

HETEROCYCLES, Vol. 106, No. 11, 2023, pp. 1837 - 1844. © 2023 The Japan Institute of Heterocyclic Chemistry  
Received, 16th August, 2023, Accepted, 4th October, 2023, Published online, 12th October, 2023  
DOI: 10.3987/COM-23-14898

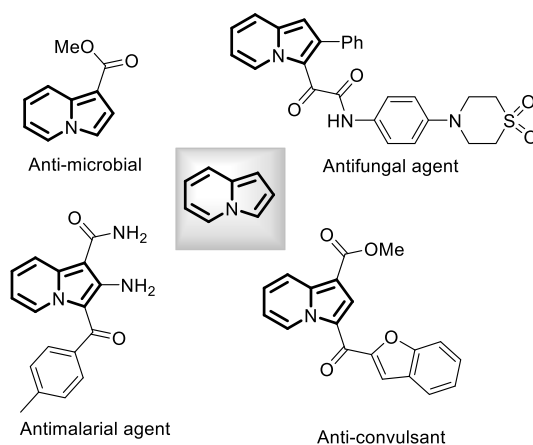
## SIMPLE BRØNSTED ACID CATALYZED THREE-COMPONENT REACTIONS FOR EFFICIENT ALKYLATION OF INDOLIZINES WITH AROMATIC ALDEHYDES AND HANTZSCH ESTERS

Jiang Geng,<sup>1</sup> Jinyi Shi,<sup>2</sup> Jin Wang,<sup>2</sup> Jiaxian Li,<sup>2</sup> Lin Jiao,<sup>2</sup> and Dongdong Guo<sup>2\*</sup>

<sup>1</sup> Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, P. R. China. <sup>2</sup> Department of Basic Courses, Shanxi Agricultural University, Taigu, 030801, P. R. China.

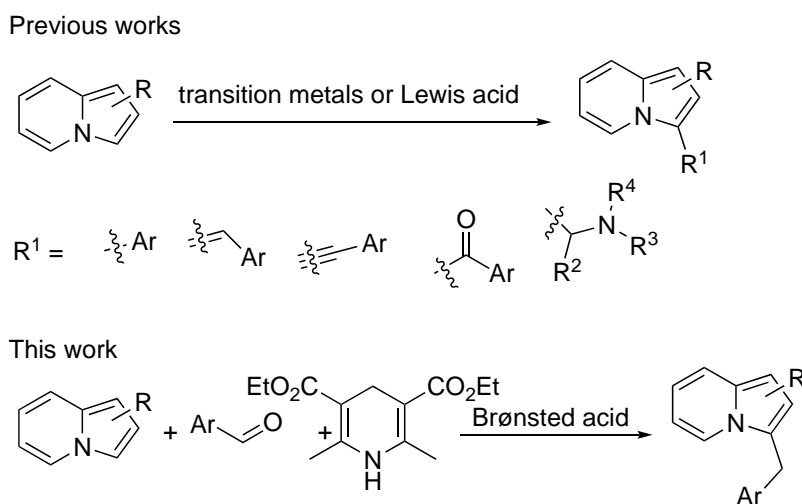
**Abstract** – An efficient three-component reaction has been developed for functionalization of indolizines with aromatic aldehydes and Hantzsch esters. Simple Brønsted acids were successfully employed as catalysts to form reactive cationic intermediate which could be efficiently trapped by Hantzsch ester. Different types of substituted indolizines could be efficiently obtained with good yields.

Nitrogen-fused bicyclic aromatic systems such as indolizine have been widely investigated to display various intriguing pharmacological activities depending on the decoration patterns of the rings with diverse functional groups (Figure 1).<sup>1</sup> For example, antifungal,<sup>2</sup> antioxidant,<sup>3</sup> antibacterial,<sup>4</sup> anticancer,<sup>5</sup> and other biological activities.<sup>6,7</sup>



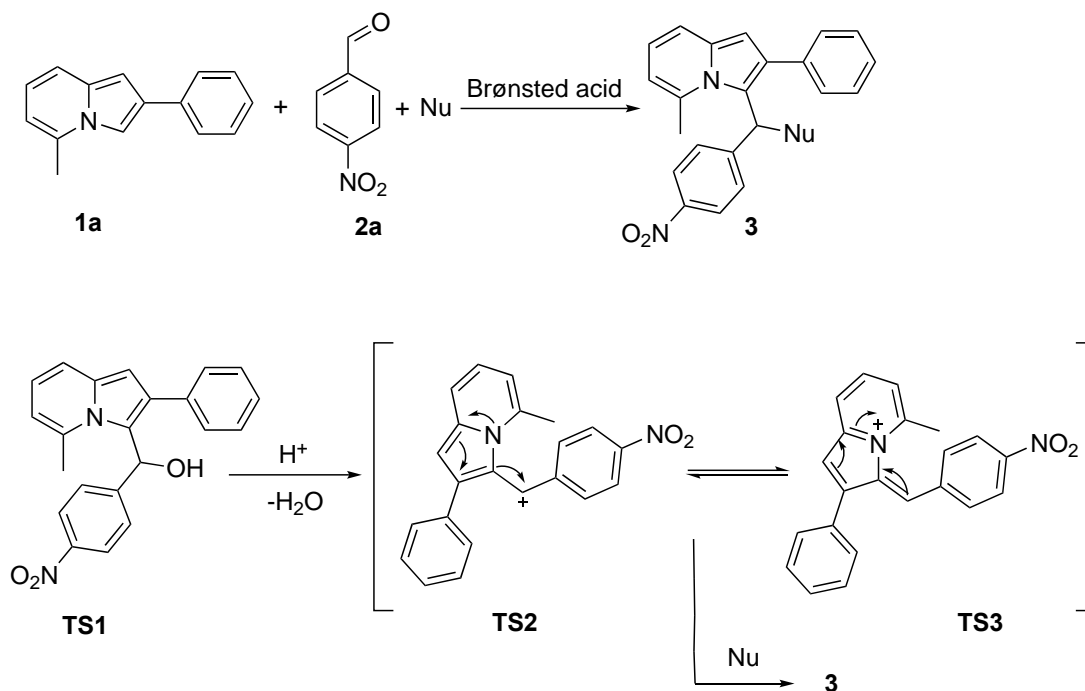
**Figure 1.** Examples of indolizine in active molecules

Meanwhile, they were also found to be potent molecular fluorescent sensor due to their excellent fluorophores with a high quantum yield.<sup>8-12</sup> Therefore, the development of efficient methods to obtain indolizines is paid much attention. Because of the importance of these molecules, some graceful methods have been developed, which could be identified as two ways: 1) construction of the indolizines rings. For example, pyridinium N-methylides reacted with electron-deficient alkynes or alkenes through 1,3-dipolar cycloaddition,<sup>13-16</sup> intramolecular cycloisomerization of pyridines catalyzed by transition metals,<sup>17-19</sup> [3+2] cyclization of pyridines and alkenyl diazoacetates catalyzed by copper,<sup>20</sup> annulation of 2-alkylazaarenes and  $\alpha,\beta$ -unsaturated carboxylic acids with copper,<sup>21</sup> I<sub>2</sub>-mediated oxidative cyclization,<sup>22</sup> multicomponent approaches;<sup>23,24</sup> 2) direct functionalization of indolizines which has also attracted considerable interest in the past decades. For instance, direct C-H bond functionalization of indolizines including arylation,<sup>25</sup> alkynylation,<sup>26</sup> and dimerization<sup>27</sup> catalyzed with transition metals, cross-coupling of indolizines and vinylarenes employing a Pd(OAc)<sub>2</sub>/Ag<sub>2</sub>CO<sub>3</sub> catalytic system to afford the branched  $\alpha$ -olefin products,<sup>28</sup> acylation of indolizines with  $\alpha,\beta$ -unsaturated carboxylic acids with palladium.<sup>29</sup> Although there are many methods available for functionalization of indolizines,<sup>30-34</sup> the development of efficient methods under mild conditions catalyzed with simple Brønsted acid catalyst are significant. Herein we developed an efficient method for functionalization of indolizines with three-component reactions (Scheme 1).



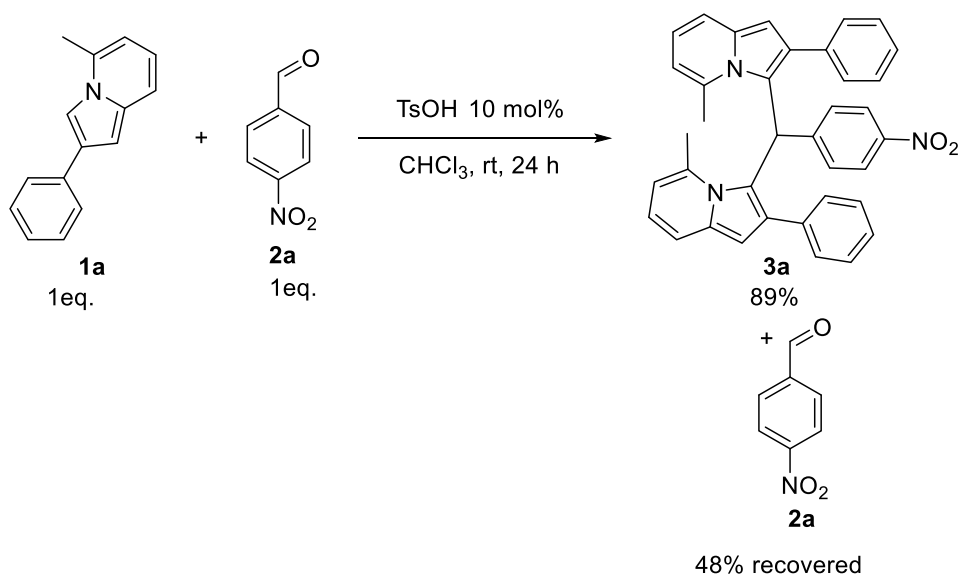
**Scheme 1.** Works for functionalization of indolizine

We reasoned that indolizine **1a** could react with aromatic aldehyde **2a** to afford product TS1 (Scheme 2), which could be dehydrated under acid conditions to result the corresponding cationic intermediates TS2 and TS3.



**Scheme 2.** Strategy for functionalization of indolizine

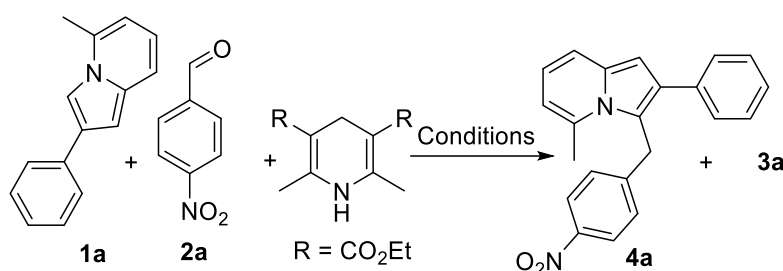
Then choose suitable nucleophiles to react with the reactive intermediates would allow for the preparation of modified indolizines **3** via the three-component reaction. To prove our hypothesis, indolizine **1a** and aromatic aldehyde **2a** were reacted under room temperature with TsOH as catalyst. To our delight, indolizine **3a** was obtained with 89% yield based on the amount of **1a**, accompanied by 48% unreacted aldehyde **2a** (Scheme 3). Therefore, we inferred that the cationic intermediates TS2 and TS3 should be formed and attacked by the indolizine itself which was also reported as efficient nucleophiles.



**Scheme 3.** Initial study of the reaction without HEH

Based on the above result, our efforts were focused on the option of suitable nucleophiles. As we know, Hantzsch ester (HEH) was a type of efficient nucleophile, which was frequently used to reduce the electrophiles such as imines, nitroolefins, cationic intermediate,<sup>35</sup> and so on. Therefore, the three-component reaction using HEH to attract the in situ formed reactive cationic intermediate was investigated (Table 1). The results demonstrated that stronger Brønsted acids such as TsOH, TfOH and TFA could catalyze the reaction to afford the corresponding product **4a** with different amount of byproduct **3a** (entries 1-4). However, acetic acid could not catalyze the reaction which might be ascribed to the slightly lower acid property (entry 2). TsOH was selected as the efficient catalyst considering the slightly higher yield of **4a**. Further screening of the reaction solvent and reaction temperatures revealed that the yield of **4a** could be increased to 92% with toluene as solvent at 60 °C (entries 5-9). Therefore the optimal reaction condition was finally set as following: 10 mol% TsOH, toluene, 60 °C, 24 h.

**Table 1.** Optimization of the reaction conditions

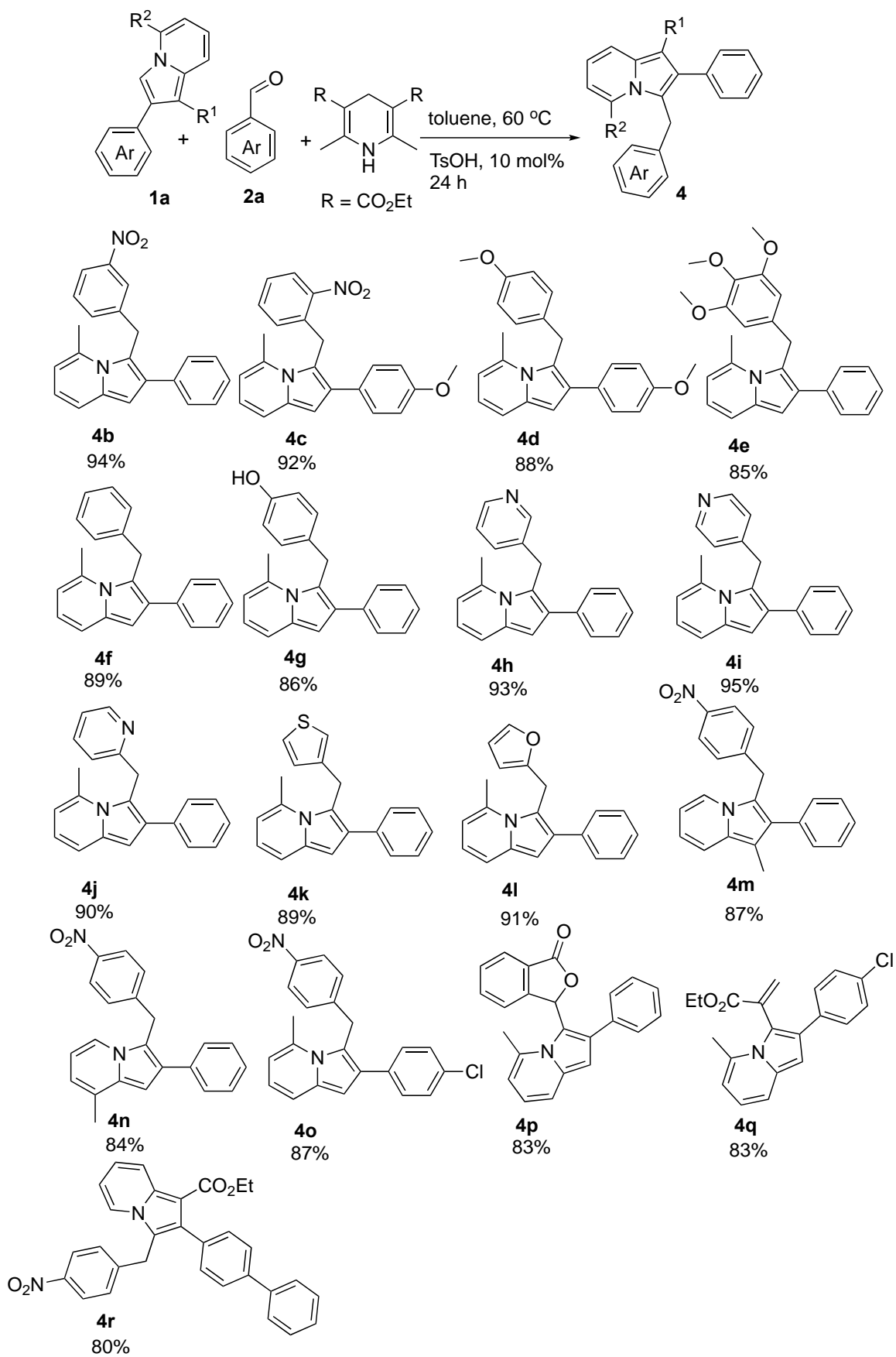


Entry	Cata.	Solv.	Tem.(°C)	Yieldb(%)	
				<b>3a</b>	<b>4a</b>
1	TsOH	CHCl <sub>3</sub>	30	15	60
2	AcOH	CHCl <sub>3</sub>	30	<5	<5
3	TfOH	CHCl <sub>3</sub>	30	10	40
4	TFA	CHCl <sub>3</sub>	30	24	48
5	TsOH	toluene	30	8	65
6	TsOH	toluene	40	7	68
7	TsOH	toluene	50	<5	78
8	TsOH	toluene	60	<5	92
9	TsOH	toluene	70	<5	92

a. the reaction was run with 0.2 mmol **1a**, 0.2 mmol **2a** and 0.26 mmol HEH in 2 mL solvent for 24 h;

b. the yield was calculated based on purification with silica-gel column chromatography.

Then we turned to investigate the reaction scope<sup>36</sup> (Scheme 4). All sorts of aromatic aldehydes were screened under the optimal reaction conditions to afford the corresponding products **4** with excellent yields (85-94%). Generally, aromatic aldehydes with electron withdrawing groups afforded the slightly higher yields (**4b-4g**).



Scheme 4. Substrate scopes of the reaction

Interestingly, aldehydes with different hetero-aromatics such as pyridine, furan and thiophene, could be efficiently used to afford the corresponding products with high yields (**4h-4l**). Meanwhile, the indolizine substrates were also investigated, which revealed that the reaction could smoothly occur to afford the corresponding products (**4c-4d**, **4m-4o**, **4r**). Interestingly, when 2-formylbenzoic acid was used as substrate, the corresponding product was lactone **4p**, which might be formed by the nucleophilic attack of the cationic intermediate with intramolecular carboxylic group. Moreover, ethyl pyruvate was also investigated. Interestingly, the product obtained was the olefin **4q** which might be formed by dehydration of the in situ formed alcohol intermediate.

In summary, we have succeeded in developing an efficient method for functionalization of indolizines under mild reaction conditions. Interestingly, all sorts of aromatic aldehydes with different types of substituents, or aldehydes with different class of hetero-aromatics were systematically used for alkylation of indolizines. Hantzsch ester could efficiently trap the reactive cationic intermediate under mild Brønsted acid condition. Further researches for functionalization of the indolizine based on such methods as well as the biological activities of the obtained indolizines are underway in our lab.

## ACKNOWLEDGEMENTS

This work was supported by Shanxi Excellent Doctor Grant Award (No.SXYBKY201737), the Science and Technology Innovation Project of Shanxi Agricultural University (No. 2017YJ38), and Science and Technology Innovation Project of Shanxi (2019L0374).

## SUPPORTING INFORMATION

Supplementary (synthesis of the indolizines,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, etc.) data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/28020/106/11>.

## REFERENCES AND NOTES

Authors are requested to submit their references according to the following format:

1. A. Mondal, N. Acharjee, and D. Palit, *Struct. Chem.*, 2023, ASAP (doi: [10.1007/s11224-023-02193-1](https://doi.org/10.1007/s11224-023-02193-1)).
2. P. Sharma, A. Kumar, S. Sharma, and N. Rane, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 937.
3. S. Teklu, L.-L. Gundersen, F. Rise, and M. Tilset, *Tetrahedron*, 2005, **61**, 4643.
4. A. Hazra, S. Mondal, A. Maity, S. Naskar, P. Saha, R. Paira, K. B. Sahu, P. Paira, S. Ghosh, C. Sinha, A. Samanta, S. Banerjee, and N. B. Mondal, *Eur. J. Med. Chem.*, 2011, **46**, 2132.
5. D. A. James, K. Koya, H. Li, G. Liang, Z. Xia, W. Ying, Y. Wu, and L. Sun, *Bioorg. Med. Chem.*

- [Lett., 2008, 18, 1784.](#)
6. R. C. Oslund, N. Cermak, and M. H. Gelb, [J. Med. Chem., 2008, 51, 4708.](#)
  7. S. Gopavaram, S. S. Mahender, L. Kyatagani, G. S. Mangubhai, K. Shivaprasad, and S. Chandrashekarappa, [J. Mol. Struct., 2023, 1286, 135561.](#)
  8. D. A. Lerner and E. M. Evleth, [Chem. Phys. Lett., 1972, 15, 260.](#)
  9. T. Mitsumori, M. Bendikov, O. Dautel, F. Wudl, T. Shioya, H. Sato, and Y. Sato, [J. Am. Chem. Soc., 2004, 126, 16793.](#)
  10. Y.-M. Shen, G. Grampp, N. Leesakul, H.-W. Hu, and J.-H. Xu, [Eur. J. Org. Chem., 2007, 3718.](#)
  11. I. Kim, H. K. Won, J. Choi, and G. H. Lee, [Tetrahedron, 2007, 63, 12954.](#)
  12. Y. Jung and I. Kim, [Tetrahedron, 2012, 68, 8198.](#)
  13. A. R. Katritzky, G. Qiu, B. Yang, and H.-Y. He, [J. Org. Chem., 1999, 64, 7618.](#)
  14. X. Fang, Y.-M. Wu, J. Deng, and S.-W. Wang, [Tetrahedron, 2004, 60, 5487.](#)
  15. N. A. Morra, C. L. Morales, B. Bajtos, X. Wang, H. Jang, J. Wang, M. Yu, and B. L. Pagenkopf, [Adv. Synth. Catal., 2006, 348, 2385.](#)
  16. Y. Liu, H.-Y. Hu, Q.-J. Liu, H.-W. Hu, and J.-H. Xu, [Tetrahedron, 2007, 63, 2024.](#)
  17. I. V. Seregin and V. Gevorgyan, [J. Am. Chem. Soc., 2006, 128, 12050.](#)
  18. I. V. Seregin, A. W. Schammel, and V. Gevorgyan, [Org. Lett., 2007, 9, 3433.](#)
  19. X. Meng, P. Liao, J. Liu, and X. Bi, [Chem. Commun., 2014, 50, 11837.](#)
  20. J. Barluenga, G. Lonzi, L. Riesgo, L. A. López, and M. Tomás, [J. Am. Chem. Soc., 2010, 132, 13200.](#)
  21. Y. Yang, C. Xie, Y. Xie, and Y. Zhang, [Org. Lett., 2012, 14, 957.](#)
  22. L. Xiang, Y. Yang, X. Zhou, X. Liu, X. Li, X. Kang, R. Yan, and G. Huang, [J. Org. Chem., 2014, 79, 10641.](#)
  23. S. U. Dighe, S. Hutait, and S. Batra, [ACS Comb. Sci., 2012, 14, 665.](#)
  24. F. Wang, Y. Shen, H. Hu, X. Wang, H. Wu, and Y. Liu, [J. Org. Chem., 2014, 79, 9556.](#)
  25. C.-H. Park, V. Ryabova, I. V. Seregin, A. W. Sromek, and V. Gevorgyan, [Org. Lett., 2004, 6, 1159.](#)
  26. I. V. Seregin, V. Ryabova, and V. Gevorgyan, [J. Am. Chem. Soc., 2007, 129, 7742.](#)
  27. J.-B. Xia, X.-Q. Wang, and S.-L. You, [J. Org. Chem., 2009, 74, 456.](#)
  28. Y. Yang, K. Cheng, and Y. Zhang, [Org. Lett., 2009, 11, 5606.](#)
  29. Y. Yang, L. Chen, Z. Zhang, and Y. Zhang, [Org. Lett., 2011, 13, 1342.](#)
  30. B. Zhao, [Org. Biomol. Chem., 2012, 10, 7108.](#)
  31. Y. Jung and I. Kim, [Org. Biomol. Chem., 2015, 13, 10986.](#)
  32. M. F. Z. J. Amaral, A. A. Baumgartner, R. Vessecchi, and G. C. Clososki, [Org. Lett., 2015, 17, 238.](#)
  33. N. N. K. Reddy, R. R. Donthiri, C. Ravi, and S. Adimurthy, [Tetrahedron Lett., 2016, 57, 3243.](#)

34. Priyanka, P. Rani, Kiran, and J. Sindhu, [ChemistrySelect, 2023, 8, e20220531](#).
35. C. Chen, H.-X. Feng, Z.-L. Li, P.-W. Cai, Y.-K. Liu, L.-H. Shan, and X.-L. Zhou, [Tetrahedron Lett., 2014, 55, 3774](#).
36. A reaction tube was charged with the iodolizine **1** (0.2 mmol, 1 equiv.), aromatic aldehyde **2** (0.2 mmol, 1 equiv.), Hantzsch ester (0.26 mmol, 1.3 equiv.), anhydrous toluene (2 mL), TsOH (10 mol%). The system was stirred under a nitrogen atmosphere at 60 °C for 24 h. Then the products were obtained by purification with flash silica gel chromatography.