

## HIGHLY DIASTEREOSELECTIVE SELF-1,3-DIPOLAR [3+3] CYCLOADDITION OF AZOMETHINE YLIDES PROMOTED BY CESIUM CATALYST

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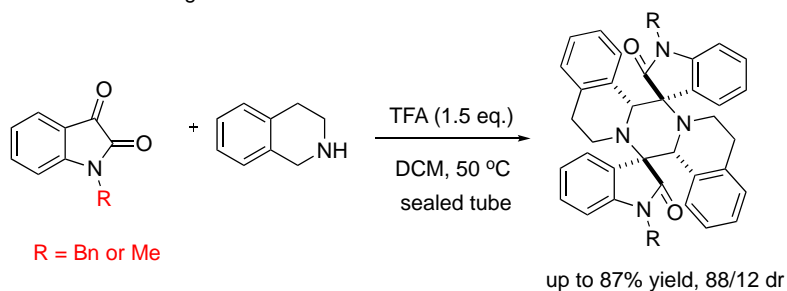
**Abstract** – A highly diastereoselective self-1,3-dipolar [3+3] cycloaddition reaction catalyzed by cesium carbonate has been established for the synthesis of 2,5-dispirooxindole-piperazines. This reaction involves the reaction of azomethine ylides derived from unprotected isatins with tetrahydroisoquinolines. The method is characterized by its simplicity, avoidance of excess external acids and high diastereoselectivity.

As privileged structures, spirocyclic oxindoles are frequently found in natural products, drugs and pharmaceutical active molecules,<sup>1</sup> rendering them significant synthetic objectives in the realms of organic and medicinal research.<sup>2</sup> In recent years, 1, 3-dipolar cycloaddition (1,3-DC) of azomethine ylides derived from isatins has attracted an increasing amount of interest owing to their distinctive ability to construct a wide array of spirooxindole ring systems.<sup>3</sup> For example, the azomethine ylides, which are formed in situ from isatin derivatives and specific amino substrates, undergo reactions with various electrophilic reagents as dipolarophiles. These reagents include electron-deficient alkenes,<sup>4</sup> alkynes,<sup>5</sup> chromane derivatives,<sup>6</sup> azirines,<sup>7</sup> or  $\alpha$ ,  $\beta$ -unsaturated ketones.<sup>8</sup> These reactions result in the formation of structurally intricate spirooxindole derivatives through multicomponent 1,3-dipolar cycloaddition reactions. Although effective and innovative approaches for the diversity-oriented synthesis of spirooxindoles have been developed, these methods typically necessitate the utilization of specific secondary  $\alpha$ -amino acids or amino compounds in conjunction with an excess of strong acid additives to generate the crucial azomethine ylides. Furthermore, although many metal salts, such as copper,<sup>9</sup> silver etc.,<sup>10</sup> have been used as catalyst for the cycloaddition of imino esters-derived azomethine ylides, the research of employing metal salts as catalyst in the transformation of isatin-derived azomethine ylides remains less-explored.<sup>11</sup>

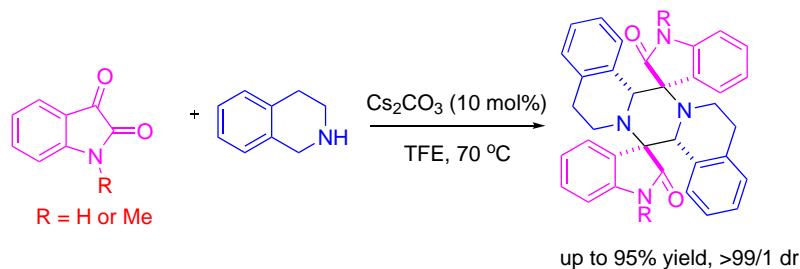
Recently, as an important advance of this research area, Yang and co-workers reported self-1,3-dipolar [3+2] and [3+3] cyclization of azomethine ylides derived from isatins with primary or cyclic secondary amines.<sup>12</sup> These findings are interesting and provide direct access to the diversified dispirooxindole scaffolds. For example, the unprecedented 2,5-dispirooxindole-piperazine skeleton<sup>13</sup> could be obtained directly from protected isatins and 1,2,3,4-tetrahydroisoquinolines (THIQs) assisted by the use of trifluoroacetic acid as additive (Scheme 1a). Indeed, the use of excess amount of external acid additives, requirement of specific protecting groups and the unsatisfactory diastereoselectivity made these reactions are still in urgent need of improvement.

Herein, we present the advancement of the self-1,3-dipolar [3+3] cycloaddition of azomethine ylides derived from isatin with THIQ facilitated by a cesium catalyst. The implementation of this catalytic approach demonstrates notable enhancements in the utility and scalability of this self-[3+3] cycloaddition, owing to its utilization of mild reaction conditions, good compatibility with various functional groups, and high diastereoselectivity.

a) Previous work: Yang *et al.*



b) This work:



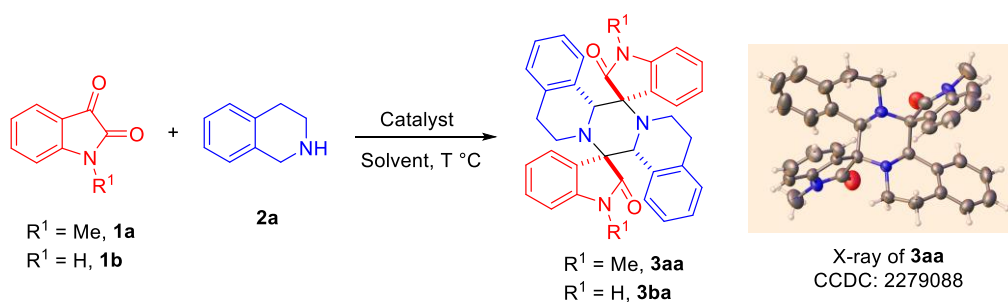
▽ easily available catalyst   ▽ operational simple   ▽ N-free isatin tolerated   ▽ high diastereoselectivity

**Scheme 1.** Cycloaddition of isatin and THIQ

We commenced our studies by optimizing the reaction conditions using N-methylisatin **1a** and 1,2,3,4-tetrahydroisoquinoline **2a** as the model substrates (Table 1). Firstly, different solvent was investigated under catalyst-free condition. When ethanol (EtOH) was used as the solvent under air in 50 °C, the self-[3+3] cycloaddition product **3aa** was obtained in 56% yield with 85/15 diastereoselectivity (dr) (Table 1, entry 1). The dr values of product **3aa** are decided by comparison with Yang's work.<sup>12</sup> The use

of methanol and isopropanol solvent failed to improve yield and diastereoselectivity (Table 1, entries 2 and 3). When the aprotic solvent tetrahydrofuran (THF) was used as the solvent, only trace amount of desired product was detected (Table 1, entry 4). Gratifyingly, under protic solvent of trifluoroethanol (TFE), the reaction was accelerated and a considerable yield and diastereoselectivity were obtained after just 16 h (Table 1, entry 6). A better result was obtained by increasing the temperature to 70 °C (Table 1, entries 7 - 8). Considering that metal salts showed effective catalytic activities for the relevant azomethine ylide research, we then turned our attention to metal salt optimization. When  $\text{Cu}(\text{OAc})_2$  or  $\text{CuBr}_2$  was used as catalyst, only trace amount of desired product was detected (Table 1, entries 9 - 10). We assumed that the copper catalyst could not activate and stabilize the azomethine ylide derived from isatin and the reason is probably due to the complexing of the exposed *N*-H group with the copper catalysts and poisoning the catalyst.<sup>14</sup> When the  $\text{ZnI}_2$  was employed, the desired product **3aa** was obtained in 70% yield with 89/11 dr (Table 1, entry 11). Attempts to enhance the yield with other metal salts were unsuccessful (Table 1, entries 12 - 15). Finally, when  $\text{Cs}_2\text{CO}_3$  was used, the yield was successfully improved to 79% with 90/10 dr (Table 1, entry 16). The *N*-free isatin was also investigated under this condition, the corresponding dispirooxindole **2ba** was obtained in 84% yield with excellent diastereoselectivity (only single isomer) (Table 1, entry 17). However, when the  $\text{CsCl}$  and  $\text{Na}_2\text{CO}_3$  were used, only 22% and 35% yield of desired products were obtained, respectively. These results suggest that both the cesium ion and carbonate ion are keys for the high efficiency of this transformation (Table 1, entries 18,19).

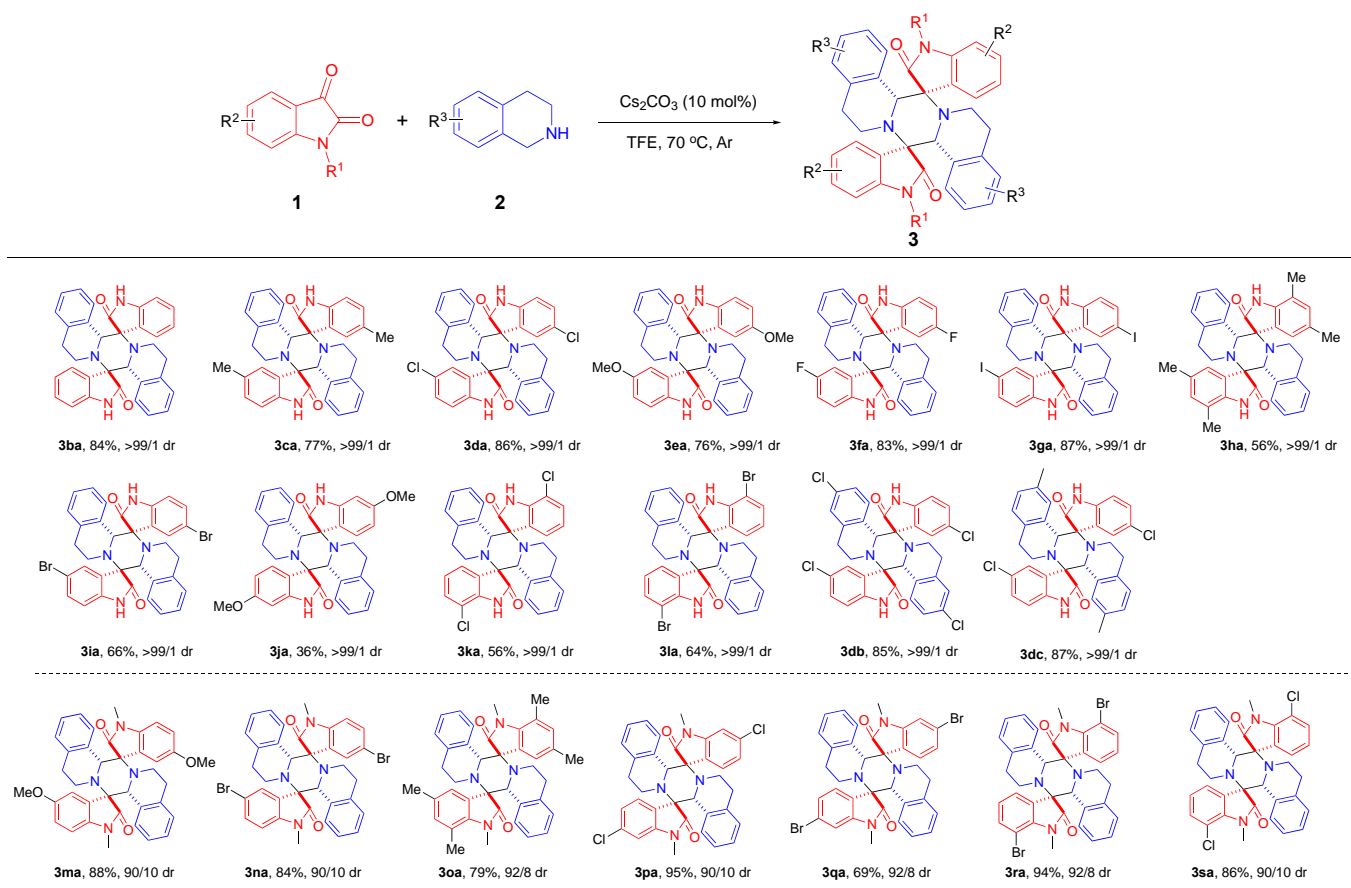
Table 1. Condition optimizations



Entry	R <sup>1</sup>	Solvent	Catalyst	T (°C)	t (h)	Yield (%)	dr
1	Me	EtOH	-	50	40	56 ( <b>3aa</b> )	85/15
2	Me	MeOH	-	50	48	29 ( <b>3aa</b> )	86/14
3	Me	<i>i</i> PrOH	-	50	48	38 ( <b>3aa</b> )	84/16
4	Me	THF	-	50	48	trace	-
5	Me	HFIP	-	50	48	24 ( <b>3aa</b> )	79/21
6	Me	TFE	-	50	16	51 ( <b>3aa</b> )	90/10
7	Me	TFE	-	60	12	53 ( <b>3aa</b> )	90/10

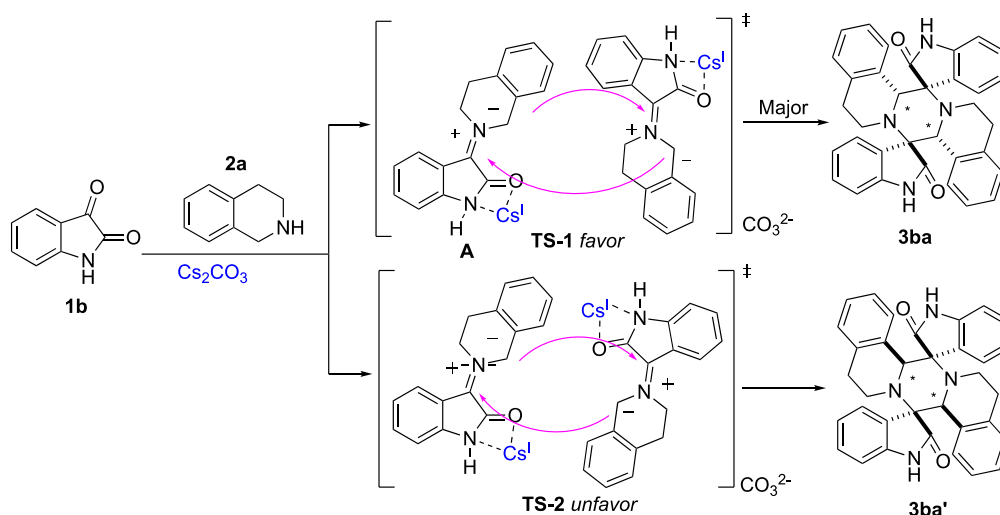
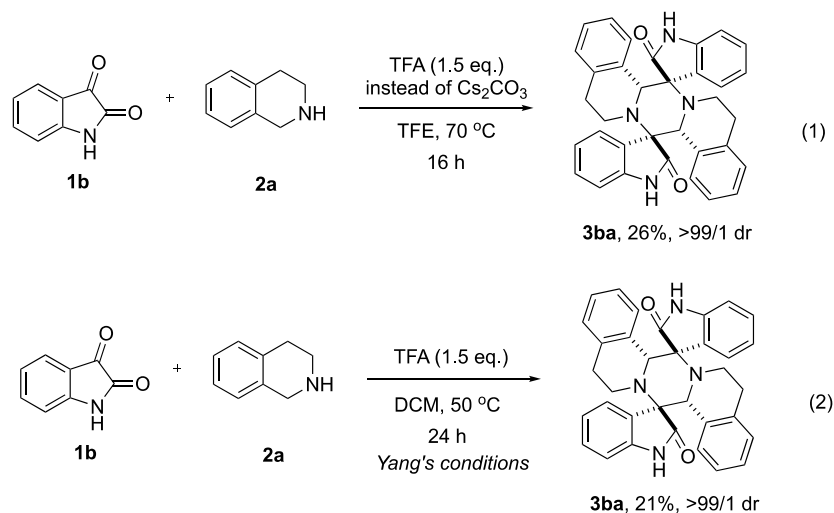
8	Me	TFE	-	70	12	61 ( <b>3aa</b> )	90/10
9	Me	TFE	Cu(OAc) <sub>2</sub>	70	16	trace	-
10	Me	TFE	CuBr <sub>2</sub>	70	16	trace	-
11	Me	TFE	ZnI <sub>2</sub>	70	16	70( <b>3aa</b> )	89/11
12	Me	TFE	AgOAc	70	16	67 ( <b>3aa</b> )	90/10
13	Me	TFE	AgBr	70	16	55 ( <b>3aa</b> )	90/10
14	Me	TFE	FeCl <sub>2</sub>	70	16	61 ( <b>3aa</b> )	90/10
15	Me	TFE	CeCl <sub>3</sub>	70	16	70 ( <b>3aa</b> )	91/9
16	Me	TFE	Cs <sub>2</sub> CO <sub>3</sub>	70	16	79 ( <b>3aa</b> )	90/10
17	H	TFE	Cs <sub>2</sub> CO <sub>3</sub>	70	16	84 ( <b>3ba</b> )	>99/1
18	H	TFE	CsCl	70	30	22 ( <b>3ba</b> )	>99/1
19	H	TFE	Na <sub>2</sub> CO <sub>3</sub>	70	30	35 ( <b>3ba</b> )	>99/1

With the optimized reaction conditions in hand, we then investigated the substrate scope of the reaction. As shown in Scheme 2, a wide range of *N*-free isatins bearing electronically different substituents on the phenyl moiety react smoothly to give self-[3+3] cycloaddition dispirooxindoles in high yields with exclusive diastereoselectivities. Electron-donating groups such as methyl (**1c** and **1h**) and methoxy (**1e** and **1j**) as well as electron-withdrawing groups such as fluoro (**1f**), chloro (**1d** and **1k**), bromo (**1i** and **1l**) and iodo (**1g**) were well tolerated under this cesium catalytic system. Moreover, 7-chloro and 8-methyl substituted tetrahydroisoquinolines tolerated the optimal conditions, giving the desired products **3db–3dc** in 85%–87% yields with >99/1 drs. Furthermore, under the optimal conditions, the use of various *N*-methyl substituted isatins with different functional substituents on the phenyl moieties afforded the corresponding products **3ma–3sa** in 69%–95% yields with 90/10-92/8 drs.



**Scheme 2.** Substrate scope of the reaction

In order to investigate the mechanism of the reaction, several control experiments have been performed. In 2015, Yang et al.<sup>12</sup> reported the self-1,3-dipolar [3+3] cyclization reaction of *N*-substituted isatins with THIQs by using excess amount of trifluoroacetic acid (TFA) as additive. In accordance with Yang's protocol, we treated *N*-free isatin **1b**, 1,2,3,4-tetrahydroisoquinoline **2a** with TFA instead of Cs<sub>2</sub>CO<sub>3</sub> under the current conditions, only 26% yield of desired product **3ba** was obtained (Scheme 3, eq. 1). When this reaction was conducted under Yang's optimal conditions, only 21% yield of product **3ba** was isolated (Scheme 3, eq. 2). Interestingly, the diastereoselectivities of the product **3ba** are both exclusive under the TFA conditions. These results suggest that the diastereoselectivity of this reaction is mainly controlled by the *N*-protecting group of the isatins and the yield of the reaction is greatly improved by the use of Cs<sub>2</sub>CO<sub>3</sub> as the catalyst. Combined with Yang et al.<sup>12</sup> proposed reaction pathway and previous relevant metal-catalyzed cycloaddition reactions of azomethine ylides researches,<sup>9-10</sup> we proposed that the coordination of azomethine ylide to cesium catalyst to form the key intermediate **A**, followed by intermolecular 1,3-dipolar [3+3] cyclization to form the 2,5-dispirooxindole-piperazine product. In this process, the cesium catalyst shows higher catalytic reactivities than that of protonic-acid TFA and the formation of *cis*-2,5-dispirooxindole-piperazine **3ba** is favored through the transition state **TS-1** (Scheme 3).



**Scheme 3.** Control experiments and proposed reaction pathway

In summary, a highly diastereoselective self-1,3-dipolar [3+3] cycloaddition of azomethine ylides derived from unprotected isatins with tetrahydroisoquinolines has been developed for the synthesis of 2,5-dispirooxindole-piperazines. This protocol, facilitated by a  $\text{Cs}_2\text{CO}_3$  catalyst, is characterized by its simplicity, high diastereoselectivity, and avoidance of excessive external acid usage.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

Supplementary (synthesis of the products,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, MS spectra, etc.) data associated with this

article can be found, in the online version, at URL:  
<https://www.heterocycles.jp/newlibrary/downloads/PDFsi/28024/106/10>.

## REFERENCES AND NOTES

1. (a) A. P. Sakla, P. Kansal, and N. Shankaraiah, *Eur. J. Org. Chem.*, 2021, 757; (b) H. Lin and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2003, **42**, 36; (c) Y. Liu, S.-J. Han, W.-B. Liu, and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740.
2. (a) R. Ahmad and F. Salim, *Stud. Nat. Prod. Chem.*, 2015, **45**, 485; (b) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748.
3. Selected examples and reviews: (a) A. K. Ganguly, N. Seah, V. Popov, C. H. Wang, R. Kuang, A. K. Saksena, B. N. Pramanik, T. M. Chan, and A. F. McPhail, *Tetrahedron Lett.*, 2002, **43**, 8981; (b) K. A. Ahrendt and R. M. Williams, *Org. Lett.*, 2004, **6**, 4539; (c) V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247; (d) M. Ghandi, A. Yari, S. J. T. Rezaei, and A. Taheri, *Tetrahedron Lett.*, 2009, **50**, 4724; (e) S. V. Karthikeyan, B. D. Bala, V. P. A. Raja, S. Perumal, P. Yogeeswari, and D. Sriram, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 350; (f) S. Dubey, A. Pal, S. Roy, S. Sasmal, A. Tamrakar, R. Jana, and T. Das, *New J. Chem.*, 2023, **47**, 8997; (g) S. V. Kumar and P. J. Guiry, *Angew. Chem. Int. Ed.*, 2022, **61**, e202205516.
4. For selected examples, see: (a) S. Vidya, K. Priya, D. V. Jayasree, A. Deepthi, and P. G. Biju, *Synth. Commun.*, 2019, **49**, 1592; (b) R. S. Kumar, A. I. Almansour, N. Arumugam, F. Mohammad, D. Kotresha, and J. C. Menendez, *Bioorg. Med. Chem.*, 2019, **27**, 2487; (c) S. Boudriga, S. Haddad, M. Askri, A. Soldera, M. Knorr, C. Strohmman, and C. Golz, *RSC Adv.*, 2019, **9**, 11082; (d) A. Dandia, S. Khan, P. Soni, A. Indora, D. K. Mahawar, P. Pandya, and C. S. Chauhan, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 2873; (e) K.-K. Wang, Y.-L. Li, R.-X. Chen, A.-L. Sun, Z.-Y. Wang, Y.-C. Zhao, M.-Y. Wang, and S. Sheng, *Adv. Synth. Catal.*, 2022, **364**, 2047.
5. M. Narayanarao, L. Koodlur, S. Gopal, S. Y. Reddy, and S. Kamila, *Synth. Commun.*, 2018, **48**, 2441.
6. (a) J. Yue, S. Chen, X. Zuo, X. L. Liu, S. W. Xu, and Y. Zhou, *Tetrahedron Lett.*, 2019, **60**, 137; (b) S. Chen, J. Yue, X. L. Liu, J. X. Wang, X. Zuo, and Y. Cao, *Synth. Commun.*, 2019, **49**, 2425.
7. A. Angyal, A. Demjen, V. Harmat, J. Wolfling, L. G. Puskas, and I. Kanizsai, *J. Org. Chem.*, 2019, **84**, 4273.
8. For selected examples, see: (a) V. Pogaku, V. S. Krishna, D. Sriram, K. Rangan, and S. Basavoju, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1682; (b) S. V. Kumar, G. U. Rani, M. Divyalakshmi, N. Bhuvanesh, S. Muthusubramanian, and S. Perumal, *Mol. Divers.*, 2019, **23**, 669; (c) M. S. Islam, H. M. Ghawas, F. F. El-Senduny, A. M. Al-Majid, Y. Elshaier, F. A. Badria, and A. Barakat, *Bioorg.*

- Chem.*, 2019, **82**, 423; (d) K. S. Mani and S. P. Rajendran, *Synth. Commun.*, 2018, **48**, 1324; (e) E. M. Hussein, Z. Moussa, N. El Guesmi, and S. A. Ahmed, *RSC Adv.*, 2018, **8**, 24116.
9. (a) L. Wei, Q. H. Li, and C. J. Wang, *J. Org. Chem.*, 2018, **83**, 11814; (b) F.-Z. Han, S.-B. Yu, C. Zhang, and X.-P. Hu, *Tetrahedron*, 2016, **72**, 2616.
  10. (a) W. Zeng and Y.-G. Zhou, *Org. Lett.*, 2005, **7**, 5055; (b) H. Yang, S.-N. Lu, Z. Chen, and X.-F. Wu, *J. Org. Chem.*, 2021, **86**, 4361.
  11. (a) Y.-R. Chen, G. Zhan, W. Du, and Y.-C. Chen, *Adv. Synth. Catal.*, 2016, **358**, 3759; (b) F. Salahi, M. J. Taghizadeh, H. Arvinnezhad, M. Moemeni, K. Jadidi, and B. Notash, *Tetrahedron Lett.*, 2014, **55**, 1515.
  12. P. J. Xia, Y. H. Sun, J. A. Xiao, Z. F. Zhou, S. S. Wen, Y. Xiong, G. C. Ou, X. Q. Chen, and H. Yang, *J. Org. Chem.*, 2015, **80**, 11573.
  13. (a) N. Mahmoodi, Q. Qian, L. Y. P. Luk, and M. E. Tanner, *Pure Appl. Chem.*, 2013, **85**, 1935; (b) M. M. C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 16077.
  14. (a) H. Ren, P. Wang, L. Wang, and Y. Tang, *Org. Lett.*, 2015, **17**, 4886; (b) Z.-Y. Li, W. Wang, J.-R. Song, R.-A. Wang, J. Shi, Q. Chi, Y. Li, H. Ren, and W.-D. Pan, *J. Org. Chem.*, 2021, **86**, 17164.