J|A|C|S COMMUNICATIONS

Published on Web 04/12/2010

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

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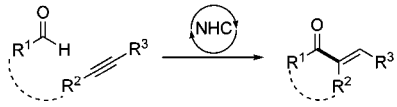
The transition-metal-catalyzed hydroacylation of alkenes is an attractive, inherently atom-economical transformation that has found many applications in organic synthesis.[1] Intriguingly, the same transformation of *activated* olefins, the Stetter reaction,[2] can also be organocatalyzed by cyanide or N-heterocyclic carbenes (NHCs).[3] Very recently, and related to the work of She et al.,[4] we reported the NHC-organocatalyzed 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).



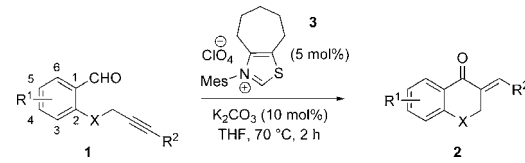
(1)

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 K_2CO_3 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 electron-donating 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-CO_2Et), with **1g** reacting ∼55 times faster than **1e**.[8,9] Thus, it is reasonable to assume that formation of the Breslow intermediate[10] is reversible under the reaction conditions and that the alkyne plays an active role in the rate-determining step, with electron-poor 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 catalysis[13] 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 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]

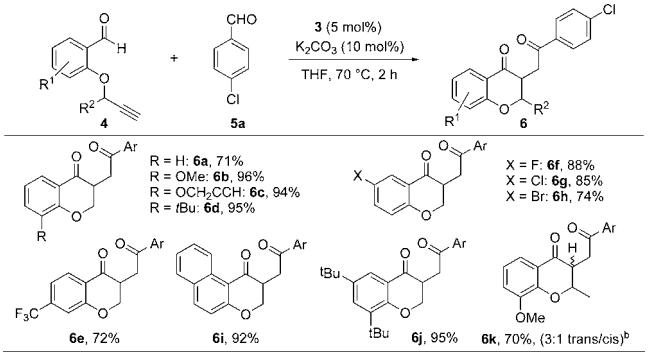
Table 1. Hydroacylation of Unactivated Alkynes[a]



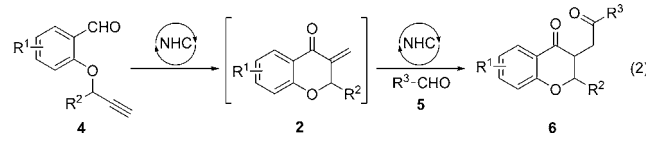
entry	X	R^1	R^2	product	yield (%)
1	O	H	Ph	**2a**	86
2	O	3-OMe	Ph	**2b**	95
3	O	5-Cl	Ph	**2c**	78
4	O	5-F	Ph	**2d**	84
5	O	H	4-$MeOC_6H_4$	**2e**	72
6	O	H	4-MeC_6H_4	**2f**	74
7	O	H	4-$EtOC(O)C_6H_4$	**2g**	78
8	O	H	2-FC_6H_4	**2h**	80
9[b]	NTs	H	Ph	**2i**	63

[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]



[a] General conditions: **4** (1.0 mmol), **5a** (1.0 mmol), **3** (5 mol %), K_2CO_3 (10 mol %), THF (2.0 mL), 70 °C, 2 h; Ar = 4-ClC_6H_4. Isolated yields are given. [b] dr based on ^{1}H NMR analysis of the crude reaction mixture.



(2)

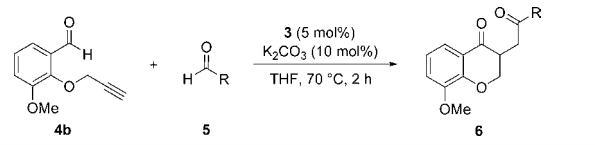
A series of substrates with different substituents on the aromatic ring of **4** was examined (Table 2). The unsubstituted parent system bearing a terminal alkyne worked well (**6a**),[16] and various electron-

10.1021/ja102130s

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 (**6l**−**q**). In what can be seen as an intramolecular competition experiment, the 2-allyloxy-substituted substrate (entry 4) was transformed into **6o** 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 electron-donating 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.

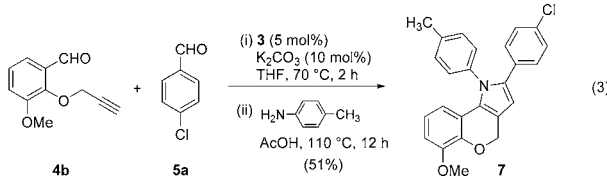
Table 3. Variation of the Coupling Aldehyde **5**[a]



entry	R	product	yield (%)
1	phenyl	**6l**	90
2	2-chlorophenyl	**6m**	66
3	2-methylphenyl	**6n**	67
4	2-allyloxyphenyl	**6o**	65
5	3-bromophenyl	**6p**	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 %), K_2CO_3 (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):



(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.

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (SPP 1179), the Alexander von Humboldt Foundation (A.T.B.), and the Deutsche Telekom Stiftung (N.E.W.) is gratefully acknowledged. The research of F.G. was supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation. We also thank Marwin Segler for assistance.

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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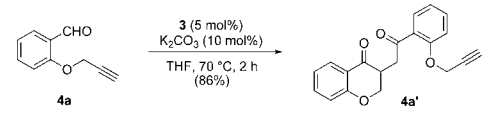

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JA102130S