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N-Heterocyclic Carbene-Catalyzed Hydroacylation of Unactivated Double Bonds

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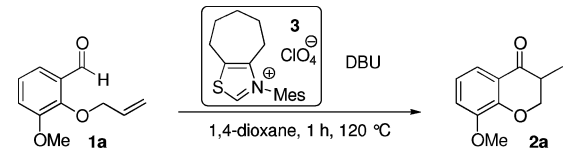
N-Heterocyclic carbene (NHC)-catalyzed umpolung reactions of aldehydes constitute an important class of organocatalysis and have found a broad range of applications in synthetic organic chemistry.[1] The corresponding nucleophilic acyl anion or homoenolate equivalent intermediates can react with various electrophiles, like aldehydes,[2] ketones,[2c,3] imines,[4] and activated, polarized C=C double bonds.[5] The latter class of reactions is especially interesting, since olefins are ubiquitous in organic chemistry. Intriguingly, however, whereas many transition-metal-catalyzed processes make use of unactivated olefin substrates, the incorporation of unactivated olefins in organocatalyzed reactions is very rare. The organocatalyzed addition of aldehydes, converted to acyl anion equivalents by umpolung, onto unactivated olefins—the hydroacylation of olefins—has not been previously reported.[6] In this Communication, we report the first NHC-organocatalyzed hydroacylation of unactivated olefins, namely the first Stetter reaction with *unactivated* olefins.

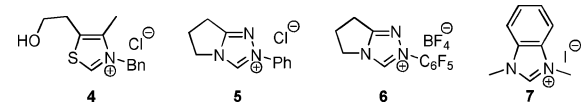
Our study commenced with the optimization of the cyclization of O-allylated *o*-vanillin **1a** to the corresponding chromanone **2a** (Table 1).[7] Among a wide range of NHCs, the carbene generated by deprotonation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) from thiazolium salt **3**[8] showed the best reactivity, within 1 h providing the desired chroman-4-one **2a** in 69% yield (based on GC; entry 1). Other common NHCs generated from **4**−**7** and other azolium salts[7] reduced the yield dramatically (entries 2−5). The excess amount of DBU with respect to **3** is essential to achieve satisfactory yields (entry 6), and a strong base is required to promote the desired reaction efficiently (entries 7−9). Finally, a longer reaction time of 2 h improved the isolated yield to 85% (entry 11).

Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **2a** (%)[b]
1	none	69
2	**4** instead of **3**	2
3	**5** instead of **3**	21
4	**6** instead of **3**	2
5	**7** instead of **3**	11
6	DBU: 20 mol % instead of 40 mol %	34
7	TEA instead of DBU	3
8	K_2CO_3 instead of DBU	32
9	KO*t*-Bu instead of DBU	69
10	10 mol % of **3**, 20 mol % DBU	65
11	**reaction time: 2 h instead of 1 h**	**81 (85)**[c]

[a] Standard conditions: **1a** (0.25 mmol), NHC·HX (20 mol %), DBU (40 mol %), 1,4-dioxane (0.5 mL), 120 °C, and 1 h. [b] GC yield using mesitylene as an internal standard. [c] Isolated yield in parentheses.



This new method can be applied to a range of substrates with different substitution patterns of the aromatic ring (Table 2). First, various electron-donating substituents at the 2-position are well tolerated (**2a**−**d**). In addition, aldehydes bearing halides on the aromatic ring readily cyclize to afford the corresponding chromanones (**2e**−**g**). Methylthioether, trimethylsilyl, phenyl, cinnamyl, and even a strongly electron-withdrawing trifluoromethyl substituent are all tolerated (**2h**−**l**). Furthermore, disubstituted aldehydes with alkyl as well as halogen and ether substitution undergo the hydroacylation in good yields (**2m**−**p**). The transformations of the naphthaldehydes **1q**,**r** resulted in smooth product formation in high yields of up to 95% (**2q**,**r**). An even more highly substituted chromanone **2s** is obtained in 77% yield. Finally, the unsubstituted parent system **1t** also works well, providing chromanone **2t**. Moreover, this novel transformation is not limited to chromanone formation, but instead, a nitrogen tether can successfully replace the oxygen linkage, giving dihydroquinolinone **2u** in 71% yield.

Next, substrates with differently substituted allyl moieties were tested. The (*E*)-crotyl-substituted substrate **8a** gave only trace amounts of chromanone **9a** (Table 3, entry 1), and the aldehyde bearing a (*Z*)-2-pentenyl group gave no substantial amount of the corresponding product **9c** at all (entry 3). Interestingly, these results indicate that simple alkyl substitution on the terminal carbon of the allyl group significantly reduces the reactivity of the double bond. Switching to a phenyl substituent (**8b**) improved the yield of the desired product **9b** to 25% (entry 2). Intriguingly, however, slightly electron-withdrawing (*Z*)-benzyloxymethyl substitution at the terminal allylic carbon led to a smooth cyclization in 93% isolated yield (entry 4). The related substrate **8e**, with two allylic ethers, could be transformed into the desired chromanone **9e** with complete chemoselectivity (entry 5). Moreover, a triple bond was also found to be compatible with this novel cyclization reaction (entry 6).

The construction of all-carbon quaternary centers[9] poses a great challenge. Gratifyingly, NHC precursor **3** catalyzed the cyclization of aldehyde substrates **10** to the chromanones **11a**−**d** with newly formed all-carbon stereocenters in the chromanone ring in excellent yields (Scheme 1). Electron-donating (**11a**) and -withdrawing (**11b**) substituents, as well as variation at the newly formed quaternary center (**11d**), were well tolerated.

Likely, the reaction is initiated by the formation of a Breslow intermediate.[10] In a concerted Conia-ene-type transition state,[11] the enamine could then add to the olefin of the allyl moiety, and at the same time the negative charge building up on the other end of the olefin is stabilized by deprotonation of the hydroxyl group.

In conclusion, we have developed a transition-metal-free[12] NHC-organocatalyzed hydroacylation of unactivated double bonds. This method readily affords biologically and pharmaceutically interesting

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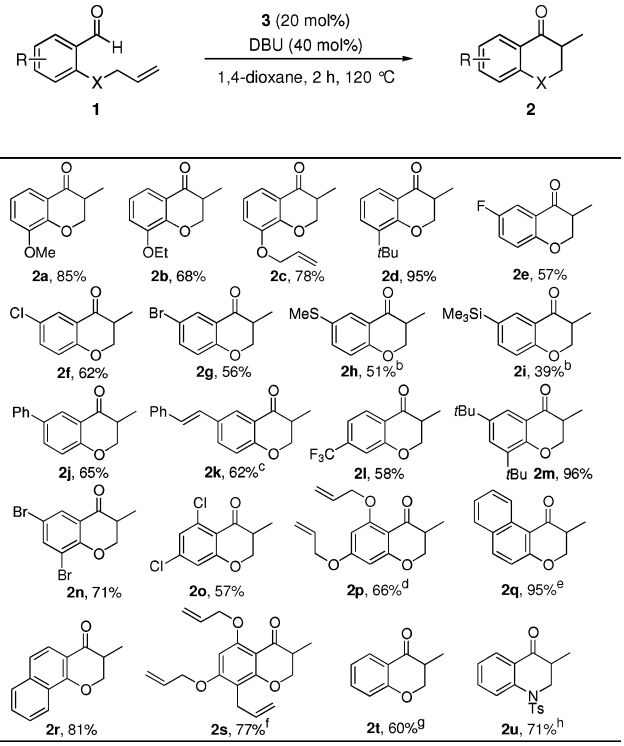
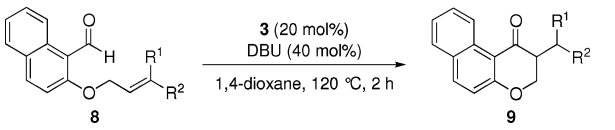
Table 2. NHC-Catalyzed Hydroacylation of Unactivated Double Bonds: Variation of the Aromatic Ring[a]



[a] General conditions: **1** (1.0 mmol), **3** (20 mol %), DBU (40 mol %), 1,4-dioxane (2.0 mL), 120 °C, and 2 h. Given are isolated yields. [b] 24 h. [c] 0.40 mmol scale. [d] 3 h. [e] Using 10 mol % of **3**, an isolated yield of 91% was obtained. [f] 0.32 mmol scale. [g] 6 h. [h] 0.69 mmol scale, 132 h.

chroman-4-ones and demonstrates an unprecedented reactivity of the catalytically generated acyl anion equivalent. Efforts to obtain further insight into the mechanism and the development of an asymmetric variant are ongoing.

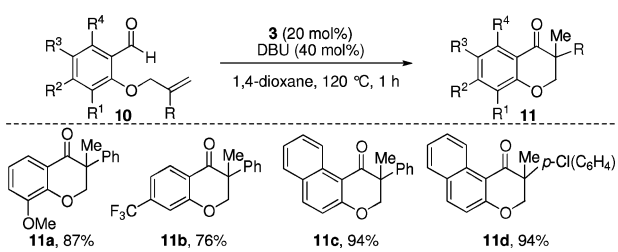
Table 3. Variation of the Allyl Moiety[a]



entry	R^1	R^2	product	yield of **9** (%)[b]
1	H	CH_3	**9a**	<5
2	H	Ph	**9b**	25
3	CH_2CH_3	H	**9c**	<5
4	CH_2OCH_2Ph	H	**9d**	93[c]
5	$CH_2OCH_2CH{=}CH_2$	H	**9e**	89[c]
6	$CH_2OCH_2C'CCH_2CH_3$	H	**9f**	83[c]

[a] General conditions: **8** (1.0 mmol), **3** (20 mol %), DBU (40 mol %), 1,4-dioxane (2.0 mL), 120 °C, 2 h. [b] Isolated yield. [c] 24 h.

Scheme 1. Formation of All-Carbon Quaternary Stereocenters



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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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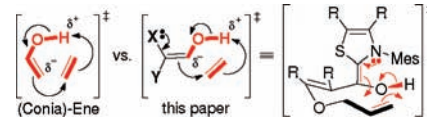
(11) For a recent example and key references on the Conia-ene reaction, see: Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. In our reaction, the NHC might generate a 1,3-enophile undergoing a concerted Conia-ene-type reaction. Despite different transition-state geometries of the Conia-ene and our reaction (six- vs five-membered, respectively), the overall similarity, including the polarity of the reacting olefins, is striking.



(12) ICP-OES (inductively coupled plasma optical emission spectrometry) analyses were performed determining the amount of transition-metal impurities in the reaction mixture. No significant amounts of any transition-metal contaminant were detected.[7]

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