

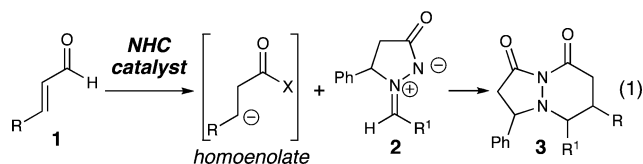
## Highly Stereoselective Formal [3 + 3] Cycloaddition of Enals and Azomethine Imines Catalyzed by *N*-Heterocyclic Carbenes

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Intermolecular cycloadditions are powerful methods for the convergent synthesis of cyclic compounds from simple precursors.<sup>1</sup> While major advances have been made in the area of metal-catalyzed cycloadditions over the past decade,<sup>2</sup> there is great potential for these reactions using organic molecules as catalysts.<sup>3</sup> In 1968, Dorn and co-workers demonstrated that 3-oxopyrazolidin-1-ium-2-ides such as **2** are stable and easily handled compounds.<sup>4,5</sup> Fu, Hayashi, and Suga have separately shown that these compounds are efficient substrates in metal-catalyzed cycloadditions to furnish five- and six-membered heterocycles.<sup>6</sup> We have been interested in developing new reactions catalyzed by *N*-heterocyclic carbenes (NHCs) derived from azolium salts.<sup>7</sup> Our recent studies, along with those of Glorius, Bode, and Nair, have shown that the combination of NHCs and  $\alpha,\beta$ -unsaturated aldehydes generates unique homoenolate species.<sup>8,9</sup> The use of an organic molecule to catalyze a formal [3 + 3] cycloaddition of azomethine imines has yet to be realized.<sup>10</sup> Herein, we report the direct synthesis of pyridazinones (**3**) by the NHC-catalyzed reaction of aldehyde (**1**) and azomethine imines (**2**, eq 1).



Our proposed pathway for this formal [3 + 3] cycloaddition involves the addition of an NHC to an  $\alpha,\beta$ -unsaturated aldehyde (**1**) to afford the extended Breslow intermediate (**I**) after addition and rearrangement (Scheme 1). The homoenolate intermediate undergoes addition to the azomethine imine (**2**) and subsequently generates enol **II**. After tautomerization of **II**, the resulting activated heteroazolium species **III** releases the NHC catalyst and affords the pyridazinone (**3**) by an intramolecular acylation.

A challenge with NHC catalysis is the presence of two separate electrophiles during a reaction. A successful process must allow for selective interaction between the carbene and the  $\alpha,\beta$ -unsaturated aldehyde. Irreversible addition of the carbene to the secondary electrophile (e.g., azomethine imine) would result in no reaction. Our studies began with cinnamaldehyde (**1a**), azomethine imine **2a**, and heteroazolium salts A–C (Table 1, entries 1–3). To our gratification, all three catalysts derived from heteroazolium salts A–C produced the desired product **4** as a *single diastereomer*.<sup>11</sup> While benzimidazolium salt **C** afforded the highest yield (39%, entry 3), the process clearly required improvement. Reactions in THF required heating to induce homogeneity (entries 4 and 5) but did not improve yields compared to  $\text{CH}_2\text{Cl}_2$ . Carefully monitoring the reaction revealed that shorter times (3 vs 24 h) significantly improve the yield of **4** (entries 6 and 7). Additionally, increasing the temperature of the reaction to 40 °C favors the [3 + 3] cycloaddition manifold with a further increase in yield (79%, entry 8). With these temperature parameters identified, an extensive re-

Scheme 1. Proposed Catalytic Pathway

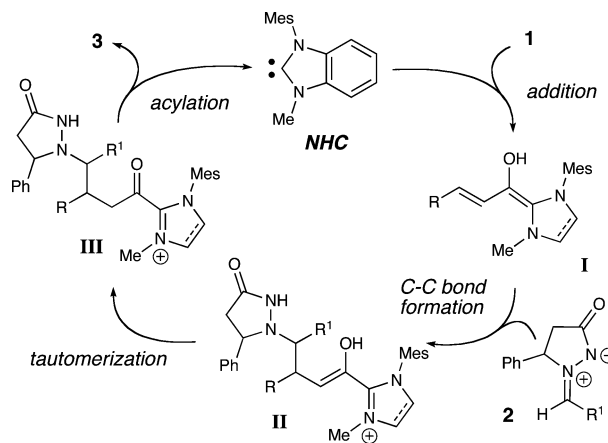


Table 1. Optimization of Conditions<sup>a</sup>

entry	catalyst	conditions	yield (%) <sup>b</sup>	dr <sup>c</sup>
1	A	$\text{CH}_2\text{Cl}_2$ , 23 °C, 24 h	35	>20:1
2	B	$\text{CH}_2\text{Cl}_2$ , 23 °C, 24 h	29	>20:1
3	C	$\text{CH}_2\text{Cl}_2$ , 23 °C, 24 h	39	>20:1
4	C	THF, 50 °C, 24 h	15	>20:1
5	C	10:1 THF/BuOH, 50 °C, 24 h	23	>20:1
6	C	$\text{CH}_2\text{Cl}_2$ , 23 °C, 3 h	45	>20:1
7	C	10:1 THF/BuOH, 50 °C, 3 h	59	>20:1
8	C	$\text{CH}_2\text{Cl}_2$ , 40 °C, 2 h	79	>20:1
9 <sup>d</sup>	C	$\text{CH}_2\text{Cl}_2$ , 40 °C, 2 h	46	>20:1

<sup>a</sup> With 2 equiv of **1a** and 1 equiv of **2a**. <sup>b</sup> Isolated yield after purification. <sup>c</sup> As determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup> With 10 mol % of **C** and 10 mol % of DBU.

examination of different azolium salts confirmed that the placement of a single *N*-mesityl substituent on the benzimidazole core is necessary for good yields. Decreasing the catalyst loading of **C** decreases the yield of **4** to 46% (entry 9).

With the optimal parameters established for this formal [3 + 3] cycloaddition process, we turned our attention to investigate the scope of this reaction (Table 2, eq 3). A survey of the  $\alpha,\beta$ -unsaturated aldehyde reveals that the process accommodates electron-donating groups on the aryl ring (entries 1–5), but electron-withdrawing groups (entry 8) do not yield products. The reaction also tolerates  $\beta$ -alkyl substituents and extended dienyl systems to afford **9** and **10** in moderate yields (entries 6 and 7). An

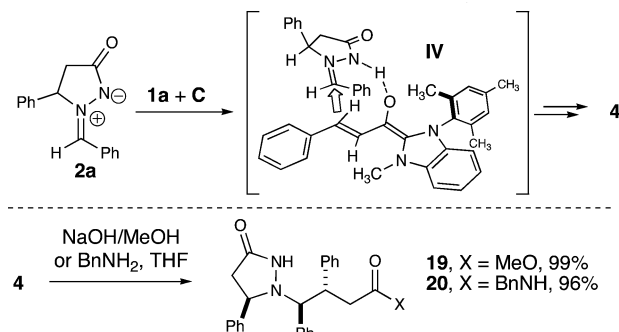
Table 2. Substrate Scope<sup>a</sup>

entry	R	R <sup>1</sup>	product	yield (%) <sup>b</sup>	dr <sup>c</sup>
1	Ph ( <b>1a</b> )	Ph ( <b>2a</b> )	<b>4</b>	79	>20:1
2	4-OMePh ( <b>1b</b> )	Ph ( <b>2a</b> )	<b>5</b>	76	>20:1
3	3-OMePh ( <b>1c</b> )	Ph ( <b>2a</b> )	<b>6</b>	79	>20:1
4	2-OMePh ( <b>1d</b> )	Ph ( <b>2a</b> )	<b>7</b>	94	>20:1
5	2-naphthyl ( <b>1e</b> )	Ph ( <b>2a</b> )	<b>8</b>	77	>20:1
6	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ( <b>1f</b> )	Ph ( <b>2a</b> )	<b>9</b>	67	>20:1
7	HC=CHCH <sub>3</sub> ( <b>1g</b> )	Ph ( <b>2a</b> )	<b>10</b>	51	>20:1
8	4-ClPh ( <b>1h</b> )	Ph ( <b>2a</b> )	<b>11</b>	0	
9	Ph ( <b>1a</b> )	4-BrPh ( <b>2b</b> )	<b>12</b>	87	>20:1
10	Ph ( <b>1a</b> )	4-FPh ( <b>2c</b> )	<b>13</b>	82	>20:1
11	Ph ( <b>1a</b> )	3-CF <sub>3</sub> Ph ( <b>2d</b> )	<b>14</b>	93	>20:1
12	Ph ( <b>1a</b> )	3-BrPh ( <b>2e</b> )	<b>15</b>	78	>20:1
13	Ph ( <b>1a</b> )	3-CH <sub>3</sub> Ph ( <b>2f</b> )	<b>16</b>	76	>20:1
14	Ph ( <b>1a</b> )	3-OMePh ( <b>2g</b> )	<b>17</b>	67	>20:1
15	Ph ( <b>1a</b> )	cyclohexyl ( <b>2h</b> )	<b>18</b>	0	

<sup>a</sup> With 2 equiv of **1** and 1 equiv of **2**, 0.25 M. <sup>b</sup> Isolated yield after purification. <sup>c</sup> Determined by 500 MHz <sup>1</sup>H NMR spectroscopy. Relative stereochemistry of **16** determined by X-ray crystallography and further assigned by analogy. See Supporting Information for details.

examination of the azomethine imine component indicates that variously substituted aryl groups are competent substrates. Electron-withdrawing groups on the aryl ring of the imine afford good to excellent yields of the pyridazinones (entries 9–12). Placing an electron-donating group on the aryl ring is also a suitable partner (entry 14), albeit in reduced yield (67%). While enolizable or 2-substituted aryl substituents at R<sup>1</sup> of **2** do not afford any pyridazinones, all productive reactions are highly diastereoselective (>20:1 dr), favoring the all *syn* stereoisomers.

The current model for the high levels of *syn* diastereoselectivity for the products invokes a hydrogen bonding assembly (**IV**) between the imine and the carbene–aldehyde adduct. The catalyst structure enforces an extended geometry of the carbene–aldehyde adduct (**I**, as the *Z(O)* enol), and this nucleophilic intermediate approaches away from the phenyl substituent on the azomethine ring.<sup>12</sup> Our initial investigations of the reactivity of the pyridazinone compounds have determined that substituted esters and amides (e.g., **19** and **20**) can be accessed in excellent yields by a highly selective ring opening upon addition of methanol or benzyl amine to a solution of the pyridazinone (**4**).<sup>13</sup>



In summary, we have developed the first formal [3 + 3] cycloaddition reaction catalyzed by *N*-heterocyclic carbenes. The addition of an *N*-mesityl benzimidazolyl carbene to an  $\alpha,\beta$ -unsaturated aldehyde generates a homoenolate intermediate that undergoes an addition/acylation sequence with an azomethine imine to afford new bicyclic heterocycles with excellent diastereoselectivity. The pyridazinone products can be manipulated to provide

esters or amides in excellent yields upon addition of alcohols or amines. Further studies generating nucleophiles with unique properties using *N*-heterocyclic carbene catalysis are ongoing.

**Acknowledgment.** Research support was generously provided by NIGMS (ROI GM73072), Abbott Laboratories, Amgen, 3M, and Boehringer Ingelheim. A.C. is the recipient of a Dow Chemical Company Fellowship. We thank FMCLithium, Sigma-Aldrich, and BASF for providing reagents used in this research, Troy Reynolds (NU) for assistance with X-ray crystallography, and Prof. Regan Thomson (NU) for helpful discussions. Funding for the NU Analytical Services Laboratory has been furnished in part by the NSF (CHE-9871268).

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0709167