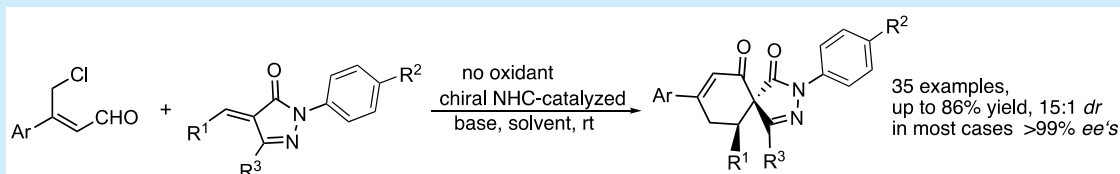


NHC-Catalyzed Asymmetric Formal [4 + 2] Annulation To Construct Spirocyclohexane Pyrazolone Skeletons

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S Supporting Information

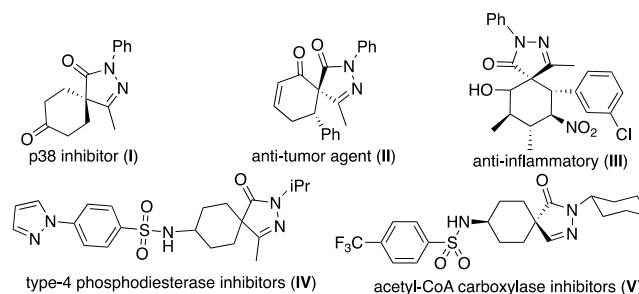


ABSTRACT: A chiral N-heterocyclic carbene (NHC)-catalyzed [4 + 2] annulation of γ -chloroaldehydes and α -arylidene pyrazolinones was developed in the absence of expensive oxidants. The reaction proceeds smoothly via a vinyl enolate intermediate to afford spirocyclohexane pyrazolones in moderate to good 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.

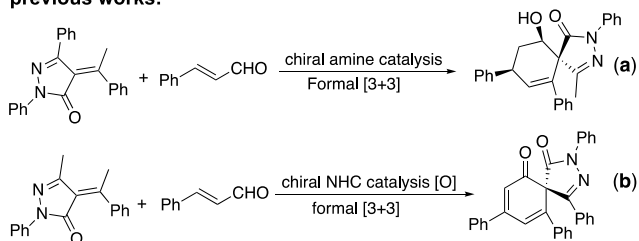
Our group has revealed the constructions of spirocyclic oxindoles via in-situ-generated vinyl enolate species in an NHC-organocatalyzed hetero-Diels–Alder reaction with isatins.¹⁷ We continue investigating the application of the NHC-organocatalyzed transformation in the synthesis of spirocyclohexane 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 -chloroaldehydes 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 -chloroaldehyde **1a** and 4-benzylidene-pyrazol-3-one **2a** by employing *N*-substituted triazolium salt as a precatalyst (Table

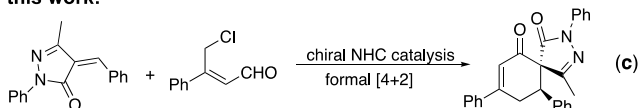
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Scheme 2. Construction of Spiropyrazolones

previous works:



this work:



1). Different chiral triazolium salt precatalysts were screened. The reaction could proceed smoothly (61% yield, >99% *ee*)

Table 1. Optimization of Reaction Conditions^a

entry	solvent	cat.	base	yield (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^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

^aUnless otherwise specified, the reaction was performed on a 0.10 mmol scale in the solvent (1.5 mL) at room temperature. ^bYields of isolated products. ^c*dr* values determined by ¹H NMR. ^d*ee* values determined by HPLC analysis on Chiralcel AD-H and OD-H columns (see the SI). ^e50 mg 4 Å molecular sieve was added. ^f3.0 equiv NaOAc was used.

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

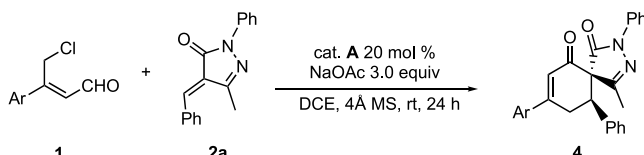
reaction with excellent enantiopurity (>99% *ee*) and good diastereoselectivity (10:1 *dr*) and in high yield (79% yield).

Table 2. Substrates Scope of Pyrazolinones^a

entry	R ¹ , R ² , R ³	yield (%) ^b	<i>dr</i> ^c	<i>ee</i> (%) ^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>i</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>i</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>i</i> -Pr (3x)	45	7:1	>99
26	Ph, H, Bn (3y)	69	8:1	>99

^aUnless otherwise specified, reactions were performed on 1a (0.10 mmol), 2 (0.10 mmol). ^bYields of isolated products. ^c*dr* values determined by ¹H NMR. ^d*ee* values determined via HPLC analysis. ^eReaction was performed on a 1 mmol scale.

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-phenylpyrazolinones was tested under optimal conditions (R¹, 3a–o). In most cases, the reactants bearing aromatic R¹ 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 (R²) on 2-phenyl ring of 4-benzylidene-5-methyl-2-phenylpyrazolinones. Spirocyclohexane pyrazolones were produced in good yield and with high enantiopurities in all of the cases. As for the substituents R³ on the five-position of pyrazolinones, both the aromatic group and the aliphatic group

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

^aUnless otherwise specified, reactions were performed on **1** (0.10 mmol), **2a** (0.10 mmol). ^bYields of isolated products. ^cdr values determined by ¹H NMR. ^dee values determined via HPLC analysis.

were tolerated in the [4 + 2] cycloaddition reaction, in which the spirocyclohexane pyrazolones 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 (SaR,10bS)-(+)-*cis*-

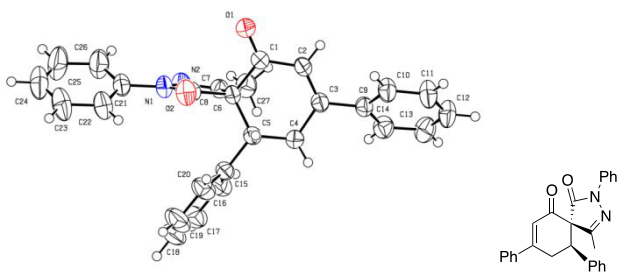
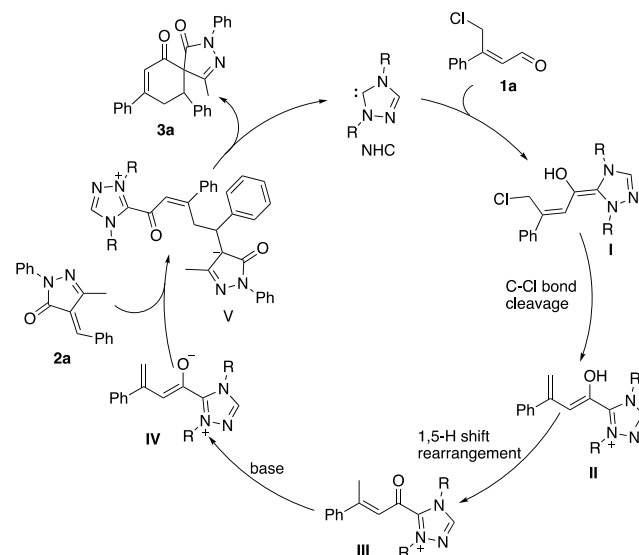


Figure 1. X-ray crystal structure of **3a**. Thermal ellipsoids are shown at 50% probability.

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**.

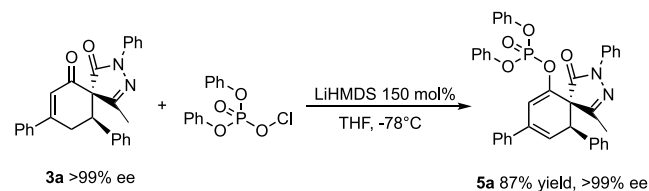
We proposed the mechanism for this formal [4 + 2] annulation of enals and α -arylidene pyrazolinones (Scheme 3). First, Breslow intermediate **I** was offered via the nucleophilic

Scheme 3. Proposed Catalytic Pathway



addition of NHC catalyst to γ -chloroenal **1a** and a 1,2-H migration to oxygen from carbon. Subsequently, enone **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 pyrazolinone derivative **2a**, generating the enantioenriched spirocyclohexane pyrazolones **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 spirocyclohexane pyrazolone **3a** with hypochlorous (diphenyl phosphoric) anhydride at -78°C in THF (Scheme 4).

Scheme 4. Transformation of Spirocyclohexane Pyrazolone **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.

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

■ Notes

The authors declare no competing financial interest.

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