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# DBU-catalyzed diastereoselective 1,3-dipolar [3+2] cycloaddition of trifluoroethyl amine-derived isatin ketimines with chalcones: synthesis of 5'-CF<sub>3</sub>-substituted 3,2'-pyrrolidinyl spirooxindoles†

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A diastereoselective 1,3-dipolar cycloaddition reaction between trifluoroethyl amine-derived isatin ketimines and chalcones was successfully achieved in the presence of DBU. A series of 5'-CF<sub>3</sub>-substituted 3,2'-pyrrolidinyl spirooxindoles were efficiently synthesized with high yields and excellent diastereoselectivities (up to 89% yield, and >99:1 dr). The *in vitro* anticancer activities of these highly functionalized spiro[pyrrolidin-3,2'-oxindole] derivatives were evaluated.

## Introduction

Pyrrolidinyl spirooxindoles have emerged as one class of privileged scaffolds commonly encountered in diverse natural products and biologically active compounds, thus establishing their medicinal significance in drug discovery and development. As a notable subtype, 3,2'-pyrrolidinyl spirooxindoles have demonstrated significant pharmacological relevance in the field of pharmaceutical research (Fig. 1).<sup>1</sup>

On the other side, the presence of fluorine atoms has been found in up to 20% of commercially available medications.<sup>2</sup> Fluorine substitutions are often applied for the strategic modifications of lead compounds. In particular, it is generally acknowledged that the introduction of a trifluoromethyl group into the  $\alpha$ -position of the pyrrolidine can effectively enhance the binding affinity of drug receptors.<sup>3</sup> Consequently, synthetic protocols of 5'-CF<sub>3</sub>-containing 3,2'-pyrrolidinyl spirooxindoles

have garnered much more attention. Among them, 1,3-dipolar [3 + 2] cycloadditions of *N*-2,2,2-trifluoroethylisatin ketimines **1** with various activated alkenes have been extensively reported in the past few years (Scheme 1a).<sup>4,5</sup> As we know, chalcones are a well-studied group of naturally occurring aromatic ketones with biological properties including anti-inflammatory and anti-cancer.<sup>6</sup> Additionally, owing to their facile synthetic accessibility and  $\alpha,\beta$ -unsaturated carbonyl conjugated system containing two electrophilic centers, they are frequently used as valuable intermediates for the formation of heterocycles, particularly five- and six-membered heterocyclic molecules.<sup>7</sup> Considering the importance of spirooxindoles, fluorine compounds, and chalcones, we hypothesized that their integration could augment the bioactivities. However, to date, there

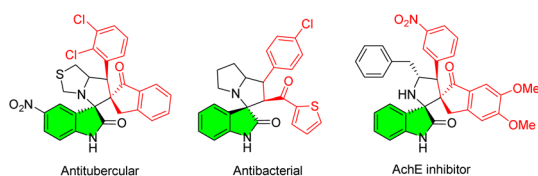
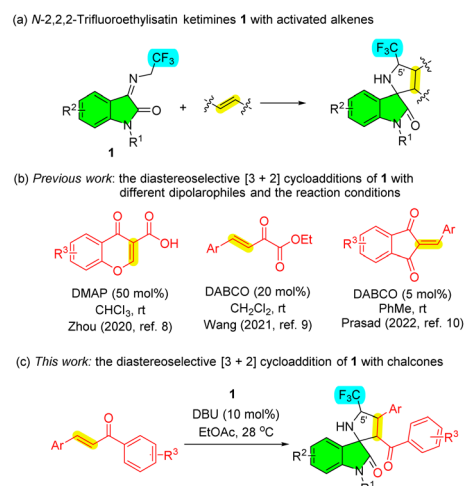


Fig. 1 Selected bioactive 3,2'-pyrrolidinyl spirooxindoles.

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Scheme 1 1,3-Dipolar [3 + 2] cycloaddition reactions of *N*-2,2,2-trifluoroethylisatin ketimines with various activated alkenes.



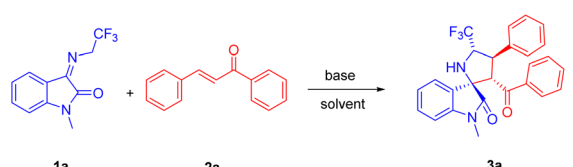
have been few successful examples employing the chalcone-type compounds as the dipolarophiles for the diastereoselective 1,3-dipolar [3 + 2] cycloaddition involving the ketimines **1** (Scheme 1b).<sup>8–10</sup> Despite the aborted cycloaddition of chalcone or its analogue with the ketimines **1** in chloroform catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),<sup>9</sup> we proposed that the alternative reaction condition would enable the utilization of chalcones for this cycloaddition (Scheme 1c).

Herein, we disclosed the DBU-catalyzed diastereoselective 1,3-dipolar [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines with chalcones in ethyl acetate to construct diverse functionalized 5'-CF<sub>3</sub>-containing 3,2'-pyrrolidine spirooxindole derivatives exhibiting promising anticancer activities.

## Results and discussion

*N*-2,2,2-Trifluoroethylisatin ketimine **1a** and chalcone **2a** were chosen as the model substrates for the envisaged [3 + 2] cycloaddition reaction (Table 1). Initially, this cyclization sequence proceeded smoothly in dichloromethane at 28 °C in the presence of K<sub>2</sub>CO<sub>3</sub>, affording the spirocyclic product **3a** in 68% yield with high dr (Table 1, entry 1). Encouraged by the outcome, a range of common inorganic and organic bases such as Cs<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N, DABCO, DBU, *t*-BuOK and DMAP were tested (entries 2–7). It was found that DBU was the best choice (entry 5).

Table 1 Optimization of the reaction conditions<sup>a</sup>



Entry	Base	Solvent	Time/h	Yield <sup>b</sup> /%	dr <sup>c</sup>
1	K <sub>2</sub> CO <sub>3</sub>	DCM	28	68	96 : 4
2	Cs <sub>2</sub> CO <sub>3</sub>	DCM	22	72	>99 : 1
3	Et <sub>3</sub> N	DCM	72	30	>99 : 1
4	DABCO	DCM	72	49	>99 : 1
5	DBU	DCM	24	83	96 : 4
6	<i>t</i> -BuOK	DCM	38	41	96 : 4
7	DMAP	DCM	16	trace	—
8	DBU	EtOAc	40 min	89	98 : 2
9	DBU	MeCN	2	82	97 : 3
10	DBU	MeOH	72	—	—
11	DBU	PhMe	18	67	>99 : 1
12	DBU	DCE	26	62	96 : 4
13 <sup>d</sup>	DBU	EtOAc	50 min	87	97 : 3
14 <sup>e</sup>	DBU	EtOAc	2.5	80	98 : 2
15 <sup>f</sup>	DBU	EtOAc	48	51	96 : 4
16 <sup>d,g</sup>	DBU	EtOAc	45 min	86	96 : 4

<sup>a</sup> Unless otherwise noted, all the reactions were performed on a 0.10 mmol scale of **1a** and **2a** (1.2 equiv.), using 20 mol% catalyst in solvent (2 mL) at 28 °C. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude mixture. <sup>d</sup> 10 mol% catalyst. <sup>e</sup> 5 mol% catalyst. <sup>f</sup> 2 mol% catalyst. <sup>g</sup> Reaction was carried out at 35 °C.

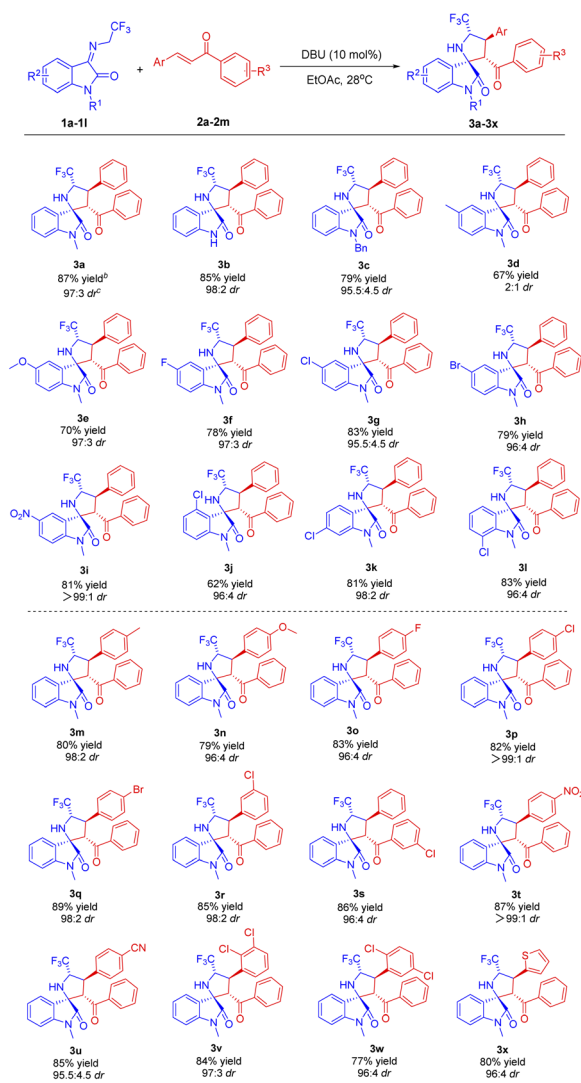
The subsequent screening of different solvents, including DCM, EtOAc, MeCN, MeOH, PhMe and DCE (Table 1, entries 5 and 8–12) indicated that EtOAc was the optimal solvent, resulting in 89% yield and 98 : 2 dr within 40 minutes (entry 8). To our delight, the reaction in MeCN could sustain high levels of yield and diastereoselectivity for a short time of 2 hours (entry 9). However, no reaction was observed in a protic solvent such as MeOH even after 72 hours (entry 10). The utilization of PhMe and DCE in the screening process resulted in diminished product yields over an extended reaction time, albeit with excellent diastereoselectivities (entries 11 and 12). With EtOAc as the solvent, upon reducing the catalyst loading to 10 mol%, both the yield and diastereoselectivity were maintained (Table 1, entry 13). Nevertheless, a significant reduction in yield and an increase in reaction time were observed when using much lower catalyst loading (entries 14 and 15). The elevation of the reaction temperature to 35 °C led to a slight decrease in yield and diastereoselectivity (entry 16). Therefore, the employment of DBU (10 mol%) as the catalyst and EtOAc as the solvent at 28 °C was identified as the optimal reaction conditions for this cycloaddition reaction.

Under the established optimum conditions, the reaction generality was next explored by conducting the [3 + 2] cycloaddition of various *N*-2,2,2-trifluoroethylisatin ketimines and chalcones (Table 2). As can be seen from Table 2, all reactions were remarkably completed within 50 minutes and demonstrated good tolerance towards a diverse array of functional groups, affording the desired products in moderate to good yields and with up to >99 : 1 diastereoselectivities.

At first, the cycloaddition of different ketimines **1a–1i** with chalcone **2a** was examined. As shown in Table 2, the reactions proceeded smoothly under the optimal reaction conditions to obtain the corresponding spirocyclic products **3a–3i** with high yields and excellent diastereoselectivities (up to 87% yield and >99 : 1 dr), except for the product **3d** with relatively lower diastereoselectivity while employing the 5-methyl substituted ketimine **1d**. Particularly, *N*-unsubstituted ketimine **1b** also exhibited notable reactivity, affording the product **3b** in high yield and exceptional diastereoselectivity (85% yield and 98 : 2 dr). Gratifyingly, both electron-donating group (–OMe) and electron-withdrawing groups (–F, –Cl, –Br and –NO<sub>2</sub>) at the 5-, 6-, or 7-position of the ketimines displayed favourable compatibility (**3e–3i**). Furthermore, the cycloaddition reactions between the ketimine **1a** and a variety of chalcones **2b–2m** could furnish the cycloadducts **3m–3w** with high yields and excellent diastereoselectivities, indicating that both electron-donating substituents (–Me and –OMe) and electron-withdrawing groups (–F, –Cl, –Br, –NO<sub>2</sub>, and –CN) at *para*- or *meta*-position on the two phenyl rings of chalcones have only a negligible impact on yield and diastereoselectivity. Notably, chalcones containing the dichloro-substituted phenyl were also tolerant in the catalytic system to afford the cycloadducts **3v** and **3w**, respectively, with good yields and excellent diastereoselectivities. In addition, the substitution of phenyl in chalcone with thienyl (**3x**) also gave satisfactory results.

A scale-up experiment was executed under the standard reaction conditions, thereby demonstrating the feasibility of

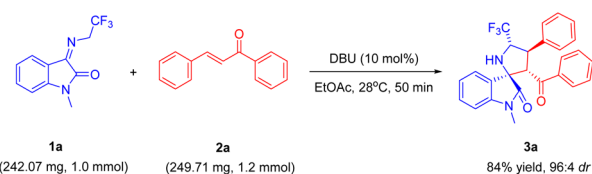
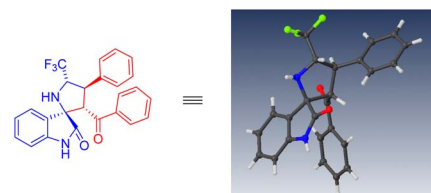


Table 2 Scope of the catalytic cycloaddition<sup>a</sup>

<sup>a</sup> Reactions were performed: **1** (0.1 mmol) and **2** (0.12 mmol), DBU (0.01 mmol), and EtOAc (2 mL) at 28 °C for 50 min. See ESI for details.  
<sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude mixture.

performing this reaction on a 10-fold amplification (Scheme 2). The yield and diastereoselectivity of compound **3a** remained consistently at a high level (84% yield and 96:4 dr), despite a slight decrease.

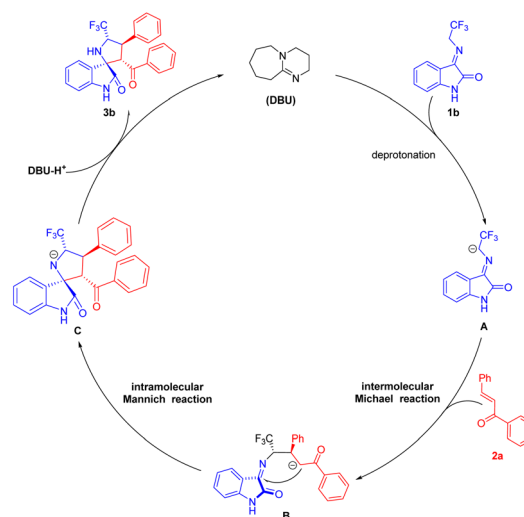
To establish the absolute configuration of the products, a single crystal of compound **3b** was obtained for X-ray

Scheme 2 Gram-scale preparation of **3a**.Fig. 2 X-ray crystal structure of compound **3b** (CCDC 2310278†).

crystallographic analysis (Fig. 2). The absolute configurations of other products were determined by analogy to **3b**.

Based on the experimental results and related literatures, we proposed a Michael/Mannich cascade reaction mechanism. As illustrated in Scheme 3, DBU initially promoted the formation of azomethine ylide **A** through deprotonation of the precursor **1b**. Then activated **1b** attacked the  $\beta$ -position of chalcone **2a** to form **B**. The  $\alpha$ -position of **2a** was negatively charged due to the breakage of the double bond, and then attacked the carbocation of **1b** to undergo a cyclization reaction to form a negatively charged transition state **C** of the nitrogen. Subsequently, 3,2'-pyrroloindyl spirooxindole product **3b** was obtained after hydrogenation.

With a diverse range of functionalized 5'-CF<sub>3</sub>-3,2'-pyrroloindole spirooxindoles successfully derived from chalcones in hand, we finally endeavored to evaluate their anticancer activities. All 24 targeted products were subjected to *in vitro* cytotoxicity tests against human gastric cancer cell line (SCG7901), followed by assessment of cell viability using MTT-based assays (for details, see ESI†). As listed in Table 3, the preliminary experimental data revealed that the selected 6 spirocyclic compounds exhibited certain cytotoxicity to SCG7901 cells with acceptable IC<sub>50</sub> values (all <35.00  $\mu$ M). Based on these results, it is anticipated that the availability of chalcone-derived CF<sub>3</sub>-containing spirooxindoles might provide promising lead compounds for further structural modification and bioactive assays.



Scheme 3 Proposed reaction mechanism.



Table 3 IC<sub>50</sub> of 3 against SCG7901 cells

Compound	IC <sub>50</sub> <sup>a</sup> (μM)	Compound	IC <sub>50</sub> (μM)
3b	33.94	3h	29.97
3d	33.02	3l	32.49
3g	30.21	3x	34.07

<sup>a</sup> Determined by MTT-based assays.

## Conclusions

In conclusion, we have developed an efficient DBU-catalyzed diastereoselective 1,3-dipolar [3 + 2] cycloaddition reaction of *N*-2,2,2-trifluoroethylisatin ketimines with chalcones in ethyl acetate. This methodology enables the construction of chalcone-derived functionalized 5'-CF<sub>3</sub>-containing 3,2'-pyrrolidine spirooxindoles in good yields and excellent diastereoselectivities (up to 89% yield and >99 : 1 dr).

## Author contributions

Conceptualization, Z.-W. Zhang and N. Lin; funding acquisition, Z.-W. Zhang and N. Lin; writing—original draft preparation, F.-J. Zhou, B.-L. Zhu, and Z.-H. Huang; writing—review and editing, Z.-W. Zhang and N. Lin.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

1 For selected reviews, see: (a) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758; *Angew. Chem.*, 2007, **119**, 8902–8912; (b) J. J. Badillo, N. V. Hanhan and

- A. K. Franz, *Curr. Opin. Drug Discov. Dev.*, 2010, **13**, 758–776; (c) B. Yu, D.-Q. Yu and H.-M. Liu, *Eur. J. Med. Chem.*, 2015, **97**, 673–698; (d) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi and J. Zhou, *ACS Infect. Dis.*, 2016, **2**, 382–392; (e) T. L. Pavlovska, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Div.*, 2016, **20**, 299–344; (f) A. J. Boddy and J. A. Bull, *Org. Chem. Front.*, 2021, **8**, 1026–1084.
- 2 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 3 K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- 4 For recent reviews on [3+2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines, see: (a) H.-Z. Gui, Y. Wei and M. Shi, *Chem.-Asian J.*, 2020, **15**, 1225–1233; (b) Z. Sun, C. Zhang, L. Chen, H. Xie, B. Liu and D. Liu, *Chin. J. Org. Chem.*, 2021, **41**, 1789–1803; (c) Y. Liu, L. Wang, D. Ma and Y. Song, *Molecules*, 2023, **28**, 2990; (d) B. Borah, N. S. Veeranagaiah, S. Sharma, M. Patat, M. S. Prasad, R. Pallepogub and L. R. Chowhan, *RSC Adv.*, 2023, **13**, 7063–7075.
- 5 For recent papers on [3+2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines, see: (a) W.-C. Yuan, L. Yang, J.-Q. Zhao, H.-Y. Du, Z.-H. Wang, Y. You, Y.-P. Zhang, J. Liu, W. Zhang and M.-Q. Zhou, *Org. Lett.*, 2022, **24**, 4603–4608; (b) R. Ma, J.-L. Zhang, X.-Q. Hu and P.-F. Xu, *Synthesis*, 2023, **55**, 1929–1939; (c) L.-Q. Li, J.-Q. Zhao, Y.-P. Zhang, Y. You, Z.-H. Wang, Z.-Z. Ge, M.-Q. Zhou and W.-C. Yuan, *Molecules*, 2023, **28**, 5372.
- 6 (a) G. Rajendran, D. Bhanu, B. Aruchamy, P. Ramani, N. Pandurangan, K. N. Bobba, E. J. Oh, H. Y. Chung, P. Gangadaran and B. C. Ahn, *Pharmaceuticals*, 2022, **15**, 1250; (b) M. A. Shalaby, S. A. Rizk and A. M. Fahim, *Org. Biomol. Chem.*, 2023, **21**, 5317–5346.
- 7 (a) S. Mastachi-Loza, T. I. Ramírez-Candeleró, L. J. Benítez-Puebla, A. Fuentes-Benites, C. González-Romero and M. A. Vázquez, *Chem.-Asian J.*, 2022, **17**, e202200706; (b) Y. N. Nayak, S. L. Gaonkar and M. Sabu, *J. Heterocycl. Chem.*, 2023, **60**, 1301–1325; (c) L. Maram and F. Tanaka, *Org. Lett.*, 2020, **22**, 2751–2755.
- 8 X. W. Liu, J. Yue, Z. Li, D. Wu, M. Y. Tian, Q. L. Wang and Y. Zhou, *Tetrahedron*, 2020, **76**, 131678.
- 9 Y. Xiong, X.-X. Han, Y. Lu, H.-J. Wang, M. Zhang and X.-W. Liu, *Tetrahedron*, 2021, **87**, 132112.
- 10 M. S. Prasad, S. Bharani, S. M. Sharief, M. Ravi, M. Sivaprakash, B. Borah and L. R. Chowhan, *RSC Adv.*, 2022, **12**, 34941–34945.

