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# Asymmetric Access to the Smallest Enolate Intermediate via Organocatalytic Activation of Acetic Ester

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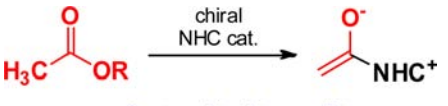
## ABSTRACT




*smallest* enolate intermediate
from acetic ester

**An NHC-catalyzed activation of acetic esters to afford enolate intermediates is disclosed. The catalytically generated triazolium enolate intermediates serve as two-carbon nucleophiles that undergo highly enantioselective reactions with enones and α,β-unsaturated imines to give α-unsubstituted δ-lactones and lactams, respectively.**

The asymmetric catalytic generation of chiral enolates and their equivalents *via* metal[1] or organic molecule-based catalysts[2] is a basic strategy in organic synthesis. Chiral enolate equivalents from acetic esters and their derivatives, the smallest enolate intermediates, have attracted much attention as two-carbon nucleophilic building blocks in synthesis. Under organic catalysis, several approaches have been developed for the catalytic generation of chiral enolate intermediates from acetaldehyde and its derivatives (Scheme 1). With a chiral amine catalyst, the List, Hayashi, and Maruoka groups reported the use of acetaldehyde as two-carbon building blocks *via* enamine intermediates (Scheme 1a).[3] With cinchona alkaloid catalysts, the groups of Wynberg and Nelson successively reported the activation of acetyl chloride to generate enolate intermediates that underwent reactions with aldehydes to afford β-lactones (Scheme 1b).[4] *N*-Heterocyclic carbenes (NHC)[5−8] have also been utilized in the catalytic generation of enolate from acetaldehyde derivatives. Bode and co-workers used

† These authors contributed equally.

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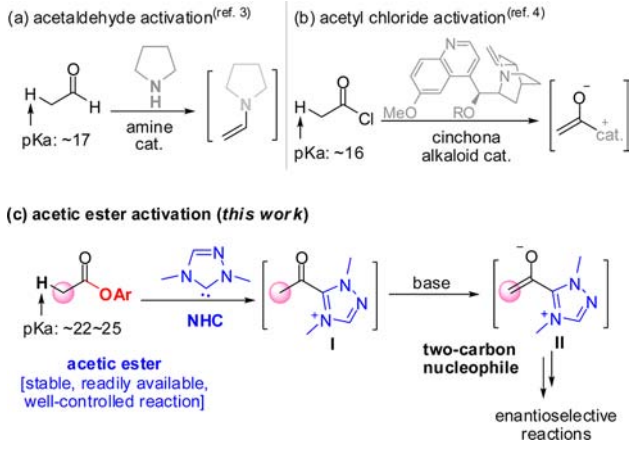
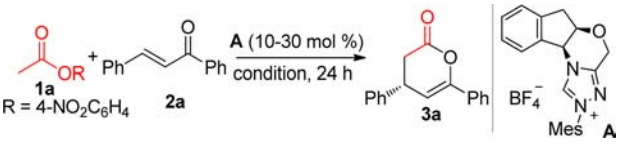
**Scheme 1.** Generation of Two-Carbon Enolate Intermediates




α-chloroacetaldehyde bisulfite adducts as enolate precursors for enantioselective reactions with enones to afford lactones.[9] Scheidt reported an internal redox transformation of α-aryloxyacetaldehyde to form an enolate intermediate for Mannich reactions.[10]

We are interested in the use of esters as substrates as they are stable, readily available, and inexpensive. Built on our success with the usual and unusual activations of esters and α,β-unsaturated esters,[11] here we report that an acetic ester can be a suitable precursor for a two-carbon enolate intermediate (Scheme 1c). As illustrated in Scheme 1c, an acetic ester reacts with an NHC catalyst to produce intermediate **I**, which on deprotonation generates enolate intermediate **II**. This catalytically generated enolate **II** undergoes enantioselective reaction with various electrophiles (see the Supporting Information for detailed mechanism). Esters are challenging substrates in part because of the lower acidity of the α-CH, when compared to the corresponding acetaldehyde and acetyl chloride. On the application side, acetic esters can be an ideal choice as they are stable and readily available.

**Table 1.** Optimization of NHC Catalyzed Annulation of Acetic Ester with Chalcone[a]

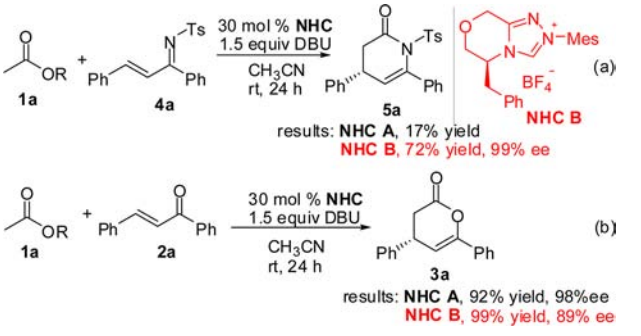



| entry | condition | yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | 30 mol % **A**, 2.0 equiv of DBU, THF | 69 | 94 |
| 2 | 30 mol % **A**, 2.0 equiv of DBU, $CH_2Cl_2$ | 80 | 99 |
| 3 | 30 mol % **A**, 2.0 equiv of DBU, $CH_3CN$ | 99 | 96 |
| 4 | 30 mol % **A**, 2.0 equiv of $Cs_2CO_3$, $CH_3CN$ | 30 | 98 |
| 5 | 30 mol % **A**, 2.0 equiv of $Et_3N$, $CH_3CN$ | trace | n.d. |
| **6** | **20 mol % A, 1.5 equiv of DBU, $CH_3CN$** | **92**[d] | **98** |
| 7 | 10 mol % **A**, 2.0 equiv of DBU, $CH_3CN$ | 88 | 96 |

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.05 mmol), **A** (10−30 mol %), base, solvent (0.5 mL), rt. [b] Yield of **3a** was estimated *via* $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] The ee of **3a** was determined *via* chiral phase HPLC analysis. [d] Isolated yield after $SiO_2$ column chromatography.

We started by using acetic ester **1a**, prepared from acetic acid and 4-nitrophenol,[11a] as the two-carbon enolate precursor. When chalcone **2a** was the electrophile, aminoindanol-derived catalyst **A**[12] was found as an effective catalyst to give product **3a** in 69% yield and 94% ee in THF (Table 1, entry 1). $CH_2Cl_2$ was also a suitable solvent while $CH_3CN$ performed the best (entries 2−3). The use of $Cs_2CO_3$ gave a much lower yield (entry 4), and $Et_3N$ was not an effective base (entry 5). We then found that the use of 20 or 10 mol % of NHC precatalyst **A** was sufficient to give good yields and excellent ee's (entries 6−7).

**Scheme 2.** Reaction Condition for α,β-Unsaturated Imines

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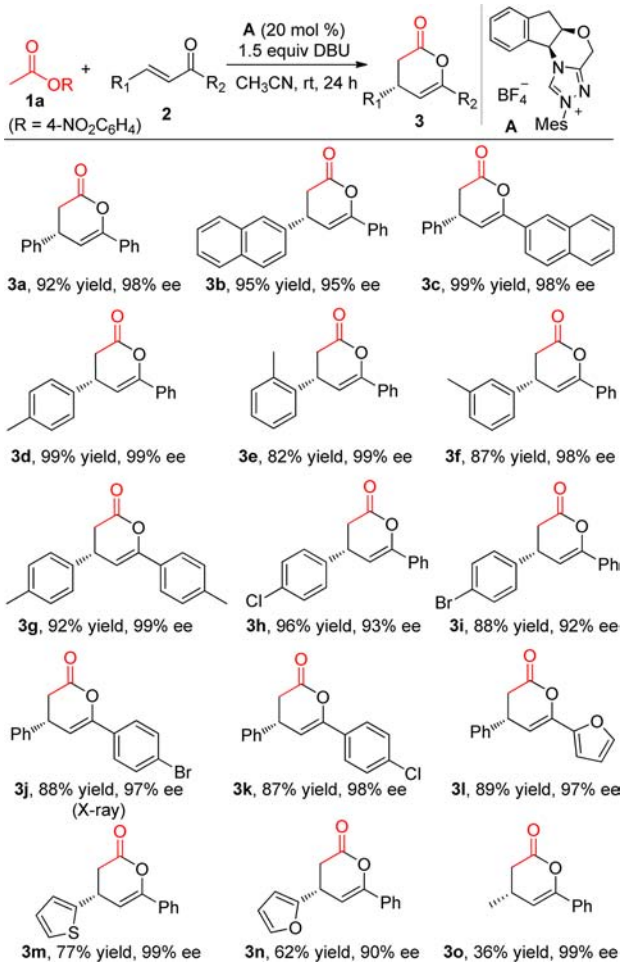
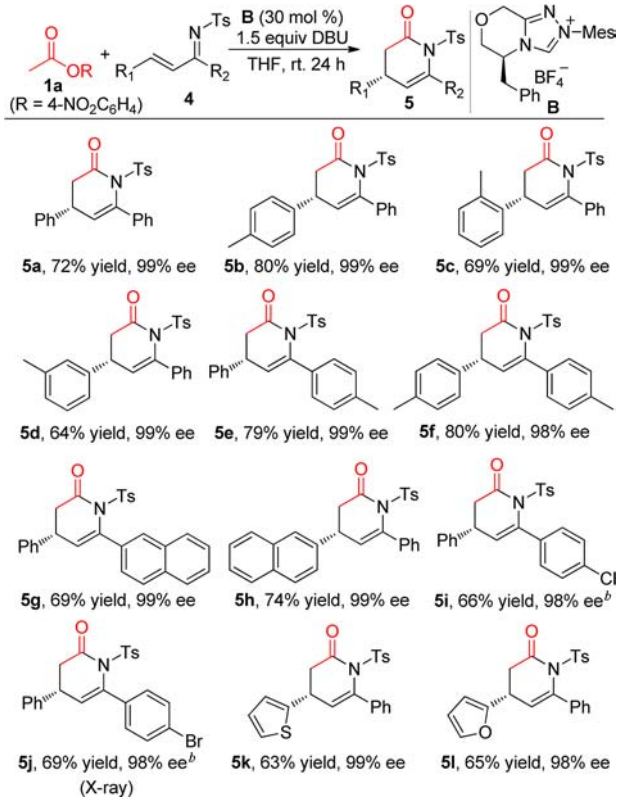
**Scheme 3.** Examples of the α,β-Unsaturated Ketones[a]




[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.10 mmol), **A** (0.02 mmol), DBU (0.15 mmol), MeCN (1.0 mL). Reported yields are isolated yields based on **2**. Enantiomeric excesses were determined via chiral phase HPLC.

**Scheme 4.** Examples of the α,β-Unsaturated Imines[a]




[a] Reaction condition: **1a** (0.10 mmol), **2** (0.05 mmol), **B** (0.015 mmol), DBU (0.075 mmol), THF (0.5 mL). Reported yields are isolated yields based on **2**. Enantiomeric excesses were determined *via* chiral phase HPLC. [b] 50 mg of 4 Å MS were added; without 4 Å MS, **5i** was obtained in 55% yield with 98% ee, and **5j** in 52% yield with 98% ee.

After identifying chalcone as an effective electrophile (Table 1), we moved to examine the use of α,β-unsaturated imine **4a** as another substrate to react with acetic ester **1a** (Scheme 2a). Interestingly, with the NHC precatalyst **A** used above, much lower yields (e.g., <20%) of lactam product **5a** were obtained after testing several conditions (Scheme 2a, NHC = **A**). Additional studies revealed that amino alcohol derived catalyst **B**[13] could catalyze this reaction of an ester and α,β-unsaturated imine with a good yield and 99% ee (Scheme 2a, NHC = **B**). It is worth noting that NHC catalyst **B** could also mediate the reaction between the acetic ester and enone to give lactone in excellent yield, albeit with a slightly dropped 89% ee (Scheme 2b).

The scope of the enone substrate was then explored. Essentially, various chalcone-type enones were effective substrates to give the corresponding enol lactone products with good yields and excellent ee (Scheme 3, **3a**–**o**). For example, replacing the β- or carbonyl phenyl group with a bulkier naphthyl substituent was well-tolerated in this reaction (**3b**, **3c**). Placing a methyl, Br, or Cl substituent on either of the phenyl groups of chalcone had little influence on the reaction yield or enantioselectivity (**3d**–**k**). Heteroaryl substituents worked fine as well, except when the β-phenyl unit was replaced with a furan ring, causing the product (**3n**) to be obtained with a reduced yield and ee (62% yield, 90% ee). The use of a β-alkyl enone could also give the product with an excellent ee, albeit with a low yield (**3o**, 36% yield).[14] The absolute configurations of the lactone products were estimated based on X-ray crystal structure analysis of **3j**.[15]

Examples of α,β-unsaturated imines used in the reactions are shown in Scheme 4. In all the reactions, the lactam products were obtained in moderate to good yields with 98–99% ee. For the unsaturated imine substrates with an

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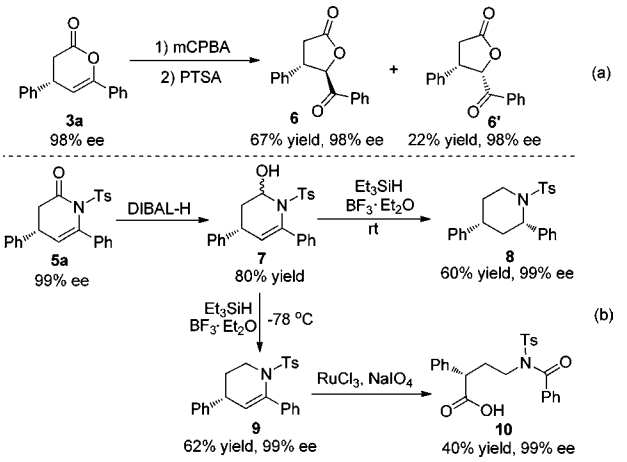
(14) Raising the reaction temperature to 40 °C gave the product **3o** in 27% yield with 98% ee. At 60 °C, the product was obtained in 24% yield with 97% ee.

(15) CCDC 921945 (**3j**) and CCDC 921945 (**5j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Scheme 5.** Synthetic Utility of the Lactone and Lactam Products




electron-withdrawing Cl/Br substituent, the addition of a molecular sieve could slightly improve the reaction yields (**5i**, **5j**), because these imine substrates could undergo hydrolysis by the trace water present in the reaction. Under this condition, alkyl substituted imines ($R_1$ and/or $R_2$ as alkyl) were not suitable substrates. The absolute configurations of the lactam products were estimated based on X-ray crystal structure analysis of **5j**.[15]

With the protocol for the asymmetric [4 + 2] annulation reaction established, we proceeded to explore the synthetic utility of the lactone and lactam products (Scheme 5). Treatment of lactone **3a** with *meta*-chloroperoxybenzoic acid (mCPBA) gave an unstable epoxide product that rearranged under acidic conditions to form butyrolactones **6** (and **6′**) that bear an important core structure found in many biologically active natural products.[16] Reduction of **5a** using diisobutylaluminium hydride (DIBAL-H) afforded hemiaminal **7** in good yield. The adduct **7** could be further transformed to piperidine **8** as a single isomer. At a low temperature (−78 °C), the hemiaminal product **7** could be selectively reduced to form tetrahydropyridine **9** in good yield.[17] Oxidation of the enamide functionality of **9** using $RuCl_3/NaIO_4$ afforded protected $\gamma$-amino acid **10**, which is useful in constructing peptide mimetics.[18]

In summary, we have developed an NHC-catalyzed generation of enolate intermediates from simple acetic ester substrates. These enolate intermediates as two-carbon building blocks readily underwent highly enantioselective reactions with $\alpha,\beta$-unsaturated ketones and imines. These reactions afforded $\alpha$-unsubstituted $\delta$-lactones and lactams that were difficult to prepare using other methods. Further mechanistic exploration and synthetic application of this smallest ester enolate intermediate are in progress.

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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.

The authors declare no competing financial interest.

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