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Enantioselective All-Carbon (4+2) Annulation by *N*-Heterocyclic Carbene Catalysis

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Supporting Information

ABSTRACT: The enantioselective vinylogous Michael/aldol cascade is an underdeveloped approach to cyclohexenes. Herein we describe a highly enantioselective (most ≥98:2 er) and diastereoselective (all ≥15:1 dr) *N*-heterocyclic carbene catalyzed cycloisomerization of acyclic dienyl esters to cyclohexyl β-lactones. Derivatizations avail cyclohexenes bearing four contiguous stereogenic centers, while mechanistic studies support olefin isomerization prior to cyclization.

Cyclohexenes are valuable motifs in medicinal and natural products chemistry, with their synthesis generally invoking application of the Diels–Alder reaction.[1] As a consequence of this pre-eminence, numerous catalytic enantioselective Diels–Alder reactions have been developed.[1c] In contrast, the enantioselective catalysis of stepwise all-carbon (4+2) annulations has received only modest attention.[2] For example, stepwise annulation of simple dienolates (i.e., **1**) with Michael acceptors (i.e., **2**) to afford cyclohexenes (i.e., **3**; eq 1 in Figure 1), despite introducing new opportunities for catalysis and target focused synthesis, is yet to be achieved via enantioselective catalysis. Presumably this deficiency is due to challenges in controlling chemoselectivity with tris-nucleophiles (**1**) and bis-electrophiles (**2**), reagents that in principle can provide intermediates **II**–**V** (and more), and hence various byproducts (Figure 1).[3] Herein we report studies on this topic that have revealed an enantioselective cycloisomerization of dienyl esters **4** to cyclohexenyl β-lactones[4] (eq 2 in Figure 1). This reaction complements existing (4+2) annulations, providing products inaccessible via the Diels–Alder reaction, while expanding the underdeveloped field of *N*-heterocyclic carbene (NHC) catalysis[5] with ester substrates.[6−8]

In earlier studies from our group, an NHC-catalyzed vinylogous Michael/aldol cascade to afford cyclohexadienes (i.e., **6**) was discovered (eq 3 in Figure 1).[9,10] Unfortunately, chemoselectivity was poorly controlled;[3] thus, the reaction terminated with stereoablative decarboxylation, had limited scope, and could not be catalyzed with homochiral NHCs. To address these limitations, we conceived an approach that takes advantage of the Curtin–Hammett principle to concurrently address chemoselectivity and enantioselectivity, the latter by either conventional transition-state control[11b] or thermodynamic models.[11c] Specifically, it was postulated that the vinylogous carbonic anhydride motif in **4**, with an appropriate NHC,[12] should provide the well-studied α,β-unsaturated acyl azolium **VI**[13] and the novel dienolate **VII**. The azolium **VI** is

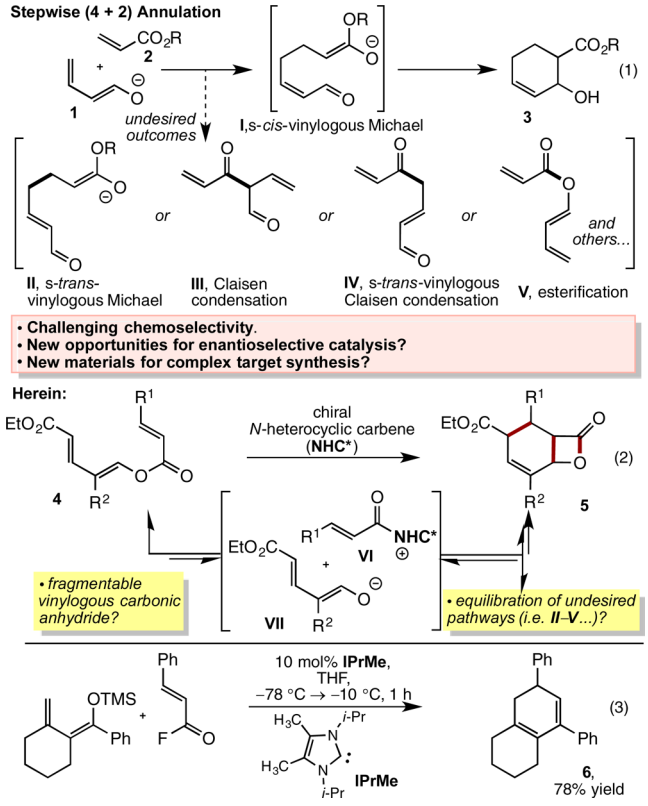

Figure 1. Background.

known to favor conjugate processes, while the moderate nucleophilicity of dienolate **VII** allows reversible reactivity, potentially permitting reaction discovery in the presence of poorly chemo- or stereoselective processes.[11]

To reduce these ideas to practice, studies commenced with ester **4a**. When it was exposed to 10 mol% IMes (**A**), β-lactone **7a** formed, implicating a transformation consistent with the intended design (eq 2), although pyranone **8a** was the major product (Table 1, entry 1). Presumably **7a** forms, rather than the isomeric β-lactone **5** (R^1 = Ph, R^2 = H), due to isomerization of the olefin into conjugation with the ester (*vide infra*). To suppress pyranone formation and favor β-lactone **7**, methyl dienyl ester **4b** was examined, providing β-lactone **7b** in 85% yield and with high diastereoselectivity (Table 1, entry 2). Changing to chiral NHCs **B**, **C**, or **D1**

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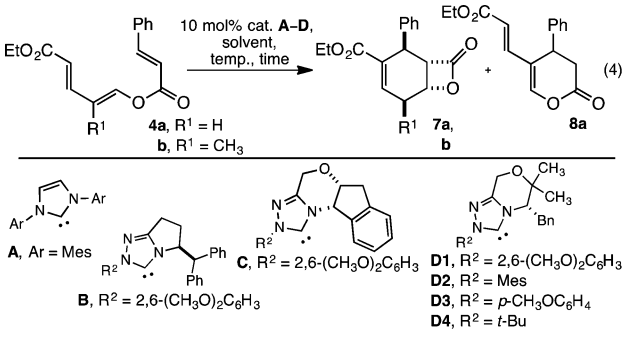
Table 1. Optimization of the Cycloisomerization of 4a,b



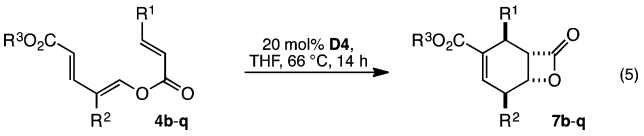
entry	cat.[a]	4	solvent/temp/time	yield[b] (%)	dr[c]	er[d]
1	**A**	**a**	THF/0 → 18 °C/ 2 h	trace (47[e])		
2	**A**	**b**	THF/rt/2 h	85	11:1	–
3	**B**	**b**	THF/rt/60 h	41	>20:1	59:41
4	**C**	**b**	THF/rt/20 h	15	>20:1	–75:25
5	**D1**	**b**	THF/rt/38 h	40	>20:1	89:11
6	**D2**	**b**	THF/rt/20 h	79	>20:1	65:35
7	**D3**	**b**	THF/rt/20 h	16	>20:1	89:11
8	**D4**	**b**	THF/66 °C/20 h	31	>20:1	97:3
9	**D4**	**b**	C_6H_6/80 °C/20 h	37	>20:1	96:4
10	**D4**[f]	**b**	THF/66 °C/20 h	–		
11	**D4**[g]	**b**	THF/66 °C/20 h	–		
12	**D4**	**b**	THF/100 °C/20 h	51	>20:1	98:2
13	**D4**[h]	**b**	THF/66 °C/14 h	71 (89[i])	>20:1	98:2

[a]Catalysts generated with KHMDS except as noted. [b]Isolated yield. [c]Diastereomeric ratio by ^{1}H NMR spectroscopic analysis. [d]Enantiomeric ratio by HPLC over chiral stationary phases. [e]Yield of **8a**. [f]**D4** generated using LiHMDS. [g]**D4** generated using NaHMDS. [h]20 mol% **D4**. [i]Yield based on recovered starting material.

provided moderately enantioenriched β-lactone **7b**[14] (Table 1, entries 3–5), with optimal selectivity obtained with **D1** (89:11 er, Table 1, entry 5). To enhance the enantioselectivity, modification of the *N*-substituent was examined,[15] and while *N*-Mes **D2** and *N*-*p*-$CH_3OC_6H_4$ **D3** failed to improve the outcome (Table 1, entries 6 and 7), *tert*-butyl **D4** provided **7b** in 97:3 er and greater than 20:1 dr (Table 1, entry 8). The reaction was comparable in benzene (Table 1, entry 9); however, it failed when the carbene was generated with NaHMDS or LiHMDS (Table 1, entries 10 and 11).[16] Performing the reaction in a sealed tube at 100 °C increased the yield (Table 1, entry 12), as did increasing catalyst loading, providing **7b** in 98:2 er, >20:1 dr, and 71% yield (Table 1, entry 13), defining conditions for subsequent studies.

To examine the generality of the reaction, a range of dienyl cinnamates (**4b–g**) were prepared. Electron-donating *ortho* or *para* substituents (Table 2, entries 2–4), and electron-withdrawing *para* substituents (Table 2, entry 5), were all tolerated, giving the expected products **7c–f** with excellent enantioselectivity (98:2 → 99:1 er). However, *ortho* bromide **4g** reacted with decreased enantioselectivity, 92:8 er (Table 2, entry 6). Substrates bearing an aliphatic R^1 substituent, i.e. **4h**, reacted smoothly with IMes (**A**) (Table 2, entry 7) but were unreactive toward the **D4** catalyst. Modification of the dienol portion commenced with ethyl dienes **4i** and **j**, giving the β-lactones in 92% and 83% yield, respectively, and identical stereoselectivity (>20:1 dr, 98:2 er) (Table 2, entries 8 and 9). The reaction with isopropyl dienes **4k** and **l** proceeded in acceptable yield but with decreased diastereoselectivity (17:1

Table 2. NHC-Catalyzed Cycloisomerization of 4b–q



entry	R^1	R^2	R^3	4/7	yield[a] (%)	dr[b]	er[c]
1	Ph	CH_3	Et	**b**	71	>20:1	98:2
2	*p*-$CH_3C_6H_4$	CH_3	Et	**c**	67	19:1	98:2
3	*p*-$CH_3OC_6H_4$	CH_3	Et	**d**	54	>20:1	98:2
4	*o*-$CH_3OC_6H_4$	CH_3	Et	**e**	60	>20:1	99:1
5	*p*-BrC_6H_4	CH_3	Et	**f**	54	>20:1	99:1
6	*o*-BrC_6H_4	CH_3	Et	**g**	51	>20:1	92:8
7[d]	$(CH_2)_4CH_3$	CH_3	Et	**h**	71	>20:1	
8	Ph	Et	Et	**i**	92	>20:1	98:2
9	*p*-$CH_3C_6H_4$	Et	Et	**j**	83	>20:1	98:2
10[e]	Ph	*i*-Pr	Et	**k**	66	17:1	92:8
11[e]	*p*-$CH_3C_6H_4$	*i*-Pr	Et	**l**	58	15:1	93:7
12	Ph	Bn	Et	**m**	88	>20:1	98:2
13	*p*-$CH_3C_6H_4$	Bn	Et	**n**	72	>20:1	99:1
14	Ph	CH_3	CH_3	**o**	71	>20:1	99:1
15	*p*-$CH_3C_6H_4$	CH_3	CH_3	**p**	69	19:1	97:3
16	Ph	CH_3	*i*-Pr	**q**	69	>20:1	98:2

[a]Isolated yield. [b]Diastereomeric ratio by ^{1}H NMR spectroscopic analysis. [c]Enantiomeric ratio by HPLC over chiral stationary phases. [d]Performed with IMes (**A**). [e]Substrates **4k,l** (~1:1) of enol diastereomers.

and 15:1) and enantioselectivity (92:8 and 93:7 er), a result potentially related to the use of diastereomerically impure substrates (Table 2, entries 10 and 11). In contrast, benzyl-substituted dienes **4m** and **n** both gave the expected products in good yield, diastereoselectivity (>20:1 dr), and enantioselectivity (98:2 and 99:1 er) (Table 2, entries 12 and 13). Unfortunately, when R^2 was a phenyl group the reaction failed, with starting materials recovered. Finally, the ethyl ester (R^3) could be replaced with either a methyl (**4o** and **p**) or isopropyl (**4q**) ester without adversely affecting the reaction outcome (Table 2, entries 14–16).

Insight into the reaction mechanism was initially derived from investigation of the fragmentation of the dienyl esters. Thus, the crossover of **4b** and **p** was conducted (eq 6 in Figure 2). While crossed products were observed, the uncrossed products dominated (**7b** + **p**:**c** + **o**, 11:5), a result consistent with fragmentation to ion-paired acyl azolium (i.e., **VI**) and dienolate (i.e., **VII**). To examine the olefin isomerization, deuterium-labeled substrates 2D-**4b** and αD-**4b** were prepared. When 2D-**4b** was subjected to the reaction conditions, 2D-**7b** formed with excellent stereoselectivity but significantly reduced yield (cf. **4b**) (eq 7 in Figure 2). Furthermore, deuterium was identified at C5, as expected with olefin isomerization following cyclization, and also at C1. When αD-**4b** was subjected to the reaction conditions, outcomes similar to those observed with the undeuterated variant (Table 2, entry 1) were obtained, although again with deuteration at C1 and C5 (eq 8 in Figure 2). To demonstrate that the deuteration pattern does not arise following β-lactone formation, αD-**7b** was resubjected to the reaction conditions and isolated unchanged. These results are consistent with olefin isomerization prior to β-lactonization. From these studies, a mechanism for the (4+2) annulation can be proposed (Figure 2). Initial addition of the NHC to carbonic anhydride **4b** gives acyl azolium **VI** and enolate *s-cis*-

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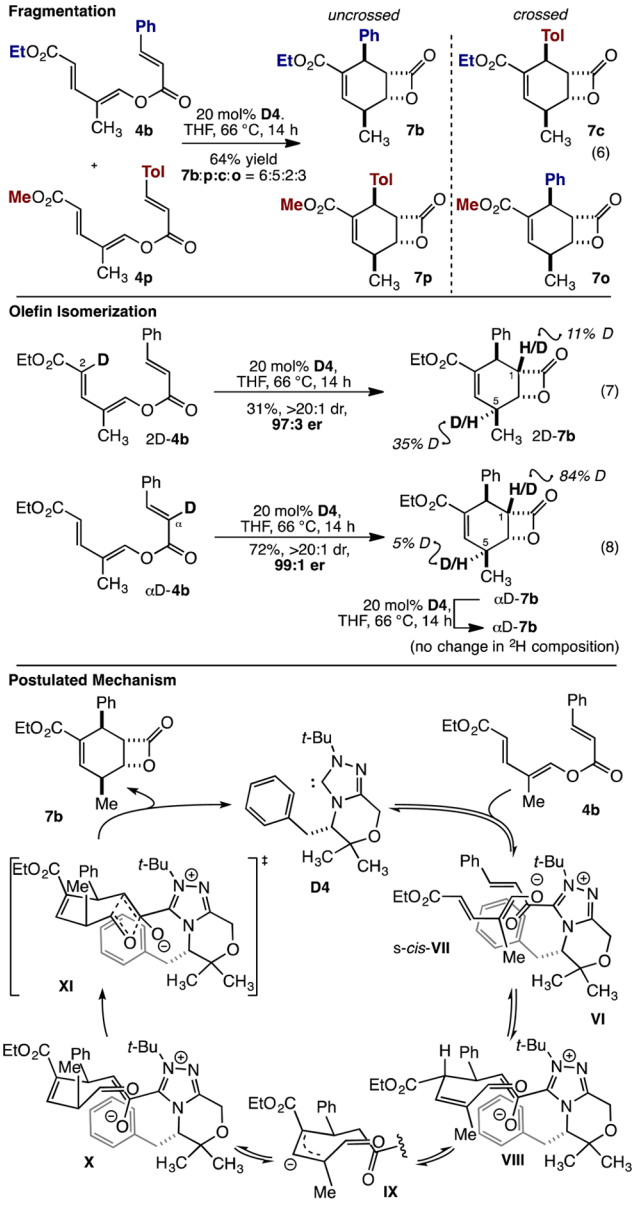


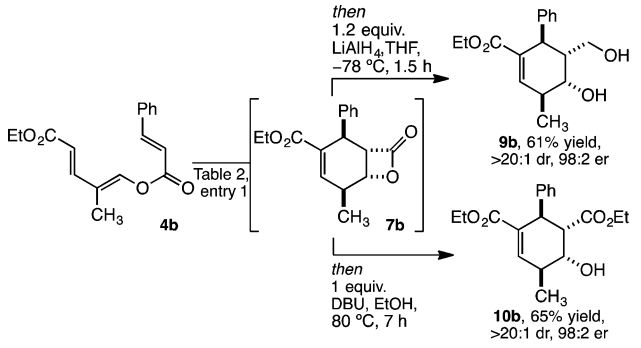
Figure 2. Mechanistic studies.

VII. Vinylogous Michael addition provides acyl azolium enolate **VIII**, which undergoes proton transfer, via **IX**, to afford **X**. β-Lactonization,[17] via a pseudo-concerted aldol/β-lactonization (transition state **XI**)[9b] or the spirocyclic pathway proposed by Scheidt and Cheong,[18] affords, following loss of **D4**, β-lactone **7b**. While the vinylogous Michael reaction of the s-*trans* conformer of **VII** is potentially viable, both the likely reversibility of the reaction and the olefin isomerization sequence provide opportunities to converge upon intermediate **X** and hence provide common product **7b**.

Finally, to examine the utility of the cyclohexyl β-lactones **7**, chemoselective derivatization using one-pot, two-step procedures was examined (Scheme 1). It was possible to reductively ring-open the β-lactone using $LiAlH_4$ at low temperature to afford diol **9b** in 61% yield, >20:1 dr, and 98:2 er, while treatment of β-lactone **7b** with ethanol and DBU provided diester **10b** with similar yield and identical stereoselectivity.

In this communication, we report the enantioselective cycloisomerization of dienyl cinnamates to enantioenriched

Scheme 1. Derivatization Studies



cyclohexenes. These products are inaccessible via Diels–Alder reactions, which would require 2H-oxet-2-one as the dienophile, a structure proposed in computational studies. Further examination of the utility of this reaction, and methods to expand the generality and catalyst activity, are topics of ongoing investigation.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, ^1H, and ^{13}C NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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