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N-Heterocyclic carbene (NHC) catalyzed annulation of enals and vinyl ketones: a novel synthesis of [2*H*]-pyranones

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This paper is dedicated with best wishes to Professor Gilbert Stork on the occasion of his 90th birthday

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ABSTRACT

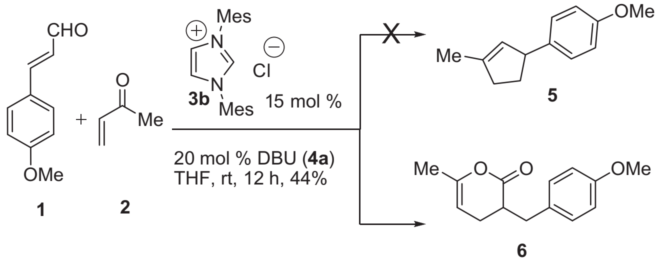
Homoenolate annulation of vinyl ketones led to the synthesis of dihydropyranones in contrast to cyclopentenes obtained by the homoenolate annulation of chalcones, another class of α,β-unsaturated ketones.

The quest for the discovery of efficient, ecofriendly catalysts for the construction of carbon–carbon bonds is a perennial issue in organic synthesis. The renaissance of organocatalysis,[1] in general, and the recognition of the unique polarity reversal (umpolung) property of *N*-heterocyclic carbenes (NHCs)[2] in particular, amply illustrate this point. Recent investigations in a number of laboratories have uncovered a variety of catalytic processes initiated by NHCs, the most interesting of these being the generation of homoenolates from enals, discovered by Glorius[3] and Bode.[4] Subsequent to their original work on the synthesis of γ-lactones, a multitude of NHC catalyzed homoenolate reactions have emerged.[5] Inter alia, the synthesis of γ-spirolactones,[6] pyrazolidinones,[7] pyridazininones,[8] spirocyclopentanones,[9] lactams,[10] and cyclopentanols[11] are noteworthy. Homoenolates have also been shown to add efficiently to nitrostyrenes[12] and sulfonimines leading to the precursors for novel γ-aminobutyric acid derivatives.[13] A reaction that intrigued us most was the NHC mediated annulation of enals with chalcones leading to cyclopentenes.[14] Our early studies were confined to the reaction of aryl enals and aryl enones. In the continuing efforts to define the scope of this reaction, we investigated the annulations of enals with vinyl ketones. To our surprise, this reaction followed a different pathway to yield [2*H*]-pyranones exclusively.[15] The results of these studies are presented in this Letter. Recently Bode[16a] and Chi[16b] have reported the formation of δ-enol lactones by the reaction of enals with γ-ketoesters and alkylidene diketones, respectively.

In an initial experiment 4-methoxy cinnamaldehyde (**1**, 1.5 equiv), IMesCl (0.15 equiv), and methyl vinyl ketone were taken in THF. After the addition of DBU (0.2 equiv), the solution was stirred for 12 h. The reaction mixture on column chromatography yielded the product as a pale brown colored liquid which was characterized as 3-(4-methoxybenzyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-one (**6**) (Scheme 1).

Subsequent to the preliminary experiments, it was found that the reaction worked more efficiently when IMesCl (**3b**) is used as the catalyst and DMAP (**4b**) as the base (Table 1).

The reaction was extended to a number of α,β-unsaturated aldehydes and the results are summarized in Table 2.



Scheme 1. Reaction of enal **1** with methyl vinyl ketone.

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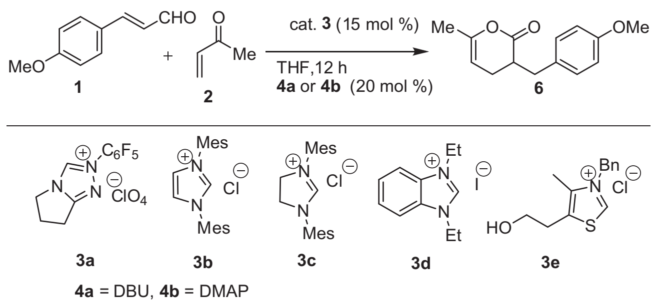
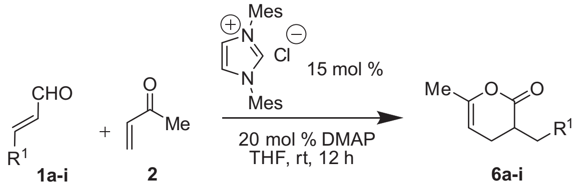
Table 1



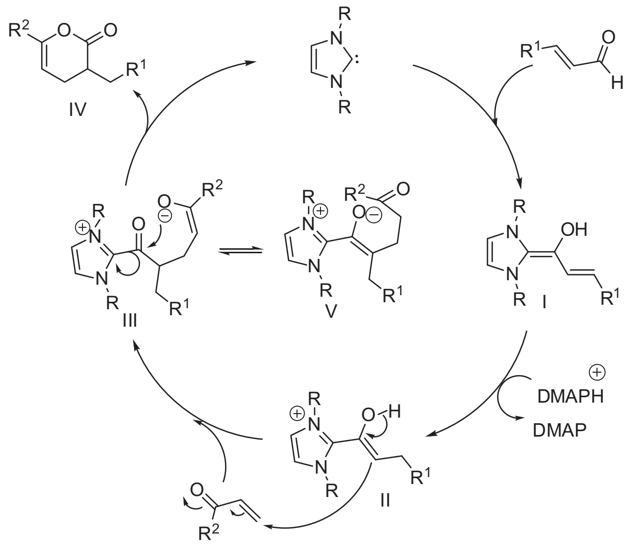
4a = DBU, 4b = DMAP

Entry	Catalyst	Base	Yield (%)
1	**3a**	**4a**	0
2	**3b**	**4a**	44
3	**3c**	**4a**	13
4	**3d**	**4a**	0
5	**3e**	**4a**	0
6	**3b**	**4b**	76
7	**3c**	**4b**	20

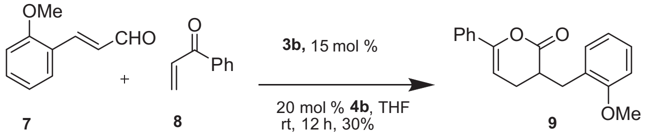
Table 2
Substrate scope[18]



Entry	R^1	Product	Yield (%)
1	Phenyl	**6a**	90
2	4-Methoxyphenyl	**6b**	76
3	2-Methoxyphenyl	**6c**	98
4	Methyl	**6d**	59
5	4-Chlorophenyl	**6e**	60
6	4-Methylphenyl	**6f**	64
7	4-Fluorophenyl	**6g**	37
8	2-Methylphenyl	**6h**	88
9	Thienyl	**6i**	51



Scheme 2. Mechanistic rationalization.



Scheme 3. Reaction of enal **7** with phenyl vinyl ketone.

A mechanistic rationalization for this unexpected reaction may be postulated as follows. The use of a weak amine base such as DMAP for the deprotonation of the NHC precatalyst generates a stronger cojugate acid (DMAPH$^+$). The homoenolate equivalent I formed initially from the enal and NHC undergoes β-protonation presumably by DMAPH$^+$, to afford enol II.[17] The latter on Michael addition to the vinyl ketone affords species III which on intramolecular *O*-acylation reaction delivers [2*H*]-pyranone (IV). It is noteworthy that isomerisation of enolate III to a more stable enolate V and subsequent intramolecular aldol-type reaction, analogous to the events observed in the case of cyclopentene formation from chalcone is precluded here since that would involve a four-membered intermediate (Scheme 2). Interestingly, no homoenolate-type reactivity was observed even in the presence of DBU (Table 1, entry 2).

It is noteworthy that a hetero-Diels–Alder reaction pathway was invoked by Bode and Chi to rationalize the formation of [2*H*]-pyranones in related transformations.[16] In view of the overwhelming steric features of II, Diels–Alder pathway is an unlikely prospect in this reaction. A Michael-initiated annulation reaction of the enol II is proposed here keeping in line with the observed reactivity of related homoenolates.[12]

In the subsequent studies, it was found that phenyl vinyl ketone also afforded an analogous product, albeit in low yield (Scheme 3).

In conclusion the homoenolate annulation to vinyl ketones leads to the synthesis of dihydropyranone derivatives in contrast to the cyclopentenes obtained by the homoenolate reaction of another class of α,β-unsaturated ketones viz., chalcones.

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Supplementary data

Supplementary data (general remarks, experimental procedure, spectral data, ^{1}H NMR and ^{13}C NMR are included) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.157.

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18. General experimental procedure: The α,β-unsaturated aldehyde (1.5 equiv), IMesCl (0.15 equiv) and vinylketone (1 equiv) were taken in THF. After addition of DMAP (0.2 equiv) the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture on column chromatography on silica gel (100–200 mesh) using 1:20 ethylacetate:hexane mixture yielded the corresponding [2*H*]-pyranone as a pale brown liquid. Spectral data of a representative compound: 3-benzyl-6-methyl-3,4-dihydro-2*H*-pyran-2-one (**6a**): IR (Neat) ν_{max}: 1711, 1451, 1362, 1161 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.29–7.14 (m, 5H), 4.89 (s, 1H), 3.33 (d, $J = 9.6$ Hz, 1H), 2.77–2.66 (m, 2H), 2.14–1.94 (m, 2H), 1.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 170.7, 149.4, 138.3, 128.9, 128.4, 126.4, 99.3, 39.9, 35.6, 23.5, 18.4. MS (LR-FAB): *m*/*z* calcd for $C_{13}H_{14}O_2$ (M+H)+: 203.10, found: 203.74.