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Lewis acid-catalyzed diastereoselective formal ene reaction of thioindolinones/thiolactams with bicyclobutanes†

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Bicyclo[1.1.0]butanes (BCBs), featuring two fused cyclopropane rings, have found widespread application in organic synthesis. Their versatile reactivity towards radicals, nucleophiles, cations, and carbenes makes them suitable for various reactions, including ring-opening and annulation strategies. Despite this versatility, their potential as enophiles in an ene reaction remains underexplored. Considering this and given the challenges of achieving diastereoselectivity in ring-opening reactions of BCBs, herein, we present a unique method utilizing BCBs as enophiles in a mild and diastereoselective Sc(OTf)₃-catalyzed formal ene reaction with thioindolinones/thiolactams, delivering 1,3-disubstituted cyclobutane derivatives in high yields and excellent regio- and diastereoselectivity. Notably, structurally different thiolactam derivatives underwent diastereoselective addition to BCBs, affording the corresponding cyclobutanes. The synthesized thioindole-substituted cyclobutanes could serve as a versatile tool for subsequent functional group manipulations.

Introduction

Through the conceptual evolution of strain release, chemists have harnessed the innate reactivity stemming from thermodynamic push and destabilization. These “spring-loaded” molecules offer an excellent framework for accessing complex molecular entities under mild conditions, eliminating the need for additional energy sources.¹ Among these, bicyclo[1.1.0]butanes (BCBs) have emerged as one of the most structurally compact cyclic compounds known, owing to their small size and high strain energy (66.3 kcal mol⁻¹). Notably, BCBs are a unique type of donor–acceptor (D–A) cyclopropane with higher strain energy compared to typical D–A cyclopropanes. Consequently, they often exhibit similar reactivity to D–A cyclopropanes in many cases.² BCBs offer a versatile platform for constructing a range of intricate bicyclic frameworks, predominantly *via* annulation reactions.³ BCBs can be engaged in dearomatization reactions as well with aromatic counterparts such as thiophenes or phenols, resulting in the formation of decorated bicyclo derivatives.⁴ Complex bicyclic scaffolds can also be achieved through functionalization of BCBs without cleaving the central C–C bond.⁵ In recent years, significant progress has been made in the development of heterolytic and

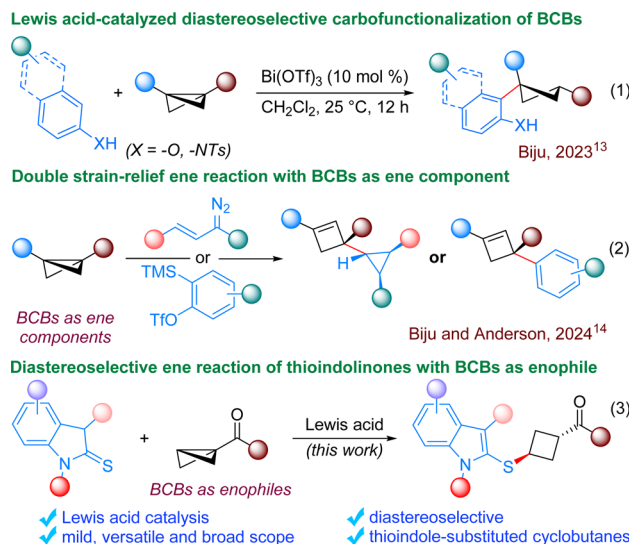
homolytic ring-opening processes involving BCBs, facilitating the foundation of structurally intricate cyclobutane derivatives.

Notably, cyclobutanes serve as crucial intermediates in chemical synthesis and found in a diverse array of natural products and other biologically relevant compounds.⁶ Specifically, 1,3-substituted cyclobutanes hold particular importance, being frequently assessed in drug discovery due to their advantageous electronic, steric, and conformational characteristics.⁷ Nevertheless, because of the challenges associated with synthesizing these small four-membered rings, the available methods for producing cyclobutanes featuring a diverse array of synthetically pertinent and pharmaceutically relevant functional groups are restricted.⁸ Hence, chemists have recently turned their attention to highly strained bicyclic systems like BCBs, aiming to discover innovative protocols to prepare these significant motifs. In 2016, Baran and co-workers reported strain-release-driven amination of BCBs for the synthesis of cyclobutyl amines, which primarily revolutionized the field.⁹ Subsequently, BCBs were used routinely for synthesizing functionalized cyclobutane derivatives. However, majority of these reactions proceed *via* radical pathway, resulting in very poor diastereoselectivity.¹⁰ Notably, Aggarwal and co-workers explored the nucleophilic reactivity of BCBs through the *in situ* formation of highly strained BCB boronates. These strained BCB boronates can react with various nucleophiles for the synthesis of trisubstituted cyclobutane derivatives with very high diastereoselectivity.¹¹ Recently, Glorius and co-workers developed photoredox-mediated thio-alkenylation of BCBs, resulting in the synthesis of functionalized cyclobutanes in high diastereoselectivity.¹² We have also devised an operationally

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Scheme 1 BCBs in ring-opening and ene reactions.

simple Lewis acid-catalyzed protocol for the diastereoselective carbofunctionalization of bicyclobutanes using naphthols (Scheme 1, eqn (1)).¹³ Although attaining high diastereoselectivity in BCB ring-opening presents a challenge, the strategic selection of appropriate reaction partners/conditions can promote high diastereoselectivity in the process.

Very recently, the Anderson group and our group demonstrated a dual strain-relief-driven ene-like reaction involving BCBs, where the *in situ* generated cyclopropenes or benzynes function as the enophiles, while BCBs serve as the ene component (eqn (2)).¹⁴ This strategy provides access to cyclopropanes or arene substituted highly decorated cyclobutenes. As enophiles are inherently electrophilic species and given the fact that BCBs are also electrophilic species, theoretically BCBs should engage as the enophile in the ene reaction. We speculated that a strategically selected reaction partner with a tendency to act as the ene component could compel BCBs to function as the enophile, contrary to the previously outlined approach.¹⁴ Literature precedents indicate that 2-thioindolinones have the potential to serve as an ene component, wherein aromaticity can serve as an additional driving force for the formation of the indole-substituted products.¹⁵ Hence, 2-thioindolinones were selected as the preferred reaction partner for the intended ene reaction. Our previous experience on the ability of Lewis acids to control the diastereoselectivity inspired us to formulate the process catalyzed by a Lewis acid.¹³ We envisioned that the coordination of BCBs by the Lewis acid could enhance the feasibility of thioindolinone addition, while the transfer of a proton from the same side of the thioindolinones could yield the desired product with high diastereoselectivity (eqn (3)). Considering the importance of 1,3-substituted cyclobutanes in mind, it was planned to use monosubstituted BCBs for our investigation.⁷ It is worth noting that the synthesis of 1-thio-3-keto disubstituted cyclobutanes from BCBs has been previously utilized in chemical biology tools, though the products were obtained with very poor diastereoselectivity.¹⁶

Results and discussion

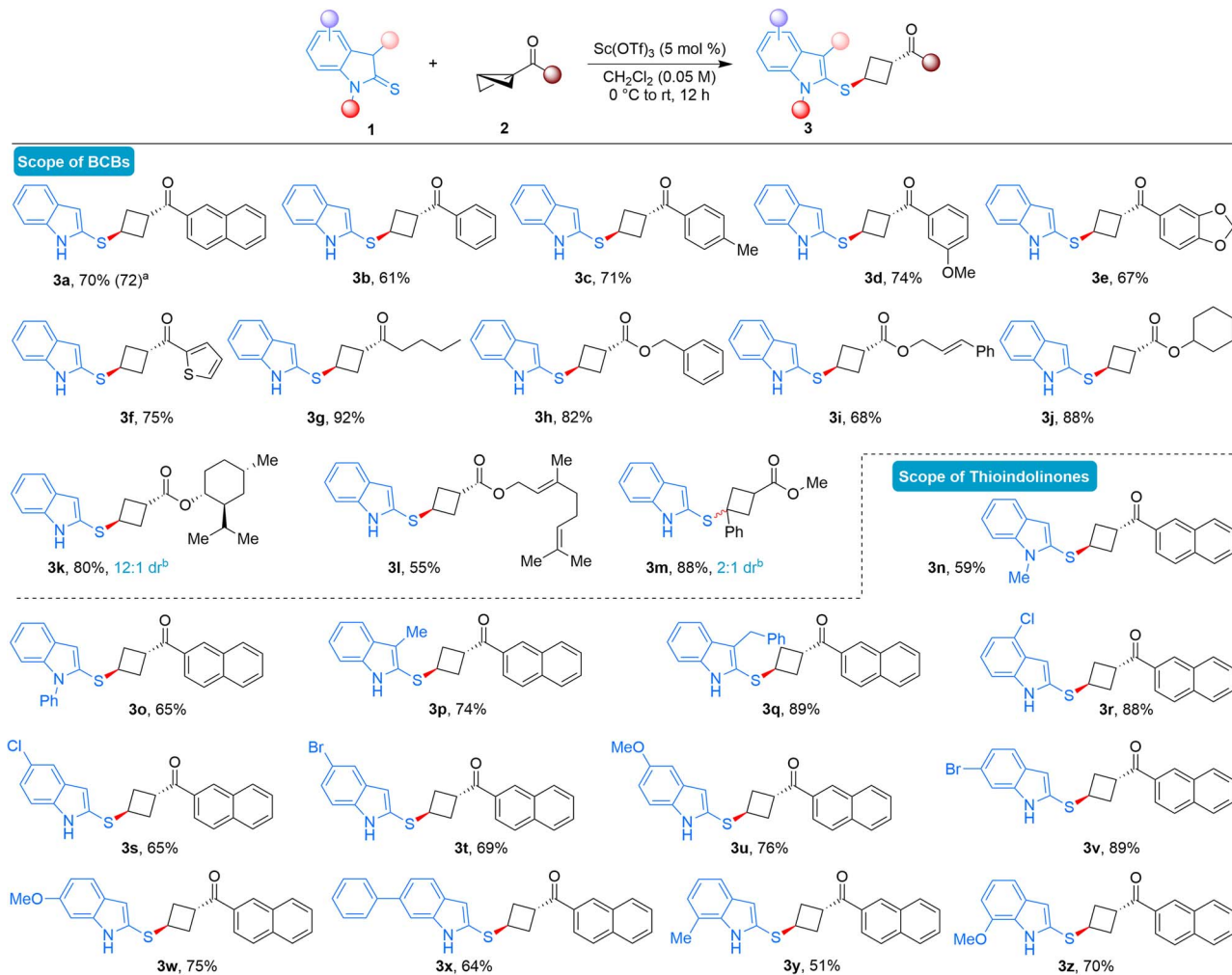
With the conceived idea in mind, the present studies were initiated by the treatment of 2-thioindolinones **1a** with the ketonaphthyl substituted BCB **2a** in the presence of $\text{Sc}(\text{OTf})_3$ (5 mol%) in CH_2Cl_2 at 25 °C. Using these conditions, the anticipated 1,3-disubstituted cyclobutane **3a** was formed in 63% yield as a single diastereomer (Table 1, entry 1). Under the present reaction conditions, $\text{Bi}(\text{OTf})_3$ was found to be ineffective to improve the yield of the product further (entry 2). Notably, employing $\text{Cu}(\text{OTf})_2$ or TMSOTf as Lewis acid catalysts resulted in the formation of the expected product with lower yield and poor diastereomeric ratio (entries 3 and 4). Augmenting the catalyst loading did not enhance the yield of product **3a** (entry 5). Changing the stoichiometry of **1a** and **2a** resulted in a decreased yield of product formation (entries 6 and 7). Conducting the reaction at 0 °C led to an improvement in the yield of **3a** to 71% (entry 8). Additionally, carrying out the reaction at 0 °C to rt furnished product **3a** in a similar yield (entry 9). Varying the solvents was not beneficial in improving the yield of the product (entries 10, 11). Hence, entry 9 was selected as the optimal condition for this diastereoselective formal ene reaction.¹⁷

With the identified reaction conditions in hand, we examined the scope and drawbacks of this diastereoselective formal ene reaction involving thioindolinones and BCBs (Scheme 2). First, the variation in BCBs was evaluated. Different keto containing bicyclo[1.1.0]butanes, featuring substitutions at various positions on the benzene ring, smoothly underwent the ring-opening reactions, resulting in the diastereoselective

Table 1 Optimization of the reaction conditions^a

Entry	Variation of the initial conditions ^a	Yield of 3a ^b (%)	dr ^c
1	None	63	>20 : 1
2	$\text{Bi}(\text{OTf})_3$ instead of $\text{Sc}(\text{OTf})_3$	40	>20 : 1
3	$\text{Cu}(\text{OTf})_2$ instead of $\text{Sc}(\text{OTf})_3$	60	2 : 1
4	TMSOTf instead of $\text{Sc}(\text{OTf})_3$	47	1 : 1
5	10 mol% $\text{Sc}(\text{OTf})_3$ instead of 5 mol%	62	>20 : 1
6	1.4 equiv of 2a instead of 1.2 equiv	57	>20 : 1
7	1.2 equiv of 1a	51	>20 : 1
8	0 °C instead of 25 °C	71	>20 : 1
9	0 °C to rt instead of 25 °C	71 (70)	>20 : 1
10 ^d	DCE instead of CH_2Cl_2	60	>20 : 1
11 ^d	THF instead of CH_2Cl_2	69	1 : 1

^a Initial conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), $\text{Sc}(\text{OTf})_3$ (5 mol%), CH_2Cl_2 (2.0 mL), 25 °C for 12 h. ^b The ¹H NMR yield of the crude products was determined using CH_2Br_2 as the internal standard and the isolated yield was given in parenthesis. ^c dr value was determined from ¹H NMR of the crude reaction mixture. ^d The reaction was performed at 0 °C to rt.

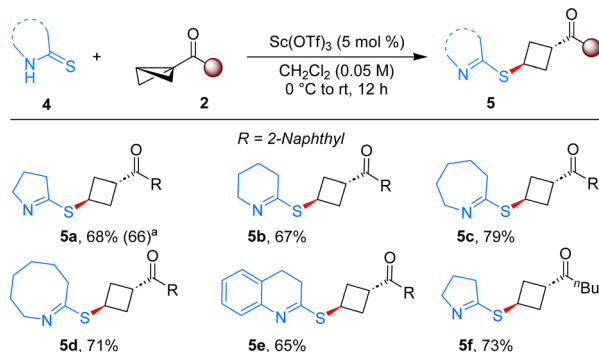


Scheme 2 Substrate scope of the reaction. Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), Sc(OTf)₃ (5 mol%), CH₂Cl₂ (4.0 mL), 0 °C to rt for 12 h. Provided are yields of isolated products. ^aYield of the experiment conducted on a 2.0 mmol scale. ^bUnless otherwise noted, dr > 20 : 1 and the dr value was determined from ¹H NMR of the crude reaction mixture.

formation of the desired thioindole-substituted cyclobutanes in good yields (**3a–3d**). The scalability of the developed ene reaction was demonstrated by isolating **3a** in a 72% yield when the reaction was conducted on a 2.0 mmol scale. Moreover, keto BCBs with disubstituted arene or heteroaryl ring were well tolerated under the present conditions, yielding the anticipated cyclobutane derivatives in good yields (**3e–3f**). BCB with butyl substitution also performed effectively, delivering the desired product **3g** in 92% yield as a single diastereomer. This diastereoselective ene reaction could be extended beyond keto BCBs as enophiles; ester substituted BCBs also furnished the desired ene product. For instance, BCBs derived from benzyl, cinnamyl, and cyclohexyl alcohols delivered the anticipated product in good to excellent yields (**3h–3j**). BCBs derived from natural products such as (–)-menthol and geraniol also furnished the desired ene products (**3k–3l**). In the case of menthol, the product was obtained in 12:1 diastereomeric ratio. Notably, BCB substituted with phenyl and ester did react under the present reaction conditions, and the desired product **3m** was formed in 88% yield and 2 : 1 dr.¹⁸

The reaction scope was subsequently assessed by employing various substituted thioindolinones. N-protected thioindolinones served as tolerable substrates under the present reaction conditions and the products were formed in moderate yields (**3n–3o**). Therefore, successful outcomes in this ene reaction are not always dependent on the presence of free N–H substituted thioindolinones. Thioindolinones substituted at the 3-position yielded the desired products in good yields (**3p–3q**). Various 4- and 5-substituted thioindolinones could also be used as substrates to obtain the corresponding 1,3-disubstituted cyclobutanes under the optimized reaction conditions (**3r–3u**). Several thioindolinones substituted at the 6-position proved to be effective substrates in this diastereoselective ene reaction, furnishing the expected products in high yields (**3v–3x**). Finally, 7-substitution also yielded the anticipated products in good yields (**3y–3z**), demonstrating that the developed BCB ring-opening reactions are effective with thioindolinones bearing substitutions at every position.

When pyrrolidine-2-thione was employed as the ene component under the present reaction conditions, the product



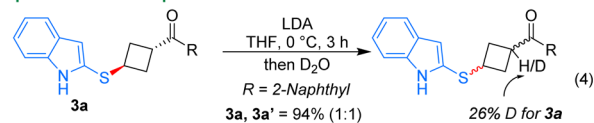
Scheme 3 Reaction with structurally different thioamides. Reaction conditions: 4 (0.20 mmol), 2 (0.24 mmol), Sc(OTf)₃ (5 mol%), CH₂Cl₂ (4.0 mL), 0 °C to rt for 12 h. Provided are yields of isolated products. ^aYield of the experiment conducted on a 1.0 mmol scale. The dr value determined from ¹H NMR of the crude reaction mixture was >20 : 1 in all cases.

5a bearing imine was formed in 68% yield in single diastereomer (Scheme 3). The distinct reactivity of indoline-2-thione compared to pyrrolidine-2-thione can be explained by the additional driving force of aromatization present in the product of indoline-2-thione, which is lacking in the latter case. This reaction was also scalable, as evident by a 1 mmol scale reaction that produced the desired product with a 66% yield. The generality of this reaction was tested with different thiones and BCBs. Thiones with different ring size delivered the anticipated products in good yields (**5b–5e**). Aliphatic ketone substituted BCB also furnished the desired product **5f** in 73% yield, thereby broadening the scope of the reaction.

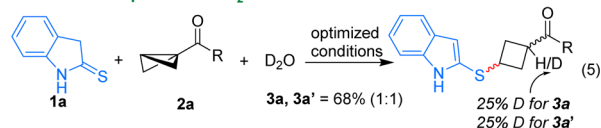
A few mechanistic experiments were conducted to gain insight into the mechanism of the described ene reaction. When the product **3a** was treated in the presence of LDA followed by quenching with D₂O, it underwent epimerization, resulting in the formation of a 1 : 1 diastereomeric mixture of **3a** and **3a'** (Scheme 4, eqn (4)). This study reveals that the observed diastereoselectivity in the described ene reaction is not governed by thermodynamic control. If thermodynamic parameters were decisive in determining diastereoselectivity, then minimal change would be expected in diastereoselectivity after the deprotonation and re-protonation steps.¹³ Furthermore, performing the reaction in the presence of D₂O also delivered a 1 : 1 diastereomeric mixture of **3a** and **3a'** (eqn (5)). This experiment suggests that the introduction of an external proton source could modify the diastereoselectivity of the product. Given the fact that the presence of such a proton source can influence diastereoselectivity, it is likely that intramolecular proton transfer occurs under the optimized reaction conditions, possibly originating from the same side of the thioindolinones.¹⁹

The reaction involving 3,3-dimethylindoline-2-thione **4g** resulted in the formation of product **5g** in 42% yield, suggesting that even without the favourable aromatization process, thiones can still undergo the reaction (eqn (6)). Notably, 1-methylpyrrolidine-2-thione did not participate in the reaction to form any products due to the absence of free N–H and

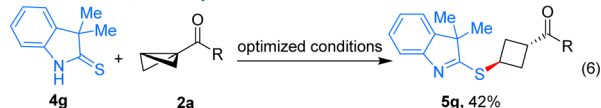
Epimerization of the product



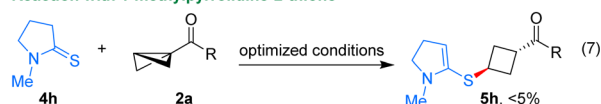
Reaction in the presence of D₂O



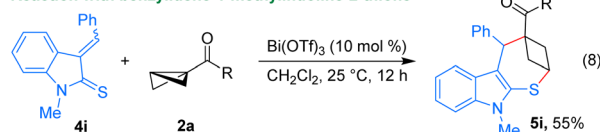
Reaction with 3,3-dimethylindoline-2-thione



Reaction with 1-methylpyrrolidine-2-thione



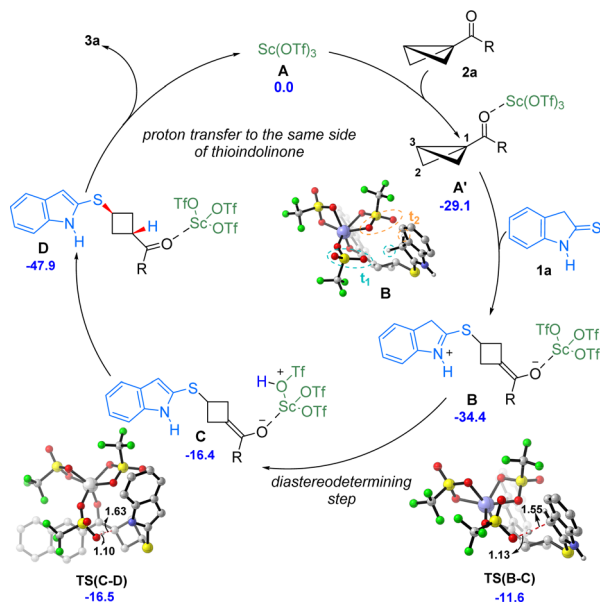
Reaction with benzylidene-1-methylindoline-2-thione



Scheme 4 Mechanistic studies.

favourable aromatization in the process (eqn (7)). Interestingly, the reaction performed using benzylidene-1-methylindoline-2-thione **4i** (which stays in a dimeric form *via* self-Diels–Alder reaction) resulted in the formation of the (4 + 3) annulated product **5i** in 55% yield. While the addition of thioamide to BCB could potentially yield the ring-opened product in this case, it is the driving force of aromatization that propels the reaction towards the formation of the annulated product.²⁰

Based on the mechanistic studies and DFT calculations a catalytic cycle for the formal diastereoselective ene reaction of thioindolinones is presented in Scheme 5. The reaction begins with the coordination of BCB **2a** with Sc(OTf)₃ to form the intermediate **A'**. Now, the 2-thioindolinone **1a** attacks the intermediate **A'** at C3 position to generate the intermediate **B**. From this intermediate several pathways can be followed, but the major pathway goes *via* the **TS(B-C)**.¹⁷ Depending upon the position of triflate, two different diastereomers can be formed. Triflate *t*₁ abstracts the proton from thioindolinone *via* **TS(B-C)** to form intermediate **C**, while proton abstraction by triflate *t*₂ *via* **TS(B-C')** leads to intermediate **C'**.¹⁷ In the final step, the proton is transferred from triflate to the C1 position of the BCB to give the product. This proton transfer is barrierless and very facile. Since the diastereomeric product formation depends upon the proton abstraction by triflate, the formation of **C** *via* **TS(B-C)** becomes the diastereo determining step of the reaction. After subsequent steps, proton abstraction by triflate *t*₁ leads to the major product while abstraction by triflate *t*₂ gives the minor product. The **TS(B-C)** is more stable than **TS(B-C')** by 1.6 kcal mol⁻¹. Furthermore, the energy difference between diastereomeric products **3a** and **3a'** was found to be only 0.2 kcal mol⁻¹, which suggests that the diastereoselectivity is

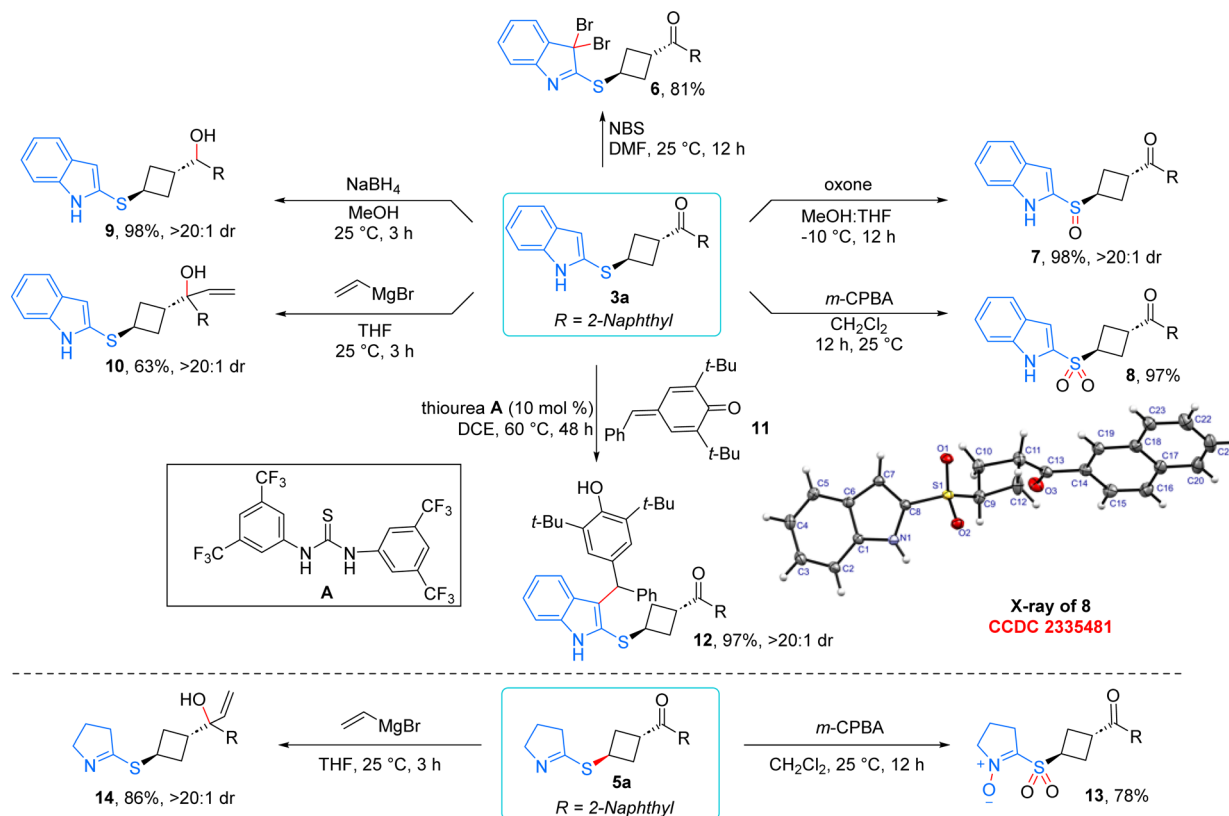


Scheme 5 Proposed catalytic cycle. Relative Gibbs free energies (ΔG) are given in kcal mol^{-1} . Distances are given in Å.

not governed by thermodynamic stability of the products. The mechanistic study also validates this result where 1 : 1 mixture of products **3a** and **3a'** is found when the reaction is carried out in the presence of LDA and D_2O . From the free energy values

and mechanistic studies, it is likely that the reaction is kinetically controlled.

The 1,3-substituted cyclobutane derivatives generated from the diastereoselective ene process provide multiple synthetic linchpins for further post synthetic modifications (Scheme 6). Treatment of **3a** with *N*-bromosuccinimide resulted in the formation of 3,3-dibromo substituted product **6** in 81% yield *via* dearomatization of the indole moiety. The sulfur centre in product **3a** was selectively converted to the sulfoxide **7** in the presence of 0.5 equivalent of oxone. Moreover, through the aid of *m*-CPBA, selective transformation of sulfone **8** was achieved in 97% yield. For sulfone **8**, the product structure was confirmed using single-crystal X-ray analysis.^{21,22} Reduction of the ketone moiety using NaBH_4 delivered the secondary alcohol derivative **9** in 98% yield with excellent dr. When **3a** was treated in the presence of vinyl magnesium bromide, the anticipated tertiary alcohol **9** was formed in 63% yield and excellent dr. In the presence of thiourea catalyst, **3a** underwent addition to *para*-quinone methide **11** *via* the third position of indole, leading to the formation of highly decorated indole scaffold **12** in 97% yield and excellent dr.²³ Notably, efforts to diversify the product under base treatment were unsuccessful as it only compromised the diastereoselectivity of **3a**. Interestingly, product **5a** could be further functionalized: *m*-CPBA oxidation yielded compound **13** by oxidizing both the sulfur and nitrogen centers.



Scheme 6 Synthetic utility of the product.

Conclusions

In conclusion, Lewis acid-catalyzed diastereoselective formal ene reaction of thioindolinones/thiolactams employing BCBs as enophiles for the synthesis of 1,3-*trans* disubstituted cyclobutanes has been realized.²⁴ The diastereoselectivity arises during the proton transfer step, presumably involving proton transfer from the same side of the thioindolinones. The present reaction is operationally simple, advances smoothly under mild conditions, and can be fine-tuned for every portion of both substrates. This reaction is not restricted to thioindolinones as the ene component; other thiones also reacted efficiently to form the functionalized cyclobutanes with excellent diastereoselectivity. Mechanistic experiments and DFT studies were performed to get insight into the possible course of the reaction. Functional group interconversions were carried out to reveal synthetic handles for additional synthetic transformations.

Data availability

Details on experimental procedures, mechanistic experiments, characterization data of all the 1,3-disubstituted cyclobutanes and X-ray data of **8**. The details are available in the ESI† of the manuscript.

Author contributions

A. G. designed the project, and performed the optimization studies, substrate scope analysis and mechanistic studies. S. D. helped in the substrate scope analysis and mechanistic studies. M. S. H. performed the DFT studies. A. G. wrote the first draft of the manuscript, which was edited by A. T. B. All authors have given approval to the final version of the manuscript. A. T. B. directed the research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) K. B. Wiberg, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 312; (b) J. Turkowska, J. Durkaab and D. Gryko, *Chem. Commun.*, 2020, **56**, 5718; (c) J. A. Milligan and P. Wipf, *Nat. Chem.*, 2016, **8**, 296; (d) A. Luque, J. Paternoga and T. Opatz, *Chem.–Eur. J.*, 2021, **57**, 4500; (e) A. Fawcett, *Pure Appl. Chem.*, 2020, **92**, 751; (f) M. A. A. Walczak, T. Krainz and P. Wipf, *Acc. Chem. Res.*, 2015, **48**, 1149; (g) C. B. Kelly, J. A. Milligan, L. Tilley and T. M. Sodano, *Chem. Sci.*, 2022, **13**, 11721.
- (a) P. Singh, R. K. Varshnaya, R. Dey and P. Banerjee, *Adv. Synth. Catal.*, 2020, **362**, 1447; (b) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504; (c) D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385; (d) A. U. Augustin and D. B. Werz, *Acc. Chem. Res.*, 2021, **54**, 1528; (e) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev.*, 2021, **121**, 227; (f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano and J. Waser, *Chem. Commun.*, 2014, **50**, 10912; (g) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (h) A. Kreft, A. Lucht, J. Grunenberg, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2019, **58**, 1955.
- (a) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, *Nature*, 2022, **605**, 477; (b) Y.-J. Liang, R. Kleinmans, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2022, **144**, 20207; (c) R. Guo, Y. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard and M. K. Brown, *J. Am. Chem. Soc.*, 2022, **144**, 7988; (d) Y. Zheng, W. Huang, R. K. Dhungana, A. Granados, S. Keess, M. Makvandi and G. A. Molander, *J. Am. Chem. Soc.*, 2022, **144**, 23685; (e) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza and D. J. Procter, *Nat. Chem.*, 2023, **15**, 535; (f) D. Ni, S. Hu, X. Tan, Y. Yu, Z. Li and L. Deng, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308606; (g) N. Radhoff, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2023, e202304771; (h) Y. Liang, F. Paulus, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2023, **62**, e20230504; (i) J. Zhang, J.-Y. Su, H. Zheng, H. Li and W.-P. Deng, *Angew. Chem., Int. Ed.*, 2024, e202318476; (j) K. Dhake, K. J. Woelk, J. Becia, A. Un, S. E. Jenny and D. C. Leitch, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204719.
- (a) H. Wang, H. Shao, A. Das, S. Dutta, H. T. Chan, C. Daniliuc, K. N. Houk and F. Glorius, *Science*, 2023, **381**, 75; (b) S. Dutta, D. Lee, K. Ozols, C. G. Daniliuc, R. Shintani and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 2789.
- (a) R. E. McNamee, A. L. Thompson and E. A. Anderson, *J. Am. Chem. Soc.*, 2021, **143**, 21246; (b) R. E. McNamee, M. M. Haugland, J. Nugent, R. Chan, K. E. Christensen and E. A. Anderson, *Chem. Sci.*, 2021, **12**, 7480.
- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (b) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515; (c) M. Wroblewski, G. Reichard, S. Paliwal, S. Shah, H. Tsui, R. Duffy, J. Lachowicz, C. Morgan, G. Varty and N. Shih, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3859; (d) K. C. Nicolaou, D. Vourloumis, S. Totokotsopoulos, A. Papakyriakou, H. Karsunky, H. Fernando, J. Gavrilyuk, D. Webb and A. F. Stepan, *ChemMedChem*, 2016, **11**, 31.
- (a) M. L. Conner and M. K. Brown, *J. Org. Chem.*, 2016, **81**, 8050; (b) K. Majima and M. Yamano, *J. Org. Chem.*, 2021, **86**, 11464.
- (a) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485; (b) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew.*

- Chem., Int. Ed.*, 2011, **50**, 7740; (c) S. Poplata, A. Troster, Y. Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748.
- 9 (a) R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *Science*, 2016, **351**, 241; (b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 3209.
- 10 (a) C. J. Pratt, R. A. Aycock, M. D. King and N. T. Jui, *Synlett*, 2020, **31**, 51; (b) G. Ernouf, E. Chirkin, L. Rhyman, P. Ramasami and J. Cintrat, *Angew. Chem., Int. Ed.*, 2020, **59**, 2618; (c) M. Ociepa, A. J. Wierzba, J. Turkowska and D. Gryko, *J. Am. Chem. Soc.*, 2020, **142**, 5355; (d) X. Yu, M. Lübbesmeyer and A. Studer, *Angew. Chem., Int. Ed.*, 2021, **60**, 675; (e) K. Das, A. Pedada, T. Singha and D. P. Hari, *Chem. Sci.*, 2024, **15**, 3182.
- 11 (a) S. H. Bennett, A. Fawcett, E. H. Denton, T. Biberger, V. Fasano, N. Winter and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 16766; (b) A. Fawcett, T. Biberger and V. K. Aggarwal, *Nat. Chem.*, 2019, **11**, 117; (c) M. Silvi and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 9511.
- 12 H. Wang, J. E. Erchinger, M. Lenz, S. Dutta, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2023, **145**, 23771.
- 13 A. Guin, S. Bhattacharjee, M. S. Harariya and A. T. Biju, *Chem. Sci.*, 2023, **14**, 6585.
- 14 A. Dasgupta, S. Bhattacharjee, Z. Tong, A. Guin, R. E. McNamee, K. E. Christensen, A. T. Biju and E. A. Anderson, *J. Am. Chem. Soc.*, 2024, **146**, 1196.
- 15 (a) P. Tang, Y.-Y. Wei, H.-J. Ma, Y. Yang and Y. Jiang, *J. Org. Chem.*, 2022, **87**, 10890; (b) X. Chen, Z.-H. Qi, S.-Y. Zhang, L.-P. Kong, Y. Wang and X.-W. Wang, *Org. Lett.*, 2015, **17**, 42.
- 16 (a) B. D. Schwartz, M. Y. Zhang, R. H. Attard, M. G. Gardiner and L. R. Malins, *Chem.-Eur. J.*, 2020, **26**, 2808; (b) K. Tokunaga, M. Sato, K. Kuwata, C. Miura, H. Fuchida, N. Matsunaga, S. Koyanagi, S. Ohdo, N. Shindo and A. Ojida, *J. Am. Chem. Soc.*, 2020, **142**, 18522; (c) A. Kaur, W. Lin, V. Dovhalyuk, L. Driutti, M. L. D. Martino, M. Vujasinovic, J.-M. Löhr, M. E. Sellin and D. Globisch, *Chem. Sci.*, 2023, **14**, 5291.
- 17 See the ESI† for details.
- 18 Disappointingly, amide BCBs did not work under the present reaction conditions.
- 19 Notably, under optimized conditions, the reaction doesn't yield 1*H*-indole-2-thiol in the absence of BCB **2a**, thereby eliminating the possibility of 1*H*-indole-2-thiols forming first and then adding to BCBs.
- 20 For a related reaction of BCBs with thioindolinones that appeared while the manuscript was under review, see: J.-J. Wang, L. Tang, Y. Xiao, W.-B. Wu, G. Wang and J.-J. Feng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405222.
- 21 CCDC 2335481† (**8**) contains the supplementary crystallographic data for this paper.
- 22 The relative stereochemistry of all products **3** and **5** was determined based on the stereochemistry observed in the crystal structure of derivative **8**.
- 23 The relative configuration of the newly generated stereocentre in **7**, **9**, **10**, **12** and **14** was not determined.
- 24 A. Guin, S. Deswal and A. T. Biju, *ChemRxiv*, preprint, 2024, DOI: [10.26434/chemrxiv-2024-gf80l](https://doi.org/10.26434/chemrxiv-2024-gf80l).