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Organocatalytic Regiodivergent Ring Expansion of Cyclobutanones for the Enantioselective Synthesis of Azepino[1,2-*a*]indoles and Cyclohepta[*b*]indoles

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01406 Read Online

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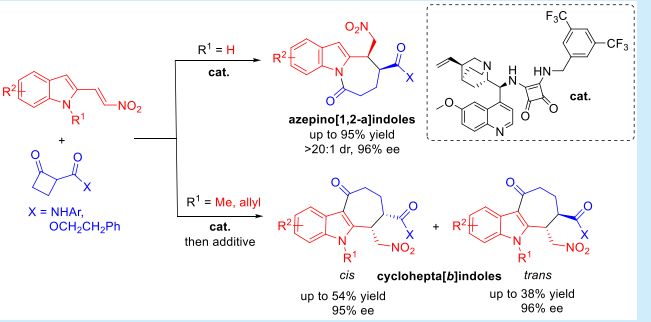
ABSTRACT: A regiodivergent organocatalytic enantioselective Michael addition/three-atom ring expansion sequence of electron-withdrawing group activated cyclobutanones with 2-nitrovinylindoles was developed. A series of azepino[1,2-*a*]indoles were obtained with exclusive regioselectivities and high diastereo- and enantioselectivities (up to >20:1 dr, 96% ee) with the application of the N1 nucleophilic site of the indole nucleus. Meanwhile, various cyclohepta[*b*]indoles could be accessed with high enantiopurity (up to 96% ee) through the Michael addition/boron-trifluoride-etherate-promoted indole C3-attack ring expansion process.



Chiral polycyclic indoles have found broad applications in medicines, pesticides, and other functional molecules.[1] Among them, azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles, containing two privileged structures, indole and a seven-membered ring, widely exist in many indole alkaloids and endow a broad spectrum of biological activities (Figure 1).[2]

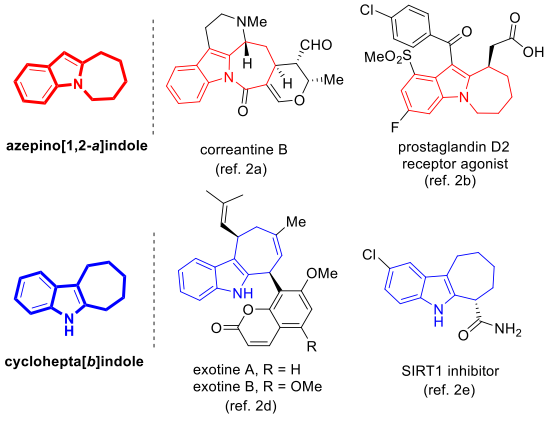


Figure 1. Representative natural products and bioactive molecules containing azepino[1,2-*a*]indoles and cyclohepta[*b*] indoles.

Despite the fact that several typical catalytic enantioselective approaches have been reported, including enantioselective sequential reactions,[3] (4 + 3) annulations,[4] and the intermolecular Rauhut–Currier reaction,[5] all of these only focus on constructing just one of the target products (azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles). The enantioselective divergent synthesis of both azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles on the strength of the same strategy remains unexplored and is highly desired.

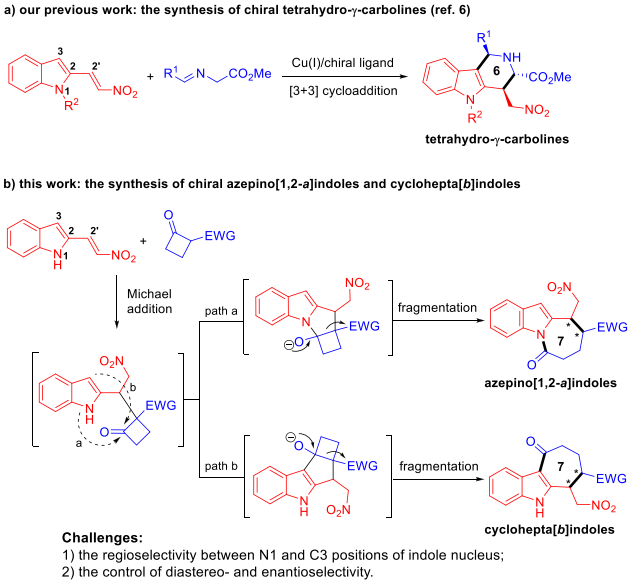
Recently, our group demonstrated 2-nitrovinylindoles as a three-atom 3C partner in copper-catalyzed asymmetric (3 + 3) annulations with azomethine ylides, which constructed tetrahydro-γ-carboline skeletons with high diastereo- and enantioselectivities (Scheme 1a).[6] 2-Nitrovinylindoles were also identified as a nitrogen–carbon–carbon (NCC) synthon in the enantioselective (3 + 2) annulations for the synthesis of chiral pyrrolo[1,2-*a*]indoles.[7] Considering the high value of azepino[1,2-*a*]indole and cyclohepta[*b*]indole in medicinal chemistry and drug discovery, we would like to develop a straightforward procedure for the divergent synthesis of enantiomerically pure azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles by using the N1 or C3 nucleophilicity and C2′ electrophilicity of 2-nitrovinylindoles. The challenges inherent in such a strategy mainly include (1) the discovery of a suitable four-atom building block, (2) the regioselectivity of the N1 and C3 positions of the indole nucleus, and (3) the control of diastereo- and enantioselectivity.

In this context, cyclobutanones attracted our attention because this class of reactants could undergo ring expansion via a carbon–carbon bond cleavage process.[8,9] However, the

Received: April 23, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01406
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Synthesis of Polycyclic Indoles via the Catalytic Enantioselective Reactions of 2-Nitrovinylindoles



enantioselective ring expansion of cyclobutanone derivatives remains a challenging task in organic synthesis. Until recently, Rodriguez, Coquerel, and coworkers reported an enantioselective Michael addition/ring expansion cascade reaction of amide activated cyclobutanones and *ortho*-amino nitrostyrenes using bifunctional aminocatalysts,[10] furnishing benzazocinone products with high enantioselectivities and good to high diastereoselectivities. Inspired by this elegant work, we envisaged that chiral azepino[1,2-*a*]indoles and cyclohepta[*b*]-indoles could be simultaneously formed via an enantioselective Michael addition/ring expansion cascade reaction of cyclobutanones and 2-nitrovinylindoles (Scheme 1b). In this process, two nucleophilic sites (N1 and C3 of indole) could add to the carbonyl group after the Michael addition step, which would deliver azepino[1,2-*a*]indoles and cyclohepta[*b*]-indoles, respectively, via a spontaneous fragmentation. Herein we report our results from this study.

To test this hypothesis, we began our study by evaluating the reaction between 2-nitrovinylindoles **1a** and 2-amide-substituted cyclobutanone **2a** with Takemoto's catalyst **C1**[11a] (Figure 2) in CH_2Cl_2 at ambient temperature (Table 1). Pleasingly, the desired reaction proceeded smoothly, and azepino[1,2-*a*]indole product **3a** was isolated in 63% yield, albeit with only 21% ee (entry 1). With this initial result in hand, a series of chiral thiourea/squaramide aminocatalysts were then screened (entries 2−9).[11] To our delight, catalyst **C8**[12] combining the 9-amino-quinine moiety with a *N*-benzylsquaramide hydrogen-bond donor delivered the best result (entry 8), and compound **3a** was gained in excellent yield (95%) with excellent diastereo- and enantioselectivity (>20:1 dr, 96% ee). Next, the solvent effect in this reaction was evaluated (see Table S1), and the chlorinated solvents provided better results, with dichloromethane as the best choice. When the catalyst loading was reduced to 5 mol %, the reaction was incomplete, even after stirring for 4 days, and product **3a** was acquired in 63% yield with 94% ee (entry 10). We note that the cyclohepta[*b*]indole product was not detected in any case.

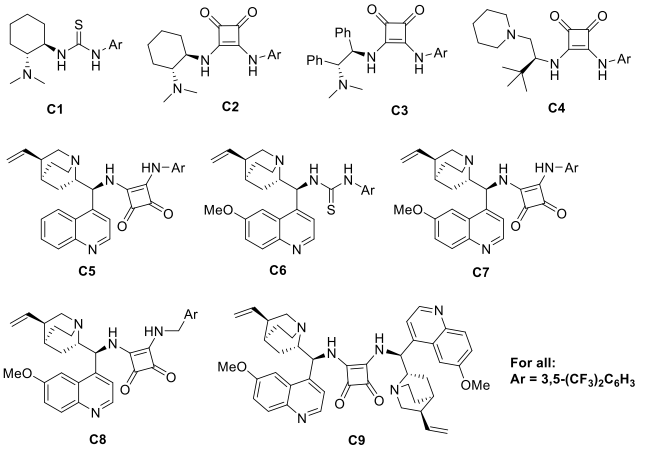


Figure 2. Bifunctional catalysts investigated in this reaction.

After optimization of the reaction conditions, the substrate scope for this diastereo- and enantioselective cascade reaction was delved. As listed in Scheme 2, a wide spectrum of cyclobutanones **2a−j** bearing different *N*-aryl secondary amide activating groups all proceeded smoothly, delivering the corresponding azepino[1,2-*a*]indole products **3a−j** in high yields (71−95%) along with high diastereo- and enantioselectivities (>20:1 dr, 88−96% ee). Noticeably, a slightly decreased enantioselectivity was observed when using the *β*-ketoamides **3g−j** with electron-donating and neutral aryl groups. This phenomenon could be attributed to the relatively low acidity of the secondary amide N−H proton,[13] which exhibited an adverse effect on the first Michael step. Significantly, the carboxylic-ester-activated cyclobutanone was also compatible under this transformation, affording product **3k** in high yield (90%) with an excellent level of diastereo- and enantioselectivity (>20:1 dr, 98% ee). It should be noted that this type of cyclobutanone was not presented in the previous report.[10]

Then, we probed the reaction scope concerning the variation of substitutions of 2-nitrovinylindoles **1** (Scheme 3). The substituent on the C3 position of the indole ring showed an adverse effect on the diastereoselectivity control, and product **3l** was attained in high yield (88%) with high enantioselectivity (92/85% ee) and moderate diastereoselectivity (6:1 dr). Methyl, methoxy, fluoro, chloro, and bromo substituents at the C5 or C6 position of the indole ring of 2-nitrovinylindoles **2** were all compatible in this cascade reaction, furnishing azepino[1,2-*a*]indoles **3m−s** in good to high yields (61−90%) with excellent diastereo- and enantioselectivities (93−96% ee, >20:1 dr). In addition, the cascade reaction with 2-nitrovinylpyrrole still proceeded smoothly, providing pyrrolo[1,2-*a*]azepine **3t** in 46% yield as a single diastereomer but with modest enantioselectivity (42% ee).

The absolute configuration of **3m** was determined to be (9*S*, 10*R*) by single-crystal X-ray diffraction analysis. In accordance with the stereochemical outcome and previous reports,[10,14] a plausible reaction pathway is depicted in Scheme 4. With the dual activation of chiral bifunctional squaramide−tertiary amine catalyst **C8**, the 2-carbamoyl cyclobutanones **2** are enolized by the tertiary amine moiety. Meanwhile, the two squaramide N−H bonds of catalyst activate the nitro group of 2-nitrovinylindole **1a** through a hydrogen-bonding interaction. The enolized cyclobutanones (*Re*-face) then add to the double bond (*Re*-face) of **1a** to favorably give intermediate **A**, which

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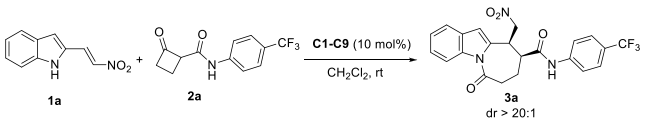
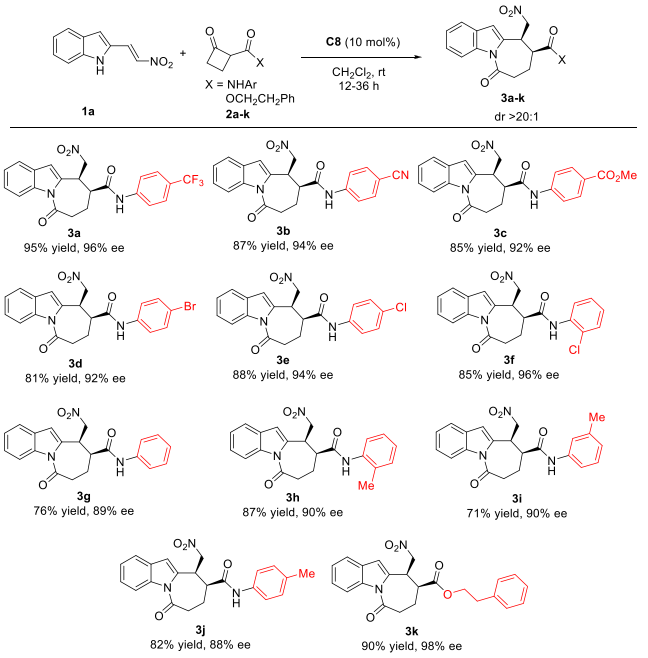
Table 1. Organocatalysts Screening[a]



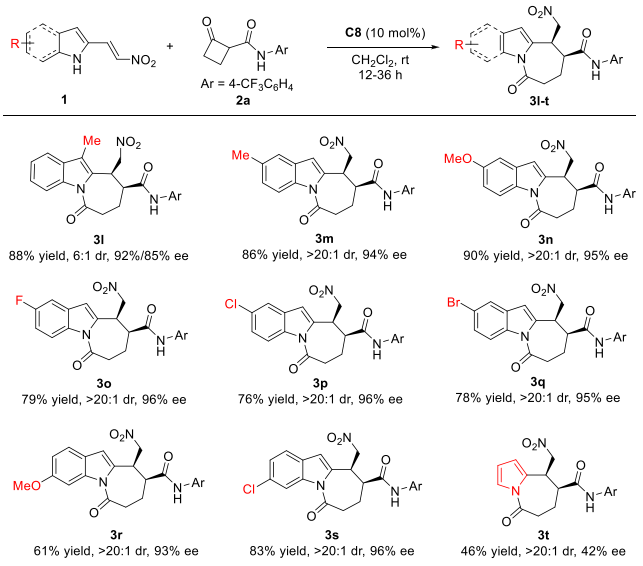
entry	catalyst	yield (%)[b]	ee (%)[c]	time (h)
1	**C1**	63	−21	12
2	**C2**	93	−58	12
3	**C3**	48	−82	36
4	**C4**	24	31	36
5	**C5**	66	83	36
6	**C6**	74	67	12
7	**C7**	54	83	36
8	**C8**	95	96	12
9	**C9**	95	77	12
10[d]	**C8**	63	94	4 d

[a]Unless others stated, reactions were carried out with **1a** (0.20 mmol), **2a** (0.22 mmol), and 10 mol % of catalyst in 2.0 mL of CH_2Cl_2 at room temperature. [b]Isolated yield after column chromatography. [c]Determined by chiral HPLC analysis; >20:1 dr was determined by ^1H NMR of the crude product. [d]Carried out with 5 mol % of **C8**.

Scheme 2. Substrate Scope of Cyclobutanones 2



Scheme 3. Substrate Scope of 2-Nitrovinylindoles 1



should be the crucial step for the enantioselectivity control. The subsequent cyclization/fragmentation affords intermediate **C**, and the protonation of amide enolate **C** would proceed through thermodynamic control, furnishing products **3** with a favorable cis configuration. Notably, this hypothesis for the diastereoselectivity control is verified by the increased diastereoselectivity after the cyclization/fragmentation/protonation step of the Michael adduct (6:1 vs >20:1 dr; see Scheme S1).

Subsequently, we would like to amplify the role of 2-nitrovinylindoles **1** as 3C building blocks in the Michael addition/ring expansion cascade process with the aim of constructing cyclohepta[*b*]indoles. Interestingly, the cascade process could be interrupted after the Michael addition step when the reaction temperature was lowered to −40 °C, and various additives were tested to promote the cyclization. Unfortunately, azepino[1,2-*a*]indole product **3a**, instead of cyclohepta[*b*]indole product **4a**, was observed in all cases. (See Scheme S1.) To solve this problem, *N*-methyl-substituted 2-nitrovinylindole **5a** was used in the reaction. The strong Lewis acid $BF_3{\cdot}Et_2O$ was directly added to the reaction mixture to promote the cyclization/fragmentation process after the Michael addition was completed (Scheme 5), and the two diastereoisomers *cis*-**6a** and *trans*-**6a** of cyclohepta[*b*]indole product were, respectively, obtained with high enantioselectivities (93% ee and 91% ee). Additionally, various substituent groups on cyclobutanones and *N*-substituted 2-nitrovinylindoles were well-tolerated in the reaction under the optimal conditions, and the corresponding cyclohepta[*b*]indole products **6b−g** were provided in good yields with high enantioselectivities (91−96% ee), albeit with modest diastereoselectivities. Furthermore, cyclohepta[*b*] pyrrole derivative **6h** was afforded in good yield with good enantioselectivities (82% ee and 85% ee) by using *N*-methyl 2-nitrovinylpyrrole. It should be noted that two diastereoisomers of cyclohepta[*b*]-

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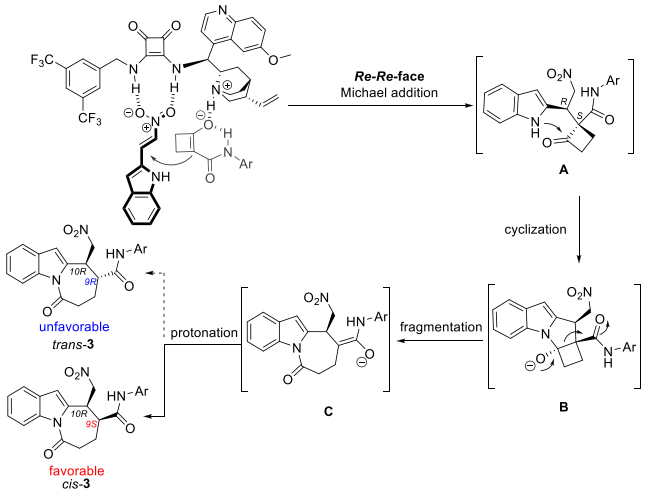
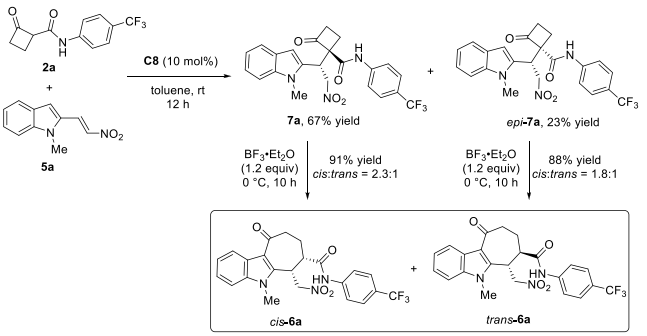
Scheme 4. Proposed Reaction Pathway for the Cascade Reaction



Scheme 6. Result of Cyclization/Fragmentation of Michael Adduct Intermediate

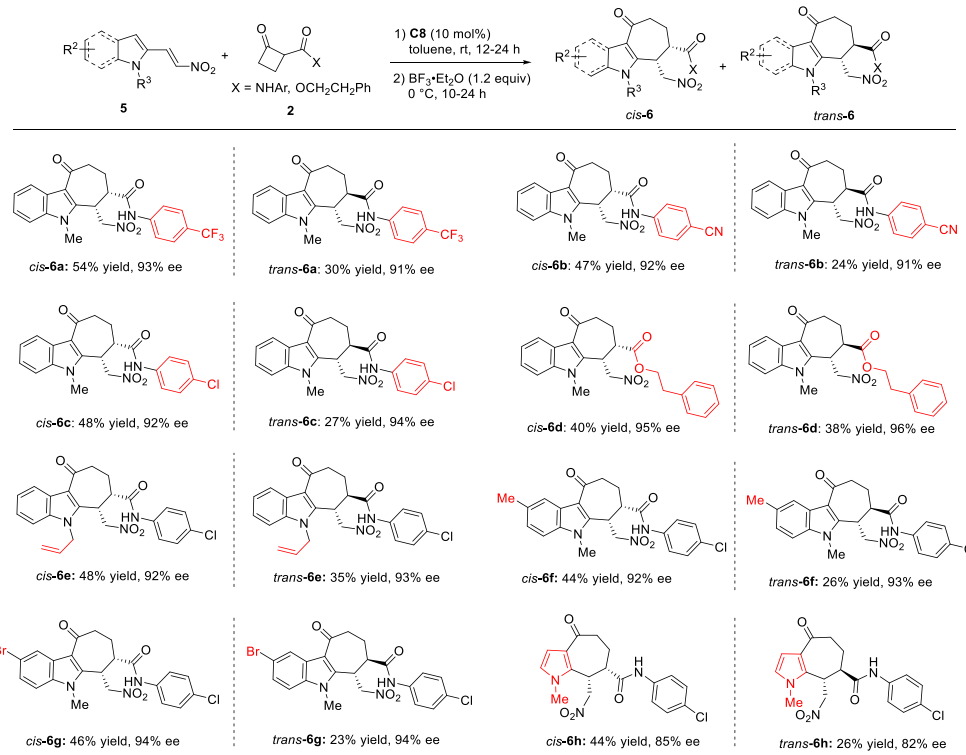


indoles in all cases could be easily separated by column chromatography.

For the purpose of confirming the stereochemical determined step in this reaction, both diastereoisomers of Michael adduct intermediate **7a** were isolated and used for the next cyclization (Scheme 6), and the mixture of products *cis*-**6a** and *trans*-**6a** was generated with similar diastereoselectivities (2.3:1 dr vs 1.8:1 dr) as **7a** or *epi*-**7a**. Therefore, by analogy to the previous case (Scheme 4), the origin of the diastereoselectivity should be derived from the protonation step of the corresponding amide enolate, and the enantioselectivity was determined by the Michael addition step. The absolute configuration of *trans*-**6g** was assigned as (6*R*, 7*R*) by single-crystal X-ray diffraction analysis, and the absolute configuration of *cis*-**6** was reasoned to be (6*R*, 7*S*).

To further evaluate the synthetic utility of the current methodology (Scheme 7), the gram-scale synthesis of azepino[1,2-*a*]indole product **3a** was achieved while maintaining the efficiency and the stereochemical outcome (90% yield, >20:1 dr, 95% ee). Furthermore, several synthetic transformations were explored. The nitro group of **3a** could be reduced in the presence of sodium borohydride/nickel(II) chloride hexahydrate without the loss of stereochemical integrity. The structurally novel tetracyclic indole compound **9** with 99% ee value could be facilely accessed via the reduction/intramolecular aminolysis of product *cis*-**6d**. Meanwhile, the reduction/intramolecular aminolysis of product **3k** afforded 2-indolyl azepine derivative **10** with excellent enantioselectivity (97% ee). We note that this class of 2-aryl

Scheme 5. Enantioselective Synthesis of Cyclohepta[*b*]indoles via the One-Pot Sequence of *N*-Substituted 2-Nitrovinylindoles 5 and Cyclobutanones 2



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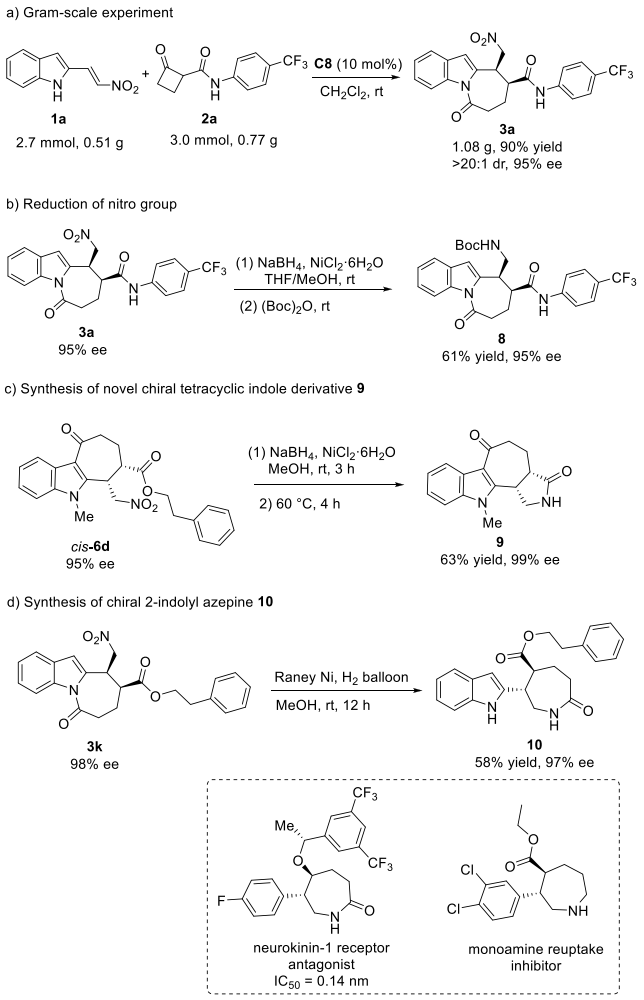
Scheme 7. Demonstration of Synthetic Utility



azepine compound exhibits critical biological activities in medicinal chemistry, such as neurokinin-1 receptor antagonistic activity and monoamine reuptake inhibitory activity.[15]

In summary, we have demonstrated a regiodivergent enantioselective sequential Michael addition/three-atom ring expansion reaction of cyclobutanone derivatives with 2-nitrovinylindoles by controlling the regioselectivity of the N1 and C3 sites of the indole nucleus in the presence of chiral bifunctional aminocatalysts. This protocol provides straightforward access to various enantiomerically pure azepino[1,2-*a*]indoles and cyclohepta[*b*]indoles with high efficiency. The salient features of the reaction include mild reaction conditions, broad substrate scopes, easy scalability, and versatile transformations of the products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01406.

Experimental details, characterization of new compounds **2**, **3**, and **6**, crystallographic data of **3m** and *trans*-**6g**, and NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1943765 and 1970016 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the National Natural Science Foundation of China (nos. 21572053 and 21772038) and the China Postdoctoral Science Foundation (nos. 2018M632037 and 2019T120310). We greatly appreciate the Research Center of Analysis and Test of East China University of Science and Technology for the assistance with the MS and NMR analysis.

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