

# Enantioselective Activation of Stable Carboxylate Esters as Enolate Equivalents *via* N-Heterocyclic Carbene Catalysts

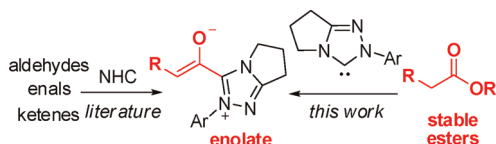
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Received March 17, 2012

## ABSTRACT



The first N-Heterocyclic Carbene (NHC) mediated activation of stable carboxylate esters to generate enolate intermediates is disclosed. The catalytically generated arylacetic ester enolates undergo enantioselective reactions with  $\alpha,\beta$ -unsaturated imines.

Asymmetric organocatalytic generation of chiral enolate equivalents is a powerful approach in organic synthesis. Ketenes are one of the most studied classes of enolate precursors. The asymmetric activation of ketenes has been realized with nucleophilic catalysts, such as planar-chiral DMAP derivatives,<sup>1</sup> cinchona alkaloids,<sup>2</sup> and chiral N-heterocyclic carbenes (NHCs).<sup>3–6</sup> A drawback of this

otherwise very successful approach lies in the relatively unstable nature of ketenes (and their carboxyl chloride precursors) that can pose operational challenges. With NHCs<sup>7</sup> as the catalysts, recently the chiral ester enolate equivalents have also been generated from functionalized aldehydes<sup>8</sup> and enals.<sup>9</sup> The overall process (the “forward” pathway) starts from enals (or functional aldehydes), goes

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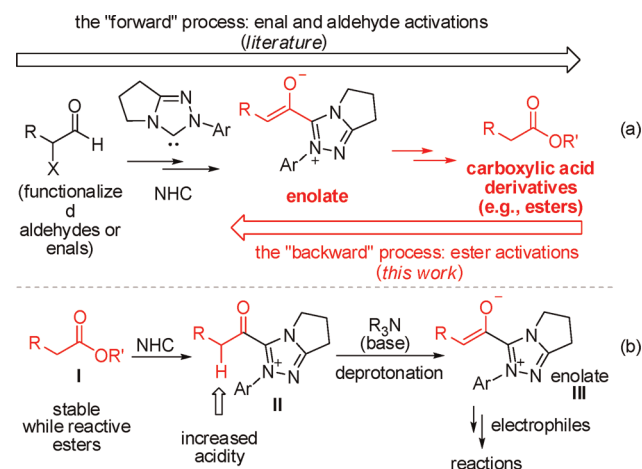
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through a few key intermediates such as enolates, and ends up as carboxylic acid derivatives (Scheme 1a).<sup>9</sup> As part of a larger program to explore and understand the rich chemistry enabled by NHC catalysis, we wondered whether the “backward” pathways starting from stable carboxylic ester substrates<sup>10</sup> could be realized (Scheme 1a). Our design is further illustrated in Scheme 1b. A stable ester (**I**) bearing a good leaving group (OR') may react with an NHC to form a more reactive intermediate (**II**) with increased acidities of the  $\alpha$  C-H's. The ester intermediate **II** subsequently undergoes a deprotonation to generate enolate **III** as a key intermediate that can react with electrophiles. In addition to intrinsic scientific values provided with asymmetric catalytic activation of esters, we expect that the use of stable carboxylic esters as substrates will offer synthetic advantages over the previously employed ketenes and aldehydes in certain cases.

We started by first identifying suitable phenylacetic esters (**I**) that could be activated by NHCs to react with  $\alpha,\beta$ -unsaturated imine **2a** as a model substrate (Table 1). The results briefed in Table 1 showed that chromatographically stable esters with good leaving groups (electro-deficient phenols) could behave as effective substrates (Table 1, entries 5–6). The use of excess base (200 mol % DIEA) was

**Scheme 1.** NHC-Mediated Activation of Stable Carboxylate Esters To Generate Enolate Intermediates: A Working Hypothesis



necessary to neutralize the acidic phenols released during the ester activations. No DIEA-catalyzed background reaction in the absence of NHC was observed (entry 7).

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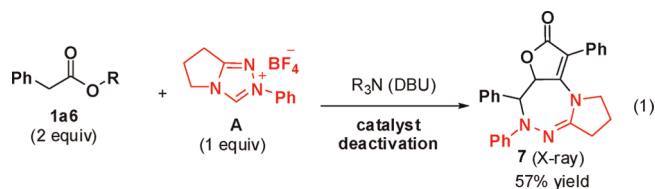
**Table 1.** Identification of Suitable Ester Substrates and Conditions

Table 1 provides data for the reaction of ester (**1**) with **2a** under various conditions. The reaction conditions are: 30 mol % **A**, DIEA (200 mol %),  $(CH_2Cl)_2$ , 70 °C, 24 h. The products are shown as **3a**. The substituents R for ester (**1**) are defined as: **1a1** (Me), **1a2** (Ph), **1a3** (p-Me-C<sub>6</sub>H<sub>4</sub>), **1a4** (2-naphthyl), **1a5** (2,4,6-trifluorophenyl), and **1a6** (4-nitrophenyl). The catalyst **A** is shown as a zwitterionic NHC.

entry <sup>a</sup>	ester ( <b>1</b> )	yield (%) <sup>b</sup>	dr <sup>c</sup>
1	<b>1a1</b>	<1 <sup>d</sup>	N.D.
2	<b>1a2</b>	<1 <sup>d</sup>	N.D.
3	<b>1a3</b>	<1 <sup>d</sup>	N.D.
4	<b>1a4</b>	~10 <sup>e</sup>	N.D.
5	<b>1a5</b>	81	10:1
6	<b>1a6</b>	83	11:1
7 <sup>f</sup>	<b>1a6</b>	<1 <sup>d</sup>	N.D.

<sup>a</sup> Reaction condition: **1** (0.15 mmol), **2a** (0.10 mmol), solvent (0.5 mL).

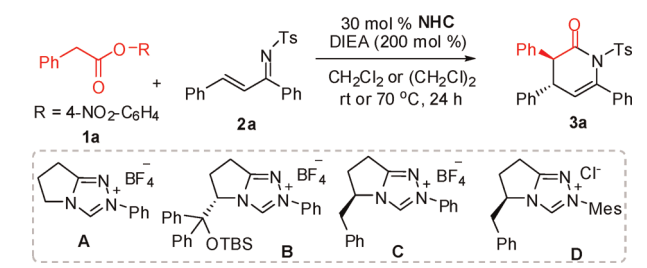
<sup>b</sup> Isolated yield (major diastereomer) based on **2a**. <sup>c</sup> Diastereomeric ratio of **3a**, determined via <sup>1</sup>H NMR analysis of unpurified reaction mixtures. Relative configuration of the product was determined via X-ray of **3b** (Scheme 3, see Supporting Information). <sup>d</sup> No detectable formation of product as indicated via TLC and crude <sup>1</sup>H NMR analysis. <sup>e</sup> Estimated via crude <sup>1</sup>H NMR analysis. <sup>f</sup> In the absence of NHC **A**. N.D. = Not determined.



Mechanistically, the enolate key intermediate (**III**, Scheme 1b) was likely formed through deprotonation of the NHC-bounded activated ester intermediate (**II**, Scheme 1b). We postulated that intermediate **II** (Scheme 1b) was formed through a direct nucleophilic addition of NHC to ester substrate **I**. Our studies (see Supporting Information (SI)) suggested that a ketene intermediate was unlikely to be involved in the reactions.<sup>11</sup> One catalyst deactivation pathway was observed during the reaction optimizations (eq 1), which further confirmed the involvement of NHC in the catalytic activation of esters to generate enolate intermediates (see SI).<sup>12</sup>

We next chose the readily available and chromatographically stable 4-nitro-phenol esters (e.g., **1a6**) to develop enantioselective reactions. With achiral precatalyst **A**, increasing the reaction temperature led to a better yield with similar dr. Triazolium-based chiral catalyst **B** was not effective even at elevated temperatures. Fortunately, by using a less bulky catalyst **C**, the product could be obtained in 59% yield and 94:6 er at rt (Table 2, entry 5). Catalyst **D** was less enantioselective than **C** (Table 2, entry 6). We next sought to improve the reaction yield and found that the use of tetraalkylammonium halides was beneficial for unclear reasons (Table 2, entry 7). By using 1 equiv of Me<sub>4</sub>NCl additive and an excess (5–10 equiv) of DIEA, the reaction could also be efficiently carried out at 0 °C to give the product with excellent yield, dr, and ee (Table 2, entry 8).

**Table 2.** Enantioselective Activation of Esters



entry <sup>a</sup>	NHC	add. <sup>b</sup>	temp (°C)	yield (%) <sup>c</sup>	dr <sup>d</sup>	er <sup>e</sup>
1	<b>A</b>	—	rt	61	7:1	—
2	<b>A</b>	—	70	83	10:1	—
3	<b>B</b>	—	70	14	N.D.	N.D.
4	<b>C</b>	—	70	72	12:1	86:14
5	<b>C</b>	—	rt	59	12:1	94:6
6	<b>D</b>	—	rt	78	10:1	84:16
7	<b>C</b>	Me <sub>4</sub> NCl	rt	87	20:1	94:6
8 <sup>f</sup>	<b>C</b>	Me <sub>4</sub> NCl	0	89	20:1	96:4

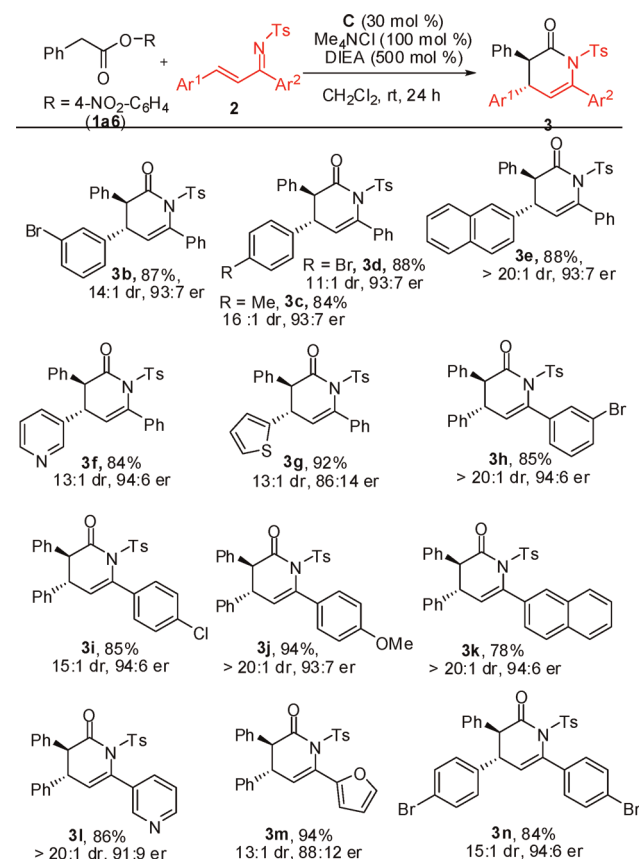
<sup>a</sup> Reaction condition: **1a6** (0.15 mmol), **2a** (0.10 mmol), solvent (0.5 mL).

<sup>b</sup> Additive (100 mol %; see SI). <sup>c</sup> Isolated yield (major diastereomer) based on **2a**. <sup>d</sup> Diastomeric ratio of **3a** determined via <sup>1</sup>H NMR analysis of unpurified reaction mixtures. <sup>e</sup> er of the major diastereomer (**3a**), determined via chiral phase HPLC analysis; absolute configuration of product was determined via X-ray of **3o** (Scheme 3; see SI). <sup>f</sup> 10 equiv of DIEA were used. N.D. = Not determined.

It is interesting to note that such formal [4 + 2] products (**3**) with a single aryl substituent at the lactam α-carbon

could not be prepared using either NHC<sup>7,13</sup> or enamine<sup>14</sup> catalysis.<sup>15</sup> For example, ketenes from monoaryl acetyl chlorides were ineffective substrates under NHC catalysis; arylacetyl aldehydes in enamine catalysis pose special challenges due to competing (and even dominated) self-aldol reactions and easy α-carbon chiral center racemization of the resulting aldehyde products.

**Scheme 2.** Scope of the Unsaturated Imine Substrate **2<sup>a</sup>**



<sup>a</sup> Reaction conditions (Table 2, entry 7).

The scope of the reaction with respect to the α,β-unsaturated imine substrates (**2**) was then examined

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(12) A conclusive kinetic picture of the reaction (Table 1) is difficult to obtain due to catalyst deactivation and other unidentified side reactions. A preliminary single-point kinetic study suggested that only one ester molecule was involved in the rate-determine step for the formation of **3**.

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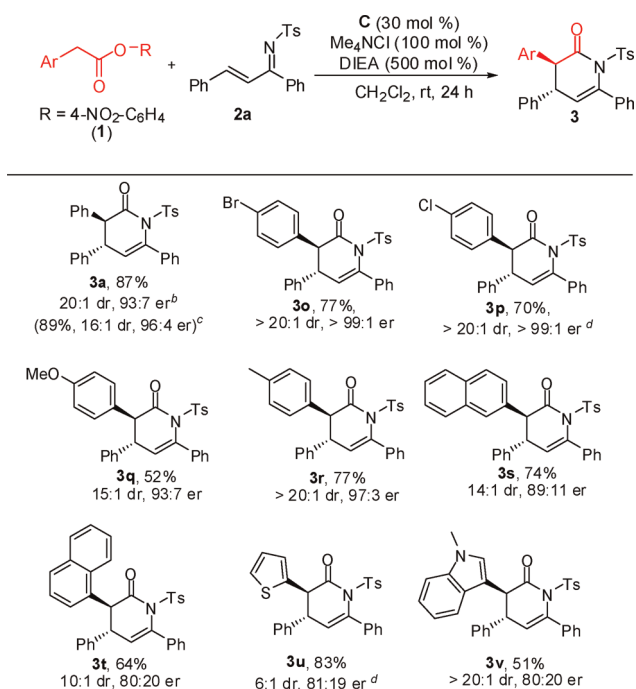
(14) Enamine catalysis approach (with nonarylacetyl aldehyde substrates): (a) Han, B.; Li, J. L.; Ma, C.; Zhang, S. J.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2008**, 47, 9971–9974. (b) Han, B.; He, Z. Q.; Li, J. L.; Li, R.; Jiang, K.; Liu, T. Y.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2009**, 48, 5474–5477.

(Scheme 2). The rt condition in the presence of an ammonium halide additive and 5 equiv of DIEA (a slight modification of Table 2, entries 7–8) could generally give products with good yields and stereoselectivities for most substrates within 24 h. The imine substrates with electron-withdrawing or -donating or heteroaryl groups at Ar<sup>1</sup> substituents were all tolerated (Scheme 2, **3a–g**). Similarly, substitutions at Ar<sup>2</sup> did not lead to significant changes in reaction outcomes (Scheme 2, **3h–n**).

We next evaluated the effects of the arylacetic ester substrates (Scheme 3). The Ar group of esters (**1**) with electron-withdrawing bromo, chloro and electron-donating methoxyl or methyl substituents were all excellent substrates, giving products with good to excellent dr's and er's (Scheme 3, **3o–r**). Sterically bulkier esters with naphthyl substituents (**3s, t**) and heteroaryl substituted esters (**3u, v**) gave products with relatively low er's without further extensive condition optimizations. We also attempted to replace the Ar substituent of ester **1** with alkyl units (e.g., PhCH<sub>2</sub>). Under conditions evaluated in this work, no product such as **3** was obtained. The esters underwent hydrolysis with the residual water present in the reaction mixture with a prolonged reaction time. It appears that a different set of conditions (base, NHC, etc.) must be developed for these esters with relatively low acidities of the  $\alpha$ -CH's.  $\alpha,\alpha$ -Disubstituted esters and the related  $\alpha,\beta$ -unsaturated ketones (such as chalcones) were also not effective substrates under current conditions.

In summary, we have developed the first NHC-catalyzed activation of stable carboxylate esters to form enolate intermediates. The catalytically generated NHC-bounded ester enolate intermediates undergo enantioselective reactions with  $\alpha,\beta$ -unsaturated imines. The catalytic process likely proceeds through a direct addition of NHC to the ester substrate without involving a ketene intermediate. We expect our studies to shed insightful light on the fundamentally challenging process of catalytic activations of stable esters to generate chiral enolate equivalents and possibly other important intermediates (e.g., homoenolates). The use of esters will also offer operationally simpler synthetic methods. Further studies with

**Scheme 3.** Scope of the Ester Substrate **1**<sup>a</sup>



<sup>a</sup> Reaction conditions: same as those in Scheme 2. <sup>b</sup> 2.0 equiv of DIEA. <sup>c</sup> 10 equiv of DIEA, and reaction at 0 °C. <sup>d</sup> 2.0 equiv of DIEA without Me<sub>4</sub>NCl, and reaction at 60 °C in 1,2-dichloroethane.

respect to the activation of other esters and mechanistic evaluations are in progress in our laboratory.

**Acknowledgment.** We are thankful for the generous financial support from Singapore National Research Foundation, Singapore Economic Development Board (EDB), GlaxoSmithKline (GSK), and Nanyang Technological University (NTU) and for help from Dr. Y. Li and Dr. R. Ganguly, Div. of Chemistry and Biological Chemistry, NTU, Singapore (X-ray structure).

**Supporting Information Available.** Experimental details. This material is available free of charge via Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

(15) After submission of this manuscript, Smith's group reported a chiral isothioureacatalyzed transformation of carboxylic acids to similar products. Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, 10.1002/anie.201109061.