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NH_4I-catalyzed C–S bond formation via an oxidation relay strategy: Efficient access to dithioether decorated indolizines

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ABSTRACT

An efficient NH_4I-catalyzed C–H/S–H cross-coupling reaction of indolizines with thiols is reported. Compared to previous methods, this environmentally friendly oxidation relay strategy uses O_2 as an oxidant to afford dithioether decorated indolizines in up to 98% yield. Promising results have been obtained, indicating the high applicability and atom economy of this method.

Introduction

Indolizines can be widely found in natural products, fluorescent materials [1], and a broad range of biologically active molecules [2], including anticancer drugs [3], antimalarial drugs, apoptosis inducers and antifungal drugs [4]. Therefore, significant effort has been devoted to the construction and modification of this important scaffold [5]. In the past few decades, C–S bond formation attracted much attention due to sulfur-containing motifs existeing in numerous pharmaceutically active compounds [6]. Transition-metal-catalyzed cross-coupling represents one of the most powerful methodologies for thiolation [7]. However, these methods use novel metal catalysts that are either expensive or damaging to the environment. Therefore, developing a highly efficient approach for the direct sulfenylation under metal-free conditions is still remains a critical goal. A variety of reagents has been applied in the past to construct C–S bonds, including thiols [8], disulfides [9], sulfinic acids [10], sodium arenesulfinates [11], *N*-thioimides [12], and sulfur powder [13]. However, despite the significant advance made in this field, few examples have been reported in the literature to date detailing dithiolation. Recently, Lenardão, Schiesser, and coworkers developed a selenium dioxide promoted synthesis of bis-sulfenlindoles (Scheme 1a) [14]. Meanwhile, Cao, Zhao, and coworkers reported KI catalyzed ditholation of indolizaines via cross-coupling of indolizaines and thiols with stoichiometric amount of peroxide TBHP as oxidant (Scheme 1b) [15]. However, these methodologies still suffer from relatively low yields and the need of highly toxic catalysts or potentially explosive peroxides. Therefore, the development of a safe and versatile method to synthesize dithioether-decorated indolizines is still highly desirable. Based on our recent work on heterocyclics [16], herein, we report a metal-free synthesis of dithioether decorated indolizines via an oxidation relay strategy.

Results and discussion

Initially, we carried out our studies with 2-phenylindolizine **1a** and 4-methylbenzenethiol **2a** as model substrates in the presence of 10 mol % of KI under oxygen atmosphere in DCE. In doing so, we obtained the desired product 2-phenyl-1,3-bis (*p*-tolylthio)indolizine **3a** in 84% yield (entry 1, Table 1). Subsequent survey on a series of solvents revealed that DCE provided the best results (entries 2–4, Table 1). Attempts of using various iodine sources, such as I_2, NaI, NH_4I, and TBAI showed that the use of NH_4I afforded the desired product **3a** in 87% yield (entries 5–8, Table 1). Decreasing the amount of NH_4I to 5 mol % could improve the yield of **3a** to

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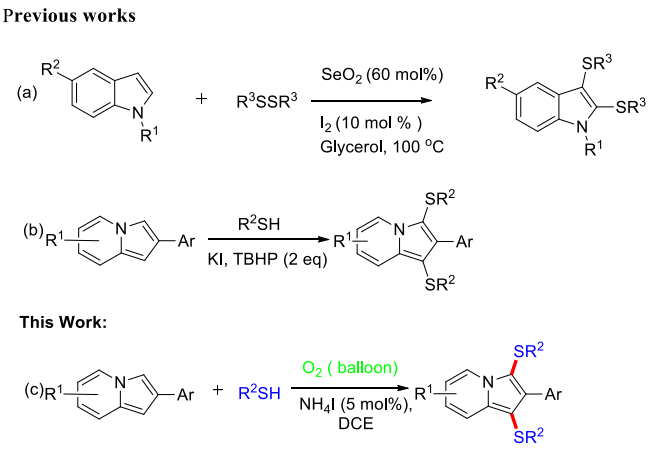
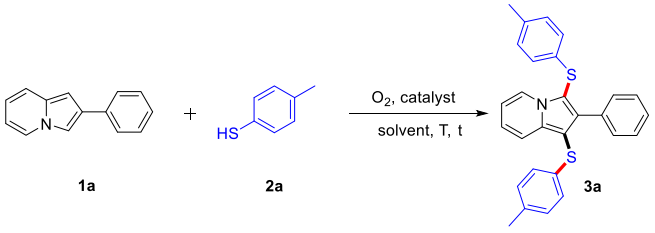


Scheme 1. Synthetic protocols of dithioether decorated indolizines.

94% (entries 9 and 10, Table 1). Further screening of the reaction temperature revealed that reaction at 60 °C resulted in the best yield (entries 11 and 12, Table 1). Increasing the amount of *p*-toluenethiol to 3 equivalents did not increase the yield of **3a** (entry 13, Table 1). Furthermore, carrying out the reaction in air afforded **3a** in only 83% yield. Decreasing the amount of thiol **2a** to 1 equivalent provided product **3a** in 37% yield. Thus, optimized reaction conditions for this model reaction (**1a** reacted with 2.1 equivalent of **2a** and 5 mol % of NH_4I in DCE under O_2 atmosphere at 60 °C) were established.

With optimized conditions in hands, we investigated the coupling of various thiols **2** with 2-phenylindolizine **1a** (Table 2). The reactions proceeded smoothly to afford dithiolated products **3** with excellent functional group compatibility. Thiols bearing either electron-donating (Me and OMe) or electron-withdrawing (F, Cl, Br, and CF_3) groups on the *para*-position of the phenyl ring of thiols displayed good reactivity, providing the corresponding products **3a–3f** in 82–94% yields. Similarly, *ortho*- and *meta*- substituted thiols with methoxy, methyl, and choloro groups could

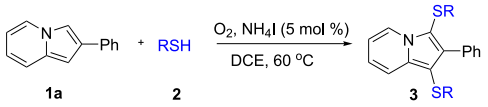
Table 1
Optimization of the reaction of **1a** and **2a**.

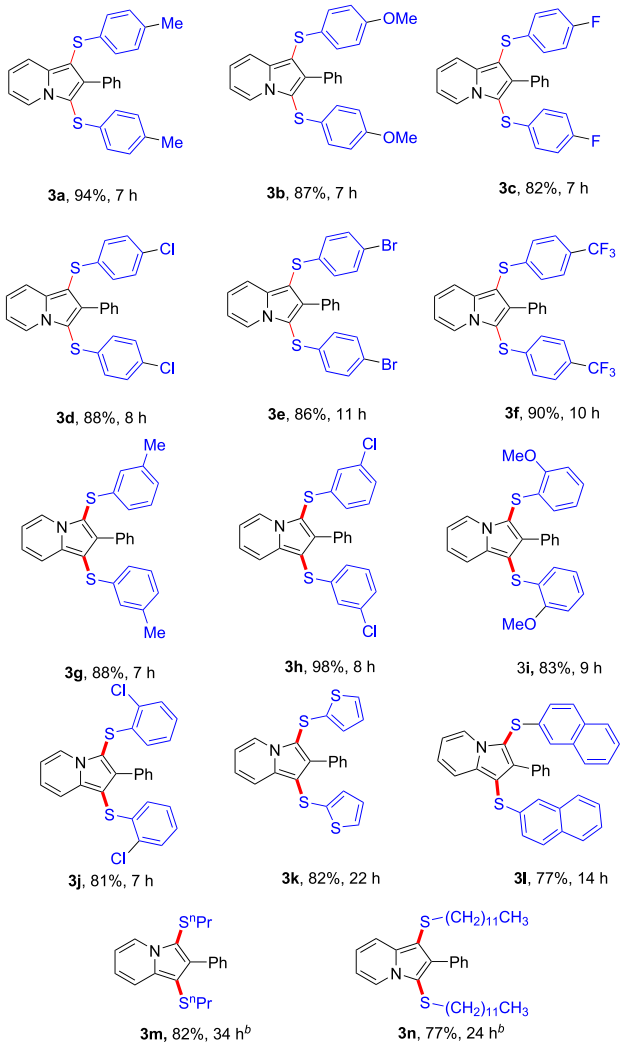


Entry	Solvent	Catalyst (10 mol %)	Time (h)	Yield (%)[b]
1	DCE	KI	6	84
2[c]	DMSO	KI	72	26
3	$MeNO_2$	KI	24	79
4[c]	MeCN	KI	72	43
5	DCE	I_2	6	72
6	DCE	NaI	7	83
7	DCE	TBAI	6	–
8	DCE	NH_4I	7	87
9[d]	**DCE**	**NH_4I**	**7**	**94**
10[e]	DCE	NH_4I	6	86
11[d,f]	DCE	NH_4I	6	82
12[d,g]	DCE	NH_4I	48	91
13[d,h]	DCE	NH_4I	7	94
14[d,i]	DCE	NH_4I	28	83
15[d,j]	DCE	NH_4I	7	37

[a]Reaction conditions: **1a** (0.26 mmol), **2a** (0.55 mmol, 2.1 eq), and catalyst (10 mol %) was reacted in solvent (1 mL) under oxygen atmosphere at 60 ℃. [b]Isolated yield. [c]The yields were determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [d]5 mol % of catalyst was used. [e]20 mol % of catalyst was used. [f]80 ℃. [g]40 ℃. [h]3 equivalents of *p*-toluenethiol was used. [i]In air. [j]**1a** (0.26 mmol), **2a** (0.26 mmol, 1 eq).

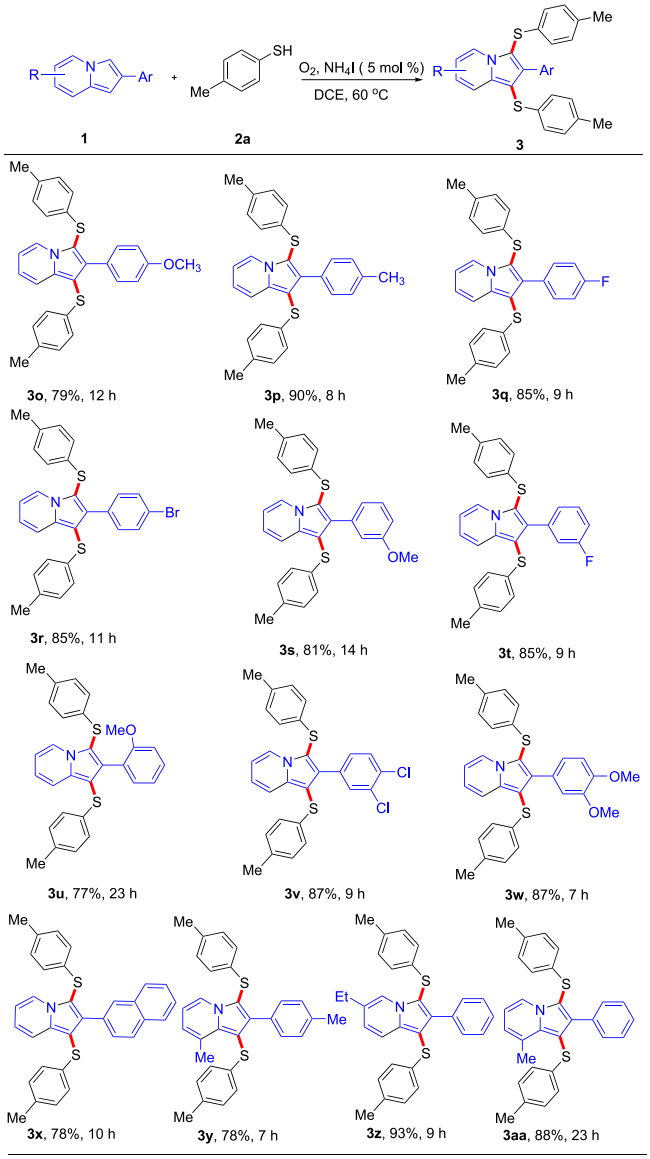
Table 2
NH_4I-catalyzed sulfenylation of 2-phenylindolizine **1a** with thiols **2**.





[a]Reaction conditions: **1a** (0.26 mmol), **2a** (0.55 mmol, 2.1 eq), NH_4I (5 mol %) in DCE (1 mL) under O_2 (1 atm) at 60 ℃. [b]10 mol % of NH_4I were used.

Table 3
NH_4I-catalyzed sulfenylation reactions of 2-phenylindolizines **1** and 4-methylbenzenethiol **2a**.



[a] Conditions: **1a** (0.26 mmol), **2a** (0.55 mmol, 2.1 eq), and NH_4I (5 mol %) in DCE (1 mL) under O_2 (1 atm) at 60 ℃.

also afford the desired products **3g-3j** in 81–98% yields. Interestingly, thiophene-2-thiol and naphthyl thiol were also found to be well tolerated in this transformation to provide **3k** and **3l** in 82% and 77% yields, respectively. Moreover, increasing the catalyst loading to 10 mol %, the use of butanethiol and 1-dodecanethiol could also afford the desired products **3m** and **3n** in good yields.

After studying various thiol species, we investigated the scope and limitation of 2-phenylindolizines **1** (Table 3). Substrates bearing either electron-donating (Me and MeO) or electron-withdrawing groups (F and Br) in *para*-, *ortho*-, and *meta*-position on the phenyl ring of 2-phenylindolizines afforded the corresponding products **3o-3u** in 77–90% yields. Moreover, dichloro- and dimethoxyl substituted 2-phenylindolizines exhibited good reactivity characteristics to produce **3v** and **3w** in 87% yield. Additionally, this reaction displayed good functional group compatibility for 2-naphthalenethiol, furnishing **3x** in 78% yield. Last but not least, substitution of the ring of indolizines was also well tolerated under standard conditions and afforded products **3y-3aa** in good to excellent yields.

Furthermore, several control experiments were carried out to generate a plausible reaction mechanism (Scheme 2). Firstly, the radical scavenger 1-oxyl-2,2,6,6-tetramethylpiperidine (TEMPO) was added to the reaction mixture. The slightly lower yield (89%) of **3a** ruled out the possibility of a radical mechanism. Secondly, no desired product **3a** was produced in the absence of NH_4I or oxygen, indicating that the NH_4I/O_2 catalytic system played a significant role in this transformation. When 5 mol % of iodine was used as a catalyst instead of NH_4I, 73% of **3a** could still be obtained under standard conditions, verifying the key role of iodine in this catalytic cycle (Scheme 2a). Thirdly, diphenyl disulfide **5a** failed to provide dithiolation product **3a**, instead, 20% of the monothiolation product **4a** was formed under standard conditions with 2-phenylindolizin, suggesting that the S–H bond plays an important role for the reaction outcome (Scheme 2b) [17]. Finally, the reaction of monothiolation product **4a** and **2a** produced **3a** in 82% yield under standard conditions, revealing that the *in situ* generated monothiolation product may represent the key intermediate in this reaction (Scheme 2c).

On the basis of the present results and former reported results [8c,18], a plausible reaction mechanism was generated as outlined in Scheme 3. Iodine ions (I^-) were oxidized by oxygen to form iodine, which then reacted with thiol **2** to produce sulfenyl iodide. This *in situ* generated intermediate reacted with 2-phenylindolizin **1** to form monothiolation product **4**. Meanwhile, diphenyl disulfide **5** may also be formed by oxidation of thiol **2** and then reacted with 2-phenylindolizin **1** to convert to the monothiolation product **4**. Due to the increase of electron density on the indolizine ring, **4** is prone to undergo a second sulfenylation to generate the final dithiolation product **3**.

Conclusion

In summary, we have developed an efficient and environmentally benign method for the dithiolation of 2-phenylindolizines. In this protocol, NH_4I was used as the catalyst and oxygen served as the sole oxidant. A variety of functionalized 2-phenylindolizines were well tolerated and provided the dithioether decorated indolizines in up to 98% yield. Further studies on the applicability of these disulfenylated products in medicinal chemistry are currently underway in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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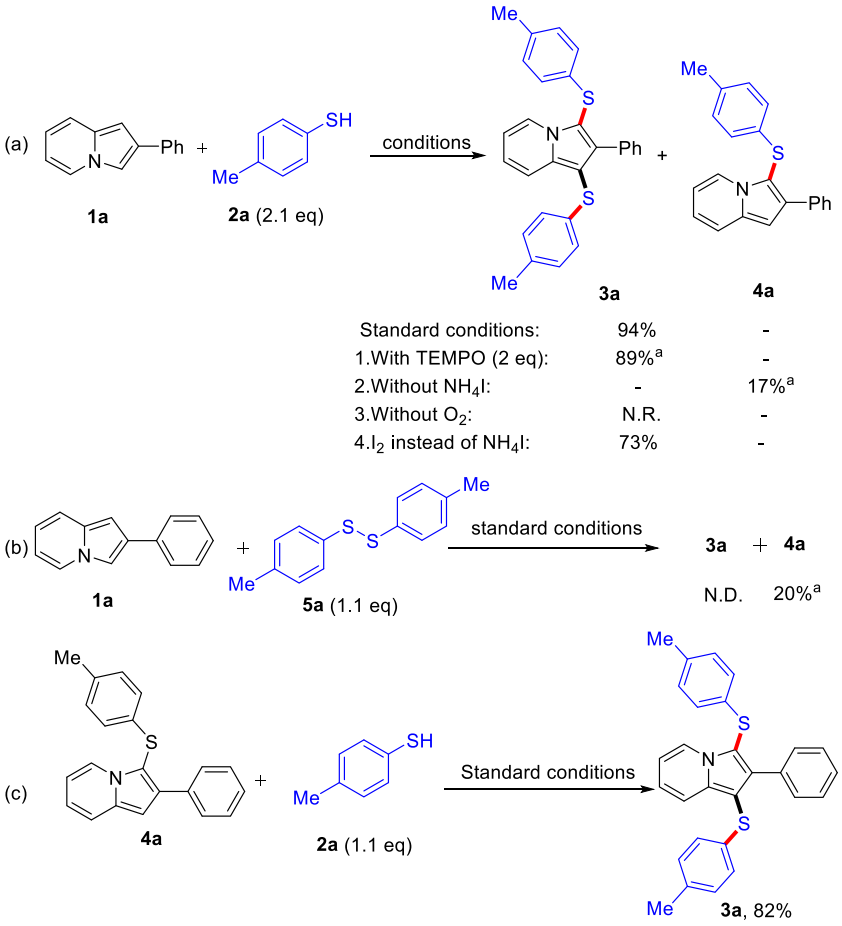
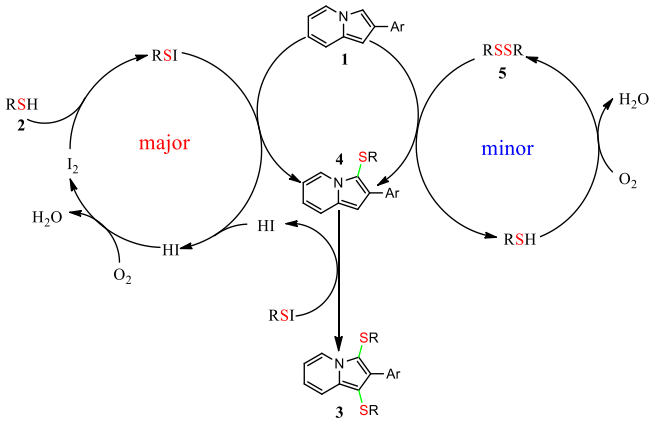
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152368.



Scheme 2. Control experiments. [a]Yields determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard.



Scheme 3. A proposed mechanism.

References

[1] (a) J. Barluenga, G. Lonzi, L. Riesgo, L.A. López, M. Tomás, J. Am. Chem. Soc. 132 (2010) 13200–13202;
(b) A.J. Huckaba, F. Giordano, L.E. McNamara, K.M. Dreux, N.I. Hammer, G.S. Tschumper, S.M. Zakeeruddin, M. Grätzel, M.K. Nazeeruddin, J.H. Delcamp, Adv. Energy Mater. 5 (2015) 1401629;
(c) D.-T. Yang, J. Radtke, S.K. Mellerup, K. Yuan, X. Wang, M. Wagner, S. Wang, Org. Lett. 17 (2015) 2486–2489;
(d) A.J. Huckaba, A. Yella, L.E. McNamara, A.E. Steen, J.S. Murphy, C.A. Carpenter, G.D. Puneky, N.I. Hammer, M.K. Nazeeruddin, M. Grätzel, J.H. Delcamp, Chem. Eur. J. 22 (2016) 15536–15542;
(e) Y. Zhang, J. Garcia-Amorós, B. Captain, F.M. Raymo, J. Mater. Chem. C 4 (2016) 2744–2747.

[2] S. Park, D.I. Kwon, J. Lee, I. Kim, ACS Combust. Sci. 17 (2015) 459–469.

[3] T. Weide, L. Arve, H. Prinz, H. Waldmann, H. Kessler, Bioorg. Med. Chem. Lett. 16 (2006) 59–63.

[4] A.F. Donnell, P.J. Dollings, J.A. Butera, A.J. Dietrich, K.K. Lipinski, A. Ghavami, W. D. Hirst, Bioorg. Med. Chem. Lett. 20 (2010) 2163–2167.

[5] (a) D. Chernyak, S.B. Gadamsetty, V. Gevorgyan, Org. Lett. 10 (2008) 2307–2310;
(b) D. Chernyak, C. Skontos, V. Gevorgyan, Org. Lett. 12 (2010) 3242–3245;
(c) J.H. Lee, I. Kim, J. Org. Chem. 78 (2013) 1283–1288;
(d) M.J. Chaichi, M. Ehsani, S. Asghari, V. Behboodi, Luminescence 29 (2014) 1169–1176;
(e) X. Wang, S.-Y. Li, Y.-M. Pan, H.-S. Wang, H. Liang, Z.-F. Chen, X.-H. Qin, Org. Lett. 16 (2014) 580–583;
(f) R.-R. Liu, J.-J. Hong, C.-J. Lu, M. Xu, J.-R. Gao, Y.-X. Jia, Org. Lett. 17 (2015) 3050–3053;
(g) M. Meazza, L.A. Leth, J.D. Erickson, K.A. Jørgensen, Chem. Eur. J. 23 (2017) 7905–7909.

[6] (a) G. De Martino, G. La Regina, A. Coluccia, M.C. Edler, M.C. Barbera, A. Brancale, E. Wilcox, E. Hamel, M. Artico, R. Silvestri, J. Med. Chem. 47 (2004) 6120–6123;
(b) G. La Regina, M.C. Edler, A. Brancale, S. Kandil, A. Coluccia, F. Piscitelli, E. Hamel, G. De Martino, R. Matesanz, J.F. Díaz, A.I. Scovassi, E. Prosperi, A. Lavecchia, E. Novellino, M. Artico, R. Silvestri, J. Med. Chem. 50 (2007) 2865–2874;
(c) S. Zhang, P. Qian, M. Zhang, M. Hu, J. Cheng, J. Org. Chem. 75 (2010) 6732–6735;
(d) G. La Regina, A. Coluccia, A. Brancale, F. Piscitelli, V. Gatti, G. Maga, A. Samuele, C. Pannecouque, D. Schols, J. Balzarini, E. Novellino, R. Silvestri, J. Med. Chem. 54 (2011) 1587–1598;
(e) E.A. Ilardi, E. Vitaku, J.T. Njardarson, J. Med. Chem. 57 (2014) 2832–2842.

[7] (a) C.-F. Lee, Y.-C. Liu, S.S. Badsara, Chem. Asian J. 9 (2014) 706–722;
(b) F. Pan, Z.-J. Shi, ACS Catal. 4 (2014) 280–288;
(c) A.N. Desnoyer, J.A. Love, Chem. Soc. Rev. 46 (2017) 197–238;
(d) D.-Q. Dong, S.-H. Hao, D.-S. Yang, L.-X. Li, Z.-L. Wang, Eur. J. Org. Chem. (2017) 6576–6592.

[8] (a) Y. Maeda, M. Koyabu, T. Nishimura, S. Uemura, J. Org. Chem. 69 (2004) 7688–7693;
(b) K.M. Schlosser, A.P. Krasutsky, H.W. Hamilton, J.E. Reed, K. Sexton, Org. Lett. 6 (2004) 819–821;

(c) Y. Jiang, J.-D. Deng, H.-H. Wang, J.-X. Zou, Y.-Q. Wang, J.-H. Chen, L.-Q. Zhu, H.-H. Zhang, X. Peng, Z. Wang, Chem. Commun. 54 (2018) 802–805.
[9] (a) W. Ge, Y. Wei, Green Chem. 14 (2012) 2066–2070;
(b) C.D. Prasad, M. Sattar, S. Kumar, Org. Lett. 19 (2017) 774–777;
(c) J. Rafique, S. Saba, M.S. Franco, L. Bettanin, A.R. Schneider, L.T. Silva, A.L. Braga, Chem. Eur. J. 24 (2018) 4173–4180.
[10] C.-R. Liu, L.-H. Ding, Org. Biomol. Chem. 13 (2015) 2251–2254.
[11] (a) Y.-M. Lin, G.-P. Lu, C. Cai, W.-B. Yi, Org. Lett. 17 (2015) 3310–3313;
(b) X. Ge, F. Sun, X. Liu, X. Chen, C. Qian, S. Zhou, New J. Chem. 41 (2017) 13175–13180.
[12] (a) M. Tudge, M. Tamiya, C. Savarin, G.R. Humphrey, Org. Lett. 8 (2006) 565–568;
(b) E. Marcantoni, R. Cipolletti, L. Marsili, S. Menichetti, R. Properzi, C. Viglianisi, Eur. J. Org. Chem. (2013) 132–140.
[13] (a) F. Xiao, S. Chen, C. Li, H. Huang, G.-J. Deng, Adv. Synth. Catal. 358 (2016) 3881–3886;
(b) J.-R. Zhang, L.-Z. Zhan, L. Wei, Y.-Y. Ning, X.-L. Zhong, J.-X. Lai, L. Xu, R.-Y. Tang, Adv. Synth. Catal. 360 (2018) 533–543.
[14] S. Thurow, F. Penteado, G. Perin, D. Alves, C. Santi, B. Monti, C.H. Schiesser, T. Barcellos, E.J. Lenardão, Org. Chem. Front. 5 (2018) 1983–1991.
[15] B. Li, Z. Chen, H. Cao, H. Zhao, Org. Lett. 20 (2018) 3291–3295.
[16] (a) X. Jiang, J. Chen, W. Zhu, K. Cheng, Y. Liu, W.-K. Su, C. Yu, J. Org. Chem. 82 (2017) 10665–10672;
(b) X. Jiang, G. Li, C. Yu, Tetrahedron Lett. 59 (2018) 1506–1510;
(c) X. Jiang, C. Zheng, L. Lei, K. Lin, C. Yu, Eur. J. Org. Chem. (2018) 1437–1442;
(d) L. Zhang, X. Zheng, J. Chen, K. Cheng, L. Jin, X. Jiang, C. Yu, Org. Chem. Front. 5 (2018) 2969–2973;
(e) X. Jiang, L. Yang, W. Yang, Y. Zhu, L. Fang, C. Yu, Org. Biomol. Chem. 17 (2019) 6920–6924;
(f) X. Jiang, B. Zhu, K. Lin, G. Wang, W.-K. Su, C. Yu, Org. Biomol. Chem. 17 (2019) 2199–2203;
(g) X. Jiang, W. Zhu, L. Yang, Z. Zheng, C. Yu, Eur. J. Org. Chem. (2019) 2268–2274;
(h) X. Jiang, L. Yang, Z. Ye, X. Du, L. Fang, Y. Zhu, K. Chen, J. Li, C. Yu, Eur. J. Org. Chem. (2020) 1687–1694.
[17] F. Penteado, C.S. Gomes, L.I. Monzon, G. Perin, C.C. Silveira, E.J. Lenardão, Eur. J. Org. Chem. (2020) 2110–2115.
[18] (a) Y. Jiang, J.-X. Zou, L.-T. Huang, X. Peng, J.-D. Deng, L.-Q. Zhu, Y.-H. Yang, Y.-Y. Feng, X.-Y. Zhang, Z. Wang, Org. Biomol. Chem. 16 (2018) 1641–1645;
(b) H.-H. Zhang, Y.-Q. Wang, L.-T. Huang, L.-Q. Zhu, Y.-Y. Feng, Y.-M. Lu, Q.-Y. Zhao, X.-Q. Wang, Z. Wang, Chem. Commun. 54 (2018) 8265–8268.