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# EtOH-mediated cascade C(sp<sup>3</sup>)-H alkylation via aromatization-driven [1,6]-hydride transfer: green and divergent synthesis of spirocyclic azepino[4,3,2-*cd*]indoles†

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The development of green and efficient methods for the construction of azepinoindole skeletons remains highly desirable yet challenging. Described herein are the EtOH-mediated cascade C(sp<sup>3</sup>)-H alkylation reactions of 4-dialkylamino-indole-3-carbaldehydes for green and divergent synthesis of spirocyclic azepino[4,3,2-*cd*]indole derivatives. This protocol proceeded through a cascade *in situ* assembly of pre-aromatics/aromatization-driven [1,6]-hydride transfer/cyclization sequence, which exhibited many advantages such as green bio-sourced EtOH as the reaction medium, metal-free and redox-neutral conditions, high step-/atom-economy, water as waste, high yields, excellent diastereoselectivities (up to >20 : 1 dr), a wide substrate scope, and diverse transformations.

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## Introduction

Nowadays, green synthetic chemistry has emerged as a prevailing research field, which advocates 12 principles of less hazardous synthesis, atom-/step-economy, benign solvents, waste prevention, and so on.<sup>1</sup> The ‘Green ChemisTREE’,<sup>1c</sup> presented by Anastas in 2018, vividly showcased a wide range of research areas stemming from green chemistry. For example, non-metal catalysis and C-H bond functionalization align with the principle of less hazardous synthesis, while one-pot cascade reactions meet the principles of atom-/step-economy and waste prevention. The bio-sourced ethanol (EtOH) satisfies the principle of benign solvents.<sup>2</sup> In view of the escalating concern about sustainability, the design of green synthetic methods, such as EtOH-mediated metal-free C-H functionalization cascade reactions, for the synthesis of high value-added molecules is undoubtedly appealing.

Azepinoindoles, which combine the privileged structures of azepine and indole, are attractive targets in both synthetic

chemistry and the medicinal industry.<sup>3,4</sup> Among the azepinoindole family, azepino[4,3,2-*cd*]indole and its derivatives have garnered considerable attention owing to their potential as vasopressin V2 antagonists, RIPK1 inhibitors, and CGRP V2 receptor antagonists (Scheme 1A).<sup>5</sup> Given their importance, efficient synthesis of such scaffolds is highly desirable; however, to our knowledge, only a limited number of methods have been documented to date (Scheme 1B).<sup>5-9</sup> One feasible strategy relies on the construction of an indole nucleus, which involves a three-step synthetic procedure *via* tandem palladium catalysis (Scheme 1B, a).<sup>6</sup> Another effective strategy depends on azepine formation through reactions of pre-functionalized 4-NO<sub>2</sub>-, 4-NH<sub>2</sub>-, and 4-NHR-indoles, including two-step AgOTf-catalyzed nucleophilic addition and Pd/C-catalyzed reductive cyclization (Scheme 1B, b),<sup>7</sup> and TsOH-catalyzed or heat-promoted intramolecular amidation (Scheme 1B, c),<sup>5,8</sup> Recently, in 2023, Guo and Xie’s group disclosed an elegant nickel-catalyzed cascade [4 + 3] annulation reaction between *N*-alkyl-4-aminoindoles and β,γ-unsaturated α-ketoesters for the synthesis of chiral azepino[4,3,2-*cd*]indole derivatives (Scheme 1B, d).<sup>9</sup> In spite of the merits of these finite but impressive works, the dependence on metal catalysis, tedious substrate pre-synthesis, multi-step procedures, and toxic reaction media may contradict the 12 principles of green chemistry. Besides, the substrate scope and product diversity seem limited and deserve an expansion to enrich the azepinoindole library. Therefore, there is an urgent need to explore a versatile method for green and divergent synthesis of azepino[4,3,2-*cd*]indoles, particularly important spirocyclic frameworks.<sup>10</sup>

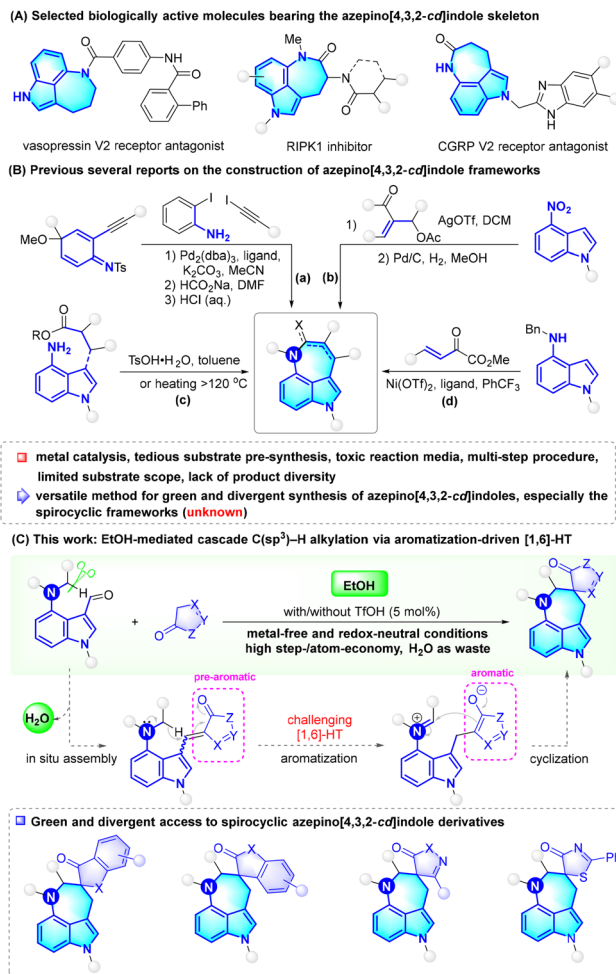
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Scheme 1 Background and outline of this work.

Direct C(sp<sup>3</sup>)-H functionalization enabled by redox-neutral [1,*n*]-hydride transfer (HT) represents an atom-/step-economic strategy for achieving molecular diversity.<sup>11</sup> The past decade has witnessed the endeavours of many reputable groups in exploring [1,*n*]-HT-involved  $\alpha$ -C(sp<sup>3</sup>)-H functionalization of amines for *N*-heterocycle synthesis.<sup>12–14</sup> However, in contrast to the well-developed synthesis of spirocyclic tetrahydroquinolines *via* [1,5]-HT, the access to spirocyclic azepinoindoles *via* [1,6]-HT is still unknown. The main reason is the lack of a class of suitable substrates that can meanwhile assemble both 7-membered azepinoindole and spirocycle *via* HT mode. In this context, we designed 4-dialkylamino-indole-3-carbaldehydes as versatile platform molecules and put forward EtOH-mediated aromatization-driven cascade C(sp<sup>3</sup>)-H functionalization reactions for green and divergent synthesis of spirocyclic azepino[4,3,2-*cd*]indole derivatives (Scheme 1C). As depicted, the transformation was expected to proceed through the *in situ* assembly of pre-aromatics, aromatization-driven [1,6]-HT, and cyclization steps. Of note, both [1,6]-HT and the final azepine formation are spatially unfavourable, posing a challenge for the proposal. As a continuous journey in one-step assembly of bioactive molecules *via* the HT strategy,<sup>12</sup> the

research findings on this subject are presented herein. This methodology featured green bio-sourced EtOH as the solvent, metal-free and redox-neutral reaction conditions, high step-/atom-economy, water as waste, and a wide substrate scope.

## Results and discussion

1-Thioaurones, characterized by their inherent tendency towards aromatization, are reactive pre-aromatic substrates that participate in various aromatization-driven cycloaddition reactions.<sup>15</sup> Therefore, we commenced our exploration by performing the model reaction between 4-(pyrrolidin-1-yl)-1-tosyl-1*H*-indole-3-carbaldehyde **1a** and benzo[*b*]thiophen-3(2*H*)-one **2a** in EtOH (Table 1). It was found that 1-thioaurone **3a** was readily afforded in 96% yield at 40 °C (Table 1, entry 1), which confirmed our assumption of *in situ* assembly of pre-aromatics. When the reactions were performed at higher temperatures, to our delight, the expected benzothiophen-3-one spirocyclic azepino[4,3,2-*cd*]indole derivative **4a** was obtained in up to 73% yield with an excellent diastomeric ratio (dr) of >20:1 (Table 1, entries 2–4). To improve the reaction efficiency, several protonic acids including PhCO<sub>2</sub>H (benzoic acid), MsOH (methanesulfonic acid), *p*-TSA·H<sub>2</sub>O (*p*-toluenesulfonic acid monohydrate), and TfOH (triflic acid) were screened (Table 1, entries 5–8). It was found that using 5 mol% TfOH resulted in the production of **4a** in 90% yield (Table 1, entry 8). In addition, the elevation of the molar amount of **2a** to 0.3 mmol led to a comparative yield (Table 1, entry 9).

After the establishment of optimized reaction conditions, we turned to investigate the substrate scope by employing a

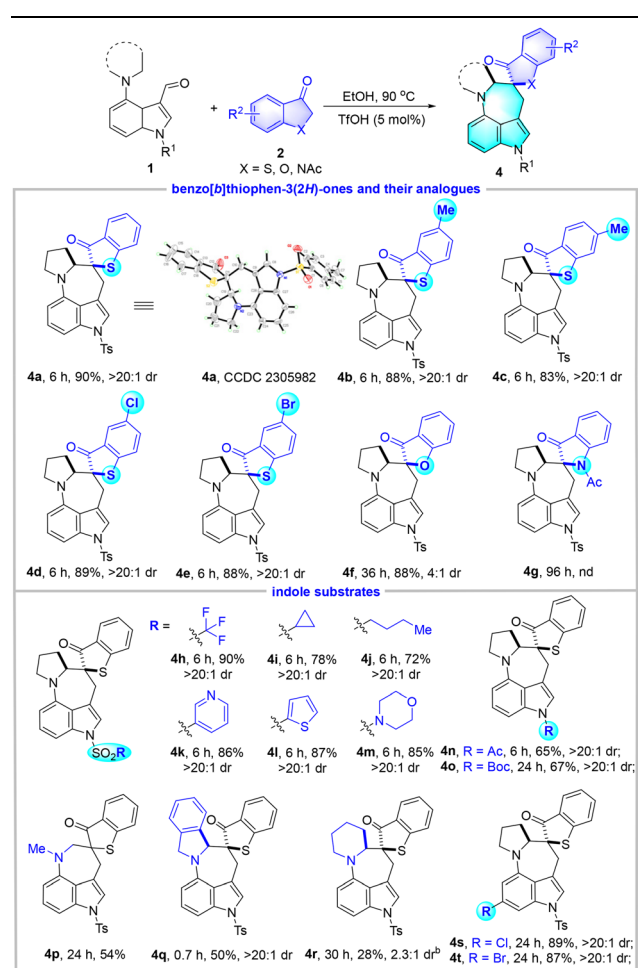
Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Additives	Temp. (°C)	Time (h)	Yield (%)	
				3a	4a
1	—	40	1	96	0
2	—	60	72	97	0
3	—	90	72	53	42
4	—	120	12	0	73
5	PhCO <sub>2</sub> H	90	72	45	45
6	MsOH	90	21	0	81
7	<i>p</i> -TSA·H <sub>2</sub> O	90	35	0	79
8	TfOH	90	6	0	90
9 <sup>b</sup>	TfOH	90	6	0	90

<sup>a</sup> Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), and solvent (2 mL) at the given temperature for the indicated time. Isolated yields after column chromatography. The dr value of **4a** was >20:1, which was determined by NMR analysis. PhCO<sub>2</sub>H = benzoic acid, MsOH = methanesulfonic acid, *p*-TSA·H<sub>2</sub>O = *p*-toluenesulfonic acid monohydrate, and TfOH = triflic acid. <sup>b</sup> **2a** (0.30 mmol).

wide range of indole substrates **1**, benzo[*b*]thiophen-3(2*H*)-ones and their analogues **2** (Table 2). For the variation of benzo[*b*]thiophen-3(2*H*)-ones, both electron-donating groups such as Me and electron-withdrawing groups such as Cl and Br on the phenyl ring were well tolerated, and products **4b–4e** were delivered in high yields (83%–89%) with excellent diastereoselectivities (>20:1 dr). Benzofuran-3(2*H*)-one was also a competent candidate for the reaction and gave **4f** in 88% yield, albeit with a moderate dr value of 4:1. However, 1-acetylidolin-3-one was found to be incompatible with this system, and the expected **4g** was not detected upon the consumption of **1a**. Afterwards, various indole substrates **1** were screened. In detail, *N*-sulfonyl indole-3-carbaldehydes that carry trifluoromethyl, cyclopropyl, *n*-butyl, pyridyl, thienyl, and morpholinyl substituents were well compatible and provided products **4h–4m** in 72%–90% yields and excellent diastereoselectivities (>20:1 dr). The *N*-Ac and *N*-Boc substrates were

**Table 2** Reaction of 4-dialkylamino-indole-3-carbaldehydes **1** with benzo[*b*]thiophen-3(2*H*)-ones and their analogues **2**<sup>a</sup>

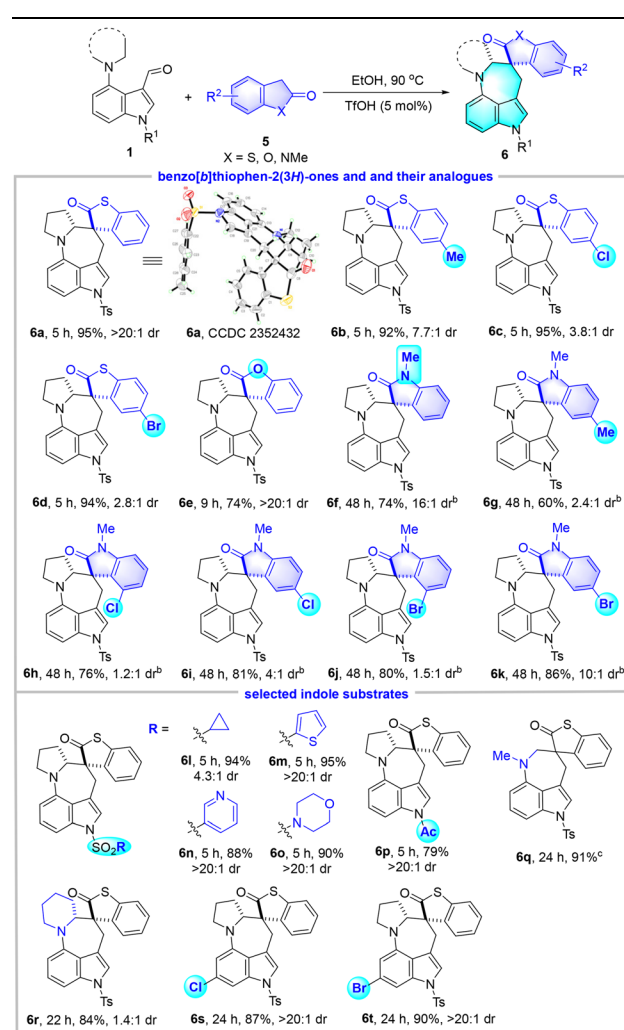


<sup>a</sup> Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), TFOH (5 mol%), and EtOH (2 mL) at 90 °C for the indicated time. Isolated yields after column chromatography. The dr was determined by NMR analysis. <sup>b</sup> At 110 °C.

also shown to be feasible to give rise to **4n** and **4o** in moderate yields. Besides pyrrolidine, both dimethylamine and isoindoline were demonstrated as viable hydride donors, allowing the synthesis of **4p** and **4q** in good yields. The challenging piperidine was also a competent donor to trigger the [1,6]-HT, although product **4r** was afforded in 28% yield with 2.3:1 dr at 110 °C. This could be rationalized by the conformational difference. Moreover, substrates that bear Cl and Br groups at the benzene ring of the indole scaffold reacted to furnish **4s** and **4t** with good results. Notably, the relative configuration of **4a** was unambiguously assigned by X-ray crystallography analysis.

In order to further broaden the substrate scope, we examined the reaction of **1a** with benzo[*b*]thiophen-2(3*H*)-one **5a** under the same conditions as above (Table 3). Satisfyingly, the

**Table 3** Reaction of 4-dialkylamino-indole-3-carbaldehydes **1** with benzo[*b*]thiophen-2(3*H*)-ones and their analogues **5**<sup>a</sup>

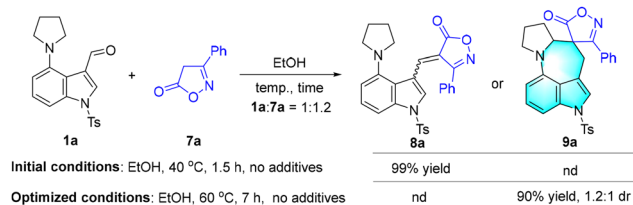


<sup>a</sup> Reaction conditions: **1** (0.20 mmol), **5** (0.24 mmol), TFOH (5 mol%), and EtOH (2 mL) at 90 °C for the indicated time. Isolated yields after column chromatography. The dr was determined by NMR analysis. <sup>b</sup> **1a** (0.3 mmol) and **5** (0.2 mmol) at 110 °C. <sup>c</sup> At 100 °C.

expected benzothiophen-2-one spirocyclic azepino[4,3,2-*cd*]indole derivative **6a** was successfully accessed in 95% yield with an excellent dr value of >20:1. The structure of **6a** was confirmed by X-ray crystallography. Then, various benzo[*b*]thiophen-2-ones and their analogues **5** as well as selected indole substrates **1** were investigated. Remarkable tolerance to different functional groups was exhibited in this EtOH system. For instance, the introduction of an electron-donating group (Me) or an electron-withdrawing group (Cl and Br) into the phenyl ring of benzo[*b*]thiophen-2-ones did not influence the reaction efficiency but resulted in much lower diastereoselectivities (**6b–6d**). Benzofuran-2(3*H*)-one was also found to be an ideal substrate and gave the desired **6e** with excellent diastereoselectivity (>20:1 dr). Moreover, in view of the significance of the spirocyclic oxindole skeleton in both synthetic and medicinal industries,<sup>16</sup> 1-methylindolin-2-ones that incorporate Me, Cl, and Br groups were tested, which proved competent to furnish spirocyclic oxindoles **6f–6k** in 60%–86% yields. Nevertheless, the introduction of substituents, regardless of their electronic effects or positions, led to reduced dr values (1.2:1–16:1). Various *N*-sulfonyl and *N*-Ac indoles could survive the reaction conditions and gave **6l–6p** in good to high yields (79%–95%). In addition, the acyclic 4-dimethylaminyl indole substrate was well-tolerated, affording the corresponding product **6q** in 91% yield, although a higher reaction temperature was required. The substrate with a piperidine motif reacted smoothly and provided **6r** in 84% yield, albeit with 1.4:1 dr. The introduction of Cl and Br groups into the indole motif had little effect on the reactions, and products **6s** and **6t** were synthesized with high yields and excellent diastereoselectivities.

Subsequently, we investigated the reaction between 3-phenylisoxazol-5(4*H*)-one **7a** and 4-(pyrrolidin-1-yl)-1-tosyl-1*H*-indole-3-carbaldehyde **1a** (Scheme 2). It was found that the pre-aromatic **8a** could be readily afforded in 99% yield in EtOH at 40 °C after 1.5 h. After adjusting the reaction temperature to 60 °C under additive-free conditions, the isoxazolone spirocyclic azepino[4,3,2-*cd*]indole derivative **9a**, to our gratification, was produced with high efficiency (90% yield, 1.2:1 dr).

Afterwards, the generality of this reaction was studied (Table 4). A series of isoxazol-5(4*H*)-ones **7** bearing electron-donating (MeO and Me) and electron-withdrawing (CF<sub>3</sub>, NO<sub>2</sub>, F, Cl, and Br) groups on the phenyl ring were subjected to the reactions with **1a**. The expected isoxazolone spirocyclic azepino[4,3,2-*cd*]indole derivatives **9b–9h** were furnished in



**Scheme 2** Conditions employed for the reaction of isoxazol-5(4*H*)-one **7a** with indole substrate **1a**.

**Table 4** Reaction between 4-dialkylamino-indole-3-carbaldehydes **1** and isoxazol-5(4*H*)-ones **7**<sup>a</sup>

**isoxazol-5(4*H*)-ones**

**9a**, 7 h, 90%, 1.2:1 dr  
**9b**, R = OMe, 7 h, 84%, 1.4:1 dr;  
**9c**, R = Me, 7 h, 88%, 1.1:1 dr;  
**9d**, R = CF<sub>3</sub>, 7 h, 80%, 1.6:1 dr;  
**9e**, R = NO<sub>2</sub>, 7 h, 89%, 2.1:1 dr;  
**9f**, R = F, 7 h, 89%, 1.5:1 dr;  
**9g**, R = Cl, 7 h, 87%, 1.5:1 dr;  
**9h**, R = Br, 7 h, 84%, 1.4:1 dr;

**9i**, 21 h, 94%, 1.2:1 dr  
**9j**, 21 h, 87%, 2:1 dr  
**9k**, 21 h, 87%, 4.8:1 dr  
**9e**, CCDC 2300404

**indole substrates**

R =

**9l**, 5 h, 95%, 1.1:1 dr  
**9m**, 12 h, 74%, 1.4:1 dr  
**9n**, 5 h, 80%, 1.4:1 dr  
**9o**, 5 h, 88%, 1.2:1 dr  
**9p**, 12 h, 90%, 1.2:1 dr  
**9q**, 12 h, 87%, 1.5:1 dr  
**9r**, 5 h, 75%, 2.1:1 dr  
**9s**, 5 h, 90%, 1.9:1 dr  
**9t**, 12 h, 77%<sup>b</sup>  
**9u**, 12 h, 66%, 3.4:1 dr  
**9v**, 12 h, nd (Int. **8b** was observed)

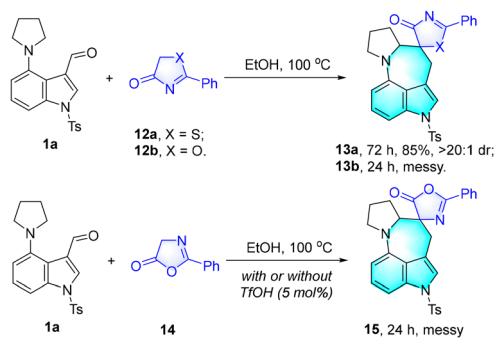
<sup>a</sup> Reaction conditions: **1** (0.20 mmol), **7** (0.24 mmol), and EtOH (2 mL) at 60 °C for the indicated time. Isolated yields after column chromatography. The dr was determined by NMR analysis. <sup>b</sup> At 100 °C.

80%–89% yields with 1.1:1–2.1:1 dr. The structure of product **9e** has been confirmed by X-ray diffraction analysis. Furyl- and thienyl-substituted isoxazolones were also found to be suitable substrates to give products **9i** and **9j** in high yields. In addition, 3-methylisoxazol-5(4*H*)-one was examined, which afforded the desired **9k** in 87% yield with a moderate dr value of 4.8:1. For indole substrates that incorporate diverse *N*-sulfonyl, *N*-Ac, and *N*-Boc groups, good to excellent yields (74%–95%) were obtained for **9l–9s**, which indicated the robustness of this method. Moreover, indole substrates that contain the motifs of dimethylamine and isoindoline at the C4 position successfully engaged in cascade C(sp<sup>3</sup>)-H alkylation to give **9t** and **9u** in good yields. When the substrate bearing the piperidine moiety was employed, the intermediate **8b** was observed and could be isolated; however, we failed to detect and isolate the desired product **9v** due to the messy reaction system. Of note, the diastereoselectivity of this transformation was not so satisfactory in spite of its advantages such as excellent functional group tolerance and high yields.

Edaravone (**10a**), 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, is a kind of free radical scavenger used for protecting

mammalian brains.<sup>17</sup> The functionalization of such a molecule is of great interest for exploring bioactive drugs. When the reaction between **1a** and edaravone **10a** was conducted under the same conditions as above, the desired edaravone spirocyclic azepino[4,3,2-*cd*]indole derivative **11a** was successfully delivered in 92% yield with excellent diastereoselectivity (>20 : 1 dr). With this exciting result in hand, we then screened a broad range of edaravone derivatives **10** (Table 5). The *N*-aryl pyrazolones **10b–10e** that bear MeO, Me, Cl, and Br groups could smoothly participate in the transformations and generated the expected **11b–11e** in high yields (90%–94%) with excellent diastereoselectivities (>20 : 1 dr). In addition, the *N*-free substrate was applicable to afford **11f** in 87% yield with >20 : 1 dr. Upon changing R<sup>2</sup> from the methyl to the cyclopropyl group, the conversion occurred at a higher temperature of 80 °C. Moreover, pyrazolones that contain electron-rich and electron-deficient phenyl and thienyl groups were well tolerated and gave **11h–11m** in 90%–94% yields with excellent diastereoselectivities (>20 : 1 dr). The relative configuration of **11l** has been unambiguously determined by X-ray diffraction analysis.

In addition, other substrates, including 2-phenylthiazol-4(5*H*)-one **12a**, 2-phenyloxazol-4(5*H*)-one **12b**, and 2-phenyloxazol-5(4*H*)-one **14**, were investigated to react with **1a** (Scheme 3). Pleasingly, the expected thiazolone spirocyclic azepino[4,3,2-*cd*]indole derivative **13a** was furnished in 85% yield with excel-



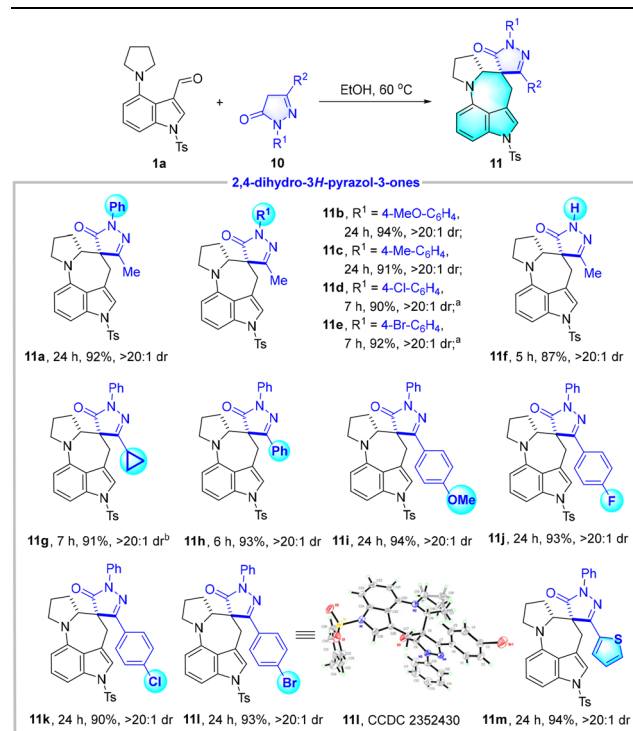
Scheme 3 Investigation of other substrates.

lent diastereoselectivity (>20 : 1 dr). However, messy reaction systems were observed for substrates **12b** and **14**, and we failed to obtain the desired products **13b** and **15**.

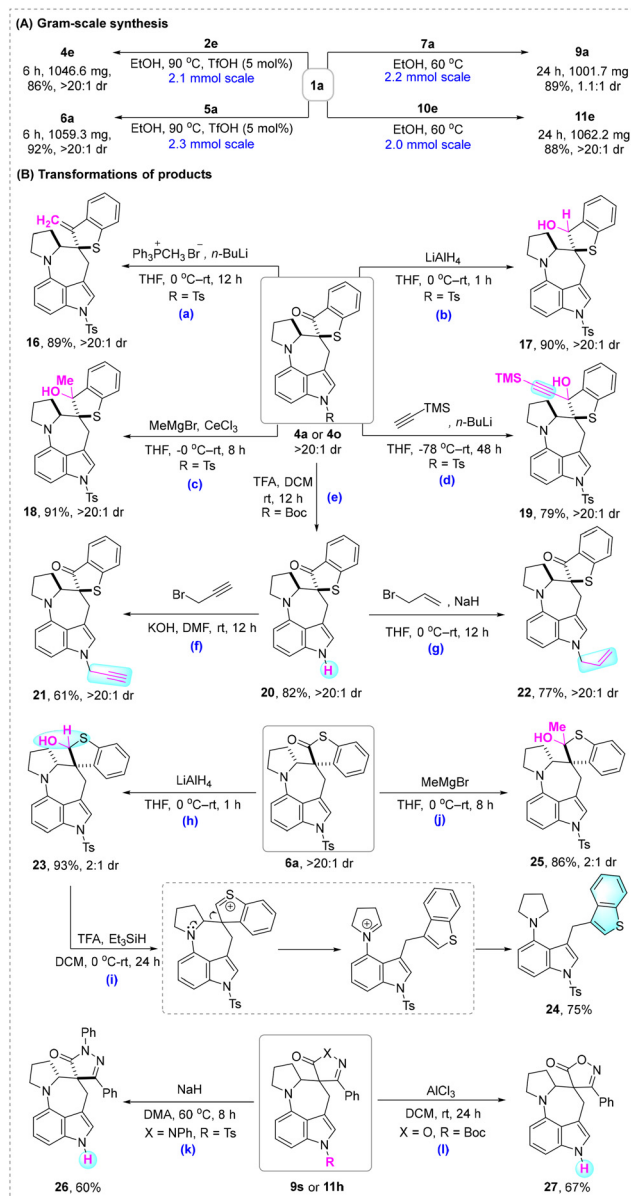
In order to demonstrate the synthetic utility of the developed EtOH-mediated cascade C(sp<sup>3</sup>)-H alkylation, gram-scale syntheses and transformations of products were performed (Scheme 4). As shown in Scheme 4A, the preparation of **4e**, **6a**, **9a**, and **11e** on a gram scale could be achieved in high yields with the maintenance of diastereoselectivities. Various derivatization reactions are depicted in Scheme 4B. The Wittig reaction of **4a** gave rise to alkene **16** in 89% yield (Scheme 4B, a), while the reduction of **4a** by LiAlH<sub>4</sub> furnished alcohol **17** in 90% yield (Scheme 4B, b). The Grignard reactions of **4a** gave tertiary alcohols **18** and **19** in high yields (Scheme 4B, c and d). The treatment of **4o** with TFA (trifluoroacetic acid) in DCM afforded the *N*-H free product **20** (Scheme 4B, e), which could be further functionalized into **21** and **22** via *N*-propargylation and *N*-allylation (Scheme 4B, f and g). Surprisingly, the reduction of **6a** by LiAlH<sub>4</sub> afforded the stable thiohemiacetal **23** in 93% yield (Scheme 4B, h), which could undergo an interesting cascade acid-catalyzed dehydration/aromatization-driven carbocation rearrangement/reduction reaction to provide 3-(benzo[*b*]thiophen-3-ylmethyl)-indole **24** in 75% yield (Scheme 4B, i). Moreover, the nucleophilic addition of MeMgBr resulted in the successful formation of thiohemiketal **25** in 86% yield (Scheme 4B, j). The *N*-H products **26** and **27** could be accessed via *N*-Ts and *N*-Boc deprotection (Scheme 4B, k and l).

To gain insights into the reaction mechanism, mechanistic studies were conducted (Scheme 5). As clearly shown in Scheme 5A, the proposed pre-aromatic intermediates **3a**, **28a**, **8a**, and **29a** were efficiently assembled in EtOH at 40 °C and isolated in nearly quantitative yields. These pre-aromatics could successfully convert into the expected products **4a**, **6a**, **9a** and **11a** under the corresponding standard conditions. These results confirmed the *in situ* generation of pre-aromatic intermediates and their capability to undergo cascade C(sp<sup>3</sup>)-H alkylation for synthesizing spirocyclic azepino[4,3,2-*cd*]indoles. Then, control experiments were performed to monitor the formation of intermediate **3a** and product **4a** in the model reaction (Scheme 5B), which provided further confirmation for the assembly of pre-aromatics and their subsequent conver-

Table 5 Reaction of 4-(pyrrolidin-1-yl)-1-tosyl-1*H*-indole-3-carbaldehyde **1a** with edaravone derivatives **10**<sup>a</sup>

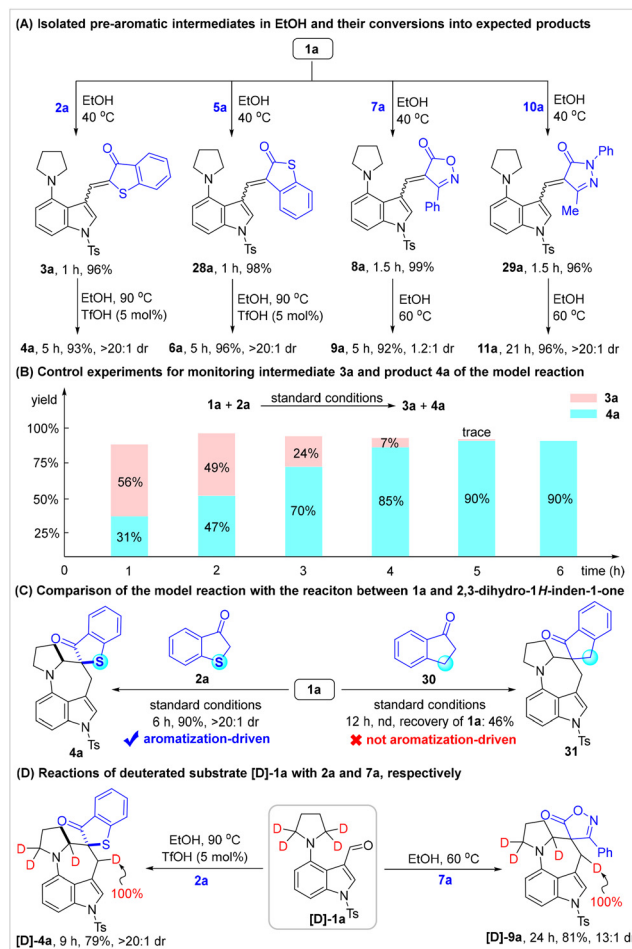


<sup>a</sup> Reaction conditions: **1a** (0.20 mmol), **10** (0.24 mmol), and EtOH (2 mL) at 60 °C for the indicated time. Isolated yields after column chromatography. The dr was determined by NMR analysis. <sup>b</sup> At 80 °C.



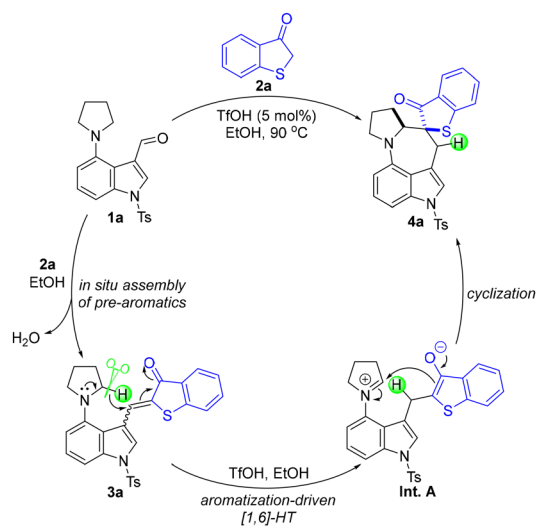
Scheme 4 Gram-scale synthesis and derivatization of products.

sions. Furthermore, the comparison of the model reaction with the control reaction between **1a** and 2,3-dihydro-1H-inden-1-one **30** was investigated under the standard conditions (Scheme 5C). It was found that no desired spirocyclic product **31** was detected in the control reaction, thus strongly supporting our proposal that aromatization acted as the driving force to facilitate and enable the cascade C(sp<sup>3</sup>)-H alkylation reaction. In addition, deuterated labelling experiments were carried out using the reactions of the deuterated substrate [D]-**1a** with **2a** and **7a**, respectively (Scheme 5D). Remarkably, the complete transfer (100%) of the [D]-label to the benzylic position of the indole was observed, which provided compelling evidence for the occurrence of the intramolecular [1,6]-HT step.



Scheme 5 Mechanistic studies.

Based on the above experimental results, a plausible reaction mechanism was proposed for the synthesis of **4a** (Scheme 6). As illustrated, the EtOH-promoted condensation



Scheme 6 Proposed mechanism.

between 4-(pyrrolidin-1-yl)-1-tosyl-1*H*-indole-3-carbaldehyde **1a** and benzo[*b*]thiophen-3(2*H*)-one **2a** achieved the *in situ* assembly of pre-aromatic 1-thioaurone **3a**, with the release of H<sub>2</sub>O as waste. Aided by the catalytic amount of TfOH in EtOH, the aromatization-driven intramolecular [1,6]-HT of **3a** occurred and yielded aromatic **Int. A**, which finally underwent intramolecular cyclization to afford product **4a**.

## Conclusions

In conclusion, the EtOH-mediated cascade C(sp<sup>3</sup>)-H alkylation reactions of well-designed 4-dialkylamino-indole-3-carbaldehydes have been realized in this work. The green and divergent synthesis of spirocyclic azepino[4,3,2-*cd*]indole derivatives, including benzothiophenone, benzofuranone, oxindole, isoxazolone, pyrazolone, thiazolone, and oxazolone spirocyclic azepino[4,3,2-*cd*]indole derivatives, was realized with good to high yields and excellent diastereoselectivities (up to >20:1 dr). The gram-scale synthesis and derivatization of products demonstrated the synthetic application potential of this methodology. The mechanistic studies proved that the transformation proceeded through a cascade *in situ* assembly of pre-aromatics/aromatization-driven [1,6]-HT/cyclization process. Many advantages of this protocol were exhibited, such as green bio-sourced EtOH as the reaction medium, metal-free and redox-neutral conditions, H<sub>2</sub>O as waste, high yields, excellent diastereoselectivities, a wide substrate scope, high step-/atom-economy, gram-scale synthesis, and diverse transformations. We were optimistic that this method would provide some inspiration for both green synthetic chemistry and drug discovery.

## Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## References

- For selected reviews on green chemistry, see: (a) S. Kar, H. Sanderson, K. Roy, E. Benfenati and J. Leszczynski, *Chem. Rev.*, 2022, **122**, 3637–3710; (b) P. T. Anastas and J. B. Zimmerman, *Green Chem.*, 2019, **21**, 6545–6566; (c) H. C. Erythropel, J. B. Zimmerman, T. M. Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata and P. T. Anastas, *Green Chem.*, 2018, **20**, 1929–1961; (d) P. T. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301–312.
- For selected reviews on bio-sourced EtOH as a green solvent, see: (a) C. J. Clarke, W.-C. Tu, O. Levers, A. Bröhl and J. P. Hallett, *Chem. Rev.*, 2018, **118**, 747–800; (b) F. G. Calvo-Flores, M. J. Monteagudo-Arrebola, J. A. Dobado and J. Isac-García, *Top. Curr. Chem.*, 2018, **376**, 18.
- For selected reviews on azepinoindole, see: (a) C.-B. Ji, X. Hu, S.-Z. Jiang and J.-H. Yang, *Eur. J. Org. Chem.*, 2022, e202201000; (b) M. Kadagathur, S. Patra, D. K. Sigalapalli, N. Shankaraiyah and N. D. Tangellamudi, *Org. Biomol. Chem.*, 2021, **19**, 738–764; (c) T. Nemoto, *Chem. Rec.*, 2019, **19**, 320–332; (d) A. C. Lindsay, S. H. Kim and J. Sperry, *Nat. Prod. Rep.*, 2018, **35**, 1347–1382; (e) T. Nemoto, S. Harada and M. Nakajima, *Asian J. Org. Chem.*, 2018, **7**, 1730–1742; (f) M. Ito, Y. Tahara and T. Shibata, *Chem. – Eur. J.*, 2016, **22**, 5468–5477.
- For selected recent reports on azepinoindole synthesis, see: (a) H. Tanaka, T. Yasui, M. Uyanik and K. Ishihara, *Org. Lett.*, 2023, **25**, 2377–2381; (b) Y.-M. Zhu, X.-P. Xu and S.-J. Ji, *Org. Lett.*, 2023, **25**, 2041–2046; (c) Y. T. H. Lam, J. Hoppe, Q. N. Dang, A. Porzel, A. Soboleva, W. Brandt, R. Rennert, H. Hussain, M. D. Davari, L. Wessjohann and N. Arnold, *J. Nat. Prod.*, 2023, **86**, 1373–1384; (d) L. Xiao, B. Li, F. Xiao, C. Fu, L. Wei, Y. Dang, X.-Q. Dong and C.-J. Wang, *Chem. Sci.*, 2022, **13**, 4801–4812; (e) C. Jagadeesh, B. Mondal, S. Pramanik, D. Das and J. Saha, *Angew. Chem., Int. Ed.*, 2021, **60**, 8808–8812; (f) W.-L. Yang, T. Ni and W.-P. Deng, *Org. Lett.*, 2021, **23**, 588–594; (g) Y. Cai, N. Shao, H. Xie, Y. Futamura, S. Panjekar, H. Liu, H. Zhu, H. Osada and H. Zou, *ACS Catal.*, 2019, **9**, 7443–7448.
- (a) J. M. Matthews, M. N. Greco, L. R. Hecker, W. J. Hoekstra, P. Andrade-Gordon, L. de Garavilla, K. T. Demarest, E. Ericson, J. W. Gunnet, W. Hageman, R. Look, J. B. Moore and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 753–756; (b) Z. Wang, S. Yang and Z. Zhao, *Patent*, 2023, WO2023040818; (c) I. M. Bell and C. A. Stump, *Patent*, 2008, WO2008153852; (d) I. M. Bell, C. A. Stump, C. R. Theberge, S. N. Gallicchio, C. B. Zartman and H. G. Selnick, *Patent*, 2007, WO2008153852.
- W. Wang, M. Yang, D. Han, Q. He and R. Fan, *Adv. Synth. Catal.*, 2020, **362**, 1281–1285.
- (a) Z. Shafiq, L. Liu, Z. Liu, D. Wang and Y.-J. Chen, *Org. Lett.*, 2007, **9**, 2525–2528; (b) Z. Shafiq, Z. Qiao, L. Liu, Q.-Y. Zheng, D. Wang and Y.-J. Chen, *Synlett*, 2009, 2965–2970.

- 8 B. Zou, C. Chen, S. Y. Leong, M. Ding and P. W. Smith, *Tetrahedron*, 2014, **70**, 578–582.
- 9 B.-Y. Xue, C.-Y. Hou, X.-B. Wang, M.-S. Xie and H.-M. Guo, *Org. Chem. Front.*, 2023, **10**, 1910–1914.
- 10 For selected reviews on applications of spirocycles, see: (a) K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150–183; (b) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, *Chem. Soc. Rev.*, 2018, **47**, 5946–5996; (c) S. Kotha, N. R. Panguluri and R. Ali, *Eur. J. Org. Chem.*, 2017, 5316–5342; (d) L. K. Smith and I. R. Baxendale, *Org. Biomol. Chem.*, 2015, **13**, 9907–9933; (e) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682; (f) J. Xie and Q. Zhou, *Acta Chim. Sin.*, 2014, **72**, 778–797; (g) K. Ding, Z. Han and Z. Wang, *Chem. - Asian J.*, 2009, **4**, 32–41; (h) T. P. I. Saragi, T. Spehr, A. Siebert, T. Fuhrmann-Lieker and J. Salbeck, *Chem. Rev.*, 2007, **107**, 1011–1065.
- 11 For selected reviews on direct C(sp<sup>3</sup>)-H functionalization via [1,*n*]-HT, see: (a) K. Mori, *Bull. Chem. Soc. Jpn.*, 2022, **95**, 296–305; (b) F. Hu, Y.-B. Shen, L. Wang and S.-S. Li, *Org. Chem. Front.*, 2022, **9**, 5041–5052; (c) Y.-B. Shen, F. Hu and S.-S. Li, *Tetrahedron*, 2022, **127**, 133089; (d) X.-D. An and J. Xiao, *Org. Chem. Front.*, 2021, **8**, 1364–1383; (e) M. C. Haibach and D. Seidel, *Angew. Chem., Int. Ed.*, 2014, **53**, 5010–5036; (f) B. Peng and N. Maulide, *Chem. - Eur. J.*, 2013, **19**, 13274–13287; (g) Y.-B. Shen, F. Hu and S.-S. Li, *Org. Biomol. Chem.*, 2023, **21**, 700–714; (h) M. Xiao, S. Zhu, Y. Shen, L. Wang and J. Xiao, *Chin. J. Org. Chem.*, 2018, **38**, 328–340; (i) Y. Chen, H. Sun, L. Wang, F. Hu and S. Li, *Chin. J. Org. Chem.*, 2023, **43**, 2323–2337.
- 12 For selected [1,*n*]-HT works of our group, see: (a) X.-D. An, D.-Y. Shao, B. Qiu and J. Xiao, *Org. Lett.*, 2023, **25**, 2432–2437; (b) L.-X. Wang, B. Qiu, X.-D. An, P.-Z. Dong, R.-B. Liu and J. Xiao, *Green Chem.*, 2021, **23**, 8181–8186; (c) S. Yang, X.-D. An, B. Qiu, R.-B. Liu and J. Xiao, *Org. Lett.*, 2021, **23**, 9100–9105; (d) K. Duan, X.-D. An, L.-F. Li, L.-L. Sun, B. Qiu, X.-J. Li and J. Xiao, *Org. Lett.*, 2020, **22**, 2537–2541; (e) K. Duan, H. Shi, L.-X. Wang, S.-S. Li, L. Xu and J. Xiao, *Org. Chem. Front.*, 2020, **7**, 2511–2517; (f) S.-S. Li, S. Zhu, C. Chen, K. Duan, Q. Liu and J. Xiao, *Org. Lett.*, 2019, **21**, 1058–1062; (g) S.-S. Li, X. Lv, D. Ren, C.-L. Shao, Q. Liu and J. Xiao, *Chem. Sci.*, 2018, **9**, 8253–8259; (h) S. Zhu, C. Chen, M. Xiao, L. Yu, L. Wang and J. Xiao, *Green Chem.*, 2017, **19**, 5653–5658; (i) D.-Y. Shao, B. Qiu, Z.-K. Wang, Z.-Y. Liu, J. Xiao and X.-D. An, *Green Synth. Catal.*, 2024, DOI: [10.1016/j.gresc.2024.01.008](https://doi.org/10.1016/j.gresc.2024.01.008).
- 13 For selected [1,*n*]-HT works of other groups, see: (a) K. Amano, T. Kawasaki-Takasuka and K. Mori, *Org. Lett.*, 2024, **26**, 1824–1827; (b) H. Okawa, T. Kawasaki-Takasuka and K. Mori, *Org. Lett.*, 2024, **26**, 1662–1666; (c) Y. Dong, F. Hu, H. Wu, F.-W. Guo, L. Wang, F.-Y. Du and S.-S. Li, *Org. Lett.*, 2024, **26**, 332–337; (d) Z. Sun, R. Hou, S.-S. Li, X. Wang, L. Wang, F. Hu and F.-W. Guo, *Org. Lett.*, 2024, **26**, 6–11; (e) D. F. León Rayo, A. Mansour, W. Wu, B.-N. Bhawal and F. Gagosz, *Angew. Chem., Int. Ed.*, 2023, **62**, e202212893; (f) F. Hu, Z. Sun, M. Pan, L. Wang, L. Xu, X.-L. Liu and S.-S. Li, *Green Chem.*, 2023, **25**, 5134–5141; (g) C. Wei, Y. Li, X. Yao, K. Zhang and L. Cai, *J. Org. Chem.*, 2023, **88**, 17144–17154; (h) F. Hu, X. Li, Z. Ding, L. Wang, C. Ge, L. Xu and S.-S. Li, *ACS Catal.*, 2022, **12**, 943–952; (i) B.-B. Zhang, S. Peng, F. Wang, C. Lu, J. Nie, Z. Chen, G. Yang and C. Ma, *Chem. Sci.*, 2022, **13**, 775–780; (j) D. Hoshino and K. Mori, *Org. Lett.*, 2021, **23**, 9403–9407; (k) K. Yokoo and K. Mori, *Org. Lett.*, 2020, **22**, 244–248; (l) S. Zhao, X. Wang, P. Wang, G. Wang, W. Zhao, X. Tang and M. Guo, *Org. Lett.*, 2019, **21**, 3990–3993; (m) J.-J. Tian, N.-N. Zeng, N. Liu, X.-S. Tu and X.-C. Wang, *ACS Catal.*, 2019, **9**, 295–300; (n) K. Mori, K. Kurihara, S. Yabe, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, 2014, **136**, 3744–3747.
- 14 (a) F. I. M. Idiris, C. E. Majesté, G. B. Craven and C. R. Jones, *Chem. Sci.*, 2018, **9**, 2873–2878; (b) S. Liu, W. Zhang, J. Qu and B. Wang, *Org. Chem. Front.*, 2018, **5**, 3008–3012; (c) S. Liu, T. Zhao, J. Qu and B. Wang, *Adv. Synth. Catal.*, 2018, **360**, 4094–4098; (d) S. Liu, J. Qu and B. Wang, *Chem. Commun.*, 2018, **54**, 7928–7931; (e) K. Ramakumar, T. Maji, J. J. Partridge and J. A. Tunge, *Org. Lett.*, 2017, **19**, 4014–4017; (f) C. W. Suh, S. J. Kwon and D. Y. Kim, *Org. Lett.*, 2017, **19**, 1334–1337; (g) K. Mori, N. Umehara and T. Akiyama, *Adv. Synth. Catal.*, 2015, **357**, 901–906; (h) Y.-Z. Chang, M.-L. Li, W.-F. Zhao, X. Wen, H. Sun and Q.-L. Xu, *J. Org. Chem.*, 2015, **80**, 9620–9627; (i) P.-F. Wang, C.-H. Jiang, X. Wen, Q.-L. Xu and H. Sun, *J. Org. Chem.*, 2015, **80**, 1155–1162; (j) K. Mori, T. Kawasaki and T. Akiyama, *Org. Lett.*, 2012, **14**, 1436–1439; (k) I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 1950–1953; (l) M. C. Haibach, I. Deb, C. K. De and D. Seidel, *J. Am. Chem. Soc.*, 2011, **133**, 2100–2103; (m) K. Mori, R. Isogai, Y. Kamei, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, 2018, **140**, 6203–6207; (n) C. Zhang, S. Murarka and D. Seidel, *J. Org. Chem.*, 2009, **74**, 419–422.
- 15 For a selected review that includes cycloaddition of pre-aromatic 1-thioaurones, see: (a) J. Huang, W. Wang, L. Zhang and X. Meng, *Chin. Chem. Lett.*, 2023, **34**, 108003. For selected recent reports, see: (b) S.-P. Yuan, P.-H. Dou, Y.-Q. Jia, J.-Q. Zhao, Y. You, Z.-H. Wang, M.-Q. Zhou and W.-C. Yuan, *Chem. Commun.*, 2022, **58**, 553–556; (c) K. Li, L. Wang, A. Yu, L. Zhu, L. Zhang, Y. Gu and X. Meng, *Chem. - Eur. J.*, 2019, **25**, 9665–9669; (d) K. Li, A. Yu and X. Meng, *Org. Lett.*, 2018, **20**, 1106–1109; (e) W. Ding, Y. Zhang, A. Yu, L. Zhang and X. Meng, *J. Org. Chem.*, 2018, **83**, 1106–1109; (f) S. Ma, A. Yu, L. Zhang and X. Meng, *J. Org. Chem.*, 2018, **83**, 5410–5419.
- 16 For selected reviews on biologically active spirocyclic oxindoles and their synthesis, see: (a) Y. Wang, A. A. Cobo and A. K. Franz, *Org. Chem. Front.*, 2021, **8**, 4315–4348; (b) G. J. Mei and F. Shi, *Chem. Commun.*, 2018, **54**, 6607–6621; (c) J. Bariwal, L. G. Voskressensky and E. V. Van Der Eycken, *Chem. Soc. Rev.*, 2018, **47**, 3831–3848; (d) T. L. Pavlovska, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Diversity*, 2016, **20**, 299–344; (e) B. Yu, D. Q. Yu and H. M. Liu, *Eur. J. Med. Chem.*, 2015, **97**, 673–

- 698; (f) M. M. M. Santos, *Tetrahedron*, 2014, **70**, 9735–9757; (g) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas, *ACS Catal.*, 2014, **4**, 743–762; (h) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104–6155.
- 17 (a) K. Okamura, T. Tsubokawa, H. Johshita, H. Miyazaki and Y. Shiokawa, *Neurol. Res.*, 2014, **36**, 65–69; (b) H. Yoshida, H. Yanai, Y. Namiki, K. Fukatsu-Sasaki, N. Furutani and N. Tada, *CNS Drug Rev.*, 2006, **12**, 9–20.