OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 7943−7947

pubs.acs.org/OrgLett

NHC-Catalyzed Asymmetric Formal [4 + 2] Annulation To Construct Spirocyclohexane Pyrazolone Skeletons

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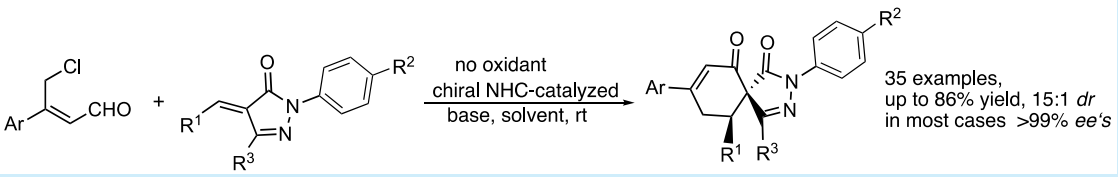
Supporting Information

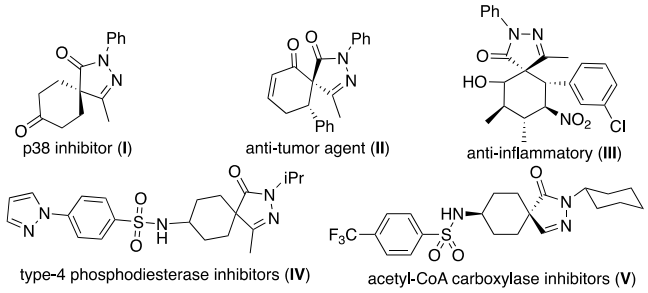


ABSTRACT: A chiral N-heterocyclic carbene (NHC)-catalyzed [4 + 2] annulation of γ-chloroenals and α-arylidene pyrazolinones was developed in the absence of expensive oxidants. The reaction proceeds smoothly via a vinyl enolate intermediate to afford spirocyclohexane pyrazolones in moderate to good yield (up to 86%) with high diastereoselectivities (up to 15:1 *dr*) and excellent enantioselectivities (up to >99% *ee*).

With special electronic properties,[1] N-heterocyclic carbenes (NHCs) were commonly described as unique ligands in organometallic catalysis.[2] Since the discovery of the isolation and crystallography of stable NHCs by Arduengo during the early 1990s,[3] multiple applications have been found in catalytic transformations, including not only organometallic catalysis but also organocatalysis.[4] Early documents concerning NHC organocatalytic transformations were focused on the entrance to acyl anion intermediates by umpolung of aldehydes.[5] In addition to this, more recent research developments have been made on the reactivity of enolate equivalents (activation of α-carbon),[6] homoenolate equivalents (activation of β-carbon),[7] and vinyl enolate equivalents (activation of γ-carbon).[8] It is worth mentioning that γ-carbon activation by NHC organocatalysis has inaugurated new access to target molecules via in-situ-generated vinyl enolate species. The construction of heterospirocyclic compounds was realized via an NHC organocatalytic strategy.[9]

The structure of pyrazol-3-one represents a simple and essential building block in a large family of clinical and listed medicines.[10] In particular, chiral spirocyclohexane pyrazolones (SCHPs) derived from pyrazol-3-ones are fundamental skeletons encountered throughout natural products and pharmaceuticals due to their broad biopharmaceutical activities.[11] As presented in Scheme 1, medicinal bioactivities have been found in SCHP skeletal compounds, such as p38 inhibitor (**I**), antitumor agent (**II**), antiinflammatory (**III**), type-4 phosphodiesterase inhibitor (**IV**), and acetyl-CoA carboxylase inhibitor (**V**).[12] Thus the construction of the chiral spiropyrazolone skeleton has been of great importance and has triggered vast investigation of their synthesis. Although the organocatalyzed reactions, such as the [1 + 2 + 2] or [1 + 4] cycloaddition reaction,[13] [1 + 5] annulation,[14] [2 + 4] annulation,[15] and [3 + 3] annulation,[16] have been described

Scheme 1. Selected Bioactive Molecules Containing Spiropyrazolone Core Structures



using attractively synthetic strategies, it is valuable to explore novel methods to construct this core structure efficiently.

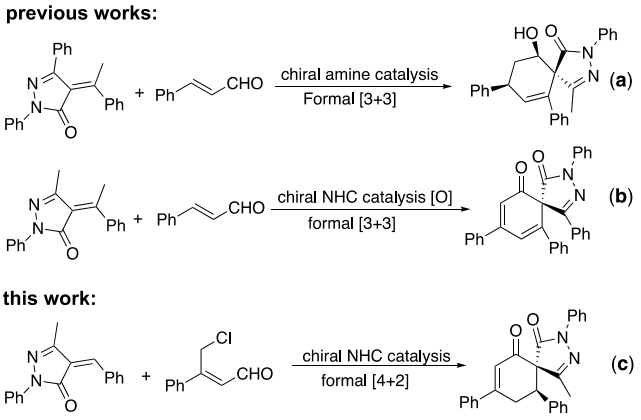
Our group has revealed the constructions of spirocyclic oxindoles via in-situ-generated vinyl enolate species in an NHC-organocatalyzed hetero-Diels−Alder reaction with isatins.[17] We continue investigating the application of the NHC-organocatalyzed transformation in the synthesis of spirocyclohexane pyrazolone skeletons (SCHPs) from the diversity of in-situ-generated vinyl enolate species (Scheme 2).[18] Biju's group has reported an asymmetric synthesis of spiropyrazolones via the formal [3 + 3] annulation of enals and α-arylidene pyrazolinones catalyzed by NHC.[19] Herein we report a different [4 + 2] annulation of γ-chloroenals and α-arylidene pyrazolinones via vinyl enolate intermediates for the enantioselective construction of carbocyclic spiropyrazolone derivatives catalyzed by NHC.

In the initial investigation, the reaction was carried out between γ-chloroenal **1a** and 4-benzylidene-pyrazol-3-one **2a** by employing *N*-substituted triazolium salt as a precatalyst (Table

Received: August 17, 2019
Published: September 12, 2019

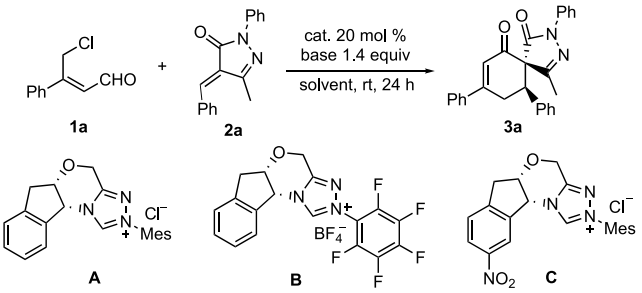
DOI: 10.1021/acs.orglett.9b02927
Org. Lett. 2019, 21, 7943−7947

Scheme 2. Construction of Spiropyrazolones



1). Different chiral triazolium salt precatalysts were screened. The reaction could proceed smoothly (61% yield, >99% *ee*) when catalyzed by *N*-mesityl-substituted triazolium (catalyst **A**) employing triethylamine as the base in tetrahydrofuran (THF), albeit with low diastereoselectivity (2:1 *dr*) (entry 1). Catalyst **B** with a penta-fluorophenyl group gave an even worse result (26% yield). When the catalyst was derived from an electron-withdrawing group on the indanol ring (catalyst **C**), it exhibited more efficient diastereoselectivity (10:1 *dr*) but was invalid on the control of stereoselectivity (70% *ee*). With mesityl-substituted triazolium salt A as the most suitable catalyst, the screening of solvents indicated that the best solvent was DCE (1,2-dichloroethane), leading to spirocyclohexane pyrazolone **3a** in high yield and with good diastereoselectivity compared with other solvents, such as toluene and DCM (dichloromethane). An inorganic base was screened to be suitable for the

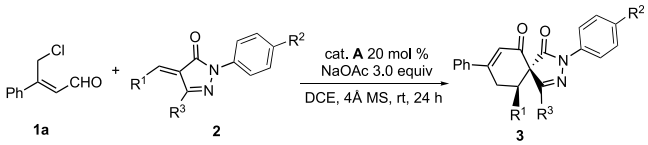
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	cat.	base	yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	THF	A	TEA	61	2:1	99
2	THF	B	TEA	26	2:1	99
3	THF	C	TEA	42	10:1	70
4	toluene	A	TEA	40	4:1	90
5	DCM	A	TEA	67	6:1	94
6	DCE	A	TEA	67	7:1	96
7	DCE	A	NaOAc	67	10:1	95
8[e]	DCE	A	NaOAc	79	10:1	95
9[e,f]	**DCE**	**A**	**NaOAc**	**79**	**10:1**	**99**

[a]Unless otherwise specified, the reaction was performed on a 0.10 mmol scale in the solvent (1.5 mL) at room temperature. [b]Yields of isolated products. [c]*dr* values determined by ^{1}H NMR. [d]*ee* values determined by HPLC analysis on Chiralcel AD-H and OD-H columns (see the SI). [e]50 mg 4 Å molecular sieve was added. [f]3.0 equiv NaOAc was used.

Table 2. Substrates Scope of Pyrazolinones[a]



entry	R^1, R^2, R^3	yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	Ph, H, Me (**3a**)	79	10:1	>99
2[e]	Ph, H, Me (**3a**)	76	10:1	>99
3	4-F-Ph, H, Me (**3b**)	66	12:1	>99
4	4-Cl-Ph, H, Me (**3c**)	69	13:1	>99
5	4-Br-Ph, H, Me (**3d**)	76	10:1	>99
6	4-Me-Ph, H, Me (**3e**)	81	9:1	>99
7	4-MeO-Ph, H, Me (**3f**)	80	10:1	>99
8	4-*i*-Pr-Ph, H, Me (**3g**)	77	9:1	>99
9	4-CF_3–Ph, H, Me (**3h**)	67	12:1	>99
10	4-NO_2–Ph, H, Me (**3i**)	60	15:1	>99
11	3-Cl-Ph, H, Me (**3j**)	65	14:1	>99
12	2-Cl-Ph, H, Me (**3k**)	40	10:1	>99
13	thiophen-2-yl, H, Me (**3l**)	75	7:1	>99
14	naphthalen-2-yl, H, Me (**3m**)	76	10:1	>99
15	cyclohexyl, H, Me (**3n**)	86	13:1	90
16	4-Ph-Ph, H, Me (**3o**)	75	10:1	>99
17	Ph, F, Me (**3p**)	64	9:1	>99
18	Ph, Cl, Me (**3q**)	62	10:1	>99
19	Ph, Br, Me (**3r**)	65	12:1	>99
20	Ph, Me, Me (**3s**)	70	8:1	>99
21	Ph, MeO, Me (**3t**)	68	9:1	>99
22	Ph, *i*-Pr, Me (**3u**)	69	9:1	>99
23	Ph, CF_3, Me (**3v**)	60	13:1	>99
24	Ph, H, Et (**3w**)	61	8:1	>99
25	Ph, H, *i*-Pr (**3x**)	45	7:1	>99
26	Ph, H, Bn (**3y**)	69	8:1	>99

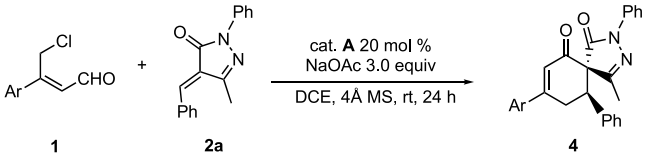
[a]Unless otherwise specified, reactions were performed on **1a** (0.10 mmol), **2** (0.10 mmol). [b]Yields of isolated products. [c]*dr* values determined by ^{1}H NMR. [d]*ee* values determined via HPLC analysis. [e]Reaction was performed on a 1 mmol scale.

reaction with excellent enantiopurity (>99% *ee*) and good diastereoselectivity (10:1 *dr*) and in high yield (79% yield).

After establishing the optimal reaction conditions, we investigated the substrate scope of the formal [4 + 2] annulation catalyzed by NHC (Tables 2 and 3). As shown in Table 2, a broad spectrum of pyrazolinones were explored and produced spirocyclohexane pyrazolone products in good yield and with excellent enantioselectivities. First, a wide range of 5-methyl-2-phenyl-pyrazolinones was tested under optimal conditions (R^1, **3a**–**o**). In most cases, the reactants bearing aromatic R^1 were well-tolerated to offer spiropyrazolones with excellent enantioselectivities (>99% *ee*), except for aliphatic-substituted pyrazolinone (**3n**, cyclohexyl, 90% *ee*). 4-Chloro-3-phenylbut-2-enal **1a** reacted flatly with 4-benzylidene-pyrazolinones carrying either electron-withdrawing (**3b**–**d**, **3h**–**k**) or electron-donating (**3e**–**g**) substituents on the phenyl ring. As for the substituent position on the phenyl ring, it showed that it has a very slight impact on the reaction results (**3c**,**j**,**k**). Second, we modified substituents (R^2) on 2-phenyl ring of 4-benzylidene-5-methyl-2-phenyl-pyrazolinones. Spirocyclohexane pyrazolones were produced in good yield and with high enantiopurities in all of the cases. As for the substituents R^3 on the five-position of pyrazolinones, both the aromatic group and the aliphatic group were tolerated in the [4 + 2] cycloaddition reaction, in which the

DOI: 10.1021/acs.orglett.9b02927
Org. Lett. 2019, 21, 7943–7947

Table 3. Substrates Scope of γ-Chloroenals[a]



entry	Ar	yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	4-F-Ph (**4a**)	68	10:1	>99
2	4-Cl-Ph (**4b**)	66	12:1	>99
3	4-Br-Ph (**4c**)	61	12:1	>99
4	4-Me-Ph (**4d**)	81	10:1	>99
5	4-MeO-Ph (**4e**)	62	9:1	>99
6	4-Ph-Ph (**4f**)	69	10:1	>99
7	3-Cl-Ph (**4g**)	63	12:1	>99
8	2-Cl-Ph (**4h**)	40	10:1	>99
9	naphthalen-2-yl (**4i**)	80	9:1	92
10	thiophen-3-yl (**4j**)	77	8:1	96

[a]Unless otherwise specified, reactions were performed on **1** (0.10 mmol), **2a** (0.10 mmol). [b]Yields of isolated products. [c]*dr* values determined by ^{1}H NMR. [d]*ee* values determined via HPLC analysis.

spiropyrazolone products were afforded in moderate to good yield and with excellent enantioselectivities (>99% *ee*) (**3a**, **3w**–**y**).

Next, we varied the γ-chloroenal substrate of the reaction (Table 3). The desired products of spirocyclohexane pyrazolones were obtained in satisfactory yield and with excellent enantioselectivities in all of the cases. The electron-donating substituents as well as the electron-withdrawing ones were well tolerated on the β-phenyl ring. The *ortho*-, *para*-, and *meta*-chlorophenyl γ-chloroenals were investigated in the reaction and gave comparable results. It seemed that the substituent position on the β-phenyl ring had a limited impact on the reaction outcome. The scope of naphthalen-2-yl- and thiophen-3-yl substituted γ-chloroenals (**4i**–**j**) afforded spirocyclohexane pyrazolones in high yield, however, with relatively lower enantioselectivities.

The absolute configuration of spirocyclohexane pyrazolone **3a** was confirmed based on the X-ray crystallographic analysis (Figure 1, CCDC 1948486). The prepared (5a*R*,10b*S*)-(+)-*cis*-*N*-mesityl-substituted triazolium salt **A** provided exclusively (5*S*,10*R*)-4-methyl-2,8,10-triphenyl-2,3-diazaspiro[4.5]deca-3,7-diene-1,6-dione **3a**.

We proposed the mechanism for this formal [4 + 2] annulation of enals and α-arylidene pyrazolinones (Scheme 3). First, Breslow intermediate **I** was offered via the nucleophilic addition of NHC catalyst to γ-chloroenal **1a** and a 1,2-H

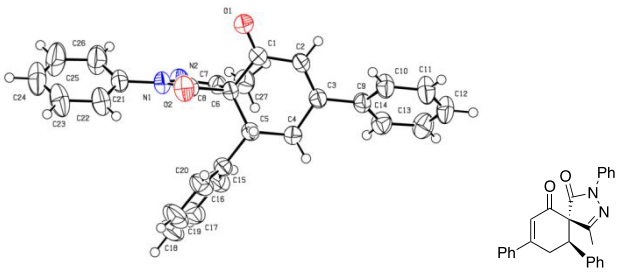
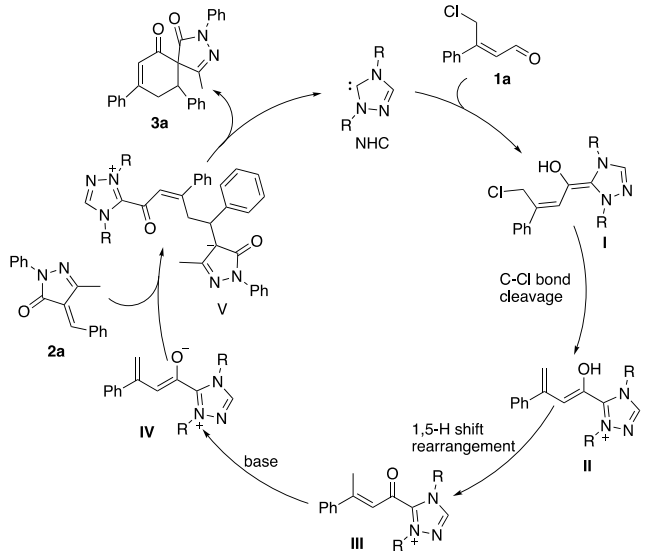


Figure 1. X-ray crystal structure of **3a**. Thermal ellipsoids are shown at 50% probability.

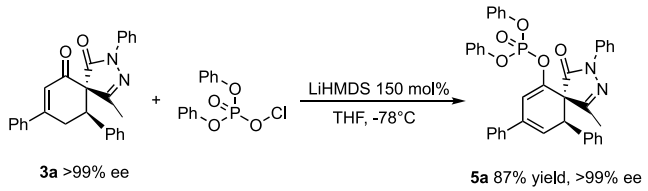
Scheme 3. Proposed Catalytic Pathway



migration to oxygen from carbon. Subsequently, enolene **II** was afforded via a tautomerization along with a C–Cl bond cleavage. Then, enone intermediate **III** was produced via an enolene–enone rearrangement along with a 1,5-H shift. After that, vinyl enolate **IV** was generated by the base capture of the acidic γ-proton. Finally, the reaction was finished by the cycloaddition of vinyl enolate **IV** with pyrazolone derivate **2a**, generating the enantioenriched spiropyrazolones **3a** and releasing NHC catalyst.

Given that the spirocyclohexane pyrazolone skeletons are important building blocks and moieties in pharmaceuticals, we tried to demonstrate the synthetic utility of this formal [4 + 2] annulation by transforming the products to other useful molecules by simple protocols. The phosphoric ester **5a** was obtained with no loss of enantiopurity (87% yield, >99% ee) by the treatment of optically enriched spiropyrazolone **3a** with hypochlorous (diphenyl phosphoric) anhydride at −78 °C in THF (Scheme 4).

Scheme 4. Transformation of Spiropyrazolone 3a



In summary, we have developed a chiral NHC-catalyzed [4 + 2] cycloaddition between γ-chloroenals with pyrazolinones in the absence of expensive oxidants. The desired spirocyclohexane pyrazolone products were obtained in moderate to good yield, with high diastereoselectivities and excellent enantioselectivities. This methodology accommodates the great prospects of constructing biologically relevant spirocyclohexane pyrazolone skeletons. Further investigations are undergoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02927.

DOI: 10.1021/acs.orglett.9b02927
Org. Lett. 2019, 21, 7943–7947

Experimental procedures, characterization data, and NMR spectra for **3a−z**, **4a−j**, and **5a** (PDF)

Accession Codes

CCDC 1948486 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.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the NSFC (21302032, 21373073, and 21672048) and the PCSIRT (IRT 1231) for financial support. G.Z. appreciates a QianJiang Scholar award from Zhejiang Province in China.

REFERENCES

(1) (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. Stable Carbenes. *Chem. Rev.* **2000**, *100*, 39. (b) Herrmann, W. A. *N*-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (c) Movassaghi, M.; Schmidt, M. A. *N*-Heterocyclic Carbene-Catalyzed Amidation of Unactivated Esters with Amino Alcohols. *Org. Lett.* **2005**, *7*, 2453.

(2) (a) Herrmann, W. A.; Weskamp, T.; Bohm, V. P. W. Metel Complexes of Stable Carbene. *Adv. Organomet. Chem.* **2001**, *48*, 1. (b) Scott, N. M.; Nolan, S. P. Stabilization of Organometallic Species Achieved by the Use of *N*-Heterocyclic Carbene (NHC) Ligands. *Eur. J. Inorg. Chem.* **2005**, *2005*, 1815.

(3) Arduengo, A. J.; Harlow, R. L.; Kline, M. A. A Stable Crystalline Carbine. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(4) (a) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (b) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by *N*-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606. (c) Moore, J. L.; Rovis, T. Insights into the Carbene Initiated Aggregation of $Fe(cot)_2$. *Top. Curr. Chem.* **2009**, *291*, 77. (d) Mahatthananchai, J.; Bode, J. W. On the Mechanism of *N*-Heterocyclic Carbene-Catalyzed Reactions Involving Acyl Azoliums. *Acc. Chem. Res.* **2014**, *47*, 696. (e) Xu, J.-H.; Zheng, S.-C.; Zhang, J.-W.; Liu, X.-Y.; Tan, B. Construction of Tropane Derivatives by the Organocatalytic Asymmetric Dearomatization of Isoquinolines. *Angew. Chem., Int. Ed.* **2016**, *55*, 11834. (f) Xiao, Z.; Yu, C.; Li, T.; Wang, X.; Yao, C. *N*-Heterocyclic Carbene/Lewis Acid Strategy for the Stereoselective Synthesis of Spirocyclic Oxindole−Dihydropyranones. *Org. Lett.* **2014**, *16*, 3632. (g) Que, Y.; Xie, Y.; Li, T.; Yu, C.; Tu, S.; Yao, C. An *N*-Heterocyclic Carbene-Catalyzed Oxidative γ-Aminoalkylation of Saturated Carboxylic Acids through in Situ Activation Strategy: Access to δ-Lactam. *Org. Lett.* **2015**, *17*, 6234.

(5) (a) Breslow, R. On the Mechanism of Thiamine Action. IV.[1] Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Sheehan, J.; Hunneman, D. H. Homogeneous Asymmetric Catalysis. *J. Am. Chem. Soc.* **1966**, *88*, 3666. (c) Stetter, H. Catalyzed Addition of Aldehydes to Activated Double Bonds—A New Synthetic Approach. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (d) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. The First Asymmetric Intramolecular Stetter Reaction. Preliminary Communication. *Helv. Chim. Acta* **1996**, *79*, 1899.

(6) (a) He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels−Alder Reactions Catalyzed by Chiral *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (b) He, M.; Uc, G. J.; Bode, J. W. Chiral *N*-Heterocyclic Carbene Catalyzed, Enantioselective Oxodiene Diels−Alder Reactions with Low Catalyst Loadings. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (c) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. Synthesis of an *N*-Mesityl Substituted Chiral Imidazolium Salt for NHC-Catalyzed Reactions. *Org. Lett.* **2008**, *10*, 957. (d) He, M.; Beahm, B. J.; Bode, J. W. Chiral NHC-Catalyzed Oxodiene Diels−Alder Reactions with α-Chloroaldehyde Bisulfite Salts. *Org. Lett.* **2008**, *10*, 3817.

(7) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *N*-Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. Organocatalyzed Conjugate Umpolung of α, β-Unsaturated Aldehydes for the Synthesis of γ-Butyrolactones. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (c) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (d) Chan, A.; Scheidt, K. A. Highly Stereoselective Formal [3 + 3] Cycloaddition of Enals and Azomethine Imines Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (e) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. Highly Diastereo- and Enantioselective Additions of Homoenolates to Nitrones Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2008**, *130*, 2416.

(8) (a) Mo, J.; Chen, X.; Chi, Y. Oxidative γ-Addition of Enals to Trifluoromethyl Ketones: Enantioselectivity Control *via* Lewis Acid/*N*-Heterocyclic Carbene Cooperative Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (b) Xu, J.; Jin, Z.; Chi, Y. Organocatalytic Enantioselective γ-Aminoalkylation of Unsaturated Ester: Access to Pipecolic Acid Derivatives. *Org. Lett.* **2013**, *15*, 5028. (c) Chen, X.; Yang, S.; Song, B.; Chi, Y. Functionalization of Benzylic $C(sp^3)$-H Bonds of Heteroaryl Aldehydes through *N*-Heterocyclic Carbene Organocatalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 11134. (d) Xu, J.; Yuan, S.; Miao, M. *N*-Heterocyclic Carbene Catalyzed [4 + 2] Annulation Reactions with in Situ Generated Heterocyclic *ortho*-Quinodimethanes. *Org. Lett.* **2016**, *18*, 3822. (e) Frogley, B. J.; Wright, L. J. A Metallaanthracene and Derived Metallaanthraquinone. *Angew. Chem., Int. Ed.* **2017**, *56*, 1.

(9) (a) Biswas, A.; DeSarkar, S.; Tebben, L.; Studer, A. Enantioselective Cyclopropanation of Enals by Oxidative *N*-heterocyclic Carbene Catalysis. *Chem. Commun.* **2012**, *48*, 5190. (b) Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *N*-Heterocyclic Carbene Catalyzed [4 + 3] Annulation of Enals and *o*-Quinone Methides: Highly Enantioselective Synthesis of Benzo-ε-Lactones. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607. (c) Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. Kinetic Resolution of Tertiary Alcohols: Highly Enantioselective Access to 3-Hydroxy-3-Substituted Oxindoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 1731. (d) Izquierdo, J.; Orue, A.; Scheidt, K. A. A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations. *J. Am. Chem. Soc.* **2013**, *135*, 10634. (e) Guo, C.; Schedler, M. C.; Daniliuc, G.; Glorius, F. *N*-Heterocyclic Carbene Catalyzed Formal [3 + 2] Annulation Reaction of Enals: An Efficient Enantioselective Access to Spiro-heterocycles. *Angew. Chem., Int. Ed.* **2014**, *53*, 10232. (f) Mahatthananchai, J.; Zheng, P.-G.; Bode, J. W. α. β-unsaturated Acyl Azoliums from *N*-Heterocyclic Carbene Catalyzed Reactions: Observation and Mechanistic Investigation. *Angew. Chem., Int. Ed.* **2011**, *50*, 1673. (g) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. Chiral *N*-heterocyclic Carbene Catalyzed Annulation of α, β-unsaturated Aldehydes with 1, 3-dicarbonyls. *Chem. Commun.* **2011**, *47*, 8670. (h) Yang, L.; Wang, F.; Chua, P. J.; Lv, Y.; Zhong, L.; Zhong, G. *N*-Heterocyclic Carbene (NHC)-Catalyzed Highly Diastereo- and Enantioselective Oxo-Diels−Alder Reactions for Synthesis of Fused Pyrano[2,3-b]indoles. *Org. Lett.* **2012**, *14*, 2894. (i) Zhang, B.; Feng, P.; Cui, Y.; Jiao, N. NHC-catalyzed C−O or C−N Bond Formation: Efficient Approaches to α, β-unsaturated Esters and Amides. *Chem.*

DOI: 10.1021/acs.orglett.9b02927
Org. Lett. 2019, 21, 7943−7947

Commun. **2012**, *48*, 7280. (j) He, L.; Guo, H.; Li, Y.-Z.; Du, G.-F.; Dai, B. *N*-Heterocyclic Carbene-Catalyzed Formal Cross-Coupling Reaction of α-Haloenals with Thiols: Organocatalytic Construction of sp^2 Carbon−Sulfur Bonds. *Chem. Commun.* **2014**, *50*, 3719. (k) Ryan, J. S.; Candish, L.; Lupton, D. W. *N*-Heterocyclic Carbene-Catalyzed [4 + 2] Cycloaddition/Decarboxylation of Silyl Dienol Ethers with α, β-Unsaturated Acid Fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 4694. (l) Candish, L.; Lupton, D. W. *N*-Heterocyclic Carbene-Catalyzed Ireland−Coates Claisen Rearrangement: Synthesis of Functionalized β-Lactones. *J. Am. Chem. Soc.* **2013**, *135*, 58.

(10) (a) Varvounis, G. Pyrazol-3-ones. Part IV: Synthesis and Applications. *Adv. Heterocycl. Chem.* **2009**, *98*, 143−224. (b) Horton, D. A.; Bourne, G. T.; Smythe, L. M. The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chem. Rev.* **2003**, *103*, 893 and references therein. . (c) Chauhan, P.; Mahajan, S.; Enders, D. Asymmetric Aynthesis of Pyrazoles and Pyrazolones Employing the Reactivity of Pyrazolin-5-one Derivatives. *Chem. Commun.* **2015**, *51*, 12890. (d) Ke, B.; Tian, M.; Li, J.; Liu, B.; He, G. Targeting Programmed Cell Death Using Small-Molecule Compounds to Improve Potential Cancer Therapy. *Med. Res. Rev.* **2016**, *36*, 983.

(11) (a) Sondhi, M.; Dinodia, M.; Singh, J.; Rani, R. Heterocyclic Compounds as Anti-Inflammatory Agents. *Curr. Bioact. Compd.* **2007**, *3*, 91. (b) Varvounis, G. Chapter 2 Pyrazol-3-ones. Part IV: Synthesis and Applications. *Adv. Heterocycl. Chem.* **2009**, *98*, 143. (c) Schmidt, A.; Dreger, A. Recent Advances in the Chemistry of Pyrazoles. Properties, Biological Activities, and Syntheses. *Curr. Org. Chem.* **2011**, *15*, 1423. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. *Chem. Rev.* **2011**, *111*, 6984.

(12) (a) Zhang, Y.; Wu, S.; Wang, S.; Fang, K.; Dong, G.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng, C.; Wang, W. Divergent Cascade Construction of Skeletally Diverse "Privileged" Pyrazole Derived Molecular Architectures. *Eur. J. Org. Chem.* **2015**, *2015*, 2030−2037. (b) Han, B.; Xu, S.; Wang, P. Chiral Pyrazolone Helical Derivative as well as Preparation Method and Application Thereof in Medicaments. CN Patent CN104610148, 2015. (c) Silay-chev, P. S.; Filimonov, V. O.; Maslivets, A. N.; Makhmu-dov, R. R. Demonstrating Analgesic Activity and Method for Obtaining Thereof. Russ. Patent, RU2577528, 2014. (d) Barnes, D.; Bebernitz, G. R.; Cohen, S. L.; Damon, R. E.; Day, R. F.; Jain, M.; Karki, R. G.; Kirman, L. C.; Patel, T. J.; Raymer, B. K.; Schuster, H. F.; Zhang, W. Cyclohexane Derivatives as Inhibitors of Acetyl-coa Carboxylase (Acc). PCT Int. Appl. WO2011067306, 2011. (e) Adolphi, H.; Dietsche, W.; Merger, F.; Beutel, P.; Huber, R. German Pat. Appl. DE 2163063, 1973. (f) Philipp, B.; Sarah, W. Amido-Substituted Cyclohexane Derivatives. PCT Int. Appl. WO2018078009, 2011. (g) Wu, S.; Li, Y.; Xu, G.; Chen, S.; Zhang, Y.; Liu, N.; Dong, G.; Miao, C.; Su, H.; Zhang, W.; Sheng, C. Novel Spiropyrazolone Antitumor Scaffold with Potent Activity: Design, Synthesis and Structureeactivity Relationship. *Eur. J. Med. Chem.* **2016**, *115*, 141.

(13) (a) Companyó, X.; Zea, A.; Alba, A.-N.; Mazzanti, R. A.; Moyano, A.; Rios, R. Organocatalytic Synthesis of Spiro Compounds via A Cascade Michael−Michael-Aldol Reaction. *Chem. Commun.* **2010**, *46*, 6953. (b) Alba, A.-N.; Zea, R. A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. Highly Stereoselective Synthesis of Spiropyrazolones. *Eur. J. Org. Chem.* **2011**, *2011*, 1318.

(14) (a) Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. Highly Enantioselective Synthesis of Spiro-[cyclohexanone-oxindoles] and Spiro[cyclohexanone-pyrazolones] by Asymmetric Cascade [5 + 1] Double Michael Reactions. *Eur. J. Org. Chem.* **2012**, *2012*, 1318. (b) Li, J.-H.; Cui, Z.-H.; Du, D.- M. Diastereo- and Enantioselective Construction of Cyclohexanone-fused Spirospyrazolones Containing Four Consecutive Stereocenters through Asymmetric Sequential Reactions. *Org. Chem. Front.* **2016**, *3*, 1087. For recent reviews on asymmetric synthesis of spiro compounds, see: (c) Rios, R. Enantioselective Methodologies for the Synthesis of Spiro Compounds. *Chem. Soc. Rev.* **2012**, *41*, 1060. Xie, X.; Huang, W.; Peng, C.; Han, B. Organocatalytic Asymmetric Synthesis of Six-Membered Carbocycle-Based Spiro Compounds. *Adv. Synth. Catal.* **2018**, *360*, 194. (d) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. Asymmetric Synthesis of Spiropyrazolones through PhosphineCatalyzed [4 + 1] Annulation. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643.

(15) (a) Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. Highly Enantioselective Cascade Synthesis of Spiropyrazolones. *Org. Biomol. Chem.* **2011**, *9*, 6519. (b) Zhang, J.-X.; Li, N.-K.; Liu, Z.-M.; Huang, X.-F.; Geng, Z.-C.; Wang, X.-W. Enantioselective Synthesis of Unsymmetrical Diaryl-Substituted Spirocyclohexanonepyrazolones through a Cascade [4 + 2] Double Michael Addition. *Adv. Synth. Catal.* **2013**, *355*, 797. (c) Chauhan, P.; Mahajan, S.; Loh, C. C. J.; Raabe, G.; Enders, D. Streocontrolled Construction of Six Vicinal Stereogenic Centers on Spiropyrazolones via Organocascade Michael/Michael/1, 2-Addition Reactions. *Org. Lett.* **2014**, *16*, 2954. (d) Li, J.-H.; Du, D.-M. Organocatalyzed Cascade Aza-Michael/Michael Addition for the Asymmetric Construction of Highly Functionalized Spiropyrazolone Tetrahydroquinolines. *Chem. - Asian J.* **2014**, *9*, 3278. (e) Yang, W.; Zhang, Y.; Qiu, S.; Zhao, C.; Zhang, L.; Liu, H.; Zhou, L.; Xiao, Y.; Guo, H. Phosphine-Catalyzed [4 + 2] Cycloaddition of Unsaturated Pyrazolones with Allenoates: A Concise Approach toward Spiropyrazolones. *RSC Adv.* **2015**, *5*, 62343. (f) Liang, J.; Chen, Q.; Liu, L.; Jiang, X.; Wang, R. An organocatalytic Asymmetric Double Michael Cascade Reaction of Unsaturated Ketones and Unsaturated Pyrazolones: Highly Efficient Synthesis of Spiropyrazolone Derivatives. *Org. Biomol. Chem.* **2013**, *11*, 1441. (g) Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J.-H.; Peng, C. Asymmetric Synthesis of Cyclohexane-Fused Drug-Like Spirocyclic Scaffolds Containing Six Contiguous Stereogenic Centers via Organocatalytic Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 561.

(16) (a) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. Direct and Enantioselective Vinylogous Michael Addition of α-Alkylidenepyrazolinones to Nitroolefins Catalyzed by Dual Cinchona Alkaloid Thioureas. *Adv. Synth. Catal.* **2014**, *356*, 2330. (b) Liu, J.-Y.; Zhao, J.; Zhang, J.-L.; Xu, P.-F. Quaternary Carbon Center Forming Formal [3 + 3] Cycloaddition Reaction via Bifunctional Catalysis: Asymmetric Synthesis of Spirocyclohexene Pyrazolones. *Org. Lett.* **2017**, *19*, 1846. (c) Yang, W.; Sun, W.; Zhang, C.; Wang, Q.; Guo, Z.; Mao, B.; Liao, J.; Guo, H. Lewis-Base-Catalyzed Asymmetric [3 + 3] Annulation Reaction of Morita−Baylis−Hillman Carbonates: Enantioselective Synthesis of Spirocyclohexenes. *ACS Catal.* **2017**, *7*, 3142.

(17) (a) Yan, J.; Shi, K.; Zhao, C.; Ding, L.; Jiang, S.; Yang, L.; Zhong, G. NHC-catalyzed [4 + 2] Cycloaddition Reactions for the Synthesis of 3′-Spirocyclic Oxindoles via a C−F Bond Cleavage Protocol. *Chem. Commun.* **2018**, *54*, 1567. (b) Lin, Y.; Yang, L.; Deng, Y.; Zhong, G. Cooperative Catalysis of *N*-heterocyclic Carbine and Brønsted Acid for A Highly Enantioselective Route to Unprotected Spiro-indoline-pyrans. *Chem. Commun.* **2015**, *51*, 8330.

(18) (a) Yan, J.; Sun, R.; Shi, K.; Li, K.; Yang, L.; Zhong, G. NHC-Catalyzed Asymmetric Benzoin Reaction in Water. *J. Org. Chem.* **2018**, *83*, 7547. (b) Yang, L.; Lv, Y.; Wang, F.; Zhong, G. Chiral NHC-catalyzed 1, 3-diploar [3 + 2] Cycloadditon of Azomethine Imines with α-Chloroaldehydes for Synthesis of Bicyclic Pyrazolidinones. *Org. Biomol. Chem.* **2018**, *16*, 4433.

(19) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3 + 3] Annulation Reaction of Enals. *Angew. Chem., Int. Ed.* **2016**, *55*, 268.

DOI: 10.1021/acs.orglett.9b02927
Org. Lett. 2019, 21, 7943−7947