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Organocatalytic Enantioselective γ-Aminoalkylation of Unsaturated Ester: Access to Pipecolic Acid Derivatives

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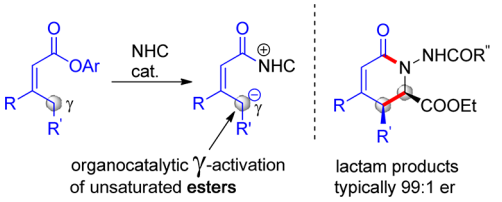
ABSTRACT



The direct γ-carbon functionalization of α,β-unsaturated esters *via* *N*-Heterocyclic Carbene (NHC) catalysis is disclosed. This catalytically generated nucleophilic γ-carbon undergoes highly enantioselective additions to hydrazones. The resulting δ-lactam products can be readily transformed to optically enriched pipecolic acid derivatives.

α,β-Unsaturated carbonyl compounds are common synthetic building blocks, of which the carbonyl, α-, and β-carbons are used as reactive sites. The γ-carbons of such unsaturated compounds, on the other hand, are typically less reactive. It is expected that a direct use of the γ-carbons should provide new opportunities for efficient access to useful molecules. Therefore, considerable efforts have been drawn to the development of asymmetric catalytic methods for the activation of γ-carbons of unsaturated carbonyl compounds.[1] These methods normally use preformed silyl dienolates as substrates or use transition metals as catalysts. Representative examples include the vinylogous aldol reactions reported by Carreira,[2] Evans,[3] Denmark,[4] and Campagne;[5] the vinylogous Mannich reactions reported by Hoveyda,[6] Shibasaki,[7] and Nakamura;[8] and the vinylogous Michael addition reactions reported by MacMillan[9] and Trost.[10] In 2006, Jorgensen and co-workers disclosed

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the γ-addition of α,β-unsaturated aldehydes to azodicarboxylates *via* dienamine organocatalysis.[11] This dienamine chemistry[12] has then been further advanced by the groups of Melchiorre,[13] Christmann,[14] Chen,[15] and Vicario.[16] With *N*-heterocyclic carbenes (NHCs)[17] or cinchona alkaloids as catalysts, Peters[18] and Ye[19] groups have activated the γ-carbons of vinyl ketenes.[20] This nice ketene-based approach, proven to be successful in a number of interesting reactions, is somewhat limited by the unstable nature of the ketene substrates.[21]

Stable carboxylic esters are readily available, inexpensive, and easy to handle. Asymmetric catalytic strategies that can directly functionalize carboxylic esters (the carbonyl, α-, β-, and γ-carbons, *etc.*) will provide useful solutions for organic synthesis. Under a larger program of organocatalytic ester activation, we developed the catalytic conversion of saturated α-aryl acetic esters as NHC-bounded enolate intermediates that led to α-functionalization

Scheme 1. NHC-Catalyzed γ-Activation of α,β-Unsaturated Esters

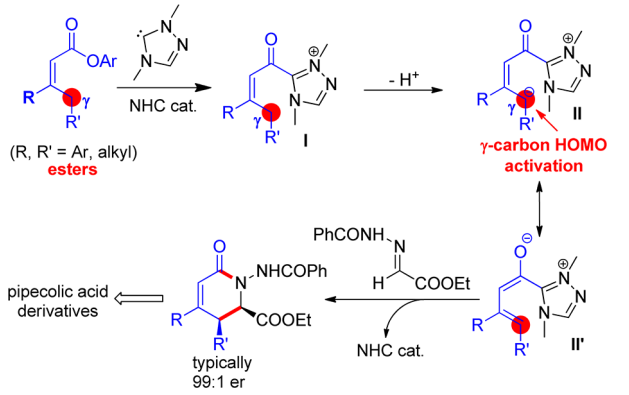
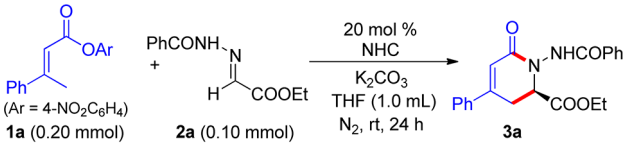
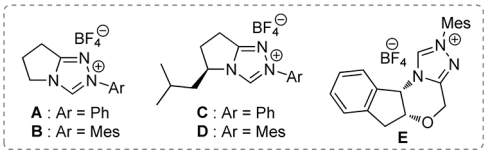


Table 1. Condition Optimization





entry	base	yield (%)[a]	er[b]
1	–, 1.5 equiv K_2CO_3	–	–
2	**A**, 1.5 equiv K_2CO_3	43	–
3	**B**, 1.5 equiv K_2CO_3	59	–
4	**C**, 1.5 equiv K_2CO_3	40	96:4
5	**D**, 1.5 equiv K_2CO_3	83	99:1
6	**E**, 1.5 equiv K_2CO_3	74	99:1
7	**D**, 1.0 equiv K_2CO_3	77	99:1
8	**D**, 0.5 equiv K_2CO_3	52	99:1
9[c]	**D** (10 mol %), 1.5 equiv K_2CO_3	81	99:1
10[c]	**D (5 mol %), 1.5 equiv K_2CO_3**	**78**	**99:1**

[a] Isolated yield based on **2a**. [b] Enantiomeric ratio of **3a**, determined *via* chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned based on X-ray structure of **3g** (see Scheme 2 and Supporting Information). [c] 0.15 mmol (1.5 equiv) of **1a** was used.

of saturated esters and an unusual β-sp^3 carbon activation of saturated esters.[22] Concurrently, we set to activate α,β-unsaturated esters *via* NHC organic catalysts for new reactions. Very recently, we realized an organocatalytic formal LUMO β-sp^2 carbon activation of α,β-unsaturated esters.[23] Here we report the first direct organocatalytic γ-carbon activation of α,β-unsaturated esters (Scheme 1). The key steps involve addition of the NHC catalyst to the

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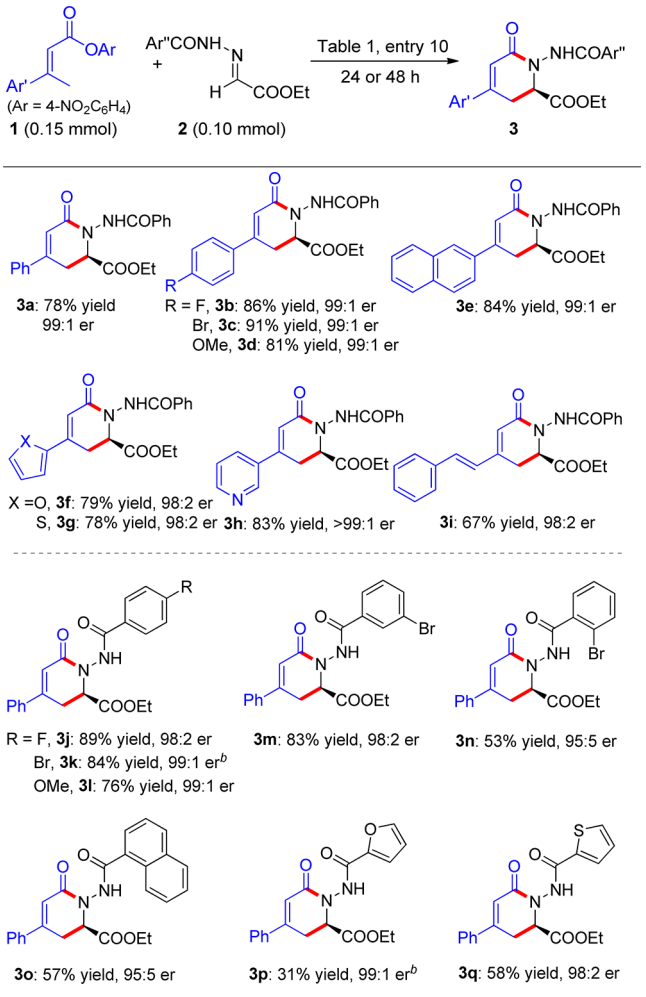
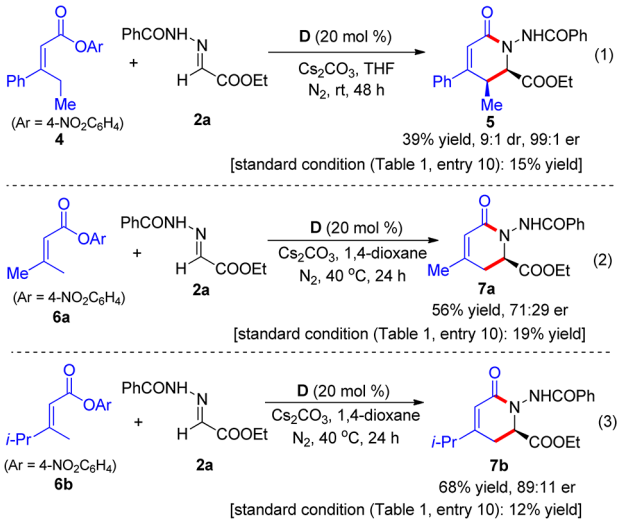
Scheme 2. Scope of Reactions[a]



[a] Reaction for 24 h for **3a**–**i**; 48 h for **3j**–**q** (except **3k** and **3p**). [b] 24 h.

ester substrate to form α,β-unsaturated ester intermediate **I**, followed by γ-CH deprotonation to form vinyl enolate intermediate **II** bearing a nucleophilic γ-carbon. The vinyl enolate intermediate **II** then undergoes nucleophilic additions to hydrazones to form optically enriched δ-lactam products. δ-Lactams are important precursors for bioactive pipecolic acid and other piperidine derivatives, such as local anesthetic ropivacaine,[24] HIV protease inhibitor palinavir,[25] thrombin inhibitor argatroban,[26] antitumor antibiotic tetrazomine,[27] and best selling pharmaceuticals such as paroxetine.[28] In the present work, we converted δ-lactam **3a** to its corresponding chiral 4-phenyl substituted pipecolic ester and acid through simple reduction and hydrolysis steps.

Scheme 3. Reactions Using γ-Alkyl and β,β′-Dialkyl Substituted α,β-Unsaturated Esters as Substrate



Key results of our initial studies using α,β-unsaturated ester **1a** and hydrazone **2a** as model substrates are briefed in Table 1. In the absence of the NHC catalyst, no formation of product **3a** was observed (Table 1, entry 1). When triazolium-based NHC catalyst **A** was used, **3a** was obtained in 43% isolated yield (entry 2). Replacing the phenyl group on the NHC catalyst with a mesityl substituent led to **3a** with an improved 59% yield (entry 3). We next moved to chiral triazolium-based NHC catalysts and found L-leucine derived catalysts **C**[29] and **D**[30] could afford **3a** in good yields and 96:4 and 99:1 er respectively (entries 4–5). Aminoindanol derived catalyst **E**[31] could also catalyze the reaction to give **3a** with similar er but lower yield (entry 6). Further studies (entries 7–10) showed that 5 mol % NHC **D** was enough to afford **3a** with 78% yield and 99:1 er.

Having established an optimal protocol for this reaction (Table 1, entry 10), we then examined the scope of the α,β-unsaturated esters bearing a β-aryl and a β′-methyl substituent (Scheme 2, **3a**–**i**). Both electron-withdrawing (**3b**, **3c**) and electron-donating (**3d**) substituents on the β-phenyl group were tolerated. Replacing the β-phenyl group with naphthyl (**3e**), heteroaryl (**3f**–**h**), or vinyl substituents were all well tolerated. The scope of the hydrazones was also studied (Scheme 2, **3j**–**q**) by using **1a** as a model ester substrate. Various aryl substituents of the hydrazones all worked well, giving products with moderate to good yields and excellent er.

We next studied the ester substrate (**4**) bearing a substituent at the γ-carbon (Scheme 3, eq 1). The desired trisubstituted δ-lactam product (**5**) could be obtained in 9:1 dr and 99:1 er, albeit with relatively low yield. In this case, a stronger base (Cs_2CO_3) was used and the reaction was

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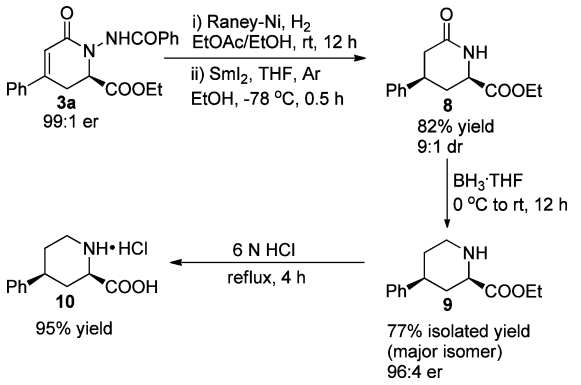
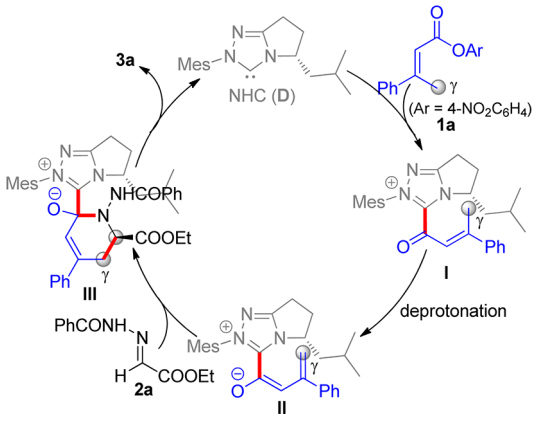
Scheme 4. Transformation of **3a** to Pipecolic Acid Derivatives



Scheme 5. Postulated Catalytic Cycle



carried out for 48 h (eq 1). β,β'-Dialkyl substituted α,β-unsaturated esters (**6a**, **6b**) were also examined (Scheme 3, eqs 2−3). The standard conditions (Table 1, entry 10) used above gave low conversion here. Further studies found that with Cs_2CO_3 as the base and 1,4-dioxane as the solvent at 40 °C, the corresponding δ-lactam product (**7a**, **7b**) could be obtained with moderate to good yields and er's (eqs 2−3).

The optically enriched δ-lactam product **3a** obtained in our studies could be readily transformed to chiral pipecolic acid and its derivatives, as illustrated in Scheme 4.

A postulated catalytic cycle is illustrated in Scheme 5. The addition of NHC to α,β-unsaturated ester **1a** forms intermediate **I**. Intermediate **I** then undergoes γ-deprotonation to afford vinyl enolate intermediate **II**. Nucleophilic γ-carbon addition of **II** to hydrazone **2a** eventually form δ-lactam product **3a** and regenerates the NHC catalyst.

In summary, we have developed the first NHC-catalyzed direct activation of the γ-carbons of α,β-unsaturated esters that undergo addition to hydrazones in a highly efficient and stereoselective manner to give δ-lactams. These lactam products could be easily transformed to optically enriched pipecolic acid derivatives using simple transformations. Further studies to extend this catalytic protocol to γ,γ-disubstituted esters, and other electrophiles are being pursued in our laboratory.

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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.