Transition-Metal-Based *Lewis* Acid Catalysis of Aza-Type *Michael* Additions of Amines to α,β-Unsaturated Electrophiles in Water

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Several transition-metal-based *Lewis* acid catalysts, especially $FeCl_3 \cdot 7\,H_2O$, $CrCl_3 \cdot 6\,H_2O$, and $SnCl_4 \cdot 4\,H_2O$, were shown to be highly effective for aza-type *Michael* reactions between electrophilic α,β-unsaturated compounds and both aliphatic and aromatic amines in aqueous solution. Advantages of the new protocol include *1*) high-yielding reactions that can be conducted at ambient temperature; *2*) the use of inexpensive, stable transition-metal salts as catalysts; and *3*) plain H_2O as an environmentally benign solvent.

Introduction. – The products of aza-type *Michael* additions, *i.e.*, β-amino carbonyl compounds and their derivatives, are often used as peptide analogs or precursors of optically active amino acids, amino alcohols, diamines, and lactams [1]. Moreover, β-amino carbonyl functionalities are ubiquitous motifs in natural products such as alkaloids and polyketides [2]. As such, the development of efficient synthetic methods leading to such compounds has attracted much attention among organic chemists [3]. However, the transition-metal-catalyzed addition of amines to C=C bonds is an unsolved, synthetically important issue [4]. Among the methods for generating β-amino carbonyl compounds, *Lewis* acid and base-catalyzed conjugate addition of N-containing nucleophiles to α,β-unsaturated compounds is one of the most simple and effective methods [5]. A number of useful procedures have been developed in the past few years [6]. In particular, various metal-catalyzed reactions have been studied in the presence of, *e.g.*, Pd compounds [7], $NaI/CeCl_3 \cdot 7\,H_2O$ [8], $Bi(NO)_3$ [9], and $Yb(OTf)_3$[1]) [10]. Recently, *Adapa* and co-workers reported aza-type *Michael* additions with $Bi(OTf)_3$ as the catalyst, a method that worked well with aliphatic amines [11]. Although recent advances have made this route more attractive, development of less expensive, simpler, 'greener', and more-efficient metal catalysts is highly desirable.

We have been interested in developing aza-type *Michael* reactions that occur with catalytic amounts of minimally toxic, readily available, and economic reagents, contributing to an environmentally benign process. Recently, we reported that $FeCl_3$ and *Lewis* base catalysts can be used for the addition of carbamates and azide ions to enones [12]. Herein, we report a new protocol that makes use of air-stable, highly efficient transition-metal salts that catalyze aza-type *Michael* reactions under mild conditions in aqueous solution, using both aliphatic and aromatic amines as the nucleophiles.

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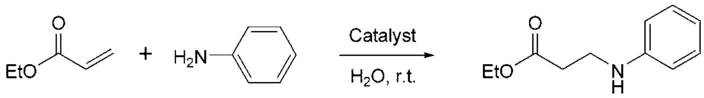
[1]) 'Tf' ('triflate') stands for 2,2,2-trifluoroacetate.

Results and Discussion. – First, we tested the catalytic properties (in terms of yield) of different transition metals towards the standardized aza-type *Michael* addition of aniline to ethyl acrylate (*Table 1*) in H_2O at ambient temperature during 15 h. Among the salts tested, $FeCl_3 \cdot 7\,H_2O$ (*Entry 2*), $CrCl_3 \cdot 6\,H_2O$ (*Entry 12*), and $SnCl_4 \cdot 4\,H_2O$ (*Entry 15*) gave fair yields (67–73%), as well as $InCl_3$ [13] (data not shown). Lower yields were obtained with the other transition-metal salts tested, Cu^{II} salts (*Entries 13* and *14*) giving rise to merely traces of product.

Table 1. *Comparison of Different Transition-Metal Salts as Catalysts in the Aqueous Aza-Type* Michael *Addition between Aniline and Ethyl Acrylate.* Standard conditions: 1 mmol ethyl acrylate, 1.2 mmol aniline, 0.1 equiv. catalyst, H_2O, r.t., 15 h.



Entry	Catalyst	Isolated yield [%]
1	$AuCl_3 \cdot 2\,H_2O$	31
2	$FeCl_3 \cdot 7\,H_2O$	72
3	$NiCl_2$	30
4	$Co(OAc)_2$	22
5	$Ni(OAc)_2$	27
6	$Zn(OAc)_2$	24
7	$Mn(OAc)_2$	25
8	$Mn(OAc)_3$	28
9	$Ni(acac)_2$	12
10	$LaCl_3$	29
11	$Ni(ClO_4)_2$	20
12	$CrCl_3 \cdot 6\,H_2O$	67
13	$Cu(OTf)_2$	Trace
14	$Cu(OAc)_2$	Trace
15	$SnCl_4 \cdot 4\,H_2O$	73
16	None	0

The inertness of aromatic amines relative to aliphatic ones was exemplified by allowing an equimolar mixture of 4-aminophenol and piperidine to react with ethyl acrylate under standard conditions. As expected, only the addition product of the *aliphatic* amine was found, and in almost quantitative yield.

Typically, only simple primary aliphatic amines can be reacted with α,β-unsaturated electrophiles in organic solvents, and only at high temperature [14], high pressure [15], or in the presence of an appropriate catalyst [16]. Whereas most aza-type *Michael* additions have been performed in organic solvents, today's environmental concerns encourage the development of 'greener' conditions [13], especially by means of metal-mediated C–C and C–X (X = heteroatom) formations [17] in aqueous media, as reported by *Xia* and co-workers [12]. Although various kinds of *Lewis* acids and bases have been tested in organic solvents, these catalysts must be used under strictly anhydrous conditions to be effective. Thus, reactions in aqueous media have the advantage, aside from being ecologically safe, that solvents and (hydrated) substrates do no longer have to be dried, but can be used directly [18]. Surprisingly, however, there are few reports on the conjugate addition of aromatic amines to α,β-unsaturated compounds in aqueous media.

Next, we tested the catalytic effect of various transition metals in the conjugate addition of *aliphatic* amines, such as benzylamine, under the same standard conditions as above (ethyl acrylate, H_2O, room temperature, 15 h). To our satisfaction, among the metal salts tested (data not shown), almost all were found to be effective catalysts, whereas the control reaction (in the absence of catalyst) gave the addition product in only 23% yield. This dramatic rate acceleration of the catalyzed reaction in H_2O may be attributed to several factors such as enforced hydrophobic interactions, and stabilization of the activated complex through solvation, H-bonding, and micellar catalysis.

With several effective catalysts in hand, we next investigated the effect of varying the structures of the reactants. Again, standard conditions (H_2O, room temperature, 15 h) were used, with $Cu(OAc)_2$, $Co(OAc)_2$, and $FeCl_3 \cdot 7\,H_2O$ as the catalysts. The results of these experiments are summarized in *Table 2*.

Interestingly, all the aliphatic amines gave excellent yields, many reactions being almost quantitative. When $BnNH_2$ or $PrNH_2$ were treated with acrylonitrile, only the mono-addition products were obtained (*Table 2*, *Entries 4* and *8*, resp.). To our surprise, the reactions of $PrNH_2$ and $BuNH_2$ with ethyl acrylate in the presence of $FeCl_3 \cdot 7\,H_2O$ or $Co(OAc)_2$ gave high yields of the disubstituted products only (*Entries 2* and *6*, resp.).

α,β-Unsaturated ketones could also be reacted in the above aza-type *Michael* addition. The resulting β-amino ketones were obtained in moderate to good yields (*Table 2*, *Entries 3* and *9*). A control experiment (in the absence of catalyst) showed no desired adduct of α,β-unsaturated ketones with aliphatic amines.

The above results indicated interesting, but also perplexing, effects of aqueous aza-type *Michael* reactions. The effects of solvent (H_2O) and different *Lewis* acids in this type of transformation will be the subject of further studies. From a synthetic point of view, the observed rate-enhancing effects can be translated into a practically useful aza-type *Michael* procedure.

Conclusions. – Several inexpensive and easy-to-handle transition-metal-salt catalysts, especially $FeCl_3 \cdot 7\,H_2O$, $CrCl_3 \cdot 6\,H_2O$, and $SnCl_4 \cdot 4\,H_2O$, among others, were found to be effective in mild aza-type *Michael* additions of aliphatic and even aromatic amines to α,β-unsaturated electrophiles (esters, ketones, and nitriles) in H_2O at ambient temperature. Our reaction protocol opens up a novel entry to the synthesis of β-amino carbonyl compounds and analogs thereof by a simple and high-yielding procedure. Also, the successful application of these inexpensive catalysts should trigger the development of *asymmetric* aza-type *Michael* reactions, as well as industrialization. Current efforts are focused on these approaches.

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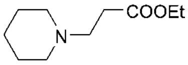
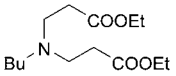
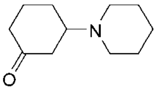
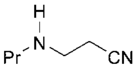
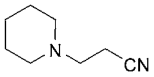
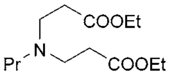
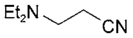
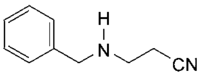
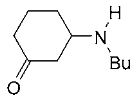
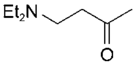
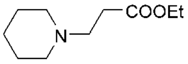
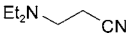
Table 2. *Transition-Metal-Catalyzed Aqueous Aza-Type* Michael *Reactions of Various α,β-Unsaturated Electrophiles with Different Aliphatic Amines.* Conditions: 1 and 1.2 equiv. of electrophile and amine, resp, 0.1 equiv. of catalyst; in H_2O at ambient temperature for 15 h.

Entry	Catalyst	Electrophile	Amine	Product	Yield[a]) [%]
1	$Co(OAc)_2$	Ethyl acrylate	Piperidine		Quant.
2	$Co(OAc)_2$	Ethyl acrylate	$BuNH_2$		92
3	$Co(OAc)_2$	Cyclohex-2-enone	Piperidine		82
4	$Co(OAc)_2$	Acrylonitrile	$PrNH_2$		92
5	$Co(OAc)_2$	Acrylonitrile	Piperidine		Quant.
6	$FeCl_3 \cdot 7\,H_2O$	Ethyl acrylate	$PrNH_2$		Quant.
7	$FeCl_3 \cdot 7\,H_2O$	Acrylonitrile	Et_2NH		Quant.
8	$FeCl_3 \cdot 7\,H_2O$	Acrylonitrile	$BnNH_2$		98
9	$FeCl_3 \cdot 7\,H_2O$	Cyclohex-2-enone	$BuNH_2$		67
10	$Cu(OAc)_2$	Methyl vinyl ketone[b])	Et_2NH		Quant.
11	$Cu(OAc)_2$	Ethyl acrylate	Piperidine		Quant.
12	$Cu(OAc)_2$	Acrylonitrile	Et_2NH		Quant.

[a]) Isolated. [b]) Systematic name: but-3-en-2-one.

Experimental Part

General. All solvents and reagents were commercially available and used as received. Thin-layer chromatography (TLC): silica gel F_{254} (pre-coated plates), visualization under UV light. Flash-column chromatography (FC): silica gel (100–200 mesh). ^{1}H- and ^{13}C-NMR spectra: at 400 and 100 MHz, resp., chemical shifts δ referenced to internal solvent signals. All compounds were fully characterized by TLC, GC, FT-IR, ^{1}H- and ^{13}C-NMR, GC-MS (*Agilent 6890N–5973N*; *HP-5MS*), and MS.

General Procedure for Aqueous Aza-Type Michael *Addition Reactions.* To a transition-metal-salt catalyst (0.1 mmol, 0.1 equiv.) in H_2O (3 ml) were added the α,β-unsaturated electrophile (1 mmol) and the amine (1.2 mmol), and the mixture was stirred for 15–24 h at r.t. Then, the mixture was extracted with CH_2Cl_2, and the combined org. layers were dried (Na_2SO_4), filtered, and evaporated. The resulting crude product was purified by FC (SiO_2).

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