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Metal-Free Synthesis of 2-Arylbenzothiazoles from Aldehydes, Amines, and Thiocyanate

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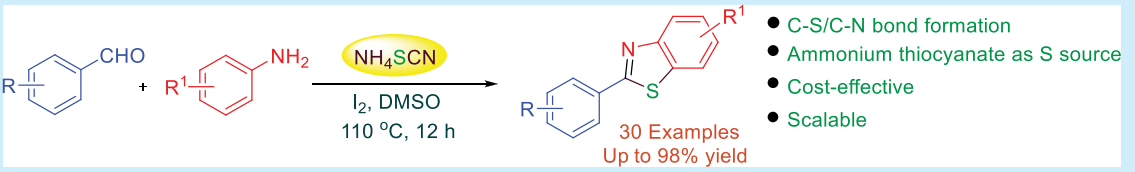
Supporting Information



ABSTRACT: A highly efficient method for the synthesis of 2-arylbenzothiazoles has been developed using readily available aromatic amines, benzaldehydes, and NH_4SCN as a sulfur source. A library of 2-arylbenzothiazoles with wide functional group compatibility has been synthesized in good yields through iodine-mediated oxidative annulation.

The C−S bond formation has attracted significant interest from organic chemists owing to the presence of the C−S bond in many essential biological and pharmaceutical compounds.[1] Benzothiazoles are generally considered to build fundamental structures of various natural products.[2] In particular, 2-arylbenzothiazole represents an important scaffold in numerous bioactive compounds such as antiparasitics, antituberculotics, antitumor agents, and calcium channel antagonists (Figure 1).[3] In addition, 2-arylbenzothiazoles

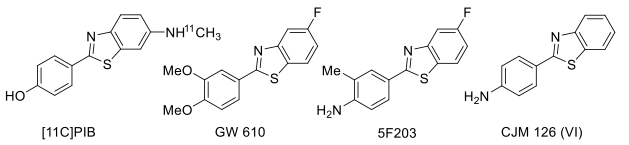
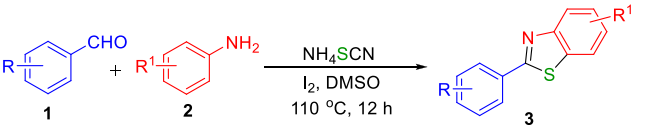


Figure 1. Bioactive compounds containing 2-arylbenzothiazole moiety.

received major attention for their potential applications in organic luminescent materials, industrial dyes, and agrochemical compounds.[4] Thus, continuous efforts have been devoted to develop new synthetic methodologies for synthesizing 2-arylbenzothiazole derivatives.[5] The reported routes to 2-arylbenzothiazoles mostly depend on the condensation of 2-aminothiophenols with aldehydes[6a−e] or ketones[6f] or carboxylic acid derivatives.[6g−j] Oxidative intramolecular cyclization of thiobenzanilides is also effective for their construction.[6k−o] However, these methods need prefunctionalized reactants like 2-aminothiophenols and thiobenzanilides which are costly and not easily available. From the synthetic and medicinal chemistry perspective, development of an efficient method for synthesis of 2-arylbenzothiazole derivatives using readily available starting materials under simple and general reaction conditions is highly desirable. To the best of our knowledge, synthesis of 2-arylbenzothiazole moieties exploring ammonium thiocyanate as the S source has not been revealed until now. In continuation of our research on C−S bond formations[7] using ammonium thiocyanate, herein we report an efficient method for the synthesis of 2-arylbenzothiazoles from readily available aromatic amines and aldehydes in the presence of iodine (Scheme 1). The reaction is a fruitful one-pot approach under mild and facile reaction conditions.

Scheme 1. Synthesis of 2-Arylbenzothiazoles



To optimize the reaction conditions, 4-methoxybenzaldehyde (**1a**, 0.5 mmol) and *p*-toluidine (**2b**, 0.5 mmol) were taken as the model substrates with ammonium thiocyanate, different iodide sources, and solvents as summarized in Table 1. Initially, the reaction was performed employing 2.0 equiv of NH_4SCN and 50 mol % of I_2 in DMSO under air at 80 °C temperature. Gratifyingly, 2-(4-methoxyphenyl)-6-methylbenzo[*d*]thiazole (**3ab**) was obtained in 32% yield after 12 h (Table 1, entry 1). Inspired by this result, the reaction temperature was increased to 110 °C, but no significant improvement was observed (Table 1, entry 2). Pleasingly, the yield of the product was increased to 93% by increasing the loading of I_2 to 1.0 equiv (Table 1, entry 3). However, no improvement was noticed by increasing the amount of I_2 to 1.5 equiv (Table 1, entry 3). Under these conditions, a 76% yield of **3ab** was obtained at 80 °C (Table 1, entry 3). A further increase of temperature to 130 °C did not give any improvement in the yield (Table 1, entry 3). Then the reaction was performed in different common solvents like

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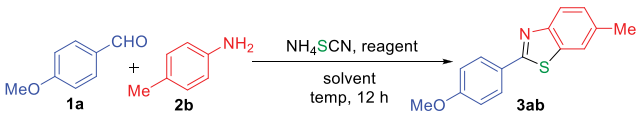
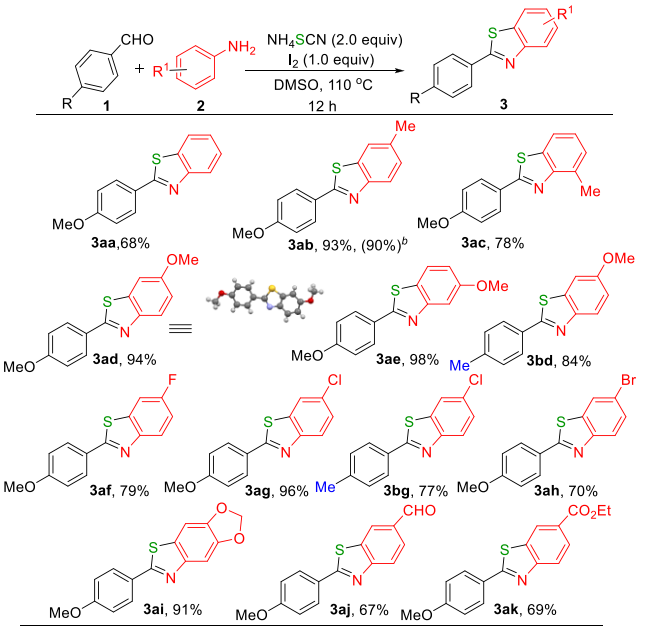
Table 1. Optimization of the Reaction Conditions[a]



entry	iodide source (equiv)	solvent	temp (°C)	yield (%)
1	I_2 (50 mol %)	DMSO	80	32
2	I_2 (50 mol %)	DMSO	110	50
3	**I_2 (1.0)**	**DMSO**	**110**	**93**, (93,[b] 76,[c] 93[d])
4	I_2 (1.0)	DCB	110	65
5	I_2 (1.0)	DMF	110	71
6	I_2 (1.0)	toluene	110	nr
7	I_2 (1.0)	PEG-400	110	trace
8	I_2 (1.0)	dioxane	110	nr
9	KI (1.0)	DMSO	110	10
10	NH_4I (1.0)	DMSO	110	20
11	TBAI (1.0)	DMSO	110	trace
12	ZnI_2 (20 mol %)	DMSO	110	60
13	I_2 (1.0)	DMSO	110	58,[e] 54[f]

[a]Reaction conditions: The reactions were carried out with **1a** (0.5 mmol), **2b** (0.5 mmol), NH_4SCN (2.0 equiv), I_2 (1.0 equiv), and solvent (2.0 mL) for 12 h under air at 110 °C. [b]1.5 equiv of I_2. [c]At 80 °C. [d]At 130 °C. [e]1.0 equiv of NH_4SCN. [f]KSCN (2.0 equiv) was used.

Scheme 2. Substrate Scope with Variation of Anilines[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), NH_4SCN (2.0 equiv), I_2 (1.0 equiv), and DMSO (2.0 mL) for 12 h at 110 °C. [b]5 mmol scale.

DCB, DMF, toluene, PEG-400, and 1,4-dioxane (Table 1, entries 4−8). However, no improvement in yield was observed compared to DMSO. Thereafter, other iodide sources like KI, NH_4I, TBAI, and ZnI_2 were checked, but these were not as effective as I_2 (Table 1, entries 9−12). Significantly, the yield was decreased on using 1.0 equiv of NH_4SCN and KSCN (2.0 equiv) as the sulfur source (Table 1, entry 13). Thus, the optimized yield of the product was obtained with 2.0 equiv of NH_4SCN in the presence of 1.0 equiv I_2 in DMSO at 110 °C (Table 1, entry 3).

After the reaction conditions were optimized, the substrate scope of this protocol was explored. At first, various substituted anilines were coupled with 4-methoxybenzaldehyde under the optimized reaction conditions, and the results are presented in Scheme 2. 2-(4-Methoxyphenyl)benzo[*d*]thiazole (**3aa**) was obtained in 68% yield from aniline. Anilines bearing electron-donating −Me and −OMe substituents at different positions efficiently reacted with 4-methoxybenzaldehyde to provide the products with high to excellent yields (**3ab**, **3ac**, **3ad**, **3ae**, and **3bd**). The structure of 6-methoxy-2-(4-methoxyphenyl)benzo-[*d*]thiazole (**3ad**) was further confirmed by single-crystal X-ray crystallographic analysis. Anilines with different halogen groups like 4-F, 4-Cl, and 4-Br produced the corresponding products in good yields (**3af**−**ah**). Benzo[*d*][1,3]dioxol-5-amine participated smoothly in this reaction to provide 91% yield (**3ai**). Anilines containing electron-withdrawing groups such as −CHO and $-CO_2Et$ were also well tolerated under the present reaction conditions, providing the desired products (**3aj** and **3ak**). Although aminobenzaldehyde may compete with methoxybenzaldehyde, which may cause the decrease in the yield of **3aj**, we were delighted that the self-coupling product was not obtained. However, 2-aminopyridine and benzyl amine did not undergo in this reaction. To demonstrate the practical applicability of the current methodology, the gram-scale reaction was also performed with the usual laboratory setup between 4-methoxybenzaldehyde (**1a**) and toluidine (**2b**). 2-(4-Methoxyphenyl)-6-methylbenzo[*d*]-thiazole (**3ab**) was obtained without a significant decrease in yield (90%).

To illustrate the general applicability of the current protocol, the substrate scope with various substituted benzaldehydes was investigated (Scheme 3). Delightfully, benzaldehyde bearing electron-donating groups such as −Me and −OMe at different positions reacted well with toluidine, affording the corresponding products (**3bb**−**eb**) in excellent yields. Halogen-containing benzaldehydes such as 4-F, 2-F, 2-Cl, 4-Br, and 2-Br afforded the desired products (**3fb**−**jb**) in excellent yields. Interestingly, 4-(dimethylamino)benzaldehyde also reacted well with toluidine and 4-chloroaniline under the present protocol to provide the products (**3kb** and **3kg**) with good yields. 4-(Methylthio)benzaldehyde underwent this reaction smoothly to afford an excellent yield of the product (**3lb**). Pleasingly, benzaldehyde with an electron-withdrawing substituent (4-NO_2, 3-NO_2, 4-CN, and 2-CHO) also successfully gave the desired products (**3mb**−**pb**) in excellent yields. 2-Naphthaldehyde also reacted efficiently to give 91% yield of the desired product (**3qb**). However, heteroaryl aldehydes (indole-3-carboxaldehyde, furan-2-carboxaldehyde, and thiophene-2-carboxaldehyde), aliphatic aldehydes (2-phenylacetaldehyde, cyclohexane carboxaldehyde, butyraldehyde, and paraformaldehyde), cinnamaldehyde, and crotonaldehyde did not afford the desired products under the present reaction conditions.

To predict the mechanistic path of this reaction, a few control experiments were carried out as shown in Scheme 4. However, 2-aminothiophenol was not the intermediate of this reaction as toluidine (**2b**) treated with NH_4SCN in the absence of aldehyde could not produce 2-amino-5-methylbenzenethiol **4**, and the starting material (**2b**) was recovered (Scheme 4a). Furthermore, the imine **5ab** was generated in a major amount when the reaction was quenched after 2 h (Scheme 4b). It was then found that the imine **5ab** could produce the final product (**3ab**) under the standard conditions (Scheme 4c). Interestingly, in the absence of I_2, addition of

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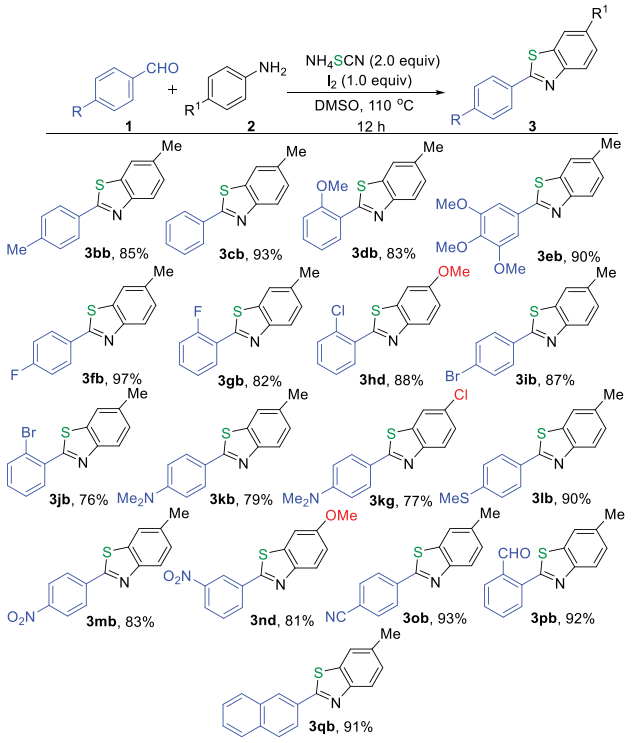
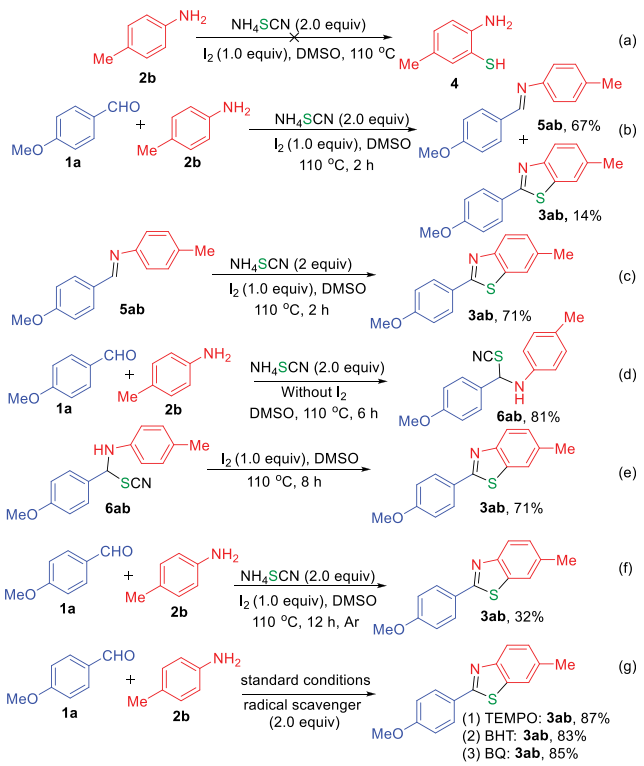
Scheme 3. Substrate Scopes with Variation of Benzaldehydes[a]



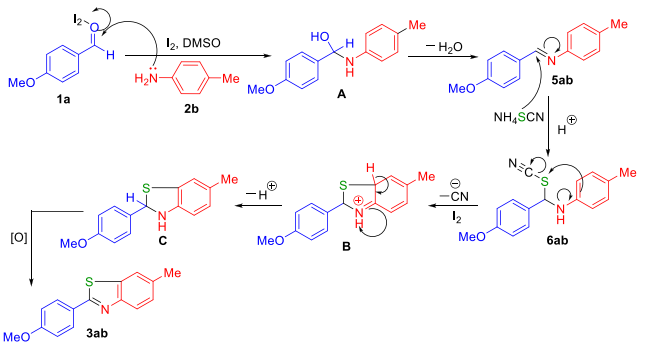
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), NH_4SCN (2.0 equiv), I_2 (1.0 equiv), and DMSO (2.0 mL) for 12 h at 110 °C.

Scheme 4. Control Experiments



thiocyanate to imine produced *N*-((4-methoxyphenyl)-(thiocyanato)methyl)-4-methylaniline, **6ab** (Scheme 4d). Significantly, **6ab** was transferred into the final benzothiazole (**3ab**) in the presence of I_2 (Scheme 4e), which indicates that **6ab** might be the intermediate of this reaction and I_2 plays a major role in the cyclization. Notably, only 32% yield of the product (**3ab**) was obtained when the reaction was carried out under Ar atmosphere (Scheme 4f). It signifies that I_2 also works as an oxidant of thiazoline to thiazole (Scheme 5), and

Scheme 5. Plausible Mechanistic Pathway



areal oxygen also plays an important role in this oxidation. Additionally, the annulation would not proceed through radical mechanism since the addition of radical scavengers like 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methyl phenol (BHT), and *p*-benzoquinone (BQ) did not inhibit the desired transformation (Scheme 4g).

On the basis of the control experimental results (Scheme 4) and previous related literature,[5f,g,i,8] a plausible reaction mechanism is proposed for the formation of 2-(4-methoxyphenyl)-6-methylbenzo[*d*]thiazole as depicted in Scheme 5. Initially, imine intermediate **5ab** is formed by the condensation of aldehyde and aniline. Next, NH_4SCN attacks the imine (**5ab**) to generate the thiacyanato intermediate **6ab**. Afterward, nucliophilic attack of aryl moiety to S atom results the formation of a cyclized intermediate **B** by eliminating the CN^- ion. Deprotonation generates dihydrobenzothiazole **C**, which likewise forms the final product (**3ab**) by oxidation. Regarding the role of the iodide source, it may be considered to activate the imine and promote the cyclization and the oxidative aromatization.[9]

In conclusion, we have demonstrated an I_2-mediated oxidative annulation of arylbenzaldehydes, aromatic amines, and ammonium thiocyanate. The reaction provides a novel synthetic route to 2-arylbenzothiazoles from easily accessible reagents. Simple reaction conditions, tolerance of a wide range of functional groups, availability of basic chemicals as starting materials, and use of NH_4SCN as sulfur source make this protocol practically applicable to synthesis a variety of benzothiazole derivatives. We believe that the present methodology would achieve much importance in synthetic organic chemistry, medicinal chemistry, material science, and also industrial chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00245.

Experimental procedures and spectral data (PDF)

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Accession Codes

CCDC 1888103 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291. (b) Castanheiro, T.; Suffert, J.; Donnard, M.; Gulea, M. *Chem. Soc. Rev.* **2016**, *45*, 494.

(2) (a) Bandyopadhyay, P.; Sathe, M.; Ponmariappan, S.; Sharma, A.; Sharma, P.; Srivastava, A. K.; Kaushik, M. P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7306. (b) Wang, X.; Sarris, K.; Kage, K.; Zhang, D.; Brown, S. P.; Kolasa, T.; Surowy, C.; Kouhen, O. F. E.; Muchmore, S. W.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2009**, *52*, 170. (c) Mortimer, C. G.; Wells, G.; Crochard, J.-P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179. (d) Facchinetti, V.; Reis, R. R.; Gomes, C. R. B.; Vasconcelos, T. R. A. *Mini-Rev. Org. Chem.* **2012**, *9*, 44.

(3) (a) Gupta, V.; Kant, V. *Sci. Int.* **2013**, *1*, 253. (b) Prajapati, N. P.; Vekariya, R. H.; Borad, M. A.; Patel, H. D. *RSC Adv.* **2014**, *4*, 60176. (c) Noel, S.; Cadet, S.; Gras, E.; Hureau, C. *Chem. Soc. Rev.* **2013**, *42*, 7747. (d) Chakraborty, M.; Jin, K. J.; Novak, M.; Glover, S. A. *J. Org. Chem.* **2010**, *75*, 5296. (e) Sun, Q.; Wu, R.; Cai, S.; Peterson, B. R.; Llewlyn, S.; Kaori, S.; Lin, Y.; He, B. *J. Med. Chem.* **2011**, *54*, 1126.

(4) (a) Hrobarikova, V.; Hrobarik, P.; Gajdos, P.; Fitilis, I.; Fakis, M.; Persephonis, P.; Zahradnık, P. *J. Org. Chem.* **2010**, *75*, 3053. (b) Serdons, K.; Bormans, G.; Verbruggen, A.; Terwinghe, C.; Vermaelen, P.; Laere, K. V.; Mortelmans, L.; Kung, H. *J. Med. Chem.* **2009**, *52*, 1428.

(5) (a) Liu, Y.; Yuan, X.; Guo, X.; Zhang, X.; Chen, B. *Tetrahedron* **2018**, *74*, 6057. (b) Natarajan, P.; Manjeet, M.; Brar, N. K.; Kaur, J. *Org. Chem. Front.* **2018**, *5*, 1527. (c) Bakthadoss, M.; Selvakumar, R. *J. Org. Chem.* **2016**, *81*, 3391. (d) Wang, X.; Qiu, X.; Wei, J.; Liu, J.; Song, S.; Wang, W.; Jiao, N. *Org. Lett.* **2018**, *20*, 2632. (e) Huang, Y.; Zhou, P.; Wu, W.; Jiang, H. *J. Org. Chem.* **2018**, *83*, 2460. (f) Huang, H.; Xu, Z.; Ji, X.; Li, B.; Deng, G.-J. *Org. Lett.* **2018**, *20*, 4917. (g) Zhu, X.; Yang, Y.; Xiao, G.; Song, J.; Liang, Y.; Deng, G. *Chem. Commun.* **2017**, *53*, 11917. (h) Ding, Q.; Huang, X.-G.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 1047. (i) Che, X.; Jiang, J.; Xiao, F.; Huang, H.; Deng, G.-J. *Org. Lett.* **2017**, *19*, 4576. (j) Deng, H.; Li, Z.; Ke, F.; Zhou, X. *Chem. - Eur. J.* **2012**, *18*, 4840. (k) Xing, Q.; Ma, Y.; Xie, H.; Xiao, F.; Zhang, F.; Deng, G.-J. *J. Org. Chem.* **2019**, *84*, 1238.

(6) (a) Pereira Araujo, D. P.; Santos Morais, V. S. S.; de Fatima, A.; Modolo, L. V. *RSC Adv.* **2015**, *5*, 28814. (b) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. (c) Cho, Y. H.; Lee, C.-Y.; Ha, D.-C.; Cheon, C.-H. *Adv. Synth. Catal.* **2012**, *354*, 2992. (d) Chen, Y.-X.; Qian, L.-F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330. (e) Kumar, A.; Sharma, S.; Maurya, R. A. *Tetrahedron Lett.* **2010**, *51*, 6224. (f) Liao, Y.; Qi, H.; Chen, S.; Jiang, P.; Zhou, W.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 6004. (g) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948. (h) Li, G.; Jiang, J.; Zhang, F.; Xiao, F.; Deng, G.-J. *Org. Biomol. Chem.* **2017**, *15*, 10024. (i) Dar, A. A.; Shadab, M.; Khan, S.; Ali, N.; Khan, T. A. *J. Org. Chem.* **2016**, *81*, 3149. (j) Sung, G. H.; Lee, I.-H.; Kim, B. R.; Shin, D.-S.; Kim, J.-J.; Lee, S.-G.; Yoon, Y.-J. *Tetrahedron* **2013**, *69*, 3530. (k) Itoh, T.; Mase, T. *Org. Lett.* **2007**, *9*, 3687. (l) Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett.* **2012**, *14*, 98. (m) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. *Org. Lett.* **2009**, *11*, 2039. (n) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (o) Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J.-X.; Wu, L.-Z.; Lei, A. *J. Am. Chem. Soc.* **2015**, *137*, 9273.

(7) (a) Dey, A.; Hajra, A. *Adv. Synth. Catal.* **2019**, *361*, 842. (b) Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 8275. (c) Mondal, S.; Samanta, S.; Hajra, A. *Eur. J. Org. Chem.* **2018**, *2018*, 1060. (d) Samanta, S.; Chatterjee, R.; Santra, S.; Hajra, A.; Khalymbadzha, I. A.; Zyryanov, G. V.; Majee, A. *ACS Omega* **2018**, *3*, 13081. (e) Bagdi, A. K.; Mitra, S.; Ghosh, M.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 3314. (f) Kibriya, G.; Mondal, S.; Hajra, A. *Org. Lett.* **2018**, *20*, 7740.

(8) (a) Liu, B.-B.; Cao, W.-B.; Wang, F.; Wang, S.-Y.; Ji, S.-J. *J. Org. Chem.* **2018**, *83*, 11118. (b) Dwivedi, V.; Rajesh, M.; Kumar, R.; Kant, R.; Reddy, M. S. *Chem. Commun.* **2017**, *53*, 11060. (c) Fan, W.; Li, Q.; Li, Y.; Sun, H.; Jiang, B.; Li, G. *Org. Lett.* **2016**, *18*, 1258.

(9) (a) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561. (b) Xue, W.-J.; Li, Q.; Zhu, Y.-P.; Wang, J.-G.; Wu, A.-X. *Chem. Commun.* **2012**, *48*, 3485. (c) Yagyu, T.; Takemoto, Y.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. *Org. Lett.* **2017**, *19*, 2506.

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