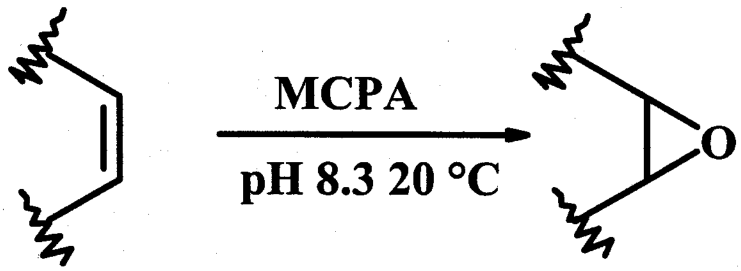
WATER PROMOTED ORGANIC REACTIONS

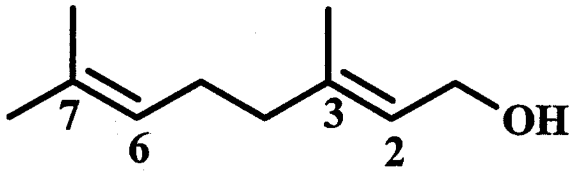
EPOXIDATION OF ALKENES



Alkene	t (h)	Yield (%)
Cyclopentene	0.5	95
Cyclohexene	0.5	90
Cyclooctene	0.5	95
Methylencyclohexane	0.5	30
(+)-3-Carene	0.5	90
1-Octene	8	95
(-)-Carvone	1	95
Styrene	1	95
α-Methylstyrene	3	70
trans β-Methylstirene	1	93
Indene	1	60

F. Fringuelli, R. Germani, F. Pizzo, G. Savelli, *Tetrahedron Lett.*, **30** 1427 (1989)
Org. Prep. Proc. Inter., **21**, 757 (1989)

EPOXIDATION OF GERANIOL IN ORGANIC SOLVENTS

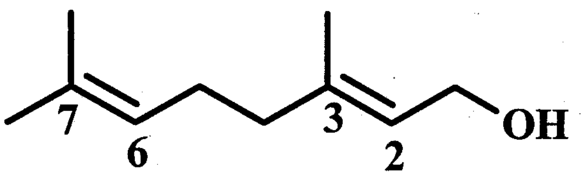


Oxidant	Reaction Conditions			Epoxides (%)		
	Solvent	Temp (°C)	Time (h)	2,3	6,7	2,3 - 6,7
MO_5.HMPT[a]	CH_2Cl_2	20	0.2	100		
Bu_2SnO/TBHP	C_6H_6	60	3	100		
$Ti(O^iPr)_4$/TBHP/DET	CH_2Cl_2	-20	0.75	100		
$VO(acac)_2$/TBHP	C_6H_6	80	4	98	2	
MCPBA	Emulsion[b]	25	20	100		
$PhSeO_3H$	MeOH	r.t.	0.5	13	87	
CH_3CO_3H	CH_2Cl_2	-5	3	43	36	21
MCPBA	CH_2Cl_2	25	1	30	57	13
MPPA	$CHCl_3$	25	2	22	52	26

[a] M = Mo (VI), W (VI); [b] n-hexane, n-octanol, water, surfactant

WATER PROMOTED ORGANIC REACTIONS

REGIOSELECTIVE EPOXIDATION OF GERANIOL WITH MPPA



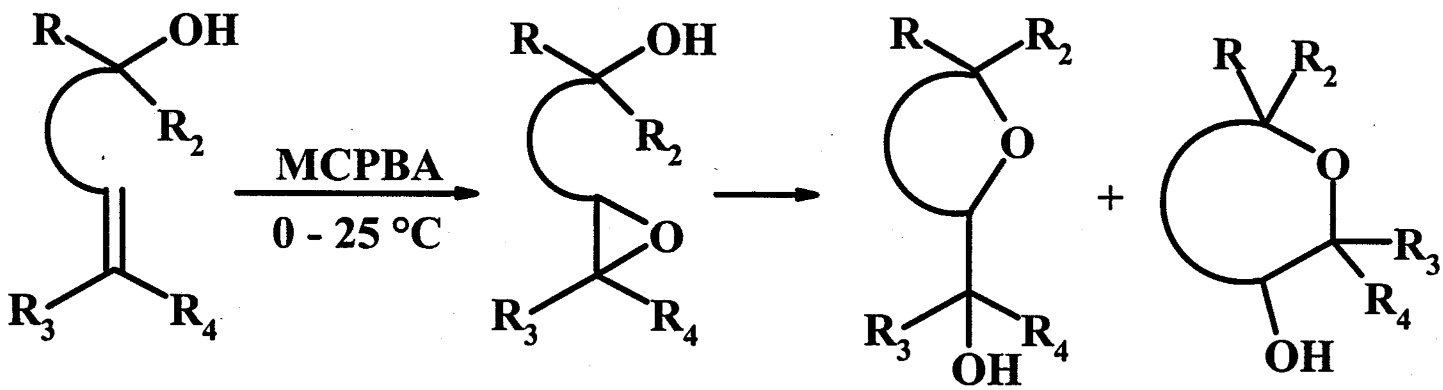
Reactions Conditions			Epoxides (%)		
pH	**T (°C)**	**t (h)**	**2,3**	**6,7**	**2,3 - 6,7**
8.3 ($NaHCO_3$)	**2**	**2**		**72**	**28**
12.5 (NaOH)	**25**	**2**	**92**		**8**
12.5 (CTAOH)	**25**	**15**	**98**		**2**

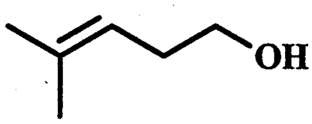
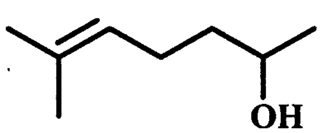
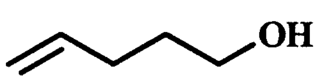
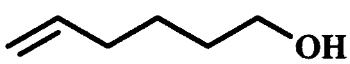
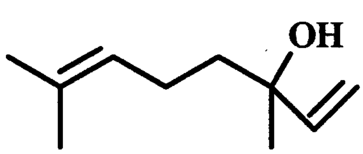
MPPA = Monoperoxyphthalic acid

F. Fringuelli, F. Pizzo, R. Germani *Synlett* 495 (1991)

WATER PROMOTED ORGANIC REACTIONS

EPOXIDATION OF HOMO AND BIS-HOMOALLYLIC ALCOHOLS



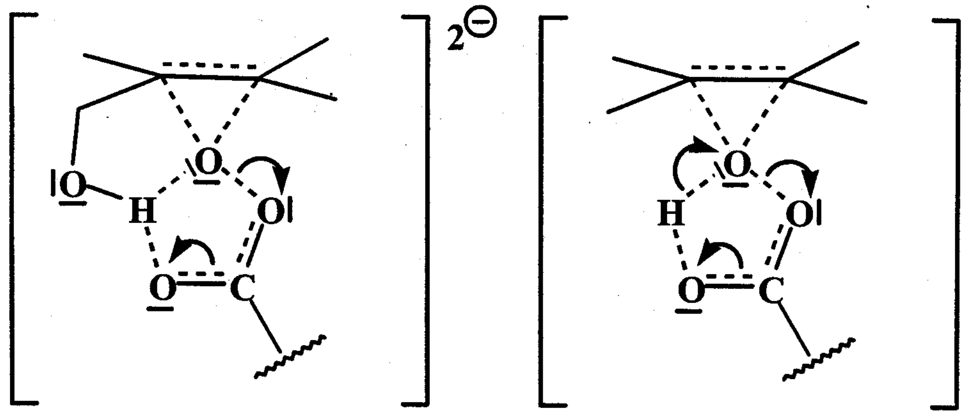
	H_2O (pH 7 - 8.3)		CH_2Cl_2	
	Epoxide (%)	Cycloadduct (%)	Epoxide (%)	Cycloadduct (%)
	100	0	90	10
	98[a]	2	10[a]	90
	56	21	40	60
	100	0	45	55
	98[a]	2	69[a]	31

a: 1,1 diastereoisomeric mixtures

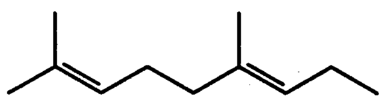
F. Fringuelli, R. Germani, F. Pizzo, M.J. Suarez: *unpublished results*

WATER PROMOTED ORGANIC REACTIONS

REGIOSELECTIVE EPOXIDATION OF ALLYLIC ALCOHOLS



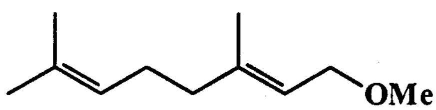
A B



(desoxygeraniol)

pH 12.5 (NaOH) → no reaction

pH 12.5 (CTAOH) → epoxides (5%)



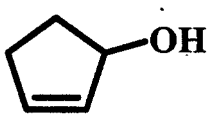
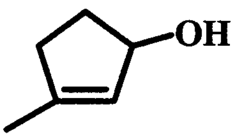
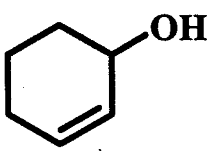
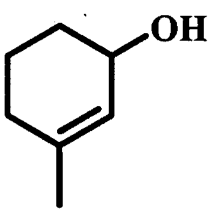
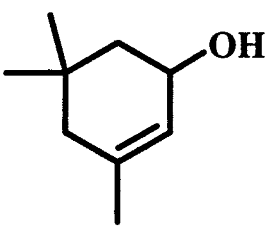
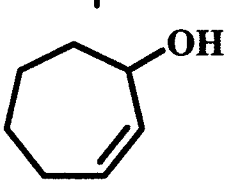
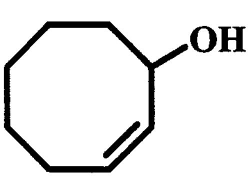
(methyl geranil ether)

pH 12.5 (NaOH) → no reaction

pH 12.5 (CTAOH) → no reaction

F. Fringuelli, R. Germani, F. Pizzo, F. Santinelli, G. Savelli *J. Org. Chem.*, **57**, 1189 (1992)

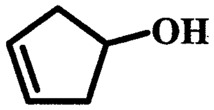
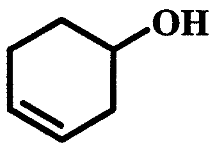
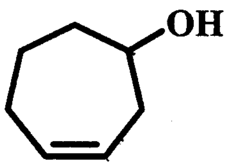
EPOXIDATION OF ALLYL-CYCLOALKENOLS

Cycloalkenol	Monoperoxyphtalic acid (MPPA)						Aryl Peroxyacid [a]		
	Water pH 8-9			Water pH 12-13			Organic Solvent		
	t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)
	3	9:1	83	6	>100:1	74	24	5.2:1	80
	0.5	9:1	86	5	99:1	80	0.5	19:1	80
	3	7:1	91	18	99:1	85	-	50:1	76
	1	10:1	90	14	>100:1	95	0.25	>100:1	100
	1	99:1	90	15	>100:1	85	15	24:1	70
	5	1:1	80	10	1:1.6	88	24	1.6:1	95
	1	1:100	86	0.5	<1:100	90	24	<1:100	81

[a] MCPBA or MPPA in CH_2Cl_2

D. Ye, F. Fringuelli, O. Piermatti, F. Pizzo *J. Org. Chem*, **62**, 3748 (1997)

EPOXIDATION OF HOMOALLYL CYCLOALKENOLS

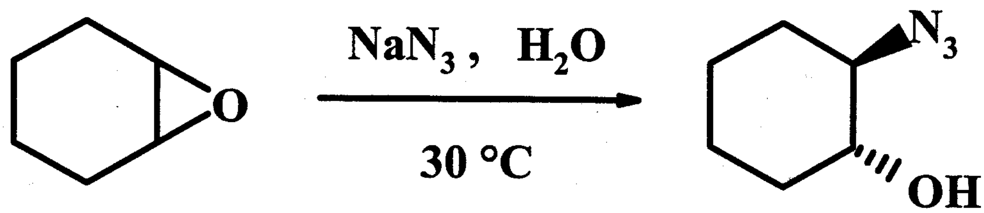
	Monoperoxyphtalic acid (MPPA)						Aryl Peroxyacid [a]		
Cycloalkenol	Water pH 8-9			Water pH 12-13			Organic Solvent		
	t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)	t (h)	cis:trans	Y (%)
	2	7:1	70	2	>100:1	68	1	24:1	70
	0.5	1:1	89	15	>100:1	48	2	85:15	90
	1	1.2:1	90	16	99:1	80	2	3:1	90

[a] MCPBA or MPPA in CH_2Cl_2

D. Ye, F. Fringuelli, O. Piermatti, F. Pizzo *J. Org. Chem*, **62**, 3748 (1997)

WATER PROMOTED ORGANIC REACTIONS

AZIDOLYSIS OF 1,2-EPOXYCYCLOHEXANE



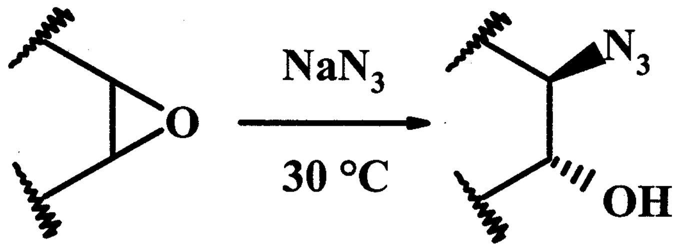
Entry	pH	salt	t(h)	Azido alcohol (%)	Diol (%)
1	9.5	-	12	100	
2	9.5	$Yb(OTf)_3$	12	100	
3	9.5	$LiClO_4$	6	100	
4	9.5	CTAB	6	97	3
5	4.2[a]	-	0.5	100[b]	
6	3.5[a]	-	0.5	87	13
7	2.5[c]	-	0.5	68	32

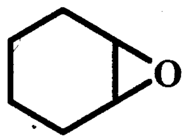
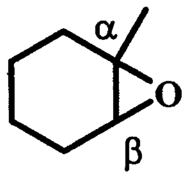
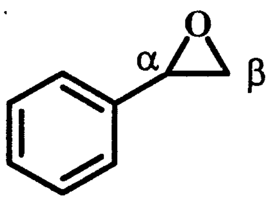
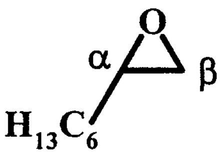
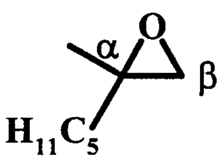
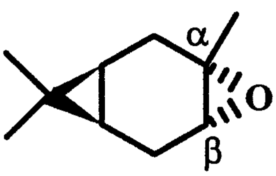
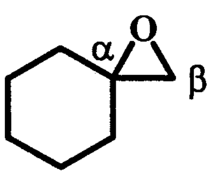
a –AcOH; b -Yield of isolated product 90%, c - H_2SO_4

F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro *J. Org. Chem.*, **64**, 6094 (1999)

WATER PROMOTED ORGANIC REACTIONS

AZIDOLYSIS BY SODIUM AZIDE OF EPOXIDES IN AQUEOUS MEDIUM AT 30 °C

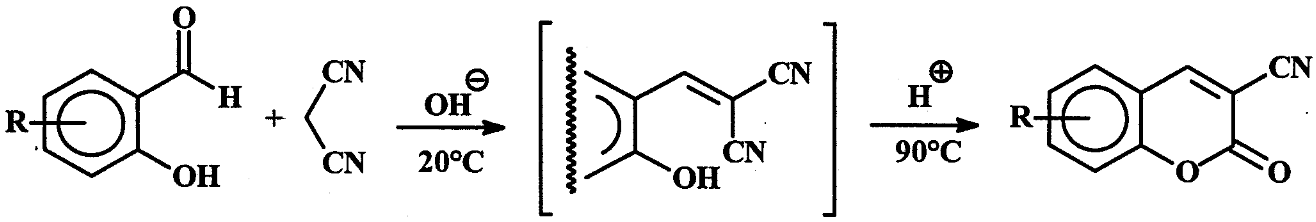


	Epoxide	pH	time (h)	regioselectivity (α/β attack)	Products (%) Azidoalcohols	Products (%) diol	yield (%)
1		9.5	12		100	-	90
		4.2	0.5		100	-	90
2		9.5	12	35/65	100	-	50
		4.2	1.5	80/20	100	-	67
3		9.5	13	97/3	100	-	90
		4.2	0.3	97/3	100	-	92
4		9.5	24	4/96	100	-	88
		4.2	4	30/70	100	-	
5		9.5	28	2/98	100	-	90
		4.2	3	85/15	96	4	70
6		9.5	60	35/65	100	-	55
		4.2	48	86/14	92	8	70
7		9.5	20	3/97	88	12	77
		4.2	1.5	70/30	94	6	58

F. Fringuelli, O. Piermatti, F Pizzo, L. Vaccaro *J.Org. Chem.* **64**, 6094 (1999)

WATER PROMOTED ORGANIC REACTIONS

ONE - POT SYNTHESIS OF 3-CYANOCOUMARINS

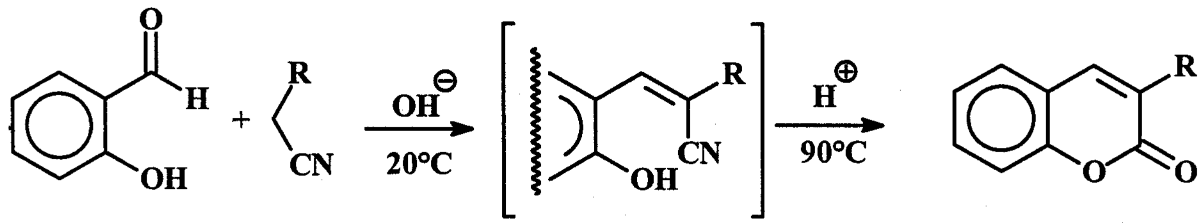


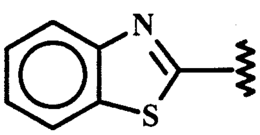
R	pH[a]	t (h)[b]	Yield (%)
H	8.3	2 - 3	90
4-OH	8.3	4 - 2	75
4-OMe	8.3	14 - 2	92
4,6-$(OMe)_2$	12.4	5 - 2	90
3-OH	8.3	4 - 1	85
5-NO_2	8.3	1 - 1	80
5,6-$(CH{=}CH)_2$	12.4	2 - 2	80

a: condensation step
b: condensation and cyclization steps

G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, *Heterocycles,* **43**, 1257 (1996)

ONE-POT SYNTHESIS OF 3-SUBSTITUTED COUMARINS



R	pH[a]	t (h)[b]	Yield (%)
CN	8.3	2 - 2.5	90
CO_2Et	8.3	3 - 2	87
NO_2	8.3	1 - 1	66
Ph	12.4	11[c]	90[d]
pNO_2-C_6H_4	8.3	20 - 4	96[d]
Ph-SO_2	8.3	20 - 4	85[d]
α-Pyridyl	12.4	3[c]	98
α-Thienyl	12.4	6 - 1	95[d]
	13.0	8 - 0.5	93[d]

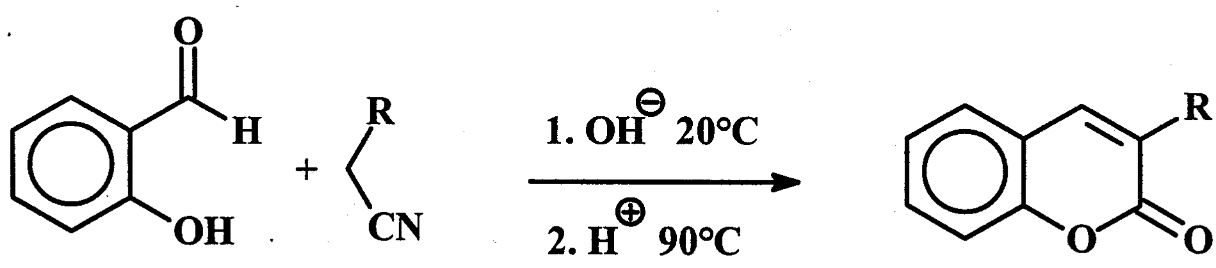
a: condesation step
b: condensation and cyclization steps
c: all the process at pH = 12.4 and at 90° C
d: in the presence of CTAB

G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, *Heterocycles,* **43**, 1257 (1996)

WATER PROMOTED ORGANIC REACTIONS

ONE-POT SYNTHESIS OF 3-SUBSTITUTED COUMARINS:

THE WATER EFFECT



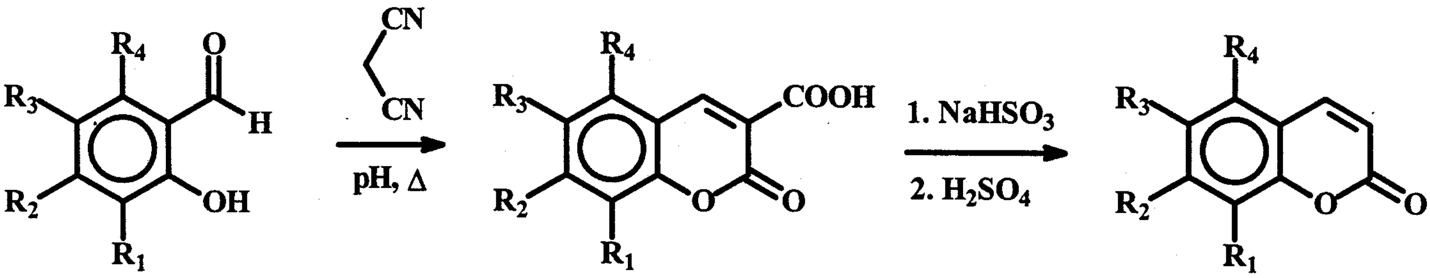
R	t (h)	Yield (%)	
		EtOH	H_2O
CN	4.5	70	90
CO_2Et	5	80	87
NO_2	2	35	66
Ph	11	traces	90[a]
α-Pyridyl	3	55	98
α-Thienyl	7	20	95[a]

a: in the presence of CTAB

G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, *Heterocycles,* **43**, 1257 (1996)

WATER PROMOTED ORGANIC REACTIONS

ONE-POT SYNTHESIS OF NATURAL COUMARINS

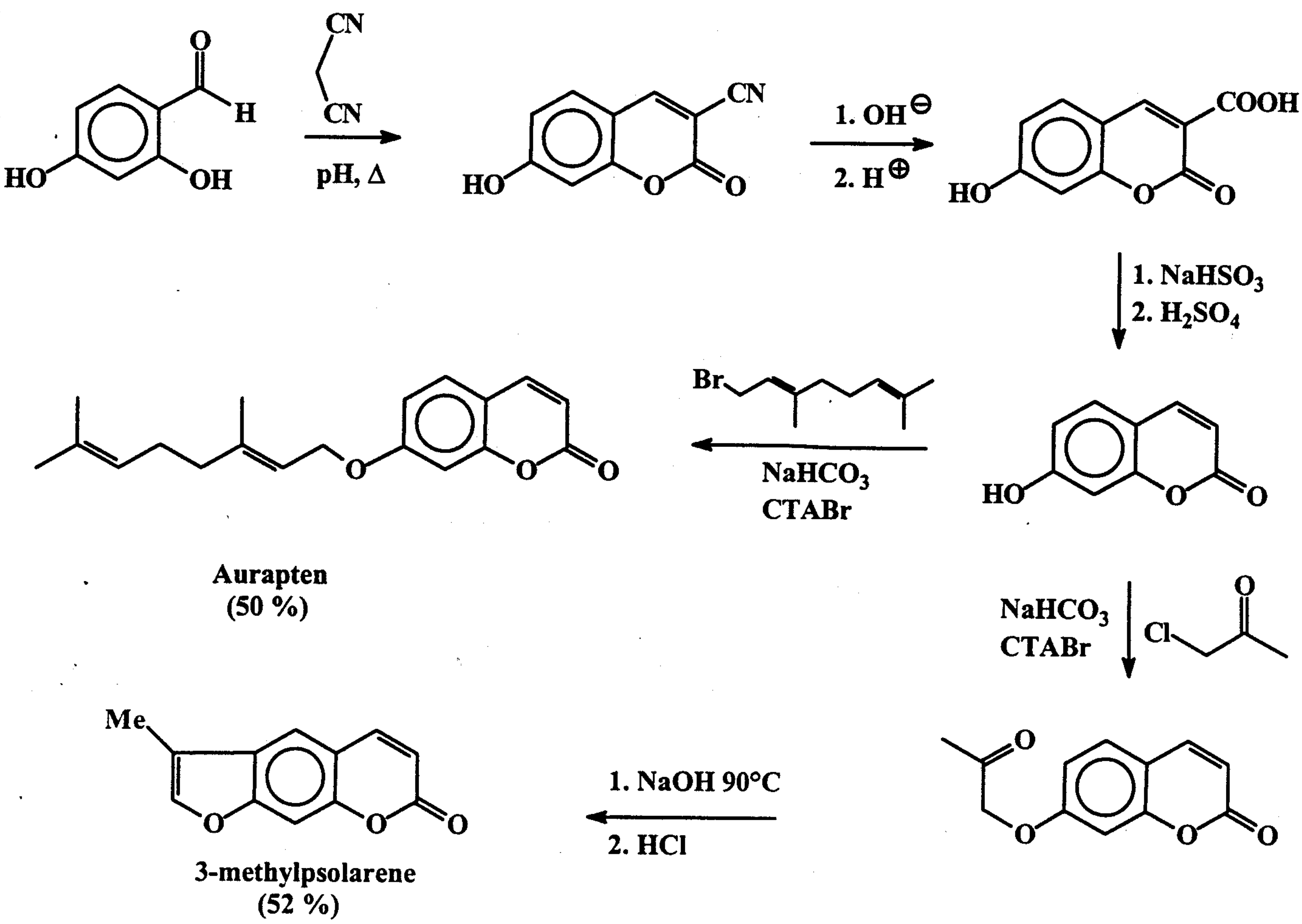


R_1	R_2	R_3	R_4	Coumarin	Yield (%)
H	OH	H	H	Umbelliferone	77
H	OMe	H	H	Herniarin	84
H	OMe	H	OMe	Limettin	50
OH	OH	H	H	Daphnetin	50
H	$-O-CH_2-O-$		H	Ayapin	70

F. Fringuelli, O. Piermatti, F. Pizzo *unpublished results*

WATER PROMOTED ORGANIC REACTIONS

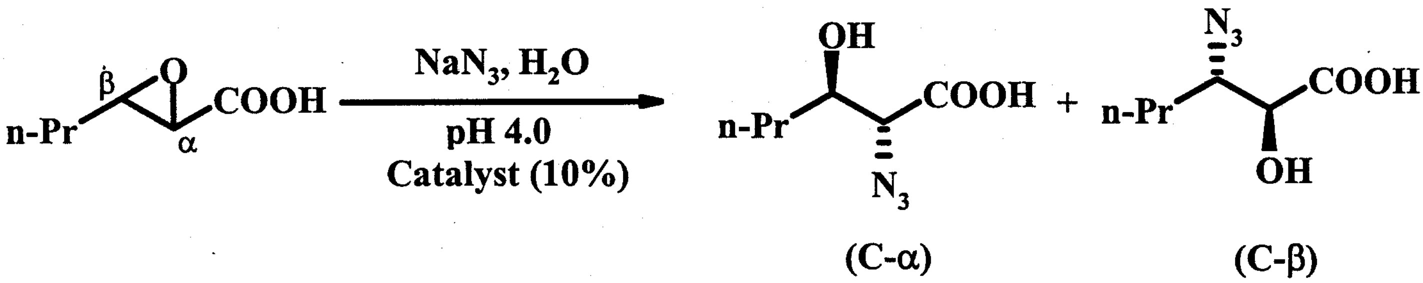
ONE-POT SYNTHESIS OF AURAPTEN AND 3-METHYLPSOLARENE



F. Fringuelli, O. Piermatti, F. Pizzo *unpublished results*

WATER PROMOTED ORGANIC REACTIONS

$Cu(NO_3)_2$ CATALYZED AZIDOLYSIS OF *trans*-α,β-EPOXYHEXANOIC ACID



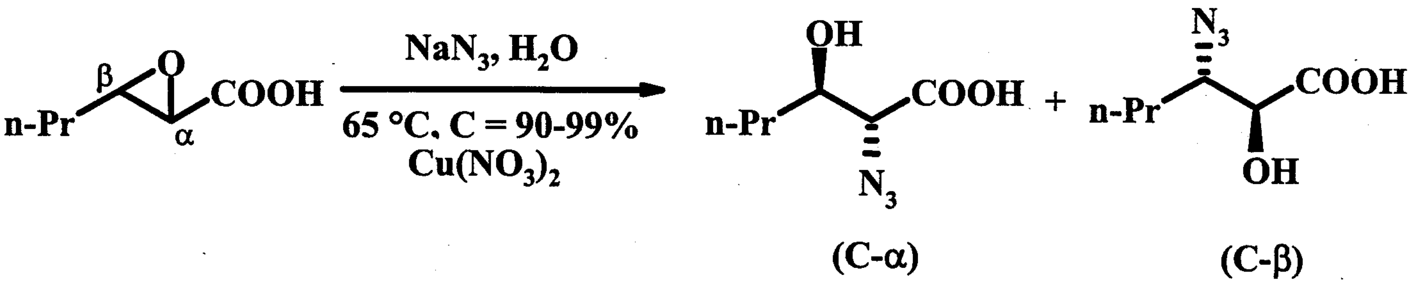
Entry	Catalyst	Medium	T(°C)	t (h)	C (%)[a]	C-α	C-β
1	-	water	30	96	40	56	44
2	NH_4Cl[b]	$MeOH/H_2O$ (8/1)	65	29	43	40	54[c]
3	$Mg(NO_3)_2$	water	30	18	15	49	51
4	$ZrCl_4$	water	30	18	65	8	92
5	$CoSO_4$	water	30	18	71	8	92
6	$Ni(NO_3)_2$	water	30	18	74	4	96
7	$Zn(NO_3)_2$	water	30	18	91	4	96
8	$Cu(NO_3)_2$	water	65	1.5	> 99	< 1	> 99
9	$Cu(NO_3)_2$	water	30	18	> 99	< 1	> 99

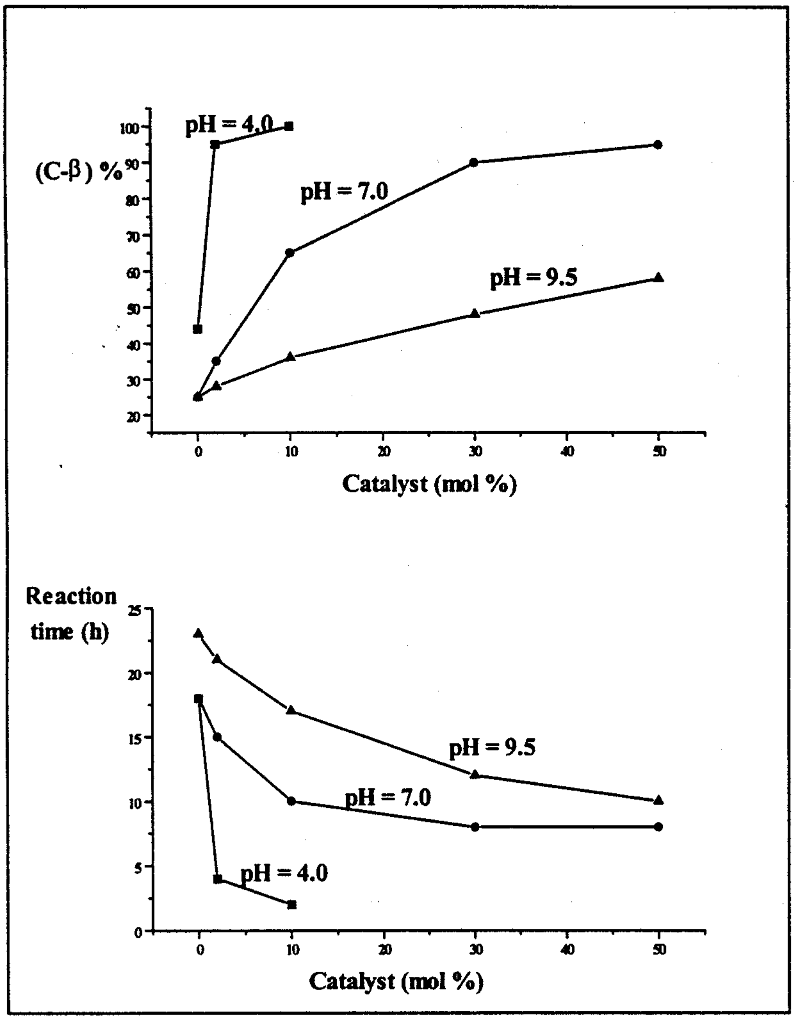
a- Conversion reaction; b- 2.2 mol/eq.; c- The remain 6% was *syn C*-α product

F. Fringuelli, F. Pizzo and L. Vaccaro, *Synlett* 311 (2000)

WATER PROMOTED ORGANIC REACTIONS

$Cu(NO_3)_2$ CATALYZED AZIDOLYSIS OF *trans*-α,β-EPOXYHEXANOIC ACID



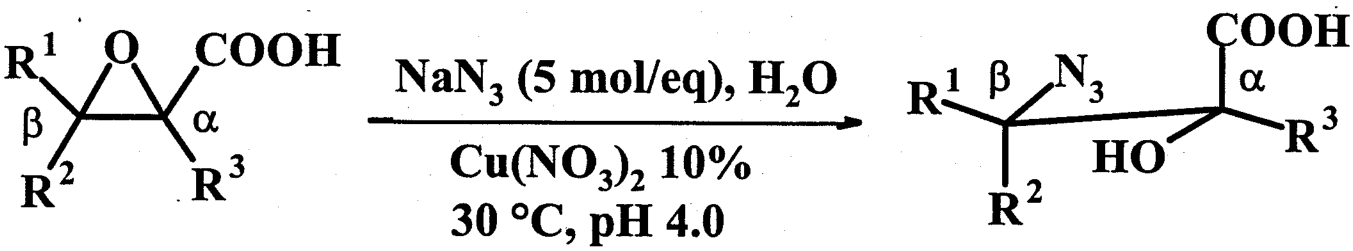


pH	% (C – β)	% Cat.	h
4.0	94	1	4
4.0	100	10	1.5
7.0	65	1	14
7.0	96	50	7
9.5	30	10	17
9.5	58	200	8
4.0	44	-	23
7.0	24	-	18
9.5	22	-	23

F. Fringuelli, F. Pizzo and L. Vaccaro, *Unpublished results*

WATER PROMOTED ORGANIC REACTIONS

$Cu(NO_3)_2$ CATALYZED AZIDOLYSIS OF α,β-EPOXYCARBOXYLIC ACIDS



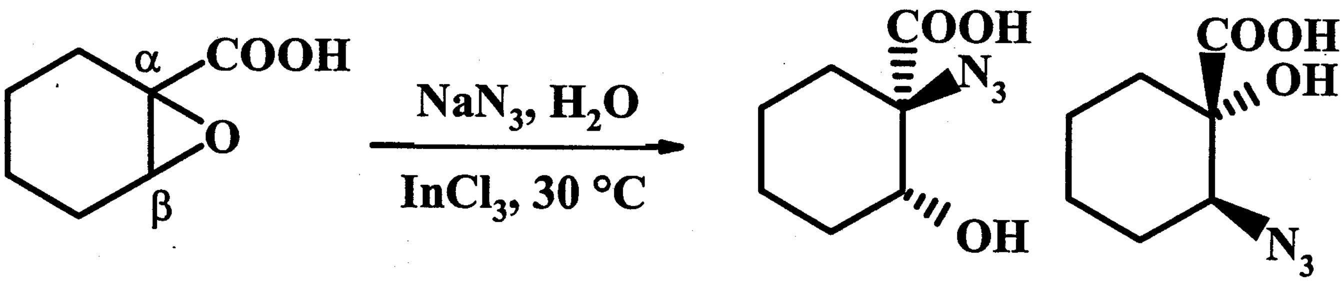
Entry	R^1	R^2	R^3	t(h)	C(%)[a]
1	H	Me	H	16	99
2	H	n-Pr	H	18	99
3	Me	Me	H	3	99
4	H	Et	Me	12	99
5	H	$CH_2(CH_2)_2CH_2$		0.25	99
6	H	Ph	H	0.25	99

a Based on GC analysis of methyl esters; Yield of isolated pure products 94-95 %

F. Fringuelli, F. Pizzo and L. Vaccaro, *Synlett* 311 (2000)

WATER PROMOTED ORGANIC REACTIONS

$InCl_3$ CATALYZED AZIDOLYSIS OF α,β-EPOXYCYCLOHEXANE CARBOXYLIC ACID



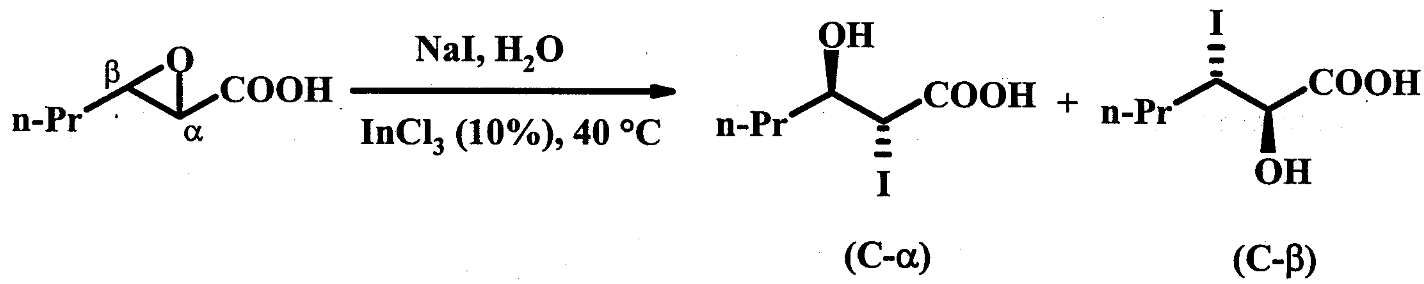
(C-α) (C-β)

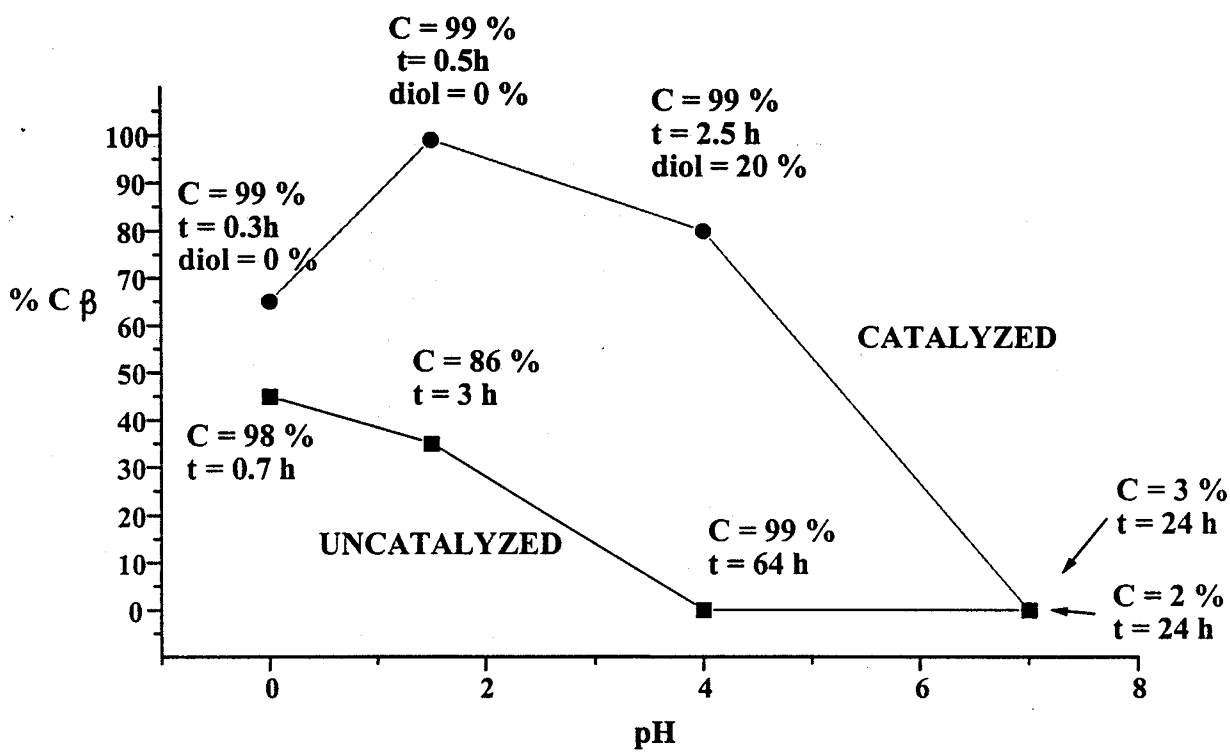
Medium	pH	$InCl_3$ (% mol)	t (h)	C(%)	(C-β)/(C-α)
MeCN	-	-	8	7	> 99/1
MeCN	-	1	8	100	> 99/1
MeCN	-	30	0.5	100	> 99/1
H_2O	7.0	-	8	50	80/20
H_2O	7.0	1	8	89	> 99/1
H_2O	7.0	30	0.5	100	98/2
H_2O	4.0	-	75	99	> 99/1
H_2O	4.0	1	1.5	100	> 99/1
H_2O	4.0	10	1/60	100	> 99/1

F. Fringuelli, F. Pizzo and L. Vaccaro, *Unpublished results*

WATER PROMOTED ORGANIC REACTIONS

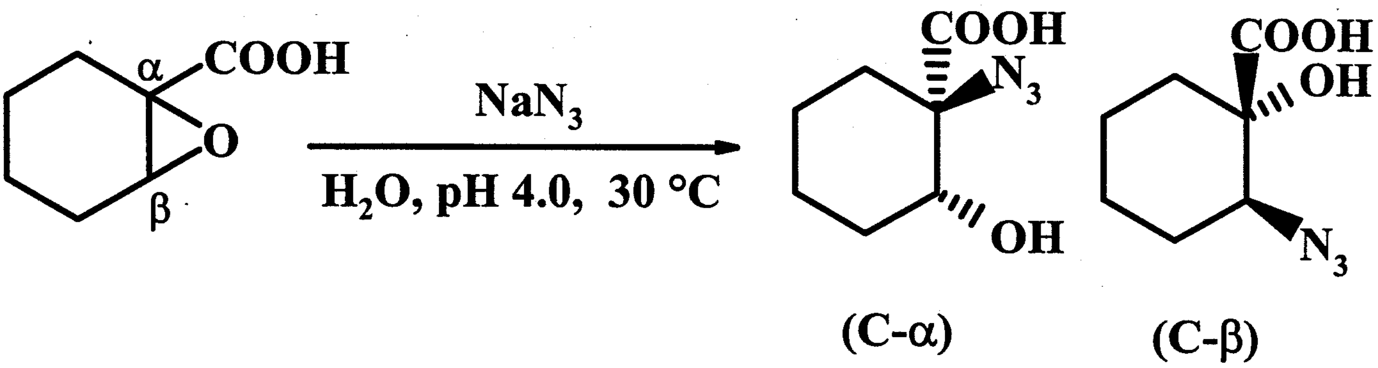
$InCl_3$ CATALYZED IODOLYSIS OF *trans*-α,β-EPOXYHEXANOIC ACID





F. Fringuelli, F. Pizzo and L. Vaccaro, *Unpublished results*

LEWIS ACIDS BELIEVED TO BE UNUSABLE IN WATER (AZIDOLYSIS OF α,β–EPOXYCYCLOHEXANE CARBOXYLIC ACID)



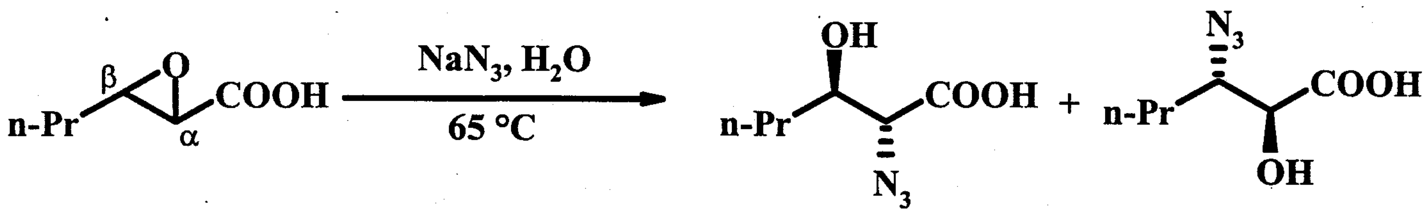
Entry	Catalyst [1 mol%]	t [h]	C[a] [%]	C-α [%]	C-β [%]	diol [%]
1	none	0.3	4	1	99	0
2	none	75	99	1	99	0
3	$Cu(NO_3)_2$	1.5	93	1	99	0
4	$InCl_3$	1.5	> 99	< 1	> 99	0
5	$AlCl_3$	0.3	> 99	< 1	> 99	0
6	$Al(NO_3)_2$	0.3	> 99	< 1	> 99	0
7	AlF_3	1	98	0	96	4

a- **Reaction Conversion; Yield of isolated products 90-95%**

F. Fringuelli, F. Pizzo and L. Vaccaro, *paper in preparation*

WATER PROMOTED ORGANIC REACTIONS

LEWIS ACIDS BELIEVED TO BE UNUSABLE IN WATER (AZIDOLYSIS OF *trans* α,β–EPOXYHEXANOIC ACID)



(C-α) (C-β)

Entry	Catalyst [1 mol%]	pH	t [h]	C[a] [%]	C-α [%]	C-β [%]	diol [%]
1	none	7.0	22	98	78	22	0
2	$Cu(NO_3)$	7.0	14	98	65	35	0
3	$AlCl_3$	7.0	22	98	69	31	0
4	$TiCl_4$	7.0	22	97	76	24	0
5	$InCl_3$	7.0	22	97	75	25	0
6	$SnCl_4$	7.0	22	98	77	23	0
7	none	4.0	24	82	54	46	0
8	$Cu(NO_3)$	4.0	4	90	6	94	0
9	$AlCl_3$	4.0	1.5	> 99	< 1	> 99	0
10	$TiCl_4$	4.0	70	75	22	35	43
11	$InCl_3$	4.0	2	> 99	< 1	> 99	0
12	$SnCl_4$	4.0	8	87	11	32	57

a- **Reaction Conversion; Yield of isolated products 90-95%**

F. Fringuelli, F. Pizzo and L. Vaccaro, *paper in preparation*

WATER PROMOTED ORGANIC REACTIONS

HYDROLYSIS CONSTANTS $K_{1,1}$ OF SOME METAL IONS

$$K_{1,1} = \frac{[M(OH)^{(x-1)}][H^+]}{[M^{x+}]}$$

Aqua ion	$pK_{1,1}$
Cu^{2+}	8.0
Al^{3+}	4.97 – 5.5
Ti^{4+}	- 0.3
In^{3+}	3 – 4
Sn^{4+}	- 0.57

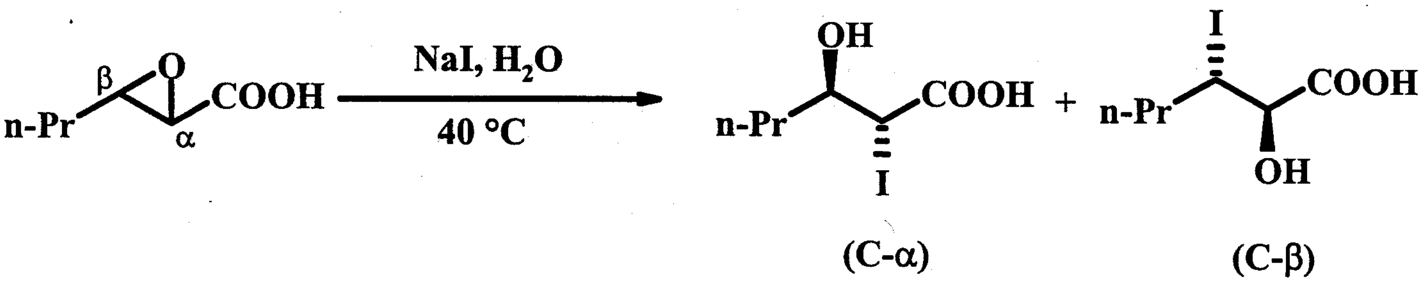
D.T Richens, The *Chemistry of Aqua Ions*, Wiley 1997

C.F. Baers, R.E. Mesmer, *The Hydrolysis of Cations,* Wiley 1976

pH	Ionic species	Active catalyst
3 – 4	Cu^{2+}, Al^{3+}, In^{3+} (aqua ions)	Yes
	Ti^{4+}, Sn^{4+} (mononuclear and polynuclear species)	No
Very low (0 – 1)	Cu^{2+}, Al^{3+}, In^{3+} (aqua ions)	Yes
	Ti^{4+}, Sn^{4+} (high concentration of aqua ions)	Yes

WATER PROMOTED ORGANIC REACTIONS

LEWIS ACIDS BELIEVED TO BE UNUSABLE IN WATER (IODOLYSIS α,β–EPOXYHEXANOIC ACID)



Entry	Catalyst [10 mol%]	pH	t [h]	C[a] [%]	C-α [%]	C-β [%]	diol [%]
1	none	4.0	64	99	99	1	0
2	$AlCl_3$	4.0	8	98	20	38	42
3	$TiCl_4$	4.0	56	95	96	4	0
4	$InCl_3$	4.0	2.5	> 99	2	78	20
5	$SnCl_4$	4.0	44	97	96	4	0
6	none	1.5	4	91	64	36	0
7	none	1.5	0.5	18	64	36	0
8	$AlCl_3$	1.5	0.5	93	2	98	0
9	$TiCl_4$	1.5	0.5	44	32	68	0
10	$TiCl_4$	1.5	2	92	33	67	0
11	$InCl_3$	1.5	0.5	> 99	2	98	0
12	$SnCl_4$	1.5	0.5	92	11	89	0

a- **Reaction Conversion. Yield of isolated products 90-95%**

F. Fringuelli, F. Pizzo and L. Vaccaro, *paper in preparation*

WATER PROMOTED ORGANIC REACTIONS

- **$AlCl_3$, $TiCl_4$ and $SnCl_4$ believed unusable to catalyze organic reactions in water, are, on the contrary, efficacious catalysts provided that they are used at suitable pH value which is related to their $pK_{1,1}$ hydrolysis constant.**

- **For the success of a Lewis-acid catalyzed organic reaction it is necessary to take in account:**

    a- The pH at which the reagents and/or products are stable

    b- The pH at which the catalyst is active

    c- The concentration of catalyst

WATER PROMOTED ORGANIC REACTIONS

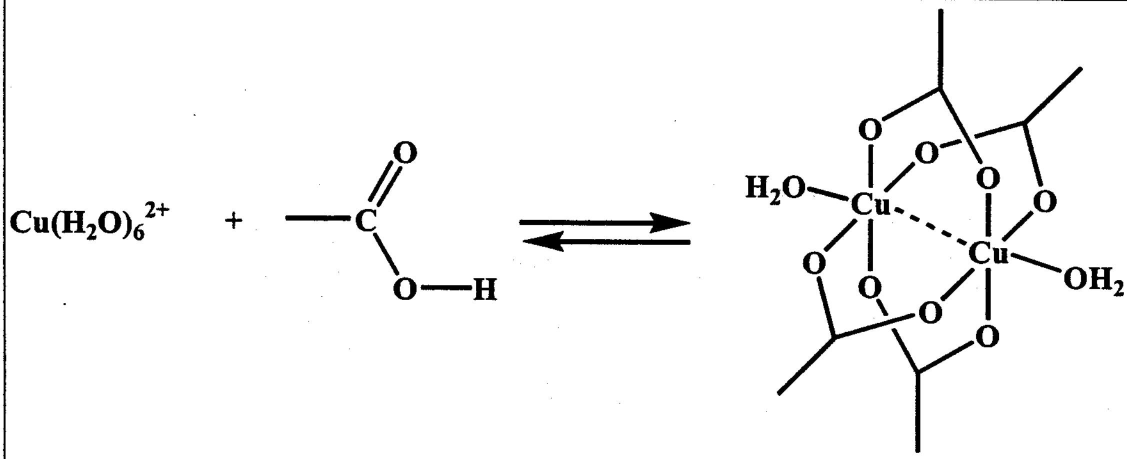
When is a metal salt water tolerant Lewis acid?

- **The term water tolerant cannot be used to indicate that the metal salt is stable in water as consequence of its slow hydrolysis rate because its dissociation is fast, the hydration of the ion occurs immediately and the distribution of species (aqua ion, mononuclear, polynuclear) is function of pH and metal salt concentration.**

- **A metal salt works as water tolerant Lewis acid when in water it generates a stable aqua ion and it shows the highest effectiveness when the pH is below its $pK_{1,1}$ hydrolysis constant.**

WATER PROMOTED ORGANIC REACTIONS

LEWIS ACID CATALYSIS



Doedens R. J. *Prog. Inor. Chem.* **1976, 21** 209