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# Conversion of α,*β*-Unsaturated Aldehydes into Saturated Esters: An Umpolung Reaction Catalyzed by Nucleophilic Carbenes

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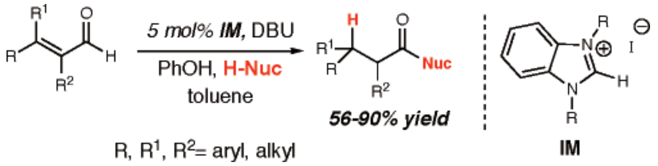
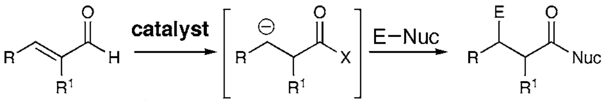
## ABSTRACT

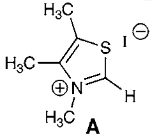


**N-Heterocyclic carbenes derived from benzimidazolium salts are effective catalysts for generating homoenolate species from α,*β*-unsaturated aldehydes. These nucleophilic intermediates can be protonated, and the resulting activated carbonyl unit is trapped with an alcohol nucleophile, thereby promoting a highly efficient conversion of an α,*β*-unsaturated aldehyde into a saturated ester. A kinetic resolution of secondary alcohols can be achieved using chiral imidazoylidene catalysts.**

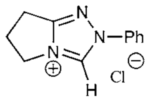
The inversion of standard functional group polarity, or Umpolung, is a powerful strategy in chemistry that facilitates the construction of organic molecules in unusual ways.[1] Established catalytic reactions that employ this unorthodox strategy include the benzoin[2] and Stetter[3] reactions in which carbonyl units of aldehydes are converted into nucleophiles upon the addition of a nucleophilic catalyst. Although the development of these carbonyl anion reactions has received significant attention, a related strategy to access catalytic “vinylogous” carbonyl anions has received considerably less attention.[4] As part of our efforts focused on the development of new nucleophile-catalyzed processes,[5] we envisioned that under appropriate organocatalytic conditions, α,*β*-unsaturated aldehydes could be converted into unique homoenolate nucleophiles with subsequent electrophilic characteristics at the carbonyl carbon.[6] Herein, we report the conversion of α,*β*-unsaturated aldehydes into homoenolates catalyzed by nucleophilic carbenes generated from ammonium salts **A**−**C** (eq 1).



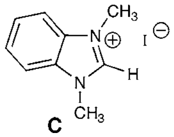
(1)



**A**



**B**



**C**

Homoenolates are important nucleophiles that are essentially the Umpolung equivalent of conjugate addition reactions (Scheme 1).[7] Although this uncommon reactivity

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[1] (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (b) Eisch, J. J. *J. Organomet. Chem.* **1995**, *500*, 101−115. (c) Pohl, M.; Lingen, B.; Muller, M. *Chem. Eur. J.* **2002**, *8*, 5289−5295.

[2] Hassner, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 541−577.

[3] Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407−496.

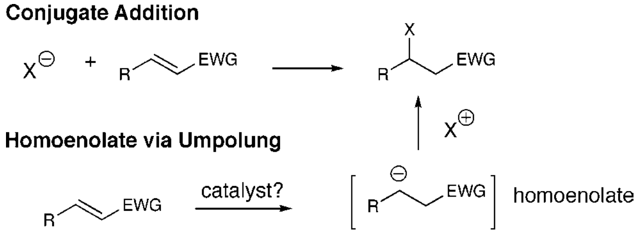
[4] For a review, see: Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541.

[5] (a) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315. (b) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363−4366. (c) A. E.; Bharadwaj, A. R.; Scheidt, K. A *Org. Lett.* **2004**, *6*, 2465−2468. (d) Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 84−85.

[6] (a) List, B. *Synlett* **2001**, 1675−1686. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175 and references therein.

10.1021/ol050100f CCC: $30.25

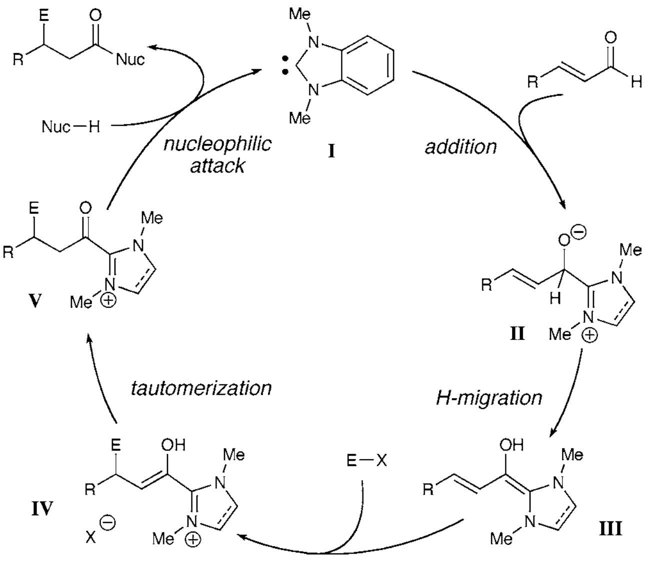
**Scheme 1.** General Umpolung Strategy



pattern has significant utility in organic synthesis, establishing the requisite nucleophilic character at the $\beta$-position of a carbonyl compound is challenging.

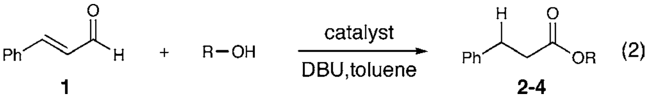
Inspired by the proposed catalytic cycle for the thiazolium-catalyzed benzoin reaction,[8] we hypothesized that the extension of carbonyl anion reactivity to a $\beta$-position could be achieved by use of an alkene in the form of $\alpha,\beta$-unsaturation (Scheme 2). The addition of a nucleophilic carbene catalyst[9] to the carbonyl compound should generate tetrahedral intermediate **II**, and subsequent hydrogen migration would generate the reactive dienamine **III**. The normal nucleophilic character of the carbonyl carbon is then extended to the $\beta$-position and, in the presence of an electrophile (E−X), should produce enol **IV**. After tautomerization of **IV** to activated ester **V**, the attack of a suitable nucleophile completes the catalytic cycle.[10,11]

**Scheme 2.** Proposed Mechanism to Generate Homoenolate Equivalents from $\alpha,\beta$-Unsaturated Aldehydes



We began our investigations of this intriguing strategy by employing the simplest electrophile, a proton (Table 1). The use of the optimal alcohol would presumably serve a double purpose as the electrophile source and subsequent nucleophile. To probe this possibility, cinnamaldehyde (**1**) and various alcohols were heated in toluene in the presence of catalytic quantities of ammonium salts **A**−**C** and DBU. With ethanol and ammonium salt **A**, we were pleased to isolate the desired ester (57%), but clearly the system required improvement. Initially, we pursued a moderate-yielding approach that utilized a single reagent as the potential proton donor and subsequent nucleophile required for catalyst turnover (entries 1 and 2).

**Table 1.** Investigation of Homoenolate Reactivity[a]



| entry | ROH[b] | catalyst (mol %) | additive[c] | yield (%) |
|---|---|---|---|---|
| 1 | EtOH | **A** (30 mol %) | | 57 (**2**) |
| 2 | PhOH | **A** (30 mol %) | | 55 (**3**) |
| 3 | BnOH | **B** (10 mol %) | PhOH | 47 (**4**) |
| 4 | BnOH | **C** (20 mol %) | PhOH | 82 (**4**) |
| 5 | BnOH | **C** (5 mol %) | PhOH | 82 (**4**) |

[a] Reactions performed with a 1:1 molar ratio of catalyst to DBU at reflux temperature. [b] Performed with 5 equiv of nuclephilic alcohol. [c] Performed with 2 equiv of proton additive.

Fortuitously, while using PhOH as the alcohol in chloroform subjected to $Al_2O_3$ filtration, but not distillation, a substantial amount of ethyl ester was observed. Our initial hypothesis for this result was that the putative activated acylation agent (i.e., **V**) was being trapped by the ethanol typically added to stabilize chloroform (not shown). Armed with the knowledge that the electrophile and nucleophile can be decoupled in this manner, we discovered that the use of imidazolium salt **C** (5 mol %) with phenol as the proton source and a second alcohol as the nucleophile affords the best yields for the reaction. This process is noteworthy since no self-condensation (benzoin) products are observed, and combinations of acids and bases in the reaction still generate effective concentrations of catalyst **I**. The combination of DBU and imidazolium salts in the presence of phenolic functionality seems to be uniquely suited for this reaction.

Encouraged by these interesting results, we proceeded to examine the ability of other alcohols to act as nucleophiles

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(7) For reviews on homoenolate equivalents, see: (a) Hoppe, D.; Kraemer, T.; Schwark, J.; Zschage, O. *Pure Appl. Chem.* **1990**, *62*, 1999−2006. (b) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365−390. For recent examples, see: Seppi, M.; Kalkofen, R.; Reupohl, J.; Frohlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 1423−1427. (c) Reuber, J.; Frohlich, R.; Hoppe, D. *Org. Lett.* **2004**, *6*, 783−786. (d) Hilgenkamp, R.; Zercher, C. K. *Org. Lett.* **2001**, *3*, 3037−3040. (e) Whisler, M. C.; Beak, P. *J. Org. Chem.* **2002**, *68*, 1207−1215.

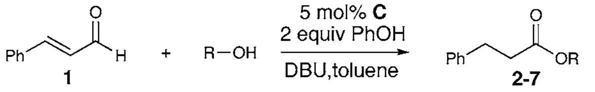
(8) (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (b) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.

(9) (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39−91. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1291−1309.

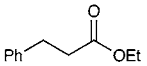
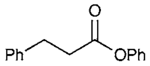
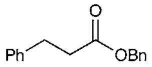
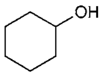
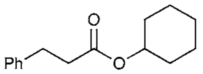
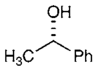
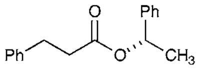
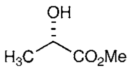
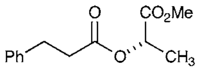
(10) Similar activated esters have been implicated in the reactions between N-heterocyclic carbenes and $\alpha$-halo aldehydes (Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519) or epoxy-aldehydes (Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127).

(11) For recent and related approaches accessing homoenolates from $\alpha,\beta$-unsaturated aldehydes for the synthesis of $\gamma$-butyrolactones, see: (a) Sohn, S. S.; Rosen, J. W.; Bode, J. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (b) Glorius, F., Burstein, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205−6208.

**Table 2.** Examination of Nucleophiles in Homoenolate Reaction[a]



(2)

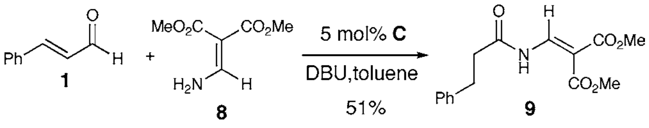
| entry | ROH[b] | time (h) | product | | yield (%) |
|---|---|---|---|---|---|
| 1 | EtOH | 4 |  | **2** | 72 |
| 2 | PhOH | 6 |  | **3** | 56 |
| 3 | BnOH | 2 |  | **4** | 82 |
| 4 |  | 6 |  | **5** | 57 |
| 5 |  | 6 |  | **6** | 77 |
| 6 |  | 6 |  | **7** | 61 |

[a] Reactions performed at 0.5 M at 100 °C. [b] Performed with 5 equiv of ROH.

in the presence of a Brønsted acid such as phenol (Table 2). Primary and secondary alcohols afford good to high yields of the corresponding esters when using cinnamaldehyde (**1**). Not surprisingly, the use of sterically demanding *tert*-butyl alcohol only afforded phenyl ester (56% yield, not shown). The generation of the phenyl ester is the default product observed when the potential nucleophile does not undergo addition. Usually with standard alcohols, this competition is not problematic. When chiral secondary alcohols are employed, the carbon stereocenter remains intact (entries 5 and 6).

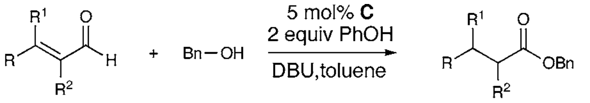
The use of typical nitrogen-based nucleophiles in this general tranformation such as sulfonamides, amides, azide, and anilines did not afford desired products. The results from this intense reaction screening underscore the crucial, and currently not well undestood, balance of acids and bases present in this process. However, during the examination of many of these potential nucelophiles, we did identify that $\beta$-amino alkylidene malonate **8** affords a modest yield of the corresponding bis-ester amide product (Scheme 3). The success and application of this unusual class of nitrogen-delivering nucleophile is currently being investigated in the context of this reaction.

**Scheme 3**

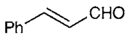
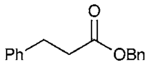
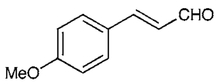
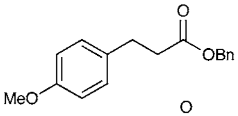
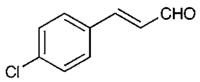
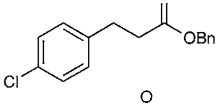
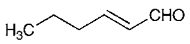
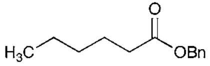
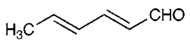
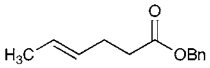
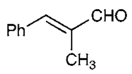
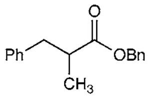
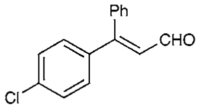
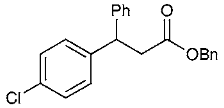
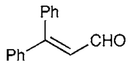
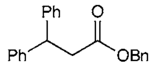
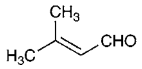


The overall reaction can successfully accommodate various $\alpha,\beta$-unsaturated aldehyde structures (Table 3). Electron-rich or electron-deficient cinnamaldehydes are good substrates for the reaction (entries 2 and 3). The use of unbranched $\beta$-alkyl substituents affords fully saturated esters in good yield (entry 4). Interestingly, the extended dienylic system of sorbaldehyde is disrupted in the reaction to afford the $\gamma,\delta$-unsaturated ester in moderate yield (entry 5).

**Table 3.** Survey of $\alpha,\beta$-Unsaturated Aldehydes[a]



(3)

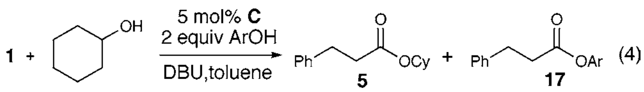
| entry | α,β-aldehyde | product | | yield (%) |
|---|---|---|---|---|
| 1 |  |  | **4** | 82 |
| 2 |  |  | **10** | 76 |
| 3 |  |  | **11** | 71 |
| 4 |  |  | **12** | 90 |
| 5 |  |  | **13** | 70 |
| 6 |  |  | **14** | 82 |
| 7 |  |  | **15** | 82 |
| 8 |  |  | **16** | 86 |
| 9 |  | no reaction | | – |

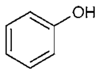
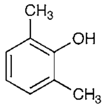
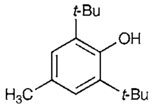
[a] Performed with 5 equiv of $PhCH_2OH$. See Supporting Information for general experimental details.

Disubstitution at the $\beta$-positions of unsaturated aldehydes leads to divergent reactivity depending on the substituents. For example, aldehydes with at least one $\beta$-aryl substituent are competent substrates (entries 6−8), but surprisingly, $\beta,\beta$-dialkyl compounds afford no product (entry 9). Efforts are currently underway to understand this differing reactivity.

Although phenols have the best level of acidity for this Umpolung process to date, various amounts of phenyl ester can be observed when employing sterically demanding alcohol nucleophiles such as cyclohexanol when just phenol is used as the proton source. This competition between phenol or hindered secondary alcohols as the nucelophile prompted us to examine more hindered proton donors with

**Table 4.** Impact of Phenol Structure on Homoenolate Reaction[a]



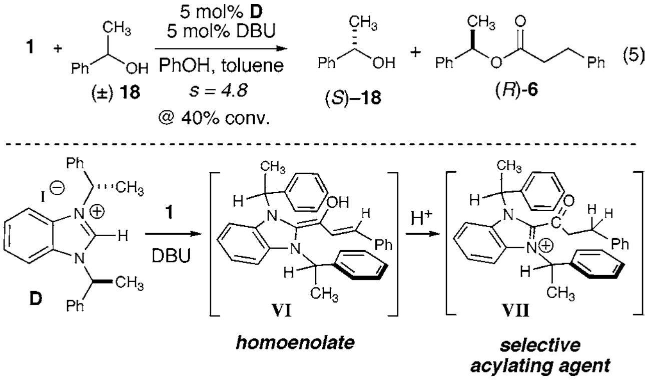
| entry | ArOH | time (h) | yield (%) of **5** | yield (%) of **17** |
|---|---|---|---|---|
| 1 |  | 6 | 57 | 26 |
| 2 |  | 6 | 58 | 20 |
| 3 |  | 6 | 65 | 0% |

[a] Reactions performed at 0.5 M at 100 °C with 5 equiv of cyclohexanol.

similar levels of acidity (Table 4, eq 4). By additional substitution at the 2- and 6-positions of the phenol architecture, the generation of phenyl ester **17** can be minimized in the reaction of 5 mol % catalyst **C** and DBU with cinnamaldehdye (**1**). By increasing the size of the substituents from 2,6-dimethylphenol (entry 2) to 2,6-di-*tert*-butyl-4-methylphenol (entry 3), the level of phenyl ester can be suppressed completely.

We hypothesized that the use of a chiral imidazolium would generate chiral activated esters capable of enantiodiscrimination. This transformation would be synthetically useful in the organocatalytic kinetic resolution of secondary alcohols while also lending credence to the participation of **V** (Scheme 4) as a viable intermediate along the catalytic cycle. To probe this possibility, chiral imidazolium salt **D**[12] was employed as the catalyst in the reaction of racemic 1-phenylethanol (**18**) and cinnamaldehyde (Scheme 3). Gratifyingly, the average *s* factor for this transformation at 40% conversion is 4.8 when using **D** as the catalyst.[13] Presumably, a chiral intermediate present in the catalytic cycle of this reaction such as **VII** has sufficient facial selectivity to undergo preferential reaction with the (*R*)-stereoisomer of 1-phenylethanol.

**Scheme 4**



In summary, the combination of α,*β*-unsaturated aldehydes and N-heterocyclic carbenes accesses unusual homoenolate reactivity under catalytic conditions. These unique nucleophilic species possess subsequent electrophilic character at the carbonyl carbon that can be trapped by a secondary nucleophile such as an alcohol. The combination of a proton donor and a separate nucleophile affords the highest yields of the resulting saturated esters. The use of a chiral imidazoylidene carbene as a catalyst in the reaction allows for the kinetic resolution of chiral secondary alcohols, thereby implicating a chiral activated ester as an intermediate in this process. Further investigations and applications of these unusual homoenolate species are being actively pursued in our laboratory and will be reported in due course.

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**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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(12) For the synthesis of **D**, see: (a) Rivas, F. M.; Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2002**, *67*, 1708−1711. (b) Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673−2676.

(13) For information on selectivity factors (*s*) in kinetic resolutions, see: (a) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley: New York, 1988; Vol. 18, pp 249−330. (b) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299. See Supporting Information for details.