OL | Organic Letters

pubs.acs.org/OrgLett Letter

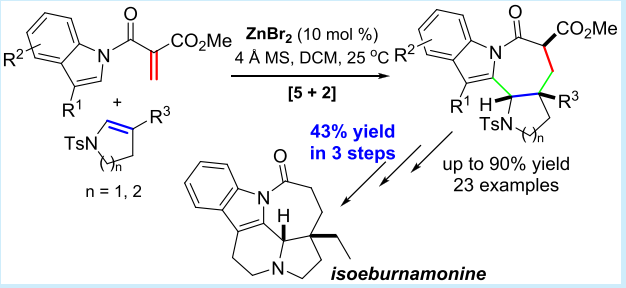
Catalytic Diastereoselective [5 + 2] Annulation of *N*-Acryloyl Indoles with Cyclic Sulfonyl Enamides: Facile Access to Isoeburnamonine

Song Wei, Long Zheng, Sunewang R. Wang,* and Yong Tang*

Cite This: *Org. Lett.* 2020, 22, 1013–1017 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: $ZnBr_2$-catalyzed stereoselective [5 + 2] annulation of *N*-acryloyl indoles with cyclic sulfonyl enamides is reported, providing a concise and efficient synthesis of isoeburnamonine, which is the key intermediate for norvincamine. Both [2 + 2] and [4 + 2] cycloadducts, depending on the ring size of the enamides, have been shown to be the important intermediates for this [5 + 2] annulation.



Donor–acceptor (D–A) cyclobutanes have proven as powerful synthetic synthons for the rapid construction of highly substituted (poly)cyclic compounds in recent years.[1−4] Remarkably, [4 + 2] cycloaddition reactions of such cyclobutane synthons with substituted indoles have been well-demonstrated in total synthesis of several bioactive indoline alkaloids, such as (±)-aspidospermidine,[5] (±)-11-demethoxy-16-*epi*-myrtoidine,[6] and (±)-akuammicine[7] by us and others (see Figure 1a). Recently, France and co-workers have reported an elegant intramolecular ring-opening cyclization of D–A cyclobutanes produced in situ from a variety of alkenes such as aromatic alkenes and vinyl sulfides to access azepino[1,2-*a*]indole cores.[8,9] However, they found that reactions with *N*-acyl enamides failed to deliver the aminated azepino[1,2-*a*]indoles that are prevalent in the core structure of bioactive indole alkaloids such as correantine B and akagerine. Motivated by our success in Lewis-acid-catalyzed stereoselective cyclizations of cyclic *N*-tosyl enamides (**1**) with activated Michael acceptors,[10] especially the [2 + 2] annulation to give the D–A amino-cyclobutanes,[10b] we attempted to prepare the troublesome aminated azepino[1,2-*a*]indoles by the use of cyclic sulfonyl enamides. We report herein the $ZnBr_2$-catalyzed diastereoselective annulation of **1** with *N*-acryloyl indoles **2** to the tetracyclic amino-azepino[1,2-*a*]indoles **3** (see Figure 1b).[11] More importantly, this method provides concise access to isoeburnamonine (**4**),[12] which is the key intermediate in total synthesis of norvincamine reported by the Winterfeldt group.[13]

Our study was commenced with the reaction between *N*-tosyl enamide **1a** (0.10 M, in DCM) and *N*-acryloyl indole **2a** (1.1 equiv) catalyzed by 10 mol % of $ZnBr_2$ at 25 °C. To our delight, a single azepino[1,2-*a*]indole diastereomer **3aa** was produced in 41% yield (Table 1, entry 1), the relative configuration of which was unambiguously confirmed by

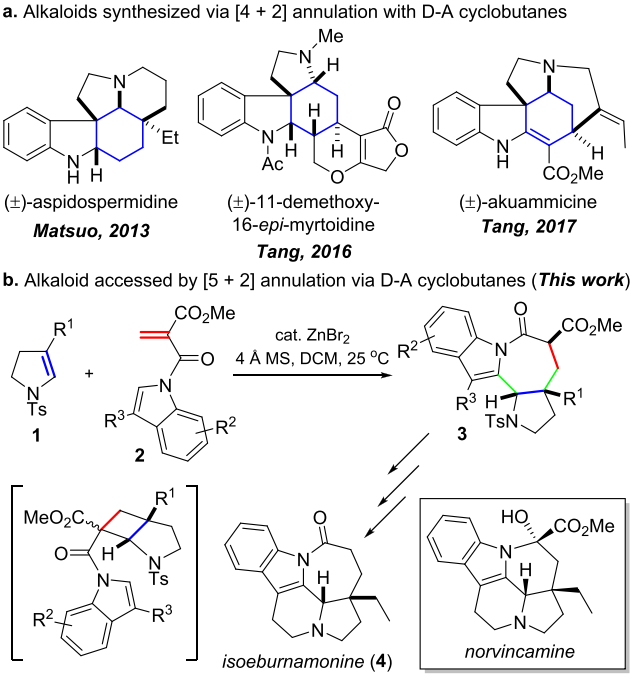


Figure 1. Cyclizations with D–A cyclobutanes for natural indole alkaloid synthesis.

Received: December 19, 2019
Published: January 23, 2020

https://dx.doi.org/10.1021/acs.orglett.9b04556
Org. Lett. 2020, 22, 1013–1017

Table 1. Optimization of Reaction Conditions[a]

entry	catalyst	time (h)	yield (conversion) (%)[b]
1[c]	$ZnBr_2$	24	41 (100)
2	$ZnBr_2$	24	74 (92)
3	$ZnCl_2$	24	51 (86)
4	$FeCl_3$	24	39 (87)
5	$Sc(OTf)_3$	24	65 (91)
6	$Yb(OTf)_3$	24	69 (90)
7	$In(OTf)_3$	24	63 (88)
8	$Cu(ClO_4)_2{\cdot}6H_2O$	24	54 (99)
9	$Zn(ClO_4)_2{\cdot}6H_2O$	24	64 (83)
10	$ZnBr_2$	48	69[d] (100)
11[e]	$ZnBr_2$	48	81[d] (100)
12[e,f]	$ZnBr_2$	17	77[d] (100)
13[g]	$ZnBr_2$	48	83[d] (100)

[a]Reaction conditions: **1a** (0.10 M, 1.0 equiv), **2a** (1.1 equiv), catalyst (10 mol %), and 4 Å MS (100.0 mg) in DCM (1.0 mL), 25 °C. [b]The conversion and the yield were determined by the ^{1}H NMR spectrum of the crude mixture with 1,1,2,2-tetrachloroethane (TTCE) as an internal standard. [c]Run without 4 Å MS. [d]Isolated yield. [e]Run with 0.24 M of **1a** in DCM (1.0 mL). [f]Run at 35 °C. [g]Run with 0.24 M of **2a** (1.0 equiv) and **1a** (1.1 equiv) in DCM (1.0 mL).

single-crystal X-ray analysis.[14] Note that the relative stereochemical outcome between the ester group and the electron-donating substituent in the alkene components was completely reversed, when compared to those reported in the work of the France group,[8a] possibly influenced by the cyclic structure. Moreover, the addition of 4 Å MS improved the yield to 74%, although the conversion of **1a** was only 92% (Table 1, entry 2). Other Lewis acids were then screened in the presence of 4 Å MS. While $Yb(OTf)_3$ showed an activity comparable to that of zinc bromide, other frequently used Lewis acidic metal chlorides, triflates, and perchlorate hydrates resulted in inferior yields of **3aa** with similar conversions (Table 1, entries 3−9). Within an extended time, **1a** was fully consumed; however, the yield of **3aa** changed slightly (Table 1, entry 10). A screening of the concentration of **1a** showed that the reaction performed at a higher concentration gave **3aa** in 81% isolated yield (Table 1, entry 11).[14] Warming the reaction at 35 °C remarkably accelerated the reaction, but a slight decrease in the yield was observed (Table 1, entry 12). To our delight, **3aa** was also isolated in good yield when *N*-acryloyl indole **2a**, which is the more-complex C5 component, was used as the limiting reagent (Table 1, entry 13). No other diastereomers were observed in the reactions examined.

With the optimal reaction conditions in hand, the scope of the [5 + 2] annulation with various *N*-tosyl enamides was studied. As shown in Figure 2, *N*-tosylated 2,3-dihydropyrroles with 4-alkyl substituents, such as methyl (**1a**), ethyl (**1b**), *n*-propyl (**1c**), allyl (**1d**), and benzyl (**1e**), reacted smoothly with **2a** at 25 °C, giving the corresponding azepino[1,2-*a*]indoles (**3aa**−**3ea**) as the single diastereomer in good to excellent yields. The allyl group in **3da** could allow for further elaboration. Interestingly, *N*-tosyl-2,3-dihydropyrrole (**1f**) was also suitable for the [5 + 2] annulation, but **3fa** was obtained in

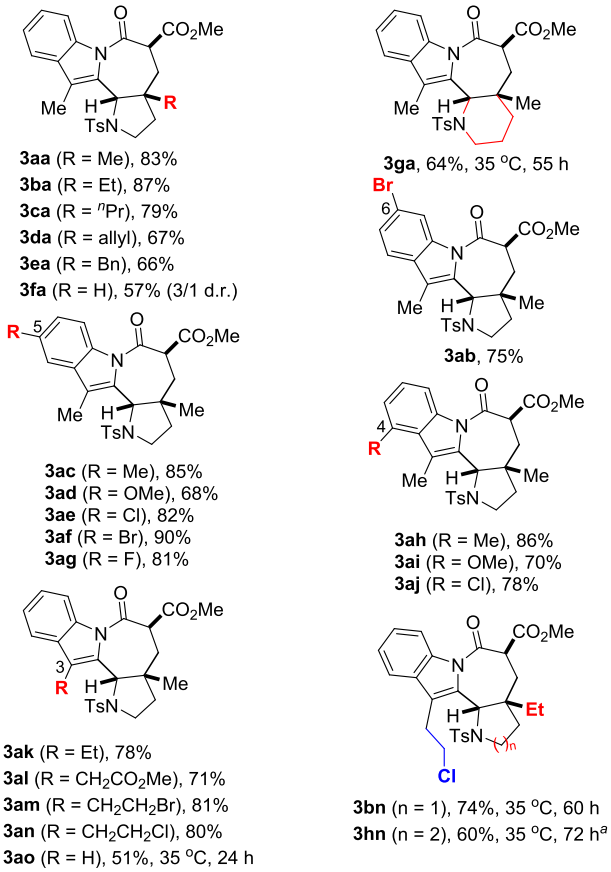


Figure 2. Scope for the [5 + 2] annulation: Unless otherwise specified, **1** (0.26 mmol), **2** (0.24 mmol), $ZnBr_2$ (10 mol %), and 4 Å MS (100.0 mg) in DCM (1.0 mL), 25 °C, 48 h. Isolated yield. [Footnote a indicates conditions including $In(OTf)_3$ (15 mol %) and 4 Å MS (30.0 mg).]

57% yield with a moderate diastereoselectivity, indicating the important role of the 4-substituents in the cyclic *N*-sulfonyl enamides for the excellent diastereomeric ratio (dr) selectivity. Unfortunately, 4-arylated *N*-sulfonyl 2,3-dihydropyrroles were unreactive, possibly because of the reduced reactivity of the double bond caused by the conjugate effect of aryls. In addition, this annulation was sensitive to the ring size of the cyclic enamide. For example, the reaction with the six-membered ring enamide **1g** was much slower even warmed at 35 °C. Moreover, like the acyclic sulfonyl enamides, the reaction with the seven-membered ring enamide *N*-tosyl-6-methyl-2,3,4,5-tetrahydro-1*H*-azepine produced a complicated mixture.

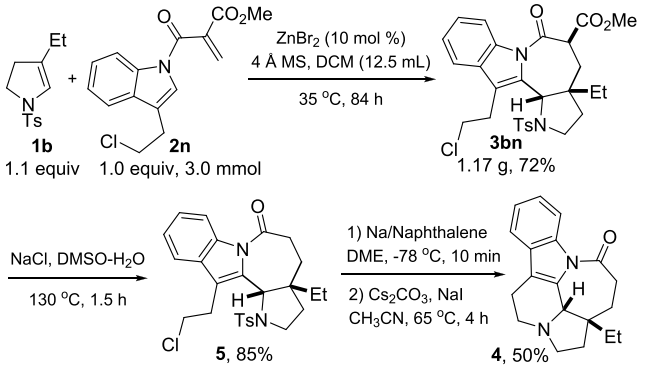
A wide range of functional groups on the indole ring of *N*-acryloyl indoles **2** were well-tolerated in the $ZnBr_2$-catalyzed [5 + 2] annulation (Figure 2). Specifically, 3-methylated substrates **2** with halo (**2b**, **2e**−**2g**, and **2j**), methyl (**2c** and **2h**), and methoxy (**2d** and **2i**) substituents on the 4-, 5-, or 6-positions of the indole ring reacted readily with **1a** under the optimal reaction conditions, diastereoselectively affording the corresponding products (**3ab**−**3aj**) in yields up to 90%. Moreover, the 3-methyl group in **2a** could be replaced by ethyl (**2k**) or the *β*-functionalized ethyl groups (**2l**−**2n**) without the significant loss of the product yields. Interestingly, the 3-unsubstituted indole **2o** was less reactive and only 51% yield of **3ao** was obtained. Given the promising further cyclization of the tethered alkyl halides in **3am** and **3an** with the pyrrolidine

https://dx.doi.org/10.1021/acs.orglett.9b04556
Org. Lett. 2020, 22, 1013−1017

ring after removal of the tosyl group, we became interested in the application of this [5 + 2] annulation for the synthesis of isoeburnamonine **4**. Thus, the reaction of **1b** and **2n** was attempted, which delightedly gave the desired product **3bn** in 74% isolated yield under slightly harsher conditions. Notably, the stronger Lewis acid $In(OTf)_3$ was used for the reaction of the less-reactive six-membered congener **1h** with **2n**, giving **3hn** in 60% yield heated at 35 °C for 72 h. As shown by the X-ray structure of **3hn**,[14] the displacement of the 3-methyl group with the long-chain 3-alkyl substituents did not affect the relative configuration of the products.

The synthetic utility of this annulation was further illustrated by a four-step synthesis of isoeburnamonine **4** in 31% overall yield (Scheme 1).[13] The synthesis started with $ZnBr_2$-catalyzed

Scheme 1. Gram-Scale Reaction and a Concise Synthesis of Isoeburnamonine 4

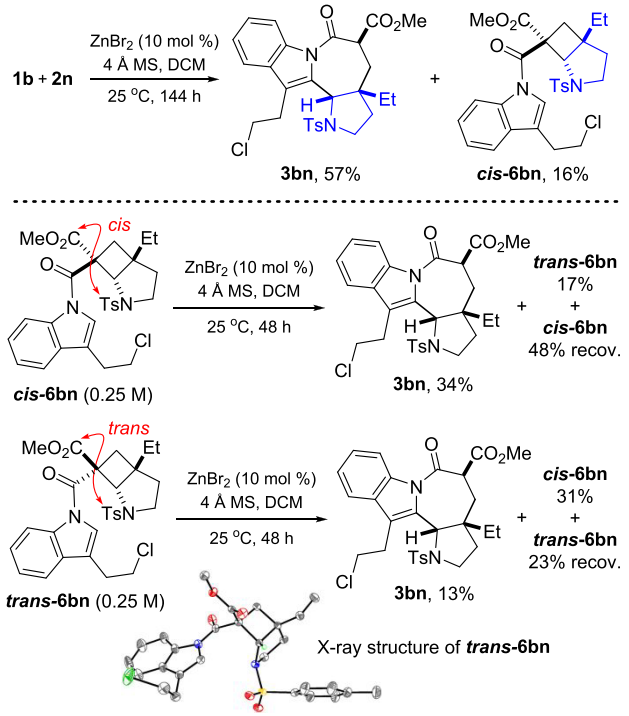


reaction of *N*-tosyl-4-ethyl-2,3-dihydropyrrole **1b** with indole **2n** on the gram scale, diastereoselectively affording 1.17 g of **3bn** in 72% isolated yield. The compound **3bn** was smoothly decarboxylated by treatment with NaCl in wet DMSO at 130 °C, giving the product **5** in 85% isolated yield. After removal of the *N*-tosyl group with Na/naphthalene, an intramolecular cyclization finally furnished the target compound **4** in 50% yield.

In the first study on the [5 + 2] annulation reported by France and co-workers,[8a] they have confirmed one of the diastereomers of the 1,1,2-trisubstituted cyclobutanes from the [2 + 2] cycloaddition as an important intermediate in the reaction. Interestingly, from the reaction of **1b** with **2n** catalyzed by $ZnBr_2$ at 25 °C for 144 h, a single *cis* diastereomer *cis*-**6bn** was isolated in 16% yield along with 57% yield of **3bn**. Moreover, its *trans* isomer *trans*-**6bn**, the molecular structure of which was further confirmed by single-crystal X-ray analysis,[14] was obtained in 17% yield when *cis*-**6bn** was subjected to catalytic $ZnBr_2$ for further transformation to **3bn** (Scheme 2). Compared with the ring expansion experiment of *trans*-**6bn** catalyzed by $ZnBr_2$, the cyclobutane *cis*-**6bn** was found to be more stable and more selective in the transformation to **3bn** (Scheme 2). Thus, in our reactions with the cyclic sulfonyl enamides, the reactivity of these cyclobutane intermediates toward the final azepino[1,2-*a*]-indole products seems to be highly dependent on their stereochemistry.

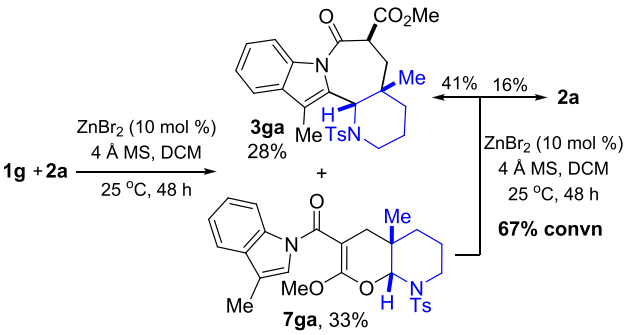
In addition to 28% yield of the desired [5 + 2] cycloadduct **3ga**, the bicyclic *N*,*O*-acetal **7ga** was isolated in 33% yield from the $ZnBr_2$-promoted reaction of the six-membered ring enamide **1g** with **2a** at 25 °C for 48 h. Surprisingly, upon further exposure to 10 mol % of $ZnBr_2$ at 25 °C for 48 h, the

Scheme 2. $ZnBr_2$-Catalyzed Formation and Ring Expansion of D−A Cyclobutane Intermediates



isolated pure compound **7ga** partially transformed to the azepino[1,2-*a*]indole product **3ga** and the original *N*-acryloyl indole **2a** in yields of 41% and 16%, respectively (Scheme 3).

Scheme 3. Isolation of a Bicyclic *N*,*O*-Acetal Intermediate

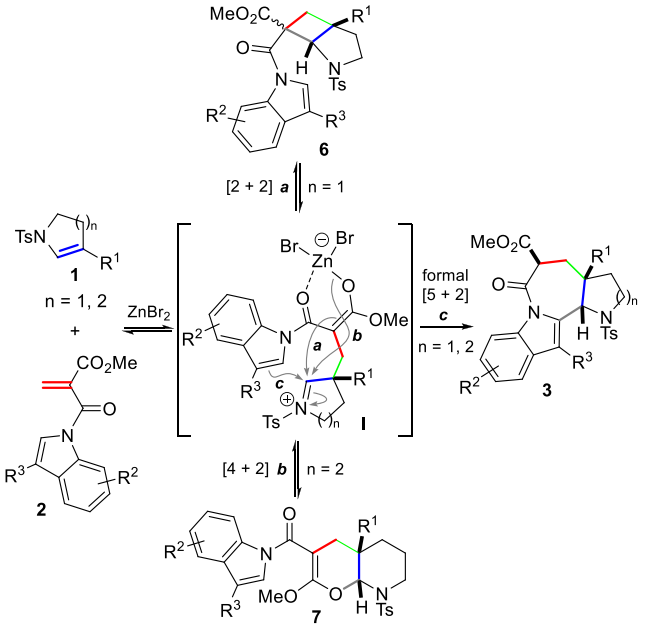


Thus, the unexpected hetero-[4 + 2] annulation product may also serve as a key intermediate for the [5 + 2] annulation, very likely depending on the ring size of the cyclic sulfonyl enamide.

Based on the above observations, a plausible mechanism via 1,4- zwitterionic intermediate **I**, which can also be regenerated from the cyclobutane (**6**) or the bicyclic *N*,*O*-acetal (**7**) intermediates that were produced, depending on the ring size of sulfonyl enamides, was proposed in Scheme 4. The facile reversibility of the $ZnBr_2$-catalyzed [2 + 2] and [4 + 2] cycloadditions between the two substrates provides a continuous supply of intermediate **I** to overcome the entropic activation barrier for the seven-membered ring formation in the [5 + 2] annulation.[15] Possibly due to the unfavored conformation, intermediate **I** with the six-membered *N*-heterocycle seems to be less reactive for the intramolecular Friedel−Crafts-type alkylation to give the product **3**. Thus, the competing formation of *N*-acryloyl indole **2a** from the [4 + 2]

https://dx.doi.org/10.1021/acs.orglett.9b04556
Org. Lett. 2020, 22, 1013−1017

Scheme 4. Proposed Mechanism for [5 + 2] Annulation



cycloadduct **7ga** was observed (Scheme 3). Accordingly, the 1,4-zwitterionic intermediates generated from larger cyclic or acyclic *N*-sulfonyl enamides may be more problematic in the seven-membered ring formation, thus giving unfruitful results.

In summary, a catalytic stereoselective [5 + 2] annulation of *N*-acryloyl indoles with cyclic sulfonyl enamides is described, providing an efficient four-step synthesis of isoeburnamonine, the key intermediate for natural product norvincamine, in 31% overall yield. The use of both the *N*-sulfonyl protecting group and the 5- or 6-membered cyclic structure of the enamides are the key for the success of this [5 + 2] annulation reaction. More interestingly, in addition to the known D−A cyclobutanes, the novel bicyclic *N,O*-acetals generated from hetero-[4 + 2] cycloaddition, depending on the ring size of the enamides, were also defined as the key intermediates for this [5 + 2] annulation reaction for the first time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04556.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1968687−1968689 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Sunewang R. Wang − *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China; Chang-Kung Chuang Institute and Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200241, China;* orcid.org/0000-0002-7099-2928; Email: rxwang@chem.ecnu.edu.cn

Yong Tang − *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China; Chang-Kung Chuang Institute, East China Normal University, Shanghai 200241, China;* orcid.org/0000-0002-5435-9938; Email: tangy@sioc.ac.cn

Authors

Song Wei − *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China*

Long Zheng − *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04556

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was sponsored by the National Natural Science Foundation of China (NSFC) (Nos. 21432011 and 21772224), the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB20000000), The Science and Technology Commission of Shanghai Municipality (No. 17JC1401200), the NSFC/RGC Joint Research Scheme (No. 21461162002) to Y.T. The authors also acknowledge Key Research Program of Frontier Sciences, CAS (No. QYZDY-SSW-SLH016), the Natural Science Foundation of Shanghai (No. 17ZR1436900) and Pujiang Program (No. 19PJ1402700) to S.R.W.

■ REFERENCES

(1) (a) Fu, N.-Y.; Chan, S.-H.; Wong, H. N. C. In *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; Wiley: Chichester, U.K., 2005; Vol. *1*, p 357. (b) Reissig, H. U.; Zimmer, R. Thrilling Strain! Donor−Acceptor-Substituted Cyclobutanes for the Synthesis of (Hetero)cyclic Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 5009. (c) De, N.; Yoo, E. J. Recent Advances in the Catalytic Cycloaddition of 1,n-Dipoles. *ACS Catal.* **2018**, *8*, 48.

(2) (a) Hu, J.-L.; Wang, L.; Xu, H.; Xie, Z.; Tang, Y. Highly Diastereoselective and Enantioselective Formal [4 + 3] Cycloaddition of Donor−Acceptor Cyclobutanes with Nitrones. *Org. Lett.* **2015**, *17*, 2680. (b) Hu, J.-L.; Zhou, L.; Wang, L.; Xie, Z.; Tang, Y. Copper Catalyzed Asymmetric [4 + 2] Annulations of D−A Cyclobutanes with Aldehydes. *Chin. J. Chem.* **2018**, *36*, 47. (c) Kuang, X.-K.; Zhu, J.; Zhou, L.; Wang, L.; Wang, S. R.; Tang, Y. Synergetic Tandem Enantiomeric Enrichment in Catalytic Asymmetric Multi-Component Reactions (AMCRs): Highly Enantioselective Construction of Tetracyclic Indolines with Four Continuous Stereocenters. *ACS Catal.* **2018**, *8*, 4991.

(3) (a) Parsons, A. T.; Johnson, J. S. Formal [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans. *J. Am. Chem. Soc.* **2009**, *131*, 14202. (b) Levens, A.; Ametovski, A.; Lupton, D. W. Enantioselective [4 + 2] Annulation of Donor−Acceptor Cyclobutanes by N-Heterocyclic Carbene Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*,

16136. (c) Garve, L. K. B.; Kreft, A.; Jones, P. G.; Werz, D. B. Synthesis of 2-Unsubstituted Pyrrolidines and Piperidines from Donor−Acceptor Cyclopropanes and Cyclobutanes: 1,3,5-Triazinanes as Surrogates for Formylimines. *J. Org. Chem.* **2017**, *82*, 9235. (d) Kreft, A.; Ehlers, S.; Jones, P. G.; Werz, D. B. Ring-Opening Reactions of Donor−Acceptor Cyclobutanes with Electron-Rich Arenes, Thiols, and Selenols. *Org. Lett.* **2019**, *21*, 6315.

(4) (a) Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. Formal [4 + 2] Cycloaddition of Alkoxy-Substituted Donor−Acceptor Cyclobutanes and Aldehydes Catalyzed by Yb(OTf)$_3$. *Org. Lett.* **2010**, *12*, 4736. (b) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. The Formal [4 + 3] Cycloaddition between Donor−Acceptor Cyclobutanes and Nitrones. *Org. Lett.* **2011**, *13*, 1528. (c) Vemula, N.; Stevens, A. C.; Schon, T. B.; Pagenkopf, B. L. The [4 + 2] Cycloaddition of Donor−Acceptor Cyclobutanes and Nitrosoarenes. *Chem. Commun.* **2014**, *50*, 1668.

(5) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.; Ishibashi, H. Regioselective Inter- and Intramolecular Formal [4 + 2] Cycloaddition of Cyclobutanones with Indoles and Total Synthesis of (±)-Aspidospermidine. *Angew. Chem., Int. Ed.* **2013**, *52*, 906.

(6) Zhu, J.; Cheng, Y.-J.; Kuang, X.-K.; Wang, L.; Zheng, Z.-B.; Tang, Y. Highly Efficient Formal [2 + 2 + 2] Strategy for the Rapid Construction of Polycyclic Spiroindolines: A Concise Synthesis of 11-Demethoxy-16-epi-myrtoidine. *Angew. Chem., Int. Ed.* **2016**, *55*, 9224.

(7) Feng, L.-W.; Ren, H.; Xiong, H.; Wang, P.; Wang, L.; Tang, Y. Reaction of Donor-Acceptor Cyclobutanes with Indoles: A General Protocol for the Formal Total Synthesis of (±)-Strychnine and the Total Synthesis of (±)-Akuammicine. *Angew. Chem., Int. Ed.* **2017**, *56*, 3055.

(8) (a) Shenje, R.; Martin, M. C.; France, S. A Catalytic Diastereoselective Formal [5 + 2] Cycloaddition Approach to Azepino[1,2-a]indoles: Putative Donor−Acceptor Cyclobutanes as Reactive Intermediates. *Angew. Chem., Int. Ed.* **2014**, *53*, 13907. (b) Parker, A. N.; Martin, M. C.; Shenje, R.; France, S. Calcium-Catalyzed Formal [5 + 2] Cycloadditions of Alkylidene β-Ketoesters with Olefins: Chemodivergent Synthesis of Highly Functionalized Cyclohepta[b]indole Derivatives. *Org. Lett.* **2019**, *21*, 7268.

(9) For a recent review on [5 + 2] cycloadditions and their synthetic application, see: Gao, K.; Zhang, Y.-G.; Wang, Z.; Ding, H. Recent Development on the [5 + 2] Cycloadditions and Their Application in Natural Product Synthesis. *Chem. Commun.* **2019**, *55*, 1859.

(10) (a) Liu, Q.-J.; Wang, L.; Kang, Q.-K.; Zhang, X. P.; Tang, Y. Cy-SaBOX/Copper(II)-Catalyzed Highly Diastereo- and Enantioselective Synthesis of Bicyclic N,O Acetals. *Angew. Chem., Int. Ed.* **2016**, *55*, 9220. (b) Wei, S.; Yin, L.; Wang, S. R.; Tang, Y. Catalyst-Controlled Chemoselective All-Alkene [2 + 2 + 2] and [2 + 2] Cyclizations of Enamides with Electron-Deficient Alkenes. *Org. Lett.* **2019**, *21*, 1458.

(11) For examples on cyclizations with sulfonyl enamides, see: (a) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. Enamide-Benzyne-[2 + 2] Cycloaddition: Stereoselective Tandem [2 + 2]-Pericyclic Ring-Opening-Intramolecular N-Tethered [4 + 2] Cycloadditions. *Org. Lett.* **2009**, *11*, 3666. (b) Gigant, N.; Gillaizeau, I. Construction of Nitrogen-Fused Tetrahydroquinolines via a Domino Reaction. *Org. Lett.* **2012**, *14*, 4622. (c) Dohi, T.; Toyoda, Y.; Nakae, T.; Koseki, D.; Kubo, H.; Kamitanaka, T.; Kita, Y. Phenol and Aniline Oxidative Coupling with Alkenes by Using Hypervalent Iodine Dimer for the Rapid Access to Dihydrobenzofurans and Indolines. *Heterocycles* **2015**, *90*, 631. (d) Zhou, L.; Yu, S.-Y.; Tang, Y.; Wang, L. Facile Stereoselective Approach to Diverse Spiroheterocyclic Tetrahydropyrans: Concise Synthesis of (+)-Broussonetine G and H. *Angew. Chem., Int. Ed.* **2019**, *58*, 15016.

(12) One epimer of eburnamonine has been previously named as "isoeburnamine" as well. See: Novák, L.; Rohál, J.; Szántay, C.; Czibula, L. Synthesis of Vinca Alkaloids and Related Compounds. VI. Synthesis of Eburanamonine and Isoburnamonine. *Heterocycles* **1977**, *6*, 1149.

(13) (a) Takayama, H.; Winterfeldt, E. Reactions with Indole Derivatives, XLIX. The Stereoselective Total Synthesis of D-Norvincamine. *Heterocycles* **1984**, *22*, 1565. (b) Bölsing, E.; Winterfeldt, E. Reactions of Indole Derivatives. XLVI. Stereoselective Route to Isoeburnamonine. *Chem. Ber.* **1981**, *114*, 1932.

(14) Experimental procedures and characterization data are provided in the Supporting Information.

(15) Byrne, L. A.; Gilheany, D. G. Simple Syntheses of Seven-Membered Rings via an Entropy/Strain Reduction Strategy. *Synlett* **2004**, 933.

https://dx.doi.org/10.1021/acs.orglett.9b04556
Org. Lett. 2020, 22, 1013−1017