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N-Heterocyclic Carbene-Catalyzed Cascade Reaction Involving the Hydroacylation of Unactivated Alkynes

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The transition-metal-catalyzed hydroacylation of alkenes is an attractive, inherently atom-economical transformation that has found many applications in organic synthesis.¹ Intriguingly, the same transformation of *activated* olefins, the Stetter reaction,² can also be organocatalyzed by cyanide or N-heterocyclic carbenes (NHCs).³ Very recently, and related to the work of She et al.,⁴ we reported the NHCorganocatalyzed hydroacylation of unactivated double bonds.⁵ Remarkably, the corresponding transition-metal-catalyzed hydroacylation reaction of alkynes,⁶ which results in the formation of valuable α,β unsaturated ketones, is much less common, and to the best of our knowledge, the NHC-organocatalyzed hydroacylation of alkynes has not been reported. The latter would be attractive, since it avoids the use of transition-metal catalysts and prevents undesired decarbonylation pathways. Herein, we report the NHC-organocatalyzed hydroacylation of unactivated alkynes, which leads to the formation of α_{β} -unsaturated chromanones (eq 1), and the application of this reaction in a unique cascade process involving hydroacylation of an unactivated triple bond followed by an intermolecular Stetter reaction (eq 2).



We commenced our study with the organocatalyzed hydroacylation of unactivated internal alkynes 1 (Table 1). Treatment of 1a with the sterically hindered carbene generated from thiazolium salt 3^7 (5 mol %) by deprotonation with K₂CO₃ resulted in smooth formation of chromanone 2a, which bears a synthetically valuable exocyclic olefin, as a single isomer in 86% yield (Table 1, entry 1). Variations on both aromatic rings were well-tolerated, providing good yields for electrondonating and -withdrawing substituents. Moreover, the reaction could also be successfully run with a nitrogen tether, furnishing quinolin-4-one 2i (entry 9). Competition experiments of differently substituted alkynes revealed that the rate increases in the order 1e (4-OMe) < 1a(4-H) < 1g (4-CO₂Et), with 1g reacting \sim 55 times faster than 1e.^{8,9} Thus, it is reasonable to assume that formation of the Breslow intermediate¹⁰ is reversible under the reaction conditions and that the alkyne plays an active role in the rate-determining step, with electronpoor alkynes reacting faster than electron-rich ones.

In view of these interesting results and since α , β -unsaturated ketones can act as substrates in the Stetter reaction, we envisioned a dually NHC-catalyzed hydroacylation cascade comprising an initial hydroacylation of an unactivated triple bond and a subsequent intermolecular Stetter reaction. Cascade catalysis, with its multiple bond-forming events, represents an efficient method for the rapid construction of organic molecules,¹¹ often reducing labor and waste and allowing the use of more readily available starting materials for a given transformation.¹² Moreover, reactions that result in reactive or labile intermediates can often only be utilized by means of cascade catalysis. Although organocatalysts play a prominent role in cascade catalysis¹³ and NHC-catalyzed reactions have found widespread applications,^{3,14} the use of NHCs in this realm of catalysis has received only scant attention.¹⁵

To test our hypothesis, we employed a second aldehyde as the coupling partner for enone 2 to yield a chromanone with a 1,4-diketone

Table 1. Hydroacylation of Unactivated Alkynes^a

	5 R ¹ 4 3 2 X	0 	$\begin{array}{c} & & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$		^{~~} R ²
entry	Х	R ¹	R ²	product	yield (%)
1	0	Н	Ph	2a	86
2	0	3-OMe	Ph	2b	95
3	0	5-Cl	Ph	2c	78
4	0	5-F	Ph	2d	84
5	0	Н	4-MeOC ₆ H ₄	2e	72
6	0	Н	4-MeC ₆ H ₄	2f	74
7	0	Н	4-EtOC(O)C ₆ H ₄	2g	78
8	0	Н	$2-FC_6H_4$	2h	80
9^b	NTs	Н	Ph	2i	63

^{*a*} General conditions: **1** (1.0 mmol), **3** (5 mol %), K_2CO_3 (10 mol %), THF (2.0 mL), 70 °C, 2 h; isolated yields are reported. ^{*b*} Run on a 0.35 mmol scale using 10 mol % **3** and 20 mol % K_2CO_3 for 4 h.

Table 2. NHC-Catalyzed Hydroacylation-Stetter Cascade: Scope of Propargylic Aldehydes



^{*a*} General conditions: **4** (1.0 mmol), **5a** (1.0 mmol), **3** (5 mol %), K₂CO₃ (10 mol %), THF (2.0 mL), 70 °C, 2 h; Ar = 4-ClC₆H₄. Isolated yields are given. ^{*b*} dr based on ¹H NMR analysis of the crude reaction mixture.

motif (eq 2). Intriguingly, in this process, many selectivity issues arose, and the formation of undesired benzoin and Stetter products could be largely suppressed by using the NHC catalyst derived from **3** (in contrast to other NHCs).⁸



A series of substrates with different substituents on the aromatic ring of **4** was examined (Table 2). The unsubstituted parent system bearing a terminal alkyne worked well (6a),¹⁶ and various electron-

donating groups at the 2-position were tolerated very well (6b-d), with isolated yields above 90% in each case. Also, aldehydes containing different halogen substituents or a trifluoromethyl group afforded the corresponding chromanones (6e-h) in good yields. Finally, a substituent on the progargylic moiety was also well-tolerated, giving the product in 70% yield with a 3:1 trans/cis ratio.

In addition, we also examined the variation of substituents on aldehyde 5 (Table 3). Benzaldehyde and other aromatic aldehydes bearing substituents in the 2- or 3-position afforded the chromanones in good yields (61-q). In what can be seen as an intramolecular competition experiment, the 2-allyloxy-substituted substrate (entry 4) was transformed into 60 in 65% yield, demonstrating the preferential attack of the acyl anion equivalent on the triple bond over the one on the double bond in the hydroacylation step. Moreover, various electrondonating and -withdrawing groups in the 4-position of the ring were well-tolerated (6r-u). Gratifyingly, heterocyclic and aliphatic aldehydes also provided good yields of the desired products (6w-x), significantly expanding the scope of this novel cascade reaction.

Table 3.	Variation	of the	Coupling	Aldehvde	5 ^a
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C OMe 4b	$\begin{array}{c} 3 (5 \pi) \\ \hline H \\ \hline \end{array} + H \\ \hline R \\ \hline \end{array} + H \\ \hline R \\ \hline THF, 7 H \\ 5 \end{array}$	nol%) 10 mol%) 0 °C, 2 h OMe	
entry	R	product	yield (%)
1	phenyl	61	90
2	2-chlorophenyl	6m	66
3	2-methylphenyl	6n	67
4	2-allyloxyphenyl	60	65
5	3-bromophenyl	6р	82
6	3-methoxyphenyl	6q	85
7	4-bromophenyl	6r	93
8	4-methylphenyl	6s	90
9	4-methoxyphenyl	6t	88
10	4-carbomethoxyphenyl	6u	77
11	1-naphthyl	6v	86
12	2-furyl	6w	85
13	isopropyl	6x	68

^a General conditions: 4b (1.0 mmol), 5 (1.0 mmol), 3 (5 mol %), K₂CO₃ (10 mol %), THF (2.0 mL), 70 °C, 2 h. Isolated yields are given.

This novel methodology was applied to the one-pot synthesis of benzopyranopyrrole derivative 7 by generation of the chromanone derivative through a hydroacylation-Stetter reaction cascade followed by condensation with *p*-toluidine (eq 3):



In conclusion, we have developed an NHC-organocatalyzed hydroacylation of unactivated alkynes to provide α,β -unsaturated ketone products.¹⁷ In addition, we have also reported a rare case of an efficient and selective dually NHC-catalyzed cascade reaction involving the hydroacylation of alkynes and a subsequent intermolecular Stetter reaction.

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Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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