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# Catalytic Generation of Activated Carboxylates from Enals: A Product-Determining Role for the Base

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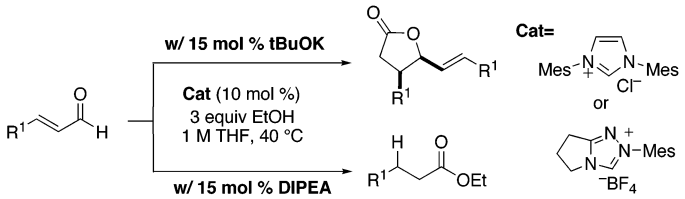
## ABSTRACT

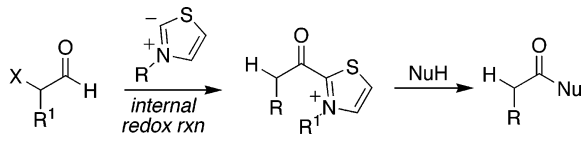



**N-Heterocycle carbenes generated in situ from imidazolium or triazolium salts and bases react with enals, leading to the catalytic generation of homoenolates. The fate of these intermediates is determined by the catalytic base: strong bases such as $^t$BuOK lead to carbon−carbon bond formation, while weaker bases allow protonation of the homoenolate and subsequent generation of activated carboxylates. This discovery, along with the design of a new triazolium precatalyst, enables the catalytic, atom-economical redox esterification of enals.**

Although the vast majority of carboxylic acid derivatives are prepared via the intermediacy of activated carboxylates, a general, catalytic method for their transient generation has not emerged.[1] This is suprising, as catalytic methods could both improve the efficiency of these widespread reactions and provide a mechanistic basis for control of the absolute stereochemistry of the products.

In the course of our ongoing studies on novel methods for the N-heterocyclic carbene (NHC)-catalyzed[2] generation of activated carboxylates via internal redox reactions (Scheme 1),[3,4] we were attracted to readily available α,β-unsaturated aldehydes as substrates for redox esterification.[5] Our initial attempts to effect this transformation led to a surprising result. While all evidence suggested that a variety of NHC catalysts reacted with enals to give **i**, carbon−carbon bond formation products predominated, and protonation was not observed, even when protic solvents were employed (Scheme 2). To determine if the observed preference for carbon−carbon bond formation was due to slow protonation of the postulated homoenolate **ii** or arose from reversible protonation, we conducted experiments in $^t$BuOD at 60 °C. Remarkably, no deuterium incorporation at the β-position was observed, implying that carbon−carbon bond formation, rather than protonation, is the preferred fate of catalytically generated

**Scheme 1.** Catalytic Generation of Activated Carboxylates via Internal Redox Reactions




(1) (a) For catalytic methods for the esterifications of carboxylic acids, see: Otera, J. *Esterification: Methods, Reactions, and Applications*; Wiley & Sons: New York, 2003. (b) Ishihara, K. Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168−4169.

(2) For NHC-catalyzed transesterifications, see: (a) Grasa, G. A.; Sing, E.; Nolan, S. P. *Synthesis* **2004**, 971−985. (b) Nyce, G. W.; Glauser, T.; Conor, E. F.; Möck, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046−3056. (c) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453−2456.

(3) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127.

(4) For the catalytic generation of activated carboxylates from α-chloroaldehydes, see: Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519.

10.1021/ol051269w CCC: $30.25 
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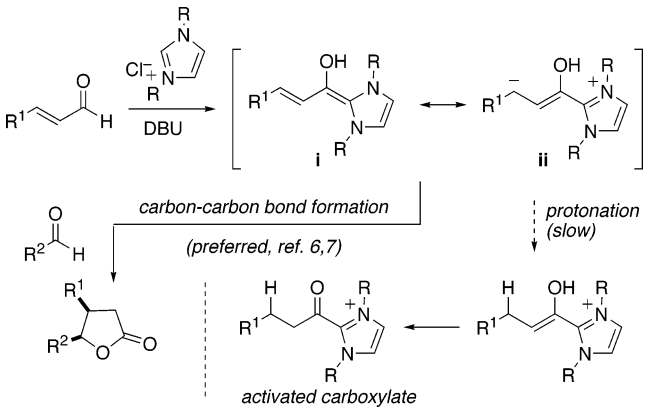
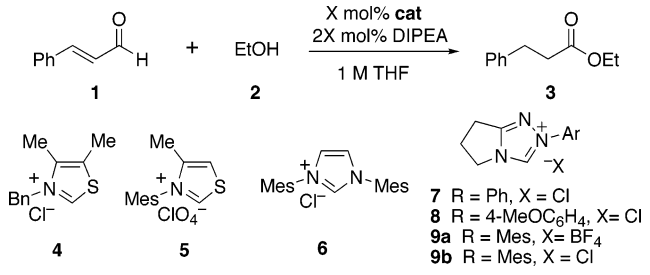
**Scheme 2.** Reaction Pathways of Catalytically Generated Activated Carboxylates



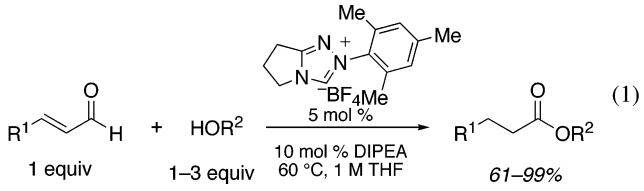

homoenolates. These observations temporarily stymied the development of a truly catalytic method for redox esterifications but contributed to our discovery that such catalytically generated homoenolates undergo facile carbon−carbon bond-forming reactions for the synthesis of $\gamma$-lactones and $\gamma$-lactams.[6,7]

Recently, Scheidt and Chan communicated a solution to the protonation of catalytically generated homonenolates using excess phenol as an added proton source.[8] While this protocol nicely achieved protonation of homoenolate equivalents generated under our usual conditions, the requirements of excess phenol, 5 equiv of the alcohol, and high temperatures limit its utility as a practical alternative to traditional coupling reagent-based esterifications. Prompted by this

**Scheme 3.** Heterocyclic Precatalysts for the Catalytic Generation of Activated Carboxylates from Cinnamaldehyde




report, we now disclose our ongoing efforts in this area, namely, the combination of substoichiometric amounts of triazolium precatalyst **9** and diisopropylethylamine (DIPEA) as a highly effective catalyst system for the direct conversion of $\alpha,\beta$-unsatured aldehydes to saturated esters (eq 1).[9] In addition to providing a practical esterification process without the use of stoichometric reagents or proton sources, our studies highlight a mechanistically revealing and product-determining role for the catalytic base.




The conversion of cinnamaldehyde to ethyl hydrocinnamate illustrates the role of the heterocyclic precatalyst in the success of this transformation (Table 1). Thiazolium salts

**Table 1.** Catalysts and Conditions for Redox Esterification[a]

| entry | catalyst (mol %) | temp (°C) | conversion[b] (%) | yield[c] (%) |
|---|---|---|---|---|
| 1 | **4** (10) | 40 | 15 | |
| 2 | **5** (10) | 40 | trace | |
| 3 | **6** (15) | 40 | 80 | 59 |
| 4 | **7** (10) | 40 | trace | |
| 5 | **8** (10) | 40 | 98 | |
| 6 | **9a** (10) | 40 | 99 | |
| 7 | **9a** (5) | 40 | 90 | 89 |
| 8 | **9a** (5) | 60 | 99 | 86 |
| 9 | **9a** (2) | 60 | 95 | 60 |
| 10[d] | **9a** (5) | 60 | 89 | 69 |
| 11 | **9b** (5) | 60 | 99 | 89 |

[a] All reactions were performed on a 0.2 mmol scale. DIPEA = diisopropylethylamine; Mes = 2,4,6-trimethylphenyl. [b] Determined by GC analysis of unpurified reaction mixtures. [c] Isolated yield following chromatography. [d] Performed with 1.2 equiv of EtOH.

**4** and **5** provided small amounts of the desired saturated ester, along with conspicuous amounts of the unsaturated ester and other byproducts. Imidazolium salt **6** (IMes-HCl) offered significant advantages, but tended to produce the unsaturated acid as a byproduct, possibly due to slow turnover of the catalyst-bound activated carboxylate. Although triazolium salt **7**, previously described by Rovis,[4] was unproductive (entry 4), methoxyphenyl analogue **8** was effective (entry 5), but with a limited range of substrates. Further studies on catalyst synthesis and screening identified triazolium precatalyst **9a** as uniquely active, effecting redox esterifications of cinnamaldehyde overnight with as little as 2 mol % of the salt and 5 mol % DIPEA as the only added reagents.[10] The counterion had no noticible effect (entry 11), although the chloride salt was hygroscopic while the tetrafluoroborate

(5) For a metal-mediated redox esterification of cinnamaldehyde, see: de Vries, J. G.; Roelfes, G.; Green, R. *Tetrahedron Lett.* **1998**, *39*, 8329−8332.

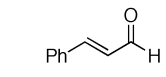
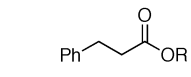
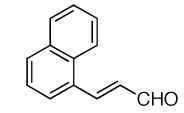
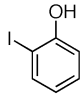
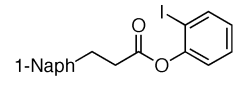
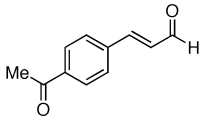
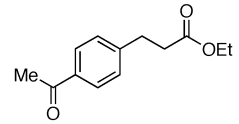
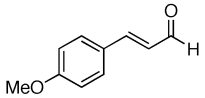
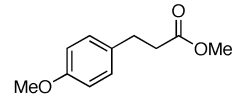
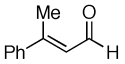
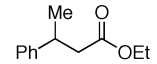
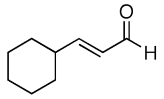
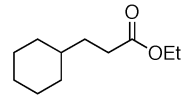
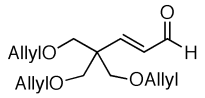
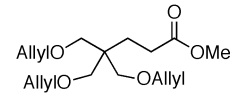
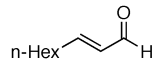
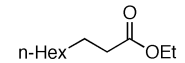
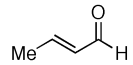
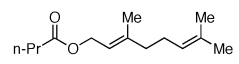
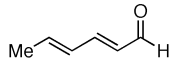
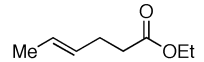
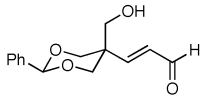
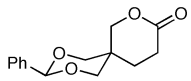
(6) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (b) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131−3134.

(7) Glorius has independently reported a related method: Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 6205−6208.

(8) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905−908.

(9) For the organocatalytic, asymmetric conjugate reduction of $\alpha,\beta$-unsaturated aldehydes to the saturated aldehydes in the presence of a hydride donor, see: (a) Ouellet, S. G.; Tuttle, J. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33. (b) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660−6662. (c) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110.

**Table 2.** Catalytic Esterifications of α,β-Unsaturated Aldehydes

| entry | enal | Nu | product | yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1** | MeOH |  **10** R = Me, **12** R = geranyl **11** R = $^i$Pr, **13** R = Bn | 97 |
| 2 | | $^i$PrOH | | 71 |
| 3 | | geraniol[c] | | 99 |
| 4 | | BnOH | | 89 |
| 5[d] |  **14** |  **15** |  **16** | 67 |
| 6 |  **17** | EtOH |  **18** | 70 |
| 7 |  **19** | MeOH |  **20** | 86 |
| 8[e] |  **21** | EtOH |  **22** | 72 |
| 9 |  **23** | EtOH |  **24** | 93 |
| 10 |  **25** | MeOH |  **26** | 85 |
| 11 |  **27** | EtOH |  **28** | 86 |
| 12 |  **29** | geraniol |  **30** | 63 |
| 13 |  **31** | EtOH |  **32** | 79 |
| 14 |  **33** | |  **34** | 89 |

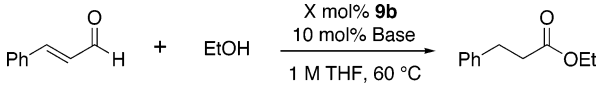
[a] Reaction conditions: 5 mol % of **9a**, 10 mol % of DIPEA, 1.0 mmol of enal, 1 M THF, 3 equiv of ROH, 60 °C, 24 h. [b] Isolated yield following chromatography. [c] Performed with 2 equiv of geraniol. [d] Performed with 1 equiv of **15**. [e] Performed with 10 mol % of **9b**, 15 mol % of DIPEA.

required no special handling. Esterifications with **9a** or **9b** and DIPEA produced no benzoin, Stetter, or lactone products and are far more efficient and selective than other combinations of heterocyclic salts and bases we have examined. Importantly, in contrast to other NHC precursors, the triazolium precatalysts are readily deprotonated by weaker bases (DIPEA, $NEt_3$), a feature critical to the success of the overall catalytic process.

Triazolium precatalyst **9** (5 mol %), in conjuction with 10 mol % DIPEA, promoted the esterification of a wide variety of unsaturated aldehydes. Primary and secondary alcohols (Table 2, entries 1−4), as well as phenols (entry 5), are competent nucleophiles. Both electron-rich and electron-deficient cinnamaldehydes (entries 4−8) serve as precursors to catalytically generated activated carboxylates, as do a broad range of aliphatic-substituted enals (entries 9−12). Intramolecular esterifications are also possible, as illustrated by the clean formation of lactone **34** (entry 14). In preliminary investigations, we have found that β,β-disubstituted enals are viable substrates (entry 8). Only α-substituted unsaturated aldehydes proved to be recalcitrant to esterifications with this catalyst system.[11]

The choice, and presence, of the amine base is critical to the success of the reaction and serves as a catalytic proton shuttle. Given that sufficient proton sources, including the alcohol substrate, are present in the reaction mixtures, the key role of the protonated amine was not immediately obvious. However, a clear correlation between the success of the reaction and the p$K_a$ of the conjugate acid emerged. While weaker amine bases, including $NEt_3$ and DIPEA, give excellent conversion (Table 3, entries 1 and 2), strong bases,

**Table 3.** Effect of the Amine Base of Catalytic Esterifications[a]




| entry | X (mol %) | base | p$K_a$ of conjugate acid in THF[13] | relative yield (%)[b] |
|---|---|---|---|---|
| 1 | 5 | $NEt_3$ | 12.5 | 99 |
| 2 | 5 | DIPEA | ~13 | 99 |
| 3 | 5 | DBU | 16.8 | 15 |
| 4 | 5 | P2-*t*-Bu | 20.9 | >5 |
| 5 | 5 | KO*t*Bu | 29.4[c] | >5 |
| 6 | 20 | KO*t*Bu | | 75 |
| 7 | 20 | DIPEA | | 99 |

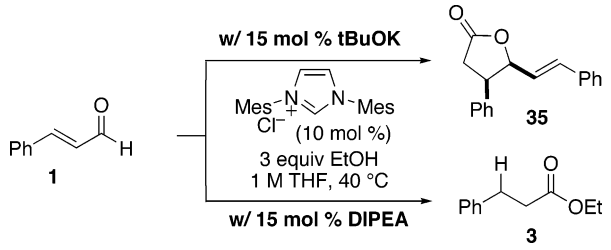
[a] Reaction conditions: X mol % of **9b**, 10 mol % of base, 0.2 mmol of enal, 1 M THF, 3 equiv of ROH, 60 °C, 15 h. [b] Relative yield of ester to starting material and other products, as determined by $^1$H NMR or GC analysis of unpuried reaction mixtures. [c] In DMSO.

including DBU, KO*t*Bu, and the phosphazine base P2-*t*Bu, show little if any products arising from protonation of the catalytically generated homoenolate species. We also considered that the triazolium salt itself could effect protonation, a pathway that would not be available in systems with strong bases that completely and irreversibly deprotonate the heterocyclic salt. Upon conducting the esterification in the presence of excess salt relative to KO$^t$Bu (entry 6), we again observed esterification products, raising the intriguing possibility that the heterocyclic salt serves as the catalytic proton shuttle.[12]

(10) (a) Synthesis of related azolium catalysts has been described: Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkins Trans. 1* **1998**, 1891−1893. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725−5728. We are grateful to Prof. Rovis for a preprint of this work.

The relative difficulty of protonating the catalytically generated homoenolates vis-à-vis carbon−carbon bond forming pathways is most evident when IMes-HCl is used as the catalyst (Scheme 4). Heating a solution of cinnamaldehyde,

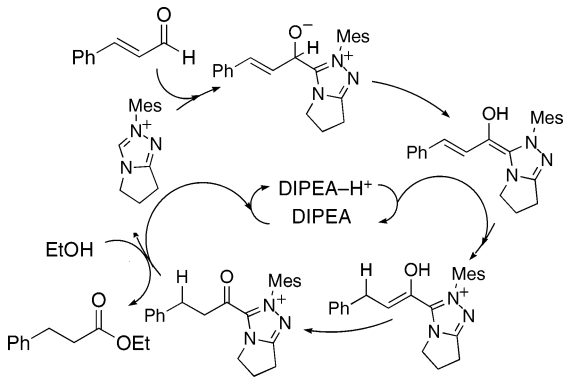
**Scheme 4.** Effect of Catalytic Base on the Fate of Catalytically Generated Homoenolate Equivalents




15 mol % IMes-HCl, 10 mol % KO*t*Bu, 3 equiv of EtOH in THF leads to lactone dimer **35** as the major isolated product; less than 5% saturated ester is formed. In contrast, the identical experiment performed with 10 mol % DIPEA gives the unsaturated ester in 60% yield, with only a trace of the lactone dimer.

This process is likely to be mechanistically similar to our previous reports of catalytically generated homoenolates and activated carboxylates with N-heterocyclic carbenes (Scheme 5).[14,15] Studies with deuterated substrates and solvents support

**Scheme 5.** Postulated Catalytic Cycle for Catalytic Redox Esterifications of Enals




this postulated catalytic cycle and disfavor a concerted hydride shift mechanism.

In summary, we have identified a critical and product-determining role for the catalytic amine base in the chemistry of homoenolates generated catalytically from enals and N-heterocyclic carbenes. In addition to revealing the unique properties of these transient intermediates, these findings were critical to the development of a catalytic method for the generation of activated carboxylates from α,β-unsaturated aldehydes under mild conditions that requires no additional coupling reagents or additives and produces no reaction byproducts.

**Acknowledgment.** This work has been supported by the National Science Foundation (CAREER Award to J.W.B.), the Camille and Henry Dreyfus Foundation, and the University of California. We thank Evie Rosen and Justin Struble for experimental assistance.

**Supporting Information Available:** Experimental procedures, characterization data, and deuterium labeling studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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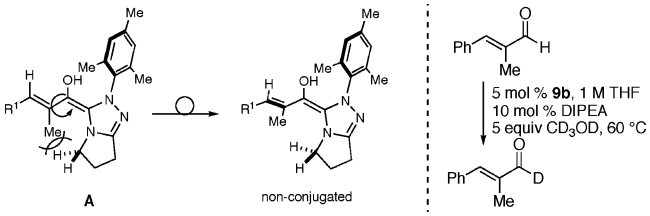
(11) We postulate that the allylic strain inherent to the key homoenolate equivalent inhibits protonation at the β-position by impeding the formation of a fully conjugated system.




We have shown, by deuterium labeling experiments, that the catalyst reacts with α-methylcinnamaldehyde to give **A** (or its geometric isomer). This process, however, is unproductive and does not promote the formation of any products other than the deuterated aldehyde.

(12) Triazolium salts **9a** and **9b** undergo rapid proton exchange even in the absence of base. For example, $^1$H NMR spectra of **9** in $CD_3OD$ show rapid exchange of the C2 proton with deuterium.

(13) (a) Rodima, T.; Kaljurand, I.; Pihl, A.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2002**, *67*, 1873−1881. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(14) The apparently related conversion of β-formyl acrylic acid to succinic acid by aqueous cyanide ion has been described: (a) Nowak, R. M. *J. Org. Chem.* **1963**, *28*, 1182−1187. (b) Franzen, V.; Fikentscher, L. *Liebigs Ann.* **1959**, *623*, 68−73.

(15) For a similar overall transformation via the stoichiometric intermediacy of TMS cyanohydrins, see: Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2002**, *43*, 5645−5647.