

# N-Heterocyclic Carbene Catalyzed Ring Expansion of Formylcyclopropanes: Synthesis of 3,4-Dihydro- $\alpha$ -pyrone Derivatives

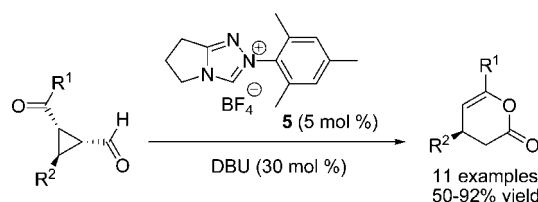
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## ABSTRACT



N-Heterocyclic carbene catalyzed ring expansion of readily accessible 2-acyl-1-formylcyclopropanes was developed. With 5 mol % of triazolium salt 5 and 30 mol % of DBU, ring expansion of various 2-acyl-1-formylcyclopropanes led to 3,4-dihydro- $\alpha$ -pyrones in good to excellent yields.

Reversing the reactivity of aldehydes (also known as umpolung<sup>1</sup>) by *N*-heterocyclic carbenes (NHCs) has become an intense area, providing an unconventional access to some important target molecules.<sup>2</sup> In recent years, NHCs were also found to catalyze various redox-type transformations of functionalized aldehydes containing reducible functionalities.<sup>3</sup> Remarkably, Bode and co-workers reported that formyl-substituted three-membered rings such as epoxides, aziridines, and cyclopropanes underwent ring opening during

redox esterifications.<sup>4</sup> Inspired by their findings, we developed the ring expansion of 4-formyl- $\beta$ -lactams, a class of four-membered ring compounds, catalyzed by a *N*-heterocyclic carbene<sup>5</sup> and its kinetic resolution version by a chiral *N*-heterocyclic carbene.<sup>6</sup> Very recently, Gravel and co-

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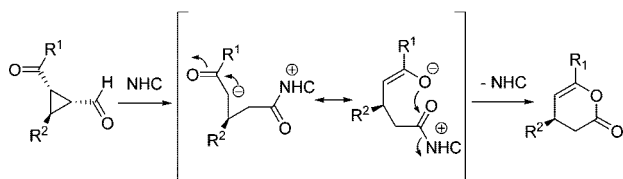
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workers realized the ring-expansion lactonization of oxacycloalkane-2-carboxaldehydes, providing functionalized five-, six-, and seven-membered lactones.<sup>7</sup> Both of the above two reactions feature the expansion of the ring size by one.

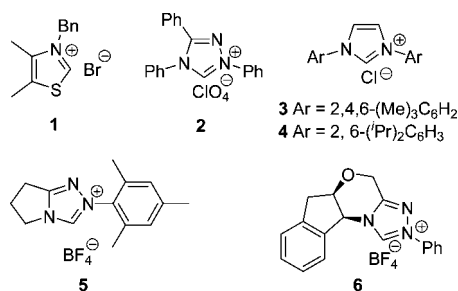
Given the fact that 3,4-dihydro- $\alpha$ -pyrones are useful intermediates for the synthesis of  $\gamma$ -lactones, substituted benzenoids, pyridones, etc.<sup>8</sup> and their efficient syntheses are however still limited,<sup>8d,9</sup> we decided to contribute a facile synthesis of 3,4-dihydro- $\alpha$ -pyrones during our work toward NHC catalysis.<sup>10</sup> This work is also inspired by the elegant work from Bode and Sohn, where in the presence of a NHC catalyst 2-acyl-1-formylcyclopropanes underwent ring opening during redox esterifications.<sup>4b</sup> The idea originated from the answer to the following question: how does the reaction proceed in the absence of the external nucleophile during Bode's ring opening of 2-acyl-1-formylcyclopropanes? We envisioned that 2-acyl-1-formylcyclopropanes in the presence of a NHC catalyst might also undergo the ring expansion affording 3,4-dihydro- $\alpha$ -pyrones, since the ketone enolate generated from the ring opening would serve as nucleophile (Figure 1). If so, this would provide a new reaction model



**Figure 1.** Possible ring expansion of 2-acyl-1-formylcyclopropanes by NHC.

with expansion of the ring size by three. Herein, we report our preliminary results from the study on this subject.

Our studies began with an initial examination of the catalytic reactivity of several NHCs (Figure 2) for the



**Figure 2.** Several readily available NHC precursors.

possible ring expansion of formylcyclopropane **7a**.<sup>11</sup> To our delight, with 20 mol % triazolium salt **5** and 30 mol % DBU in THF, the substrate **7a** was smoothly converted to 3,4-dihydro- $\alpha$ -pyrone **8a** (65% yield). Under the same conditions, several other NHCs derived from **1–4** and **6** proved

less effective.<sup>12</sup> Notably, Du and Wang recently reported a similar ring expansion reaction.<sup>13</sup> NHC derived from **3** was found efficient in their case since the more reactive substrate, ethyl 1-acetyl-2-formylcyclopropanecarboxylate, was used therein.

Further examination of the solvents, temperature, and catalyst loading led to the optimal reaction conditions: 5 mol % **5**, 30 mol % DBU, and 4 Å MS in dioxane at 65 °C. Under these conditions, various 2-acyl-1-formylcyclopropanes were tested to investigate the generality of the reaction. The results are summarized in Table 1. For the R<sup>2</sup> groups,

**Table 1.** NHC-Catalyzed Ring Expansion of Formylcyclopropanes<sup>a</sup>

entry	<b>7</b>	R <sup>1</sup> , R <sup>2</sup>	time (h)	<b>8</b> , yield (%) <sup>b</sup>
1 <sup>c</sup>	<b>7a</b>	C <sub>6</sub> H <sub>5</sub> , C <sub>6</sub> H <sub>5</sub>	24	<b>8a</b> , 92
2	<b>7b</b>	C <sub>6</sub> H <sub>5</sub> , <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	6	<b>8b</b> , 85
3	<b>7c</b>	C <sub>6</sub> H <sub>5</sub> , <i>p</i> -Br-C <sub>6</sub> H <sub>4</sub>	6	<b>8c</b> , 75
4	<b>7d</b>	C <sub>6</sub> H <sub>5</sub> , <i>m</i> -Cl-C <sub>6</sub> H <sub>4</sub>	5	<b>8d</b> , 78
5	<b>7e</b>	C <sub>6</sub> H <sub>5</sub> , H	8	<b>8e</b> , 50
6	<b>7f</b>	C <sub>6</sub> H <sub>5</sub> , Me	3	<b>8f</b> , 55
7	<b>7g</b>	C <sub>6</sub> H <sub>5</sub> , <sup><i>n</i></sup> Pr	4	<b>8g</b> , 63
8	<b>7h</b>	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> , C <sub>6</sub> H <sub>5</sub>	7	<b>8h</b> , 73
9	<b>7i</b>	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub> , C <sub>6</sub> H <sub>5</sub>	10	<b>8i</b> , 70
10	<b>7j</b>	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> , C <sub>6</sub> H <sub>5</sub>	10	<b>8j</b> , 68
11 <sup>d</sup>	<b>7k</b>	<sup><i>t</i></sup> Bu, C <sub>6</sub> H <sub>5</sub>	12	<b>8k</b> , 30

<sup>a</sup> Reaction conditions: **7** (1.0 mmol), 5 mol % **5**, 30 mol % DBU, 4 Å MS (0.1 g) in dioxane (5.0 mL) at 65 °C. <sup>b</sup> Isolated yields. <sup>c</sup> 2 mol % **5** and 5 mol % DBU were used. <sup>d</sup> **8i** was isolated in 30% yield.

substrates **7a–d** bearing phenyl with different electronic properties all underwent the ring expansion smoothly to afford the dihydro- $\alpha$ -pyrones in good yields (75–92%, entries 1–4, Table 1). The current method was also suitable for the aliphatic substituted substrates **7f**, **7g** (entries 6 and 7, Table 1). For the R<sup>1</sup> group, aryl ketones **7 h–j** bearing either an electron-withdrawing or electron-donating substituent on the phenyl group were well tolerated, with yields ranging from 68% to 73% (entries 8–10, Table 1). When an aliphatic ketone substrate such as **7k** was used, the reaction gave **8k** in 30% yield together with **8i** (30% yield) (entry 11, Table 1).

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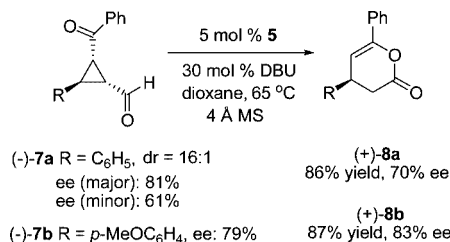
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Since the enantioenriched 2-acyl-1-formylcyclopropanes are easily accessed,<sup>11a</sup> the synthesis of optically active 3,4-dihydro- $\alpha$ -pyrones was also tested.

As shown in Scheme 1, starting from optically active substrates (–)-**7a** and (–)-**7b**, the reaction gave their

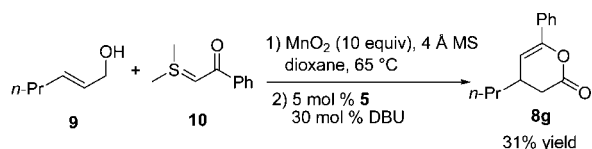
**Scheme 1.** Synthesis of Optically Active 3,4-Dihydro- $\alpha$ -pyrones



corresponding ring expansion products (+)-**8a** and (+)-**8b** in 86% and 87% yield, respectively, without notable loss of the optical purity. The ee values of (–)-**7a** and (–)-**7b** were determined by converting to their corresponding primary alcohols.<sup>11b</sup>

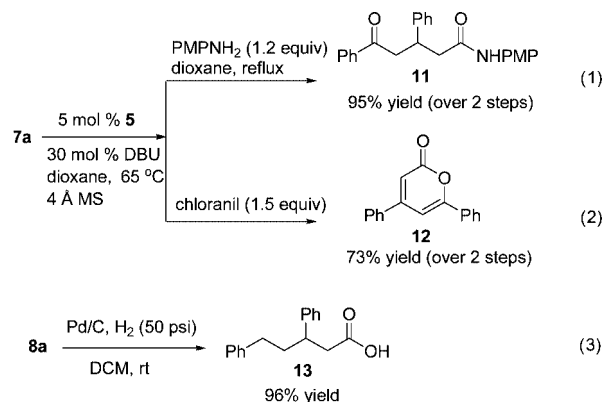
As 2-acyl-1-formylcyclopropanes could be synthesized via a one-pot procedure from allylic alcohol and 2-(dimethyl-l-sulfanylidene)- $\lambda$ -phenyl-ethanone in the presence of activated manganese dioxide, as reported by Taylor and co-workers,<sup>14</sup> we therefore tested the one-pot procedure further to include the ring expansion. To our delight, starting from allylic alcohol **9** and ylide **10**, 3,4-dihydro- $\alpha$ -pyrone **8g** could be synthesized in 31% yield via a one-pot procedure involving multiple steps (Scheme 2).

**Scheme 2.** One-Pot Synthesis of 3,4-Dihydro- $\alpha$ -pyrones from Allylic Alcohols



To demonstrate the applications of the current methodology, several ready transformations of 3,4-dihydro- $\alpha$ -pyrones were carried out (Scheme 3). The in situ generated 3,4-dihydro- $\alpha$ -pyrone **8a** from the ring expansion of **7a** would lead to ring opening product **11** and 4,6-diphenyl-2H-pyran-

**Scheme 3.** Transformations of 3,4-Dihydro- $\alpha$ -pyrones



one **12** upon treatment by *p*-anisidine in refluxed dioxane and chloranil, respectively (eqs 1 and 2). The latter is a very useful intermediate in organic synthesis.<sup>15</sup> In addition, the reductive ring-opening reaction of **8a** to carboxylic acid **13** was accomplished in excellent yield by hydrogenation on Pd/C.

In summary, we have developed a novel reaction pattern catalyzed by *N*-heterocyclic carbene where 3,4-dihydro- $\alpha$ -pyrones were synthesized efficiently from 2-acyl-1-formylcyclopropanes under mild conditions. The ready accessibility of the starting materials even in enantiopure form make the current methodology particularly attractive in organic synthesis. Further transformations of the resulting 3,4-dihydro- $\alpha$ -pyrones are ongoing.

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**Supporting Information Available:** Experimental procedures and analysis data for **7**, **8**, and **11–13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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