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

Rui Ding, Kambiz Katebzadeh, Lisa Roman,
Karl-Erik Bergquist, and Ulf M. Lindström*

Department of Organic Chemistry, Lund University,
P.O. Box 124, SE-221 00 Lund, Sweden

ulf.lindstrom@organic.lu.se

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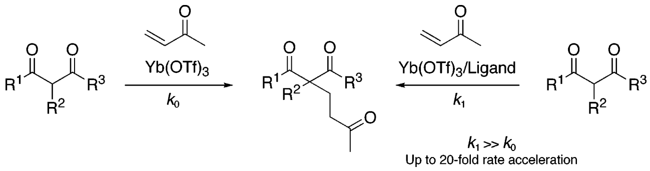

Significant rate acceleration of metal-catalyzed Michael addition reactions in water was observed upon addition of small, dibasic ligands. Ytterbium triflate and TMEDA was the most effective combination leading to a nearly 20-fold faster reaction than in the absence of ligand.

Reducing the use of hazardous solvents is one of the most important challenges in the effort to minimize pollution and risks associated with the production of chemicals. Accordingly, the development of water as a harmless alternative to organic solvents as reaction medium for organic synthesis has become an important research area.[1] Other than the environmental and economical benefits of using water, it has also been recognized that water may sometimes even be the preferred solvent in terms of synthetic efficiency. For example, using water as reaction solvent can lead to simplified work-up procedures, and the use of protecting groups to replace acidic hydrogens may be reduced or avoided completely.[2] Metal salts with Lewis acid activity in water have found extensive use in aqueous catalysis, in particular, the rare earth metals including the lanthanides (Sc(III), Y(III), Ln(III)), but also some main group elements (In(III), Pb(II)) and transition metals (Fe(II), Cu(II), Ag(I), Zn(II), Cd(II)). Their catalytic capacity in water, as demonstrated in numerous types of reactions, is ascribed to these metals having a hydrolysis constant within an optimal range and a fast exchange rate of coordinated water ligands.[3] Nevertheless, the full scope and potential of Lewis acid catalysis in water is still unclear. A significant step forward would be the realization of efficient ligand accelerated catalysis in water.[4] When a basic ligand is added to a catalytic reaction and bound to the metal the rate of the reaction can be unaffected, accelerated, or decelerated. For the majority of catalytic processes, no rate enhancement is observed. However, when a positive ligand effect on reaction rate can be found, it offers a powerful approach to increasing reaction efficiency.[5]

With the goal of developing generally useful and more efficient Lewis acid catalysts for synthesis in water, we set out to study the influence of various ligands on the rate of aqueous Lewis acid catalyzed Michael additions, one of the most important carbon–carbon bond-forming reactions in organic synthesis. However, progress toward efficient Lewis acid catalyzed Michael additions in water has been slow, and only a few examples exist where carbon nucleophiles are involved. Keller and Feringa have used $Yb(OTf)_3$ (0.1 equiv) to catalyze the conjugate addition of β-keto- and α-nitroesters to enones.[6] The reactions required 3 equiv of enone and took 3–5 days to reach completion. Kobayashi et al. used a Lewis acid–surfactant combined catalyst (LASC) to afford Michael adducts in good yields.[7] The reactions were slow (12–35 h), however, and with less than 3 equiv of acceptor the reactions became sluggish. Later, the same research group reported the use of the chiral catalyst (*R*)-Tol-BINAP/AgOTf affording the Michael adducts in good yields and ee's.[8] Nevertheless, the reactions were still run for 18–36 h using the acceptor in large excess. We now wish to report remarkable ligand acceleration effects that lead to much more efficient Lewis acid catalyzed Michael additions in water, a discovery that is of importance to the overall development of organic synthesis in aqueous media.

As a starting point for our investigation we screened various metal triflates for their ability to catalyze the Michael addition reaction between ethyl acetoacetate, **1**, and methyl vinyl ketone (MVK) to give the adduct **2** (Table 1).

The reactions were run with 10% of a metal triflate for 16 h at room temperature, after which time the ratio of adduct **2** to starting β-ketoester **1** was measured by integrating relevant peaks in the NMR spectra of the crude products. Rate constants could then be derived from the second-order rate equation (see the Supporting Information). In the absence of metal, no trace of addition product **2** was observed after 16 h (entry 1). Among the metal triflates tested, all were able to catalyze the reaction to moderate extent with 10–26% yield (based on NMR) of **1**, which corresponds to second-order rate constants between 2.2×10^{-6} and 6.2×10^{-6} M^{-1} s^{-1} (entries 2–5), except $In(OTf)_3$, the presence of which did not yield any detectable amount of **2** (entry 6). The most effective metal salt was $La(OTf)_3$ (entry 5), which proceeded with approximately three times higher rate

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* To whom correspondence should be addressed. Fax: (+46) 46 2228209.

[1] (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) *Organic Synthesis in Water*; Grieco, P., Ed.; Blackie Academic & Professional: London, 1998. (c) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (d) See also thematic issue: "Organic Reactions in Water": *Adv. Synth. Catal.* **2002**, *344* (3–4).

[2] For a recent example, see: Lindström, U. M.; Ding, R.; Hidestål, O. *Chem. Commun.* **2005**, 1773.

[3] (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.

[4] For examples of modest ligand effects in aqueous media, see: (a) Kobayashi, S.; Aoyama, N.; Manabe, K. *Chirality* **2003**, *15*, 124. (b) Kobayashi, S.; Aoyama, N.; Manabe, K. *Synlett* **2002**, 483.

[5] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.

[6] (a) Keller, E.; Feringa, B. L. *Synlett* **1997**, 842. (b) Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879.

[7] Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107.

[8] Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* **2001**, *41*, 247.

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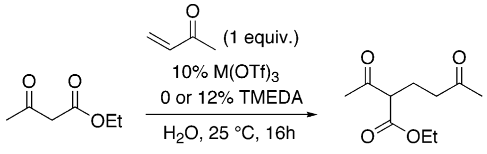
TABLE 1. Observed Yields and Rates for Lewis Acid Catalyzed Michael Additions in Water in the Absence (k_{-L}) and Presence (k_{+L}) of TMEDA[a]



1 **2**

		no TMEDA		TMEDA		
entry	catalyst	yield[b] (%)	k_{-L} (M^{-1} s^{-1})[c]	yield[b] (%)	k_{+L} (M^{-1} s^{-1})[c]	k_{rel}[d]
1		<1	$<2 \times 10^{-7}$	<1	$<2 \times 10^{-7}$	
2	$Yb(OTf)_3$	12	2.2×10^{-6}	71	4.3×10^{-5}	19.5
3	$Cu(OTf)_2$	10	1.9×10^{-6}	26	6.3×10^{-6}	3.3
4	$Sc(OTf)_3$	12	2.2×10^{-6}	23	5.2×10^{-6}	2.4
5	$La(OTf)_3$	26	6.2×10^{-6}	38	1.0×10^{-5}	1.6
6	$In(OTf)_3$	<1	$<2 \times 10^{-7}$	<1	$<2 \times 10^{-7}$	
7	TfOH[e]	<1	$<2 \times 10^{-7}$			

[a] All reactions were performed at least three times, and listed values are averages. [b] Yields are based on NMR; products not isolated. NMR detection limit was estimated to 1% conversion, which corresponds to a rate constant of 2×10^{-7}. [c] For derivation of rate constants, see the Supporting Information. [d] Ligand effect, $k_{rel} = k_{+L}/k_{-L}$. [e] No metal; only 5% of trifluoromethanesulfonic acid was used.

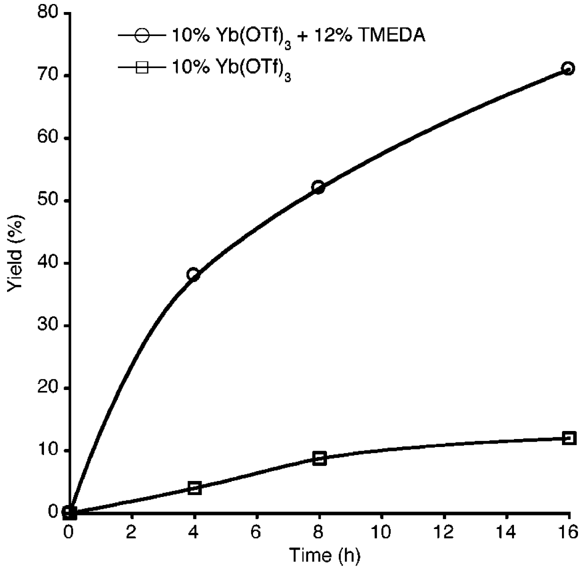


FIGURE 1. Effect of TMEDA on the reaction rate of $Yb(OTf)_3$-catalyzed conjugate addition of ethyl acetoacetate to MVK.

than either $Yb(OTf)_3$, $Cu(OTf)_2$, or $Sc(OTf)_3$ (entries 2−4). Next, to monitor the effect that a 1,2-dibasic ligand might have on the reaction rate, we performed the Lewis acid catalyzed Michael additions in the presence of 12% of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMEDA (Table 1). Gratifyingly, we found that the catalytic activities of several of the metal triflates were significantly enhanced upon addition of TMEDA. Adding equimolar amounts of **1** and MVK to a mixture of $Yb(OTf)_3$ (10%) and TMEDA (12%) gave a significantly higher second-order rate constant of 4.3×10^{-5} M^{-1} s^{-1} (entry 2).[9] Thus, the ligand acceleration effect obtained from the ratio of the rate constants is 19.5! This remarkable rate difference offers great synthetic advantages as illustrated in Figure 1 (see also Figure S1 in the Supporting Information). In the presence of TMEDA, the Michael adduct **2** is obtained in 71% yield (based on NMR) after 16 h as compared to only 12% for the ligand-free reaction.

To the best of our knowledge, this is the most significant ligand acceleration effect observed in water to date. The catalytic activities of $Cu(OTf)_2$, $Sc(OTf)_3$, and $La(OTf)_3$ were also enhanced by TMEDA, but to a significantly lower extent giving relative rate constants of 3.3, 2.4, and 1.6, respectively (entries 3−5). Again, no product was detected in the reaction with $In(OTf)_3$ (entry 6). In view of the unexpectedly large rate accelerations, and because positive ligand effects in water are relatively unexplored, we needed to convince ourselves that what we observe is true ligand accelerated metal catalysis, i.e., the active catalyst is the metal−ligand complex and not some other species formed in the reaction mixture. First, a control experiment confirmed that TMEDA alone does not catalyze the reaction (entry 1). Furthermore, to ensure that the rate acceleration was not due to trace amounts of trifluoromethanesulfonic acid (TfOH) being formed upon complexation of the metal triflate we also made a control experiment in the presence of TfOH (5%). Under these conditions no addition product was observed after 16 h (entry 7). Finally, we also performed an in situ NMR analysis that showed the presence of a complex of ytterbium and TMEDA in water and allowed the estimation of an equilibrium constant (see the Supporting Information).

Having established a plausible mechanistic origin of the observed rate accelerations, we went on to further investigate these ligand effects by screening a number of 1,2-dibasic compounds for their ability to accelerate the $Yb(OTf)_3$-catalyzed Michael addition reaction between **1** and MVK. The results are listed in Table 2.

As can be seen, all diamines and amino alcohols provided significant rate acceleration (entries 2−12), although we were not able to find a better ligand than TMEDA among these. The second best ligand was tris(hydroxyethyl)aminomethane (entry 12), with a relative rate constant of 7.3, which shows that the observed effect is not limited to 1,2-dibasic compounds and suggests the possibility that multidentate ligands may be used with advantage. 1,2-Diols seem to be poor ligands in this reaction. In fact, catechol had a clearly decelerating effect on the reaction (entry 13), while 1,2-ethanediol had almost no effect at all (entry 14).

Finally, we were able to demonstrate that other 1,3-dicarbonyl compounds also act as efficient donors in the presence of $Yb(OTf)_3$/TMEDA (Table 3).

Ethyl cyclohexanone-2-carboxylate reacted efficiently with only 1 equiv of MVK to give a quantitative yield of the expected adduct after 16 h (entry 1). We also performed this reaction using 3 equiv of MVK in order to make a direct comparison with previously described methods. Using $Yb(OTf)_3$ as catalyst and an excess of MVK, this reaction was reported to require 5 days to go to completion.[6] In the presence of TMEDA, the reaction is complete in only 6 h (entry 2)! Ethyl cyclopentanone-2-carboxylate worked nearly as efficiently providing the expected adduct in 95% yield (entry 3). Ethyl acetoacetate is slightly less reactive toward MVK but provides the addition product in 88% yield (entry 4) after 24 h. The diketone 2,4-pentanedione added to MVK in 92% yield (entry 5). 3-Methyl-2,4-pentanedione appeared to proceed equally well, although

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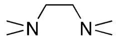
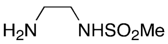
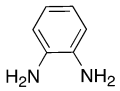
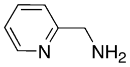
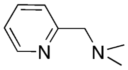
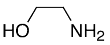
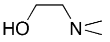
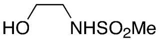
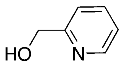
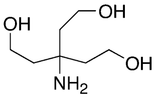
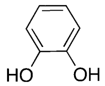
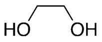
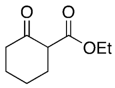
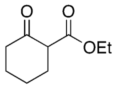
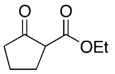
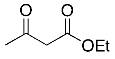
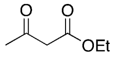
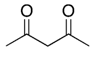
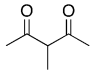
[9] For another example of ligand accelerated $Yb(OTf)_3$ catalysis, see: Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183.

TABLE 2. **Effects of Various Ligands on the Yb(OTf)$_3$-Catalyzed Michael Addition between Ethyl Acetoacetate and MVK in Water**[a]

entry	ligand	k_{+L} (M^{-1} s^{-1})[b]	k_{rel}[c]
1	-	2.2×10^{-6}	-
2		1.1×10^{-5}	5.0
3		4.3×10^{-5}	19.5
4		1.2×10^{-5}	5.5
5		1.1×10^{-5}	5.0
6		1.2×10^{-5}	5.5
7		5.9×10^{-6}	2.7
8		1.0×10^{-5}	4.5
9		1.1×10^{-5}	5.0
10		3.1×10^{-6}	1.4
11		1.0×10^{-5}	4.5
12		1.6×10^{-5}	7.3
13		1.4×10^{-6}	0.6
14		2.6×10^{-6}	1.2

[a] For reaction conditions, see Table 1. All reactions were performed at least three times. Listed rate constants are averages. [b] For derivation of rate constants, see the Supporting Information. [c] Relative to the ligand-free reaction (entry 1), $k_{rel} = k_{+L}/k_{-L}$.

TABLE 3. **Michael Additions to MVK in Water Catalyzed by Yb(OTf)$_3$/TMEDA**[a]

entry	donor	time (h)	yield[b] (%)
1		16	>99
2[c]		6	97
3		16	95
4		24	88
5[d]		2.5	85
6		16	92
7		16	84[e]

[a] For reaction conditions, see Table 1. [b] Isolated yields. [c] Three equivalents of MVK. [d] Performed at 45 °C. [e] Some impurities (<10%) remained even after repeated attempts to purify the product.

problems with purification resulted in a slightly lower yield (84%) of a product containing 5−10% of unknown impurity (entry 6). To clearly demonstrate the potential of this method for preparative purposes, we performed the reaction between ethyl acetoacetate and MVK on a gram scale. With gentle heating (45 °C), the adduct was obtained in 85% isolated yield after only 2.5 h reaction time. Unfortunately, some other potential Michael acceptors such as acrylonitrile or ethyl acrylate were unreactive to the conditions described.

In summary, we have developed an efficient, catalytic method of achieving carbon−carbon bond-forming Michael addition reactions in water. This was made possible by the pivotal find that small, dibasic ligands have remarkable, positive effects on the catalytic activity of several metal triflates in water, ytterbium triflate, in particular, which in combination with TMEDA gave an almost 20 times faster reaction compared to the ligand-free reaction. Other than providing a method that is relatively fast and high-yielding, even with equimolar amounts of donor and acceptor, the large rate differences between the ligand accelerated and the basic catalytic processes for several of the metals studied provide excellent opportunity for chiral catalysis. It is reasonable to assume that our findings on ligand accelerated catalysis reported herein can be used to improve also other Lewis acid catalyzed reactions in water and become a valuable tool in the development of asymmetric catalysis in water.

Experimental Section

Determination of Rate Constants. All reactions were performed at 25 ± 0.5 °C. Ligand (0.06 mmol, 0.12 equiv) and ytterbium triflate (0.05 mmol, 0.10 equiv) were mixed by stirring for 15 min. Water (0.5 mL) was added and the mixture stirred for another 15 min. Ethyl acetoacetate (0.5 mmol, 1 equiv) and MVK (0.5 mmol, 1 equiv) were then added. After being stirred vigorously for 16 h, the reactions were stopped by dilution with water and extraction with EtOAc (5 mL). Concentration afforded crude mixtures that were analyzed by ^{1}H NMR (acetone-d_6) to give the ratios of ethyl acetoacetate **1** to adduct **2**. All experiments were performed at least three times, and listed values are averages. The reaction rates were calculated using the formula $k' = [\mathbf{2}]_{16h}/([\mathbf{1}]_{16h}t)$, which is derived from the second-order rate equation (see the Supporting Information). When plotting 1/[**1**] against time, a straight line typical for a second-order reaction is obtained (see the Supporting Information). The data for the ligand-free reactions were obtained in an identical way. Relative rates were then obtained using the formula $k_{rel} = k'_{+L}/k'_{-L}$.

Typical Procedure for Yb(OTf)$_3$/TMEDA-Catalyzed Michael Addition. TMEDA (0.014 g, 0.12 mmol) and ytterbium triflate (0.062 g, 0.10 mmol) were stirred together for 15 min at ambient temperature, after which water (1 mL) was added and stirring continued for another 15 min. Ethyl cyclohexanone-2-carboxylate (0.170 g, 1.0 mmol) and 3-buten-2-one (0.070 g, 1.0 mmol) were then added. After being stirred for 16 h, the reaction was diluted with water and extracted with ethyl acetate (10 mL). The organic phase was dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by flash chromatography on a silica gel column pretreated with triethylamine, eluting with heptane/ethyl acetate 1:1, which afforded the desired Michael adduct (0.239 g, 100%). The analytical data of the product were identical to those reported in the literature.[10]

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Supporting Information Available: Experimental procedure optimized for preparative purposes. Sample of NMR used for determination of rate constants. Derivation of second-order rate equation. Graph showing fit of experimental data to the rate equation. Details of in situ NMR analysis of complexation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141.