Asymmetric Organocatalysis

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# NHC Organocatalytic Formal LUMO Activation of α,β-Unsaturated Esters for Reaction with Enamides**

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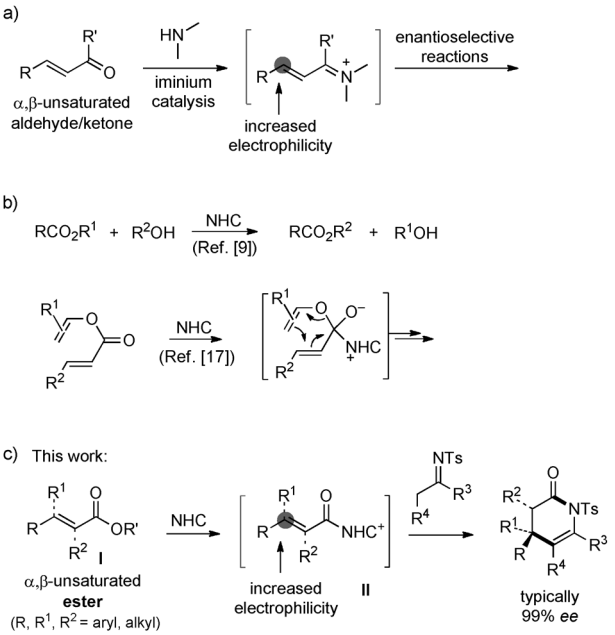
α,β-Unsaturated carbonyl compounds are basic building blocks in organic synthesis. Lewis acid catalysts bearing chiral ligands have traditionally been used for the asymmetric catalytic activation of this class of molecules as Michael acceptors.[1,2] Indeed, Lewis acid catalysis continues to be a powerful approach in which innovative solutions are still emerging. Representative examples of chiral Lewis acid catalysts include the metal–bisoxazoline complexes introduced by the research groups of Evans and Corey,[3] the multimetallic bifunctional catalysts developed by Shibasaki and co-workers,[4] the bifunctional Lewis acid/base catalysts described by Lectka and co-workers,[5] and the metal–*N*,*N*′-dioxide catalysts developed by Feng and co-workers.[6] In another direction, organocatalytic methods have received intense attention in the last decade or so. By iminium catalysis, pioneered by MacMillan and co-workers, α,β-unsaturated aldehydes and ketones can be activated as electrophiles for a set of highly enantioselective reactions (Scheme 1 a).[7] The related equally useful ester substrates, on the other hand, are outside the scope of iminium/enamine catalysis,[8] which has proved to be versatile for aldehyde and ketone substrates.

We are interested in the organocatalytic activation of readily available esters for asymmetric synthesis. N-Heterocyclic carbenes (NHCs, typically imidazolium-based NHCs) have been studied previously for the catalysis of transesterification reactions (Scheme 1 b).[9] Two mechanisms were proposed for NHC-catalyzed transesterification; one involves ester activation,[9a,b] and the other involves alcohol activation, in which NHC behaves as a base catalyst.[9c,d] Recently, we disclosed the HOMO activation of saturated α-aryl acetic esters[10] through catalysis with NHCs[11] to generate enolate intermediates for enantioselective reactions. Herein we report the formal LUMO activation of α,β-unsaturated esters by NHC catalysis for highly enantioselective reactions




***Scheme 1.*** a,b) Previously reported related approaches for the activation of carbonyl substrates with organocatalysts. c) LUMO activation of α,β-unsaturated carbonyl compounds by NHC catalysis. Ts = *p*-toluenesulfonyl.

with enamides (Scheme 1 c). The key step involves the addition of the NHC catalyst to the ester substrate **I** to form an α,β-unsaturated acyl azolium intermediate **II**. Unsaturated acyl azolium intermediates of this type were previously generated from enals,[12] α-hydroxyenones,[13] α-bromoenals,[14] ynals,[15] and α,β-unsaturated acid fluorides[16] by (oxidative) NHC catalysis. Lupton and co-workers reported an NHC-catalyzed enol ester rearrangement, which was proposed to proceed by addition of the NHC to the carbonyl group of the ester, followed by Claisen rearrangement.[17] They suggested that an α,β-unsaturated acyl azolium intermediate (such as **II**) was unlikely to be involved as a key intermediate (Scheme 1 b).[17b,d] In a related approach, Smith and co-workers recently reported the use of anhydrides as α,β-unsaturated acyl ammonium precursors with isothiourea catalysts.[18] Each of these elegant methods has its own merits and limitations. For example, with α,β-unsaturated aldehyde substrates, relatively expensive organic oxidants[12b,19] need to be used in the asymmetric oxidative NHC catalysis. The use of ynals as substrates[15a] is constrained by the limited substitution patterns (e.g. disubstitution at the α and β carbon atoms is not possible) and somewhat high cost of the ynal compounds. In our approach, the ester substrates are readily available, inexpensive, and stable (easy to handle). Various

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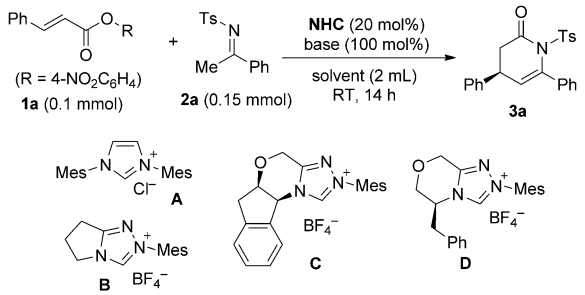
ester substrates can be used under mild conditions to afford optically pure lactam derivatives with various substitution patterns. We therefore expect this ester activation to become a rather general approach for convenient access to activated Michael acceptors for catalytic enantioselective reactions.

We started by using ester **1a** and the ketone-derived imine[20] **2a** as model substrates (Table 1). Under the basic reaction conditions, the imine substrate **2a** was observed to isomerize to the corresponding enamide nucleophile (see the Supporting Information). No formation of the desired product **3a** was observed in the absence of an NHC (Table 1, entry 1).

***Table 1:*** Optimization of the reaction conditions.

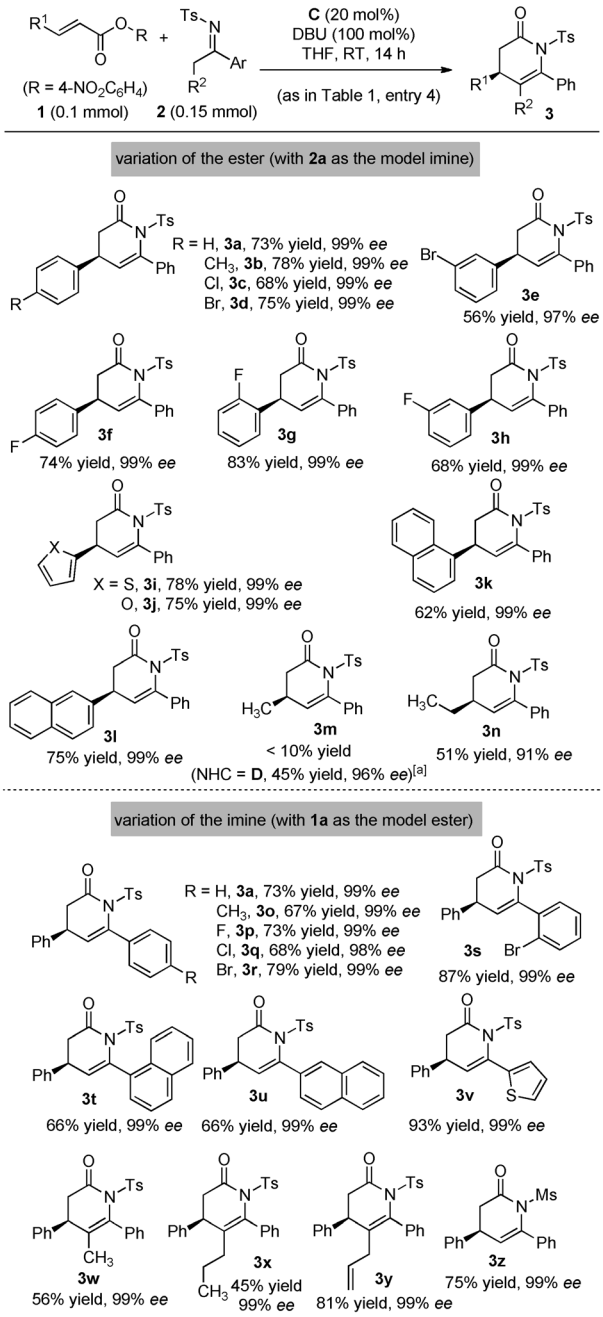



| Entry | NHC | Base, solvent | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | – | DBU, THF | – | – |
| 2 | **A** | DBU, THF | – | – |
| 3 | **B** | DBU, THF | 76 | – |
| **4** | **C** | **DBU, THF** | **73** | **99** |
| 5[c] | **D** | DBU, THF | 69 | 95 |

[a] Yield (based on **1a**) of the isolated product after $SiO_2$ column chromatography. [b] The *ee* value of **3a** was determined by chiral-phase HPLC analysis; the absolute configuration of the major enantiomer was assigned on the basis of the X-ray crystal structure of **3c** (see the Supporting Information).[23] [c] When the reaction was carried out with NHC catalyst **C** (10 mol%), **3a** was obtained in 52% yield with 99% *ee*; with 5 mol% of NHC catalyst **C**, **3a** was obtained in 29% yield with 99% *ee*. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = mesityl (2,4,6-trimethylphenyl).

The imidazolium NHC **A** did not activate the ester (Table 1, entry 2). In further studies, we found that with the triazolium salt **B** (20 mol%) as the NHC precatalyst, **3a** was formed in 76% yield (Table 1, entry 3). We next moved to chiral triazolium NHC catalysts and found that the amino-alcohol-derived catalysts **C**[21] and **D**[21a,22] catalyzed the formation of **3a** in good yield with 99 and 95% *ee*, respectively (Table 1, entries 4 and 5). We then evaluated the effects of solvents and bases. Although the combination of THF and DBU was optimal, other common organic solvents (such as $CH_2Cl_2$, toluene, $CH_3CN$) and organic/inorganic bases (such as *N*,*N*-diisopropylethylamine, 4-dimethylaminopyridine, $Cs_2CO_3$, *t*BuOK) could also be used (see the Supporting Information). The tolerance of this reaction to different NHC catalysts, bases, and solvents suggests that this chemistry may be further developed for a diverse set of reactions with different substrates.

Having established acceptable reaction conditions (Table 1, entry 4), we evaluated the scope of the reaction of β-monosubstituted unsaturated esters with imines (Scheme 2). With imine **2a** as the model nucleophile, we investigated the reaction of a variety of β-monosubstituted unsaturated esters. Both electron-donating (product **3b**) and electron-withdrawing substituents (products **3c–e**) at the *para* position of the β-phenyl group were well tolerated. A fluorine substituent could be installed at any position of the β-phenyl group (products **3f–h**). Replacement of the β-phenyl substituent with a heteroaryl (products **3i** and **3j**) or naphthyl unit (products **3k** and **3l**) had little effect on the reaction



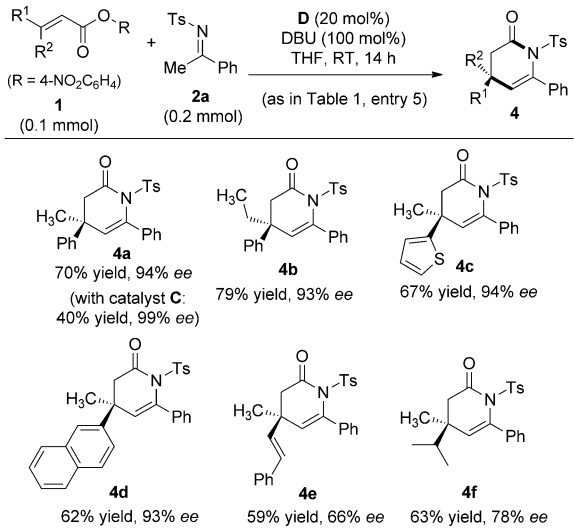

***Scheme 2.*** Scope of the reaction. [a] The NHC catalyst **D** (20 mol%) was used.

outcome. When the β-aryl group of the ester was changed to an alkyl substituent (products **3m** and **3n**), a decrease in the yield was observed. Notably, in the case of the β-methyl-substituted unsaturated ester, the NHC precatalyst **D** performed better than **C** (product **3m**).

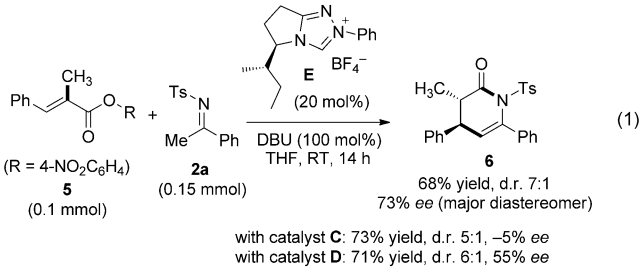
With the α,β-unsaturated ester **1a** as the model electrophile, the scope of the reaction with respect to the imine substrate was also examined. All of the (hetero)aryl imines examined afforded the corresponding lactam products **3o–v** in good yield with excellent enantioselectivity. Replacement of the methyl group of imine **2a** with another alkyl substituent (ethyl, *n*-butyl, or homoallyl) also led to the effective formation of the corresponding products **3w–y** in moderate to high yield with excellent *ee* values. We also examined imines with other N-protecting groups. Whereas an *N*-Ms-protected imine was well tolerated and afforded the product **3z** in 75% yield with 99% *ee*, the corresponding *N*-Boc enamide was not a suitable substrate. Our attempts to extend the reaction to challenging aliphatic ketimine substrates, such as the *N*-Ts imines derived from acetone and methyl isopropyl ketone, have remained unsuccessful so far. Enamide hydrolysis was observed as the major side reaction.

We next evaluated β,β-disubstituted unsaturated esters in the reaction with imine **2a** (Scheme 3). With the triazolium catalyst **C** used in the previous reactions, the reaction of the *E* β-methyl-β-phenyl unsaturated ester afforded the corresponding annulation product **4a** with high enantioselectivity (99% *ee*), but in relatively low yield (40%). Unsatisfied with this result, we went back to search for appropriate catalysts and conditions for β,β-disubstituted ester substrates. Finally, the triazolium catalyst **D** was found to mediate the reaction to afford **4a** in 70% yield with 94% *ee*. Examples of the transformation of different β,β-disubstituted unsaturated esters (to form products **4a–f**) are summarized in Scheme 3.

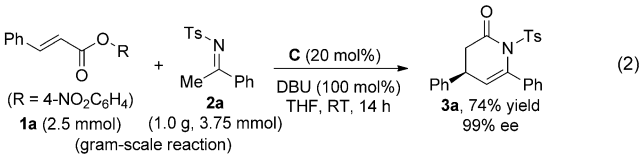



***Scheme 3.*** Activation of β,β-disubstituted unsaturated esters and their reaction with imine **2a**. The reaction was carried out at room temperature in THF (2 mL) with **1** (0.10 mmol), **2a** (2.0 equiv), an NHC (20 mol%), and DBU (1.0 equiv).

The α,β-disubstituted unsaturated ester **5** was also examined [Eq. (1)]. Under the standard reaction conditions with catalyst **C**, the desired product **6** was obtained in good yield but with poor enantioselectivity (5% *ee*). The use of catalyst **D** led to **6** in 71% yield with d.r. 6:1 and improved enantioselectivity (55% *ee*). Extensive additional studies revealed the superior performance of catalyst **E**, which provided **6** in 68% yield with d.r. 7:1 and 73% *ee*. Interestingly, catalyst **E** was ineffective for reactions of ester substrates without α substituents. For example, the reaction between **1a** and **2a** with **E** as the NHC catalyst gave **3a** in 35% yield with 34% *ee*. Interestingly, our catalytic reaction was found to be equally efficient even on a gram scale, with the formation of the lactone product **3a** in 74% yield with 99% *ee* [Eq. (2)].




(1)

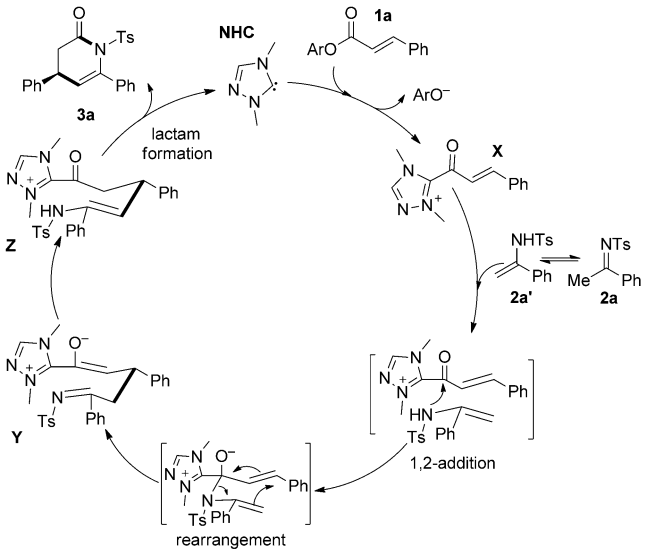



(2)

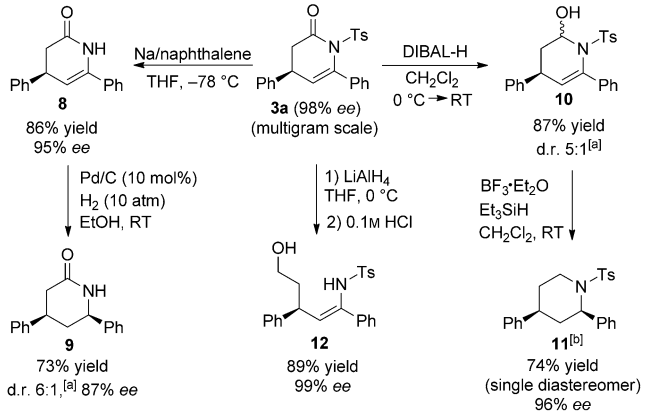
A postulated reaction pathway is summarized in Scheme 4: The addition of the NHC catalyst to ester **1a** leads to the α,β-unsaturated acyl azolium intermediate **X**. Under the basic reaction conditions, the imine substrate **2a** isomerizes to enamide **2a′**. As proposed by Bode in related studies,[24] 1,2-addition of **2a′** to **X** followed by a Claisen rearrangement affords intermediate **Y**. The tautomerization of **Y** forms **Z**, which undergoes lactam formation to yield product **3a** and regenerate the NHC catalyst.

The six-membered lactam adducts and their derivatives, such as piperidines, are basic building blocks, bioactive molecules, and commercially prescribed pharmaceuticals. Examples of such compounds include the local anesthetic ropivacaine,[25] the HIV-protease inhibitor palinavir,[26] the thrombin inhibitor argatroban,[27] the antitumor antibiotic tetrazomine,[28] and top-selling pharmaceuticals, such as paroxetine (a disubstituted piperidine).[29] The optically enriched lactam product **3a** obtained in our studies could be readily transformed by using simple protocols (Scheme 5). For example, N-deprotection of **3a** with Na/naphthalene gave **8**, which was reduced stereoselectively to the disubstituted δ-lactam **9** with little erosion of the *ee* value.[30] The reduction of




***Scheme 4.*** Postulated reaction pathway.




***Scheme 5.*** Synthetic transformations of **3a**. [a] The diastereomeric ratio was determined by $^1$H NMR spectroscopic analysis of the unpurified reaction mixture. [b] The relative configuration of **11** was assigned on the basis of its NOESY spectrum (see the Supporting Information). DIBAL-H = diisopropylaluminum hydride.

**3a** gave the cyclic N,O-acetal **10** and in a second step the disubstituted piperidine **11**.[31] The adduct **3a** could also be reduced to the aminoalcohol **12** in 89% yield with 99% *ee*.

In summary, we have developed an NHC organocatalytic strategy for the formal LUMO activation of α,β-unsaturated esters. The use of sterically demanding β,β-disubstituted esters in our catalytic approach led to optically enriched lactam products containing a quaternary stereogenic center. Given the advantages of ester substrates, we expect this organocatalytic LUMO-activation strategy to find wide application in methodology development and organic synthesis.

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