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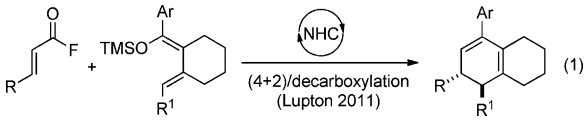
Enantioselective Synthesis of Spirocyclohexadienones by NHC-Catalyzed Formal [3+3] Annulation Reaction of Enals

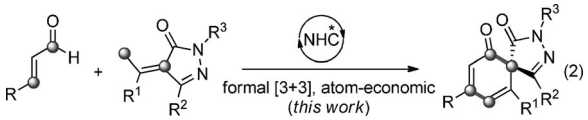
*Santhivardhana Reddy Yetra, Santigopal Mondal, Subrata Mukherjee, Rajesh G. Gonnade, and Akkattu T. Biju**

Abstract: *The enantioselective synthesis of pyrazolone-fused spirocyclohexadienones was demonstrated by the reaction of α,β-unsaturated aldehydes with α-arylidene pyrazolinones under oxidative N-heterocyclic carbene (NHC)catalysis. This atom-economic and formal [3+3] annulation reaction proceeds through a vinylogous Michael addition/spiroannulation/dehydrogenation cascade to afford spirocyclic compounds with an all-carbon quaternary stereocenter in moderate to good yields and excellent ee values. Key to the success of the reaction is the cooperative NHC-catalyzed generation of chiral α,β-unsaturated acyl azoliums from enals, and base-mediated tandem generation of dienolate/enolate intermediates from pyrazolinones.*

In recent years, N-heterocyclic carbene (NHC)-organocatalyzed transformations have emerged as a powerful synthetic tool for the rapid construction of complex and biologically relevant compounds.[1] One of the important applications of NHCs in organocatalysis is the umpolung of aldehydes,[2] which finds utility in benzoin[1a,f] and Stetter reactions.[3] The generation of NHC-bound homoenolate equivalents followed by their interception with electrophiles is another application that has received considerable attention in the last decade.[4,5] However, NHCs are also used in catalytic transformations proceeding via the normal mode (non-umpolung) of reactivity.[6] One specific example is the generation of α,β-unsaturated acyl azolium intermediates by using NHCs.[7] Nucleophiles such as enolates and enamines undergo addition of α,β-unsaturated acyl azolium in a formal [3+3] annulation reaction to give dihydropyranones and dihydropyridinones.[8,9] Interestingly, however, the reaction of dienolates with α,β-unsaturated acyl azolium has received only scant attention.

In 2011, Lupton and co-workers reported the NHC-catalyzed reaction of silyl enol ethers with α,β-unsaturated acid fluorides proceeding via the generation of dienolate and α,β-unsaturated acyl azolium intermediates [Eq. (1)].[10a] This vinylogous Michael/aldol/decarboxylation cascade enabled the synthesis of functionalized cyclohexadienes.[10b–d] Moreover, NHC-catalyzed formal [4+2] annulation of α,β-unsaturated acylchlorides with 3-alkenyloxindoles proceeding via the NHC-bound dienolates to furnish spiro carbocyclic oxindoles was demonstrated by Ye and co-workers.[11] Additionally, construction of multisubstituted benzenes by NHC-catalyzed formal [3+3] annulation of enals and enones has been uncovered by Chi and co-workers.[12] Intriguingly, the simultaneous generation of dienolate/enolate intermediates from a common precursor, followed by their interception with electrophiles has received limited attention in NHC catalysis. Herein, we demonstrate the formal [3+3] annulation reaction of α,β-unsaturated aldehydes with α-arylidene pyrazolinones under oxidative NHC catalysis for the enantioselective synthesis of pyrazolone-fused spiro-1,3-cyclohexadienones [Eq. (2)]. The dienolate/enolate intermediates generated from pyrazolinones were intercepted by the chiral α,β-unsaturated acyl azoliums generated from enals and the NHC to afford the spiro compounds in moderate to good yields and excellent enantioselectivities. In this atom-economic and efficient transformation, the desired compounds are formed by a vinylogous Michael addition/spiroannulation/dehydrogenation cascade.[13,14] The present approach stitches acyclohexadienone moiety to pharmacologically relevant pyrazolones to create an all-carbon quaternary spirocenter,[15] and related spirocyclic compounds are important synthetic targets in view of their potential applications in medicinal chemistry.[16]





The present study was initiated by the optimization of the reaction conditions for the vinylogous Michael addition/spiroannulation cascade. In an initial event, the reaction of cinnamaldehyde **1a** with α-arylidene pyrazolinone **2a** in the presence of carbene generated from the chiral triazolium salt **4**[17] under oxidative conditions by using the quinone **5** resulted in the formation of the pyrazolone-fused spiro-1,3-cyclo-

[*] S. R. Yetra, S. Mondal, S. Mukherjee, Dr. A. T. Biju
Organic Chemistry Division, CSIR-National Chemical Laboratory
Dr. Homi Bhabha Road, Pune-411008 (India)
E-mail: at.biju@ncl.res.in
Homepage: http://academic.ncl.res.in/at.biju
Dr. R. G. Gonnade
Centre for Materials Characterization
CSIR-National Chemical Laboratory
Dr. Homi Bhabha Road, Pune-411008 (India)

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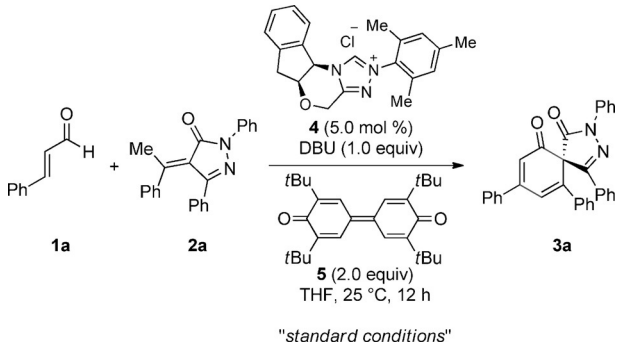
Table 1: Optimization of the Reaction Conditions.[a]

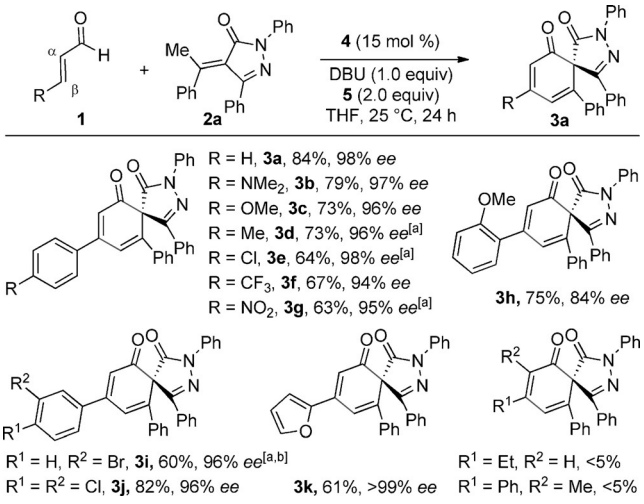


Entry	Variation of the standard conditions[a]	Yield of **3a** [%][b]	ee of **3a** [%][c]
1	none	50	98
2	Cs_2CO_3 instead of DBU	50	98
3	KO*t*Bu instead of DBU	30	90
4	DMAP instead of DBU	42	95
5	Et_3N instead of DBU	55	90
6	no base used	17	98
7	toluene instead of THF	32	98
8	CH_2Cl_2 instead of THF	35	98
9	1,4-dioxane instead of THF	45	98
10	run for 24 h	55	98
11	10 mol % **4**, run for 24 h	60	98
12	15 mol % **4**, run for 24 h	84	98

[a] Standard conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), **4** (5 mol %), **5** (2.0 equiv), DBU (1.0 equiv), THF (6.0 mL), 25 °C and 12 h. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC analysis on a chiral column. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, THF = tetrahydrofuran.

hexadienone **3a** in 50 % yield and 98 % ee (Table 1, entry 1). The reaction returned similar results when performed in Cs_2CO_3 instead of DBU (entry 2), whereas the other bases, such as KO*t*Bu and DMAP, furnished inferior results (entries 3, 4). The use of Et_3N improved the yield, but reduced the *ee* (entry 5). Interestingly, the reaction afforded 17 % **3a** in 98 % *ee* when conducted in the absence of base (entry 6).[9a,18] A quick solvent screening revealed that solvents other than THF provided reduced yield of **3a** under standard conditions (entries 7–9). The yield of **3a** was improved to 55 % while maintaining 98 % *ee* when the reaction time was extended to 24 h (entry 10). Increasing the loading of **4** increased the yield of **3a** (entry 11), and finally, with 15 mol % of **4**, **3a** was isolated in 84 % yield and in 98 % *ee* (entry 12).

The scope of the reaction was examined after deriving the optimized reaction conditions. First, we studied variation of the enals (Scheme 1). A series of α,β-unsaturated aldehydes with electron-releasing as well as electron-withdrawing groups at the 4-position of the β-aryl ring are well-tolerated and result in the formation of pyrazolone- fused spirocyclohexadienones **3a–3g** in good yields and excellent *ee* values (> 94 % *ee* in all cases). Moreover, substitution was viable at the 2-position and 3-position of theβ-aryl ring, and disubstitution was also feasible. In all the cases, the desired product was formed in good yields and moderate to excellent *ee* values (**3h, 3j**). The structure and stereochemistry of the spirocenter

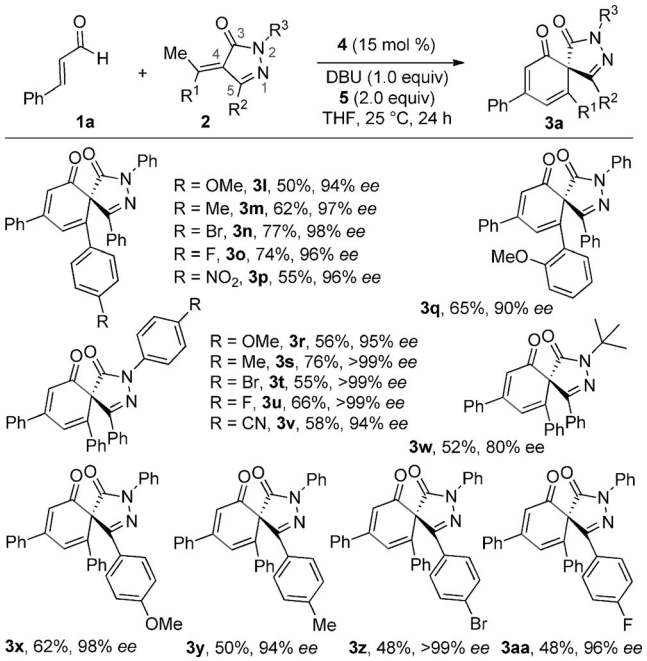


Scheme 1. Scope with respect to the α,β-unsaturated aldehydes. General conditions: **1** (0.75 mmol), **2a** (0.50 mmol), **4** (15.0 mol %), **5** (2.0 equiv), DBU (1.0 equiv), THF (12.0 mL) 25 °C and 24 h. Yields of isolated product are given and the *ee* values were determined by HPLC analysis on a chiral phase.[a] Run on 0.25 mmol scale.[b] Structure and stereochemistry confirmed by X-ray analysis.

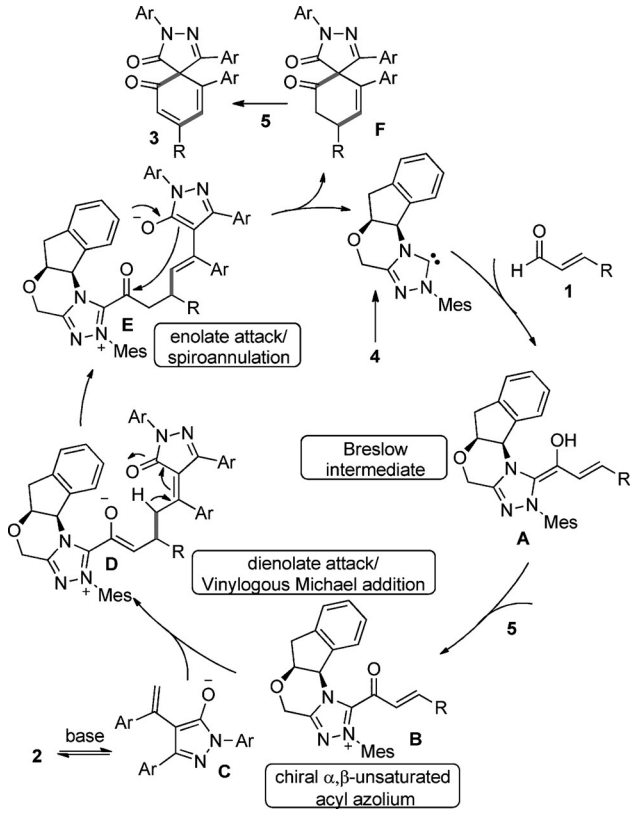
in the bromo derivative **3i** was confirmed by X-ray analysis (with the stereochemistry of the spirocentre being *S*).[19] In addition, β-furyl enal also underwent efficient annulation reaction furnishing **3k** in 61 % yield and > 99 % *ee*, thus further expanding the scope of this formal [3+3] annulation. Disappointingly, β-alkyl-substituted enals and enals with additional α or βsubstituents afforded only traces of the desired spiro compounds under the optimized conditions.

Next, we investigated variation on the α-arylidene pyrazolinone moiety (Scheme 2). Substrates with electron-releasing and electron-withdrawing groups on the arylidene moiety of **2** (R^1) underwent smooth annulation reaction to afford the spirocyclic compounds in moderate to good yields and excellent *ee* values (**3l–3q**).[20] Moreover, substitution on the N-aryl moiety (R^3) was also well-tolerated to furnish the desired product in high *ee* values (**3r–3v**). It is worth noting that tolerance of functional groups such as Br, NO_2, and CN allows further functionalization of the spirocyclohexadienones. Interestingly, the *N-tert*-butyl-substituted pyrazolinone afforded the desired product **3w** in 52 % yield and 80 % *ee*. Additionally, electron-releasing and electron-withdrawing groups at the aryl ring at the 5-position of **2**(R^2) were also well tolerated and afforded the target compounds with high *ee* values (**3x–3aa**).

A plausible mechanism for this NHC-catalyzed spiroannulation reaction is shown in Scheme 3. The carbene generated from the chiral triazolium salt **4** undergoes 1,2-addition to enal **1** followed by proton transfer to generate the nucleophilic Breslow intermediate **A**.[2] The enaminol **A** in the presence of oxidant **5** generates the key chiral α,β-unsaturated acyl azolium intermediate **B**. Simultaneously, the α-arylidene pyrazolinone **2** generates the dienolate intermediate **C** under basic conditions. Vinylogous Michael addition of **C** to the α,β-unsaturated acyl azolium **B** generates the NHC-bound enolate intermediate **D**, which upon intra-



Scheme 2. Scope with respect to the α-arylidene pyrazolinones.

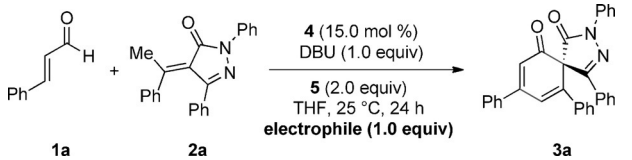


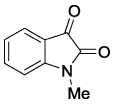
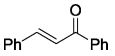
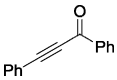
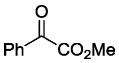
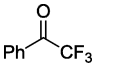
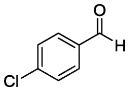
Scheme 3. Proposed mechanism of the reaction.

molecular proton transfer generates the acyl azolium **E**, which has an enolate moiety separated by a carbon tether. Intramolecular enolate C-acylation results in the formation of the spiropyrazolone **F** with regeneration of the free carbene. In the presence of excess oxidant **5**,the spiro compound **F** affords the spirocyclohexadienone product **3**.

We also examined the tolerance of this annulation reaction to commonly used electrophiles in NHC catalysis.[21] Interestingly, added electrophiles such as *N*-methyl isatin, chalcone, ynone, and α-ketoester did not affect the outcome of the annulation reaction (Table 2, entries 2–5). In all cases,

Table 2: Impact of commonly used electrophiles on this reaction.[a]



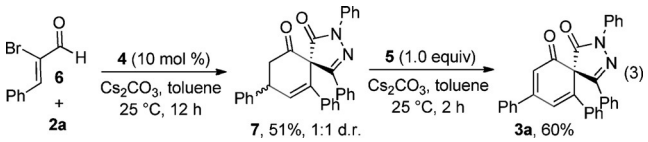
Entry	Electrophile	Yield of **3a** [%][b]	ee of **3a** [%][c]	Electrophile remaining [%][b]
1	None	84	98	–
2		82	98	99
3		70	98	83
4		84	98	90
5		80	98	95
6		65	96	63[d]
7		80	98	0

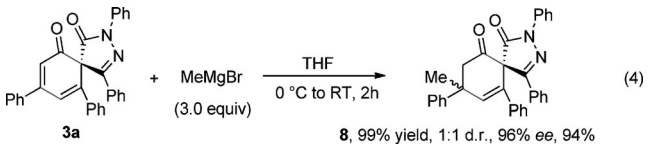
[a] Standard conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), electrophile (0.25 mmol), **4** (15 mol%), **5** (2.0 equiv), DBU (1.0 equiv), THF (6.0 mL), 25 °C and 24 h. [b] Isolated yield of **3a** and additive remaining after column chromatography. [c] The *ee* value was determined by HPLC analysis on a chiral phase. [d] Additive remaining determined by GC.

the spiro compound **3a** was formed in good yield and *ee* value. The added electrophiles did not decompose under the reaction conditions, thus indicating that the present reaction can be performed on substrates with these functionalities. The use of trifluoroacetophenone as the electrophile reduced the yield of **3a** to 65%, and only 63% of the electrophile was recovered after the reaction (entry 6). Notably, the use of 4-chlorobenzaldehyde as the electrophile did not affect the course of the reaction, but the aldehyde decomposed under the reaction conditions, thus demonstrating that a -CHO moiety is not tolerated.

To gain insight into the role of oxidant on the final oxidation step leading to **3**, we carried out the reaction of 2-bromoenal **6** with **2a** in the presence of **4** and Cs_2CO_3 as a base in the absence of the oxidant **5**. This reaction afforded the spirocyclohexenone **7** in 51% yield and 1:1 d.r. [Eq. (3)]. Moreover, treating **7** with the oxidant **5** under basic conditions furnished **3a** in 60% yield, thus indicating arole for**5** in the oxidation step. In addition, when the NHC-catalyzed

reaction of **6** and **2a** was carried out in the presence of **5**, **3a** was isolated in 70% yield, thus showing the advantages of the domino process. Finally, the spirocyclohexadienone **3a** was converted into the spirocyclohexenone **8**, which bears two all-carbon quaternary stereocenters, in 99% yield and 1:1d.r. and excellent *ee* values by treatment with MeMgBr in THF [Eq. (4)].





In conclusion, we have developed an atom-economic and NHC-organocatalyzed reaction of enals with α-arylidene pyrazolinones under oxidative conditions. This reaction resulted in the enantioselective construction of pyrazolone-fused spirocyclohexadienones in good yields and excellent *ee* values. Given the importance of pyrazolones in medicine, the spirocyclic compounds synthesized herein in enantiomerically pure form are expected to have interesting biological properties.

Acknowledgements

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Keywords: annulation reactions · asymmetric catalysis · N-heterocyclic carbenes · organocatalysis · spiro compounds

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