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 1a).[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 1b).[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[9c] through catalysis with NHC,[9d] 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 with enamides (Scheme 1c). 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-bromo-enals,[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 carboxyl 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 1b).[17a,b] 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[13b,19] need to be used in the asymmetric oxidative NHC catalysis. The use of ynals as substrates[14a] 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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**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.
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).

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 CH₂Cl₂, toluene, CH₃CN) and organic/inorganic bases (such as N,N-diisopropylethylamine, 4-dimethylaminopyridine, Cs₂CO₃, tBuOK) 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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>NHC</th>
<th>Base, solvent</th>
<th>Yield [%][a]</th>
<th>ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>DBU, THF</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>DBU, THF</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>DBU, THF</td>
<td>76</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>DBU, THF</td>
<td>73</td>
<td>99</td>
</tr>
<tr>
<td>5[c]</td>
<td>D</td>
<td>DBU, THF</td>
<td>69</td>
<td>95</td>
</tr>
</tbody>
</table>

[a] Yield (based on 1a) of the isolated product after SiO₂ 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).

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

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.
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 enamine 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

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)].

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 b-lactam 9 with little erosion of the ee value,[30] The reduction of
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 α,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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23) CCDC 932918 (3e) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


