VIP Asymmetric Catalysis

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Lewis Acid Activated Synthesis of Highly Substituted Cyclopentanes by the N-Heterocyclic Carbene Catalyzed Addition of Homoenolate Equivalents to Unsaturated Ketoesters**

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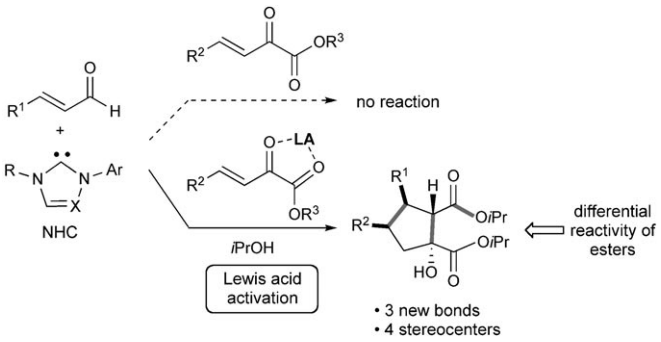
The stereoselective construction of highly functionalized small- and medium-sized carbocycles from simple substrates is an ongoing objective in organic synthesis. One approach to this goal is the use of small organic molecules that have been designed as efficient catalysts for selective cascade reactions.[1] Over the last decade, N-heterocyclic carbenes (NHCs)[2] have provided new opportunities for the development of catalytic systems based on polarity reversal or Umpolung.[3] Notably, the NHC-catalyzed generation of homoenolate equivalents from enals has emerged as a powerful tool for the synthesis of hetero- and carbocycles.[4,5]

An important discovery by Nair et al.[6] was the ability of NHCs to catalyze the addition of homoenolates to unsaturated ketones to yield 3,4-disubstituted cyclopentenes. This approach was recently extended by the addition of methanol to afford a highly substituted racemic cyclopentane with a pendent methyl ester.[5l] Although these processes expanded the reaction repertoire of carbene catalysis, the coupling partner with the enal is limited to chalcones and oxobutenoates,[7] and the products from this reaction typically have only a single alkene functional group. To advance this carbene-driven carbocycle synthesis, we envisioned that β,γ-unsaturated α-ketoesters would be a suitable class of homoenolate acceptors for the synthesis of compounds with potentially more functional groups adorning the periphery of the carbocycle framework.[8] Unfortunately, initial attempts at NHC catalysis with Lewis base activation were unsuccessful, and addition of the homoenolate intermediate to the β,γ-unsaturated α-ketoester was not observed (Scheme 1). We have been engaged recently in developing a cooperative carbene catalysis strategy by employing different Lewis acids in combination with NHCs.[9] We have shown that a Mg^{II}



Scheme 1. NHC/Lewis acid homoenolate strategy.

Lewis acid enhances the reaction rate and yield of the products in an NHC-catalyzed homoenolate addition to hydrazones.[9a] A Lewis acid in combination with carbene catalysis also completely reverses the facial selectivity of an NHC-bound homoenolate equivalent, presumably as a result of the multiple coordination sites on the metal.[9b]

Even with these advances, a major challenge in the field of carbene catalysis is to develop processes that employ new classes of electrophiles that fail as competent substrates when *only* NHCs are used. With this prospect in mind, we turned our attention to the activation of β,γ-unsaturated α-ketoesters with bidentate Lewis acids: a strategy that has proven successful in stereoselective Lewis acid catalyzed processes (Scheme 1).[10] Cooperative carbene catalysis might allow access to NHC-bound homoenolates in the presence of Lewis acids that coordinate and activate unsaturated α-ketoesters. Herein, we report the use of a Lewis acid as an essential component for an NHC-catalyzed annulation of enals with a new class of electrophiles. This reaction generates highly substituted cyclopentanols containing four contiguous stereogenic centers.

We began our studies by combining cinnamaldehyde (**1**) with (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2**) in the presence of the azolium precatalyst **A** (20 mol%), DBU (40 mol%), and $Ti(OiPr)_4$ (2 equiv). Under these conditions, cyclopentanol **3** was isolated in 69% yield as a single diastereomer (Table 1, entry 2). The excellent diastereoselectivity of this conjugate addition prompted us to develop an enantioselective version of the reaction. Use of the chiral azolium precatalysts **B**–**D** resulted in varying yields and selectivity levels (Table 1, entries 3–5). The (*S*,*R*)-aminoindanol-derived triazolium precatalyst **E**[9] furnished the desired cyclopentanol in 68% yield with a 7:1 d.r. and 90% *ee*

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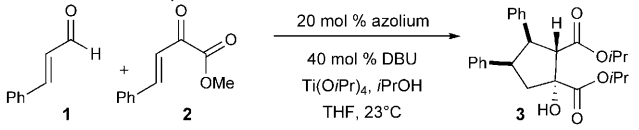
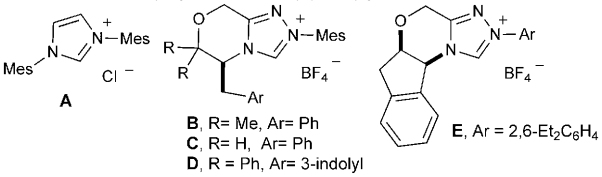
Table 1: Reaction optimization.



1 2 3

Entry	Azolium	$Ti(OiPr)_4$ [equiv]	*i*PrOH [equiv]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**A**	–	6	0[d]	–	–
2	**A**	2	–	69	>20:1	–
3	**B**	2	–	76	12:1	70
4	**C**	2	–	44	10:1	86
5	**D**	2	–	69	20:1	20
6	**E**	2	–	68	7:1	90
7	**E**	2	6	63	18:1	96
8	**E**	5	6	84	20:1	95
9	**E**	–	6	0[d]	–	–
10	**E**	–	–	0[d]	–	–

[a] Yield of the isolated product. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy (500 MHz). [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] Starting material was recovered after 48 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = mesityl (2,4,6-trimethylphenyl).

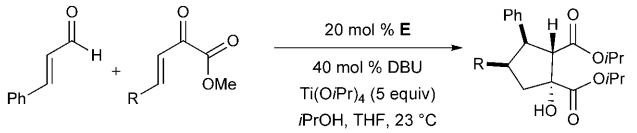


(Table 1, entry 6).[11] The addition of 2-propanol (6 equiv) promoted a faster transesterification, and surprisingly, we observed a small increase in the diastereo- and enantioselectivity to d.r. 18:1 and 96% *ee* (Table 1, entry 7).[12] A decrease in the quantity of the Lewis acid used to a substoichiometric amount resulted in incomplete conversion (results not shown).[13] An increase in the amount of the Lewis acid used to 5 equivalents led to an increase in the yield to 84% (Table 1, entry 8). When this reaction was performed under our optimized conditions but in the absence of the Lewis acid, **3** was not obtained (Table 1, entries 9 and 10). This result illustrates the importance of this Lewis acid as a key component.[14]

Having optimized the reaction conditions, we surveyed several β,γ-unsaturated α-ketoesters with varying substitution at the γ position (Table 2). Electron-withdrawing and electron-donating substituents on the aromatic ring were well-accommodated, with only a slight decrease in diastereoselectivity (13:1 d.r.) for the substrate with an *ortho*-chloro substituent (Table 2, entry 3). Heterocyclic compounds were competent substrates in the presence of Ti^{IV}; the products were obtained in moderate to good yields (52–85%) with good to excellent diastereo- and enantioselectivity (Table 2, entries 7–9). Finally, γ-cyclopropyl and γ-alkynyl substitution was well-tolerated (Table 2, entries 10 and 11), whereas only modest conversion was observed for substrates with alkyl and alkenyl groups in the γ position (results not shown).

Modification of the aldehyde component was also explored (Table 3). Electron-withdrawing groups were well-tolerated at all positions of the aromatic ring, although a slight

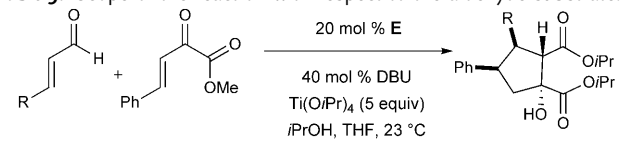
Table 2: Scope of the reaction with respect to the β,γ-unsaturated α-ketoester.[a]



Entry	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	84 (**3**)	20:1	95
2	4-Cl-C_6H_4	69 (**4**)	20:1	97
3	2-Cl-C_6H_4	72 (**5**)	13:1	95
4	4-OMe-C_6H_4	82 (**6**)	20:1	96
5	4-Me-C_6H_4	82 (**7**)	20:1	97
6	3-Me-C_6H_4	68 (**8**)	20:1	97
7	4-pyridyl	52 (**9**)	12:1	97
8	2-furyl	77 (**10**)	20:1	97
9	2-thienyl	85 (**11**)	20:1	97
10		61 (**12**)	20:1	99
11		62 (**13**)	20:1	94

[a] See the Supporting Information for details. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy (500 MHz) of the unpurified reaction mixture. [d] The *ee* value was determined by HPLC analysis using a chiral stationary phase.

Table 3: Scope of the reaction with respect to the aldehyde substrate.[a]

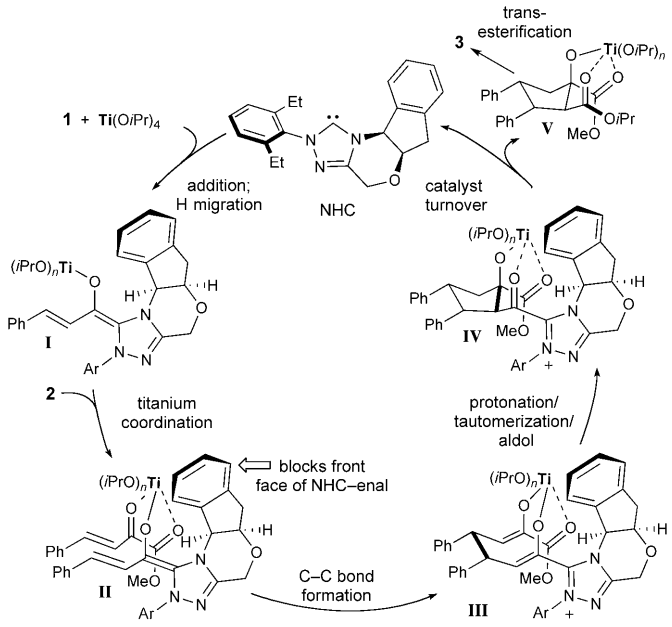


Entry	R	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	4-Cl-C_6H_4	74 (**14**)	20:1	97
2	3-Cl-C_6H_4	73 (**15**)	20:1	97
3	2-Cl-C_6H_4	68 (**16**)	10:1	98
4	4-Br-C_6H_4	75 (**17**)	20:1	96
5[e,f]	4-CO_2Me-C_6H_4	82 (**18**)	18:1	91
6	4-Me-C_6H_4	68 (**19**)	20:1	97
7	4-MeO-C_6H_4	56 (**20**)	17:1	96
8	2-MeO-C_6H_4	62 (**21**)	5:1	97
9	1-napthyl	78 (**22**)	12:1	97
10	2-napthyl	77 (**23**)	16:1	96
11[g]	4-Cl-C_6H_4	78 (**24**)	20:1	97

[a] See the Supporting Information for details. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy (500 MHz). [d] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [e] The reaction was carried out with 6 equivalents of $Ti(OiPr)_4$. [f] Transesterification to 4-CO_2iPr-C_6H_4 was observed. [g] (*E*)-Methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate was used.

decrease in diastereo- and enantioselectivity was observed in some cases (Table 3, entries 3 and 5). The presence of electron-donating groups led to moderate yields and good enantioselectivities. However, the diastereoselectivity dropped for methoxy-substituted aryl enals (Table 3, entries 7 and 8). Finally, naphthyl-derived enals furnished the desired cyclopentanols in good yields with good enantioselectivity but with slightly decreased diastereoselectivity (Table 3, entries 9 and 10).[15]

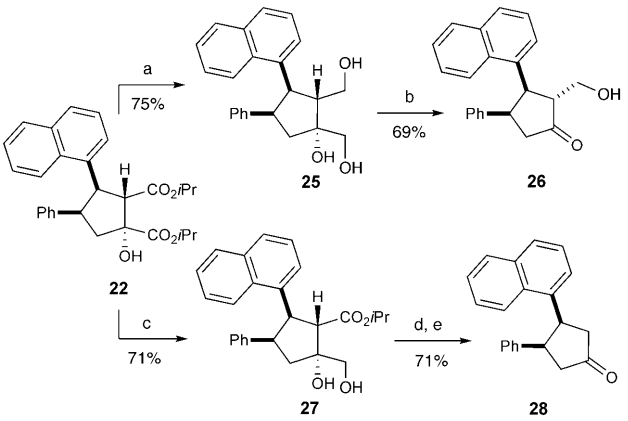
Our proposed pathway for this reaction is illustrated in Scheme 2. Initial coordination of the α,β-unsaturated aldehyde to the titanium(IV) Lewis acid, followed by the addition



Scheme 2. Proposed reaction pathway.

of the NHC, induces the formation of the extended Breslow intermediate **I**, presumably coordinated to the oxophilic titanium center. The Lewis acid concurrently coordinates to the β,γ-unsaturated α-ketoester to give **II**, thereby activating the α-ketoester and promoting the conjugate addition.[16] Following C–C bond formation, the bisenolate **III** undergoes protonation, tautomerization, and an intramolecular aldol reaction to afford intermediate **IV**. Subsequent acylation and catalyst turnover gives the mixed ester **V**, which then undergoes transesterification to furnish **3**.[17] Surprisingly, neither the β-lactone nor the cyclopentene is observed, even though the metal alkoxide and the acyl azolium moiety are *cis* in intermediate **IV**: an arrangement that could lead to an intramolecular acylation. Our current proposal is that the titanium Lewis acid prevents intramolecular acylation of **IV** as a result of the stability of the various titanium–oxygen interactions/ligations, which undergo hydrolysis upon workup and release of the product.

The synthetic utility of this annulation reaction was initially demonstrated by further elaboration of the product cyclopentanols. The treatment of bisester **22** with lithium aluminum hydride followed by silica-gel-supported sodium periodate resulted in the formation of β-hydroxyketone **26** (Scheme 3).[18] Additionally, reduction of the bisester **22** with sodium borohydride in a THF/methanol mixture at 0 °C was regioselective (>20:1) in favor of the 1,2-diol (the 1,3-diol was not observed), which was isolated in 71% yield. Subsequent oxidative cleavage under the aforementioned conditions, followed by decarboxylation in DMSO/H_2O at 130 °C, afforded the 3,4-*cis*-disubstituted cyclopentanone **28**.[19] Overall, these transformations demonstrate the utility



Scheme 3. Synthetic transformations: a) $LiAlH_4$, THF, 0–25 °C; b) $NaIO_4{\cdot}SiO_2$, CH_2Cl_2, 25 °C; c) $NaBH_4$, THF/MeOH (2:1), 0 °C; d) $NaIO_4{\cdot}SiO_2$, CH_2Cl_2, 25 °C; e) DMSO/H_2O, 130 °C. DMSO = dimethyl sulfoxide.

of the carbonyl units that remain during this novel process promoted by an NHC and a Lewis acid. These reactions also enable efficient differentiation of the two esters as well as the formation of compounds that are challenging to access otherwise, such as 3,4-*cis*-substituted cyclopentanones.

In conclusion, we have developed the first NHC-catalyzed addition of homoenolates to β,γ-unsaturated α-ketoesters. The use of $Ti(OiPr)_4$ as a mild Lewis acid compatible with NHC catalysis is essential for activation of the electrophile and promotion of the conjugate addition. This powerful NHC–Lewis acid combination enables the rapid assembly of highly substituted and functionalizable cyclopentanols from simple substrates with excellent levels of diastereo- and enantioselectivity. Furthermore, derivatization of the products provides enantiomerically enriched cyclopentanones. The two esters in the products can be differentiated by directed reduction. The powerful strategy combining Lewis basic NHC catalysis with Lewis acid activation can provide innovative ways of incorporating new reaction components and continues to be a promising area of research. New directions related to this strategy are under way and will be reported in due course.

Experimental Section

The azolium precatalyst **E** (0.2 equiv) and the γ-aryl (*E*)-α-oxobutenoic ester (3.0 equiv) were placed in an oven-dried screw-capped vial equipped with a magnetic stir bar. The vial was capped with a septum cap, removed from the dry box, and put under positive N_2 pressure. Cinnamaldehyde (32.2 mg, 0.244 mmol), THF (0.5 M), $Ti(OiPr)_4$ (5.0 equiv), *i*PrOH (6.0 equiv), and DBU (0.4 equiv) were added successively to the vial with a syringe, and the reaction mixture was stirred at room temperature under a static nitrogen atmosphere. Upon consumption of the aldehyde and transesterification (all reactions were complete within 48 h), the reaction mixture was filtered through a short plug of SiO_2 and washed with EtOAc. The solution was concentrated under reduced pressure and purified by flash chromatography (silica gel, 9% EtOAc/hexanes) to afford the corresponding cyclopentanol. Analytical data for **3**: IR (film): $\tilde{\nu}$ = 3502, 3058, 3030, 2981, 2920, 2851, 1737, 1679, 1604, 1498, 1455, 1375, 1321, 1263, 1241, 1182, 1107, 1067, 911, 742, 699 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$): $\delta = 7.06$–6.97 (m, 6H), 6.97–6.90 (m, 4H), 5.26 (sept, $J = 6.3$ Hz, 1H), 4.97 (sept, $J = 6.2$ Hz, 1H), 4.26 (dd, $J = 9.5$, 9.5 Hz, 1H), 4.05 (ddd, $J = 9.8$, 7.3, 7.3 Hz, 1H), 3.99 (s, 1H), 3.85 (d, $J = 9.2$ Hz, 1H), 2.80 (dd, $J = 13.4$, 10.1 Hz, 1H), 2.36 (dd, $J = 13.5$, 7.2 Hz, 1H), 1.45 (d, $J = 6.3$ Hz, 3H), 1.43 (d, $J = 6.3$ Hz, 3H), 1.17 (d, $J = 6.2$ Hz, 3H), 1.10 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.8$, 170.2, 140.9, 140.7, 128.7 (2C), 128.5 (2C), 127.8 (2C), 127.7 (2C), 126.1, 126.0, 81.5, 70.7, 68.5, 59.0, 50.1, 47.9, 44.3, 22.0 (2C), 21.9 ppm (2C); MS (ESI): m/z calcd for $C_{25}H_{31}O_5$: 411 $[M+H]^+$; found: 411. The enantiomeric ratio was measured by chiral-phase HPLC (Chiralcel OD-H, 5% IPA/hexanes, 0.50 mL min^{-1}, 210 nm): R_t (major) = 13.2 min, R_t (minor) = 18.7 min; 95% *ee*.

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[11] The absolute and relative configuration were determined by X-ray crystallography for compound **4** (see Table 2, entry 2) and the others were assigned by analogy (see the Supporting Information). The relative configuration of the minor diastereomer **29** was determined by X-ray crystallography and others were assigned by analogy (see the Supporting Information). CCDC 793381 (**4**) and 793382 (**29**) contain 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.

[12] The minor positive influence that 2-propanol has on the stereoselectivity is currently under investigation.

[13] A decrease in the catalyst loading (to 5 and 10 mol%) resulted in incomplete conversion (50 and 80%, respectively) after 48 h.

[14] In NMR spectroscopic experiments (^1H 500 MHz, ^{13}C 125 MHz) in which the azolium precatalyst **E**, the base DBU, and α-ketoester **2** were combined in [D_8]THF, no detectable differences were observed in the signals relative to those in the spectra of the starting material. Efforts are currently under way to understand the full role of the Lewis acid in these cooperative carbene catalytic processes.

[15] At present, the use of achiral carbene **A** and chiral Ti^{IV} complexes does not provide the desired cyclopentane products. Further investigations in this area are ongoing.

[16] For a recent computational study that supports a conjugate-addition pathway over a benzoin/oxy-Cope process, see: L. R. Domingo, R. J. Zaragozá, M. Arnó, *Org. Biomol. Chem.* **2010**, *8*, 4884.

[17] The transesterification reaction can be monitored by thin-layer chromatography or by ^{1}H NMR spectroscopy (500 MHz). The mixed ester can be isolated by flash chromatography.
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