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Nucleophilic Heterocyclic Carbene Catalyzed Annulation of Enals to Chalcones in Methanol: A Stereoselective Synthesis of Highly Functionalized Cyclopentanes[§]

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ABSTRACT

Homoenolates generated from enals by nucleophilic heterocyclic carbene (NHC) catalysis undergo annulation with chalcones in methanol to afford methyl *β*-hydroxycyclopentanecarboxylates, stereoselectively. Construction of four contiguous stereocenters in a stereoselective manner is noteworthy.

The catalysis of organic reactions by small nucleophilic molecules, generally referred to as organocatalysis,[1,2] is an area of immense topical interest in organic synthesis. Consequent to the successful studies involving stable organic molecules, the use of nucleophilic heterocyclic carbenes (NHCs) as catalysts has drawn the attention of a number of organic chemists.[3,4] The advent of NHC catalysis can be attributed to the seminal work of Breslow in 1958,[5] which categorically established the addition of NHC to aldehyde resulting in a reactivity umpoled species,[6] viz., enaminol (Breslow intermediate). The reaction of the latter to a second molecule of aldehyde delivered benzoin type product. With the exception of its role in the Stetter reaction,[7] the chemistry of the Breslow intermediate remained largely unexplored. Recently, in their pathbreaking work, Bode[8] and Glorius[9]

[§] Dedicated with best wishes to Professor (Emeritus) Alex Nickon, in honor of his original contributions to Organic Chemistry.

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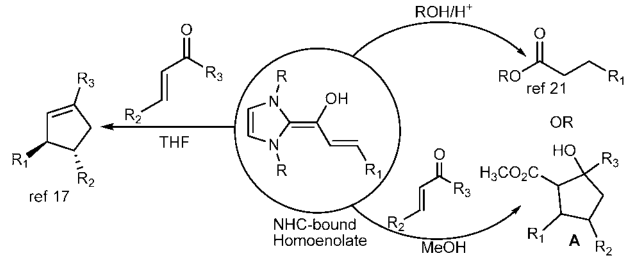
independently extended the reactivity umpolung induced by NHC to α,β-unsaturated aldehydes leading to the formation of homoenolate,[10−13] a species first described by Nickon in 1962. Investigations by different research groups, including our own, during the last five years, have demonstrated that homoenolate formed by NHC catalysis can be efficiently trapped by aldehydes and other electrophiles leading to γ-butyrolactones,[8,9] spiro-γ-butyrolactones,[14] and δ-lactones.[15] This annulation strategy has also been utilized in the synthesis of γ-lactams, bicyclic β-lactams, and β-lactones.[16] Although it was known that annulation of enals occurred exclusively at the carbonyl, in the case of chalcones the C−C π system was expected to compete effectively with the carbonyl, both for steric and electronic reasons, thus leading to a cyclopentanone. Work aimed at exploring such a possibility, however, led to the formation of a cyclopentene derivative.[17] Later, asymmetric versions of this reaction[18] as well as similar NHC-catalyzed annulation reactions were made possible by the choice of chiral NHCs.[19] Very recently, an NHC-catalyzed annulation of cinnamaldehydes to dibenzylidene cyclopentanones leading to the formation of spirocyclopentanones was also reported.[20]

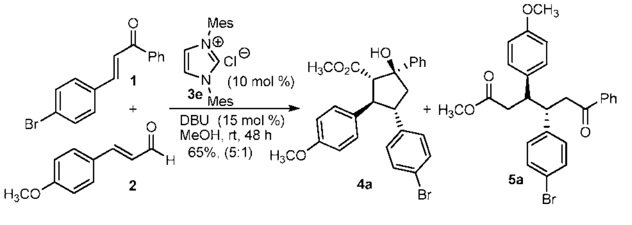
The recognition that a key step in the cyclopentene synthesis[17] (vide supra) is the intramolecular proton transfer in the adduct of homoenolate and chalcone allowed us to speculate that the results of an experiment, in which intermolecular proton transfer (from solvent) can occur, would be vastly different. With this premise, and encouraged by Scheidt's report[21] giving evidence for the existence of homoenolate in protic solvents, it was tempting to investigate the homoenolate annulation of chalcone in a protic solvent such as methanol. It was surmised that the initially formed homoenolate would either endure a redox reaction to yield a saturated ester of the enal as already reported[21] or add to the chalcone prior to protonation to afford a new enolate which would possibly undergo cyclization to deliver the tentative product **A**, thus exposing a new facet of homoenolate reactivity.

Scheme 1. Background and Hypothesis



The results of the investigations validating the concept outlined above are presented in this paper. The present studies commenced by exposing a mixture of 4-methoxycinnamaldehyde and chalcone **1**, with a catalytic amount of imidazolium salt **3e** (IMesCl) and DBU in methanol at room temperature. After 48 h, the reaction mixture was subjected to column chromatography to afford methyl β-hydroxycyclopentanecarboxylate **4a** along with a small amount of acyclic δ-ketoester **5a** (ratio 5:1) in an overall yield of 65%. The structure of the product **4a** was assigned by the use of conventional spectroscopic techniques, and final confirmation was obtained from single-crystal X-ray analysis (Figure 1).[22] It is noteworthy that only one diastereomer was formed in each case.

Scheme 2. Annulation of p-Methoxycinnamaldehyde with Chalcone



A limited number of catalysts were screened, and the results are summarized in Table 1. Low conversions were observed with benzimidazole carbene **3a** and imidazole carbene **3b**. It was found that the use of triazole carbenes

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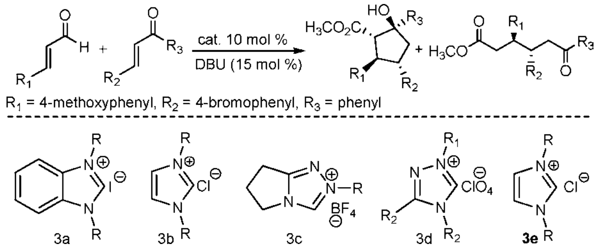
(22) Crystal structure of compound **4a** has been deposited at the Cambridge Crystallographic Data Centre and allocated the reference no. CCDC 705344.

Table 1. Catalyst Screening[a]



entry	catalyst	conditions	yield (%)[c]
1	**3a**	methanol, rt, 48 h	20
2	**3b**	methanol, rt, 48 h	10
3	**3c**	methanol, rt, 48 h	-
4	**3d**	methanol, rt, 48 h	-
5	**3e**	**methanol, rt, 48 h**	**65**
6	**3e**	methanol, 60 °C, 48 h	52
7	**3e**	ethanol, rt, 48 h	24
8[b]	**3e**	methanol, 48 h	32

[a] Except in entry 8, 1 equiv of chalcone and 2 equiv of aldehyde are used. [b] With 1 equiv of aldehyde, [c] Overall yield **3a**:R = ethyl, **3b**:R = 2,6-diisopropyl phenyl, **3c**:R = pentaflourophenyl, **3d**:R_1 = 2,4,6-trimethylphenyl, R_2 = phenyl, **3e**:R = 2,4,6-trimethylphenyl.

(**3c** and **3d**) results in a redox product of the conjugated aldehyde, as reported earlier.[21] Among the various catalysts screened, **3e** was found to be the best one, in methanol at room temperature. The reaction also worked in ethanol, albeit in low yield (entry 7).

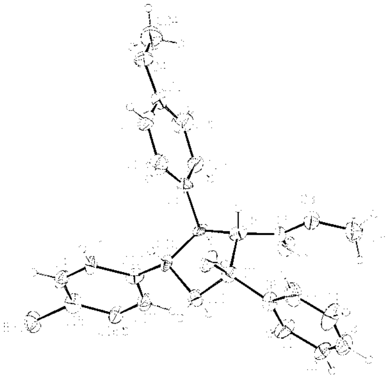
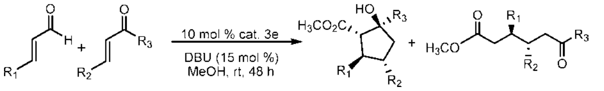


Figure 1. Single-crystal X-ray structure of **4a**.

After having identified **3e** as the most suitable catalyst, we screened different chalcones and aldehydes. It was found that various substituted chalcones underwent annulation in methanol to give methyl β-hydroxycyclopentanecarboxylate. In all cases, the acyclic compound was isolated as a minor product. The results are summarized in Table 2.

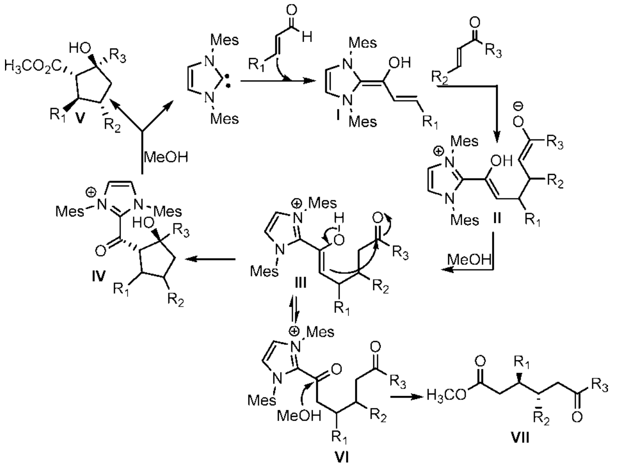
Table 2. Substrate Scope[a]



R_1	[c]R_2	products	yield (%)[b]	ratio
phenyl	4-bromophenyl	**4b** and **5b**	69	(5:1)
4-methoxyphenyl	4-chlorophenyl	**4c** and **5c**	68	(4:1)
phenyl	4-chlorophenyl	**4d** and **5d**	70	(4:1)
4-methoxyphenyl	4-fluorophenyl	**4e** and **5e**	67	(4:1)
phenyl	4-fluorophenyl	**4f** and **5f**	68	(5:1)
phenyl	phenyl	**4g** and **5g**	66	(3:1)
phenyl	2-naphthyl	**4h** and **5h**	56	(3:1)
phenyl	4-chlorophenyl	**4i** and **5i**	57	(4:1)
4-methoxyphenyl	2-thienyl	**4j** and **5j**	64	(4:1)
4-methoxyphenyl	phenyl	**4k** and **5k**	69	(3:1)
phenyl	4-methylphenyl	**4l** and **5l**	59	(2:1)

[a] One equiv of chalcone and 2 equiv of aldehyde are used. [b] Overall yield. [c] Except for **4i** and **5i**, R_3 = phenyl. For **4i** and **5i**, R_3 = 4-bromophenyl. In all cases, redox product of the enal is formed in trace amounts.[21]

Scheme 3. Postulated Catalytic Cycle



The postulated catalytic cycle for the annulation is shown in Scheme 3. In the first step, the NHC adds to enal to produce homoenolate **I**, which undergoes conjugate addition to chalcone to form enolate **II**. The latter suffers protonation to afford the intermediate **III**. This NHC-bound enol then undergoes intramolecular cyclization to the keto carbonyl followed by methanolysis to give the corresponding methyl β-hydroxycyclopentanecarboxylate as the final product with the ejection of carbene. It is noteworthy that the stereochemical outcome of the intramolecular cyclization is opposite to that observed when the reaction was conducted in THF. Evidently, the trans disposition of the ester and hydroxyl groups in **IV** preclude β-lactonization and consequent loss of carbon dioxide to yield cyclopentene.[17] Although the mechanistic underpinnings of this reaction remain to be unravelled, the reversal of stereochemistry observed in the present case may be attributed to thermodynamic control of the cyclization step in methanol. Evidently, the acyclic product **VII** is formed by the methanolysis of **VI** (which is in equilibrium with **III**) prior to cyclization. The noteworthy feature of this reaction is that the homoenolate, even when generated in the presence of a protic solvent, undergoes conjugate addition to another electrophile, viz., chalcone, in preference to protonation.

In conclusion, we have uncovered an unprecedented homoenolate annulation in methanol, initiated by conjugate addition of homoenolate to chalcone in preference to protonation. It is remarkable that this NHC-catalyzed annulation of enal with chalcones in methanol provides a simple and direct protocol for the stereoselective construction of methyl β-hydroxycyclopentanecarboxylate in a one-pot operation; the presence of four contiguous chiral centers including a quaternary one in the product is especially noteworthy. Further work is underway to gain more insight into this annulation and to explore its synthetic potential.

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Supporting Information Available: General experimental procedure, spectroscopic characterization of new compounds, and single-crystal X-ray data of compound **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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