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A Cooperative Ternary Catalysis System for Asymmetric Lactonizations of α-Ketoesters

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Abstract. A general and enantioselective *N*-heterocyclic carbene (NHC)-catalyzed lactonization of simple enals and α-ketoesters has been discovered using a new ternary cooperative catalytic system. The highly selective annulation was achieved by using a combination of a chiral NHC, a hydrogen-bond donor, and a metal salt, facilitating self-assembly of the reactive partners. A proposed model for this new mode of NHC chiral relay catalysis is supported by experimental and computational mechanistic studies.

Keywords: *N*-heterocyclic carbene; NHC; ternary catalysis; lactone; cooperative catalysis; Umpolung; homoenolate

N-heterocyclic carbene (NHC)-catalyzed homoenolate additions are unconventional methods to generate a nucleophilic β-carbon atom for the formation of C–C and C–O bonds.[1] Homoenolate annulations with carbonyl compounds give rise to enantioenriched γ-butyrolactones, which are prevalent structural motifs in natural and bioactive products,[2] as well as direct precursors to substituted tetrahydrofurans,[3] furans,[4] and nucleoside analogues.[5] While isatins,[6] acyl phosphonates,[7] and trifluoromethyl-substituted aryl ketones[8] are selective carbonyl electrophiles with NHC-homoenolate annulations, aryl aldehyde electrophiles[9] afford only moderate annulation yields and enantioselectivities, and simple alkyl ketones are not currently productive substrates (Figure 1A).[1d] The use of α-ketoesters as electrophiles for homoenolate annulations has had only limited success to date.[10] Successful examples of homoenolate additions to carbonyl groups, particularly isatins,[6a-c] have employed an additive or co-catalyst (e.g., Lewis acid (LA), Brønsted acid (BA), or hydrogen bond donor (HBD)) to enhance the enantioselectivity and yield of the reaction (Figure 1A). Cooperative NHC catalysis with compatible Lewis acid or HBD catalysts[11] to activate electrophiles for Umpolung transformations has recently emerged as a powerful strategy to access complex molecular frameworks with high selectivity.[6b, 9, 12] Despite these advances, the use of co-catalysts has not been explored for NHC-catalyzed homoenolate additions to α-ketoesters. We envisioned that under this new type of activation, a co-catalyst could potentially preorganize the α-ketoesters in a fixed geometry, generating a stereodefined ensemble in the enantiodetermining bond formation step (Figure 1B). To this end, we have developed a general and highly enantioselective annulation of enals with α-ketoesters using a novel ternary[13] cooperative chiral NHC/LA/HBD strategy.

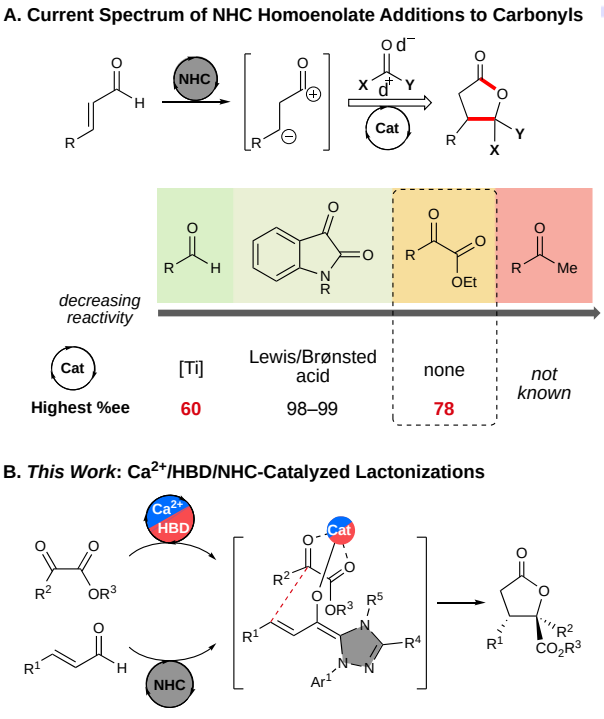

Figure 1. NHC-catalyzed lactonizations.

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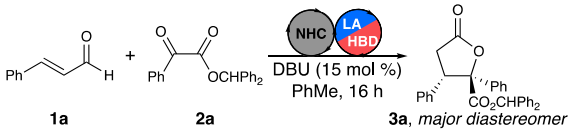
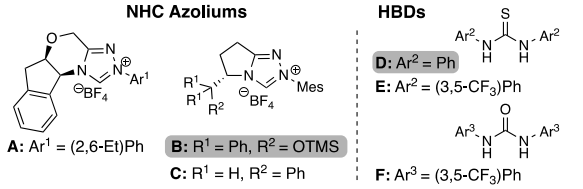
To test our hypothesis that activation of α-ketoesters using Lewis acids and HBDs may lead to improved annulation enantioselectivities, the effects of several additives were studied alongside NHC precatalysts in the title reaction (Table 1). Inspired by previous cooperatively-catalyzed NHC annulations, conditions using lithium chloride,[3e, 6b] titanium isopropoxide,[9c] scandium triflate,[12e] zinc triflate, magnesium di-tert-butoxide,[12a, 12e] and HBDs as co-catalysts were screened with no improvement to the enantioselectivity (see SI). A variety of magnesium and calcium alkoxides and HBDs were screened as co-catalysts with azolium **A**, which led to moderate enantioselectivities (32–45% ee, entries 2–3 and SI). The combination of all three catalysts increased the enantioselectivity (entry 4). Notably, while NHC and HBD cooperative systems have been relatively underexplored, the use of calcium complexes in conjunction with NHC catalysis is unreported.

Table 1. Cooperative catalysis optimization[a]



entry	NHC	LA	HBD	% yield[b]	dr	% ee[c]
1	**A**	–	–	66	2:1	33/51
2	**A**	$Mg(O^tBu)_2$	–	64	1:1	38/45
3	**A**	–	**D**	60	2:1	33/44
4	**A**	$Mg(O^tBu)_2$	**D**	67	2:1	75/38
5	**A**	$Mg(O^tBu)_2$	**E**	76	3:1	41/16
6	**A**	$Mg(O^tBu)_2$	**F**	32	3:1	15/7
7	**B**	$Mg(O^tBu)_2$	**D**	**80**	**2:1**	**88/94**
8	**C**	$Mg(O^tBu)_2$	**D**	66	2:1	4/6
9	**B**	$Ca(OMe)_2$	**D**	**75**	**2:1**	**92/91**
10	**B**	–	–	quant.	1:1	81/84
11	**B**	$Ca(OMe)_2$	–	56	1:1	46/40
12	**B**	–	**D**	15	1:1	9/6

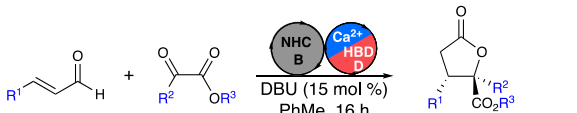


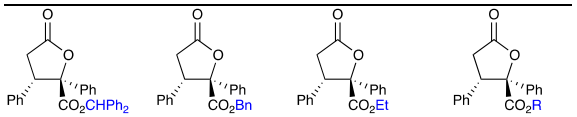
[a]Conditions: **1a** (0.08 mmol, 1 equiv), **2a** (1 equiv), NHC azolium (0.10 equiv), LA (0.15 equiv), HBD (0.15 equiv), DBU (0.15 equiv) in PhMe (0.15 M) at 23 °C for 16 h. [b]Determined by ^{1}H NMR spectroscopy with trimethoxybenzene as internal standard. [c]Determined by HPLC analysis.

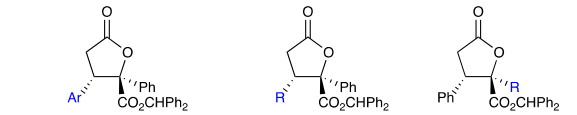
The optimization of the lactonization was continued by surveying a library of HBDs, NHC catalysts, and bases (Table 1 and SI). Contrary to most HBD-catalyzed transformations, electron-rich aromatic thioureas produced higher enantioselectivities than electron-deficient urea derivatives.[14] The use of sterically congested, electron-rich aromatic thioureas was attempted to improve the diastereoselectivity, but long reaction times and diminished diastereomeric ratios were observed (See SI). A screen of NHC catalysts revealed that triazolium **B**, first independently reported by Enders and Ye,[15] improved both the yield and %ee of the reaction (entry 7 and SI). When the silyl ether on **B** was replaced with an alkyl substituent (entry 8 and SI), the observed %ee was significantly diminished, implying that the Lewis basic site on the NHC catalyst may create a key stabilizing interaction (See SI for computational support of the proposed interaction). Employing **B** with calcium methoxide and HBD **D** (entry 9) resulted in increased %ee's for both diastereomeric products compared to lactonizations run with other or in the absence of co-catalysts (entries 7, 9–12). The best %ee and yield was observed using DBU as the base. Importantly, control reactions with no DBU resulted in *no observed product*, indicating that the metal alkoxide is not acting as a base but that it is more likely involved in organizing the transition state.

After optimization of the reaction conditions, the scope of the lactonization was explored (Table 2). Initially, different ester substituents were investigated (**3a–d**), and the observed %ee's (73–94) were higher than those previously reported. Aromatic ortho-, meta-, and para-substituted enals (**3e–3k**) effectively formed lactones with moderate to high levels of %ee (75–99). While alkyl enals expectedly afforded lower yields (35% of **3l**, 57% of **3m**),[6b, 9b, 16] they provided lactone products with good %ee's (up to 87%). Ortho-substituted aromatic α-ketoesters did not react, as reported previously,[10c, 10e] but other aromatic α-ketoesters (**3o–3q**) gave lactones with moderate to high enantioselectivities (89–98% ee). Although all of the lactonizations proceeded with modest to no diastereoselectivity (3:1–1:1), the products could be separated using column chromatography.

Table 2. Substrate Scope[a]







	Ar =				
3e	2-ClPh	70%, 1:1, 75	**3l**	R = Me	35%, 2:1, 87
3f	2-OMePh	94%, 1:1, 95	**3m**	R = *n*Pr	57%, 2:1, 73
3g	2-MePh	96%, 2:1, 98			
3h	2-furyl	90%, 1:1, 82			
3i	3-ClPh	94%, 2:1, 99			
3j	4-ClPh	89%, 2:1, 89			
3k	4-OMePh	65%, 2:1, 95[c]			

3n	R = CF_3	34%,[d] 2:1, 96
3o	R = 3-ClPh	67%, 3:1, 89
3p	R = 3-EtPh	45%,[d] 2:1, 89
3q	R = 4-MePh	64%, 2:1, 98

[a]See SI for details: dr was determined by ^{1}H NMR spectroscopy, and %ee was determined by HPLC analysis. [b]$Mg(Ot\text{-}Bu)_2$ was used instead of $Ca(OMe)_2$. [c]Absolute configuration was determined by X-ray crystallography.[17] [d]Incomplete conversion.

To gain a deeper insight into the role of each catalyst in our unique catalytic system, ^{1}H NMR and NOESY

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1D spectroscopy and ESI mass spectrometry were used to study the interactions of the electrophile, nucleophile, and additives (Figure 2).[18] The results of the ^{1}H NMR spectroscopy studies showed an unexpected upfield shift (δ 0.12–0.14 ppm) of all of the nucleophile and electrophile protons when each substrate was mixed with the co-catalysts, implying a shielding effect of the aromatic rings of the HBD to the substrates (Figure 2A).[19] The interaction of the aromatic ring of the HBD with the ester was also detected by NOESY 1D experiments, but the signal was diminished when calcium methoxide was added (Figure 2B). This is likely evidence for the binding of calcium between the carbonyls of the α-ketoester.[20] Consistent with this proposed mode of binding, no change by ^{1}H NMR spectroscopy was observed when calcium methoxide and 1,3-diphenylthiourea were mixed alone in toluene-d_8, implying that calcium is likely not activating the HBD.[21] ESI mass spectrometry revealed a mass corresponding to the catalyst–substrate complex (NHC **B** + enal), but no mass corresponding to any co-catalyst adducts.[18b, 22] Observation of this intermediate also suggests that the pendent silyl ether of NHC **B** remains silylated under the reaction conditions. Due to the heterogeneity of the reaction, kinetic studies to determine the bond order of each catalyst were problematic and DOSY experiments were unsuccessful. Based on the data, we postulate that the combination of catalysts likely forms a network, mimicking the metals and hydrogen bonds present in an enzyme pocket.[14d, 23]

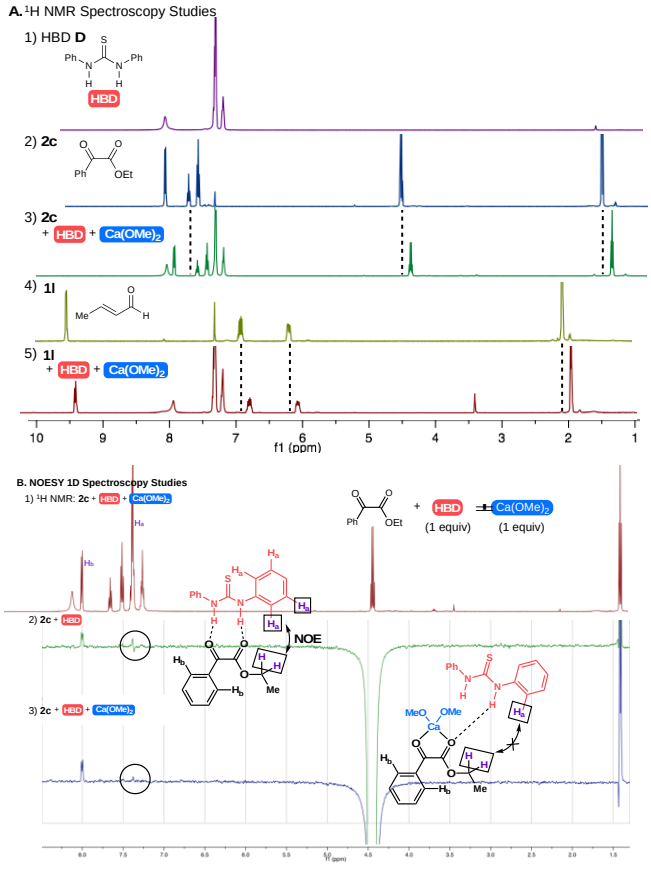

Figure 2. NMR Studies of the Lactonization. (A) ^{1}H NMR spectra ($CDCl_3$) of solutions of (1) catalyst **D**, (2) α-ketoester **2c**, (3) **2c** + **D** + $Ca(OMe)_2$, (4) enal **1l**, and (5) **1l** + **D** + $Ca(OMe)_2$. (B) NOESY 1D spectra of solutions of (2) α-ketoester **2c** + **D** and (3) **2c** + **D** + $Ca(OMe)_2$.

We next sought to enhance our model for enantioinduction in the lactonization. Experiments with modified HBDs were performed to investigate the interactions of N–H bonds and aryl substituents with the other reaction partners (Figure 3A). Parameters of the transition state that we investigated were (1) π-stacking (**G**), (2) conformation of the thiourea (**H, I**),[24] and (3) bridging of the nucleophile and electrophile (**H, I**).[25] Each modification of the optimal HBD **D** resulted in decreased selectivity, leading us to hypothesize that the H-bonding ability of the donor N–H bonds and π-stacking of the Z,Z-1,3-diphenylthiourea HBD may play crucial roles in the selectivity (see below for integrated DFT analysis).

DFT computations provided further insight into the complexation motif that may be operative in the stereodetermining C–C bond-forming transition structures (TSs). The TSs leading to the major (**TS-*(Re,Re)*-Major**) and minor (**TS-*(Si,Si)*-Minor**) enantiomers of the lactone products are shown in Figure 3B. Geometry optimizations were completed using PBE/6-31G*[26] with the energy of solvation modeled in toluene with PBE[27]/6-311+G**/SMD.[28] Dispersion corrections were also completed using the PBE D3BJ model.[29] The computed energies were further refined using PBE/6-311++G(2df,p). The computed enantioselectivity of 1.7 kcal/mol (90% ee) is in excellent agreement with experiment (1.8 kcal/mol, 92% ee, Table 1, Entry 9). Both TSs feature a Ca^{2+} ion chelated to the carbonyl groups of the α-ketoester electrophile and the oxygen atom of the anionic homoenolate nucleophile. The methoxide counterion binds to Ca^{2+}, forming a distorted tetrahedral metal center. The negative charge of the methoxide ion is further stabilized by H-bonding with the thiourea N–H groups. This binding mode corroborates the LCMS results in which the thiourea preferentially binds to methoxide rather than the substrate (See SI). Thiourea HBDs are known to interact with halides,[30] but are less frequently reported with alkoxides.[31] The formation of the thiourea–methoxide complex is critical to induce the high enantioselectivity of the reaction. The thiourea acts as a relay auxiliary, with the phenyl groups transferring the chiral information of the catalyst to the distal reactive center.[32] In **TS-*(Re,Re)*-Major**, the HBD phenyl group engages in a C–H–π interaction,[33] which is strengthened by the developing positive charge of the catalyst. This interaction is absent in the minor TS shown in Figure 3B, due to the catalyst NMes group and the pendent stereodirecting group blocking the planar azolium. Removing the HBD aryl groups (Figure 3A, **G**) eliminates the favored C–H–π interaction in **TS-*(Re,Re)*-Major** and decreases the selectivity. Methylating the thiourea (**H**) reduces the selectivity by disfavoring complexation to methoxide, thus interfering with the formation of the chiral relay

ion complex. Full methylation (**I**) completely eliminates the ability of the HBD to form the complex, and correspondingly low selectivity was observed (49% ee) in comparison to the reaction run with no HBD present (46% ee, Table 1, entry 11).

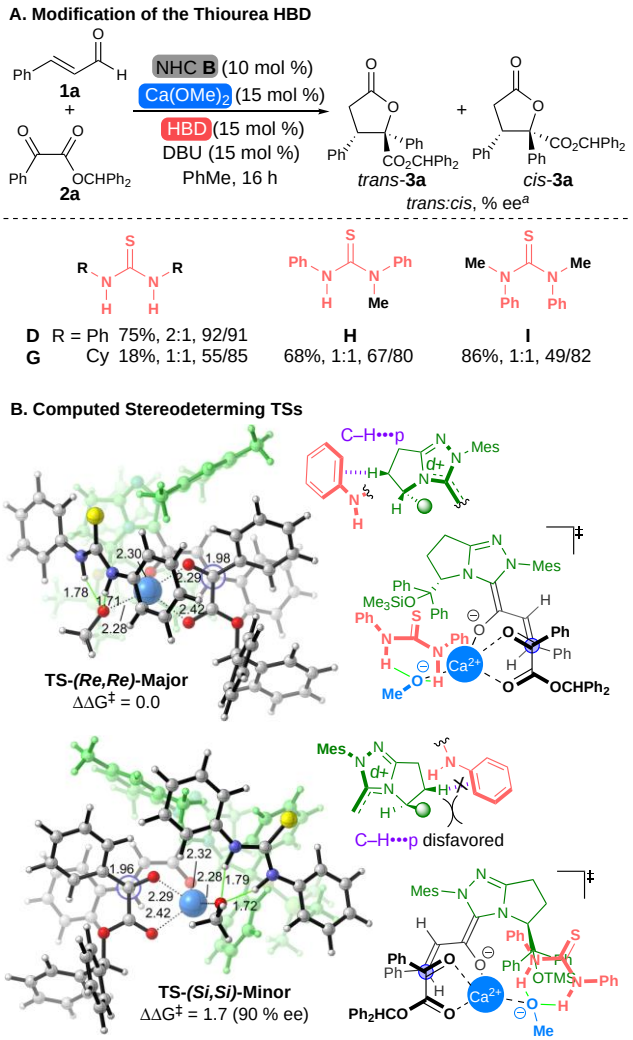

Figure 3. (A) Mechanistic studies through modifications of the HBD catalyst. (B) Computed stereodetermining TSs with catalyst **B**, HBD **D**, and $Ca(OMe)_2$ (Table 1, Entry 9). [a]dr was determined by unpurified ^1H NMR spectroscopy, and %ee was determined by HPLC analysis. NHC catalyst highlighted in green. Light green lines indicate electrostatic interactions and dashed lines show coordination to the Ca^{2+} ion. Distances are in Å and energies ($\Delta\Delta G^{‡}$) in kcal/mol.

In conclusion, an efficient asymmetric lactonization of unsaturated aldehydes with α-ketoesters using NHC/Ca^{2+}/HBD cooperative catalysis has been developed. Enals can be transformed into the corresponding enantiomerically enriched substituted γ-butyrolactones in high yield and enantioselectivity. This solution to a challenging reaction employs a new mode of cooperative catalysis. In harnessing an ensemble effect of three distinct entities with low entropic penalties, this new mode of NHC catalysis moves the efficiency of organocatalysis closer to nature's catalysis. This process broadens the scope of NHC cooperative catalysis that address less reactive substrate classes and should find applications in complex synthesis.

Experimental Section

General Procedure for the Synthesis of Lactones

In a nitrogen filled dry box, a screw-capped 1 dram vial equipped with a magnetic stirbar was charged with an α-ketoester (1 equiv), triazolium precatalyst **B** (10 mol %), HBD **D** (15 mol %), and $Ca(OMe)_2$ (15 mol %). Aldehydes (1 equiv) that are solid were also added to this same vial in the dry box. The vial was capped with a septum cap, removed from the dry box, and fitted with an argon balloon. The heterogeneous mixture was then diluted with PhMe (0.15 M), and to this mixture was added aldehyde (1 equiv), followed by DBU (15 mol %) via syringe. The reaction mixture was stirred at 23 ºC for 12–16 h. After complete conversion of the aldehyde as determined by TLC, the reaction mixture was concentrated *in vacuo*, loaded directly onto a column of silica gel, and the crude products were isolated by flash column chromatography (2–10 % EtOAc/hexanes, UV and ceric ammonium nitrate stain visualization).

Acknowledgments

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A Cooperative Ternary Catalysis System for Asymmetric Lactonizations of α-Ketoesters

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