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

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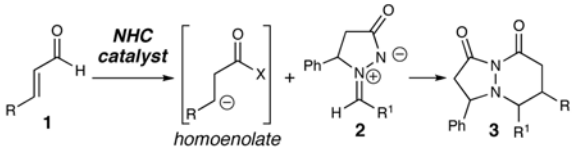
Intermolecular cycloadditions are powerful methods for the convergent synthesis of cyclic compounds from simple precursors.[1] While major advances have been made in the area of metal-catalyzed cycloadditions over the past decade,[2] there is great potential for these reactions using organic molecules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




**(1).**
Our proposed pathway for this formal [3 + 3] cycloaddition involves the addition of an NHC to an α,β-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 α,β-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*.[11] 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 4–5), but did not improve yields compared to $CH_2Cl_2$. Carefully monitoring the reaction revealed that shorter times (3 h vs. 24 h) significantly improves the

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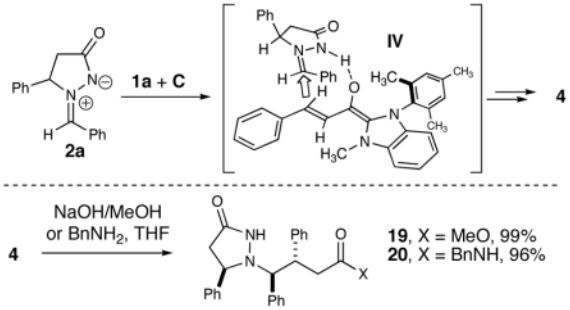
yield of **4** (entries 6–7). Additionally, increasing the temperature of the reaction to 40 °C favors the [3 + 3] cycloaddition manifold with a further increase in yield (79%, entry 8). With these temperature parameters identified, an extensive re-examination of different azolium salts confirmed that 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 out attention to investigate the scope of this reaction (Table 2, eq 3). A survey of the α,β-unsaturated aldehyde reveals 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 β-alkyl substituents and extended dienylic systems to afford **9** and **10** in moderate yields (entries 6–7). An 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 $R^1$ 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.[12] 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**).[13]




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 α,β-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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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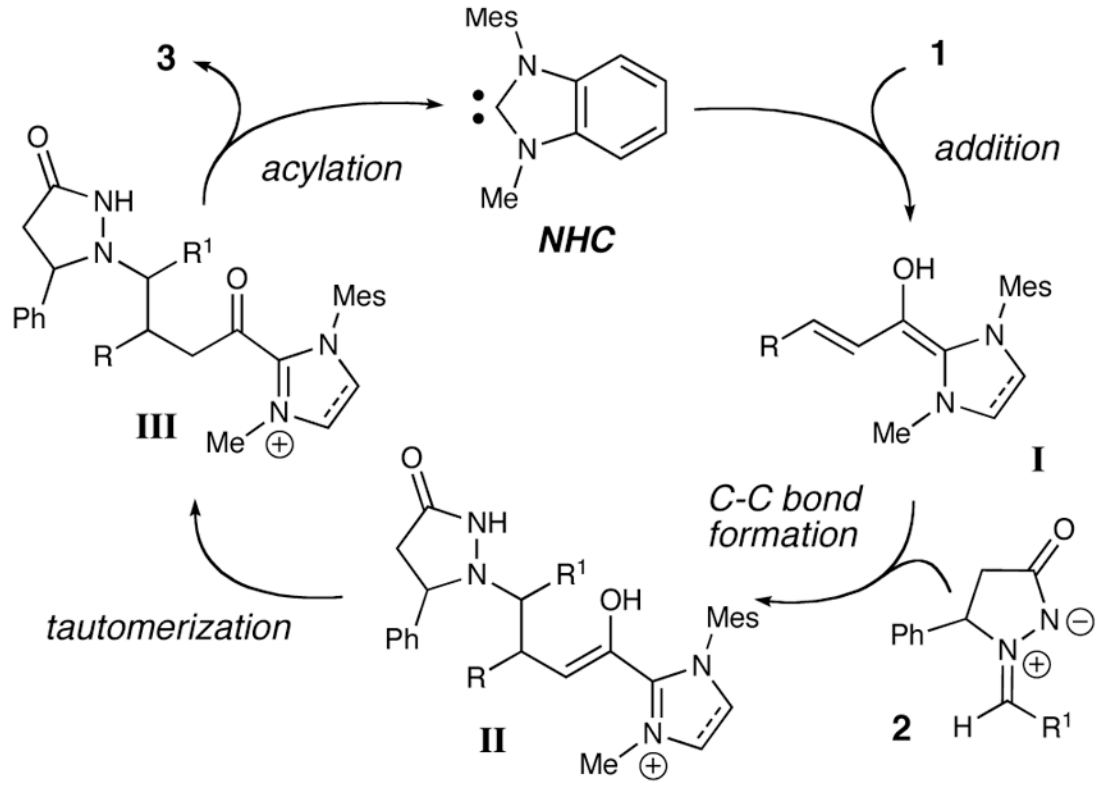
11. Azomethine imines lacking the phenyl substituent on the ring afford products, but in reduced yields.

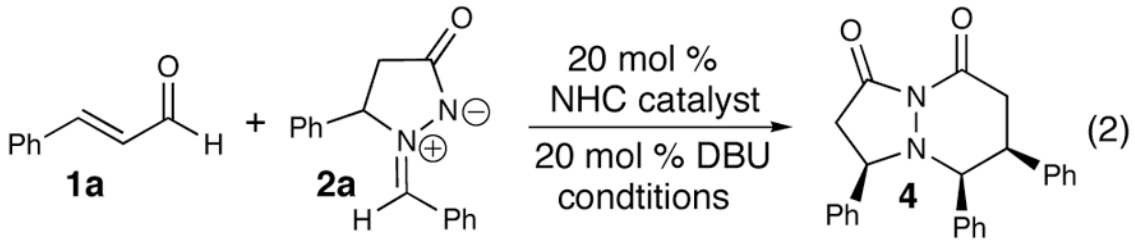
12. The *Z*(*O*) enol isomer of **I** in **IV** minimizes interactions between the *N*-mesityl group and the imine phenyl ring.
13. Laurent E, Lee SK, Pellissier N. J Chem Res Miniprint 1978:5201–5218.Additional studies on the synthetic utility of these unusual heterocycles are ongoing



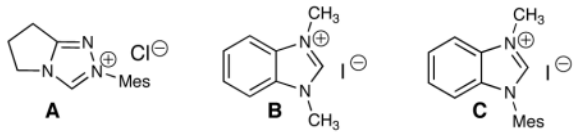

**Scheme 1.**
Proposed Catalytic Pathway

**Table 1**

Optimization of Conditions[a]




| entry | catalyst | conditions | yield (%)[b] | d.r.[c] |
|---|---|---|---|---|
| 1 | **A** | $CH_2Cl_2$, 23 °C, 24 h | 35 | >20:1 |
| 2 | **B** | $CH_2Cl_2$, 23 °C, 24 h | 29 | >20:1 |
| 3 | **C** | $CH_2Cl_2$, 23 °C, 24 h | 39 | >20:1 |
| 4 | **C** | THF, 50 °C, 24 h | 15 | >20:1 |
| 5 | **C** | 10:1 THF/$^t$BuOH, 50 °C, 24h | 23 | >20:1 |
| 6 | **C** | $CH_2Cl_2$, 23 °C, 3 h | 45 | >20:1 |
| 7 | **C** | 10:1 THF/$^t$BuOH, 50 °C, 3h | 59 | >20:1 |
| 8 | **C** | $CH_2Cl_2$, 40 °C, 2 h | 79 | >20:1 |
| 9[d] | **C** | $CH_2Cl_2$, 40 °C, 2 h | 46 | >20:1 |




[a] 2 equiv. **1a** and 1 equiv. **2a**.

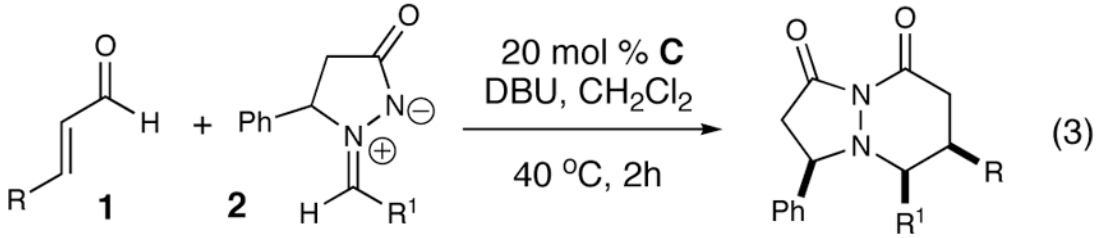
[b] Isolated yield after purification.

[c] As determined by $^1$H NMR spectroscopy.

[d] 10 mol % C, 10 mol % DBU.

**Table 2**

Substrate Scope[a]




| entry | R | $R^1$ | product | yield (%)[b] | d.r.[c] |
|---|---|---|---|---|---|
| 1 | Ph (**1a**) | Ph (**2a**) | **4** | 79 | >20:1 |
| 2 | 4-OMePh(**1b**) | Ph (**2a**) | **5** | 76 | >20:1 |
| 3 | 3-OMePh(**1c**) | Ph (**2a**) | **6** | 79 | >20:1 |
| 4 | 2-OMePh (**1d**) | Ph (**2a**) | **7** | 94 | >20:1 |
| 5 | 2-naphthyl (**1e**) | Ph (**2a**) | **8** | 77 | >20:1 |
| 6 | $CH_2CH_2CH_3$(**1f**) | Ph (**2a**) | **9** | 67 | >20:1 |
| 7 | $HC{=}CHCH_3$(**1g**) | Ph (**2a**) | **10** | 51 | >20:1 |
| 8 | 4-ClPh(**1h**) | Ph (**2a**) | **11** | 0 | - |
| 9 | Ph (**1a**) | 4-BrPh (**2b**) | **12** | 87 | >20:1 |
| 10 | Ph (**1a**) | 4-FPh (**2c**) | **13** | 82 | >20:1 |
| 11 | Ph (**1a**) | 3-$CF_3$Ph (**2d**) | **14** | 93 | >20:1 |
| 12 | Ph (**1a**) | 3-BrPh (**2e**) | **15** | 78 | >20:1 |
| 13 | Ph (**1a**) | 3-$CH_3$Ph (**2f**) | **16** | 76 | >20:1 |
| 14 | Ph (**1a**) | 3-OMePh (**2g**) | **17** | 67 | >20:1 |
| 15 | Ph (**1a**) | cyclohexyl (**2h**) | **18** | 0 | - |

[a] **2** equiv. **1** and 1 equiv. **2**,0.25 M.

[b] Isolated yield after purification.

[c] Determined by 500 MHz $^1$H NMR spectroscopy. Relative stereochemistry of **16** determined by X-ray crystallography and further assigned by analogy. See Supporting Information for details.