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Organocatalytic Activation of Alkylacetic Esters as Enolate Precursors to React with α,β-Unsaturated Imines

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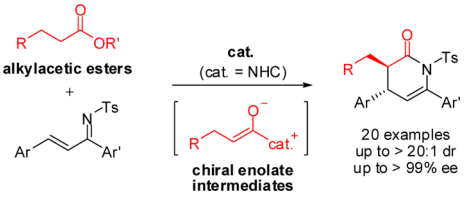
ABSTRACT



Asymmetric functionalization of alkylacetic esters and their derivatives is traditionally achieved via preformed enolates with chiral auxiliaries. Catalytic versions of such transformations are attractive but challenging. A direct catalytic activation of simple alkylacetic esters via *N*-heterocyclic carbene organocatalysts to generate chiral enolate intermediates for highly enantioselective reactions is reported.

Carboxylic esters and their derivatives are readily available and inexpensive substrates widely used in pharmaceutical and fine chemical synthesis. The versatile reactions based on ester enolates can rarely be missed while designing synthetic strategies for both small and complex molecules. Consequently, enormous efforts have been directed for the generation of chiral ester enolates and their equivalents for effective reactions. Traditionally, chiral enolates are preformed with the assistance of chiral auxiliaries, as represented by Evans oxazolidinones and their variants (Scheme 1a).[1] Catalytic approaches for asymmetric generation of enolate intermediates directly from esters are attractive but remain challenging (Scheme 1b).[2] In related efforts, aldehydes and ketones are now routinely used as enamine precursors ("enolate analogs") by employing amine organocatalysts.[3] Ketenes, activated by nucleophilic organocatalysts such as chiral DMAP derivatives,[4] cinchona alkaloids,[5] and *N*-heterocyclic carbenes,[6] can also behave as ester enolate precursors. Recently, α-functionalized aldehydes[7] and α,β-unsaturated aldehydes[8] have also been used as enolate precursors via NHC catalysis, as pioneered by Bode,[7b,8a] Rovis,[7c] Scheidt,[8c] and Glorius.[8b,9] Despite the impressive success, the (functionalized)-aldehyde and ketene substrates in these approaches pose

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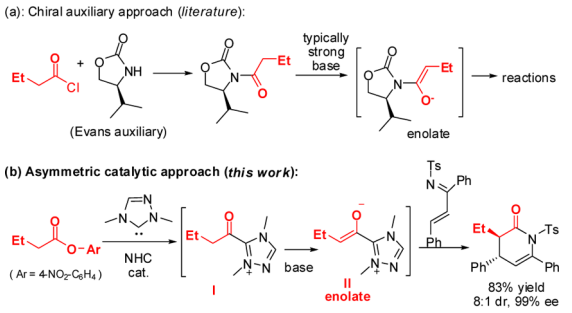
Scheme 1. Generation of Chiral Enolates from Esters



a few intrinsic limitations such as instabilities, relatively poor availabilities, and somewhat undesired synthetic steps to prepare these substrates. Carboxylic esters and acids may be superior substrates on certain aspects from the perspective of practical applications. On the fundamental side, the challenging asymmetric catalytic activation of ester is expected to generate insightful knowledge for catalyst and reaction designs.[10]

Very recently, Smith and co-workers creatively used isothioureas as nucleophilic catalysts to activate in situ formed carboxylic anhydrides as enolate intermediates for intra- and intermolecular additions to electron-deficient alkenes.[11] Our laboratory disclosed that stable esters derived from α-aryl acetic acids could be activated with NHC catalysts to generate ester enolate intermediates.[10,12] In our earlier approach,[10a,b] the ester substrate was limited to α-aryl acetic esters. In Smith's elegant study, the anhydride substrates derived from α-aryl, alkyl, and heteroacetic acids worked well.[11c] A switch to the likely more useful simple alkylacetic esters was unsuccessful, presumably due to the relatively poor electrophilicity of the alkylacetic ester (to react with the NHC catalyst) and/or the low acidity of the ester α-C−H. We now have addressed this problem and report that simple alkylacetic esters can behave as effective enolate precursors under asymmetric catalysis (Scheme 1b).

The choice of NHC with suitable nucleophilicity (as carbenes) and proper electron-withdrawing ability (as triazoliums) is crucial in order to achieve controlled ester activations. The sterics of NHC catalysts and the strength of the bases also play important roles.

Our initial study and condition optimization is summarized in Table 1 using ester **1a** with an α-ethyl substituent as a model substrate. The conditions (e.g., entry 1; cat. **A**, DIEA) used in our earlier work for α-aryl acetic ester activation[10a,b] did not lead to ester enolate generations. Instead, the ester substrate (**1a**) under the catalysis of NHC underwent hydrolysis to the corresponding carboxylic acid. This observation indicated that an initial addition of NHC to ester **1a** to form NHC-bound ester intermediate **I** did occur (in the presence of NHC, more rapid hydrolysis of esters was observed) (Scheme 1b). The failure of enolate generation was likely due to the relatively low acidity of the α-C−H of intermediate **I**. Addressing the acidity issue was not trivial as increasing the strength of the bases could lead to background reactions (e.g., base-catalyzed deprotonation of ester **1a** without involving NHC catalysts) and profound hydrolysis of the ester substrate. Fortunately, we

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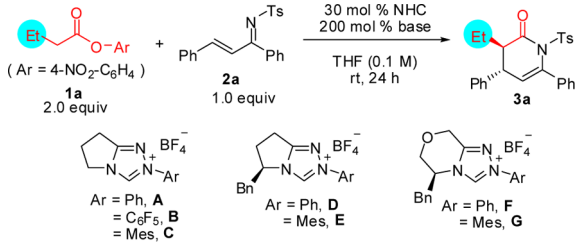
Table 1. Identification of Suitable Conditions[a]

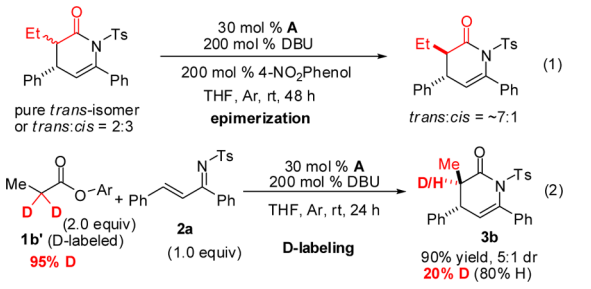


entry	NHC	base	yield[b] (%)	dr[c]	ee[d] (%) (*trans*/*cis*)
1	**A**	DIEA	<1[e]		
2	**A**	DBU	61	6:1	
3	**A**	TBD	15[f]	10:1	
4	**B**	DBU	<1[e]		
5	**C**	DBU	92	6:1	
6	**D**	DBU	54	5:1	97/87
7	**E**	DBU	<1[e]		
8	**F**	DBU	16[f]	10:1	94/86
9	**G**	**DBU**	**83**	**8:1**	**99/99**
10	**G**	DBU	57[g]	8:1	99/99

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), THF (1.0 mL). [b] Isolated yield (of combined diastereomers) based on **2a**. In all cases with DBU or TBD as the base (entries 2−10), the conversion of **1a** was over 90% as determined by ^{1}H NMR analysis of unpurified reaction mixtures; when DIEA was the base (entry 1), conversion of ester **1a** was 50%. [c] Diastereomeric ratio of **3a**, determined via ^{1}H NMR analysis of unpurified reaction mixtures. [d] ee of major/minor diastereomer of **3a**, determined via chiral-phase HPLC analysis; absolute configuration of product was determined via X-ray of **3b** (Scheme 3 and Supporting Information; CCDC 896595 contains the supplementary crystallographic data). [e] No detectable formation of product as indicated via TLC and crude ^{1}H NMR analysis. [f] Estimated via ^{1}H NMR analysis of crude reaction mixture. [g] 20 mol % of NHC catalyst **G** was used. DIEA: *N*,*N*-diisopropylethylamine, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

later found that a use of DBU in THF was effective (Table 1, entry 2). The use of stronger base (e.g., TBD, entry 3) led to significant ester hydrolysis and the reaction product **3a** was obtained in low yield. Further studies with achiral triazolium catalysts (**A**−**C**) showed that the catalysts structures could affect the reaction outcomes (entries 2, 4, and 5), although general correlations between NHC catalysts (steric and electrophilic properties) and reaction outcomes remain unclear at this moment. Chiral catalysts were then examined (entries 6−9), and triazolium precatalyst **G**, pioneered by the Glorius group,[13] was found to be optimal with regard to yield and stereoselectivities (entry 9). Both diastereomers of **3a** were obtained with 99% ee, indicating exceptional enantioinduction of the NHC catalysts for ester activations. Our studies also showed that several other common solvents (CH_2Cl_2, toluene, EtOAc, CH_3CN) and inorganic bases (e.g., Cs_2CO_3) could mediate these reactions with moderate to good yields and excellent stereoselectivities (see the Supporting Information). The fact that different solvents and bases can work for this reaction suggests that future

Scheme 2. Mechanistic Studies



extension of our ester activation approach to other reactions (electrophiles) should be feasible.

The two diastereomers of product **3a** were found to undergo facile epimerizations to each other under the catalytic conditions. The thermodynamically more stable *trans*-isomer was obtained as the major product. For example, subjecting a pure *trans*-isomer of **3a** (or a diastereomeric mixture enriched with the *cis*-isomer) to the catalytic condition[14] led to an equilibrium of *trans*/*cis*-isomers in around 7:1 ratio (Scheme 2, eq 1). In a separate NHC-catalyzed reaction using deuterium-labeled ester **1b′** (95% D) as the substrate, the corresponding product **3b** was obtained with only 20% D retained (eq 2). The loss of deuterium in the product (via H/D exchange with residual water in the reaction likely as the proton source) was likely due to epimerization of the lactam product **3b** and/or reversible interconversion between NHC-bound ester intermediate **I** and ester enolate intermediate **II** (Scheme 1b). Due to the facile epimerization of the product, it remains unknown which diastereomer (*cis*- or *trans*-**3a**) is formed more rapidly. In addition, we found that the epimerization process could readily occur in the presence (or absence) of water or 4-nitrophenol. The reactions in the absence of water were carried out in a glovebox using pretreated anhydrous solvents and reagents. As an important note, NHC-bound enolate intermediates generated from α-Cl-aldehydes or enals in cycloadditions afforded *syn*-selective lactam products, as reported by Ye[7q] and Bode.[8a] Studies to elucidate the kinetic isotope effect (e.g., using substrates **1b** and **1b′**) were difficult because the reactions were very fast (e.g., over 60% conversion for **2a** in 15 min with the formation of *trans*:*cis*-**3a** in 3:1 ratio). In the evaluation of reaction scope, we chose 24 h as the reaction time to allow equlibration of the products to reach a high dr (3:1 dr after 15 min vs 7:1 dr after 24 h).

With the optimized conditions (Table 1, entry 9) in hand, the scope of the esters was examined (Scheme 3). Both methyl- and ethyl-substituted acetic esters gave the corresponding products with good yields, drs, and excellent ee's (**3a** and **3b**). It is worth noting that the corresponding 2-propenal and 2-butenal (required for the preparation of **3a** and **3b** using literature approach in generating enolate

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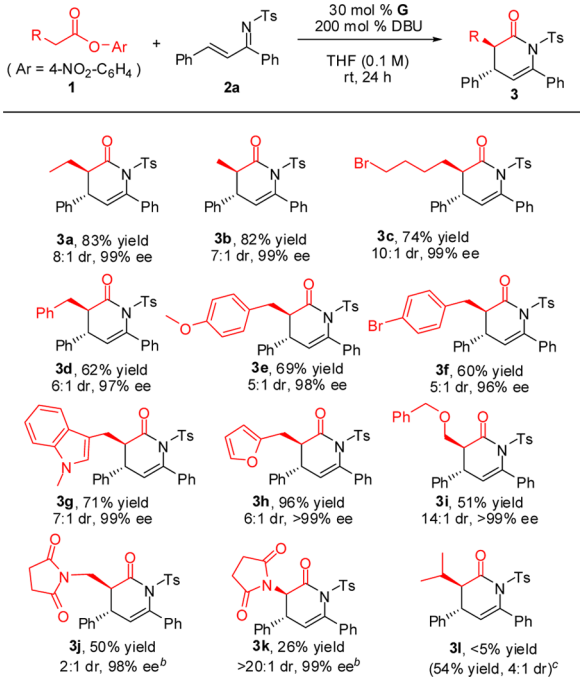
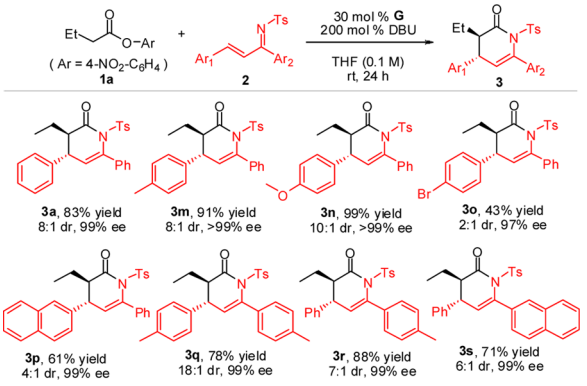
(14) Significant decomposition of product **3a** was observed when only DBU was used in THF.

Scheme 3. Examples of the Ester Substrate **1**[a]



[a] Reaction conditions are the same as in entry 9, Table 1. [b] Reaction conditions: chiral catalyst **D** (30 mol %), Me_4NCl (100 mol %), 4 Å MS (25 mg), and 1,2-dichloroethane (1.0 mL). [c] Achiral NHC **C** was used.

Scheme 4. Examples of the Imine Substrate **2**[a]



[a] Reaction conditions: same as in entry 9, Table 1.

intermediates from enals) have remained challenging substrates in NHC-enolate chemistry,[8] and very limited studies on these simple enals have been reported.[8e] The ester with a longer alkyl chain containing a terminal bromo substituent could also react well (**3c**). It should be noted that under other approaches the presence of alkyl halides is typically problematic. For example, under the typical chiral auxiliary approach, alkyl bromides (relatively reactive electrophiles) will undergo (undesired) reactions with the enolates (e.g., lithium ammonium enolates) under strong basic conditions.[15] In enamine catalysis (for aldehydes and ketones), alkyl halides will normally lead to amine catalyst deactivation.[16] The alkylacetic esters with various β-(hetero)aryl substituents were also excellent substrates (**3d**–**h**). We then evaluated esters substituted with heteroatom functional groups (which could not be activated by NHC as enolate precursors using either enals or α-functionalized aldehydes). The use of β-alkoxypropanoic acid ester could give lactam product **3i** with moderate yield, 14:1 dr, and 99% ee. The presence of an amino group (as imide) at the α- or β-carbon of the esters was also tolerated by switching to NHC precatalyst **D**, albeit with low yields (**3j** and **3k**). Ester substrates with relatively bulky substituents (e.g., β,β-disubstituted propanoic acid esters) reacted well using nonchiral NHC precatalyst **C** (**3l**, 54% yield). When chiral NHC catalysts were used, the reactivity of the bulky ester dropped significantly (e.g., NHC **G**, < 5% yield). The scope of the α,β-unsaturated imines was also examined, as shown in Scheme 4. In general, unsaturated imines with different 1,3-diaryl substituents all reacted well (**3m**–**s**, Scheme 4).

In summary, we have developed the first asymmetric organocatalytic activation of simple alkylacetic esters as ester enolate equivalents for highly enantioselective reactions. In the arena of asymmetric catalysis, especially organocatalysis, aldehydes, ketones, and ketenes (and their derivatives) have been extensively evaluated. However, the more readily available and inexpensive carboxylic acids and esters are much less studied. We hope this work on simple ester activation will lead to additional investigation on esters for the development of mechanistically interesting activation modes and practically useful chemical transformations.

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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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