Asymmetric Hydride-Transfer Reduction of Ketones

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April 23, 2002

CONTENT:

1. How did it start?

1925- Meerwein and Schmidt reduced acetaldehyde with EtOH/Al(OEt)3 *Liebigs Ann Chem.* **1925**, *37*,221

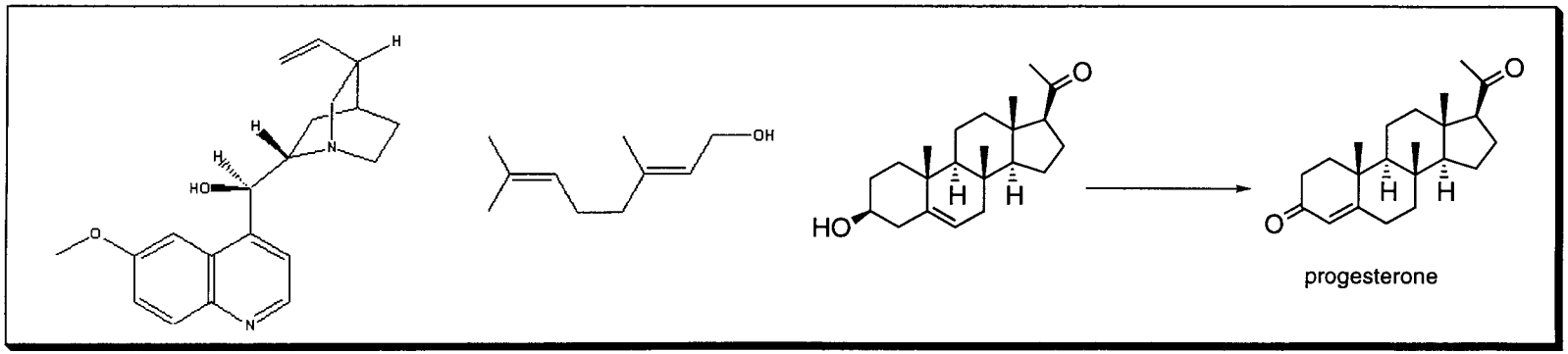
1925 -Verley reduced butyraldehyde with geraniol , $Al(OEt)_3$ *Bull.Soc.Chim.Fr.* **1925**,*37*,537

1926- Ponndorf (sec-alcohols and their aluminum alkoxides) *Angew.Chem..* **1926**,*39*,138

1937- Oppenauer used acetone and Al(Ot-Bu)3 to oxidize steroids *Recl.Trav.Chim.Pays-Bas* **1937**,*56*, 137

Introduction of easier reducible agents (quinones, benzophenones, cycloxexanone)

1945- Woodward applied KOt-Bu+Ph_2CO to oxidize Quinine *JACS* **1945**,*67*,1425



2. DECLINE

Reveiws:

1. *Org.React.* **1944,** *2,*178
2. *Org.React.* **1953,** *6,*207
3. *Synthesis* **1994,**1008

Drawbacks:

1. Typically stoichiometric use of alkoxide
2. Side-reactions
3. Reversibility ?
4. Complex metal hydrides and direct hydrogenation

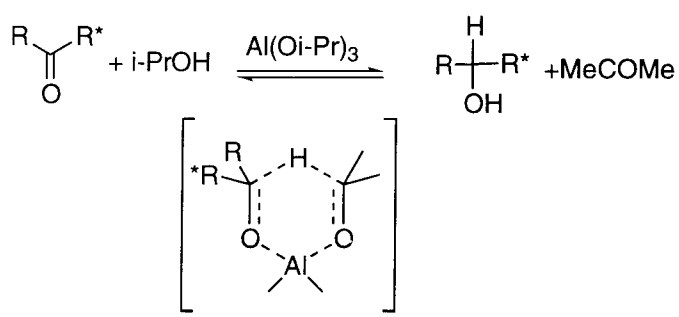
Diversity:

Alkoxides of Mg, B, Zn, Sn(IV), Ti, As(V), Fe(III), alkali metals, lanthanides

Complexes of Zr, Hf, Ir, Ru

Heterogeneous: metal oxides (Al_2O_3), zeolites

3. Mechanism



Metal:

1. Activates carbonyl

2. Serves as a template, holding two reactants together

3. Has different affinities for OH/C=O and SM/Prod

(can get deactivated)

Organic part:

1.Intramolecular Hydride-transfer

2. Easily enolizable ketones are inactive

Kinetics (Racemization)

R=Kx[ketone]/[alkoxide]

dS<0

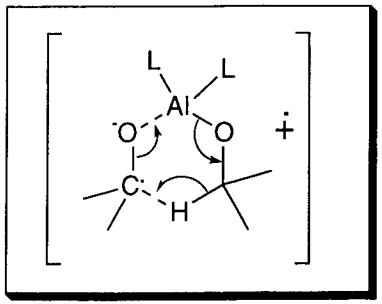
Conclusion

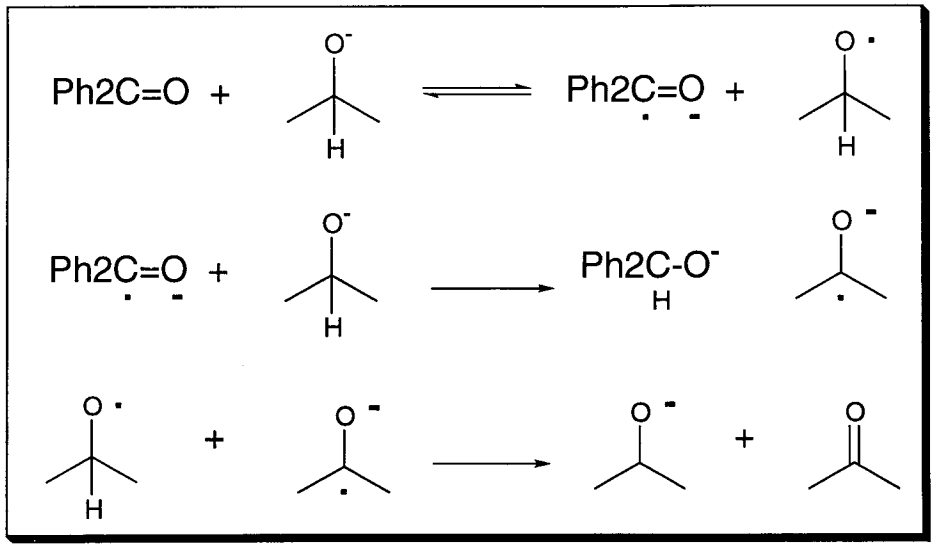
Alkoxide is associated

Ordered TS

Jackman,L.M.; MacBeth, A.K. *J.Chem.Soc.* **1952,**3253

3a. SET-mechanism.





Evidence:

1.ESR (first order decay)

2. t-BuO$^-$ +Ph2CO->ketyl radical

3. Ketyl radical reacts with LiOiPr

Couldn't find any evidence in case of aliphatic ketones

Aldol reaction observed

E.C.Ashby, *Acc.Chem.Res.* **1988,** *21,* 414

4. Thermodynamics

Polarographic determination of Red-Ox potentials.
Cox, F.W. et all *JACS* **1939,** *61,* 3364 also **1938,** *60,* 1151; Robinson C.C. et al *JACS* **1949,** *71,* 3622

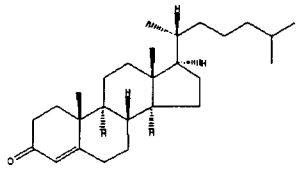
1. Highest reduction potentials/best reducing agents:

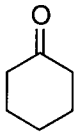
Secondary-dialkyl alcohols (e.g., i-PrOH)

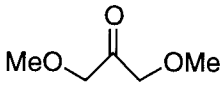
2.Highest oxidation potentials/best oxidizing agents:

Aromatic and aliphatic aldehydes

Note: if catalyst's loading is not negligible, the Red-Ox potential alone becomes less reliable







delta-4-cholestenone

63mv	162mv	270mv	350mv	
1	50	50^2	50^3	-concentration of the corresponding alcohol in equilibrium

Trends:

Alkyl groups, conjugated C=C- lower oxidation potential

Alkoxy, carbonyl, carbalkoxy groups in alpha-position- increase oxidation potential (same-for NR2, Cl, NO2)

TABLE I (*Continued*)

No.	Compound	E_s, mv.	$-\Delta F^\circ$ 25°, cal.	Equilibrated against	M. p., °C. or $n^{25}D$ Carbinol	Carbonyl	Dep. pot. (−)
57	2,7-Dichlorofluorenone	157	7.2	58Rs	161–162	192–193	0.84
	2,7-Dichlorofluorenone	157	7.2	55E			
58	Cyclohexanone	162	7.5	20B			
59	Δ^2-Cyclohexenone	162	7.5	20E			
60	3-Methoxycyclohexanone	167	7.7	20Rs	1.4638	1.4558[d]	
61	4-Methoxycyclohexanone	167	7.7	20Rs	1.4661	1.4530	
62	β-Pyridyl phenyl ketone	167	7.7	58E	67.5–69	1.6060[e]	1.22
63	*t*-Butyl phenyl ketone	169	7.8	20B			
64	*p*-Nitrobenzophenone	171	7.9	57E	73–74	136–137[e]	1.42
65	1-Chloroanthraquinone	175	8.1	57E		161–161.5	
	1-Chloroanthraquinone	174	8.0	Ref. 8			
66	Benzhydryl methyl ketone	182	8.4	20Rs	57.5–58.5	58–60	
67	Cinnamaldehyde	186	8.6	74E	1.5772	1.6120	1.08
68	Methoxyacetone	189	8.8	57Rs	1.4010	1.3955	
69	α-Tetrahydrofuryl methyl ketone	195	9.0	57Rs	1.4461	1.4361	
70	Crotonaldehyde	194	9.0	74E	1.4262	1.4355[e]	1.37
71	Benzaldehyde	197	9.1	57E	--		1.34
72	Benzoin methyl ether	199	9.2	58Rs	54–61	47–48	1.52
73	ω-Piperidinoacetophenone	203	9.4	58Rs	70.5–71.5	1.5396	1.25
74	Trimethylacetaldehyde	211	9.8	71E	54–55	1.3765	
75	Phenylglyoxal dimethyl acetal	212	9.8	58Rs	1.5097	1.5102[d]	
76	ω-Methoxyacetophenone	213	9.8	58Rs	1.5190	1.5319[e]	1.43
77	Furfuraldehyde	214	9.9	74E	1.4868	1.5248	
78	Dibenzyl ketone	216	10.0	57Rs	1.5691	35	
79	2-Methoxycyclohexanone	218	10.1	57Rs	1.4571	1.4519[d]	
80	Isobutyraldehyde	220	10.2	71E	1.3953	1.3713	
81	Isopropyl anthraquinone-2-carboxylate	219	10.2	57E	125 (*ca.*)	138–139[e]	0.55
	Isopropyl anthraquinone-2-carboxylate	222	10.2	Ref. 3			
82	Acetaldehyde	226	10.4	71E			1.87
83	*t*-Butylglyoxal	245	11.3	71E	1.4297	85	
84	Formaldehyde	270	12.5	71E			1.38
	Formaldehyde	257	11.9	Ref. 9			
85	Chloral	277	12.8	86E	55.5/13[f]	96.5/74.0[f,e]	
86	Isopropyl benzoyl formate	282	13.0	81E	1.4969	1.5035	1.05
87	Ethyl pyruvate	297	13.8	86Rs	1.4110	1.4042	1.35
88	Isopropyl pyruvate	299	13.8	86E	1.4078	1.4036	1.45
89	Ethyl oxomalonate	298	13.8	86E	1.4283	1.4190	
90	1,3-Dimethoxyacetone	350[g]		57Rs	1.4177	1.4161	
				86E			

[a] The carbonyl compound against which Cox (C), Baker (B), Rossow (Rs), Robinson (Rb), or Elofson (E) equilibrat a given compound is indicated in the fifth column of the table, by using the number of the carbonyl compound as giv for the compound in the first column of the table. The values for the methoxyacetophenones, given by Baker, Schafer,[4b] are in agreement with the potentials listed in the table for these compounds, if they are based upon a potent for fluorenone of 117 mv., rather than upon the value 150 mv. reported earlier.[4a] [b] These depolarization potenti were observed in a 0.1 *N* ammonium chloride solution, while the others reported were in a 0.05 *N* tetramethylammoni hydroxide solution. [c], [d] and [e] These ketones were reduced to the corresponding alcohols with aluminum isopropox or by catalytic hydrogenation over Raney nickel[d] or copper chromium oxide[e]. [f] Boiling points. [g] This is a minim value.

chance there is for a significant amount of a side reaction. Fluorenone is outstanding in giving rapid reactions. 2,7-Dichlorofluorenone is less reactive while isopropyl benzoylformate reacts quite slowly. Cyclohexanone reacts rapidly but is itself subject to condensation.

The determination of the oxidation potentials of Δ^4-cholestenone-3, Δ^5-cholestenone-3, Δ^2-cyclohexenone and Δ^3-cyclohexenone involves certain peculiar difficulties and uncertainties. In the classical Oppenauer oxidation of cholesterol by acetone to Δ^4-cholestenone-3 there is an intramolecular as well as an intermolecular oxidation reduction. The latter ketone may be isolated in yield of about 80% from such a reaction mixtu The reactions may be represented by the scheme

$$\Delta^5\text{-cholestenol-3} + K \rightleftharpoons \Delta^5\text{-cholestenone-3} + A$$
$$\uparrow\downarrow \qquad\qquad \uparrow\downarrow$$
$$\Delta^4\text{-cholestenol-3} + K \rightleftharpoons \Delta^4\text{-cholestenone-3} + A$$

where K represents a ketone and A the alcol corresponding to it.

Cholesterol (Δ^5-cholestenol-3) is oxidized

15

TABLE I

SUMMARY OF OXIDATION POTENTIALS

No.	Compound	E_s, mv.	$-\Delta F^\circ$ 25°, cal.	Equilibrated against[a]	M. p., °C. or $n^{25}D$ Carbinol	Carbonyl	Dep. pot. (−)
1	Δ^4-Cholestenone	63	2.9	20E	140.5–141	80–81[c]	1.30[b]
2	α-Hydrindone	73	3.4	20Rb	66–68	41–42[d]	1.55
3	α-Tetralone	80	3.7	20Rs	1.5643	1.5662	1.67
4	Camphor	82	3.7	20B			
5	Δ^2-Cyclohexenone	85	3.9	20E	1.4828	1.4853	1.55[b]
6	*p*-Methoxyacetophenone	99	4.6	20Rb	1.5330	1.5310[e]	1.70
7	Di-isopropyl ketone	100	4.6	39C			
8	Di-*n*-butyl ketone	101	4.6	39C			
9	Di-*n*-propyl ketone	101	4.6	39C			
10	Di-isobutyl ketone	102	4.7	39C			
11	Di-ethyl ketone	110	5.1	39C			
12	Acenaphthenone	110	5.1	20Rb	144.5–145.5	120.5–121.5	
13	*n*-Propyl phenyl ketone	113	5.2	39C			
14	3,5-Dimethoxyphenyl *n*-butyl ketone	114	5.3	20Rb	1.5166	42–43[e]	1.56
15	1,4-Diphenylbutanone-1	115	5.3	20E	47.5–48	56–57[e]	
16	*p*-Methylacetophenone	115	5.3	20Rb	1.5186	1.5310[d]	1.66
17	Methyl cyclohexyl ketone	116	5.4	20B			
18	*n*-Butyl phenyl ketone	116	5.4	39C			
19	*n*-Amyl phenyl ketone	117	5.4	39C			
20	Fluorenone	117	5.4	58B	151–152	83–84	1.07[b]
	Fluorenone	119	5.5	55E			
21	Methyl phenyl ketone	118	5.4	20B			
22	Ethyl phenyl ketone	118	5.4	39C			
23	2-Fluorenyl methyl ketone	119	5.5	20Rb	137–138	128–129	1.51[b]
24	β-Acetonaphthone	120	5.5	20E	73–73.5	54.5–55[e]	1.65
25	*m*-Methoxyacetophenone	120	5.5	20Rb	1.5316	1.5383	1.65
26	1,3-Diphenylpropanone-1	121	5.6	20E	1.5685	72.5–73	1.61
27	Isopropyl 9-fluorenone-4-carboxylate	121	5.6	58Rb	93.5–95	89–90.5[e]	1.04[b]
28	Ethyl 9-fluorenone-4-carboxylate	121	5.6	58Rb		103	
29	Methyl *t*-butyl ketone	121	5.6	20B			
30	α-Furyl methyl ketone	122	5.6	20Rs	1.4763	1.5043	1.63
31	Ethyl methyl ketone	123	5.7	20B			
32	Methyl isopropyl ketone	123	5.7	20B			
33	Cyclopentanone	123	5.7	20B			
34	Xanthone	124	5.7	20B			
35	Isopropyl phenyl ketone	125	5.8	39C			
36	1-Naphthyl phenyl ketone	128	5.9	20Rb	86–87	76	1.46[b]
37	*m*-Tolyl phenyl ketone	128	5.9	20Rb	54–55	1.5965	1.57[b]
38	Dimethylfulvene	129	6.0	20B			
39	Diphenyl ketone	129	6.0	20B			
	Diphenyl ketone	126	5.8	55E			
40	*p*-Bromoacetophenone	129	6.0	20Rb	1.5689	49–51[e]	1.57
41	Phenyl benzyl ketone	136	6.3	20Rs	67–68	55.5–56	1.60[b]
42	Ethyl *p*-acetylbenzoate	136	6.3	20Rb	1.5062	54–56	1.35[b]
43	β-Hydrindone	139	6.4	20Rb	70–70.3	57–57.5	
44	Benzyl methyl ketone	140	6.5	20Rs	1.5187	1.5139	
45	Methyl 9-fluorenone-2-carboxylate	140	6.5	58Rb	118–119.5	184–185[e]	1.02[b]
46	2-Chlorofluorenone	141	6.5	58Rs	142–143	122–123	1.06[b]
47	*o*-Methoxyacetophenone	141	6.5	20Rb	1.5312	1.5378[e]	1.63
48	Ethyl benzoylacetate	147	6.8	20Rb	1.5107	102–3/1[f]	1.49[b]
49	Isopropyl *m*-benzoylbenzoate	149	6.9	58Rb	180–1/2[f]	1.5723[e]	1.38
50	*m*-Nitroacetophenone	152	7.0	20Rb	63	79.5–81[e]	0.80–1.67
51	Ethyl *p*-benzoylbenzoate	152	7.0	58E		54.5–55.5	1.27[b]
52	Isopropyl *p*-benzoylbenzoate	153	7.1	58E	51–52	55.5–56	1.26[b]
53	*t*-Butyl *p*-benzoylbenzoate	152	7.0	58E		49–50	1.27[b]
54	Δ^5-Cholestenone-3	153	7.1	20E	148		
55	9,10-Anthraquinone	154	7.1	Ref. 8			
56	β-Tetralone	155	7.2	20Rs	1.5632	1.5557	

5. Choice of Metal-Alkoxide

From 65% ionic character for the alkoxides of Al, Ti, Zr to 90% for alkali metals and lanthanides

The more ionic- the easier ligand exchange

Al is good for easy preparation and exelent solubility in ROH and CnHm, but requires stoichiometric amount.

***Rate of ligand exchange (water)*, s^{-1}:** Al(1)<Mg(10^5)<Lanthanides (10^8-9)<Li(10^11) [1]

Al :=>stoichiometric amount (however, see 5b)

Protic acids rate-increase [2] CF3COOH
(50 mol% relative to $Al(Oi\text{-}Pr)_3$ (used 5 mol%)), aldol reaction

Addition of 30 mol% of $Al(Oi\text{-}Pr)_2Cl$ increases the rate too
(LA-character increased)

Na, K- low charge density;

Li-small coordination number

Useful for oxidation of N-containing compds.

[1] - Ohtaki, H.; Radnai, T *Chem.Rev.* **1993,** *93,* 1157

[2]- Rathke, M.W et al *J.Org.Chem.* **1977,** *42,* 826

5a. Choice of Metal-Alkoxide

Lanthanides:

Hard acids, coordination numbers 8-12

Used in 10 mol% amount ($Sm(Ot\text{-}Bu)I_2$ [1], $Ln(Oi\text{-}Pr)_3$ [2,3]) La(III) is the most active [3], $Gd(Oi\text{-}Pr)_3$ is 1000 times as active as Al [2]

Cp_2ZrH_2 can be used in 2 mol % amount.[4]

Ir- complexes were used with Ir loading 0.005 mol% [5]

Ru-complexes. See slides 8b,c

[1]-Namy, J.L. et al *J.Org.Chem.* **1984,** *49,* 2045

[2]-Okano, T. et al *Chem.Lett.* **1987,** 181

[3]- Kagan, H.B. *Tetrahedron Lett.* **1991,** *32,* 2355

[4] Ogawa, M.J. et al. *J.Org.Chem.* **1986,** *51,* 240

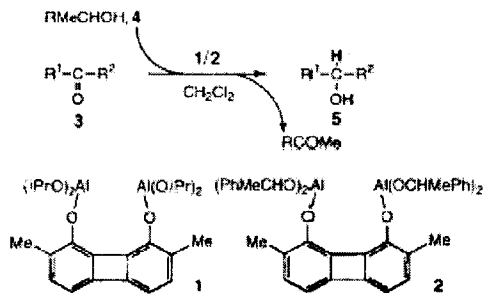
[5] Vinzi, F. et al *J.Mol. Cat.* ***1983,*** *18*, 359

5b. Choice of Metal-Alkoxide

Table 1. Catalytic MPV reduction of carbonyl substrates with 1 or 2.

Substrate	Al reagent (mol %)	Hydride source (equiv)	t[h]	Yield [%][a]
PhCHO	$Al(OiPr)_3$ (100)	–	1	34
PhCHO	$Al(OiPr)_3$ (10)	iPrOH (1)	2	10
PhCHO	1 (100)	–	(5 min)	99
PhCHO	1 (5)	iPrOH (1)	1	81
PhCHO	1 (5)	iPrOH (3)	1	96
$PhCH(CH_2)_2C{=}O$	$Al(OiPr)_3$ (100)	–	1	(trace)
$PhCH(CH_2)_4C{=}O$	1 (5)	iPrOH (1)	1	91
$PhCH(CH_2)_4C{=}O$	1 (5)	iPrOH (1)	2	99
$PhC(O)CH_2Cl$	$Al(OiPr)_3$ (100)	–	2	– [b]
$PhC(O)CH_2Cl$	1 (5)	iPrOH (1)	2	75
$PhC(O)CH_2Cl$	1 (5)	iPrOH (1)	10	89
$PhC(O)CH_2Cl$	2 (5)	PhMeCHOH (1)	2	99
$CH_3(CH_2)_6COCH_3$	$Al(OiPr)_3$ (100)	–	5	– [b]
$CH_3(CH_2)_6COCH_3$	1 (5)	iPrOH (3)	5	50
$CH_3(CH_2)_6COCH_3$	2 (5)	PhMeCHOH (1)	5	73
$CH_3(CH_2)_6COCH_3$	2 (5)	PhMeCHOH (3)	5	89
$CH_3(CH_2)_6COCH_3$	2 (5)	PhMeCHOH (6)	5	99
$PhCH{=}CHCOCH_3$	1 (5)	iPrOH (1)	5	31[c]
$PhCH{=}CHCOCH_3$	2 (5)	PhMeCHOH (6)	5	70[d]

[a] Yield of isolated product. [b] No reaction. [c] Yield of 1,2-reduction product.



Scheme 2. Catalytic MPV reduction of aldehydes and ketones with 1 or 2.

5 Mol% cat loading, RT

Double e-philic activation

Also asymmetric

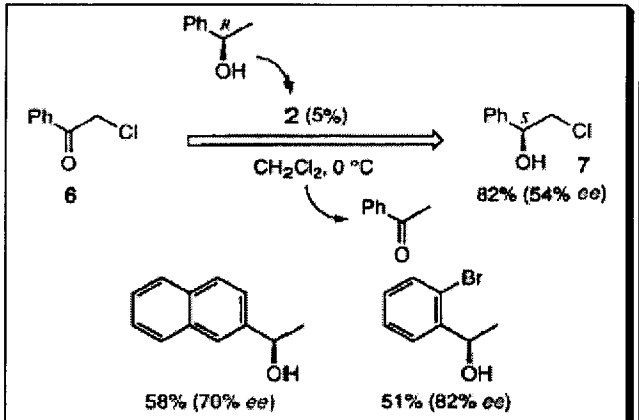
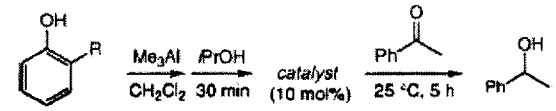
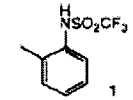
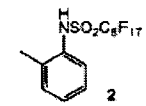
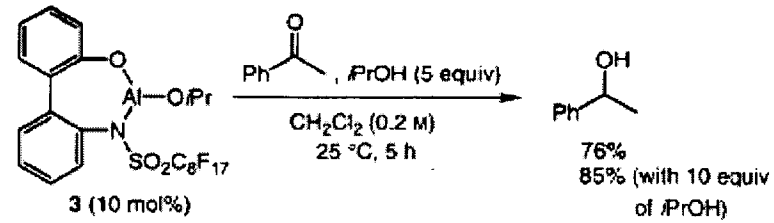


Table 1. Catalytic MPV reduction of acetophenone with various aluminum catalysts.[a]



Entry	R	iPrOH [equiv]	Yield [%][b]
1	H	5	n.r.[c]
2	COOH	5	n.r.[c]
3	OH	5	8
4	$NHSO_2CH_3$	5	9
5	$NHSO_2CF_3$	5	30
6		5	46
7	 1	5	65
8	 2	5	76
9	2	10	85

[a] The MPV reduction of acetophenone was conducted with several aluminum catalysts (10 mol %) and iPrOH (distilled from CaH_2) in freshly distilled CH_2Cl_2 at 25 °C for 5 h. [b] Yield of isolated product. [c] n.r. = no reaction.



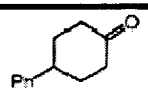
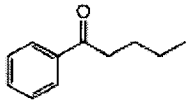
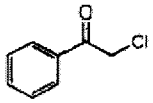
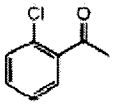
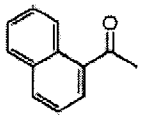
Scheme 2. Efficient catalytic MPV reduction of acetophenone in the presence of the new aluminum alkoxide 3.

Maruoka, K. et al. *Angew.Chem.Int.Ed.* **1998,** *37,* 2347

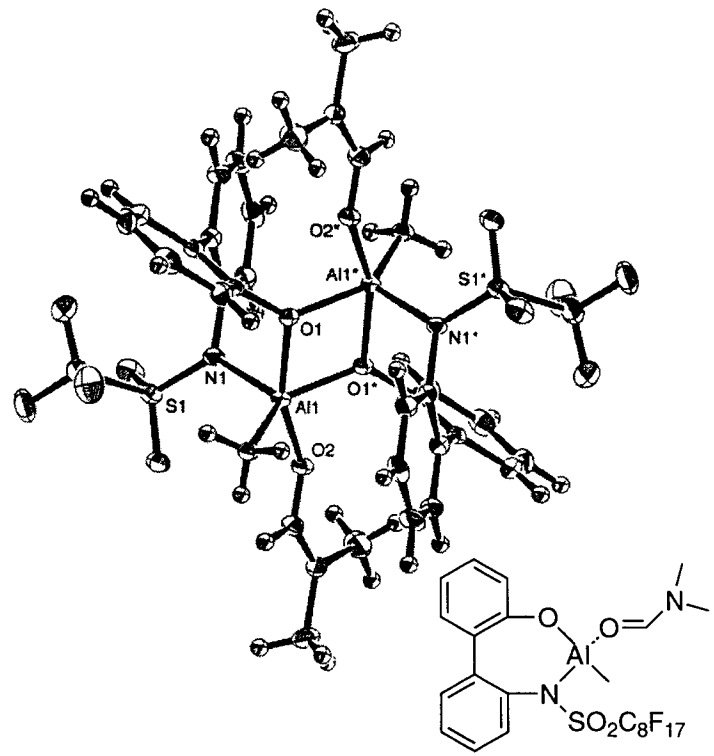
Maruoka, K. et al. *Angew.Chem.Int.Ed.* **2001,** *40,* 3610

5c. Choice of Metal-Alkoxide

Table 2. Catalytic MPV reduction of ketone substrates with new aluminum catalyst 3[a] and scale-up experiments with 5 g of starting ketones.[b]

Entry	Substrate	Conditions [°C]	Conditions [h]	Yield[c] [%]	Scale-up reaction conditions [°C]	Scale-up reaction conditions [h]	Scale-up reaction yield [%][c]
1		25	0.5	99[d]	25	2	99[d]
2	$CH_3(CH_2)_6COCH_3$	25	5	97	25	5	94
3	$(CH_3(CH_2)_3)_2C{=}O$	25	5	92	25	5	91
4		25	3.5	85	25	5	82
5		25	5	99	25	5	98
6		25	1	99	25	3.5	99
7		25	5	97	25	9	95

[a] The MPV reduction of various ketone substrates was effected with **3** (10 mol%) and *i*PrOH (10 equiv, distilled from CaH_2) in freshly distilled CH_2Cl_2 (0.2 M) under the indicated reaction conditions. [b] The reaction was carried out in reagent grade CH_2Cl_2 (1.0 M) and distilled *i*PrOH (10 equiv) in the presence of **3** (5 mol%), prepared from $Al(OiPr)_3$ and **2**, under the given conditions. [c] Yield of isolated product. [d] The *cis*/*trans* ratio was 17:83. Scale-up: 5g ketone, 5 mol % cat



Dimeric Structure

Pentacoordinate Al-Center

7-membered ring

No mecanism proposed

Maruoka, K. et al. *Angew.Chem.Int.Ed.* **2001,** *40,* 3610

6. Preparation of Catalyst.

1. Reaction of metal with ROH (Al and Ln require some form of activation ($HgCl_2$, I_2 etc))

2. MX_n+ROH. Can require NH3 or alkali metal alkoxide to complete.

3. $M(OR)_n$+R*OH. The affinity of metal: $1^0>2^0>3^0$

4. 2SmI2+(t-BuO)2->2Sm(Ot-Bu)I2 [1]

5. $LaCl_3$*7H2O+7 $HC(OMe)_3$->$LaCl_3$*4MeOH $\xrightarrow[\text{-MeOH^}]{\text{i-PrOH}}$ $LaCl_3$*3 i-PrOH $\xrightarrow[\text{-LiCl}]{\text{BuLi}}$ La(Oi-Pr)$_3$ [2]

6. AlMe3+ROH->$Al(OR)_nMe_{3-n}$ (can regulate value of n)

[1]. Namy, J.L. et al *J.Org.Chem.* **1984,** *49,* 2045

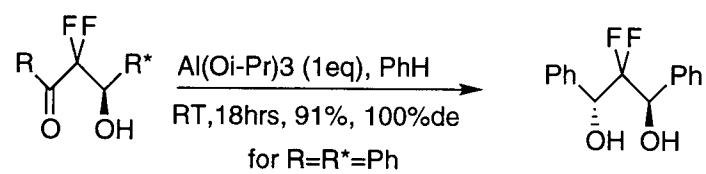
[2]. Merbach, A. et al *Helv. Chim. Acta* **1972,** *55*, 44

7.Selectivity.

1. Chemoselectivity:

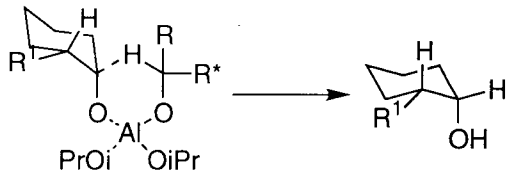
2^0-ROH are oxidized more easily than 1^0-ROH (**thermodynamics=>Al?**). Protection can be used.

2. Diastereoselectivity:



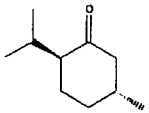
Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990,** *63,* 1185. No mechanism proposed

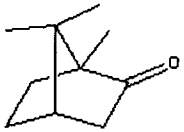
7a.Selectivity.



R1	Cis, %
2-Me	50
3-Me	55
4-Me	33
4-iPr	40
4-iPr-2-en	39
(-)-menthone	70
(+)-camphor	70
Yields>90%	

Alcohol used	Cis, %
sec-BuOH	75
4-Me-pentane-2-ol	72
3,3-Me-butane-2-ol	86
Yields >94%	

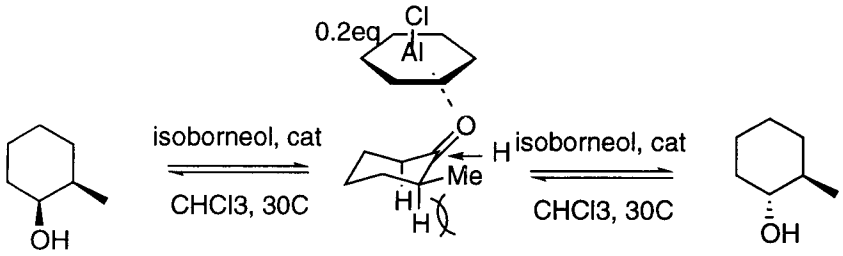


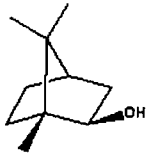


Jackman,L.M. et al.*J.Chem.Soc.* **1949,** 2641

Initial cis-selectivity can be increased by the use of bulky reducing alcohols , $Al(Os\text{-}Bu)_3$. Or by dilution.

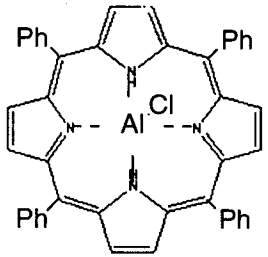
Hach, V. *J.Org.Chem.* **1973,** *38,* 293





1eq
No excess of alcohol!!

tetraphenylporphynatoaluminium chloride



0.2 eq

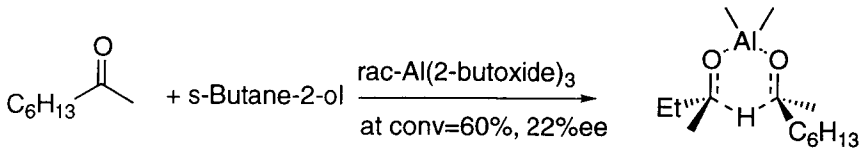
t, (h)	A	B	C
0	0	100	0
0.3	86	7	7
5	5	0	95 ← 1:2 in case $Al(Oi\text{-}Pr)_3$

Konishi, K. et al. *J.Chem.Soc., Chem.Commun.* **1988,** 643

8. Enantioselectivity.

1. First succesive use of chiral alcohol.

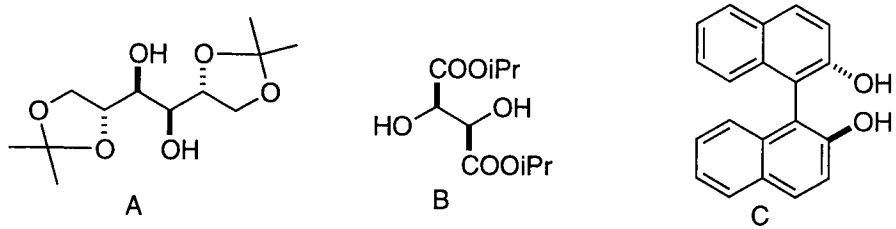
Large excess of the alcohol used, no data on the catalyst loading



Doering, W. von E.;Young, R.W. *JACS,* **1959,** *72,*631

2. First succesive use of chiral catalysts.

La, Eu,Yb; 10 mol%, 1-2 eq of Chiral ligand. RCOMe (R=Pr,Ph,t-Bu)

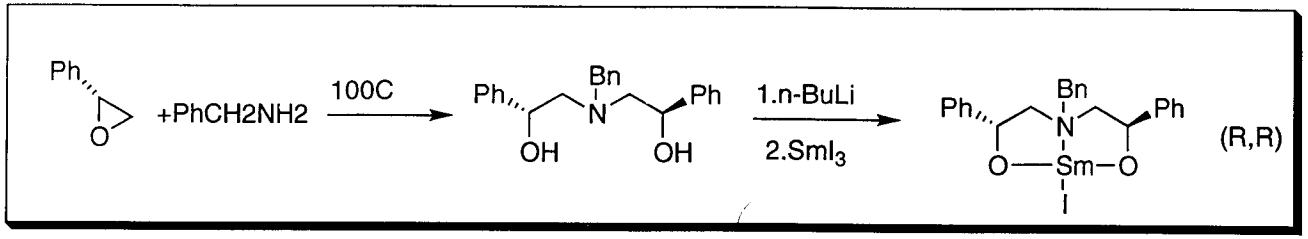


The best ee is for La(OtBu)$_3$ and cat A: up to 32% ee for R=Ph

J. Huskens et al. *Recl.Trav.Chim.Pays-Bas,* **1994**, *113,* 489

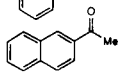
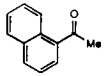
8a. Enantioselectivity.

Chiral catalysts, Ln(III)



Conditions: 5mol % cat, 25 eq of acetone, THF,1hr, RT
No TS proposed. Bulkier R->less ee.

Table I. Enantioselective MPV Reduction of Aryl Methyl Ketones[a]

entry	substrate		% ee (config)[b]	% conversion[c]
1		X = Cl	97 (*R*)[c,e]	100 (96)
2		X = H	96 (*R*)[d]	83 (74)
3		X = OMe	96 (*R*)[f]	100 (95)
4		X = Cl	94 (*R*)[f]	91 (88)
5		X = OMe	92 (*R*)[d]	43 (36)
6		X = NO_2	94 (*R*)[g]	100 (77)
7		X = Cl	68 (*R*)[d,e]	95 (78)
8		X = H	73 (*R*)[f]	66 (63)
9			96 (*R*)[h]	84 (82)
10			97 (*R*)[e,i]	98 (95)

[a] Reactions were carried out on a 2-mmol scale using the conditions given in the text. Products were isolated after complete conversion or 24 h. [b] Absolute configuration assigned by comparison of product rotations to literature values except where noted. [c] Conversions were determined by GLC. Values in parentheses are isolated yields. [d] Enantiomeric purity was determined by chiral GLC assay (Chiraldex G-TA). [e] Absolute configuration was assigned by the method of Trost (Trost, B. M. *et al. J. Org. Chem.* **1986**, *86*, 2370–2374). [f] Enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel-OD). [g] Enantiomeric purity was determined by ^{1}H NMR spectroscopic assay of the derived Mosher ester. [h] Enantiomeric purity was determined by chiral HPLC assay (Bakerbond, DNBPG).

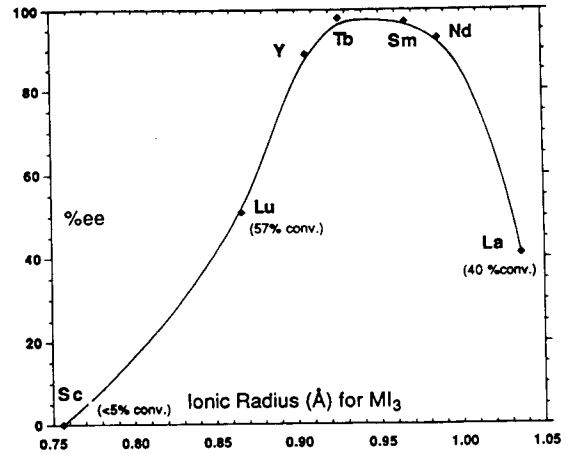


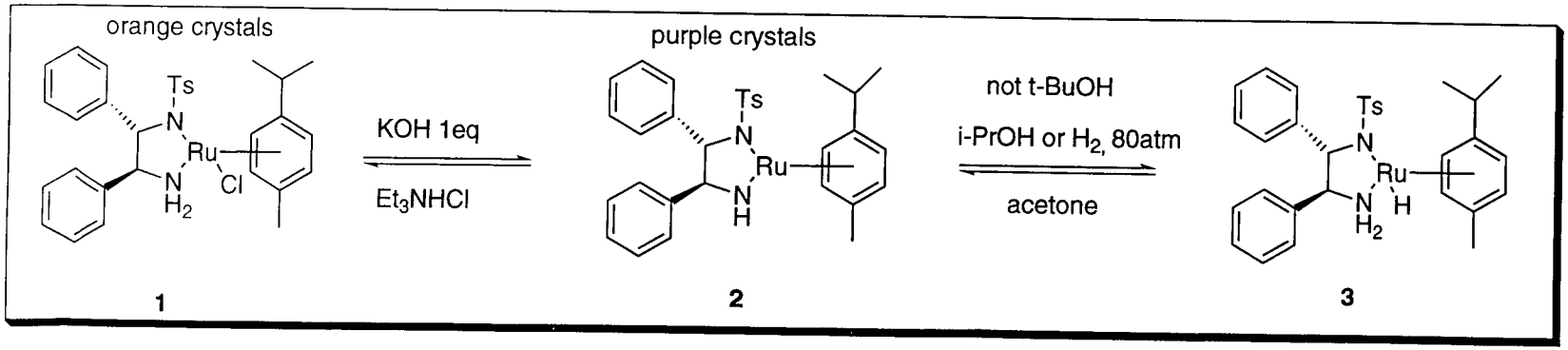
Figure 1. Enantioselective reduction of **1** by catalysts derived from **3** and MI_3 (2-propanol, 24 h, 25 °C).

Non-linear effects:80% ee of (R,R) gives the same ee of the product as 100% (R,R).
ee doesn't change upon prolonged exposure to the catalytic system.
Proposed binding of substrate to cat. in case of o-methoxyaryl.

Evans, D.A. et al. *JACS* **1993,** *115,* 9800

8b. Enantioselectivity.

Chiral catalysts, Ru(II)



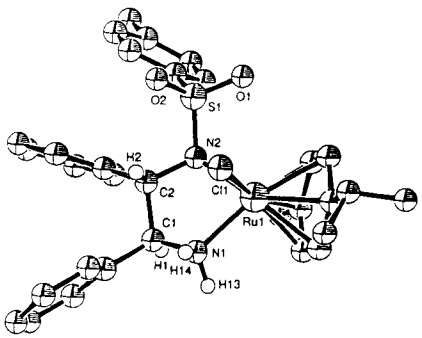


Figure 1. Molecular structure of 1 in the crystal. All hydrogen atoms except for the proton of the amine ligand and those at the carbon atoms in the chelate backbone and one crystal water molecule have been omitted for the sake of clarity. Selected distances [Å] and angles [°]: Ru–Cl 2.435(4), Ru–N1 2.117(9), Ru–N2 2.144(8), RuCl···HN 2.57; N1-Ru-N2 79.4(3), Ru-N1-C1 112.8(7), Ru-N2-C2 111.6(6).

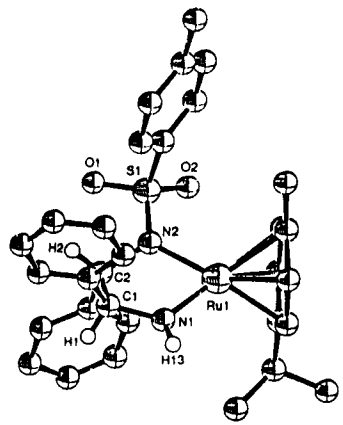


Figure 2. Molecular structure of 2 in the crystal. All hydrogen atoms except for the proton of the amide ligand and those at the carbon atoms in the chelate backbone have been omitted for the sake of clarity. Selected distances [Å] and angles [°]: Ru–N1 1.897(6), Ru–N2 2.065(6), N1–H13 0.88(6); N1-Ru-N2 78.9(2), Ru-N1-C1 121.2(5), Ru-N2-C2 114.9(4).

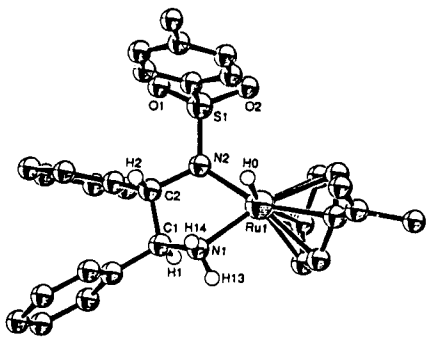


Figure 3. Molecular structure of 3 in the crystal. All hydrogen atoms except for the hydride at ruthenium, the two protons of the amine ligand, and those at the carbon atoms in the chelate backbone, as well as two water molecules in the lattice have been omitted for the sake of clarity. Selected distances [Å] and bond angles [°]: Ru–H0 1.40(1), Ru–N1 2.110(1), Ru–N2 2.139(9), N1–H13 0.90(1), N1–H14 0.7(1), RuH0···H14N1 2.29; N1-Ru-N2 78.3(4), Ru-N1-C1 108.7(7), Ru-N2-C2 113.0(7).

Noyory, R. et al. *Angew.Chem.Int.Ed.Engl.* **1997**, *36*, 285

8c. Enantioselectivity.

Chiral catalysts, Ru(II)

Reduction of acetophenone:

MeOH, EtOH, i-PrOH, (R,S)-,(R)- and (S)-2-BuOH, all gave (S)-1-Ph-Ethanol 95(+/- 0.5)%ee. Neutral conditions!

Me2CDOH gave (S)-PhCD(OH)Me, mix with non-deuturated->k_H/k_D=1.5

R=k[cat]x[i-PrOH]x[C_2D_6CO]^n (0<n<1) Saturation at higher concentrations (H-transfer is RDS). $(CD_3)_2CO$+i-PrOH.

~0.2 mol % of cat.

Kinetic resolution:

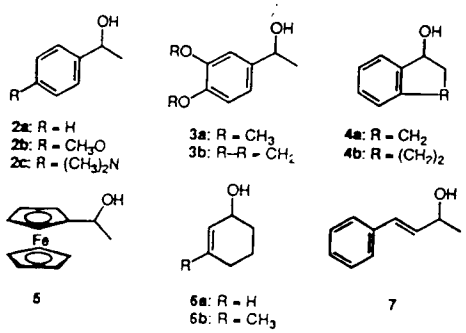
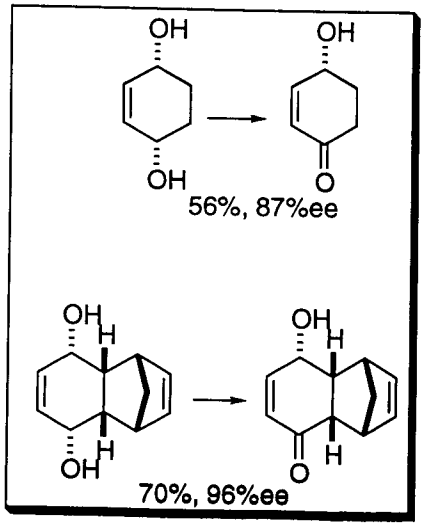


Table 1. Kinetic resolution of alcohols by chiral Ru^{II} complexes in acetone [a].

Substr.	Cat.	S/C	Time [h]	Unreacted substrate: Recovery [%]	ee [%]	Config.	k_f/k_s [b]
2a	(S,S)-1a	500	36	50	92	R	>80
2a	(S,S)-1b	500	30	51	94	R	>100
2b	(S,S)-1a	500	22	47	92	R	>30
2c	(S,S)-1b	500	30	44	98	R	>30
3a	(S,S)-1b	500	36	47	97	R	>50
3b	(S,S)-1b	500	24	47	97	R	>50
4a	(S,S)-1a	500	6	46	97	R	>40
4b	(S,S)-1a	500	6	49	99	R	>50
5	(S,S)-1b	200	36	51	98	R	>100 [c]
6a	(S,S)-1a	500	4.5	43	93	R	14 [c]
6b	(S,S)-1a	500	5	46	95	R	>20 [c]
7	(S,S)-1a	500	40	49	45	R	4

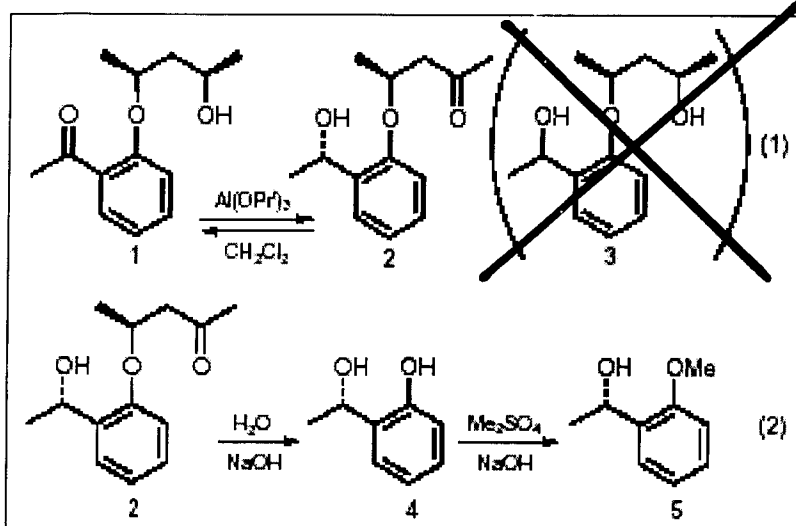
[a] The reaction was carried out at 28 °C in a 2 M acetone solution of the substrate (5–10 mmol). [b] The ratio was estimated based on the final conversion and enantiomeric purity of the recovered alcohol unless otherwise specified. [c] For accuracy, the ratio was determined at 10–20% conversion.



Noyory, R. et al. *Angew.Chem.Int.Ed.Engl.* **1997**, *36*, 285, also p.288

9. Enantioselectivity.

Aluminum catalysts, chiral hydride source



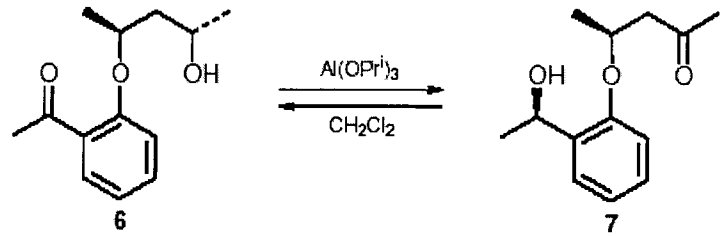
68% of (2), 100%ee, 32% of (1) recovered, no (3)

2eq of Al(Oi-Pr)$_3$, 20hrs

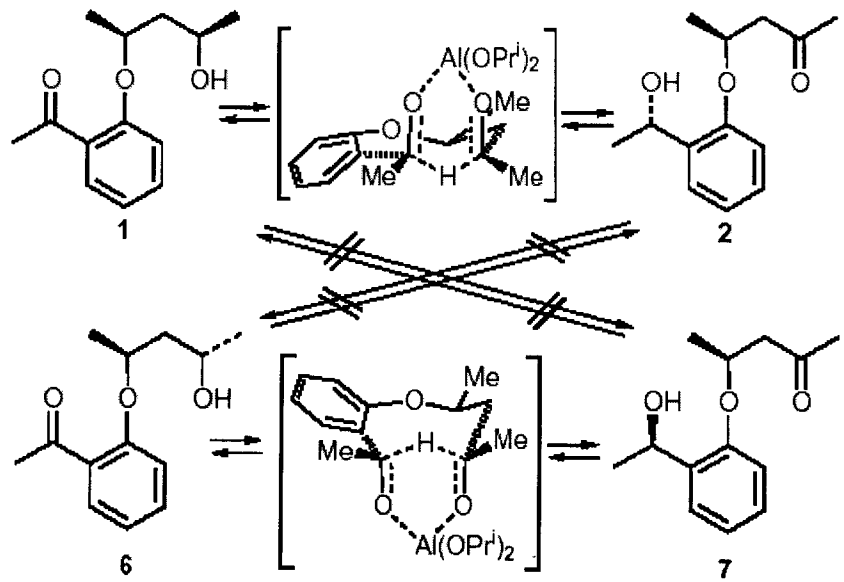
Same ratio (4 days, 4eq of Al)=> eq. with K=2,

complete stereodiff. in the reverse step.

Previously- stereocontrol- only under kinetic cond.



67% of (6),100%ee, 33% of SM recovered

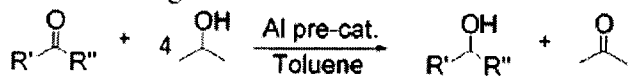


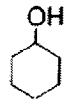
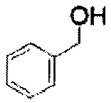
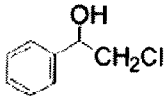
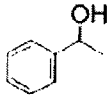
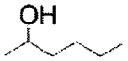
Fujita, M. et al. *Chem. Commun.*, **1997,** 1631

9a. Enantioselectivity.

Aluminum catalysts, chiral hydride source

Table 1. Catalytic MPV Reduction Using Simple Alkylaluminum Reagents



entry	product	Al pre-catalyst (10 mol%)		yield(%)	time(h)
1		a	$AlMe_3$	82	3
		b	$AlMe_2Cl$	96	2
		c	$AlMeCl_2$	5	12
		d	$Al(O^iPr)_3$	7	12
2		a	$AlMe_3$	91	2
		b	$AlMe_2Cl$	60	1
		b'	$AlMe_2Cl$ (neat ^iPrOH)	85	4
		c	$AlMeCl_2$	6	12
		d	$Al(O^iPr)_3$	3	12
3		a	$AlMe_3$	99	12
		b	$AlMe_2Cl$	65	12
4		a	$AlMe_3$	51	12
		a'	$AlMe_3$ (65 °C)	80	12
		b	$AlMe_2Cl$	55	12
		d	$Al(O^iPr)_3$	0	12
5		a	$AlMe_3$	11	12
		b	$AlMe_2Cl$	50	12
		d	$Al(O^iPr)_3$	0	12

[a] Reaction conditions: Al pre-catalyst in 21 μM concentration, rt, N_2.

In situ generated catalyst (NMR), aggregtion state

aged (6 days)- 20% decrease in activity

$AlMe_2Cl$ (LA) better for e-rich (entries 1,5)

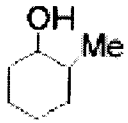
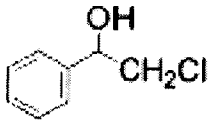
Simple catalyst, catalytic amount

Nguyen, S. T., et al. *Org. Lett.* **2001,** *3,* 2391

9b. Enantioselectivity.

Aluminum catalysts, chiral hydride source

Stereoselective MPV Reduction and Effect of Ligand Additives

product	entry	Al Reagent (10 mol%)	ligand	hydride source (equiv)	product selectivity cis/trans	ee(%)[d]
	1[b]	$AlMe_2Cl$	5,10,15,20-tetraphenyl porphyrin (slide 7a)	^iPrOH(4)	20/80	---
	2[a]	$AlMe_2Cl$	—	^iPrOH(4)	20/80	---
	3[c]	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol (slide 5b)	*enantiopure*-α-methyl-2-napthyl methanol(1)	—	70
	4[a]	$AlMe_3$	----	*enantiopure*-α-methyl-2-napthyl methanol(1)	—	68
	5[c]	$AlMe_3$	2,7-Dimethyl-1,8-biphenylene-diol (slide 5b)	*enantiopure-sec-o*-bromophenethyl alcohol(1)	—	82
	6[a]	$AlMe_3$	----	*enantiopure-sec-o*-bromophenethyl alcohol(1)	—	86-81[e]

a Reaction conditions: toluene (1 mL), 1,2,4,5-tetramethylbenzene (internal standard), N2, Al reagent (21*10^-6 mol, 10 mol %), substrate (10 equiv), either chiral hydride source (1 equiv, 0 C) or iPrOH (4 equiv, rt).b Reference 10 reports a cis/trans ratio of 8/92. Al(TPP)Cl under our reaction conditions (rt) yields a cis/trans ratio of 20/80.c Taken from ref 11; reactions carried out at 0 C.d The absolute configuration of the major enantiomer of the product is opposite that of the chiral hydride source.e As would be expected for a reversible reaction, the enantioselectivity of the product decreases slowly over time.

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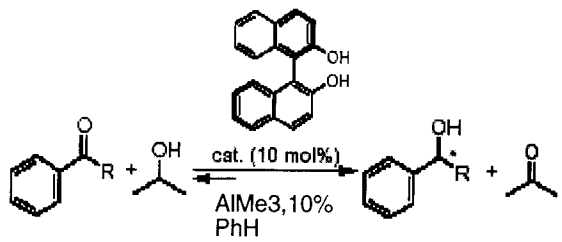
10. Enantioselectivity.

Chiral aluminum catalysts



(2)

Table 1. Asymmetric MSPV reduction.[a]

Entry	R	2-Propanol (equivalents[b])	Product Yield [%]	Product ee [%]
1	CH_2Cl	4	99	80 (*R*)[c]
		4	99	80 (*S*)[d]
2	CH_2Br	4	99	83 (*S*)[d]
3	CH_2CH_3	4	30	50 (*R*)[c]
		15	80	46 (*R*)[c]
4	$CH_2CH(CH_3)_2$	4	32	53 (*S*)[d]
		15	35	35 (*S*)[d]
5	$CH(CH_3)_2$	4	20	61 (*S*)[d]
		15	46	50 (*S*)[d]
6	CH_3	4	54	30 (*R*)[c]
		4	58	28 (*S*)[d]
		15	80	25 (*R*)[c]
7	CH_2OCH_3	4	95	8 (*R*)[c]
8	acetonaphthone[e]	4	41	48 (*S*)[d]
		15	43	46 (*S*)[d]

[a] Reaction conditions: BINOL (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), and toluene (500 μL); room temperature, N_2 for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reaction with (*S*)-(−)-BINOL. [e] acetonaphthone is the whole reactant, not an R group (not shown in Eq. (2)).

1. More e-rich ketone- lower yield, ee.

2. Excess i-PrOH increases the yield

3. Methoxy-group, disrupts chiral TS

4.Bulkier Ar- higher ee.

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10a. Enantioselectivity.

Chiral aluminum catalysts

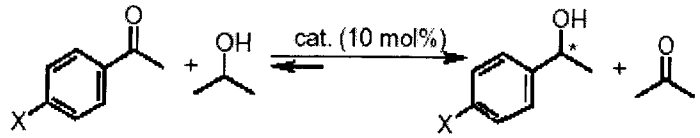
Better yields, same ee.

Favorable equilibrium:10%(R)-BINOL,

20eq i-PrOH, 20eq Acteone, (R)-phenylethanol

decreased ee from 98 to 93%

Table 2. Electronic effect on the MSPV reduction.[a]



(3)

Entry	X	2-Propanol (equivalents[b])	Product Yield [%]	*ee* [%]
1	H	4	54	30 (*R*)[c]
		15	80	25 (*R*)[c]
2	CH_3	4	44	30 (*R*)[c]
		15	62	20 (*S*)[d]
3	F	4	55	30 (*R*)[c]
		15	55	30 (*R*)[c]
4	Cl	4	70	30 (*R*)[c]
5	Br	4	70	30 (*R*)[c]

[a] Reaction conditions: BINOL (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), and toluene (500 µL); room temperature, N_2 for 16 h. [b] based on substrate. [c] *R* isomer obtained from reactions with (*R*)-(+)-BINOL. [d] *S* isomer obtained from reactions with (*S*)-(−)-BINOL.

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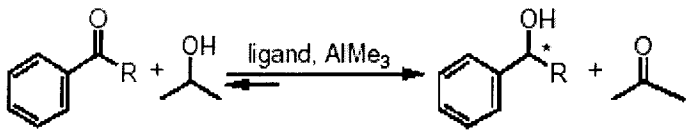
10b. Enantioselectivity.

Chiral aluminum catalysts, role of the ligand.

Table 3. Effect of ligand additive on the MSPV reduction.[a]



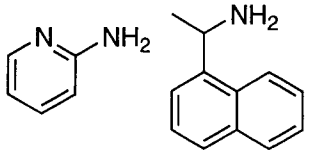
(4)

	R = Me				R = CH_2Cl		
Ligand	Ligand:$AlMe_3$	Yield [%]	*ee* [%]	Ligand	Ligand:$AlMe_3$	Yield [%]	*ee* [%]
BINOL	1:1	54	30	BINOL	1:1	99	80
BINOL	2:1	0	–	BINOL	2:1	0	–
1	1:1	58	0	**1**	1:1	99	15
1	2:1	40	0	**1**	2:1	90	12
1	4:1	20	0	**1**	4:1	60	0
2	1:1	25	0	**2**	1:1	90	10
3	1:1	7	0	**3**	1:1	25	0

[a] Reaction conditions: ligand **1–3** (0.02 mmol), $AlMe_3$ (0.02 mmol), ketone (0.20 mmol), *i*PrOH (0.80 mmol), and toluene (500 µL); room temperature, N_2 for 16 h.

1. Excess of the ligand-detrimental

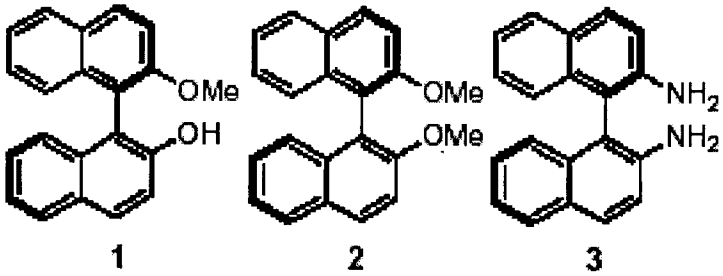
2. Primary amines-low yield



-prevent at all

3. Ligand (1) -same yield, no ee

4. Even (2) works, but worse



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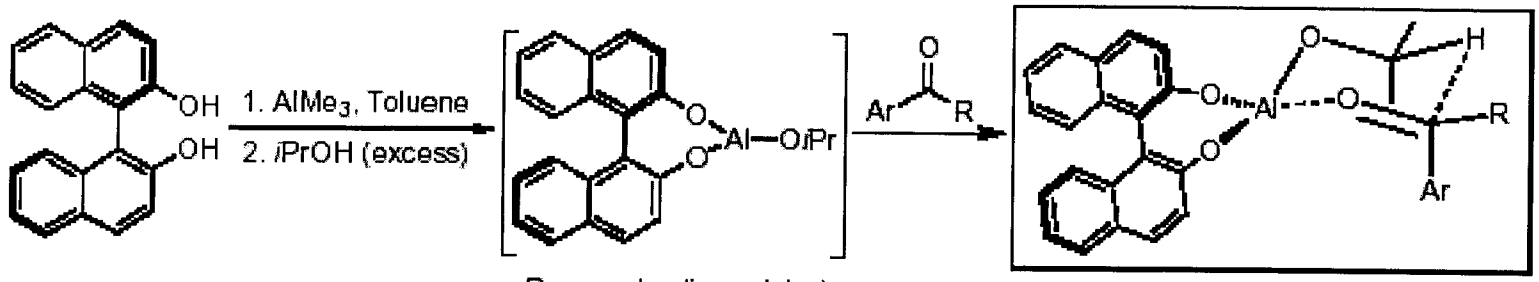
10c. Enantioselectivity.

Chiral aluminum catalysts



Proposed active catalyst

Proposed transition state for the stereoselective MSPV reaction.

1. Active catalyst tructure proposed see above. [(BINOL)AlMe(THF)] gave the same yield and ee with alpha-Br-acetophenone and i-PrOH

2. 2 sites bound to BINOL, two -to the reagents. If not- lower yield/ee

3. Excess i-PrOH competes with BINOL, => higher yield, but lower ee (not much, however)

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11. CONCLUSIONS:

1. An old reaction with a lot to discover.

2. Kinetic or thermodinamic control:

- stoichiometric amount of $Al(Oi\text{-}Pr)_3$ vs. catalitic amounts of not so tightly bound promoters.

3. Chemo-, diastereo-, enantioselectivity:

-the best reducing agents (dialky ketones; a,b-unsaturated);

-the best oxidizing agents (acetone, cyclohexanone, diaryl ketones, aldehydes); 1 or more equivalents;

-cis-substituted cycloalkanols under kinetic control vs. trans- under thermodinamic;

-use of chiral alcohols or catalysts (MPV- or hydride-type).

4. Usually basic conditions, but can be neutral:

-from alkali metal alkoxides, through Al-alkoxides, to Ru(II)-based catalysts;

5. Environmentally friendly, cheap, industrially convenient (heterogenious variant).

6. Very tough to compete with metal hydrides and direct hydrogenation.