J|A|C|S COMMUNICATIONS

Published on Web 03/21/2006

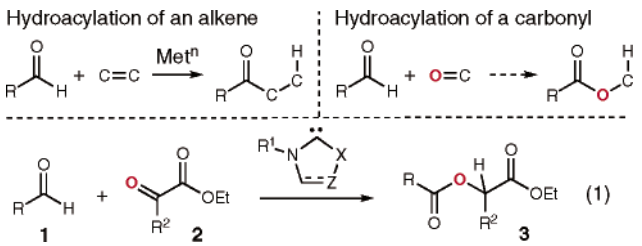
Hydroacylation of Activated Ketones Catalyzed by *N*-Heterocyclic Carbenes

Audrey Chan and Karl A. Scheidt*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208

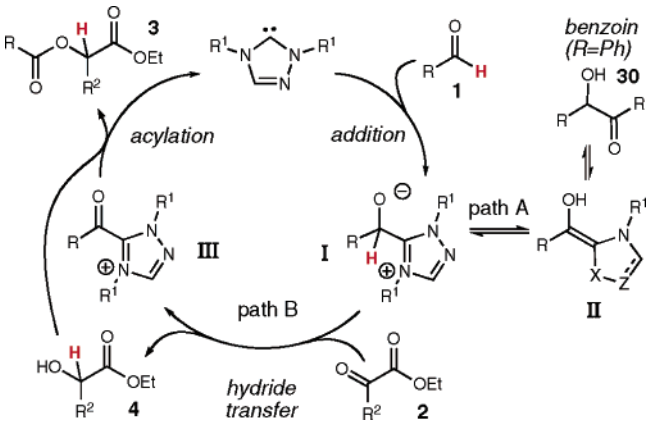
Received February 3, 2006; E-mail: scheidt@northwestern.edu

Direct methods for the selective oxidation of σ bonds are powerful bond-forming strategies in organic synthesis. One established approach to selectively oxidize C−H bonds utilizes transition metals capable of undergoing oxidative addition pathways.[1] The rhodium(I)-catalyzed intramolecular hydroacylations of alkenes, reported from many laboratories including Bosnich, Larock, Jun, Brookhart, Shair, Fu, and Morehead, functionalize aldehydic C−H bonds for the synthesis of carbocycles.[2] Interestingly, the development of analogous catalytic hydroacylation processes involving aldehydes and carbonyl π systems has not received the same attention.[3] We have been interested in developing approaches in which an organic molecule promotes multiple bond-forming steps in a single catalytic cycle.[4] Herein, we report the hydroacylation of α-keto esters (**2**) with aldehydes (**1**) catalyzed by *N*-heterocyclic carbenes (eq 1). In this process, the carbene facilitates selective catalytic oxidation of a C−H bond with concomitant reduction of a ketone.



The interaction of *N*-heterocyclic carbenes[5] with aldehydes has been extensively employed in the development of carbonyl anions, mainly in the additions of these *Umpolung* species[6] to aldehydes (benzoin reaction)[7] and conjugate acceptors (Stetter reaction).[8] A common premise in these processes is that the tetrahedral intermediate (**I**) resulting from the addition of the NHC to an aldehyde usually generates a "Breslow intermediate" structure (**II**, path A, Scheme 1).[9] However, an alternative course potentially involves

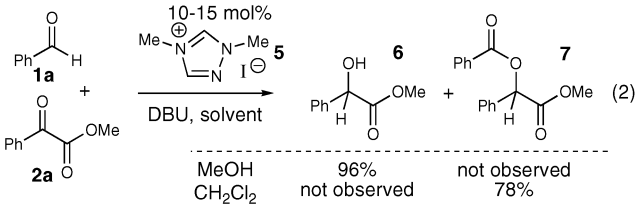
Scheme 1. Proposed Reaction Pathway



the collapse of this intermediate to afford an acyl heteroazolium species (**III**) with concomitant formation of a hydride equivalent (path B). We envisioned that this Cannizzaro-type[10] reducing equivalent could be harnessed to reduce ketones.[11] The resulting alcohol (**4**) produced after a reduction step can undergo an acylation event with the acyl iminium species formed in situ (**III**), thus promoting catalyst turnover and yielding an overall hydroacylation process catalyzed by an organic molecule. Importantly, the aldehdye and activated ketone are separate components, thereby providing for a *metal-free* reaction with broader potential reaction scope than the related Al(III)-promoted Tishchenko disproportionation reaction.[12]

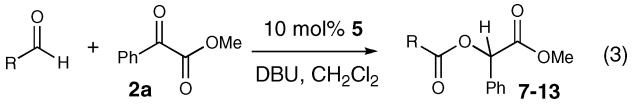
To explore this transformation, a protic solvent (MeOH) was employed to decouple the reduction and acylation events (Scheme 2). After examining various heteroazolium salts and potential ketone

Scheme 2. Protic and Aprotic Reaction Conditions with Keto Ester **1**



electrophiles, the combination of α-keto ester (**2a**) with benzaldehyde (**1a**) in the presence of 15 mol % triazolium salt **5** and DBU produces methyl mandalate (**6**) in excellent yield (96%).[13] Gratifyingly, the use of an aprotic solvent, such as dichloromethane, and 10 mol % **5** affords the hydroacylation product (78%, **7**), which is the product expected from path B in Scheme 1.

Table 1. Examination of Aldehydes in Hydroacylation



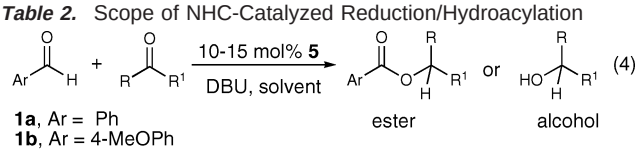
entry	R	compd	yield (%)
1	Ph	**7**	78
2	4-MeO−Ph	**8**	77
3	4-F−Ph	**9**	71
4	4-Me-Ph	**10**	72
5	2-Naphthyl	**11**	70
6	2-Furyl	**12**	73
7	$Ph(CH_2)_2$	**13**	0

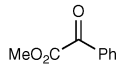
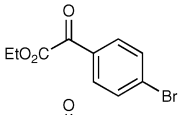
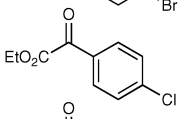
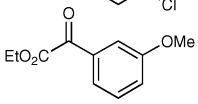
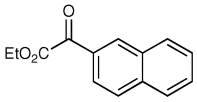
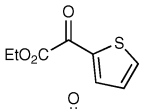
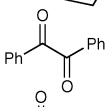
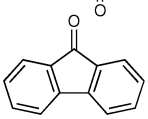
A survey of aldehydes for this process (Table 1, eq 3), indicates that aromatic substituents afford high yields of the corresponding products. The process is tolerant of electron rich aldehydes, while the yields are generally lower when electron-deficient systems are employed. To date, the use of enolizable aldehydes yields predominantly benzoin products.

We have also examined the scope of the reaction with regard to the activated ketone component (Table 2, eq 4). Substituted aromatic keto esters provide the desired esters resulting from overall hydroacylation in good yield when dichloromethane is used as the solvent. By switching the media to ethanol, the corresponding alcohols are

10.1021/ja060833a CCC: $33.50 © 2006 American Chemical Society

Table 2. Scope of NHC-Catalyzed Reduction/Hydroacylation

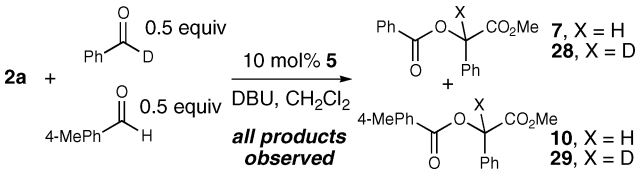


entry	ketone	solvent	product[a]	yield (%)
1		CH_2Cl_2 MeOH	ester (**8**) alcohol (**6**)	77% 96%
2		CH_2Cl_2 EtOH	ester (**14**) alcohol (**15**)	87% 80%
3		CH_2Cl_2 EtOH	ester (**16**) alcohol (**17**)	81% 75%
4		CH_2Cl_2 EtOH	ester (**18**) alcohol (**19**)	72% 84%
5		CH_2Cl_2 EtOH	ester (**20**) alcohol (**21**)	78% 89%
6		CH_2Cl_2 EtOH	ester (**22**) alcohol (**23**)	73% 71%
7		CH_2Cl_2 EtOH	ester (**24**)[b] alcohol (**25**)	83% 93%
8		CH_2Cl_2 EtOH	ester (**26**) alcohol (**27**)	0% 75%[c]

[a] Protic solvent reactions employed **1a** and aprotic solvent reaction used **1b**. [b] Aldehyde **1a** was used. [c] Performed at 40 °C.

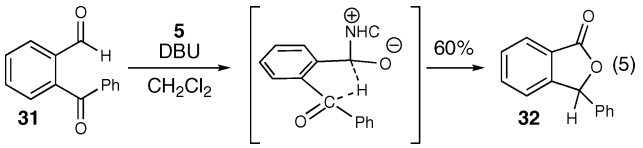
produced directly in the reaction along with the benzoic ester. Currently, these conditions do not generate hydroacylation/reduction products with enolizable keto esters. For less active ketones (e.g., entry 8), only protic conditions are successful in the reduction, and investigations to understand this divergent reactivity are underway.

Our preliminary investigations have provided information about the operative reaction pathway in Scheme 1. The experiment using deuterium-labeled benzaldehyde and 4-methyl benzaldehyde in CH_2Cl_2 generates all potential products (**7**, **10**, and **28**−**29**). This observation strongly supports that the reduction and acylation steps are separate events. The combination of benzoin (**30**, Scheme 1) and keto ester (**2a**) in the presence of **5** and DBU affords the hydroacylated product **7** in 63% yield, indicating that path A is reversible and potential intermediates such as **I** or **II** can enter into catalytic cycle (path B).[14]



This NHC-catalyzed hydroacylation is also successful in an intramolecular manifold (eq 5). The exposure of **31** to **5** delivers the benzofuranone **32** in moderate yield under aprotic conditions.

In summary, we have demonstrated that hydroacylations of activated ketones can be catalyzed by *N*-heterocyclic carbenes. This



process occurs via separate reduction and acylation steps in which the organocatalyst is responsible for two key bond-forming steps of the catalytic cycle. Further investigations of the generality of this catalytic process and the development of asymmetric variants are currently ongoing and will be reported in due course.

Acknowledgment. Support has been generously provided by Northwestern University, the PRF (Type-G), Abbott Laboratories, Amgen, 3M, and Boehringer-Ingelheim (New Investigator Awards). A.C. is the recipient of a Dow Fellowship. We thank FMCLithium, Sigma-Aldrich, and BASF for reagent support, Troy Reynolds (NU) for assistance with X-ray crystallography, and Dr. Steve Wittenberger (Abbott) for helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The use of *N*,*N*′-dimethylbenzimidazolium iodide as a precatalyst affords only 15% of **6**, while 1,4,5-trimethylthiazolium iodide yields 76%.

(14) The heteroazolium-catalyzed benzoin reaction has been shown to be reversible, see refs 6 and 8.

JA060833A