OL Organic Letters

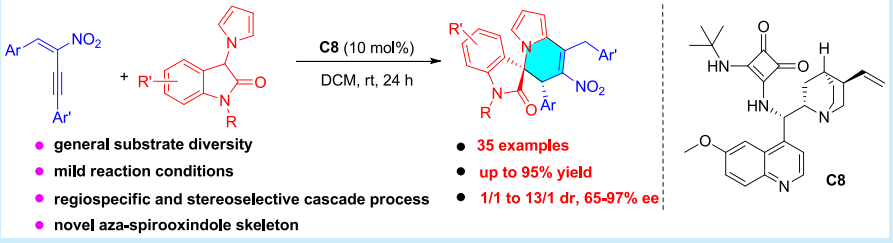
pubs.acs.org/OrgLett Letter

Organocatalytic Asymmetric Synthesis of Aza-Spirooxindoles via Michael/Friedel–Crafts Cascade Reaction of 1,3-Nitroenynes and 3-Pyrrolyloxindoles

Qijian Ni,* Xuyang Wang, Da Zeng, Qianling Wu, and Xiaoxiao Song*

Cite This: *Org. Lett.* 2021, 23, 2273–2278 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: An asymmetric [3+3] cyclization of nitroenynes and 3-pyrrolyloxindoles has been realized with a chiral bifunctional squaramide catalyst. This Michael/Friedel–Crafts cascade strategy provides a facile and efficient access to enantioenriched polycyclic aza-spirooxindoles with 32–95% isolated yields and excellent stereocontrol under mild reaction conditions.

The aza-spirooxindole unit has been one of the most common structural scaffolds in numerous bioactive natural products (Figure 1).[1] For example, (−)-vincatine represents one type of *Aspidosperma* alkaloid.[2] SOID-8 could inhibit melanoma cell proliferation and induce apoptosis of melanoma cells.[3] Cipargamin, which is now under Phase II clinic trials, has proven to be a new class of potent, fast-acting, and dose-dependent antimalarial drug candidate.[4] Compound **IV** has demonstrated potent capability in inhibiting MDM2–p53 interaction.[5] Accordingly, considerable efforts have recently been devoted to the stereoselective construction of functionalized aza-spirooxindole scaffolds in the past decades,[6] especially focused on the asymmetric and highly efficient access to spiropyrrolidine oxindoles through formal [3+2] cyclizations.[7] However, the development of the asymmetric methodology for the construction of spiropiperidinyl oxindole received less attention, which is in stark contrast to its prevalence in natural products and pharmaceuticals.[8] On the contrary, the 3-pyrrolyloxindoles, as efficient Michael donors, are useful synthetic building blocks for the preparation of diverse 3,3′-disubstituted oxindoles under organocatalysis.[9] Moreover, the pyrrole moiety bearing an oxindole at the C3 position enabled Friedel–Crafts reaction with diverse electrophiles, thus providing an attractive and straightforward strategy

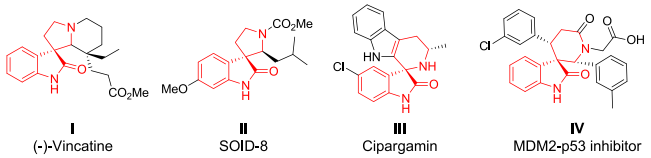
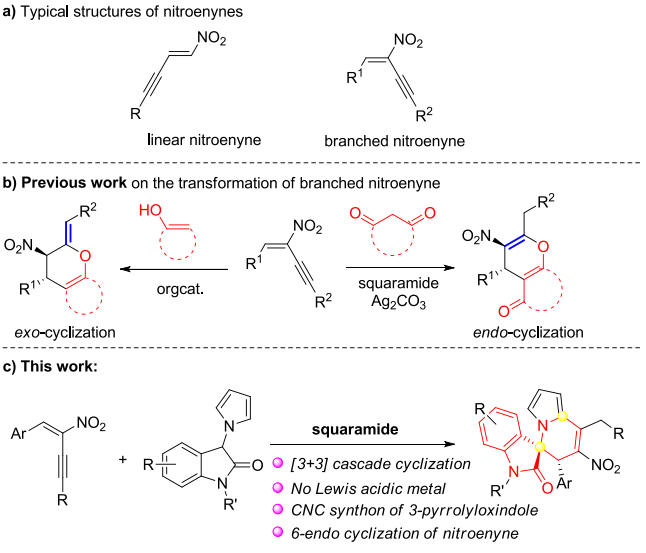


Figure 1. Examples of aza-spirooxindoles in bioactive compounds.

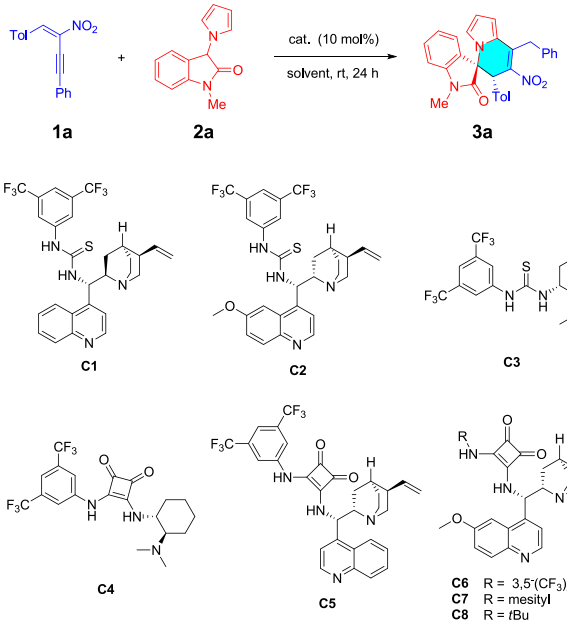
Scheme 1. Synthetic Strategies for Nitroenynes



Received: February 3, 2021
Published: March 3, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00409
Org. Lett. 2021, 23, 2273–2278

Table 1. Reaction Optimization[a]



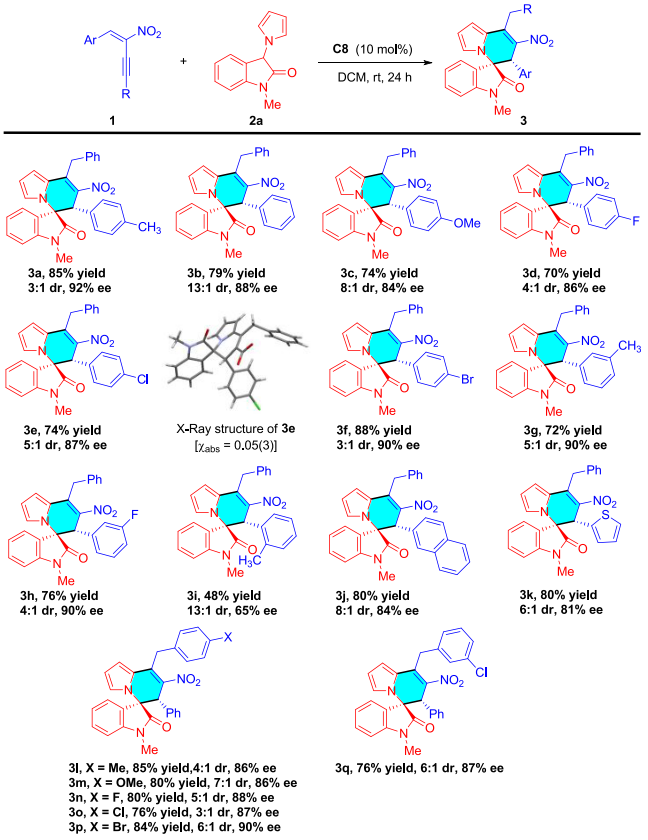
entry	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**C1**	DCM	92	1.7:1	12
2	**C2**	DCM	63	2.5:1	18
3	**C3**	DCM	97	1.7:1	0
4	**C4**	DCM	87	3.8:1	75
5	**C5**	DCM	97	2.6:1	81
6	**C6**	DCM	98	1.9:1	84
7	**C6**	DCE	98	2.0:1	79
8	**C6**	TBME	87	2.5:1	82
9	**C6**	toluene	88	2.4:1	83
10	**C6**	$CHCl_3$	95	2.4:1	82
11	**C6**	THF	98	1.5:1	79
12	**C6**	$PhCF_3$	90	2.0:1	80
13	**C6**	CCl_4	98	2.0:1	80
14	**C6**	PhCl	88	2.1:1	81
15[e]	**C6**	DCM	90	2.0:1	74
16[f]	**C6**	DCM	95	2.4:1	81
17	**C7**	DCM	42	3.2:1	54
18	**C8**	DCM	85	3.0:1	92

[a]General conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (1.2 equiv), catalyst (10 mol %) in 1 mL of solvent, 24 h, rt. [b]Isolated yields. [c]Determined on the basis of the masses of the isolated diastereomers. [d]Determined by HPLC. [e]With 10 mol % Ag_2O. [f]At 0 °C for 72 h.

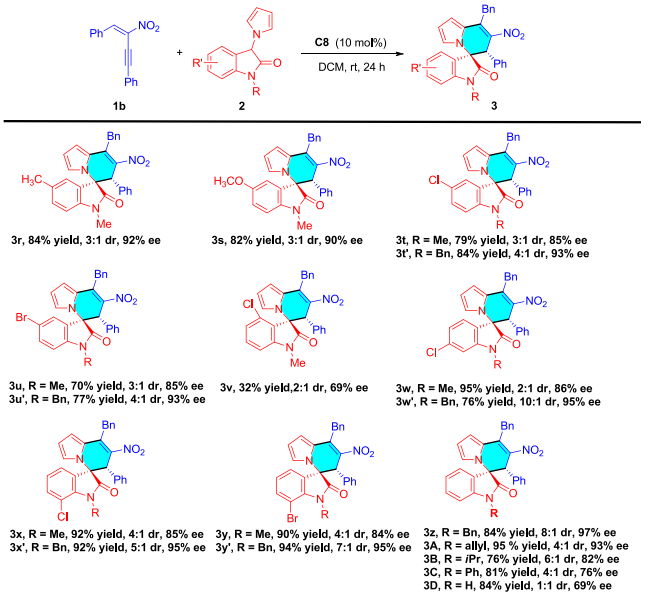
for the construction of chiral spiropiperidinyl oxindoles through asymmetric [3+3] cyclization. To the best of our knowledge, very few studies involved this intriguing compound as a CNC three-atom synthon in asymmetric [3+*n*] cyclization reactions.[10]

Electron-poor 1,3-enynes have been investigated as a valuable synthon for building highly functionalized skeletons. Among them, 1,3-enynes with a strong electron-poor nitro group at the C1 (linear) position have widely served as Michael acceptors to produce heterocyclic compounds in a combination of organo and metal catalysts (Scheme 1a).[11] In contrast, another type of nitroenyne bearing a nitro group at the C3 (branched) position, which also possessed two electrophilic sites as an ideal 3C atom synthon, gained limited attention for the preparation of diverse heterocycles.[12] Recently, several elegant asymmetric approaches involving

Scheme 2. Scope of Substrate Nitroenynes



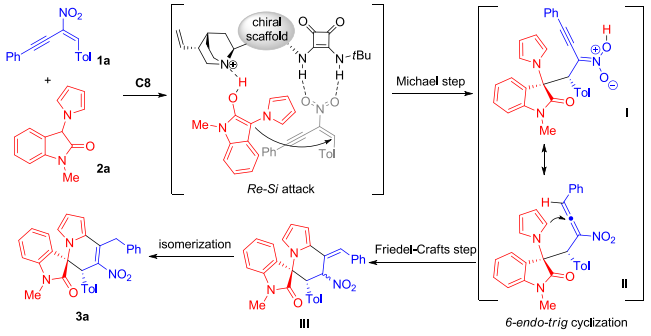
Scheme 3. Scope of Substrate 3-Pyrrolyl-oxindoles



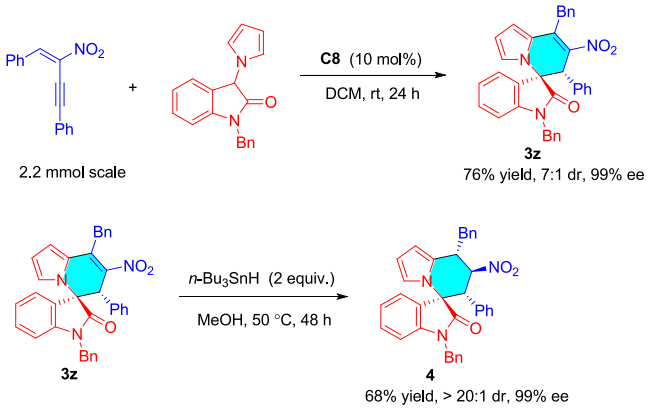
the domino Michael/6-*exo*-*dig* cyclization reactions of branched nitroenynes with a variety of bisnucleophiles have been successfully realized by using organocatalysts (Scheme 1b, left).[13] Notably, Shi and co-workers developed an enantioselective tandem Michael/6-*endo*-*trig* cyclization of branched nitroenynes with 1,3-cyclodiones under organo and silver metal catalysis (Scheme 1b, right).[14] Motivated by the broad applicability of spiropiperidinyl oxindole scaffolds and the potential of organocatalytic transformation of nitroenyne,

https://dx.doi.org/10.1021/acs.orglett.1c00409
Org. Lett. 2021, 23, 2273−2278

Scheme 4. Proposed Reaction Mechanism



Scheme 5. Scale-Up and Further Transformations



we envisoned that the branched nitroenynes could also be employed as biselectrophiles to trigger the asymmetric cascade cyclization with 3-pyrrolyloxindoles in the presence of bifunctional organocatalysts to produce the spiropiperidinyl oxindole derivatives (Scheme 1c). The challenge of this design arises from the control of the regioselective and stereoselective Michael/Friedel−Crafts cascade process, especially the endo-cyclization without the addition of Lewis acidic metal.

To test the feasibility of our reaction design, we probed a model reaction between branched nitroenyne **1a** and 3-pyrrolyloxindole **2a** under a bifunctional organocatalyst in DCM. As shown in Table 1, with thioureas **C1**−**C3** as the catalysts, the reactions gave the desired aza-spirooxindole **3a** in 63−97% yields and acceptable dr with poor enantioselectivity at ambient temperature (Table 1, entries 1−3, respectively). The screening of other chiral bifunctional organocatalysts (**C4**−**C6**) was then carried out. To our delight, bifunctional squaramide **C6** was shown to be an effective catalyst, delivering spiropiperidinyl oxindole **3a** in 98% yield with 84% ee and 1.9:1 dr (entry 7). The subsequent solvent screening and the addition of Ag_2O as an additive did not improve the stereoselectivity, albeit with comparable reactivity (entries 8−15). Decreasing the reaction temperature to 0 °C had no effect on the enantioselectivity. Finally, we focused our attention to varying the type of sterically hindering groups on the squaramide moiety. Gratifyingly, quinine-derived squaramide **C8** (entry 18), bearing a *tert*-butyl N substituent, resulted in the best outcome, producing the desired **3a** in a good yield of 85% with 3:1 dr and 92% ee.

With the optimized conditions in hand, the scope of various branched nitroenynes (**1**) for the cyclization with **2a** was first examined (Scheme 2). The reactions of branched nitroenyne bearing a *para* or *meta* substituent on the aryl group afforded **3b**−**3h** in high yields with 84−92% ee and 3:1 to 13:1 dr. The substituent at the *ortho* position furnished **3i** in a moderate yield of 48% with 13:1 dr and 65% ee, possibly due to steric hindrance upon a Michael step. The 2-naphthyl or furyl group instead of an aryl ring was also compatible with this methodology to produce **3j** and **3k** in 80% yield with high stereocontrol. Moreover, this protocol could also be applied to various substituents at the alkyne tether, affording **3l**−**3q** in 76−85% yields with 86−90% ee and 3:1 to 7:1 dr. In addition, the absolute configuration of the resulting **3** was determined by the X-ray analysis of **3e**.[15]

We then turned our attention to the scope of substituted 3-pyrrolyloxindoles **2**. As shown in Scheme 3, this catalytic strategy was compatible with several substituents on the aromatic ring of oxindole. The electronic properties of the substituents at the C5 position of oxindole rings showed a weaker effect on this transformation, and either electron-rich groups (CH_3 and OCH_3) or electron-poor groups (Cl and Br) gave the target cycloadducts **3r**−**3u** with good yields (70−84%), diastereoselectivity (3:1), and high enantioselectivities (85−92% ee). Similarly, good results were obtained with the substituent at the C6 or C7 position of oxindoles (**3w** and **3y**). We also tested the substituent at the C4 position, which decreased the reactivity (**3v**) and enantioselectivity because of the steric hindrance. Interestingly, a switch of the N substituent from methyl to benzyl led to a positive effect on the stereoselectivity and afforded product **3z** in 84% yield, 8:1 dr, and 97% ee (vs **3b**). Extensive study indicated that the *N*-benzyl-substituted 3-pyrrolyloxindoles could deliver the corresponding products with better stereocontrol (**3t** vs **3t′**, **3u** vs **3u′**, and **3w**−**3y** vs **3w′**−**3y′**). Further study of the N protection indicated that the *N*-allyl substituent also afforded **3A** with a comparable result. Variation of the N substituent with *i*-Pr, phenyl, or H could also give the corresponding products **3B**−**3D** in good yield and enantioselectivity. However, N protection with electron-poor groups, such as Boc or Cbz, failed to afford the desired products.

A plausible catalytic reaction model for this cascade cyclization was proposed. As illustrated in Scheme 4, the reaction was initiated from the deprotonation of 3-pyrrolyloxindole **2a** by the quinuclidine nitrogen of **C8**, which resulted in formal indol-2-ol. Meanwhile 3-nitroenyne **1a** was activated by double H-bonding between the squaramide moiety and the nitro group of **1a**. The formal indol-2-ol then underwent a Michael addition from the *Re*-face. The nitroenyne approaches with its *Si*-face because of the bulky *N*-*tert*-butyl group on **C8**. Presumably, the *N*-benzyl group of **2** shielded the *Si*-face attack to afford better enantioselectivity. The subsequent proton transfer of intermediate **I** resulted in allenyl **II** as its resonance form. After that, the pyrrolyl moiety of **2a** was added to nitroallene **II** in a 6-*endo*-*trig* intramolecular Friedel−Crafts cyclization. The further isomerization of **III** gave rise to the target aza-spirooxindole **3a**.

To demonstrate the practicability of the cascade cyclization, a scale-up synthesis of **3** was conducted on a 2.2 mmol scale, giving the desired **3z** in 76% yield with maintained dr and ee values. Additionally, the treatment of **3z** with *n*-Bu_3SnH selectively reduced the C=C bond and afforded product **4** in 68% yield with excellent stereoselectivity. The absolute stereochemistry of **4** at the two new chiral centers was confirmed by NOESY analysis (Scheme 5).

https://dx.doi.org/10.1021/acs.orglett.1c00409
Org. Lett. 2021, 23, 2273−2278

In summary, we have developed a facile and practical asymmetric cascade Michael/Friedel−Crafts reaction between branched nitroenynes and 3-pyrrolyloxindoles using a quinine-derived squaramide organocatalyst. It demonstrated an alternative utility of nitroenyne in 6-*endo*-*trig* cyclization and provided a straightforward access to various structurally spiropiperidinyl oxindole in good to high yields and enantioselectivities. This novel approach features mild reaction conditions, is metal-free, and features excellent functional group compatibility. Further studies of the enantioselective transformation of nitroenyne are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00409.

General procedures, product characterization, copies of NMR spectra, and HPLC chromatograms (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a**−**3z**, **3A**−**3D**, and **4** (ZIP)

Accession Codes

CCDC 2034090 contains 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

Qijian Ni − *Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, Anhui, P. R. China*; orcid.org/0000-0002-3135-1271; Email: qijianni@ahnu.edu.cn

Xiaoxiao Song − *Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, Anhui, P. R. China*; Email: xsong@ahnu.edu.cn

Authors

Xuyang Wang − *Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, Anhui, P. R. China*

Da Zeng − *Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, Anhui, P. R. China*

Qianling Wu − *Key Laboratory of Functionalized Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecule-Based Materials (State Key Laboratory Cultivation Base), College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, Anhui, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00409

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for the financial support from the National Natural Science Foundation of China (22001010), the Anhui Provincial Natural Science Foundation (1908085QB55), and the Scientific Research Foundation of the Higher Education Institutions of Anhui Province (KJ2019A0499).

■ REFERENCES

(1) (a) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (b) Yu, B.; Yu, D.-Q.; Liu, H.-M. Spirooxindoles: Promising scaffolds for anticancer agents. *Eur. J. Med. Chem.* **2015**, *97*, 673−698. (c) Ye, N.; Chen, H.; Wold, E. A.; Shi, P.-Y.; Zhou, J. Therapeutic Potential of Spirooxindoles as Antiviral Agents. *ACS Infect. Dis.* **2016**, *2*, 382−392. (d) Bhunia, S.; Chaudhuri, S.; Bisai, A. Total Syntheses of Pyroclavine, Festuclavine, Lysergol, and Isolysergol via a Catalytic Asymmetric Nitro-Michael Reaction. *Chem. - Eur. J.* **2017**, *23*, 11234−11238. (e) Babu, K. N.; Roy, A.; Singh, M.; Bisai, A. Thiourea-Catalyzed Enantioselective Malonate Addition onto 3-Sulfonyl-3′-indolyl-2-oxindoles: Formal Total Syntheses of (−)-Chimonanthine, (−)-Folicanthine, and (+)-Calycanthine. *Org. Lett.* **2018**, *20*, 6327−6331. (f) Yang, Y.-T.; Zhu, J.-F.; Liao, G.; Xu, H.-J.; Yu, B. The Development of Biologically Important Spirooxindoles as New Antimicrobial Agents. *Curr. Med. Chem.* **2018**, *25*, 2233−2244. (g) Zhou, L.-M.; Qu, R.-Y.; Yang, G.-F. An overview of spirooxindole as a promising scaffold for novel drug discovery. *Expert Opin. Drug Discovery* **2020**, *15*, 603−625.

(2) (a) Danieli, B.; Lesma, G.; Palmisano, G.; Gabetta, B. Ozonation in alkoloid chemistry: a mild and selective conversion of vincadifformine into vincamine. *J. Chem. Soc., Chem. Commun.* **1981**, 908−909. (b) Ali, E.; Roy, S.; Chakraborty, P. K.; Pakrashi, S. C. Synthesis and absolute stereochemistry of (−)-vincatine. *Tetrahedron Lett.* **1983**, *24*, 2497−2500. (c) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R.; Tollari, S. Absolute configuration of (−)-vincatine, the unique 2,16-seco Aspidosperma alkaloid. *J. Org. Chem.* **1984**, *49*, 547−551.

(3) Tian, Y.; Nam, S.; Liu, L.; Yakushijin, F.; Yakushijin, K.; Buettner, R.; Liang, W.; Yang, F.; Ma, Y.; Horne, D.; Jove, R. Spirooxindole Derivative SOID-8 Induces Apoptosis Associated with Inhibition of JAK2/STAT3 Signaling in Melanoma Cells. *PLoS One* **2012**, *7*, e49306.

(4) (a) Mathebula, B.; Butsi, K. R.; van Zyl, R. L.; Jansen van Vuuren, N. C.; Hoppe, H. C.; Michael, J. P.; de Koning, C. B.; Rousseau, A. L. Preparation and antiplasmodial activity of 3′,4′-dihydro-1′H-spiro(indoline-3,2′-quinolin)-2-ones. *Chem. Biol. Drug Des.* **2019**, *94*, 1849−1858. (b) Bouwman, S. A. M.; Zoleko-Manego, R.; Renner, K. C.; Schmitt, E. K.; Mombo-Ngoma, G.; Grobusch, M. P. The early preclinical and clinical development of cipargamin (KAE609), a novel antimalarial compound. *Travel Med. Infect. Dis.* **2020**, *36*, 101765.

(5) (a) Ding, Q.; Liu, J.-J.; Zhang, Z. Patent Appl. WO2007104714A1, 2007. (b) Chen, L.; Ding, Q.; Liu, J.-J.; Yang, S.; Zhang, Z. Patent Appl. US7495007B2, 2009.

(6) For selected recent reviews, see: (a) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. Strategies for the enantioselective synthesis of spirooxindoles. *Org. Biomol. Chem.* **2012**, *10*, 5165−5181. (b) Hong, L.; Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3,3′-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **2013**, *355*, 1023−1052. (c) Mei, G.-J.; Shi, F. Catalytic asymmetric synthesis

of spirooxindoles: recent developments. *Chem. Commun.* **2018**, *54*, 6607−6621.

(7) For selected reports on the construction of spiropyrrolidine oxindoles, see: (a) Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Wang, R. Catalytic Asymmetric Michael Addition/Cyclization of Isothiocyanato Oxindoles: Highly Efficient and Versatile Approach for the Synthesis of 3,2′-Pyrrolidinyl Mono- and Bi-spirooxindole Frameworks. *Chem. - Eur. J.* **2013**, *19*, 1184−1188. (b) Narayan, R.; Potowski, M.; Jia, Z.-J.; Antonchick, A. P.; Waldmann, H. Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. *Acc. Chem. Res.* **2014**, *47*, 1296−1310. (c) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. *ACS Catal.* **2014**, *4*, 743−762. (d) De, S.; Das, M. K.; Bhunia, S.; Bisai, A. Unified Approach to the Spiro(pyrrolidinyl-oxindole) and Hexahydropyrrolo[2,3-b]indole Alkaloids: Total Syntheses of Pseudophrynamines 270 and 272A. *Org. Lett.* **2015**, *17*, 5922−5925. (e) Li, B.; Gao, F.; Feng, X.; Sun, M.; Guo, Y.; Wen, D.; Deng, Y.; Huang, J.; Wang, K.; Yan, W. Highly Efficient Enantioselective Synthesis of Bispiro[benzofuran-oxindole-pyrrolidine]s through Organocatalytic Cycloaddition. *Org. Chem. Front.* **2019**, *6*, 1567−1571. (f) Gui, H.-Z.; Wei, Y.; Shi, M. Recent Advances in the Construction of Trifluoromethyl-Containing Spirooxindoles through Cycloaddition Reactions. *Chem. - Asian J.* **2020**, *15*, 1225−1233.

(8) For selected examples, see: (a) Huang, Y.-M.; Zheng, C.-W.; Zhao, G. Organocatalyzed aza-Michael−Michael cascade reactions to construct spirooxindole tetrahydroquinolines with all-carbon chiral centers. *RSC Adv.* **2013**, *3*, 16999−17002. (b) Yang, W.; Du, D.-M. Cinchona-based squaramide-catalysed cascade aza-Michael-Michael addition: enantioselective construction of functionalized spirooxindole tetrahydroquinolines. *Chem. Commun.* **2013**, *49*, 8842−8844. (c) Yang, M.-C.; Peng, C.; Huang, H.; Yang, L.; He, X.-H.; Huang, W.; Cui, H.-L.; He, G.; Han, B. Organocatalytic Asymmetric Synthesis of Spiro-oxindole Piperidine Derivatives That Reduce Cancer Cell Proliferation by Inhibiting MDM2-p53 Interaction. *Org. Lett.* **2017**, *19*, 6752−6755. (d) Jayakumar, S.; Louven, K.; Strohmann, C.; Kumar, K. A Tunable and Enantioselective Hetero-Diels-Alder Reaction Provides Access to Distinct Piperidinoyl Spirooxindoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 15945−15949. (e) Tang, Q.-G.; Cai, S.-L.; Wang, C.-C.; Lin, G.-Q.; Sun, X.-W. Organocatalytic Aza-Michael/Michael Cyclization Cascade Reaction: Enantioselective Synthesis of Spiro-oxindole Piperidin-2-one Derivatives. *Org. Lett.* **2020**, *22*, 3351−3355. (f) Rehan, M.; Flegel, J.; Heitkamp, F.; Pergomet, J. L.; Otte, F.; Strohmann, C.; Kumar, K. Asymmetric Synthesis of 3,3′-Piperidinoyl Spirooxindoles and Discovery of Stereospecific Cycloadducts as Novel Hedgehog Pathway Modulators. *Synthesis* **2020**, *52*, 3140−3152.

(9) For representative examples employing 3-pyrrolyloxindoles as Michael donors, see: (a) Cui, B.-D.; You, Y.; Zhao, J.-Q.; Zuo, J.; Wu, Z.-J.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. 3-Pyrrolyl-oxindoles as efficient nucleophiles for organocatalytic asymmetric synthesis of structurally diverse 3,3′-disubstituted oxindole derivatives. *Chem. Commun.* **2015**, *51*, 757−760. (b) You, Y.; Wu, Z.-J.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. Enantioselective Synthesis of 3,3-Disubstituted Oxindoles Bearing Two Different Heteroatoms at the C3 Position by Organocatalyzed Sulfenylation and Selenenylation of 3-Pyrrolyl-oxindoles. *J. Org. Chem.* **2015**, *80*, 8470−8477. (c) You, Y.; Wu, Z.-J.; Chen, J.-F.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. Organocatalytic Asymmetric Michael Addition of 3-Pyrrolyloxindoles to β-Phthalimidonitroethene for the Synthesis of 3,3′-Disubstituted Oxindoles Bearing Contiguous 3,α,β-Triamino Functionality. *J. Org. Chem.* **2016**, *81*, 5759−5765. (d) Deng, Y.-H.; Zhang, X.-Z.; Yu, K.-Y.; Yan, X.; Du, J.-Y.; Huang, H.; Fan, C.-A. Bifunctional tertiary amine-squaramide catalyzed asymmetric catalytic 1,6-conjugate addition/aromatization of para-quinone methides with oxindoles. *Chem. Commun.* **2016**, *52*, 4183−4186. (e) Ge, Z.-Z.; Yang, L.; You, Y.; Wang, Z.-H.; Xie, K.-X.; Zhou, M.-Q.; Zhao, J.-Q.; Yuan, W.-C. Asymmetric dearomatization of 2-nitrobenzofurans by organocatalyzed one-step Michael addition to access 3,3′-disubstituted oxindoles. *Chem. Commun.* **2020**, *56*, 2586−2589.

(10) For seminal studies of [3+n] cyclization of 3-pyrrolyloxindoles, see: (a) You, Y.; Cui, B.-D.; Zhou, M.-Q.; Zuo, J.; Zhao, J.-Q.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. Organocatalytic Asymmetric Michael/Friedel-Crafts Cascade Reaction of 3-Pyrrolyl-oxindoles and α,β-Unsaturated Aldehydes for the Construction of Chiral Spiro[5,6-dihydropyrido[1,2-a]pyrrole-3,3′-oxindoles]. *J. Org. Chem.* **2015**, *80*, 5951−5957. (b) Fan, W.-T.; Li, N.-K.; Xu, L.; Qiao, C.; Wang, X.-W. Organo-Catalyzed Asymmetric Michael-Hemiketalization-Oxa-Pictet-Spengler Cyclization for Bridged and Spiro Heterocyclic Skeletons: Oxocarbenium Ion as a Key Intermediate. *Org. Lett.* **2017**, *19*, 6626−6629. (c) Zhang, T.; Cui, B.; Han, W.; Wan, N.; Bai, M.; Chen, Y. Sequential Nucleophilic C(sp^3)-Benzylation/C(sp^2)−H Arylation for the Synthesis of Spiro[oxindole-3,5′-pyrrolo[2,1-a]isoquinolines]. *Eur. J. Org. Chem.* **2017**, *2017*, 3179−3186. (d) Li, N.-K.; Fan, W.-T.; Zhang, J.-Q.; Sun, B.-B.; Chen, J.-B.; Wang, X.-W. Diastereodivergent synthesis of bispirooxindoles via asymmetric Friedel-Crafts/aldol cascade reaction: co-catalyst effects on diastereoselective outcomes. *Chem. Commun.* **2018**, *54*, 2260−2263.

(11) For selected examples of linear nitroenynes, see: (a) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. Enantioselective One-Pot Organocatalytic Michael Addition/Gold-Catalyzed Tandem Acetalization/Cyclization. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923−8926. (b) Li, X.; Li, X.; Peng, F.; Shao, Z. Mutually Complementary Metal- and Organocatalysis with Collective Synthesis: Asymmetric Conjugate Addition of 1,3-Carbonyl Compounds to Nitroenynes and Further Reactions of the Products. *Adv. Synth. Catal.* **2012**, *354*, 2873−2885. (c) Enders, D.; Hack, D.; Chauhan, P.; Deckers, K.; Raabe, G.; Mizutani, Y. Combining silver- and organocatalysis: an enantioselective sequential catalytic approach towards pyrano-annulated pyrazoles. *Chem. Commun.* **2015**, *51*, 2266−2269. (d) Kaya, U.; Chauhan, P.; Hack, D.; Deckers, K.; Puttreddy, R.; Rissanen, K.; Enders, D. Enantioselective synthesis of 4H-pyranonaphthoquinones via sequential squaramide and silver catalysis. *Chem. Commun.* **2016**, *52*, 1669−1672. (e) Cao, Z.-Y.; Zhao, Y.-L.; Zhou, J. Sequential Au(i)/chiral tertiary amine catalysis: a tandem C-H functionalization of anisoles or a thiophene/asymmetric Michael addition sequence to quaternary oxindoles. *Chem. Commun.* **2016**, *52*, 2537−2540. (f) Kaya, U.; Chauhan, P.; Deckers, K.; Puttreddy, R.; Rissanen, K.; Raabe, G.; Enders, D. Asymmetric Synthesis of Tetrahydrobenzofurans and Annulated Dihydropyrans via Cooperative One-Pot Organo- and Silver-Catalysis. *Synthesis* **2016**, *48*, 3207−3216. (g) You, Z.-H.; Chen, Y.-H.; Wu, X.-N.; Liu, Y.-K. Lactols in Asymmetric Sequential Organo- and Gold-Catalysis: Synthesis of Densely Functionalized Epimeric Bicyclic O,O-Acetals. *Adv. Synth. Catal.* **2017**, *359*, 4260−4266.

(12) For selected examples of branched nitroenynes, see: (a) Bharathiraja, G.; Sakthivel, S.; Sengoden, M.; Punniyamurthy, T. A Novel Tandem Sequence to Pyrrole Syntheses by 5-endo-dig Cyclization of 1,3-Enynes with Amines. *Org. Lett.* **2013**, *15*, 4996−4999. (b) Bharathiraja, G.; Sengoden, M.; Kannan, M.; Punniyamurthy, T. Expedient synthesis of tetrasubstituted pyrroles via a copper-catalyzed cascade inter-/intramolecular cyclization of 1,3-enynes carry a nitro group with amines. *Org. Biomol. Chem.* **2015**, *13*, 2786−2792. (c) Bharathiraja, G.; Sathishkannan, G.; Punniyamurthy, T. Domino Synthesis of Tetrasubstituted Thiophenes from 1,3-Enynes with Mercaptoacetaldehyde. *J. Org. Chem.* **2016**, *81*, 2670−2674. (d) Ran, G.-Y.; Wang, P.; Du, W.; Chen, Y.-C. α-Regioselective [3 + 2] annulations with Morita-Baylis-Hillman carbonates of isatins and 2-nitro-1,3-enynes. *Org. Chem. Front.* **2016**, *3*, 861−864. (e) Huang, W.-Y.; Gurubrahamam, R.; Chen, K. An Unprecedented Organocascade Synthesis of Functionalized Bicyclic Nitrones from 2-Aminomalonate Derived Nucleophiles and 1-Nitro-1,3-Enynes via Allenes Formation and Subsequent Rearrangement. *Adv. Synth. Catal.* **2019**, *361*, 170−175. (f) Ge, J.; Ding, Q.; Wang, X.; Peng, Y. Three-Component Cascade Synthesis of Fully Substituted Trifluoromethyl Pyrroles via a Cu(II)/Rh(III)-Promoted Aza-Michael Addition/Trifluoromethylation Cyclization/Oxidation Reaction. *J. Org. Chem.*

https://dx.doi.org/10.1021/acs.orglett.1c00409
Org. Lett. 2021, 23, 2273−2278

2020, *85*, 7658−7665. (g) Ge, J.; Ding, Q.; Long, X.; Liu, X.; Peng, Y. Copper(II)-Catalyzed Domino Synthesis of 4-Benzenesulfonyl Isoxazoles from 2-Nitro-1,3-enynes, Amines, and Sodium Benzenesulfinate. *J. Org. Chem.* **2020**, *85*, 13886−13894.

(13) For recent reports of cyclization of branched nitroenynes, see: (a) Biswas, S.; Dagar, A.; Mobin, S. M.; Samanta, S. DABCO catalyzed domino Michael/hydroalkoxylation reaction involving α-alkynyl-β-aryl nitroolefins: excellent stereoselective access to dihydropyrano[3,2-c]chromenes, pyranonaphthoquinones and related heterocycles. *Org. Biomol. Chem.* **2016**, *14*, 1940−1945. (b) Gurubrahamam, R.; Gao, B.-F.; Chen, Y. m.; Chan, Y.-T.; Tsai, M.-K.; Chen, K. Organocascade Synthesis of Annulated (Z)-2-Methylenepyrans: Nucleophilic Conjugate Addition of Hydroxycoumarins and Pyranone to Branched Nitro Enynes via Allene Formation/Oxa-Michael Cyclization/Alkene Isomerization Sequence. *Org. Lett.* **2016**, *18*, 3098−3101. (c) Xiao, Y.; Lin, J.-B.; Zhao, Y.-N.; Liu, J.-Y.; Xu, P.-F. Exploring the Reactivity of Nitro-Activated 1,3-Enynes in an Organocatalytic One-Pot, Three-Component Coupling Reaction: A Tandem Catalytic Approach to a Novel 3-Nitrochroman Scaffold. *Org. Lett.* **2016**, *18*, 6276−6279. (d) Rana, N. K.; Jha, R. K.; Joshi, H.; Singh, V. K. Enantioselective access to tetrahydropyrano[2,3-c]pyrazoles via an organocatalytic domino Michael-hydroalkoxylation reaction. *Tetrahedron Lett.* **2017**, *58*, 2135−2139.

(14) Xing, Z.-M.; Song, L.-L.; Li, F.-X.; Xu, N.-S.; Wang, L.-F.; Shi, Z.-F.; Cao, X.-P. Organocatalytic Enantioselective Tandem Michael Addition and Cyclization Reaction of Trisubstituted 2-Nitro-1,3-enynes with Cyclic 1,3-Diketones. *Adv. Synth. Catal.* **2017**, *359*, 1892−1900.

(15) CCDC 2034090 contains the supplementary crystallographic data for compound **3e** reported in this paper.

https://dx.doi.org/10.1021/acs.orglett.1c00409
Org. Lett. 2021, 23, 2273−2278