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Oxidative Nucleophilic Cyclization of 2-Alkynylanilines with Thiophenols under Metal-Free Conditions

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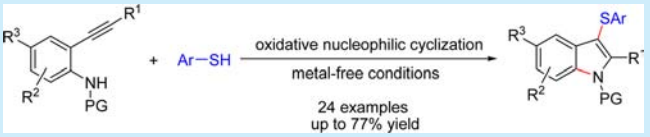
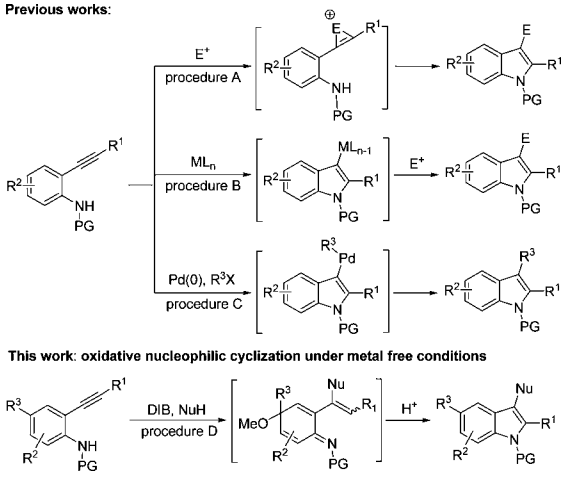
Supporting Information

ABSTRACT: An oxidative nucleophilic cyclization of 2-alkynylanilines with thiophenols under metal-free conditions was developed. The one-pot two-step reaction involves a $PhI(OAc)_2$-mediated oxidative dearomatization and a Brønsted acid promoted nucleophilic cyclization. DFT calculations were performed to understand the reaction pathway.



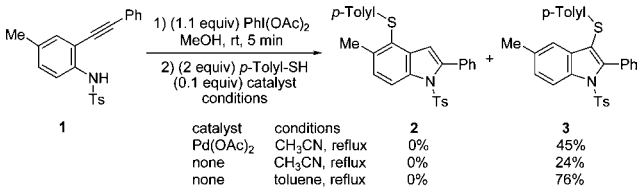
Due to their remarkable biological and medicinal activities, 3-substituted indoles are of synthetic importance. 2-Alkynylanilines are versatile precursors to prepare substituted indoles as a result of their ready availability.[1] The direct electrophilic cyclization[2] (Scheme 1, procedure A) and the transition metal-assisted electrophilic cyclization of 2-alkynylanilines (Scheme 1, procedure B)[3−8] are the most widely employed methods. These reactions enable the incorporation of an electrophile in the 3-position of indoles. Recently, the transition-metal-catalyzed cascade cyclization/coupling reactions (Scheme 1, procedure C) have been developed.[9] These tactics provide an alternative way to access 3-substituted indoles. At times, the high cost and the toxicity of transition metals limit the utility of such methods. In this paper, we present our preliminary results on the unprecedented *metal-free oxidative nucleophilic cyclization* of 2-alkynylanilines with nucleophiles (Scheme 1, procedure D).

Scheme 1. Synthesis of 3-Substituted Indoles from 2-Alkynylanilines



Dearomatization of aromatic compounds is one of the most powerful tools in the synthesis of complex molecules.[10] Our recent studies[11] revealed that the dearomatization strategy of 2-alkynylanilines[12] might offer a unique opportunity to build 4-substituted indoles through oxidative dearomatization and subsequent metal-catalyzed cascade cyclization/Michael addition/aromatization. However, when we examined the reaction of *N*-Ts 4-methyl-2-(2-phenylethynyl)benzenamine **1** with 4-methylbenzenethiol using $Pd(OAc)_2$ as the catalyst, the reaction gave rise to 3-sulfenylindole **3** as the major product instead of the expected 4-sulfenylindole **2** (Scheme 2). The structure of compound **3** was confirmed by its single-crystal diffraction analysis.[13] Moreover, the formation of compound **3** was still observed when some other different types of metal salts such as Au(I), Pt(II), Rh(II), Cu(II), Zn(II), Sc(III) Au(III), and Fe(III) were employed. These experiments indicated that the presence of a metal catalyst might not be essential to the formation of 3-sulfenylindole. Indeed, the reaction in the absence of an added catalyst also produced compound **3** in 24% yield. After screening of solvents and temperatures for the second step reaction, the isolated yield of 3-sulfenylindole **3** was improved to 76% when the reaction was conducted in toluene at reflux.

Scheme 2



The potential therapeutic value of 3-sulfenylindoles in many diseases[14] inspired us to investigate the possible pathway of this

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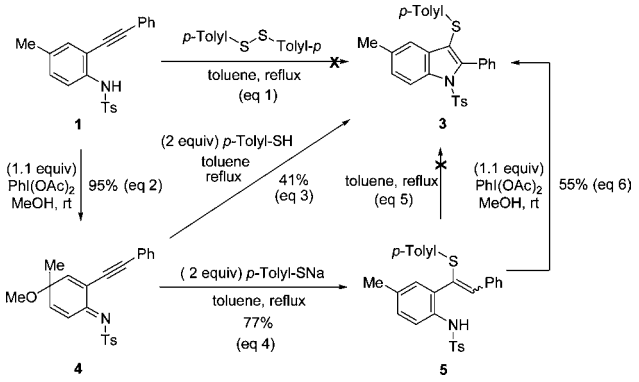
reaction and explore its synthetic utility.[15] When compound **1** was mixed with 4-methylbenzenethiol in toluene at reflux, no reaction was observed. The groups of Larock and Zhang have developed the electrophilic cyclization of 2-alkynylaniline derivatives with arylsulfenyl chlorides or disulfides with the aid of *n*-Bu_4NI,[2c,d] $PdCl_2$,[16] or Fe/I_2.[2e] To rule out the possibility of electrophilic cyclization, we examined the reaction of compound **1** with 1,2-di-*p*-tolyldisulfane, but no reaction was observed (Scheme 3, eq 1). The $PhI(OAc)_2$-mediated oxidative

Scheme 3. Search for Mechanistic Insight

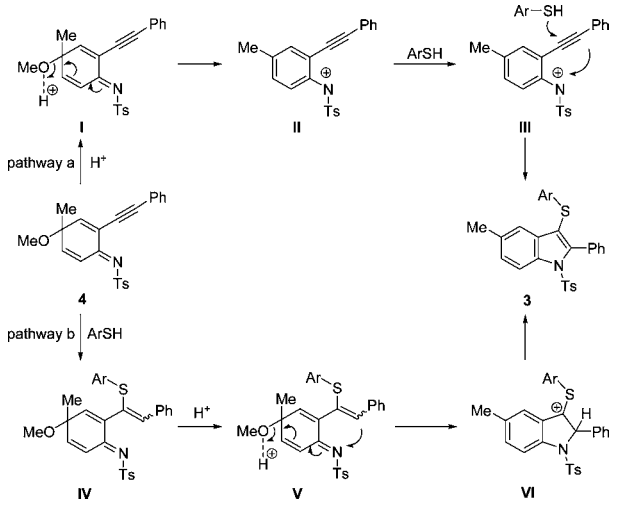


dearomatization produced 2-alkynylcyclohexadienimine **4** in 95% yield (Scheme 3, eq 2). The reaction of compound **4** with 4-methylbenzenethiol under the standard conditions afforded compound **3**, but only in 41% yield (Scheme 3, eq 3). This experiment indicated that the second step of the one-pot reaction might be promoted by acetic acid generated from the metabolism of (diacetoxyiodo)benzene in the oxidative dearomatization step. Moreover, when sodium 4-methylbenzenethiolate was used instead of 4-methylbenzenethiol, the formation of 3-sulfenylindole was not observed, but compound **5** was isolated in 77% yield (Scheme 3, eq 4). Treating compound **5** in toluene at reflux did not lead to the conversion to 3-sulfenylindole even with the aid of $Pd(OAc)_2$ (Scheme 3, eq 5). But it is noteworthy that, when compound **5** was mixed with 1.1 equiv of $PhI(OAc)_2$ in methanol at room temperature, the conversion occurred and gave rise to compound **3** in 55% yield (Scheme 3, eq 6).

The above experiments indicated that there are at least two possible reaction pathways for the formation of 3-sulfenylindole from the dearomatized product (Scheme 4). In pathway a, the proton promotes the departure of the methoxyl group of 2-alkynylcyclohexadienimine to form an intermediate **II**. The positive charge on the nitrogen atom of this intermediate induces a cascade cyclization and nucleophilic addition by thiophenol. In pathway b, the nucleophilic addition to the triple bond of 2-alkynylcyclohexadienimine occurs before the aromatization and the cyclization. With the aid of acid, the generated intermediate **IV** undergoes a tandem cyclization and aromatization to produce 3-sulfenylindole.

To further understand the reaction pathway, density functional theory (DFT) calculations were performed.[17] The primary results revealed that, compared with the nucleophilic addition to the triple bond (the total barrier is 36.9 kcal mol^{-1}), the relative free energy (69.3 kcal mol^{-1}) of the intermediate having a positive charge on the nitrogen atom is much higher. This means that the nucleophilic cyclization favors pathway b to a large extent. As shown in Figure 1, the detailed reaction

Scheme 4. Possible Reaction Pathways



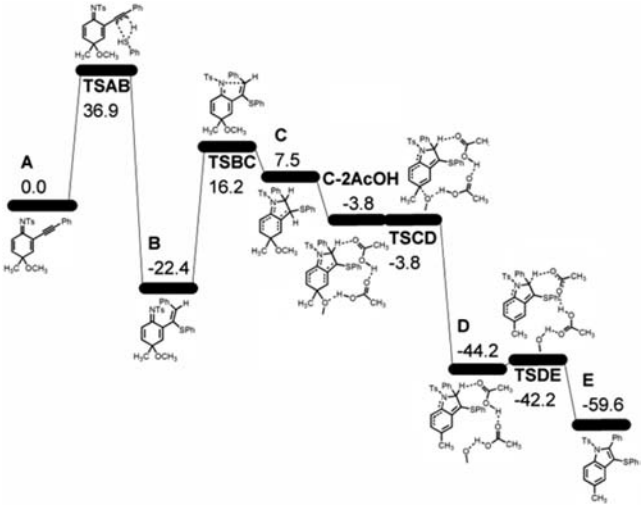


Figure 1. Free-energy reaction profile (kcal mol^{-1}) from the dearomatized product to 3-sulfenylindole, calculated at the PCM (Toluene) B3LYP/6-31++G(d,p)//B3LYP/6-31G(d) level. TS = transition state.

pathway is indicated. The reaction is initiated by an asynchronous concerted electrophilic addition of thiophenol to the triple bond of 2-alkynylcyclohexadienimine via **TSAB** to form the key intermediate **B**. This is the rate-determining step. Subsequent cyclization of **B** affords a bicyclic intermediate **C**. With the aid of acetic acid, the departure of a methoxyl group (**TSCD**) and the elimination of a proton (**TSDE**) lead to the formation of the thermodynamically stable 3-sulfenylindole.

Moreover, the NBO (natural bond orbital) analysis of the structure of 2-alkynylcyclohexadienimine revealed that its C-8 position is more positively charged (0.09) compared to the C-3 (−0.23) position (Figure 2). The corresponding condensed Fukui function also shows that the nucleophilic attack will occur at the C-8 position.[18]

The species of protecting group at the nitrogen atom of 2-alkynylaniline has a big influence on the reaction. The tosyl group proved to be the best (Scheme 5). The scope of this metal-free oxidative nucleophilic cyclization was further explored, and the results are summarized in Table 1. For most cases, the one-pot two-step reaction proceeded smoothly

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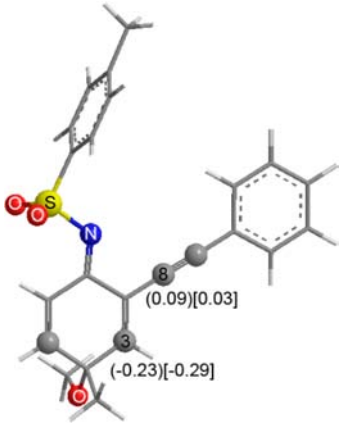
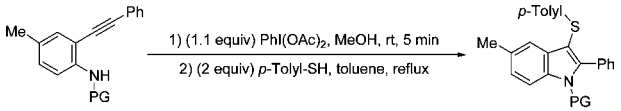


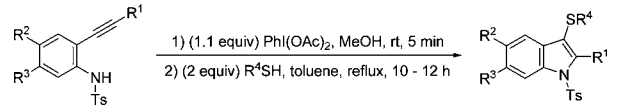
Figure 2. Optimized structure of 2-alkynylcyclohexadienimine. The numbers in the parentheses are the NBO charges on atoms, and the numbers in square brackets are the condensed Fukui functions.

Scheme 5



PG = Ts **3** (76%)
PG = Ms **6** (47%)
PG = Bz **7** (26%)
PG = Bn **8** (0%)

Table 1. Oxidative Nucleophilic Cyclization of 2-Alkynylanilines with Thiophenols



entry	R^1	R^2	R^3	R^4	product (%)[a]
1	C_6H_5	Me	H	4-MeC_6H_4	**3** (76)
2	4-MeC_6H_4	Me	H	4-MeC_6H_4	**9** (75)
3	4-$MeOC_6H_4$	Me	H	4-MeC_6H_4	**10** (72)[b]
4	4-ClC_6H_4	Me	H	4-MeC_6H_4	**11** (65)
5	4-$CF_3C_6H_4$	Me	H	4-MeC_6H_4	**12** (61)
6	4-$NO_2C_6H_4$	Me	H	4-MeC_6H_4	**13** (59)
7	2-thiophene	Me	H	4-MeC_6H_4	**14** (77)[b]
8	*n*-Bu	Me	H	4-MeC_6H_4	**15** (0)
9	CO_2Et	Me	H	4-MeC_6H_4	**16** (0)
10	C_6H_5	Et	H	4-MeC_6H_4	**17** (75)[b]
11	C_6H_5	*i*Pr	H	4-MeC_6H_4	**18** (73)[b]
12	C_6H_5	*n*Bu	H	4-MeC_6H_4	**19** (71)[b]
13	C_6H_5	H	H	4-MeC_6H_4	**20** (51)[b,c]
14	C_6H_5	Me	Me	4-MeC_6H_4	**21** (69)[b]
15	C_6H_5	Me	Br	4-MeC_6H_4	**22** (0)
16	C_6H_5	Me	H	2-MeC_6H_4	**23** (75)
17	C_6H_5	Me	H	3-MeC_6H_4	**24** (75)[b]
18	C_6H_5	Me	H	3,5-$Me_2C_6H_3$	**25** (71)[b]
19	C_6H_5	Me	H	C_6H_5	**26** (72)[b]
20	C_6H_5	Me	H	4-$MeOC_6H_4$	**27** (55)
21	C_6H_5	Me	H	4-BrC_6H_4	**28** (73)
22	C_6H_5	Me	H	4-ClC_6H_4	**29** (71)
23	C_6H_5	Me	H	4-FC_6H_4	**30** (62)
24	C_6H_5	Me	H	*n*-Bu	**31** (0)

[a]Reported yields are of the isolated products. [b]Benzoic acid (1 equiv) was added. [c]The isolated product was 5-methoxy 3-sulfenylindole.

leading to the corresponding 3-sulfenylindoles in moderate to good yields. In some cases, 1 equiv of benzoic acid was added to promote the nucleophilic cyclization. The R^1 group at the alkynyl moiety of 2-alkynylanilines could be not only an electron-rich but also an electron-poor aryl group (Table 1, entries 1−7). It is noteworthy that 2-alkynylanilines bearing an electron-poor alkynyl group are normally not good substrates for electrophilic cyclization. Interestingly, when the R^1 group was an *n*-butyl group, the reaction did not produce 3-sulfenylindole, but gave rise to a 4-sulfenylindole in 45% yield (Table 1, entry 8). The condensed Fukui function analysis of 2-alkynylcyclohexadienimine bearing an *n*-butyl group supports the experimental fact as well. The condensed Fukui functions for the corresponding C-3 and C-8 positions are 0.09 and −0.07, respectively. This means that, for this substrate, the C-3 position is a more favored site for the nucleophilic attack. When the R^1 group was an ester group, the reaction is complex (Table 1, entry 9). The para-substituent of 2-alkynylanilines could be an ethyl, an isopropyl, or a *n*-butyl group (Table 1, entries 10−12). When the R^2 group of 2-alkynylaniline was a hydrogen atom, 2 equiv of $PhI(OAc)_2$ were used in the oxidative dearomatization step to generate 4,4-dimethoxy-2-alkynylcyclohexadienimine, and the one-pot reaction provided 5-methoxy 3-sulfenylindole **20** in 51% yield (Table 1, entry 13). When 5-bromo 2-alkynylaniline was used as a substrate, the oxidative dearomatization was very complex (Table 1, entry 15). A range of thiophenols could be used as a nucleophile to be introduced in the C-3 position of indole. However, compared to the high reactivity of thiophenols, butane-1-thiol was not a suitable nucleophile, and it only served as a reductant to reduce 2-alkynylcyclohexadienimine to 2-alkynylaniline.

In conclusion, we have developed an oxidative nucleophilic cyclization of 2-alkynylanilines with thiophenols under metal-free conditions. This method provides an alternative way to prepare 3-substituted indole derivatives. The current direction is aimed at extending the reaction scope and investigating the reaction mechanism, and these results are forthcoming.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, copies of ^1H and ^{13}CNMR of new compounds, X-ray diffraction structure and crystallographic data of compound **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

(c) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.

(2) (a) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (b) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzláez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (c) Chen, Y.; Cho, C.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802. (d) Chen, Y.; Cho, C.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (e) Du, H.-A.; Tang, R.-Y; Deng, C.-L.; Liu, Y.; Li, J.-H.; Zhang, X.-G. *Adv. Synth. Catal.* **2011**, *353*, 2739. (f) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (g) Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274.

(3) For examples on the palladium-catalyzed reaction, see: (a) Wang, Q.; Huang, L.; Wu, X.; Jiang, H. *Org. Lett.* **2013**, *15*, 5940. (b) Álvarez, R.; Martínez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; de Lera, A. R. *Chem.—Eur. J.* **2010**, *16*, 12746. (c) Janreddy, D.; Kavala, V.; Kuo, C.-W.; Kuo, T.-S.; He, C.-H.; Yao, C.-F. *Tetrahedron* **2013**, *69*, 3323. (d) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 8770. (e) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662.

(4) For examples on the gold-catalyzed reaction, see: (a) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265. (b) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212. (c) Arcadi, A.; Pietropaolo, E.; Alvino, A.; Michelet, V. *Org. Lett.* **2013**, *15*, 2766. (d) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284.

(5) For examples on the platinum-catalyzed reaction, see: (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (b) Li, X.; Wang, J.-Y.; Yu, W.; Wu, L.-M. *Tetrahedron* **2009**, *65*, 1140. (c) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670.

(6) For an example on the rhodium-catalyzed reaction, see: Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329.

(7) For examples on zinc-catalyzed reaction, see: (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (b) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803. (c) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731.

(8) For an example on the silver-catalyzed reaction, see: Liu, J.; Xie, X.; Liu, Y. *Chem. Commun.* **2013**, *49*, 11794.

(9) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Iazzetti, A. *Org. Biomol. Chem.* **2012**, *10*, 9142. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal.* **2006**, *348*, 1301. (d) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213. (e) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (f) Arcadi, A.; Cianci, R.; Ferrara, G.; Marinelli, F. *Tetrahedron* **2010**, *66*, 2378.

(10) For reviews on dearomatization, see: (a) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (c) López Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andújar Sánchez, C. M.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580. (d) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (e) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (f) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (g) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (h) Ding, Q.; Ye, Y.; Fan, R. *Synthesis* **2013**, *45*, 1.

(11) (a) Yang, M.; Tang, J.; Fan, R. *Chem. Commun.* **2012**, *48*, 11775. (b) Zhang, L.; Li, Z.; Fan, R. *Org. Lett.* **2012**, *14*, 6076. (c) Yang, M.; Tang, J.; Fan, R. *Org. Lett.* **2013**, *15*, 3464. (d) Zhang, C.; Chen, J. J.; Fan, R. *Org. Lett.* **2014**, *16*, 816. (e) Feng, X.; Wang, H.; Yang, B.; Fan, R. *Org. Lett.* **2014**, *16*, 3600.

(12) For examples on dearomatization of anilines, see: (a) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325. (b) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215. (c) Quideau, S.; Pouységu, L.; Ozanne, A.; Gagnepain, J. *Molecules* **2005**, *10*, 201. (d) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (e) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629. (f) Giroux, M.-A.; Guérard, K. C.; Beaulieu, M.-A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871.

(13) Crystallographic data for compound **3** are available free of charge from the Cambridge Crystallographic Data Centre, accession number CCDC 1035533.

(14) (a) Ragno, R.; Coluccia, A.; La Regina, G.; De Martino, G.; Piscitelli, F.; Lavecchia, A.; Novellino, E.; Bergamini, A.; Ciaprini, C.; Sinistro, A.; Maga, G.; Crespan, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 3172. (b) La Regina, G.; Edler, M. C.; Brancale, A.; Kandil, S.; Coluccia, A.; Piscitelli, F.; Hamel, E.; De Martino, G.; Matesanz, R.; Díaz, J. F.; Scovassi, A. I.; Prosperi, E.; Lavecchia, A.; Novellino, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2007**, *50*, 2865. (c) Cianchi, F.; Cortesini, C.; Magnelli, L.; Fanti, E.; Papucci, L.; Schiavone, N.; Messerini, L.; Vannacci, A.; Capaccioli, S.; Perna, F.; Lulli, M.; Fabbroni, V.; Perigli, G.; Bechi, P.; Masini, E. *Mol. Cancer Ther.* **2006**, *5*, 2716.

(15) For examples on the synthesis of 3-sulfenylindoles: (a) Yang, F.-L.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4929. (b) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.* **2006**, *8*, 565. (c) Schlosser, K. M.; Krasutsky, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.* **2004**, *6*, 819. (d) Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 7688. (e) Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anikumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 2434.

(16) Guo, Y.-J.; Tang, R.-Y; Li, J.-H.; Zhong, P.; Zhang, X.-G. *Adv. Synth. Catal.* **2009**, *351*, 2615.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

(18) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1999. (b) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.