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CATALYSIS OF THE SPECIFIC MICHAEL ADDITION :
THE EXAMPLE OF ACRYLATE ACCEPTORS

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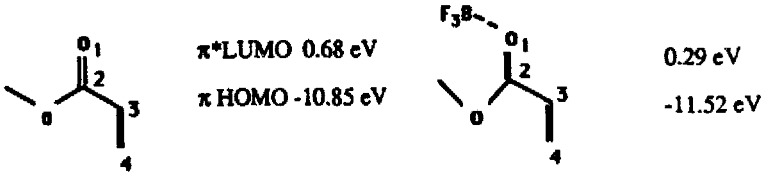
Summary : Lewis acids, ferric chloride in particular, catalyze the addition of amine nucleophiles to acrylates. Yields are very good, under mild conditions. Exclusive 1,4-addition occurs, and polymerization is avoided.

We return to the Michael reaction[1]. We had earlier provided with xonotlite doped with potassium t-butoxide an efficient basic catalyst for the reaction of charged nucleophiles as Michael donors[2]. We address here the important complementary question of catalysis of the Michael reaction, with a neutral nucleophile , and when the acidic catalyst interacts with the Michael acceptor.

We opted for catalysis of the Michael addition of amine nucleophiles to acrylates, for two strong reasons. One is the wealth of biochemical reactions one such 1,4-adduct, β-alanine, undergoes : as a neutal inhibitory transmitter; as a precursor of malonyl-CoA, of carnosine, and of coenzyme A via panthothenic acid[3]. The other is the high yield (90%) access these 1,4-amino adducts from primary amines give to β-lactams[4].

Molecular orbital calculations (MINDO-3)[5] gave us a further inducement. With methyl acrylate as the model (Table 1) complexation at O-1 by BF_3 as the prototypical Lewis acid brings down significantly the Michael acceptor LUMO, i.e. the orbital accommodating the electron pair from the nucleophile.



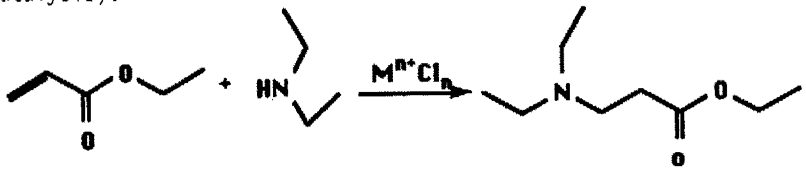
	coeff.	charge	coeff.	Δ	charge	Δ
O-1	-0.2936	-0.5671	-0.2797	0.0139	-0.5532	0.0139
C-2	0.4440	0.8490	0.5298	0.0858	0.8545	0.0055
C-3	0.4936	-0.1396	0.4140	-0.0796	-0.1565	-0.0169
C-4	-0.6659	0.0858	-0.6381	0.0278	0.1138	0.0280

Table 1 - Calculation of Free and BF_3-Complexed Methyl Acrylate : coefficients in the Π^*- Type LUMO and Atomic Charge.

The charge at C-2 is more than five times greater than the charge at C-4. Yet, orbital control[6] will favor C-4 with an atomic orbital coefficient greater than that at C-2 by 20%. These conclusions are consonant with ab initio calculations at the 6-21 G and 6-21 G* levels of lithium and borane complexation of methyl acrylate[7]. We did not attempt a full exploration of the s-cis/s-trans preference at the semi-empirical level of our calculations.

Accordingly, we chose as our model reaction addition of diethylamine (3 mmol) to ethyl acrylate (3 mmol). We study its results as a function of catalyst type : hard Lewis acids (Table 2), borderline or soft Lewis acids (Table 3), and various heterogeneous catalysts (Table 4).

Experimental. The reactions are carried out with 3 mmol of each of the reactants in 40 mL of solvent, methylene chloride generally. The catalysts are the stated metallic chlorides of best commercial purity, or the K10 montmorillonite (Süd-Chemie) exchanged with various metallic chlorides using our standard procedure[8], or the likewise copper(II)-exchanged Y zeolithe. Workup proceeds, either by filtration through a silicagel column followed by concentration under a rotary evaporator (homogeneous catalysis); or by filtration followed by rotary evaporation (heterogeneous catalysis).



Reaction: Time,h	Temp.,°C	Cat.(mol eq.)	% Yield
64	25	-	68
42	25	$FeCl_3$(0.1)	96
21	25	$FeCl_3$(0.1)	61
18	25	$AlCl_3$(1.0)	72
39	25	LiCl(0.1)	79
42[a]	25[a]	LiCl(0.1)	83
38	25	$TiCl_4$(0.5)	polym.

[a] in acetonitrile

Table 2 : Hard Lewis Acid Catalysis of 1,4-Addition of Diethylamine Onto Ethyl Acrylate, in Methylene Chloride Solution.

Reaction :Time,h	Temp.,°C	Cat.(mol eq)	% Yield
64	25	$HgCl_2$(0.1)	93
24	25	ZnI_2(0.3)	63
144	25	$ZnCl_2$(0.5)	61
24	25	$CuCl_2$(0.5)	polym.
24	40	HgCl(0.25)	50
20[a]	78[a]	HgCl(0.25)	81
48[b]	25[b]	HgCl(0.25)	66
48[c]	110[c]	CuCl(0.15)	83
168	25	CuCl(0.5)	58

[a] in acetonitrile [b] in diethyl ether [c] in toluene

Table 3. Borderline and Soft Lewis Acid Catalysis of 1,4-Addition of Diethylamine Onto Ethyl Acrylate, in Methylene Chloride Solution.

Reaction :Time, h	Temp.,°C	Cat.(amount,g)	% Yield
24	25	K10/Li$^+$(0.4)	75
144	25	zeolithe Y/Cu^{2+}(0.4)	81
28[a]	25[a]	K10/Co^{2+}(0.4)	65
27[a]	110[a]	K10/Fe^{3+}(0.4)	80
24	25	K10/Li$^+$(0.4)	-

[a] in toluene

Table 4. Heterogeneous Catalysis of 1,4-Addition of Diethylamine Onto Ethyl Acrylate, in Methylene Chloride Solution.

The uniform result is 1,4 addition. It has to be put into perspective; this is the background for the dual reactivity of α,β-unsaturated carbonyls as either 1,2- or 1,4 (Michael)-acceptors :

(i) *steric hindrance of the Michael acceptor at* C-4 drives the addition to the 1,2-mode[9], at C-2 makes it occur predominantly in the 1,4-mode[10];

(ii) *kinetic versus thermodynamic control*, HCN additions give either the 1,2 kinetic product or the 1,4 thermodynamic product[11]. Heathcock has given the textbook example of the switch from predominant (97:3) 1,2-addition under kinetic control at -78°C to predominant (96:4) 1,4-addition under thermodynamic control at +25°C[10];

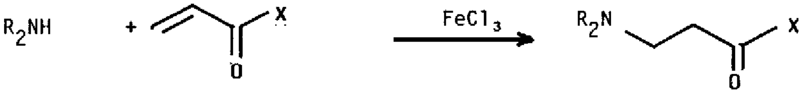
(iii) *orbital control by the hardness of the nucleophile.*
Soft nucleophiles, such as flattened carbanions with delocalized charge or phosphorus, seek out the larger atomic orbital coefficient at C-4 in the unperturbed Michael acceptor. Hard nucleophiles, such as pyramidal carbanions with localized charge, add to a different Michael acceptor that has been polarized by attachment to O-1 of the counterion and whose bigger relevant atomic orbital coefficient is now at C-2[6,12-14].

Conditions have been evolved so that addition occurs exclusively 1,4. Gilman reagents R_2CuLi and higher-order cuprates $R_2Cu(CN)Li_2$ have this feature, which has been used for instance, in combination with boron trifluoride activation, for addition to a highly hindered position, in the context of a coriolin synthesis[15-16]

The exclusive 1,4-addition observed here is probably due simply to the reaction being under thermodynamic rather than kinetic control. And this is consistent with the usual pattern of α,β-unsaturated esters giving more 1,4-addition than do enones. The important finding is that Lewis acids do catalyze addition of the secondary amine significantly nevertheless, and in catalytic amounts. Ferric chloride gives a quantitative yield (96%) of the adduct under very mild reaction conditions.

We investigated the generality of this useful finding studying the addition reaction of various amines to Michael acceptors with ferric chloride as catalyst (Table 5).

Amino adducts were readily formed in high yields. Secondary amines gave exclusively 1,4-amino adducts. With the primary amine n-butylamine a di-adduct was formed in addition to the mono-adduct. The best results were obtained with the Michael acceptor ethylacrylate. Only the too reactive acrolein gave polymers.



	amines	X	% Yield
a	Diethylamine	OEt	96
b	Diethylamine	Me	82
c	Diethylamine	H	polym
d	Piperidine	OEt	97
e	Piperidine	Me	90
f	Morpholine	OEt	90
g	Morpholine	Me	87
h	Pyrrolidine	OEt	95
i	Pyrrolidine	Me	88
j	n-Butylamine	OEt	79

Table 5 : Ferric chloride catalysis of 1,4-addition of amines onto Michael acceptors in methylene chloride solution.

Experimental : The reactions are carried out as above but with the same amount of catalyst (0.1 mol.eq) during 42 h at 25 °C in 20 mL of dry methylene chloride. The mixture is washed with saturated aqueous sodium sulfate and evaporated. The ^{1}H nmr spectral data are as follows :

^{1}H nmr ($CDCl_3$) δ

a	4.13 (2H,q,OCH_2), 2.80 (2H,t,NCH_2), 2.46 (4H,q,CH_2NCH_2), 2.44 (2H,t,CH_2CO), 1.26 (3H,T,CH_3), 1.03 (6H,t,CH_3)
b	2.69 (2H,t,NCH_2), 2.52 (4H,t,CH_2NCH_2), 2.40 (2H,t,CH_2CO), 1.89 (3H,s,CH_3CO), 0.96 (6H,t,CH_3)
d	4.05 (2H,q,OCH_2), 2.58 (2H,t,CH_2N), 2.41 (2H,t,CH_2N), 2.31 (4H,t,CH_2N), 1.51-1.34 (6H,m,CH_2), 1.17 (3H,t,CH_3)
e	2.50 (4H,s,$CO(CH_2)_2N$), 2.24 (4H,t,CH_2N), 2.03 (3H,s,CH_3), 1.46-1.30 (6H,m,CH_2)
f	4.07 (2H,q,OCH_2), 3.62 (4H,t,CH_2OCH_2), 2.61 (2H,t,NCH_2), 2.40 (6H,t,CH_2), 1.17 (3H,t,CH_3)
g	3.66 (4H,t,CH_2O), 2.61 (4H,s,$N(CH_2)_2CO$), 2.41 (4H,t,CH_2N), 2.14 (3H,s,CH_3)
h	4.10 (2H,q,OCH_2), 2.74 (2H,t,NH_2), 2.49 (6H,t,CH_2), 1.74 (4H,m,CH_2), 1.22 (3H,t,CH_3)
i	2.66 (4H,m,$N(CH_2)_2CO$), 2.47 (4H,m,CH_2N), 2.14 (3H,s,CH_3), 1.76 (4H,m,CH_2)
j	4.10 (2H,q,CH_2O), 2.84-2.35 (6H,m,CH_2), 1.71 (1H,s,NH), 1.43-1.28 (4H,m,CH_2), 1.22 (3H,t,CH_3), 0.88 (3H,t,CH_3)

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