

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

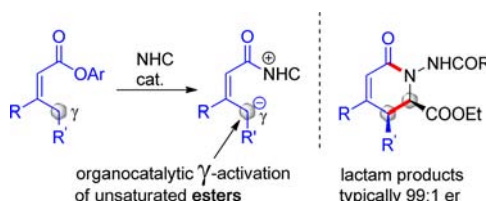
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ABSTRACT



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 MacMillan⁹ and Trost.¹⁰ In 2006, Jørgensen and co-workers disclosed

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the γ -addition of α,β -unsaturated aldehydes to azodicarboxylates *via* dienamine organocatalysis.¹¹ This dienamine chemistry¹² 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, Peters¹⁸ and Ye¹⁹ 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

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

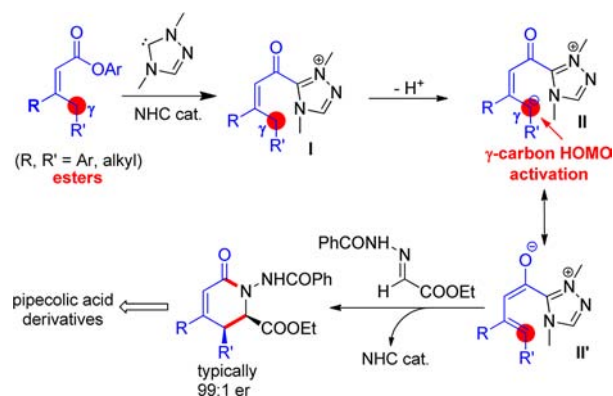


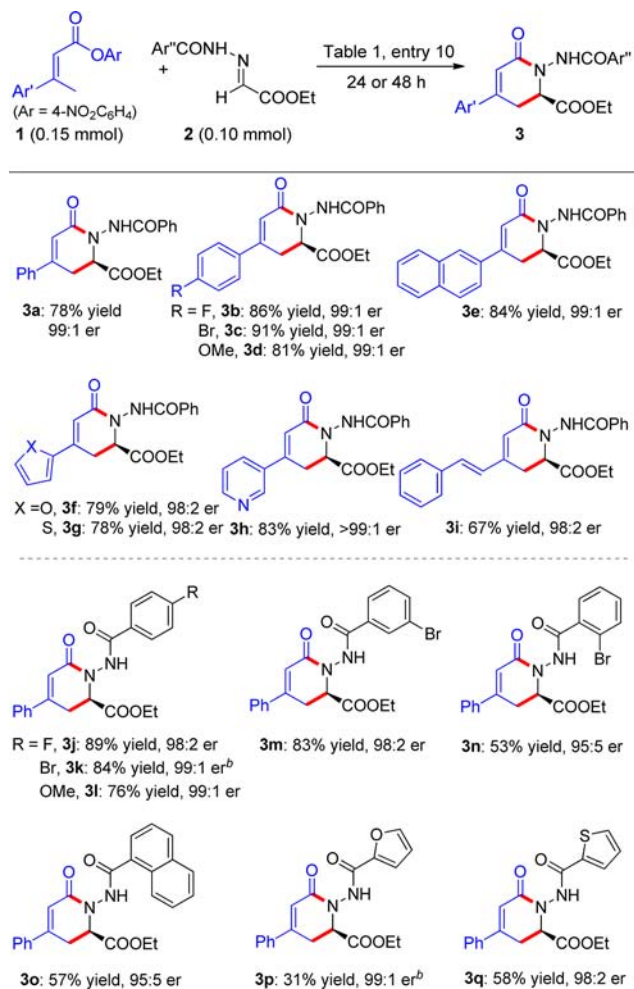
Table 1. Condition Optimization

entry	base	yield (%) ^a	er ^b
1	—, 1.5 equiv K ₂ CO ₃	—	—
2	A, 1.5 equiv K ₂ CO ₃	43	—
3	B, 1.5 equiv K ₂ CO ₃	59	—
4	C, 1.5 equiv K ₂ CO ₃	40	96:4
5	D, 1.5 equiv K ₂ CO ₃	83	99:1
6	E, 1.5 equiv K ₂ CO ₃	74	99:1
7	D, 1.0 equiv K ₂ CO ₃	77	99:1
8	D, 0.5 equiv K ₂ CO ₃	52	99:1
9 ^c	D (10 mol %), 1.5 equiv K ₂ CO ₃	81	99:1
10 ^c	D (5 mol %), 1.5 equiv K ₂ CO 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 -sp³ 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 -sp² 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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^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 piperidinic 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 piperidinic ester and acid through simple reduction and hydrolysis steps.

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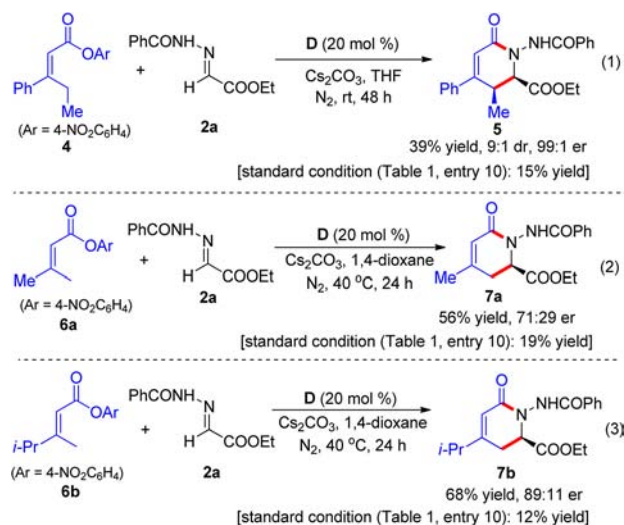
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Scheme 3. Reactions Using γ -Alkyl and β,β' -Dialkyl Substituted α,β -Unsaturated Esters as Substrate



Key results of our initial studies using α,β -unsaturated ester **1a** and hydrazine **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.

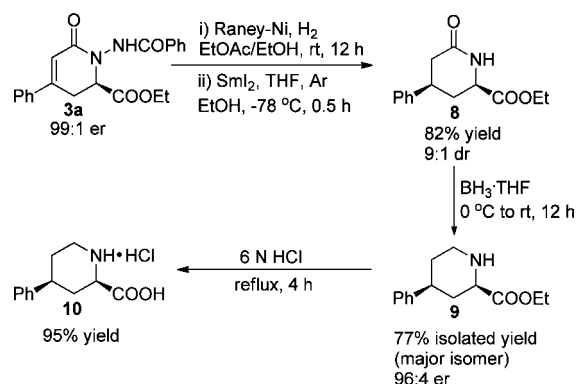
We next studied the ester substrate (**4**) bearing a substituent at the γ -carbon (Scheme 3, eq 1). The desired trisubstituted δ -lactam product (**5**) could be obtained in 9:1 dr and 99:1 er, albeit with relatively low yield. In this case, a stronger base (Cs_2CO_3) was used and the reaction was

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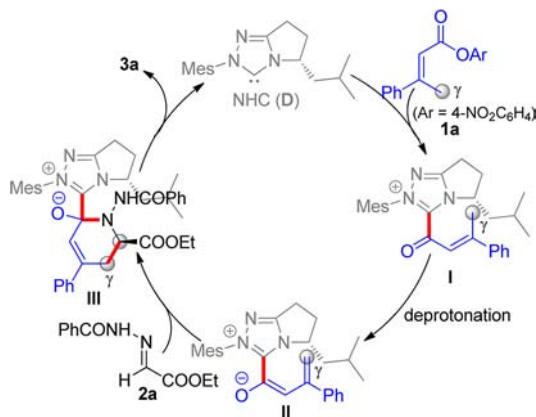
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Scheme 4. Transformation of **3a** to Pipecolic Acid Derivatives



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 Cs₂CO₃ 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.