

Asymmetric Inverse-Electron-Demand Hetero-Diels–Alder Reaction of Six-membered Cyclic Ketones: An Enamine/Metal Lewis Acid Bifunctional Approach**

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The combination of organocatalysis with metal catalysis has emerged as a potentially powerful tool in organic synthesis.^[1] This new concept aims to achieve organic transformations that cannot be accessed by organocatalysis or metal catalysis alone. In our effort to combine organo-enamine catalysis with metal Lewis acid catalysis, we have developed a new class of bifunctional enamine/metal Lewis acid catalysts.^[2] These bifunctional catalysts displayed unusually high activity and high stereoselectivity in asymmetric direct aldol reactions. The challenge in the development of Lewis acid/Lewis base catalytic systems lies in the acid-base quenching reaction that leads to catalyst inactivation.^[3] A common and elegant approach to solving this problem is the use of a soft acid along with a hard base, or vice versa. Based on this approach, organo-enamine catalysis has been successfully combined with Cu^I,^[1c,d] Ag^I,^[1e] Pd⁰,^[1f–h] and Au^I.^[1i,j] We use a different strategy to solve the acid-base problem. This new strategy complements the mixed soft/hard approach. In our system, the Lewis base (primary or secondary amine) is tethered to a chelating ligand, which serves as a “trap” for the incoming metal. In this way, the base and the metal Lewis acid are brought into close proximity in one molecule without interacting with each other (Figure 1). The bifunctional enamine/metal Lewis acid catalysts have two unique advantages. First, a large number of metals can be introduced. The

Lewis acidity can be easily tuned by simply using a different metal, thereby offering great flexibility to this system. For example, stronger Lewis acids, such as La^{III}, can be used to activate the enamine acceptor more strongly. Second, the bifunctional catalysts can potentially convert an intermolecular reaction into a much more efficient intramolecular reaction. In addition, the intramolecular bifunctional nature of the catalysts would also enhance the stereoselectivity of the reaction. With these catalysts, we intend to develop new carbon–carbon or carbon–heteroatom bond-forming reactions involving difficult organic transformations. Herein, we report the first example of a highly chemo- and enantioselective inverse-electron-demand hetero-Diels–Alder (HDA) reaction of cyclic ketones with β,γ -unsaturated- α -ketoesters catalyzed by primary-amine-based enamine/metal Lewis acid bifunctional catalysts.

Asymmetric inverse-electron-demand hetero-Diels–Alder (IED/HDA) reactions of electron-rich alkenes with an electron-deficient α,β -unsaturated ketone offers a valuable synthetic entry into dihydropyran derivatives, which are chemically and biologically of significant importance, allowing the construction of up to three stereogenic centers in one operation.^[4] In most of the inverse-electron-demand HDA reactions, enol ethers derived from aldehydes act as the electron-rich alkenes (dienophiles). Very recently, enamine-based organocatalytic asymmetric inverse-electron-demand HDA reactions, in which an in situ formed enamine from a chiral pyrrolidine and an aldehyde serves as the dienophile, have been made possible.^[5] Ketones are much less reactive compared to aldehydes because of electronic and steric reasons. Asymmetric HDA reactions of ketones, in particular cyclic ketones, have remained a long-standing challenge.^[4,6] We are interested in developing a catalytic asymmetric enamine-based IED/HDA reaction of simple ketones with enones, as it would greatly generalize this method, and open it up to much wider exploitation.

To achieve this we believe that the activation of enones should extend beyond hydrogen-bond methods,^[5,7,8] for example, by using a strong metal Lewis acid.^[4,9] In contrast, the formation of a less congested enamine intermediate using a primary amine catalyst may also contribute to or facilitate this transformation. The primary-amine-based enamine/metal Lewis acid bifunctional catalysts developed in our laboratory^[2] appear to be ideal candidates to tackle this difficult problem. We envision that the primary amine/metal Lewis acid bifunctional catalyst would engage enone **3** and the cyclic ketone **2** intramolecularly (Scheme 1). The primary amine would form an enamine in situ with the ketone (**A**) and the

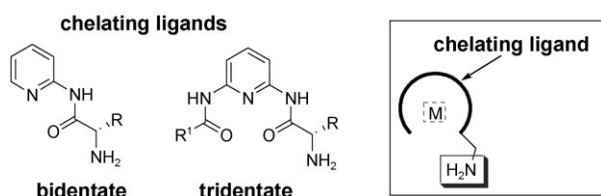
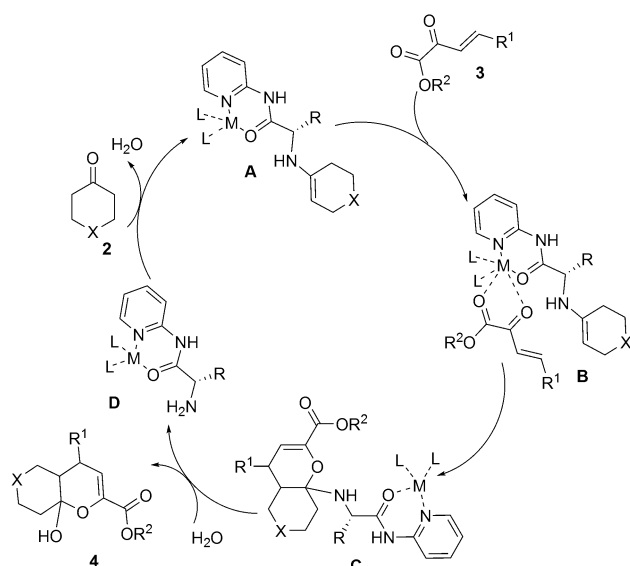


Figure 1. Illustration of primary amine/metal Lewis acid bifunctional catalysts.

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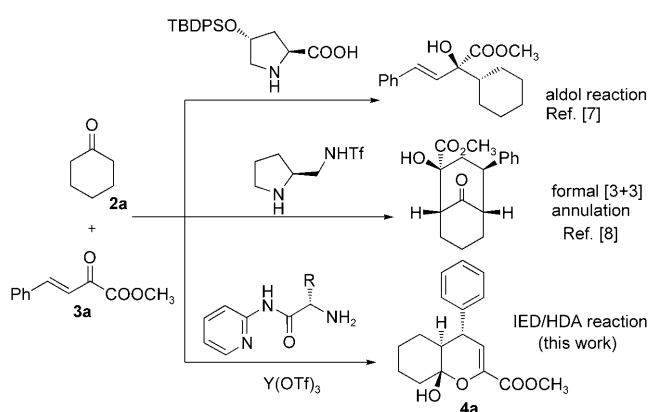
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Scheme 1. The proposed catalytic cycle of the HDA reaction catalyzed by primary amine/metal Lewis acid bifunctional catalyst. L = ligand.

metal could strongly activate enone **3** through chelation (**B**). The activated enone would react with the enamine, thus leading to the formation of cyclic aminal **C**; hydrolysis of **C** will generate the HDA product hexahydrochromene **4**, and release the catalyst to complete the catalytic cycle.

Initially, the primary amine/metal Lewis acid bifunctional catalysts were applied to the reaction of cyclic ketones with enones. The IED/HDA reaction of cyclic ketones with enones will lead to the formation of a novel class of fused dihydropyran derivatives (hexahydrochromenes), creating three stereogenic centers including a quaternary carbon center (Scheme 2, bottom). However, it has been reported that cyclohexanone reacted with enone **3a** in the presence of a proline-derived catalyst, thereby leading to a highly enantioselective aldol reaction (Scheme 2, top);^[7] in contrast, a novel asymmetric formal [3+3] annulation reaction occurred between the same reactants using a different proline derivative as the catalyst, forming a bicyclo [3,3,1] skeleton (Scheme 2, middle).^[8] Another uncertainty involved in the



Scheme 2. Comparison of organocatalysts with the bifunctional catalyst in the reaction of cyclohexanone with enone **3a**. TBDPS = *tert*-butyldiphenylsilyl, Tf = trifluoromethanesulfonyl.

IED/HDA reaction is the stability of the HDA product **4a**.^[5,6] It was not clear to us if **4a** was stable enough to be isolated, or if further stabilization of **4a**, for example, through the protection of the hydroxy group, was needed. To investigate the possibility of a HDA reaction, we first pursued screening of the metal using ligand **1a** (Table 1). The catalysts were prepared by stirring the ligand and the metal salt in solvent for 1–4 hours before addition of the substrates. The reaction of cyclohexanone **2a** and enone **3a** was carried out in THF in the presence of **1a** and a metal salt at room temperature. Whereas Cu(SbF₆)₂, Sc(OTf)₃ and Eu(fod)₃ essentially yielded the aldol product **5a** (entries 1, 4, and 5), we were intrigued to discover that La(OTf)₃, Yb(OTf)₃, and Y(OTf)₃ produced the desired HDA product **4a** (entries 2, 3, and 6). To our surprise, the HDA product **4a** displayed remarkable stability. Y(OTf)₃ was selected as the metal for solvent screening because of the higher chemo-, diastereo-, and enantioselectivity of the resulted HDA reaction. A range of solvents were examined (entries 6–11). Toluene gave the highest chemoselectivity but moderate enantioselectivity of **4a** (entry 8), THF and CH₃CN resulted in good chemoselectivity and very good enantioselectivity (entries 6 and 9), and when MeOH was used, only the aldol product **5a** was isolated (entry 11).

As indicated in Table 1, the aldol reaction was the major competing reaction with the HDA reaction.^[7] The formal [3+3] annulation product^[8] was not observed. The hydrolysis of the aminal **C** (Scheme 1) appeared to be a key step to

Table 1: Optimization of HDA reaction.^[a]

Entry	Metal	Solvent	<i>t</i> [h]	Yield [%] ^[b]	d.r. ^[c]	4a/5a ^[d]	ee [%] ^[d]
1	Cu(SbF ₆) ₂	THF	72	72	—	0:100	—
2	La(OTf) ₃	THF	16	95	4:1	95:5	49
3	Yb(OTf) ₃	THF	36	61	3:1	70:30	70
4	Sc(OTf) ₃	THF	60	60	—	0:100	—
5	Eu(fod) ₃	THF	60	37	—	0:100	—
6	Y(OTf) ₃	THF	16	61	7:1	92:8	83
7	Y(OTf) ₃	CH ₂ Cl ₂	36	75	4:1	96:4	75
8	Y(OTf) ₃	Toluene	36	74	4:1	> 99:1	67
9	Y(OTf) ₃	CH ₃ CN	36	70	4:1	92:8	85
10	Y(OTf) ₃	Neat	36	76	4:1	58:42	82
11	Y(OTf) ₃	MeOH	72	31	—	< 1:99	—
12 ^[e]	Y(OTf) ₃	CH ₃ CN	36	50	5:1	91:9	82
13 ^[f]	Y(OTf) ₃	CH ₃ CN	72	20	—	8:92	—
14 ^[g]	Y(OTf) ₃	CH ₃ CN	72	20	—	4:96	—
15 ^[h]	Y(OTf) ₃	CH ₃ CN	72	38	4:1	83:17	80

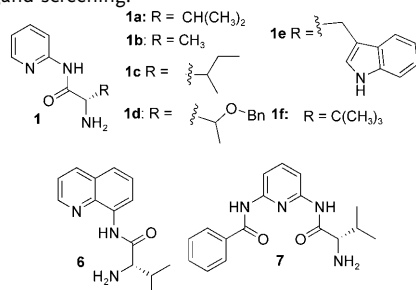
[a] Reaction conditions: enone **3** (0.2 mmol) and cyclohexanone (0.5 mL), room temperature in 1 mL of solvent. [b] Yield of the isolated HDA products. [c] Determined by ¹H NMR spectroscopy.^[10] [d] Determined by HPLC analysis using a chiral stationary phase. [e] 50 mg of silica gel was added. [f] 5 equivalents of H₂O was added. [g] 10 equivalents of H₂O was added. [h] 100 mg of 4 Å M.S. was added. fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadiene, M.S. = molecular sieves, THF = tetrahydrofuran.

complete the HDA catalytic cycle, and we found that the water generated in situ in this reaction played a critical role in the hydrolysis. When molecular sieves were included in the reaction (Table 1, entry 15), the HDA reaction was noticeably slower and the yield decreased significantly, suggesting that water was essential for the HDA reaction; however, when extra water was added to the reaction, the reaction path was switched to favor the aldol reaction (entries 13 and 14). In contrast to the amins formed from secondary amines, the hydrolysis of amination **C**, which was generated from a primary amine, did not require the presence of silica;^[5] inclusion of silica did not facilitate the reaction (entry 12).

Having established the possibility of an inverse-electron-demand HDA reaction of cyclohexanone **2a** and enone **3a**, we screened a series of primary-amine-based ligands (**1**, **6**, and **7**; Table 2) to enhance the activity and stereoselectivity. Ligand **1**, **6**, and **7** were prepared through the coupling reaction of the corresponding amine and N-protected L-amino acids with subsequent deprotection (see the Supporting Information for experimental details). While all ligands showed activity toward the HDA reaction, **1f** displayed the best chemo- and enantioselectivity; however, the diastereoselectivity was a little low (entry 8). Lowering the temperature to 4 °C lead to excellent chemo- and enantioselectivity, but also with a slight decrease in diastereoselectivity (entry 9). When the solvent was changed from CH₃CN to THF at 4 °C, the diastereoselectivity significantly increased, whilst excellent chemo- and enantioselectivity were maintained (entry 10).

The substrate scope of this reaction was explored by the reaction of four six-membered cyclic ketones with various substituted enones (Scheme 3). The β,γ-unsaturated-α-

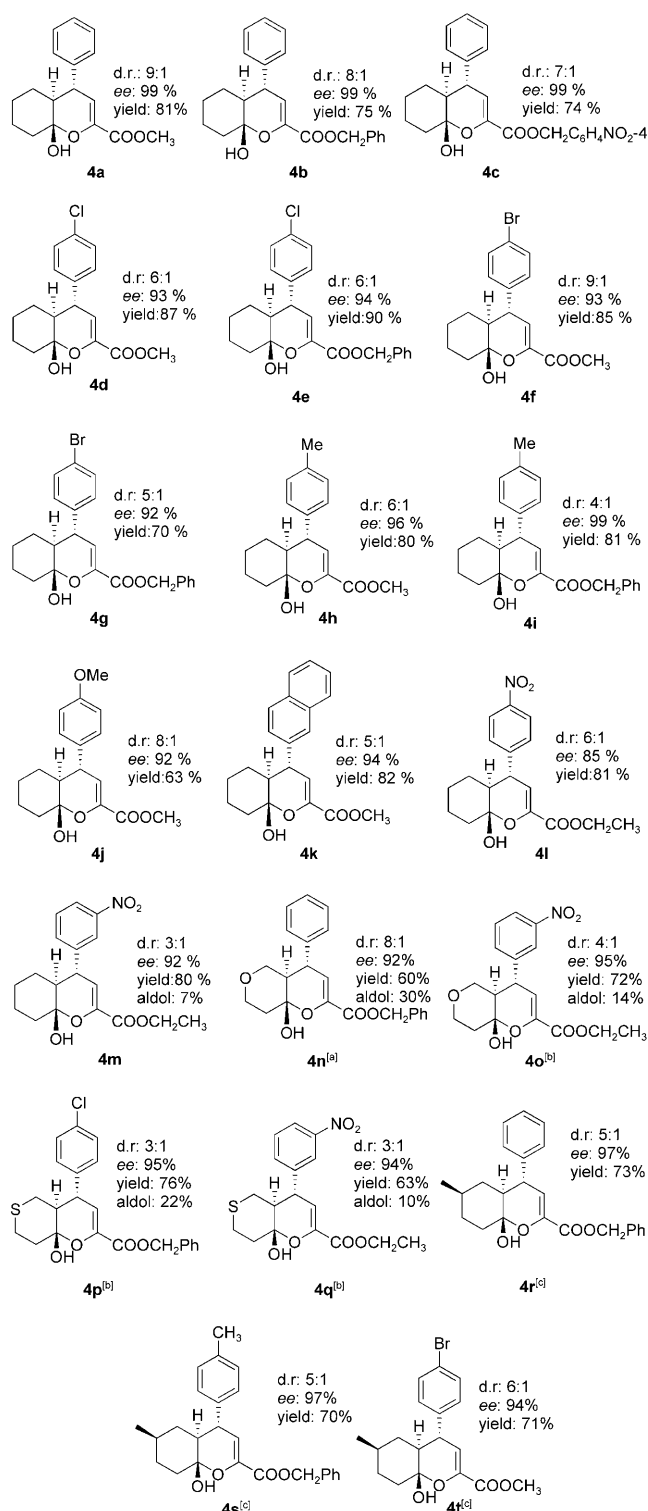
Table 2: Ligand screening.^[a]



Entry	Ligand	Solvent	t [h]	Yield [%] ^[b]	d.r. ^[c]	4a/5a ^[c]	ee [%] ^[d]
1	1a	CH ₃ CN	36	70	4:1	92:8	85
2	1b	CH ₃ CN	36	21	13:1	50:50	66
3	1c	CH ₃ CN	36	72	4:1	95:5	80
4	1d	CH ₃ CN	48	48	4:1	75:25	48
5	1e	CH ₃ CN	36	64	6:1	88:12	71
6	6	CH ₃ CN	72	51	—	10:90	—
7	7	CH ₃ CN	36	54	6:1	85:15	67
8	1f	CH ₃ CN	36	91	3:1	98:2	92
9	1f ^[e]	CH ₃ CN	72	86	2.5:1	>99:1	>99
10	1f ^[e]	THF	84	81	9:1	>99:1	>99

[a] Reaction conditions: enone **3a** (0.2 mmol) and cyclohexanone (0.5 mL) at room temperature in 1 mL of solvent. [b] Yield of the isolated HDA products. [c] Determined by ¹H NMR spectroscopy.^[10] [d] Determined by HPLC analysis using a chiral stationary phase. [e] Run at 4 °C. Bn = benzyl.

ketoesters with both electron-donating and electron-withdrawing aromatic substituents at the γ position reacted



Scheme 3. Substrate scope. The reaction was performed with 0.2 mmol of enone and 0.5 mL of cyclic ketone at 4 °C in 1 mL of THF unless otherwise mentioned. [a] 5.0 equivalents of cyclic ketone was used at 4 °C. [b] 5.0 equivalents of cyclic ketone was used at room temperature. [c] Only two diastereomers were detected by ¹H NMR analysis of the crude reaction mixture, similar to the reactions of cyclohexanone.

smoothly with cyclohexanone to give the HDA product **4** in very good to excellent enantioselectivity (**4a–4m**, 85–99% *ee*), and good to very good diastereoselectivity (d.r. 3:1 to 9:1). No aldol product was detected in either of the reactions except the reaction of the γ -3-nitrophenyl-substituted enone (**4m/5m** = 12:1). The reactions of 4-methylcyclohexanone with enones were also highly chemo- and stereoselective (**4r–4t**, no aldol product, d.r. 5:1 to 6:1, 94–97% *ee*), noting four stereogenic centers were created in these reactions. Both dihydropyran-4-one and dihydrothiopyran-4-one underwent HDA reaction smoothly with enones, generating the fused dipyrans in good stereoselectivity (**4n–4q**, d.r. 3:1 to 8:1, 92–95% *ee*); however, the aldol products were also isolated as the minor product in 10–30% yields.

Only two *endo* diastereomers were detected for the HDA products as determined from the ^1H NMR spectra of the crude reaction mixtures, even though three to four stereogenic centers were generated in these inverse-electron-demand HDA reactions. The HDA reactions were highly π -facial diastereoselective, and the final diastereomers were produced from the hydrolysis in the last step (see Scheme 1).^[10] The structure and relative stereochemistry of the major diastereomer was determined by ^1H and ^{13}C NMR spectroscopy, including DEPT, COSY, NOESY, HSQC, and NOE methods (see the Supporting Information). The absolute configuration of **4g** was established as 4*R*, 4*aS*, 8*aR* by X-ray crystallography (Figure 2).^[11] All the rest of the compounds were assumed to have similar configurations as **4g**.

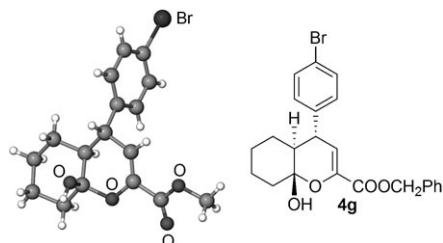


Figure 2. X-ray crystal structure of **4g**.

The bifunctional nature of the catalysts was revealed by the fact that neither the ligand **1a** nor the metal ($\text{Y}(\text{OTf})_3$) alone could catalyze the reaction. The proposed transition-state **B** (Figure 3), featuring an *endo*-selective mode of reaction, matches well with the relative stereochemistry at C4 and C4*a*. The big *R* (*tert*-butyl) group shields the *Re* face of the enamine, thus the activated enone attacks from the *Si* face, accounting for the absolute configuration of the final products.

In conclusion, the novel concept of enamine/metal Lewis acid bifunctional catalysis was introduced for the first time to the HDA reactions, offering a convenient and viable approach to meeting the long-standing challenge of asymmetric HDA

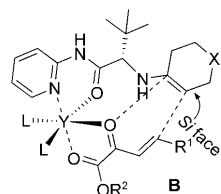


Figure 3. Proposed transition state of the IED/HDA reaction catalyzed by enamine/metal Lewis acid bifunctional catalysts.

reaction of cyclic ketones. The IED/HDA reactions were highly chemo- and enantioselective. It is worth noting that a stereochemically well-controlled quaternary carbon center was formed in this reaction. We believe that the strong activation of the activated enone **3** through chelation to the metal and the intramolecular nature of the bifunctional catalyst contribute to the high activity and stereoselectivity of the HDA reactions. In addition, a new approach has been introduced to the emerging field involving combination of organocatalysis and metal catalysis. In depth investigation and detailed mechanistic study of this reaction is underway. The application of these catalysts in other important organic reactions will be reported in due course.

Experimental Section

General procedure: A mixture of $\text{Y}(\text{OTf})_3$ (16 mg, 0.03 mmol, 15 mol %), ligand **1f** (12.4 mg, 0.06 mmol, 30 mol %), cyclohexanone (0.5 mL), and THF (1.0 mL) was stirred at room temperature for 4 h. The reaction mixture was then cooled to 4 °C. Enone **3** (0.2 mmol) was added. The resulting mixture was stirred at 4 °C until the reaction was complete (monitored by TLC). The reaction mixture was filtered through a short silica gel plug to remove the catalyst. After removal of the solvent, ^1H NMR analysis of the mixture was recorded to determine the chemoselectivity and the diastereoselectivity. The mixture was purified through column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 6:1) to give the pure products.

The *ee* values were determined by HPLC analysis using a chiral stationary phase. Racemic HDA products were prepared under the same conditions using racemic ligand **1a**, which was obtained from racemic valine.

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- [10] The minor diastereomer of the HDA products was identified as an epimer (at C8a) of the *endo* product that resulted from the hydrolysis in the last step (refer to Scheme 1). See the Supporting Information for relevant experiments and NMR spectroscopy.
- [11] The crystal was obtained from the major enantiomer of **4g** (> 99% *ee* after recrystallization). Crystal data for **4g** at 100 K: orthorhombic, space group $P2_12_12_1$; $a = 7.5414(2)$, $b = 9.8212(2)$, $c = 20.9811(4)$ Å; $\alpha = 90.00^\circ$, $\beta = 90.00^\circ$, $\gamma = 90.00^\circ$; $V = 1553.98(6)$ Å³, $Z = 4$, $\mu(\text{CuK}\alpha) = 3.747 \text{ mm}^{-1}$, 10525 reflections (2709 unique) collected with $4.21 < \theta < 67.58^\circ$, $R_{\text{int}} = 0.0314$; $R1 = 0.0339$, $wR2 = 0.0867$ refined on F^2 . CCDC 806477 (**4g**) 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.