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Synthesis of *o*-Aminophenols via a Formal Insertion Reaction of Arynes into Hydroxyindolinones

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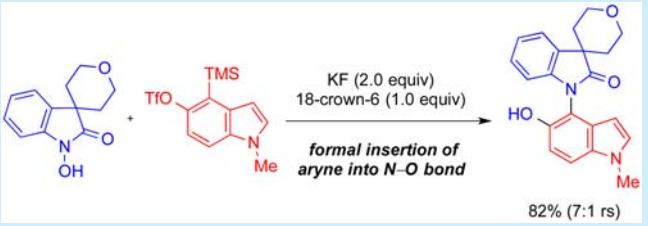
Supporting Information

ABSTRACT: A novel approach toward the synthesis of sterically hindered *o*-aminophenols has been achieved by a formal aryne insertion into hydroxyindolinones. This transformation offers a rapid and efficient entry to diverse *o*-aminophenol scaffolds under mild transition-metal-free conditions. The reaction involves the addition of hydroxyindolinones to arynes followed by a chemo- and regioselective [1,3]-rearrangement. Furthermore, the reactions of *N*-hydroxyindoles and arynes were found to provide the C3-aryl indole products via an alternative [3,3]-rearrangement pathway.



o-Aminophenols represent a valuable structural motif found in a wide range of natural products, materials, and ligands (Figure 1).[1] Traditional preparation of *o*-aminophenols includes the

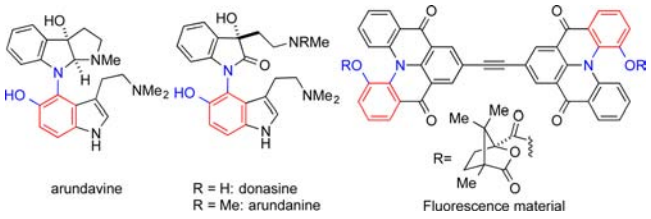
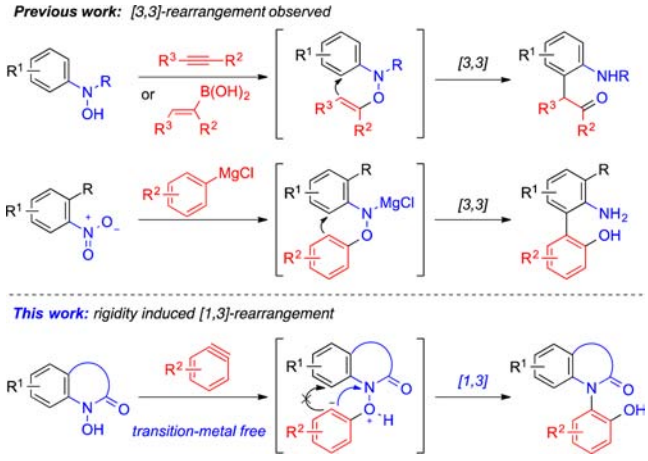


Figure 1. Examples of sterically hindered *o*-aminophenols in natural products and dyes.

S_NAr reaction of 1-fluoro-2-nitroarenes[2] or the nitration of phenols[3] followed by reduction of the nitro group. These methods often suffer from either low efficiencies or multiple-step syntheses.[4] Effective construction of this scaffold has been achieved by transition-metal-catalyzed transformations, such as Ullman, Buchwald–Hartwig, and Chan–Lam couplings,[5] as well as direct *ortho*-aryl C–H functionalization of either phenols to form C–N bond or anilines to form C–O bonds, respectively.[6] However, these metal-catalyzed coupling reactions often need elevated temperatures and prolonged time, especially for the synthesis of sterically hindered *o*-aminophenols. A rapid access to *o*-aminophenols under mild conditions by a transition-metal-free approach[7] would be desired, especially for sterically hindered *o*-aminophenols (e.g., arundavine, donasine, arundanine,[8] and fluorescent dye[9] shown in Figure 1).

Herein, we report the development of a metal-free formal aryne insertion approach to access *o*-aminophenols from hydroxyindolinones. Along with our ongoing interest in aryne chemistry[10] and electrophilic amination,[11] we envisioned that the sterically hindered *N*-(*o*-hydroxylaryl)aniline motif could be attained via the addition of *N*-hydroxylanilines to an aryne intermediate followed by [1,3]-rearrangement (Scheme 1).

Scheme 1. Rearrangements of *N*-Arylhydroxylamines



This strategy is appealing as the simultaneous difunctionalization of an aryne is extremely useful for the synthesis of complex and sterically hindered arene derivatives.[12] However, the control of the chemo- and regioselectivity in this proposed transformation is challenging. For example, *N*-arylhydroxylamines are known to undergo [3,3]-rearrangement (Scheme 1).[13] Additionally, the aminophenol product could react further with a second aryne, which needs to be minimized in the desired transformation.[14] Thus, several *N*-hydroxylamines were tested for reactivity with benzyne precursor to examine the chemo- and regioselectivity.[15] Encouragingly, the reaction of

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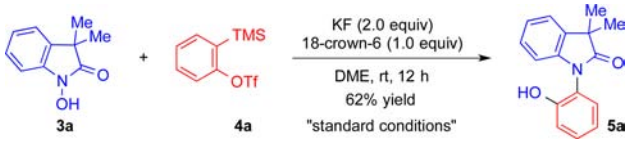
cyclic *N*-hydroxylamide **3a** led to the desired *o*-aminophenol product **5a** with excellent chemo- and regioselectivity (Table 1). The observed [1,3]-rearrangement, as a formal intra-

Table 1. Optimization for the Formal Hydroxyindolinone–Benzyne Insertion via Nucleophilic Addition/[1,3]-Rearrangement Sequence[a]



entry	variations from standard conditions	yield[b] (%)
1	MeCN instead of DME	54
2	CH_2Cl_2 instead of DME	0
3	toluene instead of DME	<5
4	without 18-crown-6	<5
5	CsF instead of KF/18-crown-6	45
6	**4a** 1.5 equiv instead of 1.0 equiv	56
7	**40 °C instead of rt**	**60**[c]
8	add $Cu(OAc)_2$ (0.1 equiv)	51
9	add AgOAc (0.1 equiv)	17
10	add PhCOOH (0.1 equiv)	56

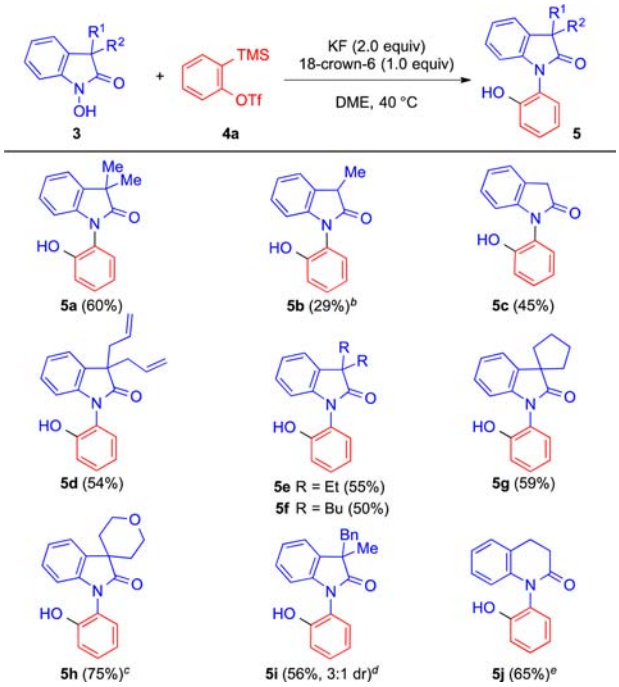
[a]Reactions run on 0.1 mmol scale. [b]Yields determined by ^{1}H NMR with CH_2Br_2 as an internal standard. No other rearrangements observed. [c]Isolation yield. Reaction completed in 4 h.

molecular electrophilic amination, was possibly facilitated by the introduction of the amide functionality to enhance the electrophilic nature of nitrogen, in comparison to hydroxyamines. Furthermore, the structural rigidity of cyclic amides might impede the $\pi-\pi$ stacking conformation required for the transition state of a [3,3]-rearrangement, thus favoring the desired [1,3]-rearrangement product.

Upon further optimization of this formal insertion of hydroxyindolinone **3a** with benzyne precursor **4a**, the desired 1-(2-hydroxyphenyl)indolinone **5a** was obtained in 62% yield in the presence of KF/18-crown-6 in DME at room temperature (Table 1, standard conditions). The use of other solvents such as MeCN, toluene, and CH_2Cl_2 diminished the yields of **5a** (Table 1, entries 1–3). In the absence of 18-crown-6 or with the replacement of KF/18-crown-6 by CsF, the reaction became sluggish (Table 1, entries 4 and 5), suggesting the rate of benzyne formation strongly influences the efficiency of this transformation. However, increasing the equivalence of benzyne precursor **4a** did not improve efficiency of the reaction (Table 1, entry 6). Elevated temperature accelerated the reaction, but it did not result in a higher yield of **5a** (Table 1, entry 7). Lewis acids and Brönsted acids were also examined for their potential to activate arynes or facilitate the rearrangement, yet little effect was observed with either $Cu(OAc)_2$ or $PhCO_2H$, while AgOAc dramatically decreased the reaction efficiency (Table 1, entries 8–10). Thus, entry 7 was chosen as the optimal reaction conditions.

With established conditions, the generality and efficiency of different hydroxyindolinones **3** were examined for this transformation (Scheme 2). Overall, the desired products were formed in all the reactions of benzyne precursor **4a** in moderate to good yields with different hydroxyindolinones. A range of functional groups was well tolerated in this transformation, including phenols, ethers, and alkenes. Interestingly, the C3- substituent of hydroxyindolinone **3** was

Scheme 2. Scope of Hydroxyindolinones for the Formal Insertion Reaction with Benzyne[a]



[a]Reaction conditions: **3** (0.5 mmol, 1.0 equiv), **4** (1.1 equiv), DME (3 mL), 6–12 h. Isolation yields shown. [b]NMR yield determined with CH_2Br_2 as an internal standard. [c]Run in DME/MeCN (4 mL, 3:1). [d]dr = diastereomeric ratio, determined by ^{1}H NMR. [e]Structure confirmed by X-ray analysis.

found to influence the efficiency of the reactions. For example, indolinones with two substituents at the C3-position (**5a** and **5d–5i**), especially **5h** bearing a tetrahydropyran ring, were formed in higher yields than indolinones with one or no substituent at the C3-position (**5b** and **5c**). It is worth noting that the diastereomeric outcome of product **5i** was likely influenced by the configuration of the remote stereocenter at C3-position.[16] Finally, six-membered dihydroquinolinone **5j** was readily formed in this transformation in an even higher yield than the analogous five-membered indolinone **5c**.

Different aryne precursors were also examined in this transformation (Scheme 3). The results indicate that both electron-donating and electron-withdrawing groups on arynes were well tolerated in this transformation and also affected the efficiency and regioselectivity of this reaction. For example, indolinones bearing electron-donating dimethoxy groups (i.e., **5k**, **5n** and **5q**) were formed in much higher yields than difluorinated product **5l**. In addition, **5m**, derived from aryne containing a *p*-methyl group, was formed in a 3:2 regioselectivity while **5o** and **5r**, derived from naphthyl arynes, were obtained in higher regioselectivity. Additionally, the reactions between a hydroxyindolinone and an indolyne were viable and provided bisindoles **5p** and **5s** in good yields with a 7:1 regioselectivity. The observed regioselectivity in our studies is consistent with the outcome of nucleophilic addition reactions of arynes.[17] Among these results, particularly attractive is the framework of **5p** and **5s**, which resembles the core structure of many indole alkaloids (e.g., donasine and arundanineare in Figure 1).[8] This suggests the potential of this method for the synthesis of indole-containing complex natural products and derivatives.

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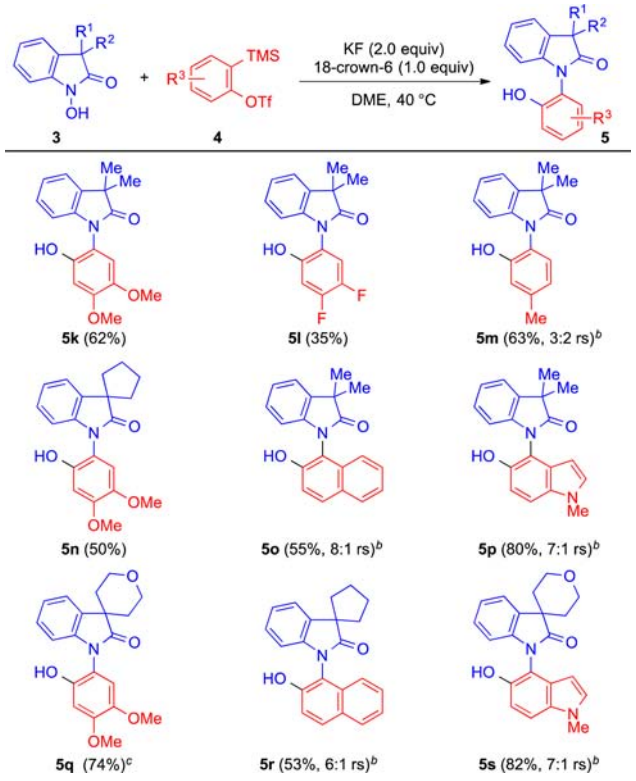
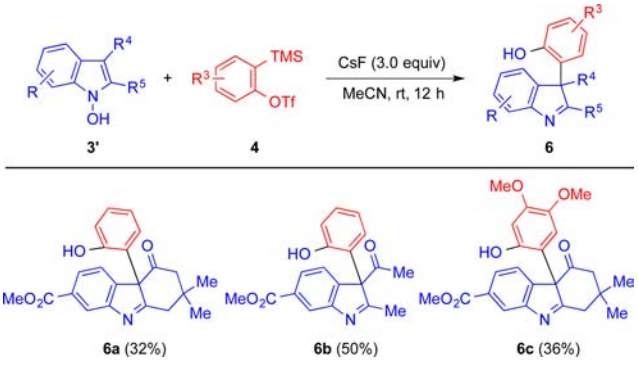
Scheme 3. Scope of Arynes for the Formal Insertion Reaction with Hydroxyindolinones[a]



[a]Reaction conditions: **3** (0.5 mmol, 1.0 equiv), **4** (1.1 equiv), DME (3 mL), 6−12 h. Isolation yield shown. [b]Major product shown. Isolation yields include both isomers. rs = regioselectivity, ratio determined by ^{1}H NMR. [c]Run in DME/MeCN (4 mL, 3:1).

We next examined *N*-hydroxyindoles **3′**, which have subtle structural and electronic difference from hydroxyindolinones **3**, as substrates for this transformation (Scheme 4). Indeed, the

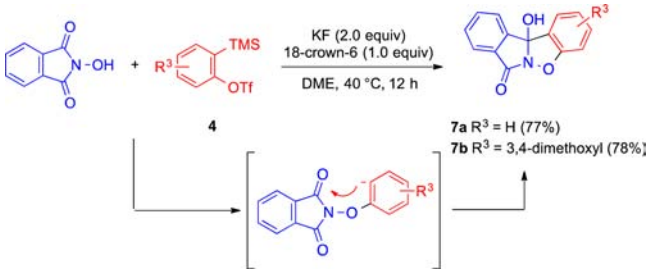
Scheme 4. Hydroxyindole−Aryne Addition and the [3,3]-Rearrangement



C3-aryl indole was formed as the major product, presumably via a [3,3]-rearrangement, instead of the expected *ortho*-aminophenol products.[18] We found that the use of CsF in MeCN favored the alternative [3,3]-rearrangement and also explored this reaction on several indole substrates. Albeit with moderate yields, the successful formation of **6a−c** suggests that this reaction allows for a rapid entry to C3-aryl indole skeletons embodied in many indole alkaloids as well as a good functional group tolerance. Especially interesting is the reactivity switching between [1,3]- and [3,3]-rearrangements in the formation of *N*-arylation and *C*-arylation products.[19]

Finally, *N*-hydroxyphthalimide, as another type of hydroxyamide substrate, was examined in the reaction with aryne precursors **4** (Scheme 5). Interestingly, these reactions led to

Scheme 5. Construction of Hydroxylactams by Addition of *N*-Hydroxyphthalimide to Arynes/Cyclization Sequence



the formation of **7a,b**.[20] In this case, 1-hydroxy-2-phthalimide intermediates, generated upon the addition to arynes, possess a more electrophilic carbonyl group and thus were prone to undergo the nucleophilic cyclization onto the carbonyl, rather than a [1,3]- or [3,3]-rearrangement.

In summary, we have developed a novel and efficient synthesis of *o*-aminophenols via the addition of hydroxyindolinones to arynes followed by a chemo- and regioselective [1,3]-rearrangement. It offers a mild transition-metal-free approach to rapidly construct *o*-aminophenol scaffolds, presenting useful applications in the synthesis of sterically hindered aminophenol-containing natural products, materials, and ligands.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03147.

Experimental procedures, additional screening data, characterization data for new compounds including ^{1}H and ^{13}C NMR spectra, and crystallographic data for **5j** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For *o*-aminophenol scaffolds in natural products, see: (a) Bringmann, G.; Kajahn, I.; Reichert, M.; Pedersen, S. E. H.; Faber, J. H.; Gulder, T.; Brun, R.; Christensen, S. B.; Ponte-Sucre, A.; Moll, H.; Heubl, G.; Mudogo, V. *J. Org. Chem.* **2006**, *71*, 9348. (b) Warabi, K.;

DOI: 10.1021/acs.orglett.5b03147
Org. Lett. 2015, 17, 6130−6133

Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765. (c) Zhang, H.-P.; Kakeya, H.; Osada, H. *Tetrahedron Lett.* **1997**, *38*, 1789. For selected examples in drugs, materials, and ligands, see: (d) Everitt, B. J.; Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J.-C.; Sokoloff, P. *Nature* **1999**, *400*, 371. (e) Mukherjee, C.; Pieper, U.; Bothe, E.; Bachler, V.; Bill, E.; Weyhermüller, T.; Chaudhuri, P. *Inorg. Chem.* **2008**, *47*, 8943.

(2) For recent examples, see: (a) Guo, B.; Fan, H.; Xin, Q.; Chu, W.; Wang, H.; Huang, Y.; Chen, X.; Yang, Y. *J. Med. Chem.* **2013**, *56*, 2642. (b) Wu, J.; Chen, W.; Xia, G.; Zhang, J.; Shao, J.; Zhang, C.; Yu, W.; Weng, Q.; Liu, H.; Hu, M.; Deng, H.; Hao, Y.; Shen, J.; Yu, Y.; Tan, B. *ACS Med. Chem. Lett.* **2013**, *4*, 974.

(3) For recent examples, see: (a) Funel, J.-A.; Brodbeck, S.; Guggisberg, Y.; Litjens, R.; Seidel, T.; Struijk, M.; Abele, S. *Org. Process Res. Dev.* **2014**, *18*, 1674. (b) Brucelle, F.; Renaud, P. *J. Org. Chem.* **2013**, *78*, 6245.

(4) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Wender, P. A.; Verma, V. A. T.; Paxton, J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(5) For selected examples, see: (a) Lange, J. H. M.; Hofmeyer, L. J.F.; Hout, F.A. S. S.; Osnabrug, J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101. (b) Konkel, M. J.; Packiarajan, M.; Chen, H.; Topiwala, U. P.; Jimenez, H.; Talisman, I. J.; Coate, H.; Walker, M. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3950. (c) Phillips, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J. H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137. (d) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613.

(6) (a) Zhang, Z. J.; Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Org. Lett.* **2014**, *16*, 3292. (b) Yang, X.; Shan, G.; Rao, Y. *Org. Lett.* **2013**, *15*, 2334. (c) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 9651.

(7) For a related transition-metal-free direct *ortho*-amination of phenols, see: Louillat-Habermeyer, M.-L.; Jin, R.; Patureau, F. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 4102.

(8) (a) Wassel, G. M. *Planta Med.* **1982**, *45*, 164. (b) Khuzhaev, V. U. *Chem. Nat. Compd.* **2004**, *40*, 196. (c) Khuzhaev, V. U.; Zhalolov, I.; Turgunov, K. K.; Tashkhodzhaev, B.; Levkovich, M. G.; Aripova, S. F.; Shashkov, A. S. *Chem. Nat. Compd.* **2004**, *40*, 261. (d) Khuzhaev, V. U.; Zhalolov, I. Z.; Levkovich, M. G.; Aripova, S. F.; Shashkov, A. S. *Russ. Chem. Bull.* **2004**, *53*, 1765.

(9) Cyphersmith, A.; Surampudi, S.; Casey, M. J.; Jankowski, K.; Venkataraman, D.; Barnes, M. D. *J. Phys. Chem. A* **2012**, *116*, 5349.

(10) (a) Hendrick, C. E.; McDonald, S. L.; Wang, Q. *Org. Lett.* **2013**, *15*, 3444. (b) Hendrick, C. E.; Wang, Q. *J. Org. Chem.* **2015**, *80*, 1059.

(11) (a) McDonald, S. L.; Wang, Q. *Chem. Commun.* **2014**, *50*, 2535. (b) McDonald, S. L.; Wang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 1867. (c) McDonald, S. L.; Hendrick, C. E.; Wang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 4667. (d) McDonald, S. L.; Wang, Q. *Synlett* **2014**, *25*, 2233. (e) Shen, K.; Wang, Q. *Chem. Sci.* **2015**, *6*, 4279.

(12) For recent reviews, see: (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (d) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214. (e) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (f) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725. For examples, see: (g) Nakayama, J.; Tajiri, T.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907. (h) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (i) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (j) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (k) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (l) Pena, D.; Perez, D.; Guitian, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (m) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (n) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (o) Liu, Y. L.; Liang, Y.; Pi, S. F.; Li, J. H. *J. Org. Chem.* **2009**, *74*, 5691. (p) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (q) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (r) Laczkowski, K. Z.; Garcia, D.; Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960. (s) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946. (t) Hoye, T. R.; Baire, B.; Niu, D. W.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (u) Saito, N.; Nakamura, K.; Shibano, S.; Ide, S.; Minami, M.; Sato, Y. *Org. Lett.* **2013**, *15*, 386. (v) Shen, C. R.; Yang, G. Q.; Zhang, W. B. *Org. Lett.* **2013**, *15*, 5722. (w) Shi, J. R.; Qiu, D. C.; Wang, J.; Xu, H.; Li, Y. *J. Am. Chem. Soc.* **2015**, *137*, 5670.

(13) (a) Tabolin, A. A.; Ioffe, S. L. *Chem. Rev.* **2014**, *114*, 5426. (b) Cox, J. R.; Dunn, J. M. F. *Tetrahedron Lett.* **1963**, *4*, 985. (c) Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858. (d) Ram, R. N.; Soni, V. K. *J. Org. Chem.* **2013**, *78*, 11935. (e) Wang, Y. Z.; Liu, L. Z.; Zhang, L. M. *Chem. Sci.* **2013**, *4*, 739. (f) Kumar, M.; Scobie, M.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *Org. Lett.* **2013**, *15*, 724. (g) Wang, H. Y.; Anderson, L. L. *Org. Lett.* **2013**, *15*, 3362. (h) Gao, H.; Ess, D. H.; Yousufuddin, M.; Kurti, L. *J. Am. Chem. Soc.* **2013**, *135*, 7086.

(14) (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99. (b) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (c) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169. (d) Huang, X.; Zhang, T. *J. Org. Chem.* **2010**, *75*, 506.

(15) Several different *N*-aryl hydroxylamines were examined for the proposed transformation. Only the cyclic *N*-hydroxyl amide (i.e., **3a**) led to the formation of the desired *o*-aminophenol product. See the Supporting Information for details.

(16) Nakazaki, A.; Mori, A.; Kobayashi, S.; Nishikawa, T. *Tetrahedron Lett.* **2012**, *53*, 7131.

(17) (a) Liu, Z. J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. (b) Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267. (c) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96. (d) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett* **2011**, *2011*, 2599.

(18) Somei, M.; Kawasaki, T.; Fukui, Y.; Yamada, F.; Kobayashi, T.; Aoyama, H.; Shinmyo, D. *Heterocycles* **1992**, *34*, 1877.

(19) (a) Varoglu, M.; Corbett, T. H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **1997**, *62*, 7078. (b) Raju, R.; Piggott, A. M.; Conte, M.; Aalbersberg, W. G. L.; Feussner, K.; Capon, J. R. *Org. Lett.* **2009**, *11*, 3862.

(20) For related reactions of *N*-hydroxyphthalimide with electron deficient alkynes, see: (a) Zhou, Q. F.; Chu, X. P.; Ge, F. F.; Wang, Y.; Lu, T. *Adv. Synth. Catal.* **2013**, *355*, 2787. (b) Xie, J. N.; Yu, B.; Guo, C. X.; He, L. N. *Green Chem.* **2015**, *17*, 4061.

DOI: 10.1021/acs.orglett.5b03147
Org. Lett. 2015, 17, 6130−6133