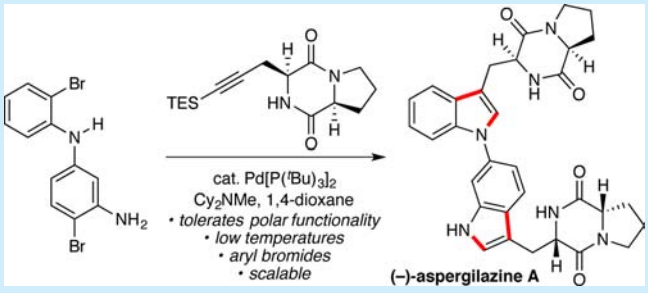
A Mild and General Larock Indolization Protocol for the Preparation of Unnatural Tryptophans

Kangway V. Chuang, Madeleine E. Kieffer, and Sarah E. Reisman*

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology Pasadena, California 91125, United States

Supporting Information

ABSTRACT: A mild and general protocol for the Pd(0)-catalyzed heteroannulation of *o*-bromoanilines and alkynes is described. Application of a Pd(0)/P(^{t}Bu)$_3$ catalyst system enables the efficient coupling of *o*-bromoanilines at 60 °C, mitigating deleterious side reactions and enabling access to a broad range of useful unnatural tryptophans. The utility of this new protocol is demonstrated in the highly convergent total synthesis of the bisindole natural product (−)-aspergilazine A.



The development of new methods to prepare unnatural tryptophan derivatives is an important endeavor with interdisciplinary applications. In the context of natural product synthesis, a large number of alkaloids contain tryptophan subunits embedded explicitly or implicitly within their structures;[1] in chemical biology, functionalized tryptophan derivatives have emerged as important molecules for studying protein function and dynamics.[2] Although subtle perturbations to this core amino acid may seem trivial, the preparation of the requisite tryptophan building block often constitutes a substantial synthetic undertaking. The Pd-catalyzed heteroannulation reaction between *o*-bromoanilines and serine-derived alkynes represents a convergent approach to unnatural tryptophan derivatives, yet its versatility has thus far been limited due to challenges of reactivity and functional group tolerance. Herein, we describe the development and application of a Pd-catalyzed synthesis of structurally complex and synthetically useful tryptophan derivatives from widely available *o*-bromoanilines. Using this method, a concise synthesis of the bisindole alkaloid (−)-aspergilazine A is reported.

The Pd(0)-catalyzed heteroannulation of disubstituted alkynes with *o*-haloanilines,[3] commonly known as the Larock indole synthesis, is a powerful method for the preparation of 2,3-disubstituted indoles.[4−6] Larock's original conditions, which employ a "ligandless" Pd catalyst in conjunction with an inorganic base and chloride salt additive, were developed for *o*-iodoanilines and remain the most widely utilized (Figure 1A).[7] In 2004, Senanayake and co-workers expanded the scope of this transformation to include *o*-chloro- and *o*-bromoanilines by employing a bidentate phosphine ligand, 1,1′-bis-di-*tert*-butylphosphinoferrocene (dtbpf), at elevated temperatures (110−130 °C), providing simple indoles in good yield and high regioselectivity (not shown).[8]

Despite these advances, efforts to employ the Larock indole synthesis in complex settings, particularly using alkynyl

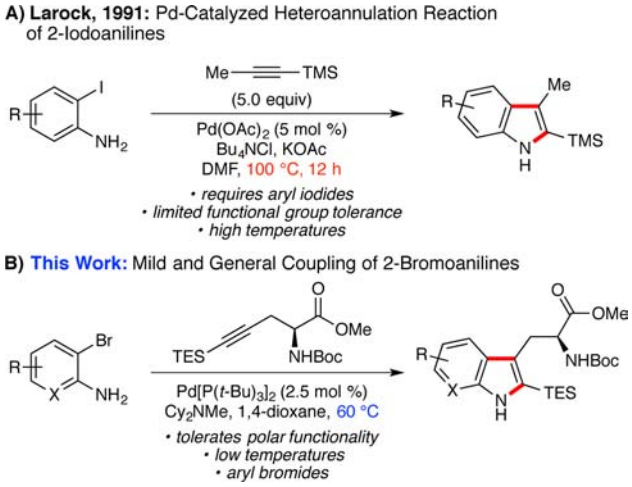


Figure 1. Larock indole synthesis.

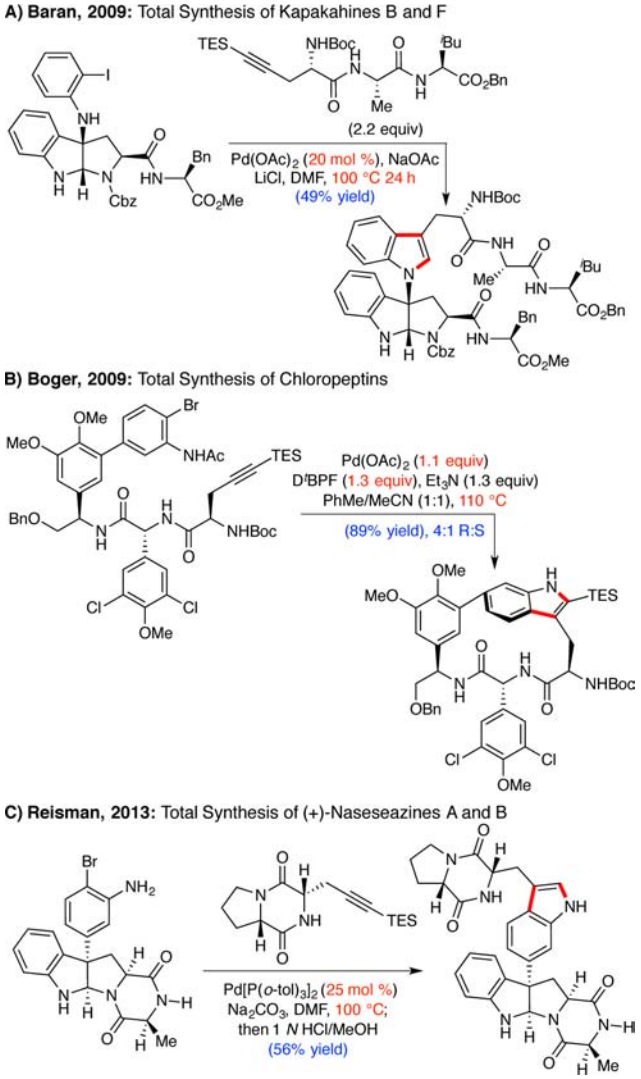
substrates containing peptide functionality and *o*-bromoanilines, reveal significant limitations in the state of the art. For example, Baran's elegant synthesis of (+)-kapakahine B necessitated prolonged reaction times (24 h) and increased catalyst loadings (20 mol %) under Larock's standard conditions (Scheme 1A).[5c] Similarly, Boger's landmark synthesis of the chloropeptins, which employed an intramolecular Larock macrocyclization of an aryl bromide, required excess [Pd] and dtbpf (1.1 and 1.3 equiv, respectively) to effect high yields (Scheme 1B).[6a]

We also encountered challenges during our efforts to implement a late-stage indole annulation for the total syntheses of the C3-arylpyrroloindolines (+)-naseseazines A and B (Scheme 1C). Specifically, poor catalyst turnover and low yields

Received: August 18, 2016
Published: September 6, 2016

DOI: 10.1021/acs.orglett.6b02477
Org. Lett. 2016, 18, 4750−4753

Scheme 1. Challenging Larock Indolizations in Natural Product Synthesis



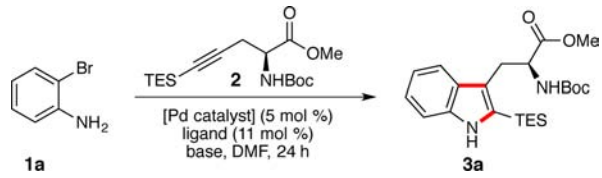
were obtained using substoichiometric [Pd], while the use of higher catalyst loadings or higher temperatures resulted in hydrodehalogenation, epimerization of the diketopiperazine, poor regioselectivity, and low mass recovery.[9] Following extensive experimentation, we determined that use of 25 mol % of $Pd[P(o\text{-}tol)_3]_2$ in conjunction with Na_2CO_3 provided the product in 56% isolated yield. Although only two turnovers of [Pd] were achieved, this report represents the first Larock indole synthesis using an *o*-bromoaniline with substoichiometric Pd in the context of a complex polypeptide substrate.[10]

Given our general interest in the synthesis of indole alkaloids,[11] we sought to develop a mild and reliable Pd-catalyzed synthesis of tryptophan derivatives that addresses the challenges outlined above. Specifically, we hoped to identify conditions that would (1) enable the general use of widely available *o*-bromoanilines, (2) proceed with synthetically useful catalyst loadings, and (3) deliver tryptophan products at lower temperatures in order to mitigate deleterious side reactivity.

In assessing the existing limitations of the Larock indole synthesis, we hypothesized that the poor reactivity of *o*-bromoanilines under the originally disclosed ligandless conditions was likely due to slow rates of oxidative addition. Although this elementary step could be enabled by the use of an electron-donating phosphine ligand,[12] it was recognized that such ligands might slow the rate of subsequent alkyne insertion. We reasoned that sterically demanding phosphines, which have been demonstrated to favor Pd–monophosphine complexes,[13] could serve to balance these opposing effects by providing a vacant coordination site to facilitate alkyne insertion.

Our studies commenced with the coupling between *o*-bromoaniline (**1a**) and alkyne **2**[14] to afford tryptophan **3a**. Treatment of a mixture of **1a** and **2** with 5 mol % of $Pd(OAc)_2$ and Na_2CO_3 at 100 °C, Larock's original conditions,[3] provided **3a** in 27% yield (Table 1, entry 1). A survey of conditions

Table 1. Optimization Studies



entry	[Pd cat.]	ligand	base	temp (°C)	yield[b] (%)
1	$Pd(OAc)_2$		Na_2CO_3	100	27
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	100	17
3	$Pd(OAc)_2$	DavePhos	Na_2CO_3	100	8
4	$Pd(OAc)_2$	PCy_3	Na_2CO_3	100	<5
5	$Pd(OAc)_2$	dtbpf	Na_2CO_3	100	<5
6	$Pd[P(o\text{-}tol)_3]_2$		Na_2CO_3	100	70
7	$Pd[P(^tBu)_3]_2$		Na_2CO_3	100	78
8	$Pd[P(^tBu)_3]_2$		Na_2CO_3	60	85
9	$Pd[P(^tBu)_3]_2$		Cy_2NMe	60	85
10[e]	$Pd[P(^tBu)_3]_2$		Cy_2NMe	60	84 (87)[d]
11[c,e]	$Pd_2(dba)_3$	$P(^tBu)_3$	Cy_2NMe	60	83

[a]Reactions conducted on 0.1 mmol scale with 2.0 equiv of alkyne **2** and 2.5 equiv of base in DMF (0.5 mL). [b]Yield determined by ^1H NMR analysis of the crude reaction mixture relative to an internal standard. [c]1:1 [Pd]/ligand used. [d]Isolated yield on 0.3 mmol scale. [e]Reaction performed in 1,4-dioxane.

previously reported in the literature to promote Larock indolizations, including the addition of 11 mol % of PPh_3, PCy_3, DavePhos, or dtbpf (the optimal ligand in Senanayake's report),[8] suppressed the reaction (entries 2–5). The preformed complex $Pd[P(o\text{-}tol)_3]_2$, our most successful catalyst in the synthesis of the naseseazines,[9] delivered **3a** in 70% yield.

Increasing the steric demand of the ligand through the use of $Pd[P(^tBu)_3]_2$[13] further increased the yield (Table 1, entry 7). Pleasingly, lowering the temperature to 60 °C enabled a clean reaction and provided the product in 85% yield (entry 8). Use of the soluble organic base Cy_2NMe in 1,4-dioxane furnished **3a** with comparable efficiency (entries 9 and 10). Generation of the catalyst from a 1:1 [Pd]/ligand ratio was also feasible and improved the initial rate of the reaction (entry 11). To the best of our knowledge, this reaction represents the lowest temperature Larock indolization of *any o-haloaniline* reported to date.

As shown in Figure 2, the reaction exhibits excellent scope: both electron-rich (**3b–d**) and electron-deficient (**3e–l**) *o*-bromoanilines react efficiently to provide an array of unnatural tryptophan derivatives. Substitution is readily tolerated at all positions of the aniline substrate, including at nitrogen, although the preparation of 4-substituted indoles requires slightly elevated temperatures to achieve acceptable reaction rates (**3c** and **3i**).

DOI: 10.1021/acs.orglett.6b02477
Org. Lett. 2016, 18, 4750–4753

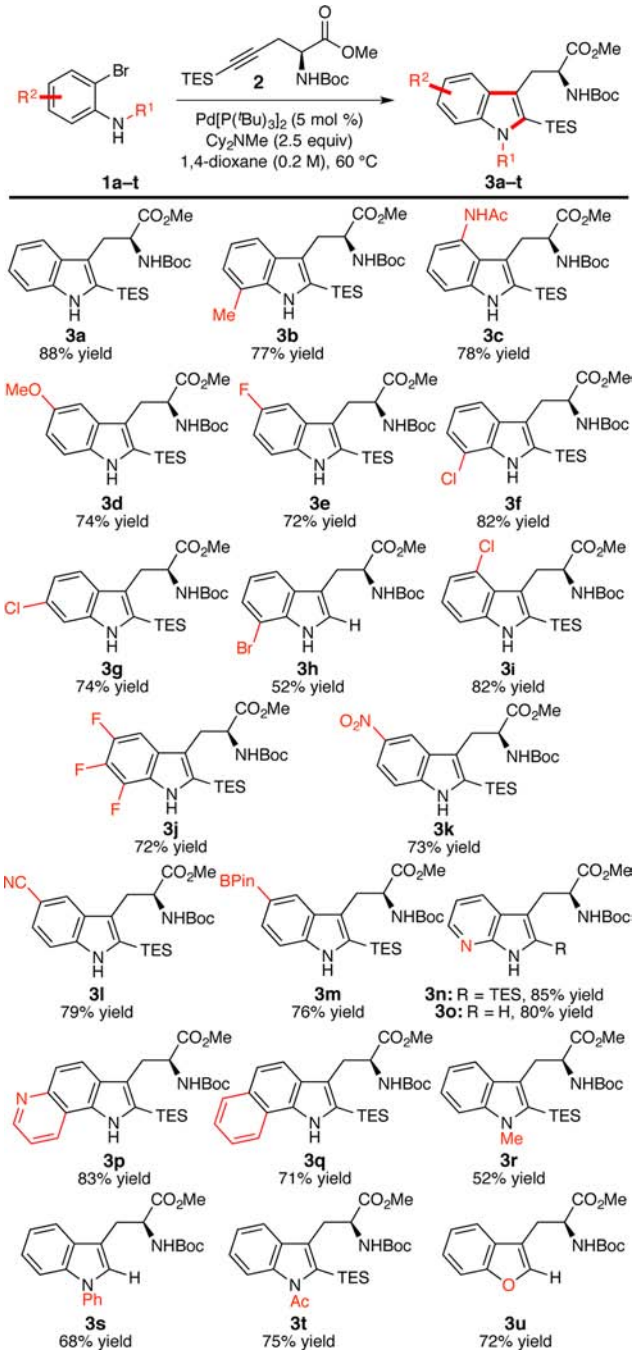


Figure 2. Substrate scope of the *o*-bromoaniline. Reactions were conducted with **1** (1.0 equiv), **2** (2.0 equiv), and Cy_2NMe (2.5 equiv) in 1,4-dioxane (0.2 M) at 60 °C; the isolated yields of **3** are reported. For compounds **3c** and **3i**, the reaction was performed at 80 °C. For compounds **3h**, **3s**, and **3u**, desilylation with 1 M TBAF or 1 N HCl in MeOH was performed prior to chromatography. The synthesis of **3o** was conducted on 5.0 mmol scale with 2.5 mol % of $Pd[P(^tBu)_3]_2$ and 1.5 equiv of **2** and then desilylated with 1.0 M TBAF.

Halogenated substrates react with excellent chemoselectivity for the aryl bromide over the aryl chloride; a variety of useful chlorinated (**3f,g,i**) and fluorinated (**3e,j**) tryptophans are readily prepared. Lewis-basic heterocycles also perform well under these conditions (**3n,o**). It is noteworthy that tryptophan **3o**, prepared here in two steps from commercially available materials, has recently been reported as a new fluorescent probe with useful photophysical properties.[15] Finally, these conditions can be extended to *o*-bromophenol to provide direct access to a substituted benzofuran derivative (**3u**). Importantly, chiral SFC analysis of the products verifies that this reaction proceeds without racemization, providing all products in enantiopure form.[16] The 2-triethylsilyl group is easily removed using aqueous acid or fluoride sources or, alternatively, can serve as a useful functional handle for a variety of transformations.[17]

To investigate the scope of the alkyne, several dipeptide-and diketopiperazine-based substrates were prepared and subjected to the reaction conditions (Figure 3). In all cases, the products are obtained in good yields and with no observed epimerization of the α-stereocenters.

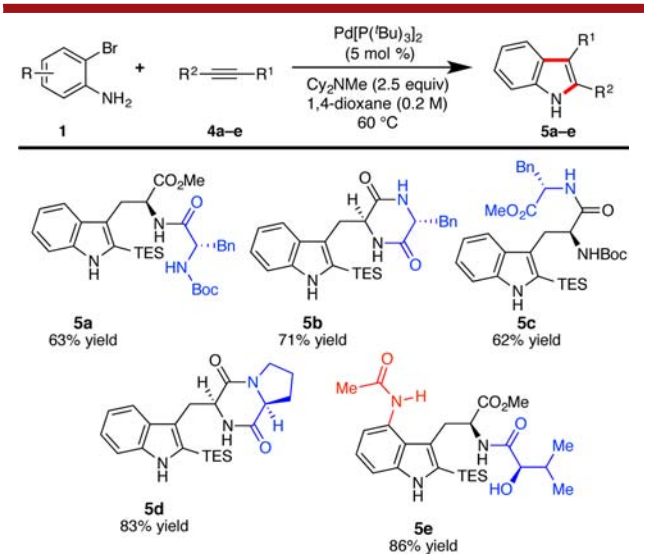


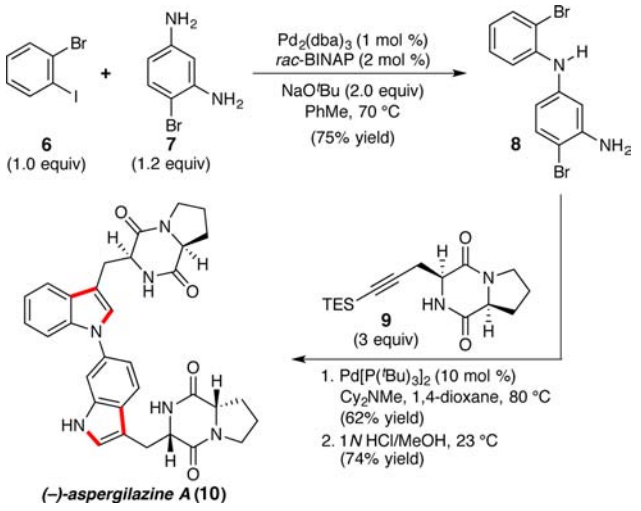
Figure 3. Substrate scope of the alkyne. Reactions were conducted with **1** (1.0 equiv), **4** (2.0 equiv), and Cy_2NMe (2.5 equiv) in 1,4-dioxane (0.2 M) at 60 °C; isolated yields of **5** are reported. For compound **5e**, the reaction was performed at 80 °C.

The synthetic studies described above utilize 5 mol % of catalyst for ease of operation; however, individual couplings can be conducted on preparatively useful scales with lower catalyst loadings. For example, the coupling between 2-amino-3-bromopyridine (**1n**) and alkyne **2** was carried out on 5 mmol scale using 2.5 mol % of $Pd[P(^tBu)_3]_2$ and 1.5 equiv of alkyne, which upon desilylation with 1 M TBAF in THF provided 1.28 g (80% yield) of 7-azatryptophan (Figure 2, **3o**).[18]

To further highlight the utility of this protocol, we sought to complete a total synthesis of the dimeric diketopiperazine natural product (−)-aspergilazine A (**10**),[19,20] which is characterized by its novel C6-to-N1 bisindole linkage (Scheme 2). We envisioned that **10** would be ideally suited for a sequential indolization strategy that would allow assembly of the natural product in a direct and convergent manner. To this end, the requisite dibromide (**8**) was prepared via Buchwald−Hartwig coupling of 1-bromo-2-iodobenzene (**6**) with diamine **7**.[21] Subjection of a mixture of dibromide **8** and alkyne **9** to 10 mol % of $Pd[P(^tBu)_3]_2$ and 2.5 equiv of Cy_2NMe in 1,4-dioxane at 80 °C furnished bis(triethylsilyl)-(−)-aspergilazine A in 62% isolated yield, representing an average reaction efficiency of 79% per indolization. Subsequent HCl-mediated desilylation cleanly provided the natural product. Importantly, the success of this strategy hinges largely on the ability of this new protocol to enable the coupling of 2-bromoanilines; the preparation of the diiodinated analogue of diarylamine **8** via C−N bond formation

DOI: 10.1021/acs.orglett.6b02477
Org. Lett. 2016, 18, 4750−4753

Scheme 2. Total Synthesis of (−)-Aspergilazine A



is a considerably more challenging synthetic undertaking. This highly convergent synthesis proceeds in an overall yield of 21% from commercially available starting materials and underscores the utility of this methodology in the direct preparation of complex molecular scaffolds.

In summary, we have developed a mild and general protocol for the Pd-catalyzed synthesis of functionalized tryptophan derivatives. The reaction proceeds with low catalyst loadings, displays excellent substrate scope, and is readily scalable to provide gram quantities of synthetically useful unnatural tryptophans. Furthermore, the synthetic utility of this transformation has been demonstrated in the concise synthesis of the natural product (−)-aspergilazine A.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02477.

Experimental data, characterization information, and spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: reisman@caltech.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Scott Virgil of Caltech for helpful discussions, the Caltech Center for Catalysis and Chemical Synthesis for access to screening facilities and analytical equipment, and Sigma−Aldrich for a kind donation of chemicals. We gratefully acknowledge Jordan Beck and Lauren Chapman of Caltech for their assistance in the preparation of this manuscript. Fellowship support was provided by the National Science Foundation (Graduate Research Fellowship to M.E.K. and K.V.C., Grant No. DGE-1144469). S.E.R. is an American Cancer Society Research Scholar and a Heritage Medical Research Foundation investigator. Financial support from the NIH (NIGMS RGM097582A) and the donors of the ACS Petroleum Research Foundation is gratefully acknowledged.

■ REFERENCES

(1) For representative reviews, see: (a) Veale, C. G. L.; Davies-Coleman, M. T. *Alkaloids: Chemistry and Biology* **2014**, *73*, 1−64. (b) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57−58.

(2) For the use of tryptophan derivatives as biological probes, see: (a) Royer, C. A. *Chem. Rev.* **2006**, *106*, 1769. (b) Lepthien, S.; Hoesl, M. G.; Merkel, L.; Budisa, N. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 16095. (c) Zhong, W.; Gallivan, J. P.; Zhang, Y.; Li, L.; Lester, H. A.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 12088.

(3) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Chen, Y.; Markina, N. A.; Yao, T.; Larock, R. C. *Org. Synth.* **2011**, *88*, 377.

(4) (a) Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2781. (b) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525. (c) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339.

(5) (a) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886. (b) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360. (c) Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119. (d) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716.

(6) (a) Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Takizawa, S.; Shimamura, H.; Tomishima, M.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 16036. (b) Shimamura, H.; Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776. (c) Breazzano, S. P.; Boger, D. L. *J. Am. Chem. Soc.* **2011**, *133*, 18495. (d) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. *J. Am. Chem. Soc.* **2013**, *135*, 1600.

(7) For recent reports utilizing Larock's original conditions, see: (a) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902. (b) Danner, P.; Morkunas, M.; Maier, M. E. *Org. Lett.* **2013**, *15*, 2474. (c) Tao, P.; Liang, J.; Jia, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 5735. (d) Miyamoto, H.; Hirano, T.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron* **2013**, *69*, 9481.

(8) (a) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (b) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573.

(9) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557.

(10) For elegant syntheses in complex systems using *o*-iodoanilines, see ref 5a−d. For examples using stoichiometric [Pd] *o*-bromoanilines, see ref 6a−c.

(11) Wang, H.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 6206.

(12) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010.

(13) (a) Littke, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (b) Littke, A.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (c) Littke, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (e) Littke, A.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (f) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343. (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(14) Readily prepared on decagram scale following the protocol of Baran and co-workers; see ref 5b.

(15) For an eight-step synthesis of the analogous *o*-nitrobenzyl carbamate protected compound, see: Talukder, P.; Chen, S.; Arce, P. M.; Hecht, S. M. *Org. Lett.* **2014**, *16*, 556.

(16) See the Supporting Information for additional details.

(17) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80.

(18) The previously reported yield was 63%; see ref 8a.

(19) Cai, S.; Kong, X.; Wang, W.; Zhou, H.; Zhu, T.; Li, D.; Gu, Q. *Tetrahedron Lett.* **2012**, *53*, 2615.

(20) For a recent total synthesis of (−)-aspergilazine A, see: Boyd, E. M.; Sperry, J. *Org. Lett.* **2014**, *16*, 5056.

(21) Garcia-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676.

DOI: 10.1021/acs.orglett.6b02477
Org. Lett. 2016, 18, 4750−4753