Expanding the Scope of Lewis Acid Catalysis in Water: Remarkable Ligand Acceleration of Aqueous Ytterbium Triflate Catalyzed Michael Addition Reactions.

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SUPPORTING INFORMATION

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1. General Experimental Details

Deionized water was used in all reactions. All metal triflates and ligands are commercially available compounds, or simple derivatives thereof, and used as received from the supplier. Purification of products was done by flash chromatography performed on normal phase silica gel, 35-70 μ , 60Å. Purity has been documented by providing a ^{13}C -NMR spectra for each of the products (see below). All products are known compounds and gave consistent ^1H - and ^{13}C -NMR data.¹

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¹ Christoffers, J. *J. Chem. Soc., Perkin Trans. I* **1997**, 3141.

2. Procedure for preparative gram-scale synthesis of **2**.

TMEDA (0.11 g, 0.92 mmol) and ytterbium triflate (0.48 g, 0.77 mmol) were stirred together for 15 min at ambient temperature, after which water (7.5 mL) was added and stirring continued for another 15 min. Ethyl acetoacetate (1.0 g, 7.68 mmol) and 3-buten-2-one (0.81 g, 11.52 mmol) were then added. The reaction tube was capped and the reaction mixture was stirred for 2.5 h at 45 °C. The reaction was diluted with water and extracted with ethyl acetate (30 mL). The organic phase was dried over MgSO_4 , filtered and concentrated. The crude product was purified by flash column chromatography (heptane/ethyl acetate 2:1), which afforded the desired product **2** (1.31 g, 85%).

3. NMR Analysis of Michael Additions

Reactions were analyzed for conversion of ethyl acetoacetate into product by integrating the peaks of α -protons in the ^1H -NMR (300 MHz, acetone- d_6). Below is a representative image of a typical experiment from the ligand screen study.

4. Derivation of Rate Constants from Second Order Rate Equation

Rate of formation of products = $k [\text{A}][\text{B}]$

$[\text{A}] = [\text{B}]$ i.e. we use a 1:1 ratio of ethyl acetoacetate and MVK

$$\begin{aligned}
 d[\text{P}]/dt &= k'[\text{A}]^2 \\
 [\text{P}]_t &= [\text{A}]_0 - [\text{A}]_t \\
 d([\text{A}]_0 - [\text{A}]_t)/dt &= k'[\text{A}]^2 \\
 -d[\text{A}]_t/dt &= k'[\text{A}]^2 \\
 -\int d[\text{A}]_t/[\text{A}]^2 &= k' \int dt \\
 \{1/[\text{A}]_t\} &= k't \\
 k't &= 1/[\text{A}]_t - 1/[\text{A}]_0
 \end{aligned}$$

In the reactions, $[\text{A}]_0 = 1\text{M}$, then

$$k't = 1/[\text{A}]_t - 1$$

During the reaction, $[\text{A}]_t + [\text{P}]_t = 1$,

$$[\text{A}]_t = 1 - [\text{P}]_t, \text{ then}$$

$$k't = 1/(1 - [\text{P}]_t) - 1$$

$$= [\text{P}]_t/(1 - [\text{P}]_t)$$

$$= [\text{P}]_t/[\text{A}]_t$$

The ^1H -NMR shows the ratio of ethyl acetoacetate to product at time t . This ratio is the same as $[\text{P}]_t/[\text{A}]_t$. Hence, the reaction rate constant can be calculated by the following equation:

$$k' = [\text{P}]_t/([\text{A}]_t)$$

If k'_{+L} and k'_{-L} are the rate constants for the reaction in presence and absence of ligand, respectively, then the relative rate is k'_{+L}/k'_{-L} .

5. Kinetic study

A simple kinetic study confirmed the observed reaction as being second order.

Figure S1. Plot showing an excellent fit of experimental data to the second order rate equation as derived above.

6. Preliminary ^1H NMR studies on solutions of $\text{Yb}(\text{OTf})_3$ and TMEDA in D_2O

In order to determine if a complex is formed between $\text{Yb}(\text{OTf})_3$ and TMEDA in water solution we studied the chemical shift of TMEDA in D_2O , 10 mM, throughout a titration with $\text{Yb}(\text{OTf})_3$, 10 mM. A Bruker Avance 500MHz spectrometer, operated with XWINNMR 2.6 software, was used in this study and the sample temperature was kept at 300K. The chemical shift scale was kept, for each sample, as calculated from the deuterium lock software. This resulted in a residual water resonance at 4.656 ppm for pure TMEDA in D_2O , 10 mM.

The addition of $\text{Yb}(\text{OTf})_3$ to a solution of TMEDA in D_2O caused a change in chemical shift of the methylene and the methyl resonances of TMEDA. The induced shift shows a linear response for the 0.25 molar equivalents of $\text{Yb}(\text{OTf})_3$ that was added, (Figure S2 and Table S1).

Figure S2. ^1H NMR spectra of TMEDA in D_2O , 10 mM, throughout a titration with $\text{Yb}(\text{OTf})_3$, 10 mM. Details on the titration is found in Table S1.

Table S1. Chemical shift at 300K of TMEDA methylene and methyl proton after titration of a 10 mM D₂O solution with Yb(OTf)₃, 10 mM.

[Yb(OTf) ₃]/[TMEDA]	δ_{CH_2} [ppm]	δ_{CH_3} [ppm]
0.000	2.427	2.148
0.013	2.447	2.162
0.026	2.464	2.174
0.051	2.491	2.193
0.128	2.618	2.284
0.256	2.802	2.415

The bound shift for the complex of Yb³⁺ and TMEDA was estimated using two different approaches. Assuming an initial formation of a 1:1 complex and taking into account the linear relationship between the addition of Yb(OTf)₃ and the induced shift, bound shifts were estimated for the hypothetical 1:1 complex from a linear interpolation to 1 equivalent of Yb(OTf)₃, using measured data. The resulting bound shifts, $\Delta^{B1}(CH_2) = 1.471$ ppm and $\Delta^{B1}(Me_3) = 1.050$ ppm, can be expected to be close to the shifts for a 1:1 complex having an equilibrium constant $K \gg 1$. Bound shifts were also estimated from measurement of the chemical shift of TMEDA in the presence of a large excess of Yb(OTf)₃. Thus 20 μ L of TMEDA in D₂O, 10 mM, was added to 780 μ L of Yb(OTf)₃, 10 mM. The resulting bound shifts were; $\Delta^{B2}(CH_2) = 0.732$ ppm and $\Delta^{B2}(Me_3) = 0.505$ ppm.

When the relation of the induced shift $\Delta\delta$ to the bound shift Δ^{B1} , $\Delta\delta / \Delta^{B1}$, is plotted against [Yb(OTf)₃] / [TMEDA] the measured data matches a linear response, as would be expected from data for the formation of a 1:1 complex having an equilibrium constant $K \gg 1$, (Figure S3). Using the bound shifts $\Delta^{B1}(CH_2)$ and $\Delta^{B1}(Me_3)$ we calculated the hypothetical equilibrium constants to 103 M⁻¹ and 96 M⁻¹ respectively from the Δ^{B2} measurement. The graph of $\Delta\delta / \Delta^{B1}$ as a function of [Yb(OTf)₃] / [TMEDA] for the formation of a 1:1 complex with $K = 100$ is drawn in Figure S3.

Figure S3. Plot of fractional shift of (x) CH₂ and (o) CH₃ in TMEDA against the relative concentration of [Yb(OTf)₃]/[TMEDA]. The dotted line is the graph for the formation of a 1:1 complex having bound shifts Δ^{B1} and an equilibrium constant $K = 100$.

This preliminary study shows the presence of a complex of Yb(OTf)₃ and TMEDA in water and that the equilibrium constant for the formation of the complex $K > 100$. However, more data has to be collected in order to describe the complex further.

7. ^{13}C -NMR spectra demonstrating purity of products.

Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate:

Ethyl 2-oxo-1-(3-oxobutyl)cyclopentanecarboxylate:

Ethyl 2-acetyl-5-oxohexanoate:

3-Acetylhepta-2,6-dione (mixture of tautomers):

3-Acetyl-3-methylhepta-2,6-dione (containing 5-10% impurities):