NHC-Catalyzed Reactions of Aryloxyacetaldehydes: A Domino Elimination/Conjugate Addition/Acylation Process for the Synthesis of Substituted Coumarins
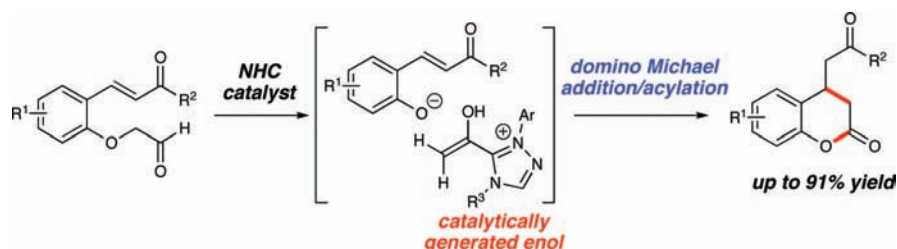
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ABSTRACT

N-Heterocyclic carbenes (NHCs) catalyze a domino Michael addition/acylation reaction to form 3,4-dihydrocoumarins. The reaction proceeds through addition of the NHC to an aryloxyaldehyde followed by elimination of a phenoxide leaving group, generating an enol intermediate. This transient nucleophile generated in situ performs a 1,4-addition onto a conjugate acceptor, and the carbene catalyst is regenerated upon acylation of the phenoxide anion resulting in formation of 3,4-dihydrocoumarins.

Enolates are essential intermediates in chemistry and biology due to their high utility in carbon−carbon bond-forming reactions.[1] The catalytic, in situ generation of enolates or enols has become increasingly important due to their efficiency in synthesis and emerging environmental concerns. Consequently, significant effort in this area has been directed toward metal-catalyzed processes[2] that allow for the addition of the corresponding metalloenolate to various electrophiles.[3] More recently, attention has turned toward the formation of enolates using only organic molecules as catalysts.[4] Numerous groups[5−8] have employed secondary amines to catalyze enantioselective aldol, Michael, and Mannich reactions

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through the generation of a reactive enamine intermediate.[9] We report here that N-heterocyclic carbenes (NHCs) catalyze the formation of enolates/enols through an elimination process of α-aryloxy aldehydes. The capture of these nucleophiles leads to substituted coumarins by a domino Michael addition/acylation process (eq 1 in Scheme 1).


Scheme 1. General Concept
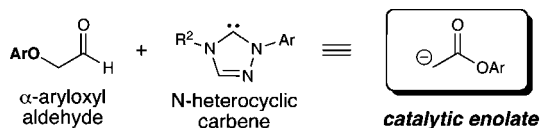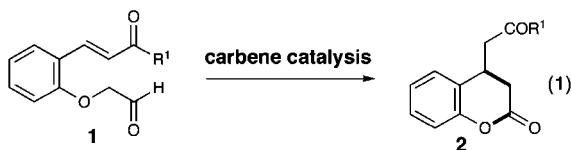
In our recent carbene catalysis studies to access enols by the protonation of homoenolates,[10] we became interested in whether new carbon−carbon bond-forming reactions were possible using reactive acetate-type enol-NHC intermediates from α-aryloxyacetaldehydes. This concept is distinctive since the phenol in the α-position serves an important dual purpose: first to facilitate generation of the enol equivalent and second to liberate the carbene catalyst through an acylation event.[11] We hypothesized that this process could be evaluated with an aldehyde containing a tethered conjugate acceptor in the *ortho*-position.[12] The likely pathway involves initial addition of the NHC to aldehyde 1 (Scheme 2).[13] A formal 1,2-shift of the aldehyde proton results in elimination of phenoxide/phenol derivative III and concomitant formation of enol equivalent II. A Michael addition could then occur which, when followed by intramolecular O-acylation, promotes regeneration of the carbene catalyst. A delicate balance of leaving group ability and nucleophilicity of the α-position substituent is crucial. A catalytic process is untenable if these factors are not optimal in this new type of "rebound" process. For example, a strong leaving

Scheme 2. Proposed Reaction Pathway
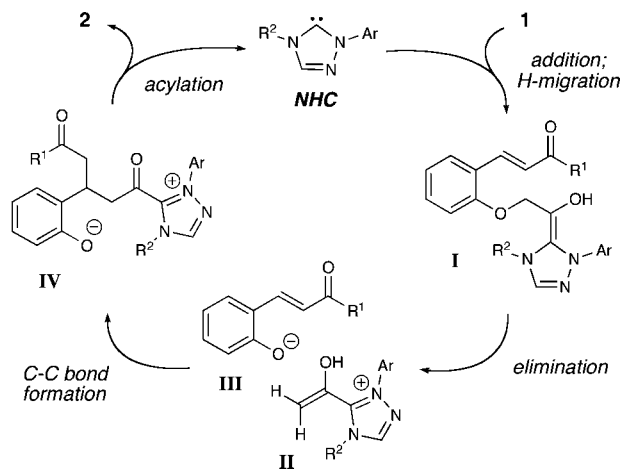
group (e.g., chloride or sulfonate) would potentially initiate the reaction faster (I to II and III) but would fail to turn over the catalyst due to weak nucleophilicity (IV to 2).

Enone 1a was chosen to explore this carbene-catalyzed enolate formation strategy and leads to the formation of 3,4-dihydrocoumarin products.[14] Substituted coumarins and related compounds are biologically active,[15] and access to this particular substitution pattern by Michael additions to the parent coumarin remains challenging.[16] For example, to the best of our knowledge, there are no general and high-yielding reports of conjugate additions of enolates to coumarins. While combining enone 1a with imidazolium or benzimidazolium salts in the presence of base produced a minor amount of the desired product (entries 1 and 2, Table 1), a large increase in yield was observed when triazolium precatalyst C[17] was used with DBU (entry 5). Further optimization revealed that acetonitrile was the best solvent (60% yield, entry 6). In this particular case, the moderate yield was due to decomposition from prolonged exposure to silica gel. Indeed, quick filtration through SiO₂ provided an improved 83% yield of pure desired product 2a (entry 7).

With azolium salt C identified as the most efficient precatalyst to promote this well-orchestrated domino process, we investigated the scope of the reaction. Electron-withdrawing (Table 2, entry 3) and electron-donating aryl ketones (entries 4 and 5), as well as naphthyl ketones (entry 6), are accommodated by the reaction conditions. Electron-with-

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Table 1. Optimization of Conditions

entry	azolium salt	conditions	yield[b]
1	A	0.1 M CH$_2$Cl$_2$, 1.0 equiv i-Pr$_2$EtN	<5
2	B	0.1 M CH$_2$Cl$_2$, 1.0 equiv i-Pr$_2$EtN	<5
3	B	0.1 M CH$_2$Cl$_2$, 10 mol % DBU	<5
4	C	0.1 M CH$_2$Cl$_2$, 1.0 equiv i-Pr$_2$EtN	<5
5	C	0.05 M CH$_2$Cl$_2$, 10 mol % DBU	39
6	C	0.05 M CH$_3$CN, 10 mol % DBU	60
7	C	0.02 M CH$_3$CN, 10 mol % DBU	83

[a] All reactions performed on 0.2 mmol scale. [b] Isolated yields.

Table 2. Substrate Scope

entry	R^1	R^2	product	yield (%)[a]
1	1a H	Ph	2a	83
2	1a H	Ph	2a	79[b]
3	1b H	4-Br-C$_6$H$_4$	2b	77
4	1c H	4-Me-C$_6$H$_4$	2c	84
5	1d H	4-OMe-C$_6$H$_4$	2d	80
6	1e H	2-Naphthyl	2e	90
7	1f OMe	Ph	2f	68
8	1g Me	Ph	2g	80
9	1h Br	Ph	2h	77
10	1i F	Ph	2i	91
11	3		4	66
12	5		6	66
13	7		8	70[c]

[a] Isolated yields. [b] 5 mol % of C and DBU. [c] dr 1.3:1 as observed by 500 MHz ^{1}H NMR spectroscopy.

drawing and -donating groups (entries 7−12) can also be placed on the aromatic ring in a variety of patterns. The 3,4-dihydrocoumarin derived from substrate **7** (entry 11) is formed in good yield, although the diastereoselectivity with achiral NHCs is marginal. Additionally, catalyst loading can be decreased to 5 mol % without diminishing the yield (entry 2). Currently, substitution at the α-position of the aldehyde is not accommodated under the reaction conditions. The use of saturated substrates, which replace the phenoxide leaving group with an alkoxide, results in no reaction. From these data, it seems that normal alcohols are not sufficiently stabilized to undergo the first step of the catalytic cycle, i.e., elimination from the initial carbene•aldehyde adduct **I**. An extensive survey of known chiral azolium salts as catalysts in this reaction provides products in moderate yields but low levels of enantioselectivity (<10% ee). Importantly, the discovery of this new process provides a strong impetus to develop new chiral catalysts to provide optically active substituted coumarins.
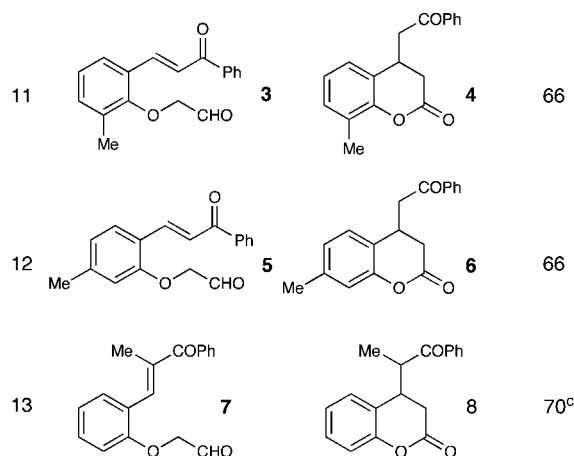
Our investigations of the proposed pathway have focused on probing alternative pathways to the one depicted in Scheme 1. The possibility of the acylation of the phenol by **II** occurring prior to the Michael addition was strongly discounted by subjecting **9** to reaction conditions. No reaction was observed, thereby supporting that intermediate **II**, a catalytic enolate equivalent, undergoes C−C bond formation prior to C−O bond formation (Scheme 3).

A cross-over experiment was performed (Scheme 4) to determine the fate of the enol (**II**) that is potentiallly formed in situ. When compounds **1g** and ^{18}O-labeled **1j** were subjected to the optimized reaction conditions in a single flask, a mixture of compounds **2a**, **2g**, **10**, and **11** was obtained (as observed by HRMS).[18] The randomized distri-

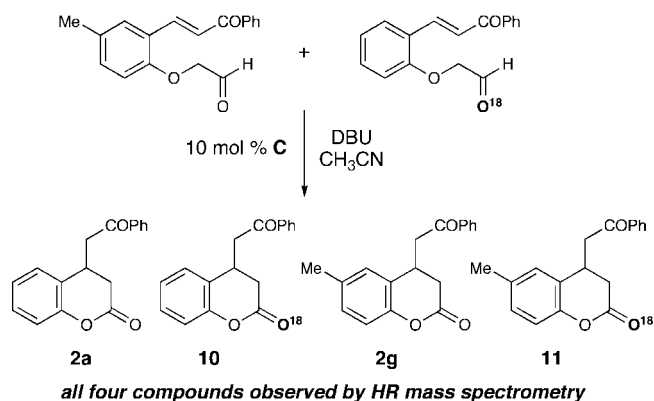(18) See Supporting Information for details.

bution of the labeled oxygen and methyl group on the aryl ring lends additional support to a pathway involving a bimolecular Michael addition in which the α-aryloxy acetaldehyde fragments to form a reactive enol.

In conclusion, we have developed a new carbene-catalyzed domino process to generate substituted coumarins. A reactive enol is generated catalytically through the addition of an N-heterocyclic carbene to an α-aryloxy aldehyde followed by elimination of a phenoxide ion. The resulting enol

Scheme 3. Reaction Pathway Investigation

possible reaction intermediate

azolium salt **C**
DBU, CH$_3$CN
→ *no reaction* (2)

C−O bond formation occurs **after** C−C bond formation

Scheme 4. Cross-Over Experiment

all four compounds observed by HR mass spectrometry

intercepts a conjugate acceptor, thereby forming a 3,4-dihydrocoumarin after acylation of the phenoxide/phenol by the acyl azolium intermediate. This new concept of leaving group "rebound" has been developed in the context of carbene catalysis to access enolate reactivity in situ and yield an efficient synthesis of important oxygenated heterocycles. One can envision incorporating additional groups beyond phenols with this rebound capacity that will undoubtedly broaden the scope and utility of this process. Our mechanistic investigations employing both the subjection of potential intermediates to the reaction conditions and cross-over experiments using isotopically labeled substrates support a sequential elimination/C−C formation/C−O acylation pathway. There are many promising potential uses of enols derived from a carbene-catalyzed elimination process, and our continued investigations in this area will be reported in due course.

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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