Catalysis in Water

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α-Amino Acid Induced Rate Acceleration in Aqueous Biphasic Lewis Acid Catalyzed Michael Addition Reactions**

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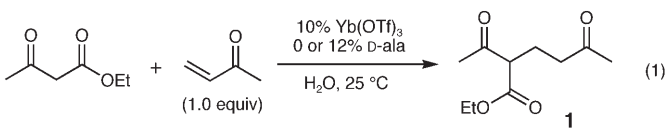
Water is of increasing importance as a cheap, safe, and environmentally benign reaction medium.[1] Indeed, aqueous biphasic catalysis is one of the most promising strategies towards more economical and greener processes.[2] However, progress in the development of efficient catalysts that are also highly water-soluble has been slow.[1e] With regard to the natural abundance of α-amino acids, it is somewhat surprising that their use as ligands in Lewis acid catalysis remains largely unexplored. A likely explanation is their low solubility in the organic solvents used ubiquitously for metal-catalyzed reactions. In water, however, the solubility of α-amino acids is not limiting, and their potential as ligands in aqueous Lewis acid catalysis deserves exploration.[3]

The Michael addition is one of the most important C–C bond-forming reactions. Although transition-metal-catalyzed Michael addition reactions in organic solvents have been developed with a great deal of success,[4] catalytic efficiency and substrate scope in aqueous media have so far been limited.[5] Recent significant advances have been the use of solid-phase Lewis acid catalysis[6] and our own discovery that small 1,2-dibasic ligands, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) in particular, can have a remarkable effect on aqueous Michael addition reactions catalyzed by ytterbium triflate.[7] Herein we report our first results on the use of α-amino acids as rate-accelerating ligands.

First, we set out to measure the effect of alanine on the catalytic activity of ytterbium triflate in the aqueous biphasic reaction between ethyl acetoacetate and methyl vinyl ketone (MVK) to afford adduct **1** [Eq. (1)]. The result was a quite extraordinary effect on the initial (for the first 120 min) second-order rate constant (Figure 1). The use of $Yb(OTf)_3$ (10%) alone led to a very slow reaction ($k = 1.3 \times 10^{-4}\,\text{M}^{-1}\,\text{min}^{-1}$). However, the inclusion of alanine (12%) resulted in a remarkable rate acceleration ($k = 1.79 \times 10^{-2}\,\text{M}^{-1}\,\text{min}^{-1}$), which corresponds to a relative second-order rate of 138 for the reaction in the presence of alanine.[8] This positive ligand effect is to our knowledge one of the strongest disclosed for any metal-based Lewis acid catalyzed reaction.[9–11] The large difference in initial rate constants offers a considerable synthetic advantage. After 16 h, the ligand-accelerated reaction afforded **1** in 96% yield, whereas a yield of only 12% was observed for the reaction without alanine. The ligand-free reaction was reported previously to take 5 days to reach completion.[5d]



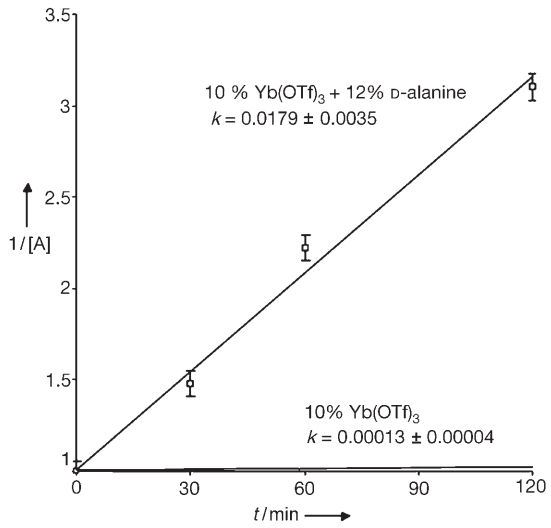


Figure 1. Initial second-order rate constants, *k*, of the aqueous biphasic Michael addition [Eq. (1)] in the presence and absence of D-alanine.[8] [A]: concentration of ethyl acetoacetate.

We then applied the $Yb(OTf)_3$/alanine combination in reactions between various donors and acceptors (Table 1). The products were isolated in high yields (88–97%) after relatively short reaction times (2–3 h) when nearly equivalent

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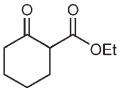
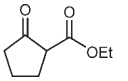
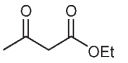
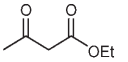
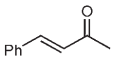
Table 1: Michael addition reactions in aqueous suspension catalyzed by $Yb(OTf)_3$/D-alanine.

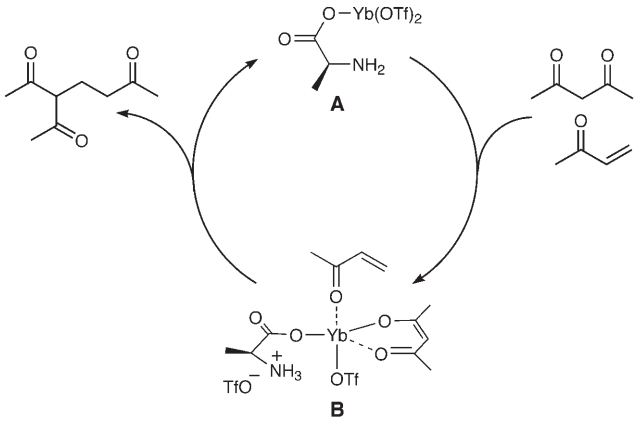
Entry	Donor	Acceptor	Cond.[a]	*t* [h]	Yield [%][b]
1			A	3	96
2			A	3	97
3			A	2	88
4			A	2	90
5			B	4	78
6			B	24	94
7			B	24	90
8			B	30	41

[a] Reaction conditions: A) donor (1 mmol), acceptor (1.1 mmol), $Yb(OTf)_3$ (0.1 mmol), D-alanine (0.12 mmol), NaOH (0.12 mmol), water (1 mL), 60 °C; B) donor (1 mmol), acceptor (3 mmol), $Yb(OTf)_3$ (0.2 mmol), D-alanine (0.24 mmol), NaOH (0.24 mmol), water (2 mL), 60 °C. [b] Yield of the isolated product.

amounts of the donor and MVK were used (Table 1, entries 1–4). Although the use of internal olefins as acceptors is normally much more challenging than the use of terminal olefins, the desired product was isolated in 78% yield from the reaction between ethyl acetoacetate and 2-cyclohexen-1-one (3 equiv) after only 4 h (Table 1, entry 5). High yields (90–94%) were observed for the addition of acetylacetone to cyclic enones if the reaction times were extended to 24 h (Table 1, entries 6 and 7). Even the unreactive acceptor benzalacetone underwent a slow but clean Michael addition with acetylacetone to provide the adduct in 41% yield after 30 h, along with recovered starting material (Table 1, entry 8).

A ligand acceleration effect of the magnitude observed in this study is counter-intuitive. In fact, a negative ligand effect, that is, rate deceleration, is the most commonly observed outcome of the addition of a basic ligand to a Lewis acid catalyzed reaction.[12] Although a significant amount of research has gone into understanding transition-metal-catalyzed addition reactions of 1,3-dicarbonyl compounds to enones,[13] as well as α-amino acid–lanthanide complexation,[14] any discussion about ligand effects must start by recognizing and disproving other potential catalytic pathways. Is the rate acceleration really due to ligand–metal binding and not to some alternative mechanism? First, we eliminated the possibility that small amounts of acid, potentially formed upon hydrolysis of the metal salt, had a catalytic effect; no addition product **1** was observed after 16 h at 25 °C in the presence of triflic acid (5%). Second, a series of experiments in which the Michael addition was performed under "organocatalytic" conditions (see the Supporting Information) gave the products with very low yields and *ee* values. These results gave us confidence that an enamine mechanism is not a significant contributor to the acceleration or to the enantioselectivities we observe (see below).[15]

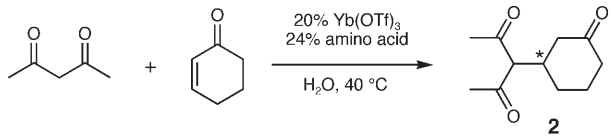
We propose that the α-amino acid accelerates the reaction by acting as a ligand. The deprotonated amino acid first displaces one of the labile triflate ligands of $Yb(OTf)_3$ to give **A** (Scheme 1); a considerable amount of experimental data



Scheme 1. Formation of the postulated "amino acid activated" catalytic complex **B** that leads to the addition product.

exists to support the formation of 1:1 complexes between lanthanides and α-amino acids in water.[14] Upon the addition of the reactants, another triflate ligand is displaced by a bidentate β-ketoenolate to give complex **B**. Simultaneous coordination of the enone brings the reactants into proximity for the addition step. A clue to the origin of the large ligand effect may then be derived from a recent study by Christoffers and co-workers, who showed that the coordination of negatively charged ligands can enhance significantly the reactivity of a β-ketoenolate towards an electrophile, presumably by weakening the covalent character of its M–O bond.[13b] The authors showed that the coordination of common counterion ligands, such as Cl^-, leads to fast protonation of the enolate by the acidic reaction mixture and a retarded reaction rate. In our system, however, the dibasic character of the α-amino acid ligand may give a kinetic advantage to the reaction between the β-ketoenolate and a coordinated electrophilic Michael acceptor.

We then screened a number of α-amino acids for their ability to induce asymmetry in the reaction between acetylacetone and 2-cyclohexen-1-one. The observed *ee* values of adduct **2** were modest (16–53% *ee*; Scheme 2). Nevertheless, our results compare favorably to the best previously reported *ee* value of 36% for aqueous Lewis acid catalysis with native α-amino acid ligands.[3a] Higher enantioselectivities have been attained by using synthetically modified α-amino acids (76% *ee*)[3a] or by using a cosolvent (56% *ee*).[16] Unexpectedly, the sterically more demanding α-amino acids valine and isoleucine gave similar results (38% *ee*) to that with alanine



Scheme 2. $Yb(OTf)_3$/α-amino acid catalyzed asymmetric Michael addition between acetylacetone and 2-cyclohexen-1-one (amino acid, *ee* value of **2**: Asn, 16%; Gln, 18%; Ser, 22%; Leu, 25%; Phe, 32%; Pro, 33%; Trp, 36%; Val, 38%; Ile, 38%; Ala, 39%; Ala (60°C), 53%).

(39% *ee*), the sterically least demanding α-amino acid.[17] To our further surprise, we observed higher enantioselectivity in the reaction with alanine at 60°C (53% *ee*) than at 40°C (39% *ee*). This atypical relationship between temperature and selectivity was also observed in the addition of acetylacetone to benzalacetone (15% *ee* at 60°C versus 9% *ee* at 40°C).[18] An explanation for this observation cannot be derived from our current knowledge of the mechanism, but the phenomenon may stem from variations in solubility with temperature and/or a mechanism dominated by entropy effects.[19] The lowest *ee* values were observed when α-amino acids with polar side chains were used (Asn, Gln, Ser; 16–22% *ee*).

Finally, we performed a recycling experiment under aqueous biphasic conditions (Figure 2). Ethyl 2-oxocyclohexanecarboxylate (6.3 mmol) and MVK (6.9 mmol) were added to a solution of the catalyst (10% Yb, 12% D-Ala), and the resulting suspension was stirred at 60°C for 8.5 h. When the stirring was stopped, the mixture separated slowly into two distinct phases. Following the facile separation of the mixture in a separating funnel, the aqueous catalytic phase was returned to the reaction flask, and another batch of reactants was added. Five such cycles provided consistently complete conversion of the reactants into the desired adduct **3**, without the use of an organic solvent. Remarkably, no product was detected in the absence of the catalyst.

In conclusion, we have shown that natural α-amino acids have significant potential as chiral ligands for aqueous biphasic Lewis acid catalysis. A ligand acceleration factor of 138 was measured for alanine in an ytterbium triflate catalyzed Michael addition. High-yielding reactions were observed with various donors and a wider range of acceptors than could be used previously under conditions of aqueous, non-solid-phase Lewis acid catalysis. The enantioselectivities of the reactions were the highest observed with native α-amino acids as ligands for Lewis acids in water alone. Still in its infancy, aqueous biphasic Lewis acid catalysis has tremendous potential in the development of more economical and more environmentally friendly processes. We will pursue the opportunities revealed herein in terms of the large ligand effect and the efficient and extremely simple recycling of the catalyst. However, we first require deeper insight into the mechanism behind the rate acceleration and the atypical relationship between reaction temperature and selectivity.

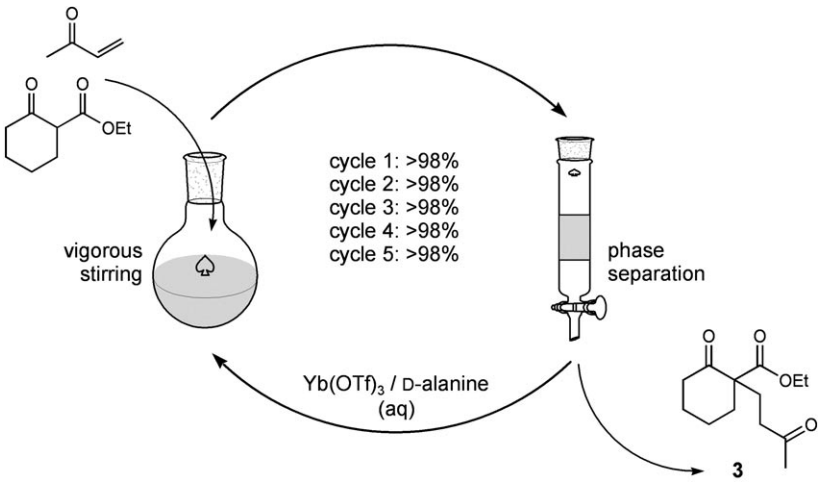


Figure 2. The high water solubility of the $Yb(OTf)_3$/alanine catalyst allows simple isolation of the Michael adduct and repeated recycling of the catalytic aqueous phase.

Experimental Section

Typical procedure: D-Alanine (6.3 mg, 0.07 mmol) and ytterbium triflate (36.5 mg, 0.06 mmol) were stirred in aqueous NaOH (0.06 M, 1.2 mL) in a round-bottomed flask for 15 min at room temperature. Ethyl 2-oxocyclohexanecarboxylate (94 μL, 0.59 mmol) and methyl vinyl ketone (53 μL, 0.65 mmol) were then added. The reaction flask was sealed, and the mixture was stirred vigorously at 60°C for 3 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (6 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography of the residue on silica gel (heptane/ethyl acetate 2:1) afforded **3** (136 mg, 96%).

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