Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

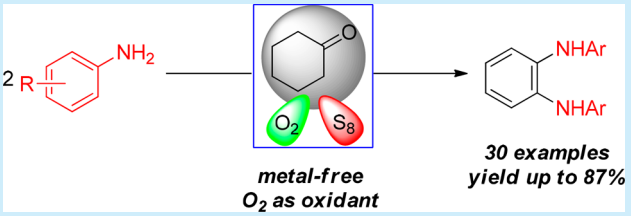
Synthesis of *o*-Arylenediamines through Elemental Sulfur-Promoted Aerobic Dehydrogenative Aromatization of Cyclohexanones with Arylamines

Zhen Wang, Xiangui Chen, Hao Xie, Dahan Wang, Huawen Huang,* and Guo-Jun Deng*

Key Laboratory for Green Organic Synthesis and Application of Hunan Province, Key Laboratory of Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China

Supporting Information

ABSTRACT: Herein, the first elemental sulfur-promoted aerobic dehydrogenative aromatization of cyclohexanones is described that provides novel access to synthetically useful *o*-arylenediamines. This protocol complements previous palladium- and iodine-catalyzed diarylamine formation from cyclohexanones and anilines.



Org. Lett.

Transition-metal-catalyzed cross coupling has proven to be one of the most powerful tools for arylation and the construction of functionalized aromatic compounds.[1] Among the well established named coupling reactions, all of them require prefunctionalized arylating reagents that include aryl halides,[2] organoboranes,[3] arylsiloxanes,[4] and others.[5] Accordingly, highly excessive or stoichiometric amounts of additives such as base are generally required. In the past decade, cyclohexanones have been emerging as environmentally friendly and versatile arylation reagents.[6] The versatility of cyclohexanones as aryl sources is reflected by the broad range of functionalized aromatic products they now provide, which include phenols,[7] aromatic amines,[8] aromatic ethers,[9] biarenes,[10] and some kinds of benzoheterocycle[11] (Figure 1a−d). Also, the strategy of dehydrogenative aromatization of

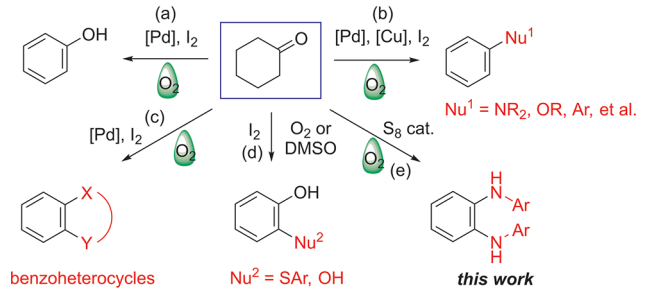


Figure 1. Dehydrogenative aromatization of cyclohexanones.

cyclohexanones has been flexibly enabled by optional metal or metal-free catalytic systems. For example, Stahl and co-workers demonstrated a palladium-catalytic aerobic system in which dehydrogenative aromatization of cyclohexanones occurred effectively to give phenols,[7a−c] while Jiao et al. developed a viable iodine-based catalytic system for the same reaction.[7d,e] As a relatively sustainable chemical process, metal-free iodine-catalyzed dehydrogenative aromatization of cyclohexanones has been successfully applied in the preparation of 3,3′,4,4′-tetrahydroxybiphenyl, an aggregation inhibitor of Alzheimer's amyloid-β peptide (Aβ), by a pathway that had higher atom- and step-economy over a traditional palladium-catalyzed Suzuki coupling.[7d]

Our recent research has revealed that cyclohexanones can couple with amines to permit 1,2-difunctionalization/C−N bond formation under sulfur-based aerobic conditions.[12] However, dehydrogenative aromatization did not occur, thus leading to the formation of tetrahydrobenzimidazoles in these systems (Figure 2a−b). When we tried anilines as coupling

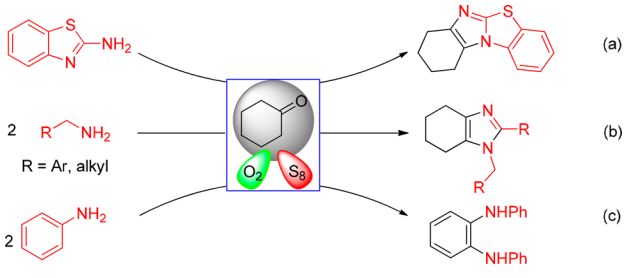


Figure 2. Coupling of cyclohexanones and amines in sulfur-promoted aerobic systems.

partners, *o*-phenylenediamines were detected as the main products. In a reaction complementary to previous work, herein, we report the first sulfur-enabled dehydrogenative aromatization of cyclohexanones, which provides a novel access to *o*-phenylenediamines[13] from cyclohexanones and arylamines (Figure 2c). Compared with the established methods for palladium- and iodine-catalyzed coupling of

Received: July 27, 2018

DOI: 10.1021/acs.orglett.8b02387
Org. Lett. XXXX, XXX, XXX−XXX

cyclohexanones and amines,[8] the present dehydrogenative aromatization of cyclohexanone proceeds through a 1,2-difunctionalization with two molecules of arylamine, and again, oxygen serves as the co-oxidant.

To initiate our study, cyclohexanone **1a** and aniline **2a** were used as the model substrates (Table 1). In the absence of any

Table 1. Optimization of Reaction Conditions[a]

entry	catalyst (mol %)	additive	solvent	yield[b] (%)
1			toluene	trace
2	S_8 (12.5)		toluene	34
3	I_2 (20)		toluene	trace
4	KI (100)		toluene	7
5	S_8 (12.5)		DMSO	8
6	S_8 (12.5)		DMF	24
7	S_8 (12.5)		NMP	17
8	S_8 (12.5)		PhCl	24
9	S_8 (12.5)		*o*-xylene	27
10	S_8 (12.5)	AcOH	toluene	50
11	S_8 (12.5)	BzOH	toluene	62
12	S_8 (12.5)	TsOH	toluene	trace
13	S_8 (12.5)	H_3PO_4	toluene	13
14	S_8 (12.5)	HCl	toluene	53
15	S_8 (18.75)	BzOH	toluene	61
16	S_8 (6.25)	BzOH	toluene	48
17[c]	S_8 (12.5)	BzOH	toluene	9
18[d]	S_8 (12.5)	BzOH	toluene	19
19[e]	S_8 (12.5)	BzOH	toluene	70 (75)[g]
20[f]	S_8 (12.5)	BzOH	toluene	58

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.7 mmol), catalyst, additive (0.2 mmol), solvent (0.6 mL), 120 °C under O_2, 24 h. [b]Isolated yield, trace amounts were determined by GC–MS. [c]Under Ar. [d]Under air. [e]130 °C. [f]140 °C. [g]Yield on a 10 mmol scale.

catalyst or additive, the mixture was heated in toluene under oxygen to form trace amounts of *o*-phenylenediamine **3aa** (entry 1). The addition of elemental sulfur (S_8) dramatically enhanced the transformation to produce **3aa** in 34% yield (entry 2). Notably, the previously utilized iodine (I_2) as well as iodide gave a very low yield in this reaction (entries 3 and 4). Testing of other solvents such as DMSO, DMF, NMP, PhCl, and *o*-xylene gave inferior results to toluene for the present dehydrogenative aromatization (entries 5–9). To our delight, some organic acids as additives could increase the reaction yield (entries 10–12). Among them, benzoic acid (BzOH) facilitated the generation of **3aa** in 62% yield (entry 11), while inorganic acids such as H_3PO_4 and HCl gave negative results (entries 13 and 14). We also screened the amount of S_8 added (entries 15 and 16), the reaction atmosphere (entries 17 and 18), and the temperature (entries 19 and 20) and found that elevating the reaction temperature to 130 °C further enhanced the transformation, affording the target product **3aa** in 70% yield (entry 19). Notably, the gram-scale reaction has proven to be even slightly higher yielding in this reaction system.

With the optimized reaction conditions in hand, we next explored the substrate scope of the present dehydrogenative aromatization. For substituted cyclohexanones (Figure 3), the 3-methyl reactant **1b** gave the product **3ba** in good yield with

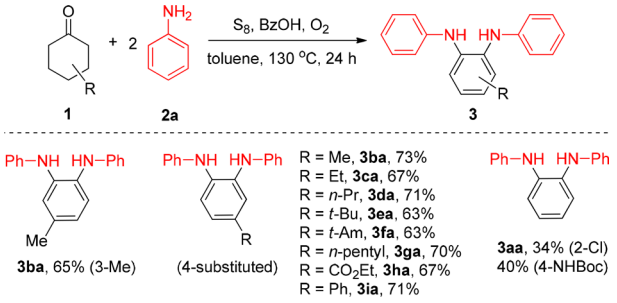


Figure 3. Scope of cyclohexanones.

high levels of regioselectivity. This result revealed the strong effect of steric hindrance in the speculative *α*-functionalization/C–N coupling of cyclohexanones. Cyclohexanones bearing C4-substituents afford the corresponding products in generally moderate yields with good tolerance of a variety of functionalities, in which both electron-donating alkyls (**3ca–ga**) and electron-withdrawing esters (**3ha**) had minimal influence on the reaction yields. Notably, 4-NHBoc as well as 2-Cl cyclohexanone gave the same product **3aa**, with both functional groups eliminated in the reaction procedure.

Subsequently, the scope and generality of the anilines utilized was studied (Figure 4). In this regard, a broad range of

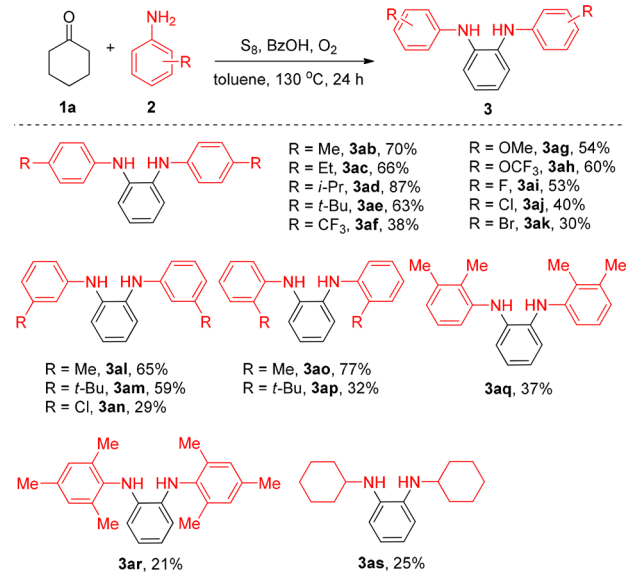


Figure 4. Scope of anilines.

functionalities attached at the benzene ring were compatible, with alkyls, trifluoromethyl, methoxyl, and halo (F, Cl, Br) tolerated to afford the corresponding products in moderate to good yields (**3ab–ap**). Among them, electron-deficient (trifluoromethyl)aniline (**3af**) as well as halo-substituted anilines (**3ai–ak**, **3an**) gave comparatively low yields of products. Moreover, while *o*-toluidine generated the desired **3ao** in good yield, more bulky 2-(*tert*-butyl)aniline (**3ap**) dramatically decreased the yield to 32%, revealing an obvious steric hindrance effect. Multiple methyl-substituted anilines gave **3aq** and **3ar** in 37% and 21% yields, respectively. Unfortunately, secondary anilines such as *N*-methylaniline did not work in this system. Finally, among others of aliphatic amines tested, only cyclohexanamine worked, albeit in 25% yield.

DOI: 10.1021/acs.orglett.8b02387
Org. Lett. XXXX, XXX, XXX–XXX

The synthetic utility of the present system was further explored by the cross coupling of two different anilines, which smoothly transited into the *o*-phenylenediamine products (Figure 5).

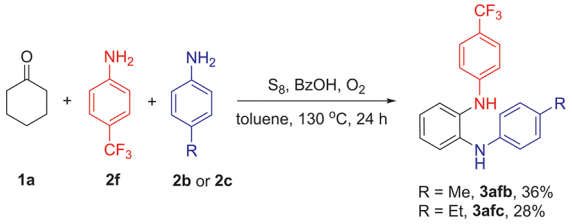


Figure 5. Cross coupling with two different anilines.

The reaction mechanism of the dehydrogenative aromatization of cyclohexanones with two molecules of anilines was preliminarily studied by some control experiments (Figure 6).

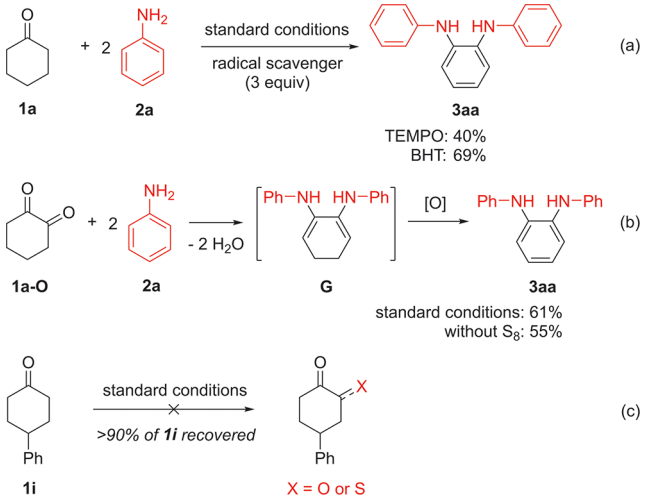


Figure 6. Control experiments.

First, the radical clock experiments revealed that the addition of a radical scavenger such as TEMPO and butylated hydroxytoluene (BHT) into the reaction system did not inhibit the transformation, with no observation of any radical-trapping intermediates (Figure 6a). Furthermore, we suspect that cyclohexane-1,2-dione (**1a-O**) may be the intermediate by α-oxidation of cyclohexanone, which proceeds through condensation with aniline to afford cyclohexa-1,3-diene **E** followed by dehydrogenative aromatization. This compound indeed gave the target product **3aa** under the standard conditions or in the absence of S_8 (Figure 6b), which indicates that intermediate cyclohexa-1,3-diene **G** is probably involved in the reaction and the final dehydrogenative aromatization process is enabled by only oxygen. Finally, the treatment of 4-phenylcyclohexanone **1i** under our standard conditions did not afford any α-oxidation products, and the majority of it was recovered (Figure 6c).

Based on the experimental results and the well-known Willgerodt–Kindler reaction[14] (coupling of ketones, amines, and elemental sulfur), a plausible reaction mechanism was proposed (Figure 7). The condensation of **1a** and **2a** affords enamine **A**, which attacks sulfur (S_n) to generate intermediate **B**. Subsequently, intermediate **C** is formed by the elimination of S_{n-1}. Intermolecular nucleophilic cyclization followed by the

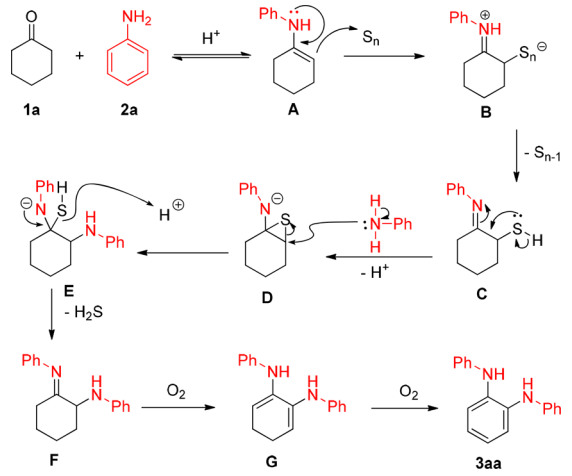


Figure 7. Possible reaction mechanism.

aniline attack generates intermediate **E**. Then elimination of H_2S occurs to afford α-aminoimino **F**. This process could clarify why 1 equiv of sulfur is needed for this reaction. Finally, the aromatization proceeds through two-step dehydrogenative oxidation of **F** via cyclohexa-1,3-diene **G**.

In summary, we have developed a novel elemental sulfur-promoted aerobic system for dehydrogenative aromatization/coupling of cyclohexanones with anilines. In reaction complementary to previous diarylamine formation, this reaction affords access to *o*-arylenediamines from simple and readily available starting materials. This elemental sulfur-based protocol may inspire other cases of functionalization and dehydrogenative aromatization of cyclohexanones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02387.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hwhuang@xtu.edu.cn.
*E-mail: gjdeng@xtu.edu.cn.

ORCID

Huawen Huang: 0000-0001-7079-1299
Guo-Jun Deng: 0000-0003-2759-0314

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support by the National Natural Science Foundation of China (21572194, 21602187), the Collaborative Innovation Center of New Chemical Technologies for Environmental Benignity and Efficient Resource Utilization, and the Scientific Research Fund of Hunan Provincial Education Department (16B251) is gratefully acknowledged.

DOI: 10.1021/acs.orglett.8b02387
Org. Lett. XXXX, XXX, XXX–XXX

REFERENCES

(1) For recent reviews, see: (a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333. (b) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163.

(2) (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (e) Touré, B. B.; Lane, B. B.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (f) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (g) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (h) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (i) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (j) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644. (k) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929. (l) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471. (m) Wang, L.; Yi, W. B.; Cai, C. *Chem. Commun.* **2011**, *47*, 806. (n) Huang, Y. B.; Lin, Z. J.; Cao, R. *Chem. - Eur. J.* **2011**, *17*, 12706. (o) Truong, T.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 4243.

(3) (a) Yang, S.; Sun, C.; Fang, Z.; Li, B.; Li, Y.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (b) Zhao, J. L.; Zhang, Y. H.; Cheng, K. *J. Org. Chem.* **2008**, *73*, 7428. (c) Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4235.

(4) Liang, Z. J.; Yao, B. B.; Zhang, Y. H. *Org. Lett.* **2010**, *12*, 3185.

(5) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (b) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (c) Chen, Y. X.; Guo, S. B.; Li, K. N.; Qu, J. P.; Yuan, H.; Hua, Q. R.; Chen, B. H. *Adv. Synth. Catal.* **2013**, *355*, 711. (d) Mochida, K.; Shimizu, M.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 8350. (e) Cornella, J.; Lu, P. F.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506. (f) Wu, M.; Luo, J.; Xiao, F.; Zhang, S.; Deng, G.-J.; Luo, H.-A. *Adv. Synth. Catal.* **2012**, *354*, 335.

(6) Girard, S. A.; Huang, H.; Zhou, F.; Deng, G.-J.; Li, C.-J. *Org. Chem. Front.* **2015**, *2*, 279.

(7) (a) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209. (b) Diao, T.; Pun, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8205. (c) Pun, D.; Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8213. (d) Liang, Y. F.; Li, X.; Wang, X.; Zou, M.; Tang, C.; Liang, Y.; Song, S.; Jiao, N. *J. Am. Chem. Soc.* **2016**, *138*, 12271. (e) Liang, Y. F.; Song, S.; Ai, L.; Li, X.; Jiao, N. *Green Chem.* **2016**, *18*, 6462.

(8) (a) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 1692. (b) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M. O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, *14*, 5606. (c) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, *14*, 5488. (d) Barros, M. T.; Dey, S. S.; Maycock, C. D.; Rodrigues, P. *Chem. Commun.* **2012**, *48*, 10901. (e) Sutter, M.; Duclos, M. C.; Guicheret, B.; Raoul, Y.; Métay, E.; Lemaire, M. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1463. (f) Cao, X.; Bai, Y.; Xie, Y.; Deng, G.-J. *J. Mol. Catal. A: Chem.* **2014**, *383*, 94.

(9) (a) Simon, M. O.; Girard, S. A.; Li, C.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7537. (b) Sutter, M.; Sotto, N.; Raoul, Y.; Métay, E.; Lemaire, M. *Green Chem.* **2013**, *15*, 347. (c) Sutter, M.; Lafon, R.; Raoul, Y.; Métay, E.; Lemaire, M. *Eur. J. Org. Chem.* **2013**, *2013*, 5902.

(10) (a) Zhou, F.; Simon, M. O.; Li, C.-J. *Chem. - Eur. J.* **2013**, *19*, 7151. (b) Chen, S.; Liao, Y.; Zhao, F.; Qi, H.; Liu, S.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 1618.

(11) (a) Xiao, F.; Liao, Y.; Wu, M.; Deng, G.-J. *Green Chem.* **2012**, *14*, 3277. (b) Liao, Y.; Jiang, P.; Chen, S.; Xiao, F.; Deng, G.-J. *RSC Adv.* **2013**, *3*, 18605. (c) Kim, D.; Min, M.; Hong, S. *Chem. Commun.* **2013**, *49*, 4021. (d) Zhao, J.; Huang, H.; Wu, W.; Chen, H.; Jiang, H. *Org. Lett.* **2013**, *15*, 2604. (e) Cao, X.; Cheng, X.; Bai, Y.; Liu, S.; Deng, G.-J. *Green Chem.* **2014**, *16*, 4644. (f) Chen, J.; Li, G.; Xie, Y.; Liao, Y.; Xiao, F.; Deng, G.-J. *Org. Lett.* **2015**, *17*, 5870. (g) Chen, X.; Xie, Y.; Li, C.; Xiao, F.; Deng, G.-J. *Eur. J. Org. Chem.* **2017**, *2017*, 577.

(12) (a) Xie, Y.; Wu, J.; Chen, Y.; Huang, H.; Deng, G.-J. *Green Chem.* **2016**, *18*, 667. (b) Xie, Y.; Chen, X.; Wang, Z.; Huang, H.; Yi, B.; Deng, G.-J. *Green Chem.* **2017**, *19*, 4294. (c) Tan, J.; Ni, P.; Huang, H.; Deng, G.-J. *Org. Biomol. Chem.* **2018**, *16*, 4227. (d) Nguyen, T. B.; Retailleau, P. *Adv. Synth. Catal.* **2017**, *359*, 3843. (e) Chen, X.; Wang, Z.; Huang, H.; Deng, G. *Adv. Synth. Catal.* **2018**, DOI: 10.1002/adsc.201800765. For original elemental sulfur-promoted C−N bond formation, see: (f) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. *J. Org. Chem.* **2009**, *74*, 3566.

(13) For the synthesis of *o*-arylenediamines, see: (a) Wenderski, T.; Light, K. M.; Ogrin, D.; Bott, S. G.; Harlan, C. J. *Tetrahedron Lett.* **2004**, *45*, 6851. (b) Jiménez-Pérez, V. M.; Ibarra-Rodríguez, M.; Muñoz-Flores, B. M.; Gómez, A.; Santillan, R.; Hernández Fernadez, E.; Bernès, S.; Waksman, N.; Ramírez Duron, R. *J. Mol. Struct.* **2013**, *1031*, 168. (c) Wang, H.; Xia, Y.; Lv, S.; Xu, J.; Sun, Z. *Tetrahedron Lett.* **2013**, *54*, 2124. (d) Li, L.; Qiu, D.; Shi, J.; Li, Y. *Org. Lett.* **2016**, *18*, 3726.

(14) Priebbenow, D. L.; Bolm, C. *Chem. Soc. Rev.* **2013**, *42*, 7870.

DOI: 10.1021/acs.orglett.8b02387
Org. Lett. XXXX, XXX, XXX−XXX