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Asymmetric Lewis Acid Catalysis in Water: α-Amino Acids as Effective Ligands in Aqueous Biphasic Catalytic Michael Additions

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This article explores the potential of native α-amino acids as chiral ligands in aqueous asymmetric Lewis acid catalysis, employing the C–C bond forming Michael addition as a model reaction. Some insights are provided regarding the details of $Yb(OTf)_3$/α-amino acid-catalyzed Michael additions in water through new kinetic data as well as studies on how both yield and selectivity are influenced by variations in metal/ligand ratio, pH, temperature, and structure of the α-amino acid. Through this investigation it was found that reaction conditions that require only 5 mol-% of the Lewis acid, provides enantiomeric excesses of up to 79 % and is applicable to a wider range of donors and acceptors than previously demonstrated. Importantly, it was also demonstrated that the α-amino acid complexed ytterbium catalyst might have potential for large-scale applications as it displays not only large ligand accelerations, but also good solubility and stability in water. It can be recycled multiple times without appreciable loss of activity. The result is a promising example of a water-compatible chiral Lewis acid.

Introduction

The use of homogeneous metal-based catalysts to promote chemical reactions in terms of both rate and selectivity is of great importance in organic synthesis. For example, complexation of transition metals with chiral ligands has been a successful strategy to achieve various catalytic enantioselective reactions that have found wide application in fine chemicals production.[1–3] The vast majority of these methods were developed for use under anhydrous conditions because of the notorious lability of organometallics towards water. In recent years, however, the surge of interest in the use of water as an economical and environmentally benign reaction medium for organic reactions[4–8] has called for the development of transition-metal catalysts that display solubility, stability, and efficacy in water. It is clear that for the full potential of water as reaction solvent to be realized aqueous metal catalysts are required that can at least match the efficacy of traditional metal catalysts developed for non-aqueous media. Accordingly, research efforts in this area have intensified in the last decade and some progress has been made. A recent review by Li on C–C bond-forming reactions in aqueous media, many of which are metal-mediated, listed nearly 1000 references.[9]

Lewis acid catalysis is one of the most useful strategies for enhancing the rate and selectivity of a synthetic reaction, so that it may be carried out under milder conditions and with fewer by-products. In addition, the coordination properties of Lewis acidic metals make them suitable for use in asymmetric catalysis through the complexation of chiral, basic ligands to the central metal ion. A significant step forward in the area of aqueous synthesis and catalysis would be the development of Lewis acid catalysts that present high stability, activity, and selectivity in an aqueous environment. However, making the solvent switch to water for Lewis acid catalyzed reactions is a formidable challenge. The first reports on the use of water-compatible Lewis acids, employing lanthanide triflates, were reported by Kobayashi and co-workers in 1991.[10] It is, however, only in the most recent decade that the rational design of water-compatible Lewis acid catalysts has been properly addressed. The seminal work is a paper by Kobayashi and co-workers from 1998 where a large number of metal salts were tested for their efficiency in promoting aqueous aldol reactions.[11] A basic understanding of which characteristics of a metal salt that are important for Lewis acid activity in water, such as having a hydrolysis constant (K_h) within a certain range and a high water-exchange rate constant (WERC), crystallized from this study. The first enantioselective Lewis acid catalyzed reaction in water was disclosed as late as in 1998.[12,13]

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A few years ago, we began an investigation aimed at developing more efficient Lewis acid catalysts for synthesis in water. The aim was to study the influence of various ligands on the catalytic activity of various metal salts in water. While ligand complexation to a Lewis acid metal in organic media is commonly associated with reaction rate deceleration, we reasoned that the aqueous medium might be particularly amenable to ligand-accelerated catalysis.[14] Assuming that tightly coordinated water ligands become more labile upon complexation of an organic ligand, this should lead to a higher rate of exchange with substrate molecules and consequently to higher reaction rates. By the same rationale, ligand complexation in water could also lead to more stable catalysts by reducing the rate of decomposition through hydrolysis. A simple illustration of this concept is outlined in Figure 1. Indeed, positive ligand effects such as increased hydrolytic stability[15] and rate accelerations[16] are commonly noted in papers on aqueous Lewis acid catalysis, although quantitative data have rarely been given.

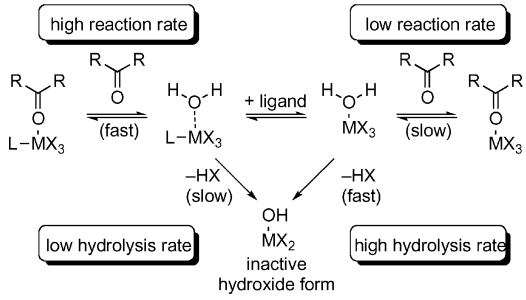


Figure 1. Schematic illustration of the potential influence of a ligand on the activity and hydrolytic stability of a Lewis acidic metal in aqueous media.

As a model reaction for studying ligand effects in water the Michael addition reaction, which is one of the most important carbon–carbon bond-forming reactions in organic synthesis, was chosen. While a great deal of success has been achieved with catalytic Michael additions in organic solvents,[17–19] progress towards efficient Lewis acid catalyzed Michael additions in water has been slow. Until very recently aqueous catalytic Michael additions required long reaction times and a large excess of acceptor in order to get high yields of adduct.[20–23] Recent significant advances have come from Kaneda and co-workers on solid phase Lewis acid catalysis[24] and from our own research. In 2006, we reported our first results on ligand-accelerated aqueous biphasic catalysis of C–C bond forming Michael additions.[25] In this study we screened some metal triflates for their ability to catalyze the Michael addition reaction between ethyl acetoacetate, **1**, and methyl vinyl ketone (MVK) to give **2** using TMEDA as ligand (Scheme 1).

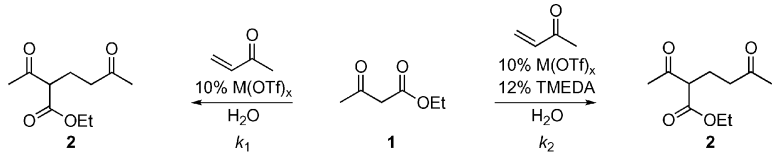
Having established the potential of $Yb(OTf)_3$ in ligand-assisted aqueous Michael additions a study of the effect of α-amino acids as ligands in these reactions were carried out. With respect to their natural abundance and role in biocatalysis, as integral parts of enzymes, the use of native α-amino acids as chiral ligands in catalysis has been relatively little explored.[26] In recent years, α-amino acids have been studied as organocatalysts and applied as such in a variety of reactions in organic as well as aqueous media.[27] On the other hand, we find it surprising that metal-amino acid complexes, although physically well-characterized through a number of studies,[28] have found so little application in the area of organic synthesis. A reason for this may be the limited solubility of such complexes in the organic solvents traditionally used for synthetic applications.

In a recent communication, we disclosed our initial results on the use of α-amino acids as ligands in aqueous biphasic Lewis acid catalyzed Michael additions.[29] Remarkably, in the presence of D-alanine, the second-order rate constant for the ligand-assisted reaction between **1** and MVK was increased by a factor of 138 compared to the ligand-free reaction. That is seven times the ligand effect we observed for the same reaction when TMEDA was used as ligand. It is to the best of our knowledge one of the strongest ligand effects reported for any Lewis acid catalyzed reaction. In addition, the initial enantioselectivities we obtained, albeit modest (up to 53%) were the highest observed for any reaction using natural α-amino acids as Lewis acid ligands in water. Herein we provide further insight into the details of $Yb(OTf)_3$/α-amino acid-catalyzed Michael additions in water through additional kinetic data as well as studies on how both yield and selectivity are influenced by variations in pH, temperature, and type of α-amino acid.

Results and Discussion

Determination of Reaction Order and Rate-Determining Step

We previously established the reaction between **1** and MVK catalyzed by 10 mol-% $Yb(OTf)_3$ and 12 mol-% D-alanine as following typical second-order kinetics for the first 2 h. Thus, we used the initial (2 h) rate constants to determine the rate difference between the ligand-assisted and ligand-free reaction. This was reasonable because after



Ligand effect (k_2/k_1): $Yb(OTf)_3$ = 19.5, $Cu(OTf)_2$ = 3.3, $Sc(OTf)_3$ = 2.4, $Ln(OTf)_3$ = 1.6

Scheme 1. Ligand acceleration in Lewis acid catalyzed aqueous biphasic Michael addition.

2 h we already had 57% conversion of starting material into adduct **2**. In the present study, to determine the reaction order with respect to each of the reactants, we performed the reaction under pseudo-first-order conditions for the nucleophiles, **1**, and MVK. As can be seen in Figure 2, when plotting ln 1/[**1**] or ln 1/[MVK] against the reaction time straight lines typical of first-order rates are obtained.

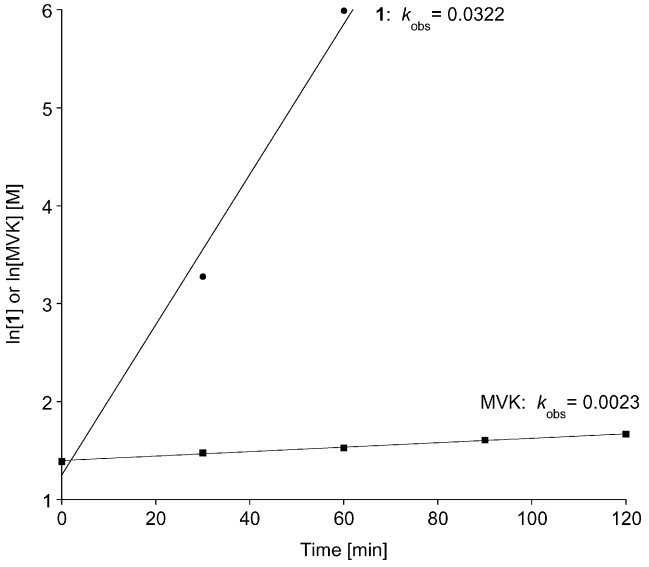
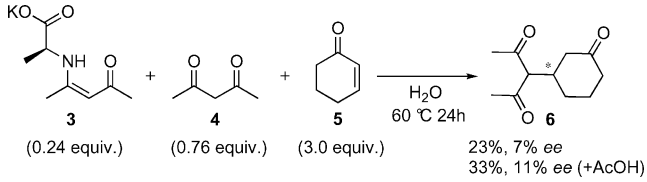


Figure 2. Graph illustrating first-order behavior with respect to both donor and acceptor.

The large difference in observed rates, $k_{obsd.}$[**1**]/$k_{obsd.}$[MVK] = 14, did not allow us to make an unambiguous assignment of these experiments as first order. Being run at the same concentrations we had expected the two experiments to have similar rates if they were of true first order, but a large excess of donor (**1**/MVK, 10:1) had a relatively modest effect on the overall reaction rate, while an excess of acceptor (MVK/**1**, 10:1) had a much greater influence on the reaction rate. When MVK was used in large excess, the first step of the reaction (formation of a metal-diketonato complex) became saturated, meaning that all activated **1** reacted instantly with MVK and the reaction order of **1** went from first order towards zero order. The fact that $k_{obsd.}$[**1**] is much larger than $k_{obsd.}$[MVK] indicates that the rate-limiting step is not formation of the metal-diketonato complex, but the step involving formation of the new C–C bond. Recent mechanistic studies on transition-metal-catalyzed Michael additions of 1,3-dicarbonyl compounds to enones in organic solvents have shown initial reaction rates to be almost independent of the substrate concentrations (zero order in both donor and acceptor).[30] This difference in kinetic behavior between aqueous and organic media may be ascribed to the fact that metal complexes are more labile in water and thus more liable to take part in concentration-dependent equilibria. For example, as shown by Kobayashi,[11] the activation of a carbonyl oxygen by a metal in aqueous media is limited by the concentration-dependent rate of exchange with coordinated water ligands on the metal.

Lewis Acid Catalyzed vs. Organocatalytic Mechanism

Considering recent work on metal-free reactions using amino acids as organocatalysts,[27] any suspicion that an organocatalytic enamine-based mechanism was a major contributor to the results was investigated. To determine this some experiments under "enforced" organocatalytic conditions were performed. Enamine adduct **3** (Dane's salt) of acetylacetone (**4**), and alanine were prepared according to a literature procedure.[31] Subjecting **3** to a reaction with the Michael acceptor 2-cyclohexen-1-one (**5**) (Scheme 2), in the absence or presence of a Brønsted acid, afforded poor yields (23% and 33%) and *ee* values (7% and 11%) of the adduct **6**. These results, together with other supporting observations throughout our studies (see below) made us confident that an organocatalytic enamine mechanism was not significantly involved in our reactions.

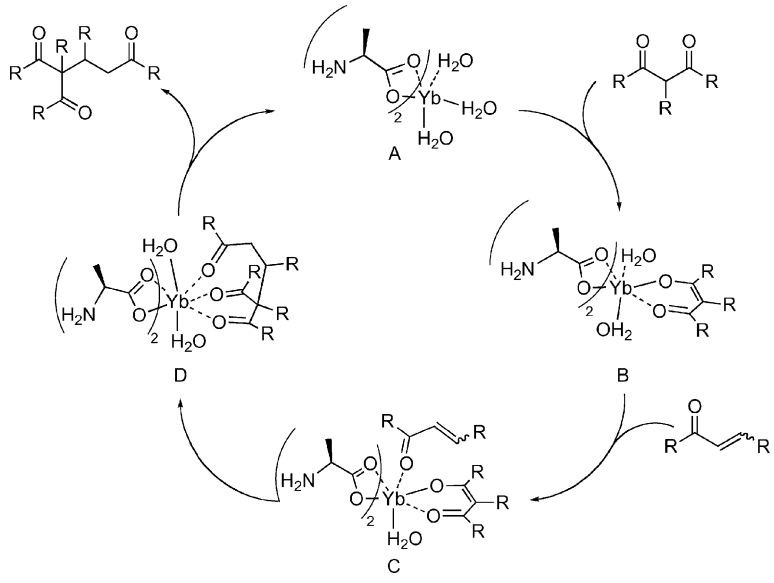


Scheme 2. Aqueous Michael addition under "enforced" organocatalytic conditions.

Proposed Mechanism/Influence of the Basic Amino Group on Rate and Selectivity

To successfully arrive at more efficient reaction conditions an improved understanding of the large ligand effect and the significant level of stereocontrol that we observe was required. On the basis of our own observations and extensive literature precedence,[22,30,32] a tentative mechanism for the reaction (Scheme 3) is proposed. It suggests that when $Yb(OTf)_3$ is dissolved in aqueous medium, water will become the major ligand and the counterion (OTf^-) will exist in solution. Then the deprotonated amino acid first displaces one of the water ligands to give **A**. These types of 1:2 complexes between lanthanides and α-amino acids in water are well studied and have been subjected to extensive review.[28] Upon addition of the reactants another water ligand is displaced by a bidentate β-keto enolate to give complex **B**, which is planar and may be stabilized by π-delocalization. Through ligand exchange with water, the enone will then coordinate to a vacant site on the metal to form the reactive complex **C**. Subsequent bond formation affords the metal-Michael adduct complex, **D**, and finally ligand exchange with a new donor molecule releases the product.

We believe that the origin of the enantioselectivity and the large rate acceleration is the effective coordination of a chiral dibasic ligand (the deprotonated amino acid) to the Lewis acidic metal. It has been shown that negatively charged ligands can significantly enhance the reactivity of a metal bound β-keto enolate towards electrophiles, presumably by weakening the covalent character of its M–O



Scheme 3. Proposed mechanism for the $Yb(OTf)_3$/α-amino acid catalyzed aqueous Michael addition.

bond.[30a] With common counterion ligands (e.g. Cl^-) this leads to fast protonation of the enolate by the acidic reaction mixture and a decrease in reaction rate. In the present system, however, the dibasic character of the α-amino acid ligand may give a kinetic advantage to the reaction between the β-keto enolate and a coordinated electrophilic Michael acceptor. According to this mechanistic proposal, we should find the reaction to be highly sensitive to variations in pH. To obtain support for this hypothesis we performed two lines of experiments. First, we monitored the dependence of enantioselectivity on the pH of the $Yb(OTf)_3$/D-alanine-catalyzed reaction between acetylacetone (**4**), and 2-cyclohexen-1-one (**5**). Second, we varied the pK_a of the amino group by adding one or two *N*-methyl groups to D-alanine and observed the impact of these changes on both yield and *ee* of **6**. In addition, to include an example of a monobasic ligand, an experiment was performed with D-lactic acid in place of D-alanine. We found that when using alanine as ligand, the *ee* of **6** varied significantly with the pH of the catalyst solution, but interestingly the optimal pH range within which to obtain the best enantioselectivity was quite narrow (Figure 3).

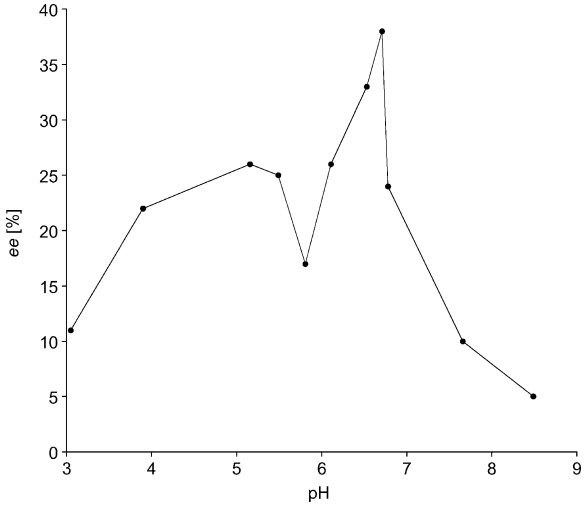
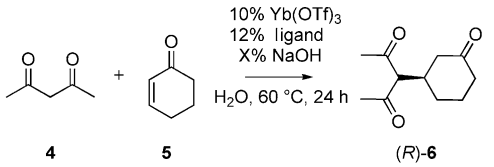


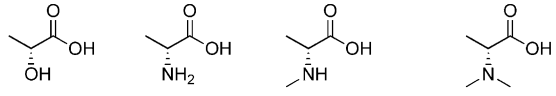
Figure 3. Graph illustrating the observed influence of pH on the enantiomeric excess of Michael adduct (*R*)-**6**.

At pH 6.7, an *ee* of 38% was observed while at pH 6.1 the *ee* dropped to 26% and at pH 5.8 it was only 17%. Above pH 7, the *ee* plunged to low levels (pH 7.7 = 10% *ee*, pH 8.5 = 5% *ee*), most likely due to increased importance of the base-catalyzed pathway that leads to racemic product. The rapid drop in *ee* below pH 4 can be ascribed to increased protonation of the carboxylate ion leading to weaker metal ion complexation. We argue that the optimal pH around 6.7 is high enough for nitrogen–metal coordination to effectively compete with *N*-protonation, but low enough to avoid the non-selective, base-catalyzed pathway. Another prominent feature of the *ee* vs. pH graph in Figure 3 is that two maxima are observed. This suggests a change in the reaction mechanism with a change in pH. The results from the Michael reaction between **4** and **5** with structurally varied ligands are collected in Table 1.

As expected, the reaction with deprotonated lactic acid (Entry 1) afforded a much lower conversion (12%) and *ee* (6%) of **6** than the reference reaction with D-alanine (Entry 2, 93% yield, 57% *ee*), clearly showing the importance of the basic amino group for the rate effects and selectivities observed. Somewhat surprisingly, however, the reactions with the ligands *N*-methyl-D-alanine (Entry 3), or *N*,*N*-dimethyl-D-alanine (Entry 4), also led to much lower yields (20% and 18%, respectively) and *ee* values (19% and 5%, respectively). This indicated that, while the basicity of the amino group is important, making the nitrogen too basic might have a negative influence on both rate and selectivity.

Table 1. Effects of varying the structure of the chiral ligand.





Entry	Ligand	Yield (%)[a]	*ee* (%)[b]
		1 equiv. NaOH	
1	D-lactic acid	12	6
2	D-alanine	93	57
3	*N*-methyl-D-alanine	20	19
4	*N*,*N*-dimethyl-D-alanine	18	5
		pH-control (6.70)	
5	D-alanine	93	57
6	*N*-methyl-D-alanine	25	21
7	*N*,*N*-dimethyl-D-alanine	31	25

[a] Not isolated. Determined by NMR spectroscopy. [b] Determined by chiral HPLC.

In an attempt to evaluate the steric influence of the extra *N*-methyl groups on rates and selectivities, we performed additional experiments where the pH was adjusted (pH = 6.70) to compensate for differences in the p*K*a of the amino groups (Entries 6 and 7). Slightly higher yields (25% and 31% for *N*-methyl- and *N*,*N*-dimethyl-D-alanine, respectively) were observed compared to the reactions without pH-adjustment. The *ee* values also increased after adjusting the pH to 6.70. As expected, the effect was significantly larger with *N*,*N*-dimethyl-D-alanine. The results obtained after pH-adjustment suggested that the electronic influence of the basic nitrogen was largely offset by steric effects imposed by the methyl groups.

Effect of Ligand/Metal Ratio on Yield and Enantioselectivity

In order to get a clearer picture of how yields and selectivities were influenced by variations in ligand/metal ratio, we performed the reaction between **4** and **5** with varying amounts of L-alanine and $Yb(OTf)_3$. Because there is a good correlation between yield and conversion, the latter was used to analyze the reactions. First, we ran the reactions with 2–30 mol-% of L-alanine while keeping the amount of $Yb(OTf)_3$ constant at 10 mol-%. These results are illustrated in Figure 4. As can be seen, the conversion of the Michael adduct **6** increases steadily up to a ligand/metal ratio of about 2.4, after which the yield is not improved much and even falls again at a ligand/metal ratio of 3.0. The trend for the enantiomeric excess follows the trend in yield up to a ligand/metal ratio of 1.2.

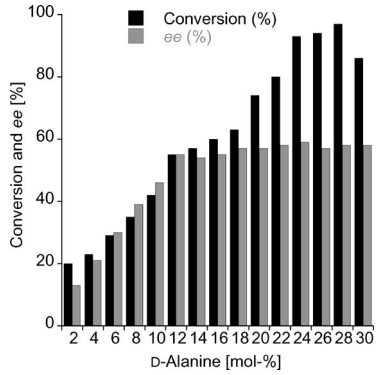


Figure 4. Graph demonstrating the influence of ligand concentration on yield and *ee* with 10 mol-% $Yb(OTf)_3$. Reactions were performed at 60 °C for 18 h with **4** (1 mmol), **5** (3 mmol), D-alanine (0.02–0.30 mmol) and $Yb(OTf)_3$ (0.10 mol) in water (1 mL) at pH 6.70.

No significant changes in enantioselectivities were observed in the reactions with higher ligand/metal ratios. As one of our goals of the present investigation was to significantly reduce the amount of Lewis acid required, we continued by studying the reaction between **4** and **5** in the presence of only 5 mol-% of $Yb(OTf)_3$ and 12 mol-% ligand (Table 2).

Table 2. Influence of metal/ligand ratio on yield and *ee* in the reaction between **4** and **5** to give (*R*)-**6**.[a]

Entry	$Yb(OTf)_3$ [mol-%]	D-Ala [mol-%]	*T* [°C]	Yield[b] [%]	*ee*[c] [%]
1	10	12	60	93	57
2	5	12	60	46	57
3	5	10	70	98	60
4	5	11	70	97	63
5	5	12	70	100	63
6	5	13	70	100	63
7	5	14	70	100	64
8	5	15	70	100	64

[a] All reactions were run twice and listed values are averages. Reactions were performed with **4** (1 mmol), **5** (3 mmol), in water (1 mL) at pH 6.70 for 18 h. [b] Not isolated. Determined by NMR spectroscopy. [c] Determined by chiral HPLC.

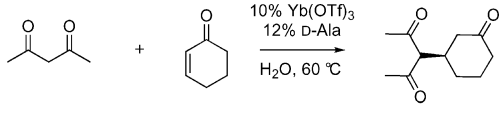
Initially, we found that there was a significant drop in yield from 93% to 46% upon reducing the loading of Lewis acid from 10 mol-% to 5 mol-% (Entries 1 and 2). The enantioselectivity, however, did not change. In order to compensate for the reduced yield we increased the reaction temperature to 70 °C. Gratifyingly, under otherwise identical conditions, we now observed quantitative conversion of **4** into **6** (Entry 5). Then, by varying the amount of ligand from 10–15 mol-% (ligand/metal ratio 2–3, Entries 3–8) we were able to confirm that a ligand/metal ratio of 2.4 that we had arrived at earlier (see above) was optimal in the range studied. Higher ratios did not give any significant improvement (Entries 6–8). The ratio may be explained due

to the dynamic character of the catalytic process i.e. the excess of ligand is necessary to keep the system saturated and thus more efficient. Interestingly, slightly higher *ee* values were obtained in the reactions run at 70 °C than in the reactions run at 60 °C. This unusual reversed temperature effect will be addressed further below.

Effect of the Reaction Temperature on Yield and Selectivity

In order to investigate how the *ee* values and yields were changed with reaction time, eight Lewis acid catalyzed reactions between **4** and **5** were performed (Table 3).

Table 3. Investigation of *ee* values and yields with reaction time of the $Yb(OTf)_3$/D-alanine-catalyzed reaction between **4** and **5**.[a]



4 **5** (*R*)-**6**

Time [h]	Yield (%)	*ee* (%)
1	8	47
2	14	49
4	23	47
8	30	51
12	40	45
16	52	50
20	67	49
24	92	52

[a] All experiments were performed twice and reported values are averages.

The data in Table 3 demonstrates that the enantiomeric excesses were not changed to any larger extent during the reaction. Even after 1 h when only 8% conversion was achieved the *ee* was 47% compared to 52% *ee* after 24 h and almost complete conversion (92%). This confirmed that the enantiomeric excess was obtained immediately and no racemization occurred during the reaction.

Influence of Various α-Amino Acids on Yield and Enantioselectivity

While we have previously screened a number of α-amino acids for their ability to induce asymmetry in the studied reaction, these first experiments used 20 mol-% $Yb(OTf)_3$ and 24 mol-% of amino acid.[12] In our current investigation we decided to screen a much wider selection of α-amino acids for their efficacy as chiral ligands, and to employ our optimized catalytic conditions 5 mol-% $Yb(OTf)_3$ and 12 mol-% α-amino acid.

The results are collected in Table 4. Gratifyingly, out of 17 reactions only two, those with threonine and cysteine, afforded yields (36% and 24%, respectively, Entries 11 and 13) that were lower than observed in the reaction with alanine (46%, Entry 1). Two of the reactions, using tryptophan and histidine, even gave complete conversion of starting material into adduct (Entries 6 and 17).

Table 4. Influence of α-amino acid structure and temperature on enantioselectivity in the Michael addition reaction between **4** and **5**.[a]

Entry	Amino acid	Yield (%)[b]	*ee* (%, *S*)[c]
1	D-Ala	46	57 (*R*)
2	L-Val	72	63
3	L-Ile	78	61
4	L-Phe	97	50
5	D-Pro	60	70 (*R*)
6	L-Trp	100	56
7	L-Met	96	43
		average: 78	average: 57
8	L-Gln	67	49
9	L-Ser	53	46
10	L-Asn	79	35
11	L-Cys	24	24
12	L-Tyr	46	39
13	L-Thr	36	17
		average: 51	average: 35
14	L-Asp	61	8
15	L-Glu	83	14
		average: 72	average: 11
16	L-Lys	94	27
17	L-His	100	20
		average: 97	average: 24

[a] All reactions were run at least twice and listed values are averages. Reactions were performed at 60 °C for 24 h with **4** (1 mmol), **5** (3 mmol), amino acid (0.12 mmol) and $Yb(OTf)_3$ (0.05 mol) in water (1 mL) at pH 6.70. [b] Not isolated. Determined by NMR spectroscopy. [c] Determined by chiral HPLC.

Somewhat surprisingly, considering that alanine is the sterically least demanding of all the chiral α-amino acids, only three α-amino acids were able to induce a higher *ee* than alanine in this reaction, namely valine (63%, Entry 2), isoleucine (61%, Entry 3) and proline (70%, Entry 5). Unfortunately, none of these also provided high conversion. It is important to note that in this study, the use of L-amino acids exclusively led to (*S*)-**6** and that the use of D-amino acids afforded the enantiomeric (*R*)-**6**. While the yields and selectivities observed in this study vary significantly among all of the ligands tested, it is very interesting to note that if the α-amino acids are listed according to the character of their side-chain, one finds distinct groupings in terms of yields and *ee* values. As for the yields, the following ranking of side-chain character is observed, with average yields for the groups in parenthesis: basic (97%)>non-polar (78%)>acidic (72%)>polar (51%). In terms of enantioselectivities, the order is different (average *ee* in parenthesis): non-polar (57%) > polar (35%) > basic (>24%) acidic (11%) side-chains. Correlating α-amino acid structure with reactivity/selectivity of the catalyst will be important in the design of synthetic amino acid derivatives with optimized ligand properties.

Influence of Temperature on Enantioselectivity

That the enantioselectivity so clearly changes with the polarity of the amino acid side-chain serves as an indication that solvation effects are important in the enantiodifferentiating step of the reaction. If this is true, the Gibbs acti-

vation energy for this step is expected to have a large entropic contribution because solvation effects are usually considered to be entropy-driven.[33] To find support for this, we returned to the discovery that the enantioselectivity increases with temperature. Reversed temperature effects in enantioselective reactions, while unusual, are not entirely unknown, and have been explained by analyzing the enthalpy and entropy factors of the reaction [Equation (1)].[34–37] Given that the observed effects are linear, the differential Eyring equation [Equation (2)] can be used to obtain the differential activation enthalpy ($\Delta\Delta H^{\ddagger}_{R-S}$) and entropy ($\Delta\Delta S^{\ddagger}_{R-S}$) values.[38]

$$\ln(k_R/k_S) = \ln[(100 + \%\ ee)/(100 - \%\ ee)] \quad (1)$$

$$\ln(k_R/k_S) = \Delta\Delta S^{\ddagger}_{R-S}/R - \Delta\Delta H^{\ddagger}_{R-S}/\text{r.t.} \quad (2)$$

Figure 5 shows the Eyring plot, i.e., the temperature effect on enantioselectivity, for the 5 mol-% $Yb(OTf)_3$/12 mol-% D-alanine-catalyzed reaction between **4** and **5**. As can be seen, the *ee* increases in a linear fashion from 25% *ee* at 30 °C up to 67% *ee* at 90 °C, a difference of 42% *ee*!

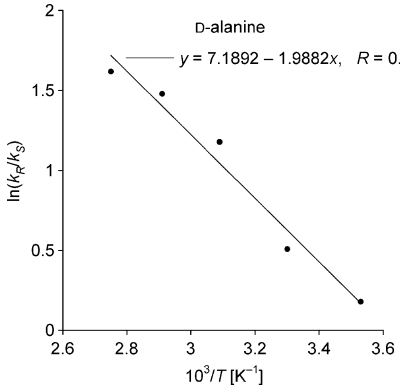


Figure 5. Eyring-plot for the $Yb(OTf)_3$/D-alanine-catalyzed Michael reaction between **4** and **5**.

Considering the known susceptibility of many Lewis acidic transition metals to hydrolysis in water, it is an unexpected, and quite remarkable, observation that the optimal reaction temperature for a Lewis acid catalyzed reaction in water is close to the boiling point of water! Using the data shown in Figure 5 it was then possible to extract the differential activation enthalpy ($\Delta\Delta H^{\ddagger}_{R-S}$) and entropy ($\Delta\Delta S^{\ddagger}_{R-S}$) values from Equation (2). Not surprisingly, we found a large entropy contribution ($\Delta\Delta S^{\ddagger}_{R-S}$ = 59.7 $J\,K^{-1}\,mol^{-1}$) to the differential Gibbs energy of activation, which serves to explain the selectivity enhancement with increasing temperature. The differential enthalpy term was found to be of the same sign ($\Delta\Delta H^{\ddagger}_{R-S}$ = 16.5 $kJ\,mol^{-1}$). These data provided some preliminary insight into the origin of the relationship between enantioselectivity and reaction temperature. Because a linear relationship was found over the temperature range studied, the enantioselectivities observed are likely the results of a single enantiodifferentiating mechanism. Assuming that the two reaction pathways leading to the two possible enantiomers proceed through the same type of reaction mechanism, our data show that the diastereomeric transition state that leads to the major enantiomer has a lower Gibbs' free energy of activation because of an unusually large entropic factor. This indicates that a difference in solvation of the diastereomeric transition states is a crucial factor in determining the stereoselectivity of this reaction. Further investigation of the reversed temperature effect will be reported in due course.

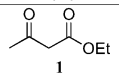
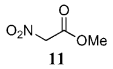
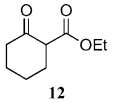
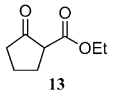
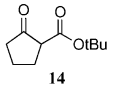
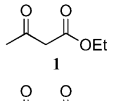
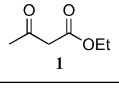
Drawing from the positive results obtained by increasing the temperature in the reaction using L-alanine as ligand, we then proceeded to test the reaction with D-proline as ligand at 90 °C as that had provided the highest *ee* (70%) at 60 °C. Fortunately, again a significant temperature effect was observed and (*R*)-**6** was obtained in quantitative yield and 79% *ee* after 10 h at 90 °C. As far as we know, this is the highest *ee* value reported for a metal-catalyzed synthetic reaction that uses a native α-amino acid as ligand. As expected for enantiomeric ligands of equal optical purity, replacing D-proline with L-proline afforded the opposite enantiomer (*S*)-**6** with the same *ee* (79%).

$Yb(OTf)_3$/L-Proline as Catalyst in Aqueous Michael Addition Reactions Between Various Donors and Acceptors

Having arrived at the conclusion that a combination of 5 mol-% $Yb(OTf)_3$ and 12 mol-% L-proline provides both high yield and enantioselectivity, we proceeded to apply these conditions in reactions between various donors and acceptors. These results are listed in Table 5. Michael acceptors with 1,2-substituted double bonds are more challenging acceptors than 1,1- or 1-substituted acceptors. Until our recent discovery of the $Yb(OTf)_3$/amino acid catalysts no examples of this type had been reported using homogeneous Lewis acid catalysis in water. Under the present conditions mostly good yields were obtained with such acceptors in acceptable reaction times. We were also able to decrease the amount of acceptor needed. 1.1 Equivalents were sufficient although the reaction is faster with 3 equiv. of the acceptor. This was also evidenced in the kinetic studies. In the reaction between ethyl acetoacetate (**1**), and 2-cyclohexen-1-one (**5**), an isolated yield of 77% of the expected adduct with an *ee* of 71% was obtained after 12 h (Entry 1). Higher yields may be obtained if the reaction times are extended, such as in the addition of acetylacetone (**4**) to **5**, which provided the Michael adduct in both high yield (94%) and *ee* (79%) (Entry 2). The addition of acetylacetone to 2-cyclopenten-1-one (**7**), gave a moderate yield (61%) and *ee* (49%) (Entry 3).

Benzalacetone (**8**), is a synthetically useful, but less reactive Michael acceptor. Under optimized conditions it underwent a slow Michael addition with acetylacetone to afford the corresponding adduct in 70% yield and 19% *ee* after 24 h, along with recovered starting material (Entry 4). Nitroalkenes may also act as acceptors. β-Nitrostyrene (**9**), reacted with acetylacetone to afford the Michael product in 29% isolated yield, and a similar *ee* (17%) as the adduct with benzalacetone (Entry 5). The low yield was explained

Table 5. Aqueous biphasic Michael additions catalyzed by Yb(OTf)$_3$/L-Pro.[a]

Entry	Donor	Acceptor	Time (h)	Yield(%)[b]	*ee* (%)[c]
1	 **1**	 **5**	12	77	70
2	 **4**	 **5**	21	94	79
3	 **4**	 **7**	21	61	49
4	 **4**	 **8**	24	70	19
5	 **4**	 **9**	14	29[d]	17
6	 **10**	 **5**	14	74	<10[e]
7[f]	 **11**		4	87	59
8[f]	 **12**		6	95	<5
9[f]	 **13**		5	99	<5
10[g]	 **14**		10	84	<5
11[h]	 **1**	 **15**	24	0	0
12[h]	 **1**	 **16**	24	0	0

[a] Conditions: 1 mmol donor, 1.1 mmol acceptor, 0.05 mmol Yb(OTf)$_3$, 0.12 mmol L-proline, 0.12 mmol NaOH, 1 mL of water, 90 °C. All experiments were run at least twice and listed yields and *ee* values are averages. [b] Isolated yields after flash column chromatography. [c] Determined by chiral HPLC except Entry 8 and 9, which were determined by chiral GC. [d] Low yield because the addition product undergoes further reactions. [e] An exact value could not be obtained because of overlapping peaks. [f] Run as for [a] but with at 60 °C. [g] Run as for [a] but with 3.0 mmol acceptor. [h] Conditions: 1 mmol donor, 3.0 mmol acceptor, 0.20 mmol Yb(OTf)$_3$, 0.24 mmol L-alanine, 0.24 mmol NaOH, 1 mL of water, 90 °C.

by the initial adduct undergoing further reactions. In this study we also found that the scope of donors can be expanded beyond the typical 1,3-dicarbonyl donors, which significantly increases the synthetic potential. First, the structurally rigid donor **10** undergoes addition to **5** in a 74% yield (Entry 6). Obviously, because of its geometry this donor cannot coordinate both of its carbonyl oxygen atoms to the metal simultaneously, which may serve to explain the low *ee* observed (<10%). As an example of a reaction with a non-1,3-dicarbonyl donor, methyl nitroacetate (**11**), adds efficiently to MVK in 87% yield and 59% *ee* after only 4 h at 60 °C (Entry 7).[22] This could be a useful Entry into α-alkylated amino acids and other nitrogen containing compounds. In the reactions between MVK and the five- and six-membered cyclic donors **12** and **13** relatively short reaction times at 60 °C were required to obtain excellent isolated yields (95 and 99%, respectively, Entries 8 and 9). Unfortunately, and somewhat surprisingly, we obtained both of these products in racemic or near-racemic form (<5% *ee*). It has been reported that some quaternary carbon centers formed by Michael addition of dicarbonyls may be susceptible to racemization.[39] To examine whether the lack of enantioselectivity in this reaction was due to racemization after initial asymmetric induction by the chiral catalyst, we performed the addition between **13** and MVK using another procedure known to be enantioselective.[40]

The isolated enantiomerically enriched addition product was then subjected to prolonged heating (18 h, 90 °C) in the presence of 5 mol-% Yb(OTf)$_3$ and 12 mol-% L-proline. No significant racemization was observed, which demonstrated that the addition product was stable under the present conditions and that the low *ee* was likely a direct result of low asymmetric induction in the reaction. In opposite to the previous examples (except Entry 7) the stereogenic center is created in the donor in these cases. In contrast to these results, Kobayashi have previously reported asymmetric Ag^{I}-catalyzed Michael additions in water using similar donors.[41] They highlighted the importance of the structure of the ester moiety for achieving high *ee*. In the reaction between the *tert*-butyl ester derivative **14** and MVK they had obtained as high as 83% *ee*. To see if a change in the ester structure would have a beneficial effect on *ee* with our catalyst, we subjected **14** to our catalytic conditions. Unfortunately, no significant *ee* was observed (Entry 10). At this point we have no further explanation to the lack of asymmetric induction with the Yb(OTf)$_3$/L-proline catalyst in these reactions. Last to be examined were some more sterically demanding acceptors. As seen in Table 5 (Entry 11 and 12) neither mesityl oxide (**15**), nor 3-methyl-2-cyclohexen-1-one (**16**), underwent any reaction, not even under enforced conditions. High temperature and high catalyst loading together with prolonged reaction times gave no conversion of the starting material. By using basic conditions these substrates undergoes Michael reactions smoothly. Obviously the explanation should be sought in the mechanism. In our proposed mechanism both acceptor and donor are coordinated to the same metal center and if the donor is di-substituted at the 3-position this may create a steric hindrance that prevent the bond-forming step.

Stability and Leaching of the Aqueous Yb(OTf)$_3$/L-Proline Catalyst

As demonstrated in preliminary communication, the aqueous phase containing the Yb(OTf)$_3$/amino acid complex can be recycled a number of times without appreciable loss of activity. In other words, it appears as if the ligand stabilizes the complex towards hydrolytic decomposition

into catalytically inactive and water-insoluble ytterbium hydroxide. These characteristics are highly desirable, if not required, for aqueous biphasic catalysis to become more generally useful in a large-scale applications. In order to quantify these practically useful ligand effects, we performed some simple but clarifying experiments. First, an aqueous catalytic solution of 5 mol-% $Yb(OTf)_3$ and 12 mol-% L-proline was prepared, but rather than immediately adding the reactants to the mixture, the catalyst solution was set aside at room temperature for 7 d. After this time, visual inspection of the solution did not reveal any precipitation of water-insoluble ytterbium hydroxide. The reactants (**4** and **5**) were then added and the reaction was performed as before. Quite remarkably, the yield and enantiomeric excess of **6** was identical compared to the experiment where the reactants were added to the reaction immediately after mixing $Yb(OTf)_3$ and L-proline. Second, an aqueous solution of $Yb(OTf)_3$ without amino acid was prepared for direct comparison. After 7 d at room temperature a significant amount of precipitation was formed, which upon quantification revealed that at least 30% of the original $Yb(OTf)_3$ had been converted into insoluble and catalytically inactive ytterbium hydroxide. This is compelling evidence of the stabilizing influence of the α-amino acid ligand on the Lewis acid. The $Yb(OTf)_3$ solutions in the presence and absence of ligand are pictured in Figure 6.

Figure 6. Aqueous solutions of $Yb(OTf)_3$ without added ligand (left tube) and with added L-proline (right tube).

Finally, we were interested in determining the extent of metal leaching in these reactions. The fact that we were able to recycle the aqueous catalytic phase multiple times without any observable decrease in activity suggested that no major decomposition of the metal catalyst was taking place between cycles. In order to quantify the amount of metal leaching from the aqueous phase, we performed the reaction between **12** and MVK with 1 gram of donor and analyzed the organic product phase for inorganic residues. It was found that the product phase, which spontaneously separated from the aqueous phase upon termination of stirring and after cooling, contained as little as 0.2% inorganic residues. This result indicated that the aqueous catalytic phase, in theory, can be recycled tens of times without serious loss of activity.

Conclusions

In the present work, we have been able to further evaluate the potential of ligand-assisted Lewis acid catalysis in water through an elaborate study on the use of α-amino acids as ligands in $Yb(OTf)_3$-catalyzed aqueous biphasic Michael addition reactions. Several developments and discoveries were made during the course of our study.

Through an extensive series of experiments involving optimization of metal/ligand ratios and reaction temperature we were able to reduce the amount of $Yb(OTf)_3$ used from our original 10–20 mol-% to only 5 mol-%. The rate-accelerating effect on $Yb(OTf)_3$-catalyzed Michael additions initially observed with alanine was shown to be a general effect associated with α-amino acids as it was found also with all of the other 16 α-amino acids tested in this study, albeit to varying degrees. After screening a range of α-amino acids we were able to relate the structure of a ligand to its influence on activity and selectivity. Some further insight into the ligand effects on rate and selectivity through studies of the influence of pH and temperature on the reactions was obtained. An unexpected discovery from this study was the large increase in enantioselectivity with increasing temperature. An Eyring plot showed that the unusual effect displays a linear behavior in the temperature range between 10–90 °C. Calculation of the differential activation enthalpy and entropy for this reaction revealed a large entropic contribution to the overall Gibbs energy of activation for the enantiodifferentiating step. This result, in combination with the large dependence of yields and selectivities on the polarity of the amino acid side-chain, suggests a very strong influence of solvation effects in determining the outcome of these reactions. From a practical point of view we developed a process, which is faster, more general, and require less amounts of reactants and catalyst than previously reported.[22,23] Although, the reactions in this article are performed in a small scale including extractive work-up and chromatographic purification there is a potential to avoid these techniques when applied at larger scale. The work presented herein is an example of the academic relevance in exploring water as a reaction medium as its distinctive and unique solvent properties may lead to the discovery of new types of reactions and thus to expand the scope of organic synthesis. Our search for better enantioselectivities and applications will be reported in due course.

Experimental Section

General Experimental Details: Deionized water was used in all reactions. All reagents and ligands are commercially available compounds, or simple derivatives thereof, and used as received from the supplier. Conversions were determined by ^1H NMR at 400 MHz in $CDCl_3$ or [D_6]acetone. Enantiomeric excesses were determined by HPLC with chiral column Chiralpak AD-H, *n*-hexane/2-propanol unless otherwise stated. Purification of products was performed by flash column chromatography on normal phase silica gel, 35–70 μ, 60 Å. All products are known compounds and gave consistent ^1H and ^{13}C NMR spectroscopic data. For documentation of purity

a ^{1}H NMR spectrum for each of the products is included in the Supporting Information

Determination of Reaction Order in Acceptor and Donor: See Figure 2. NaOH (0.06 M, 0.12 equiv.) was added to a mixture of D-alanine (5.3 mg, 0.06 mmol) in a Radley tube and the mixture was stirred for 15 min at room temperature and then ytterbium trifluoromethanesulfonate (31.0 mg, 0.05 mmol) was added. Ethyl acetoacetate (63 μL, 0.5 mmol) and methyl vinyl ketone (406 μL, 5.0 mmol) were then added. The reaction tubes were capped and the reaction mixtures were stirred vigorously for 30, 60, 90 and 120 min, respectively at 25 ±0.5 °C. The reaction mixture was then diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude mixture was analyzed by ^{1}H NMR ([D$_6$]acetone), which afforded the ratios of **1** to ethyl 2-ethanoyl-5-oxohexanoate (**2**). $\mathbf{1}_0$ = 100%, ln[**1**]$_0$ = 1.39, $\mathbf{1}_{30}$ = 15%, ln[**1**]$_{30}$ = 3.28, $\mathbf{1}_{60}$ = 1%, ln[**1**]$_{60}$ = 5.99, $\mathbf{1}_{90}$ = 0%, $\mathbf{1}_{120}$ = 0%. The rate constant for MVK was obtained in an identical way by using ethyl acetoacetate (633 μL, 5.0 mmol) and methyl vinyl ketone (40 μL, 0.5 mmol). The crude mixture was analyzed by ^{1}H NMR ([D$_6$]acetone), which afforded the ratios of MVK to ethyl 2-ethanoyl-5-oxohexanoate 2. MVK_0 = 100%, ln[MVK]$_0$ = 1.39, MVK_{30} = 91%, ln[MVK]$_{30}$ = 1.48, MVK_{60} = 87%, ln[MVK]$_{60}$ = 1.53, MVK_{90} = 80%, ln[MVK]$_{90}$ = 1.61, MVK_{120} = 75%, ln[MVK]$_{90}$ = 1.67. When plotting ln[1] and ln[MVK] against time, a straight line, typical for a first-order reaction, is obtained.

Reaction Under "Enforced" Organocatalytic Conditions: See Scheme 2.

3-(3-Oxocyclohexyl)pentane-2,4-dione (6): A) Without Acetic Acid: Compound **3**[36] (50.2 mg, 0.24 mmol) was stirred in H_2O (1 mL) and then acetylacetone (78 μL, 0.76 mmol) and 2-cyclohexene-1-one (291 μL, 3.0 mmol) were added. The reaction mixture was stirred vigorously for 24 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude mixture was analyzed for conversion by ^{1}H NMR ($CDCl_3$) and for enantiomeric excess by chiral HPLC (2-propanol/hexane, 1:6.5), which afforded 23% conversion and 7% *ee* (*S*). **B) With Acetic Acid:** Compound **3**[28] (50.2 mg, 0.24 mmol) was stirred in H_2O (1 mL) and then acetic acid (19.5 μL, 0.34 mmol), acetylacetone (78 μL, 0.76 mmol) and 2-cyclohexene-1-one (291 μL, 3.0 mmol) were added. The reaction mixture was stirred vigorously for 24 h at 60 °C. The reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude mixture was analyzed for conversion by ^{1}H NMR ($CDCl_3$) and for enantiomeric excess by chiral HPLC (*n*-hexane/2-propanol, 6.5:1), which afforded 33% conversion and 11% *ee* (*S*).

Influence of pH on Enantioselectivity: See Figure 3. Deionized water (2 mL) was added to a mixture of amino acid (0.24 mmol) and ytterbium trifluoromethanesulfonate (0.20 mmol). The reaction mixtures were stirred in Radley tubes for 15 min at room temperature. The pH of the solutions was measured to 5.16 and one tube was kept at this pH. The pH of the other ten tubes was adjusted by either adding HCl (1.0 M) or NaOH (0.2 M) giving pH 3.05, 3.9, 5.49, 5.81, 6.11, 6.53, 6.71, 6.78, 7.66 and 8.49. Acetylacetone (1 mmol) and 2-cyclohexen-1-one (3 mmol) were then added. The reaction tubes were capped, and the mixtures were stirred vigorously at 40 °C for 22 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The enantiomeric excess of the crude product was determined by chiral HPLC (*n*-hexane/2-propanol, 87:13).

Michael Addition with D-Lactic Acid and *N*-Mono- and: *N*,*N*-Dimethylated Alanine as Ligands: See Table 1. **a) No pH Adjustment:** The ligand (0.12 mmol) was stirred in NaOH (0.2 M, 0.12 equiv.) in a Radley tube for 15 min at room temperature and then ytterbium trifluoromethanesulfonate (0.10 mmol) was added. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tube was capped, and the mixture was stirred vigorously at 60 °C for 24 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (6 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The conversion and enantiomeric excess of the crude product were determined by ^{1}H NMR ($CDCl_3$) and chiral HPLC (*n*-hexane/2-propanol, 87:13), respectively. **b) With pH Adjustment:** These experiments were performed in an identical fashion except the pH was adjusted to 6.70 before addition of the reactants.

Influence of Metal/Ligand Ratio on Yield and *ee*: See Table 2. To a mixture of D-alanine (0.10 mmol–0.15 mmol) and ytterbium trifluoromethanesulfonate (0.05 or 0.10 mmol) in deionized water (1.0 mL) was added NaOH (0.2 M) until the solution reached pH 6.70. The reaction mixtures were stirred in Radley tubes at room temperature for 15 min. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tubes were capped, and the mixtures were stirred vigorously at 60 °C or 70 °C for 18 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (6 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The conversion and enantiomeric excess of the crude product were determined by ^{1}H NMR ($CDCl_3$) and chiral HPLC (*n*-hexane/2-propanol, 87:13), respectively.

Change in *ee* Values and Yields with Reaction Time: See Table 3. NaOH (0.2 M) was added to a mixture of D-alanine (0.12 mmol) and ytterbium trifluoromethanesulfonate (0.05 mmol) in deionized water (1.0 mL) until the solution reached pH 6.70. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tube was capped and the reaction was stirred vigorously for 1–24 h at 60 °C. The reaction mixture was then diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The conversion and enantiomeric excess of the crude product were determined by ^{1}H NMR ($CDCl_3$) and chiral HPLC (*n*-hexanes/2-propanol, 87:13), respectively.

Procedure for Screening Ligand/Metal Ratios: See Figure 4. NaOH (0.2 M) was added to a mixture of D-alanine (0.02 mmol–0.30 mmol) and ytterbium trifluoromethanesulfonate (0.10 mmol) in deionized water (1.0 mL) until the solution reached pH 6.70. The reaction mixtures were stirred in Radley tubes at room temperature for 15 min. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tubes were capped, and the mixtures were stirred vigorously at 60 °C for 18 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (6 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The conversion and enantiomeric excess of the crude product were determined by ^{1}H NMR ($CDCl_3$) and chiral HPLC (*n*-hexane/2-propanol, 87:13), respectively.

Yb(OTf)$_3$-Catalyzed Michael Additions Using Various Amino Acids as Ligands: See Table 4. NaOH (0.2 M) was added to a mixture of amino acid (0.12 mmol) and ytterbium trifluoromethanesulfonate

(0.05 mmol) in deionized water (1.0 mL) until the solution reached pH 6.70. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tube was capped and the reaction was stirred vigorously for 24 h at 60 °C or for 10 h at 90 °C. The reaction mixture was then diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)-pentane-2,4-dione. The conversion and enantiomeric excess of the crude product were determined by ^1H NMR ($CDCl_3$) and chiral HPLC (*n*-hexanes/2-propanol, 87:13), respectively.

Procedure for the "Eyring Plot Reactions": See Figure 5. NaOH (0.2 M) was added to a mixture of amino acid (0.12 mmol) and ytterbium trifluoromethanesulfonate (0.05 mmol) in deionized water (1.0 mL) until the solution reached pH 6.70. Acetylacetone (1.0 mmol) and 2-cyclohexen-1-one (3.0 mmol) were then added. The reaction tube was capped and the reaction was stirred vigorously for 24 h at 30 °C, 50 °C, 70 °C or 90 °C. The reaction mixture was then diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated to give 3-(3-oxocyclohexyl)pentane-2,4-dione. The enantiomeric excess of the crude product was determined by chiral HPLC (*n*-hexane/2-propanol, 87:13).

Details for Michael Reactions Between Various Donors and Acceptors: See Table 5.

General Procedure: L-proline (0.12 mmol) was stirred in NaOH (0.030 M, 1 mL) in a Radley tube for 15 min at room temperature and then ytterbium trifluoromethanesulfonate (0.05 mmol) was added. Donor (1.0 mmol) and acceptor (1.1 mmol) were then added. The reaction tube was capped, and the mixture was stirred vigorously at 60 °C or 90 °C for 4 h to 24 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (6 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. Flash column chromatography of the residue on silica gel afforded the Michael adduct. The enantiomeric excess was determined by chiral HPLC (*n*-hexane/2-propanol, 87:13).

Ethyl (*S*)-3-Oxo-2-(3-oxocyclohexyl)butanoate: See Table 5, Entry 1.[42] Following the general procedure, ethyl acetoacetone (127 μL, 1.0 mmol) and 2-cyclohexen-1-one (106 μL, 1.1 mmol) were reacted at 90 °C for 12 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 2:1 + 2% triethylamine) afforded the product (174 mg, 77%, 70% *ee*).

(*S*)-3-(3-Oxocyclohexyl)pentane-2,4-dione: See Table 5, Entry 2.[43] Following the general procedure, acetylacetone (103 μL, 1.0 mmol) and 2-cyclohexen-1-one (106 μL, 1.1 mmol) were reacted at 90 °C for 21 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 2:1 + 2% triethylamine) afforded the product (184 mg, 94%, 79% *ee*).

(*S*)-3-(3-Oxocyclopentyl)pentane-2,4-dione: See Table 5, Entry 3.[44] Following the general procedure, acetylacetone (103 mL, 1.0 mmol) and 2-cyclopenten-1-one (92 μL, 1.1 mmol) were reacted at 90 °C for 21 h. Flash chromatography on silica gel (*n*-hexane/ethyl acetate, 3:2 + 2% triethylamine) afforded the product (111 mg, 61%, 49% *ee*).

3-Acetyl-4-phenylheptane-2,6-dione: See Table 5, Entry 4.[45] Following the general procedure, acetylacetone (103 μL, 1.0 mmol) and benzalacetone (161 mg, 1.1 mmol) were reacted at 90 °C for 24 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 2:1) afforded the product (172 mg, 70%, 19% *ee*).

(*S*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione: See Table 5, Entry 5.[46] Following the general procedure, acetylacetone (103 μL, 1.0 mmol) and *trans*-β-nitrostyrene (164 mg, 1.1 mmol) were reacted at 90 °C for 14 h. Flash chromatography on silica gel (dichloromethane) afforded the product (72 mg, 29%, 17% *ee*).

3-Hydroxy-2-(3-oxocyclohexyl)cyclohex-2-enone: See Table 5, Entry 6.[47] Following the general procedure, 1,3-cyclo-hexanedione (112 mg, 1.0 mmol) and 2-cyclohexen-1-one (106 mL, 1.1 mmol) were reacted at 90 °C for 14 h. Flash chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1 + 2% triethylamine) afforded the product (154 mg, 74%, <10% *ee*).

Methyl 2-Nitro-5-oxohexanoate: See Table 5, Entry 7.[48] Following the general procedure, methyl nitroethanoate (92 μL, 1.0 mmol) and methyl vinyl ketone (89 μL, 1.1 mmol) were reacted at 60 °C for 4 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 4:1) afforded the product (164.6 mg, 87%, 59% *ee*).

Ethyl 2-Oxo-1-(3-oxobutyl)cyclohexanecarboxylate: See Table 5, Entry 8.[49] Following the general procedure, ethyl cyclohexanone-2-carboxylate (160 μL, 1.0 mmol) and methyl vinyl ketone (89 μL, 1.1 mmol) were reacted at 60 °C for 6 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 2:1 + 2% triethylamine) afforded the product (228.5 mg, 95%, <2% *ee*).

Ethyl 2-Oxo-1-(3-oxobutyl)cyclopentanecarboxylate: See Table 5, Entry 9.[49] Following the general procedure, ethyl 2-oxocyclopentanecarboxylate (145 μL, 1.0 mmol) and methyl vinyl ketone (89 μL, 1.1 mmol) were reacted at 60 °C for 5 h. Flash column chromatography on silica gel (*n*-heptane/ethyl acetate, 2:1 + 2% triethylamine) afforded the product (224.3 mg, 99%, <2% *ee*).

***tert*-Butyl 2-Oxo-1-(3-oxobutyl)cyclopentanecarboxylate:** See Table 5, Entry 10.[50] Following the general procedure, *tert*-butyl 2-oxocyclopentanecarboxylate (220 mg, 1.2 mmol) and methyl vinyl ketone (295 μL, 3.0 mmol) were reacted at 90 °C for 10 h. Flash chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1) afforded the product (256 mg, 84%, <5% *ee*). HPLC [1:99 *n*-hexane/2-propanol, 0.44 mL/min, 280 nm, $t_R(1)$ = 31.3 min, $t_R(2)$ = 33.7 min, broad overlapping peaks].

Determination of Inorganic Residues in the Product Phase of the Michael Addition Between 12 and MVK: The product phase (1.0319 g) from the reaction between **12** and MVK, performed according to the procedure described above, was placed in a crucible that previously had been heated at 600 °C for 30 min and then cooled in a dessicator. Concentrated sulfuric acid (1 mL, p.a. quality) was added to the sample. The mixture was heated gently on a hot plate until the sample was thoroughly charred. The sample was then heated at 600 °C overnight. The crucible was cooled in a dessicator and then weighed. The mass of residual inorganics was 0.00204 g, which corresponded to 0.2% of the total sample weight.

Supporting Information (see also the footnote on the first page of this article): ^1H NMR spectra of all products. Determination of absolute configuration of **6**.

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