ATOM EFFICIENCY & CATALYSIS IN ORGANIC SYNTHESIS

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Lecture presented at the 8th Ischia Advanced School of Organic Chemistry
Ischia, September 26-October 1, 1998

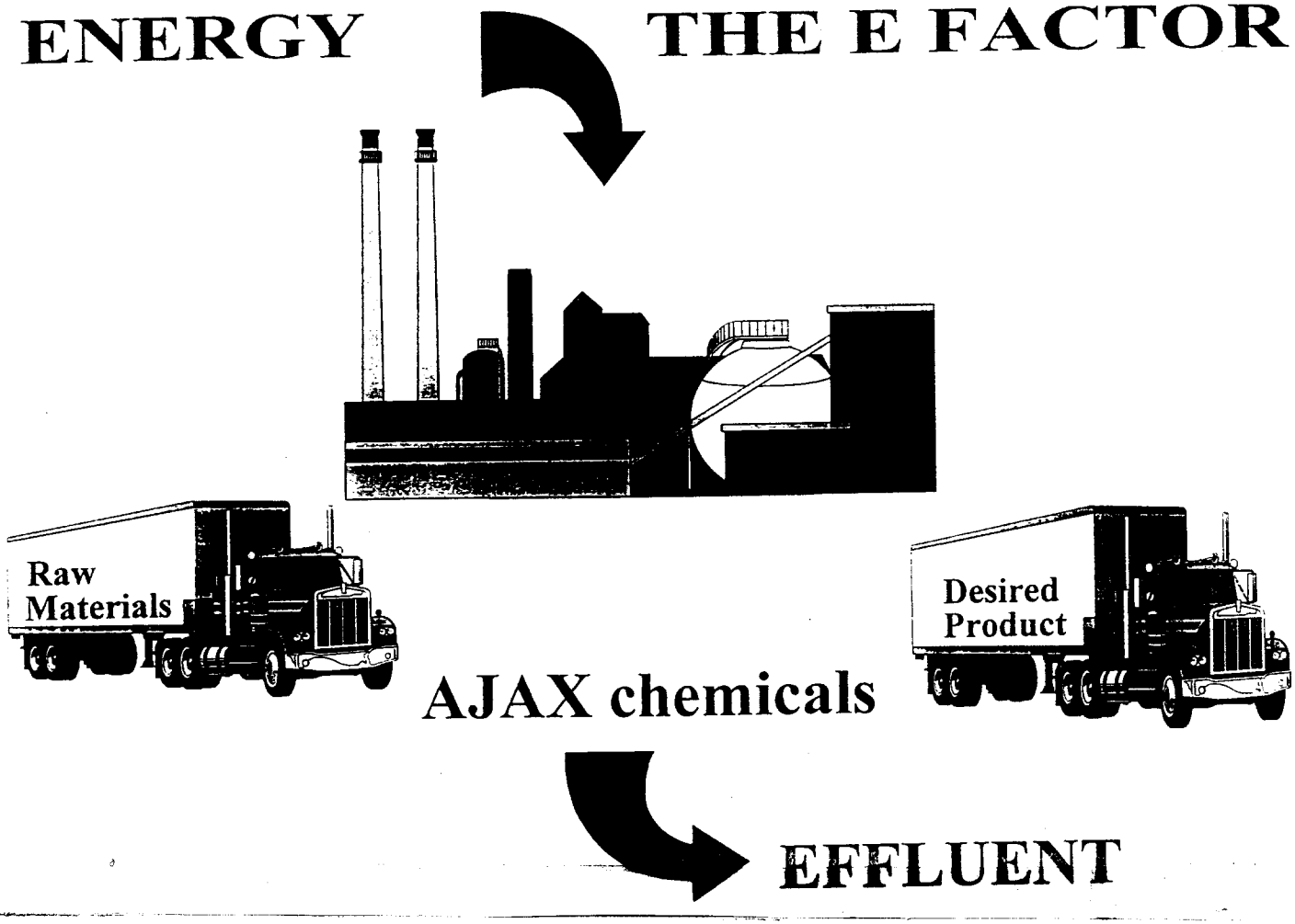
ATOM EFFICIENCY & CATALYSIS IN ORGANIC SYNTHESIS

OUTLINE

Environmental Acceptibility: The E Factor

Industry Segment	Product Tonnage	E factor kg waste/ kg product
Oil refining	10^6 - 10^8	< 0.1
Bulk Chemicals	10^4 - 10^6	<1 - 5
Fine Chemicals	10^2 - 10^4	5 - 50
Pharmaceuticals	10 - 10^3	25 - >100

R.A. Sheldon, Chem. Ind. (London) 1997, 12 and 1992, 903



Atom Efficiency: Stoichiometric vs Catalytic Oxidation

Stoichiometric:

$3\ PhCH(OH)CH_3 + 2\ CrO_3 + 3\ H_2SO_4 \longrightarrow 3\ PhCOCH_3 + Cr_2(SO_4)_3 + 6\ H_2O$

Atom efficiency = 360 / 860 = 42 %

Catalytic :

$PhCH(OH)CH_3 + 1/2\ O_2 \xrightarrow{Catalyst} PhCOCH_3 + H_2O$

Atom efficiency = 120 / 138 = 87 %
Byproduct: H_2O

R.A. Sheldon, J. Chem. Tech. Biotechnol., 68 (1997) 381

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Alcohol oxidation

CrO_3 | MnO_2 | $Pb(OAc)_4/py$ | Ag_2CO_3 | $PH_3Bi(CO)_3$

$(CH_3)_2S/Cl_2$ | $DMSO/(COCl)_2$ | $DMSO/(C_6H_{11}N=)_2C$ | $Al(Opr^i)_3/Me_2CO$

Pt/O_2

Chromic acid is one of the most versatile of the available oxidizing agents.....One of the most important uses of chromic acid in organic synthesis is in the oxidation of alcohols, particularly secondary alcohols to ketones.

CrO_3/H_2SO_4 Jones

$(py)_2CrO_3$ Collins

$(pyH)^+ClCrO_3^-$ Corey

W. Carruthers, Some Modern Methods of Organic Synthesis, 3rd edn., Cambridge Univ. Press, 1986

Clean Catalytic Technologies

Hydrogenation

$$PhCOCH_3 + H_2 \xrightarrow{\text{catalyst}} PhCH(OH)CH_3$$

100% atom efficiency

Oxidation

$$PhCH(OH)CH_3 + 1/2\ O_2 \xrightarrow{\text{catalyst}} PhCOCH_3 + H_2O$$

87% atom efficiency

Carbonylation

$$PhCH(OH)CH_3 + CO \xrightarrow{\text{catalyst}} PhCH(CH)_3CO_2H$$

100% atom efficiency

Environmental = Elegance Quotient, EQ

Environmental Quotient = E x Q

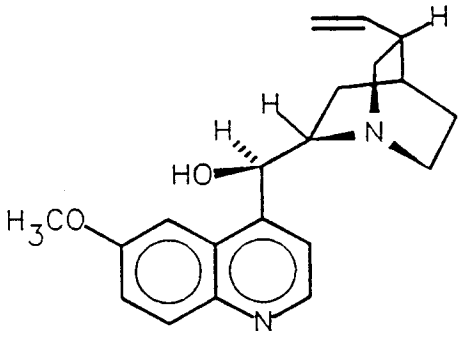
E = kg waste / kg product
Q = unfriendliness quotient

e.g. NaCl: Q=1
Cr-salts: Q =100 or 1000?

R.A. Sheldon, Chemtech., 1994, 38; J. Mol. Catal. A, 107 (1996), 75

INDUSTRIAL ORGANIC SYNTHESIS

W.H. PERKIN
QUININE SYNTHESIS (1856)



Quinine

$C_{20}H_{24}N_2O_2$

Concept:

$$2\ C_{10}H_{13}N + 3\ "O" \xrightarrow{K_2Cr_2O_7} C_{20}H_{24}N_2O_2 + H_2O$$

ALLYL TOLUIDINE — QUININE

N.B. BENZENE STRUCTURE, *A. Kekulé (1865)*

J.J. BERZELIUS (1779-1848)

ORGANIC CHEMISTRY (1807)

Urea synthesis (Wohler) — 1828

First synthetic dye, Aniline purple (Perkin) — 1856

↓

DYESTUFFS INDUSTRY (based on coal-tar)

↓

FINE CHEMICALS

CATALYSIS (1835)

ca. 1900 Catalysis definition (Ostwald)

Catalytic hydrogenation (Sabatier)

ca. 1920 Petrochemicals

↓

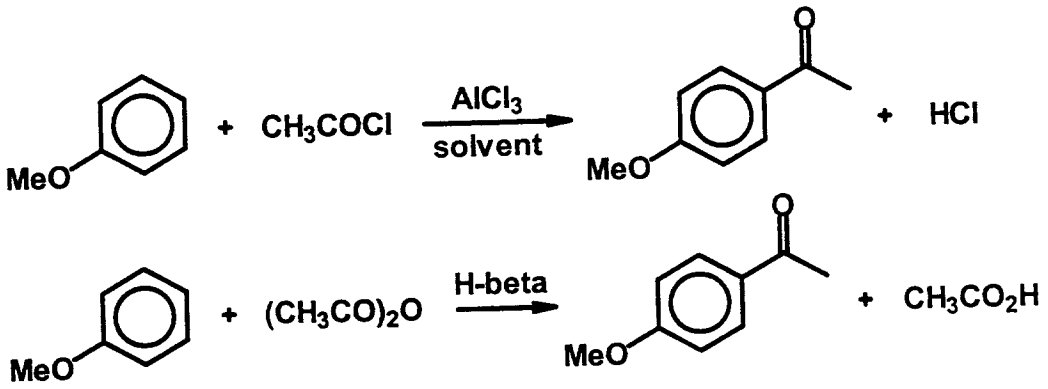
1936 Catalytic cracking
1949 Catalytic reforming
1955 Ziegler-Natta catalysts

↓

BULK CHEMICALS AND POLYMERS

→ CATALYSIS IN ORGANIC SYNTHESIS ←

Zeolite-catalyzed Friedel-Crafts Acylation



Homogeneous	Heterogeneous
$AlCl_3$ > 1 equivalent	H-beta, catalytic & regenerable
Solvent (recycle)	No solvent
Hydrolysis of products	No water necessary
85-95% yield	> 95% yield / higher purity
4.5 kg aqueous effluent per kg	0.035 kg aqueous effluent per kg

S. Ratton, Chem. Today (Chim. Oggi), March/April, 1998, 33

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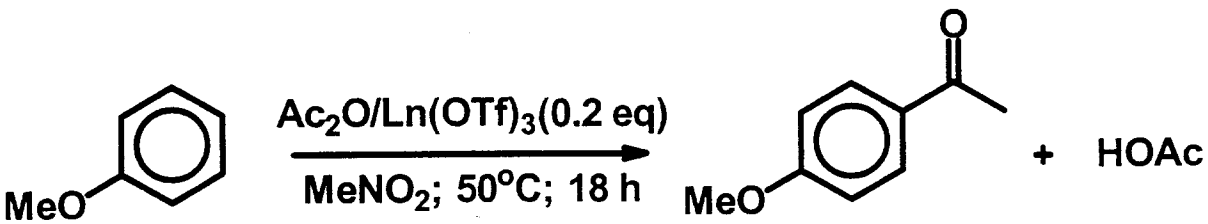
Lanthanide Triflates: Recyclable F/C Acylation Catalysts



Ln	Yield(%)	Ln	Yield(%)
La	41	Dy	85
Pr	87	Ho	79
Nd	79	Er	78
Sm	80	Tm	84
Eu	78	Yb	99
Gd	78	Lu	81

PhH unreactive

A.Kawada, S. Mitamura, S.Kobayashi, Chem. Comm., 1993, 1157

Lanthanide Triflate-Catalyzed Aromatic Nitration

$$ArH + HNO_3 \xrightarrow[ClCH_2CH_2Cl,\ reflux,\ 12\ h]{Yb(OTf)_3\ (10\ m\%)} ArNO_2 + H_2O$$

- Avoids spent acid problem of conventional nitration (HNO_3/H_2SO_4)

ArH	Conv. (%)	Product distribution (%)		
		o	*m*	*p*
Benzene	> 75			
Toluene	> 95	52	7	41
Bromobenzene	92	44	tr	56
Nitrobenzene	0	-	-	-
p-Xylene	> 95		n/a	

F.J. Waller, D. Ramprasad, A.G.M. Barrett and D.C. Braddock, Catalysis of Organic Reactions, F.E. Herkes, Ed., 1998, p. 289

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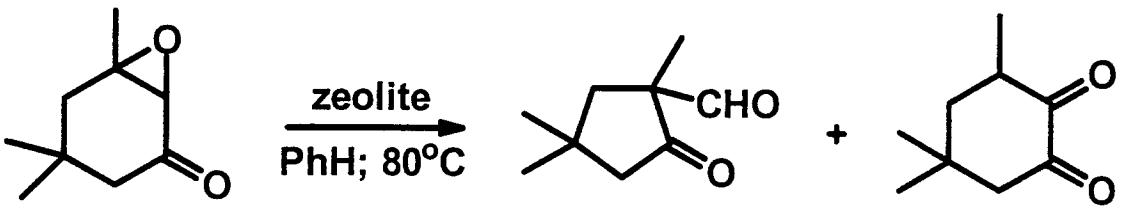
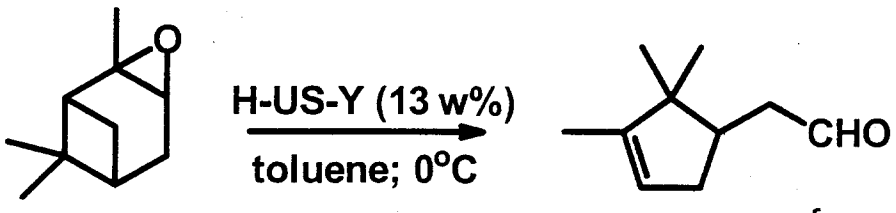
Zeolite-Catalyzed Epoxide Rearrangements



fragrance intermediate

H-MOR	85%	5%
H-BEA	71%	11%

J.A. Elings, H.E.B. Lempers and R.A. Sheldon, Stud. Surf. Sci. Catal., 105 (1997) 105

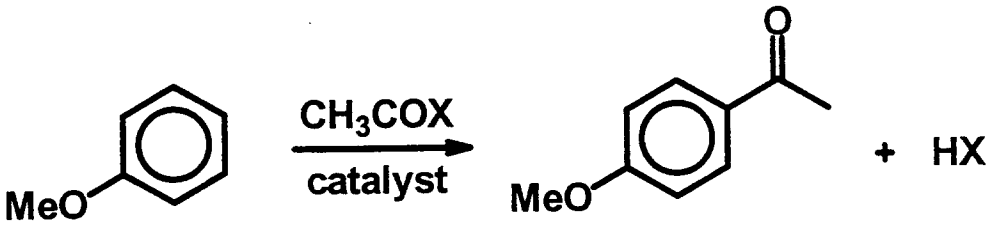


80% yield

fragrance intermediate

A.T. Liebens, C. Mahaim and W.F. Hoelderich, Stud. Surf. Sci. Catal., 108 (1997) 587

Friedel-Crafts Acylation



	$AlCl_3$	H-beta	$H_3PW_6Mo_6O_{40}$	$Yb(Otf)_3$
X	Cl	OAc	Cl	OAc
Solvent	CS_2	-	-	CH_3NO_2
S/C (g/g)	0.7	2.9	2.6	8.5
Productivity (g/g/h)	0.26	25	7	0.4
Volume yield (g/l	47	162	51	17
STY (g/l/day)	560	648	303	22
E factor (g/g)	3	0.4	0.24	0.43
Atom efficiency (%)	25	71	80	71
Byproducts	$AlCl_3.nH_2O$ HCl	HOAc	HCl	HOAc

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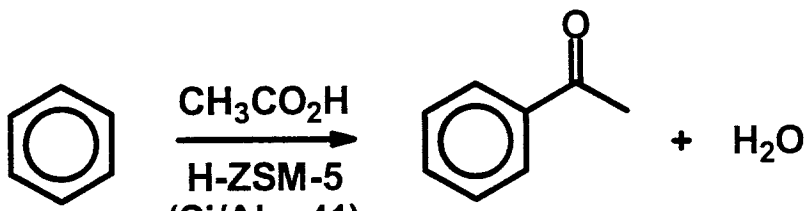
Friedel-Crafts Acylation: Gas Phase



Conv. (HOAc) = 43%
Selectivity = 91%

PhH/HOAc = 2:1 Feed rate = 2 ml/h (2 g catalyst) Tubular reactor

- TOF = 46 $mmol.s^{-1}$ mol^{-1} Al x 10^{-3}
- No deactivation in 2 h on stream
- Byproducts di- and triacetylbenzenes

A.P. Singh and A.K. Pandey, J. Mol. Catal. A: Chemical, 123 (1997) 141

Ether Synthesis via Reductive Alkylation

Classical Route (Williamson Ether Synthesis)

$$R^1CH_2Cl + R^2ONa \longrightarrow R^1CH_2OR^2 + NaCl$$

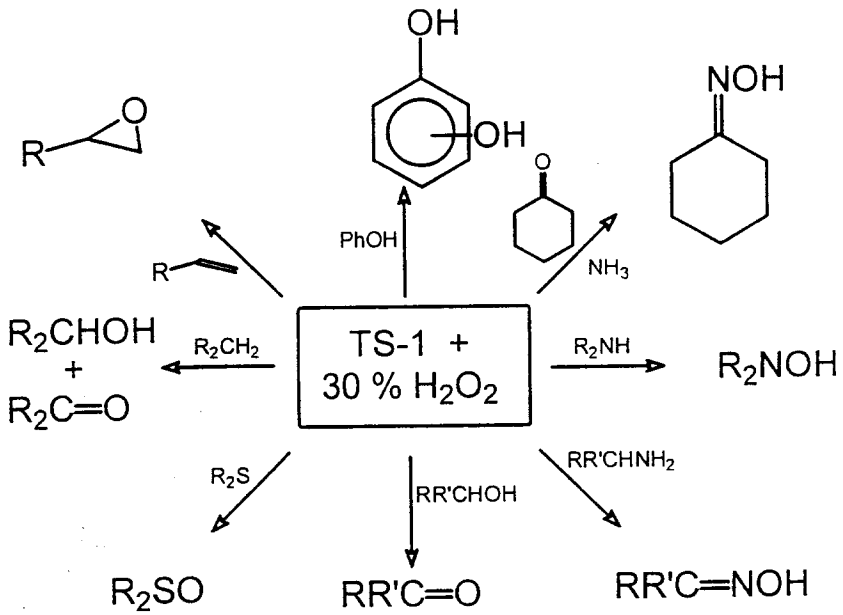
A.W. Williamson, J. Chem. Soc., 4 (1852) 106

Catalytic *O*-Alkylation

$$R^1CHO + R^2OH + H_2 \xrightarrow{Pd/C} R^1CH_2OR^2 + H_2O$$

F. Fache, V. Bethmont, L. Jacquot and M. Lemaire, Recl. Trav. Chim. Pays-Bas, 115 (1996) 231

TS-1 Catalyzed Oxidations with H_2O_2

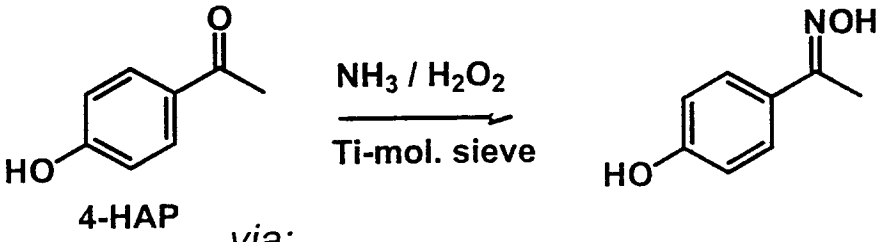


Hydrophobic molecular sieve (5.6 x 5.3 Å)

Hydrophobicity index ($\varkappa_{octane}/\varkappa_{H2O}$) TS-1 = 3.4 Ti/SiO_2 = 0.1

B. Notari, Stud. Surf. Sci. Catal., 37 (1988) 413

PARACETAMOL INTERMEDIATE VIA AMMOXIMATION

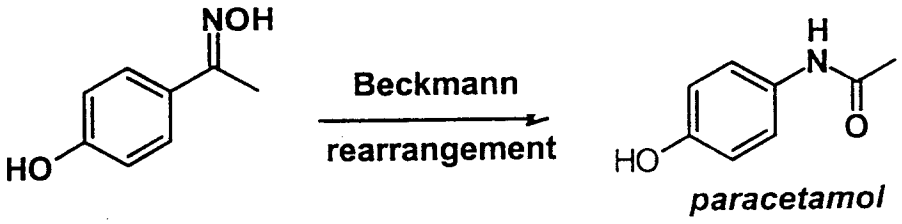


4-HAP

via:

$NH_3 + H_2O_2 \xrightarrow{\textit{Ti-mol. sieve}} NH_2OH + H_2O$

Catalyst	*4-HAP conv (%)*	*Oxime sel. (%)*
TS-1	50	100
Ti-Al-Beta	30	80
Ti-ZSM-48	17	67



paracetamol

J. Le Bars, J. Dakka and R.A. Sheldon, Appl. Catal. A.: General, 36 (1996) 69-80.

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Acetic Acid via Methanol Carbonylation

$$CH_3OH + CO \xrightarrow[150\text{-}200^oC,\ 30\text{-}60\ bar]{\text{catalyst}} CH_3CO_2H$$

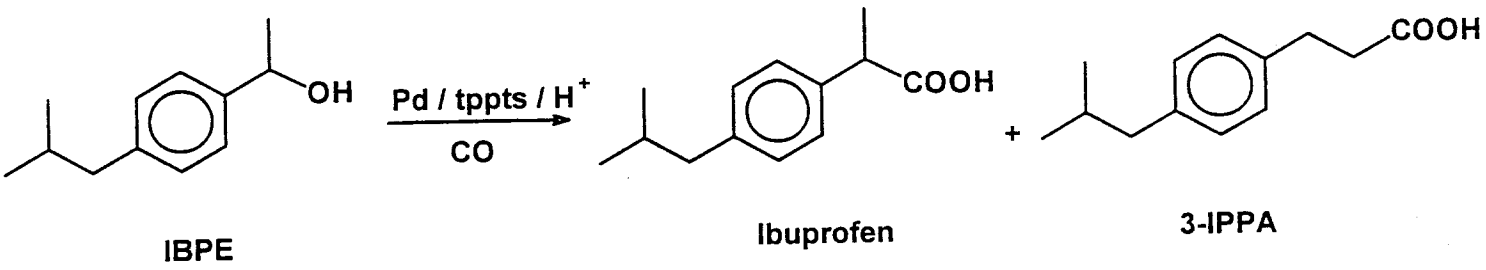
Rh^I/I^- Monsanto (1966)
Ir^I/I^- BP (1996)

- 100% atom efficient / high selectivity (> 99%)
- Cheap raw materials
- 3.5×10^6 tons worldwide (ca. 60% of total)
- Ir gives higher rates / more stable catalyst

Price $/oz. (1991)
Rh: 3500
Ir: 60

P.J. Watson, Catalysis of Organic Reactions, F.E. Herkes, Ed., 1998, 369

The BHC Ibuprofen process

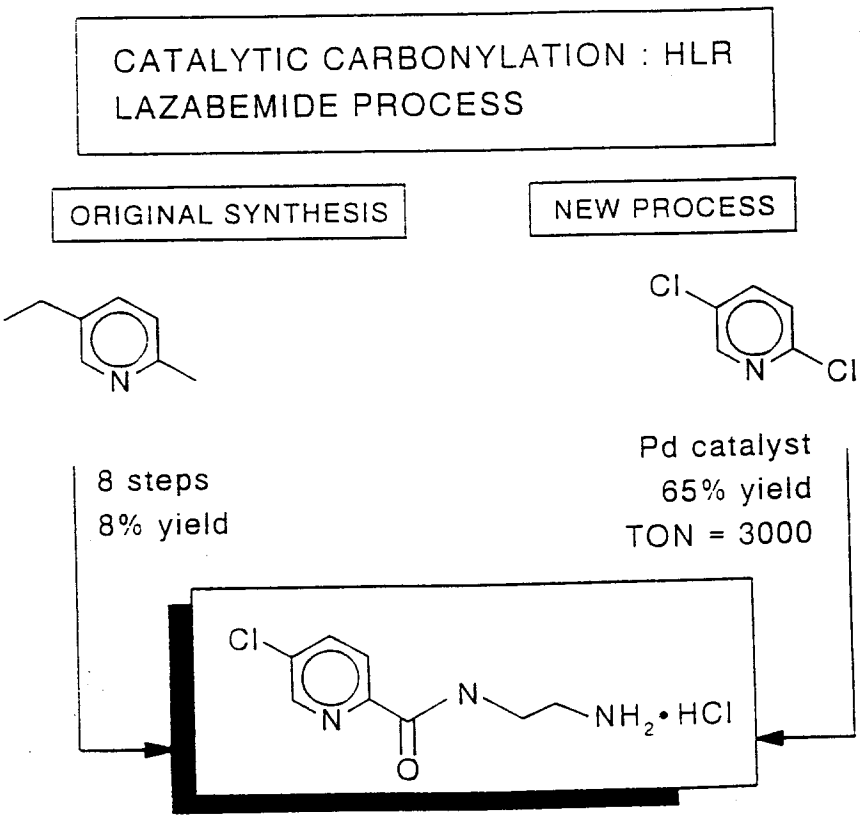


IBPE — Ibuprofen — 3-IPPA

Cumbersome catalyst removal

99% conversion
96% selectivity
T.O.F.= 375 h^{-1}
3,500 tpa

V. Elango *et al*, *US Patent 4 981 995* (**1991**) to Hoechst Celanese



Lazabemide
(anti-Parkinsonian drug)

R. Schmid, [illegible], 50, 110, (1996)

Homogeneous vs Heterogeneous Catalysis

	Homogeneous	Heterogeneous
Advantages	- Mild reaction conditions - High activity & selectivity - Efficient heat transfer	- Facile separation of catalyst and products - Continuous processing
Disadvantages	- Cumbersome separation & recycling of catalyst - Not readily adapted to a continuous process	- Heat transfer problems - Low activity and / or selectivity

➡ **Homogeneous liquid / liquid biphasic catalysis**

Water as a reaction medium

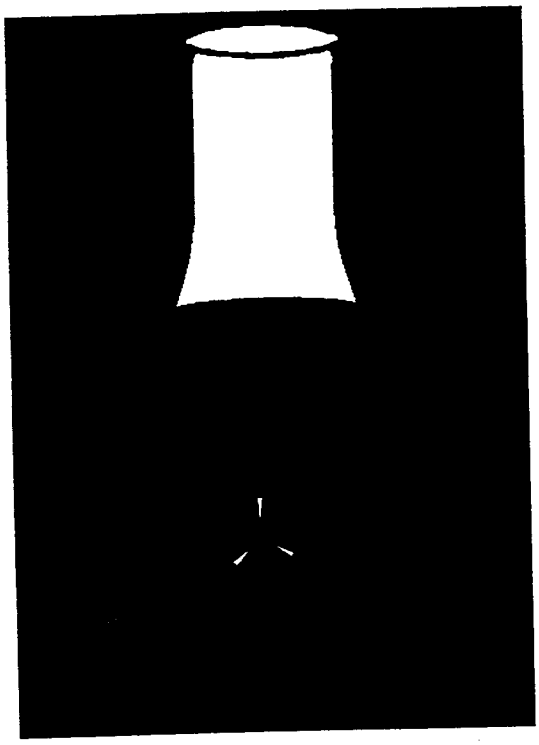
Economically & Environmentally attractive

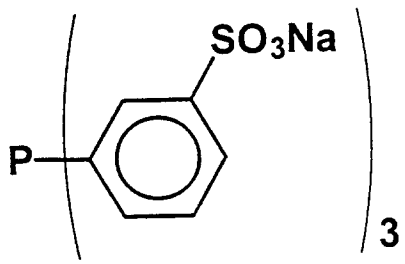
- Inexpensive and abundantly available
- Non-inflammable and non-toxic
- Odorless and colorless
- Environmentally friendly

Highly polar reaction medium

- Novel reactivity
- Facile product separation and catalyst recycling
- Reduced product contamination

Sodium salt of tri-*m*-sulfonatotriphenylphosphine (tppts)

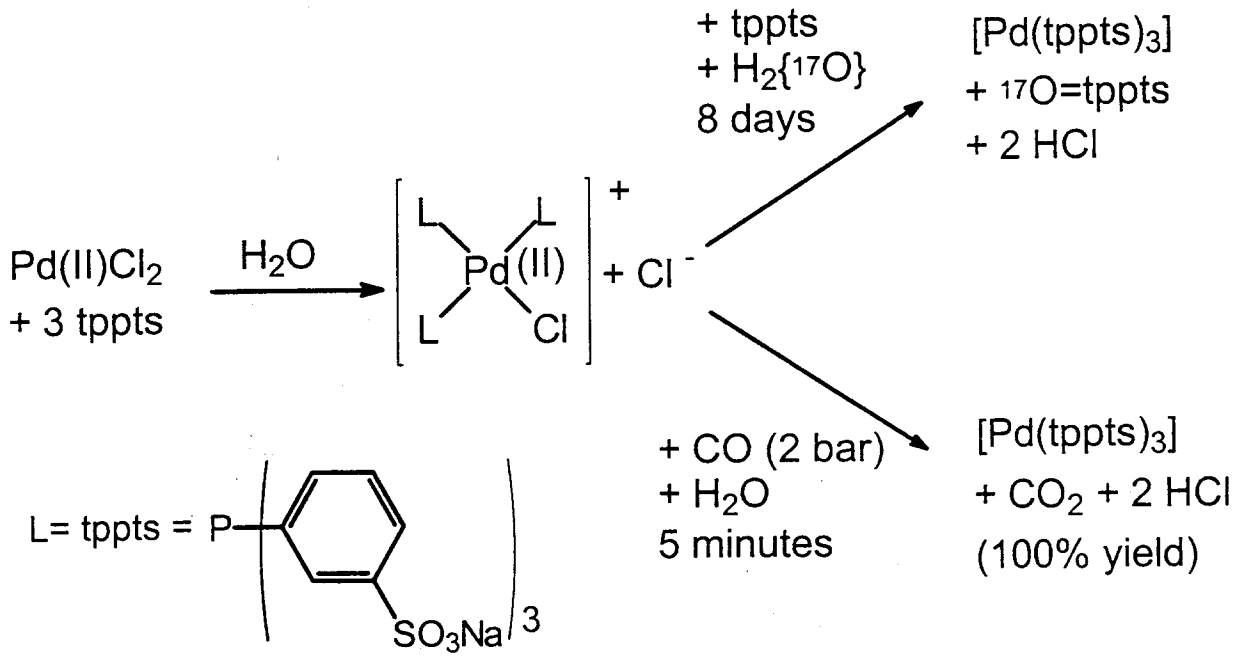




- Solubility in water: 1100 g / L

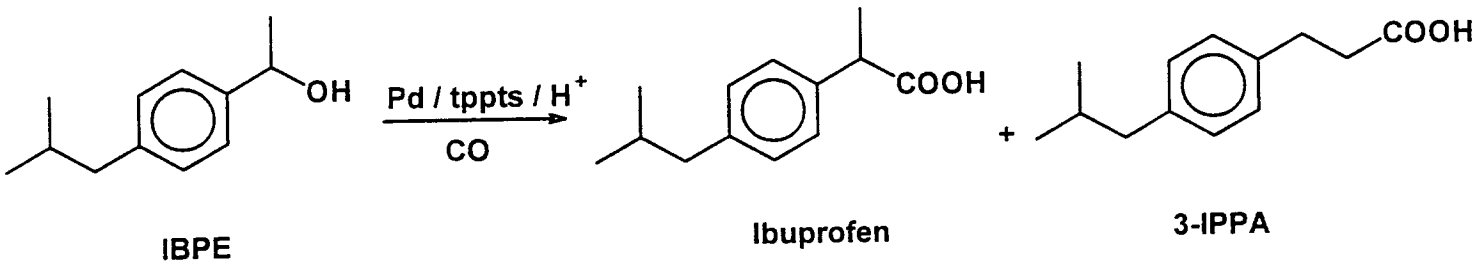
E.G. Kuntz, **1974**

^{17}O-, ^{31}P- and ^{35}Cl NMR study of the redox reaction between $PdCl_2$, tppts and H_2O



G. Papadogianakis, L. Maat, J.A. Peters and R.A. Sheldon, *Chem. Commun.*, **1995**, *1105*

Biphasic carbonylation of 1-(4-isobutylphenyl)ethanol

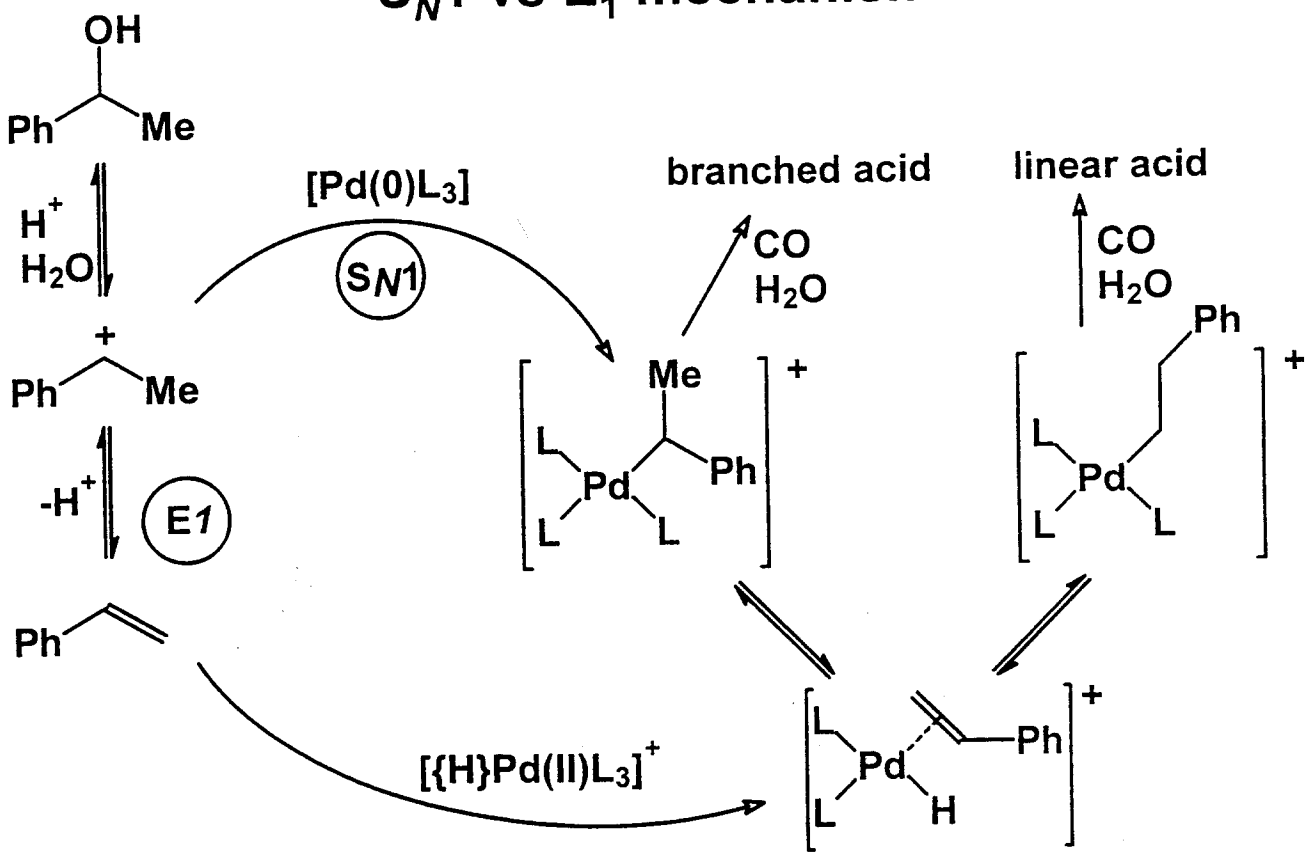


IBPE Ibuprofen 3-IPPA

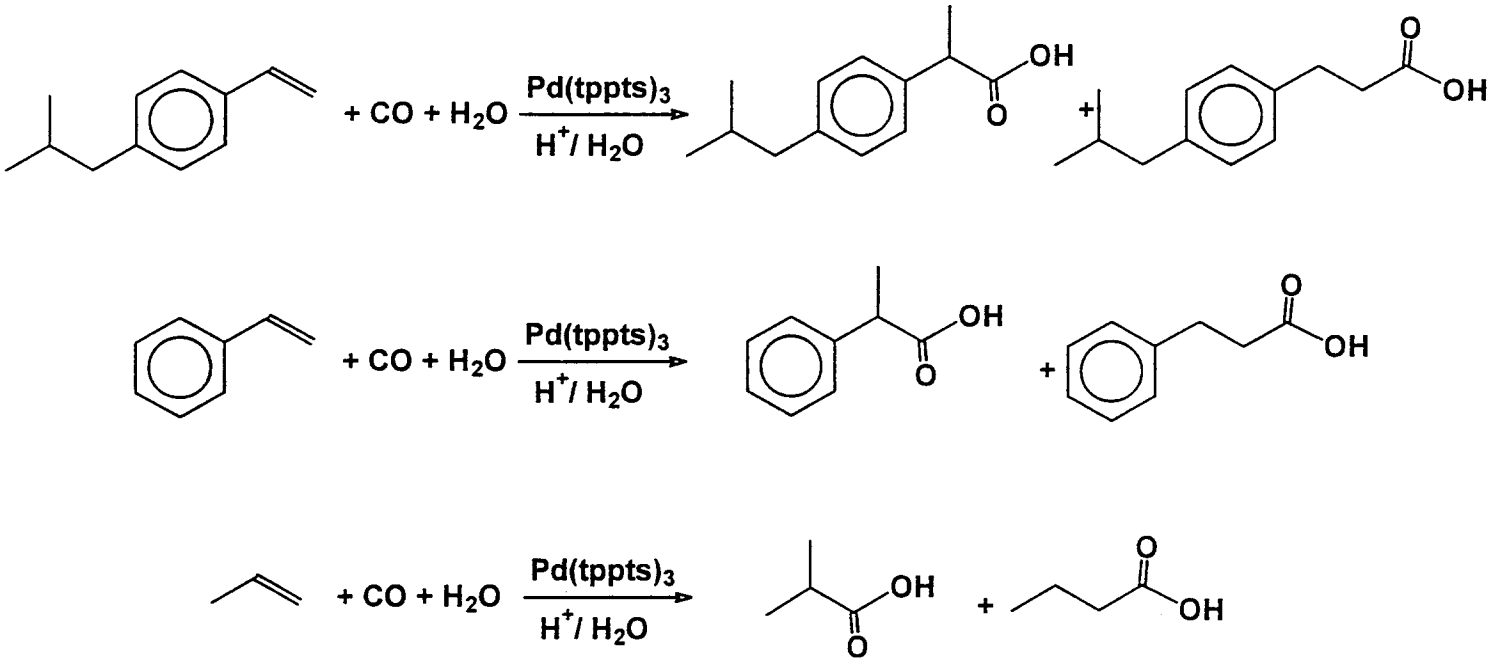
conversion: 83%
selectivity to ibuprofen: 82%
Low activity (TOF = 2.3 h^{-1})

G. Papadogianakis, L. Maat and R.A. Sheldon,
Patent appl. US 08/346,027 (**1994**) to Hoechst Celanese Corp.

S_N1 vs E_1 mechanism

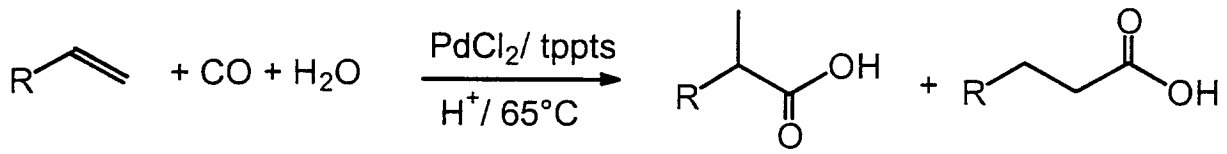


Hydrocarboxylation of α-olefins



G. Papadogianakis, G. Verspui, L. Maat and R.A. Sheldon, *Catal. Lett.*, **1997**, 47, *43*

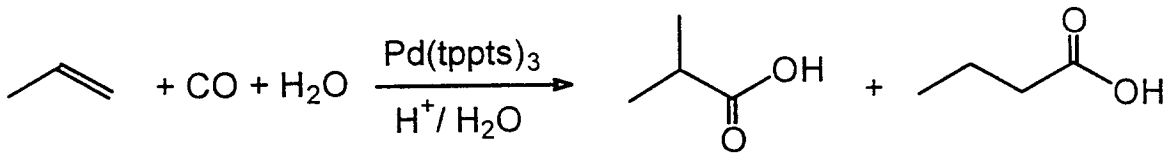
Pd / tppts catalyzed hydrocarboxylation of α-olefins[a]



Olefin	Olefin/Pd	t (h)	Conversion (mol%)	Selectivity (mol%) iso	n	TOF (h^{-1})
IBS[b]	50	10	62	74	14	3
Styrene[b]	50	10	100	56	33	5
Styrene	250	3	59	73	27	49
Propene[c]	250	3	41	38	62	34

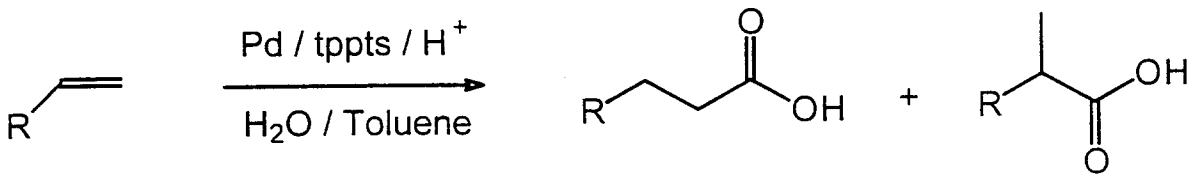
[a] *0.20 mmol $PdCl_2$, tppts/Pd=4 (except runs 1 and 2 P/Pd=8), ([Pd]=1.41 mM), 50 mM p-toluenesulfonic acid, 50 bar; 65°C.* [b] *Formation of heavy ends, presumably polymers of IBS or styrene.* [c] *One phase after the reaction.*

Pd / tppts catalyzed hydrocarboxylation of propene[a]

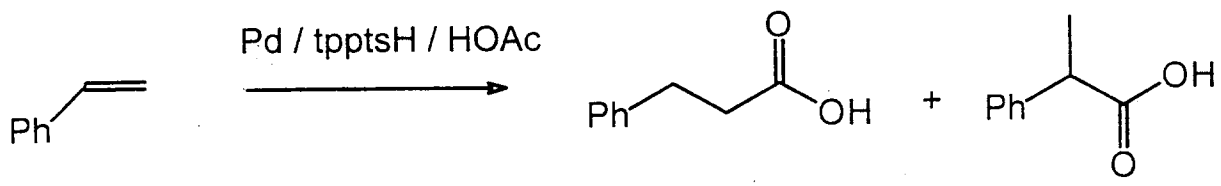


Ligand	HOTs (mmol)	T (°C)	Conv. (mol%)	Selectivity mol% iso	n	TOF (h^{-1})
TPPTS	**0**	110	12	43	57	239
TPPTS	**29**	110	70	42	58	1390
TPPTS	**60**	110	64	42	58	1284
TPPTS	29	**120[b]**	63	43	57	2507
PPh_3[c]	29	110	12	43	57	246

[a] 0.20 mmol $PdCl_2$, [tppts/Pd=4] ([Pd]=1.41 mM), Olefin/Pd=1000, 50 bar, 30 minutes.
[b] Reaction time 15 minutes. [c] PPh_3 [P/Pd= 4], in 1.4-dioxane/water (87/13m/m)

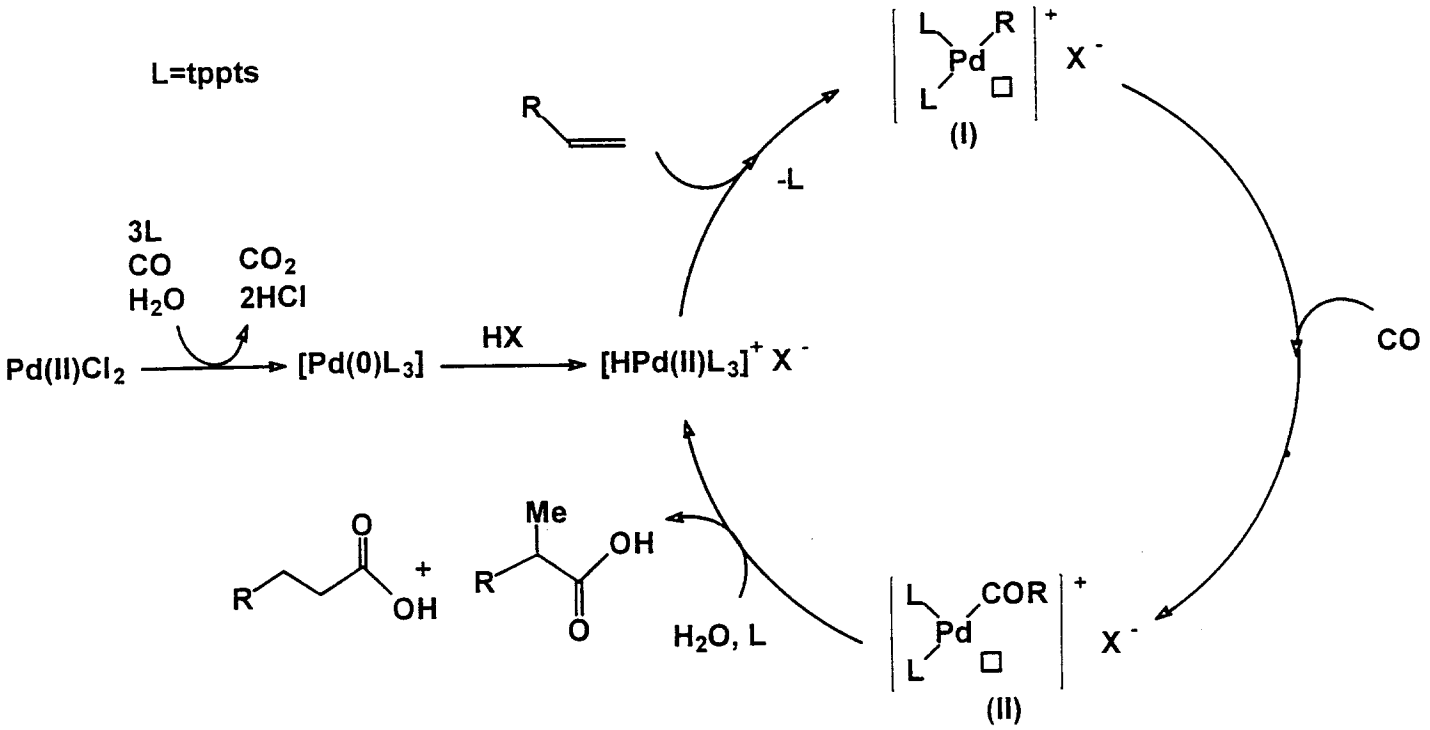


S. Tilloy, E. Monflier, F. Bertroux, Y. Castanet and A. Mortreux, *New. J. Chem.*, **1997**, 21, *529*

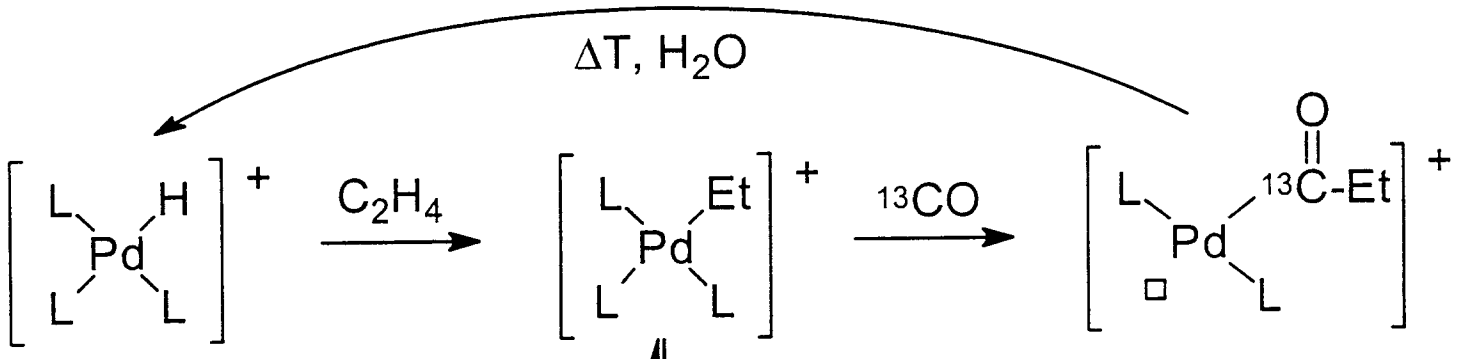


B. Xie, Y. Kou and Y. Ying, *Fenzi Cuihua*, **1997**, 11, *81*

Proposed mechanism for the hydrocarboxylation of α-olefins



Intermediates, characterized by ^{1}H-, ^{13}C- and ^{31}P-NMR



Stable at r.t.

^{1}H: -6.55 ppm (dt)
$^{2}J_{HPtrans}$ = 174 Hz
$^{2}J_{HPcis}$ = 15 Hz

^{31}P: 27.0 ppm (d, 2P)
20.3 ppm (t, 1P)
$^{2}J_{PP}$ = 29 Hz

Decomposes at T>0°C

^{31}P: 31,1 ppm (d, 2P)
15,2 ppm (t, 1P) $^{2}J_{PP}$ = 40 Hz

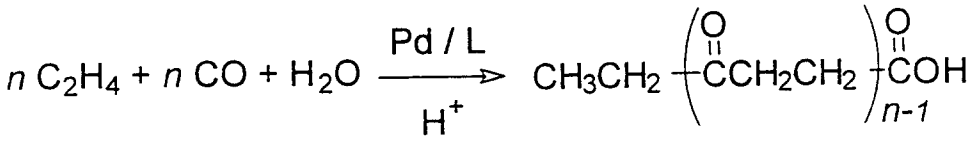
~~and: 27.0 ppm (s, 2P)~~

Stable at r.t.

^{13}C: 235.1 ppm
(s, broad)

^{31}P: 18.9 ppm
(s, broad, 2P)

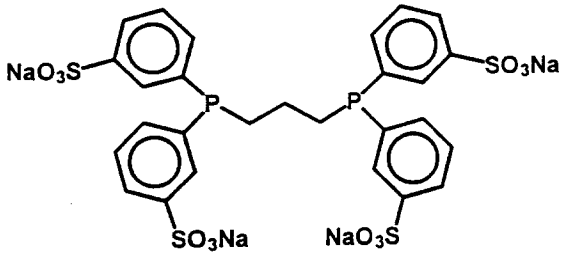
Pd-catalyzed hydrocarboxylation of ethene



L= tppts: n = 1, 2, 3, 4 (T.O.F.= 1000)

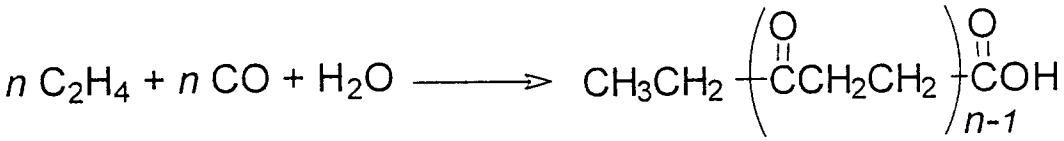
L= DPPPr-S: n = 100 - 200 (T.O.F.= 7500)

DPPPr-S:

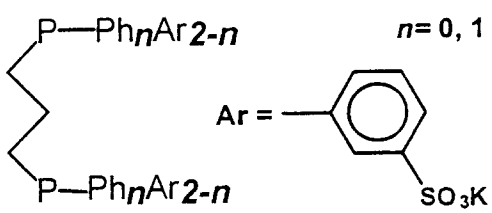


G. Verspui, G. Papadogianakis and R.A. Sheldon, *Chem. Commun., in press*
G. Verspui, G. Papadogianakis and R.A. Sheldon, *Patent appl. NL 100 74 22* (**1997**)

Copolymerization of CO and ethene in water



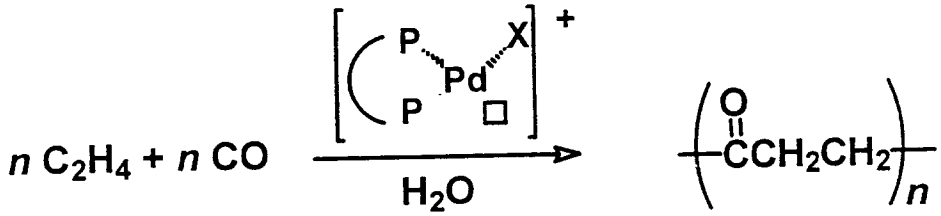
4.86 mmol $[Pd(MeCN)_4(BF_4)_2]$ per liter (517 ppm Pd)
"Ligand" / Pd : 1/1
69 bar total pressure (CO:Ethene = 1:1), 50 °C
470 g Polymer / g Pd in 22 hours



"The palladium(II) center in water is less accessible to the incoming monomers than in organic solvents due to the strong coordination of water molecules."

Z. Jiang, A. Sen, *Macromolecules*, **1994**, 27, *7215*

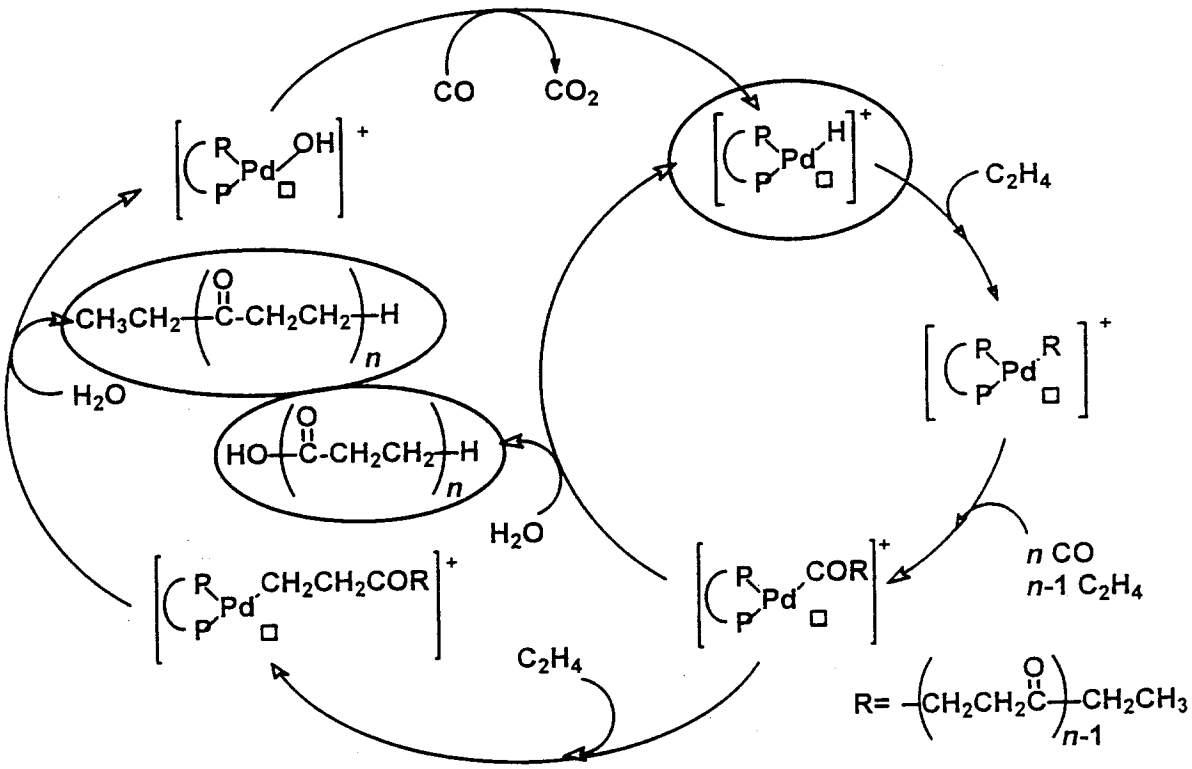
Optimum results in the Pd / DPPPr-S system



- Ligand / Pd ratio: 1 / 1
- pH < 5.0
- Bronsted acid concentration 7 mmol/L (50 equiv. per Pd)
- Weakly or non-coordinating anions

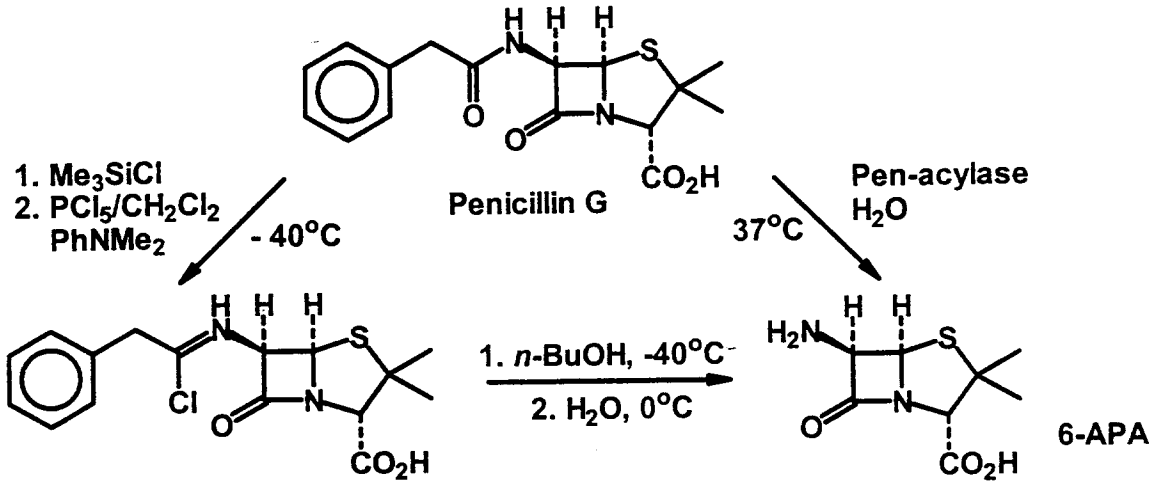
> 4,0 kg copolymer per g Pd per hour (90°C, 40 bar)

Pd / DPPPr-S catalyzed copolymerization of CO and ethene: Suggested mechanism



Adapted from:
E. Drent, J.A.M. van Broekhoven, M.J. Doyle, *J. Organomet. Chem.*, 1991, 417, 235

Enzymatic vs Chemical Process for 6-APA



Key improvements: Enhanced enzyme production and immobilization

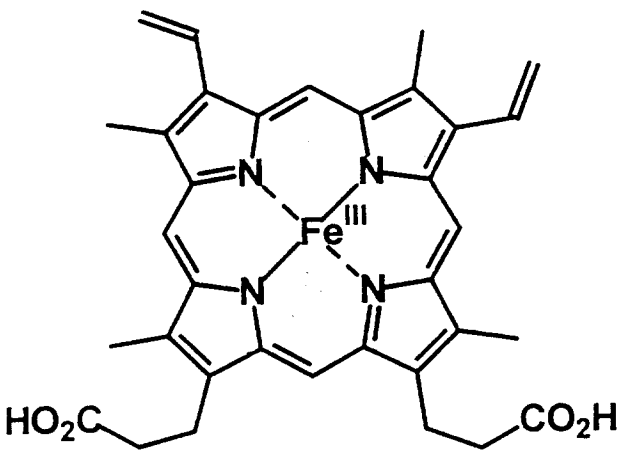
Process	Chemical	Enzymatic
Reagents (kg/kg 6-APA)	Me_3SiCl (0.6), PCl_5 (1.2), $PhNMe_2$ (1.6) *n*-BuOH (8.4 l), NH_3 (0.2)	Pen-acylase (1-2) NH_3 (0.09)
Solvent (l/kg 6-APA)	CH_2Cl_2 (8.4)	H_2O (2)

Ullmann's Encyclopedia of Industrial Chemistry, 5th edn. vol. B 8, p.302

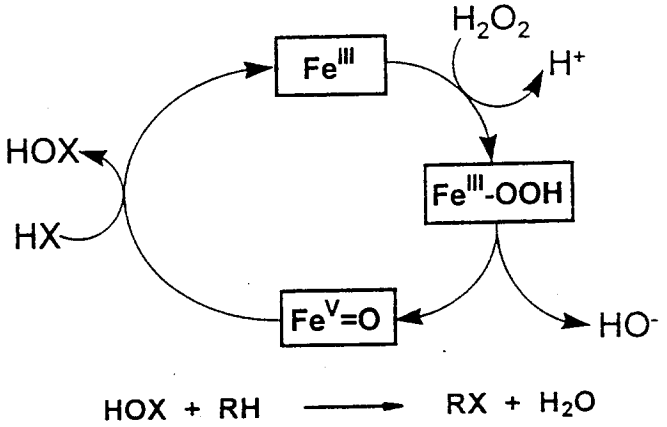
Chloroperoxidase : CPO EC 1.11.1.10

$$RH + HX + H_2O_2 \xrightarrow{CPO} RX + 2H_2O$$

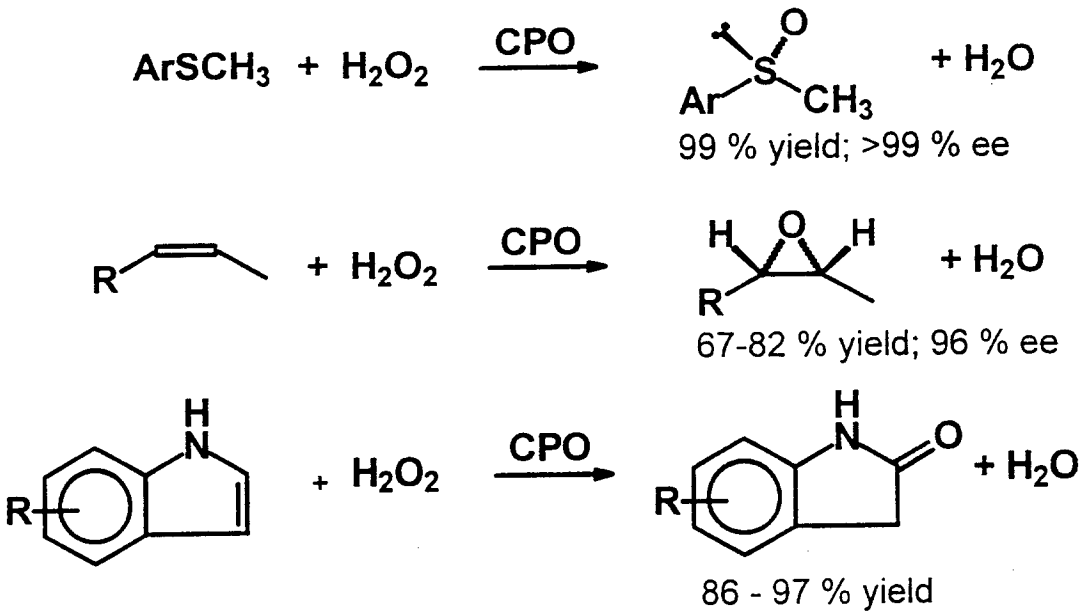
X = Cl, Br or I



Ferriprotoporphyrin IX

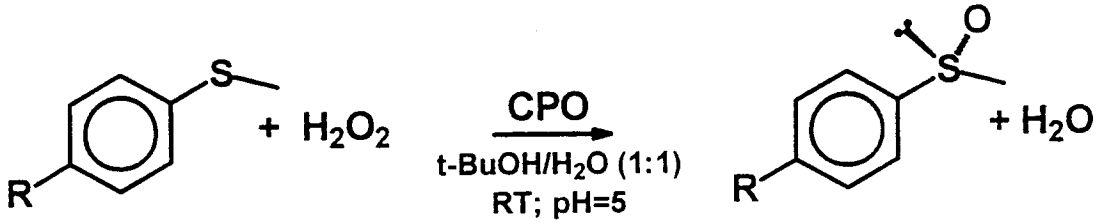


CPO-Catalyzed Oxygen Transfer

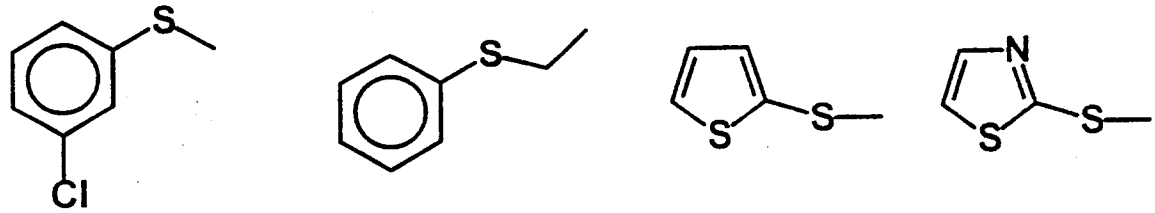


M.P.J. van Deurzen, F. van Rantwijk and R.A. Sheldon, Tetrahedron, 53 (1997) 13183

CPO-Catalyzed Enantioselective Sulfoxidation



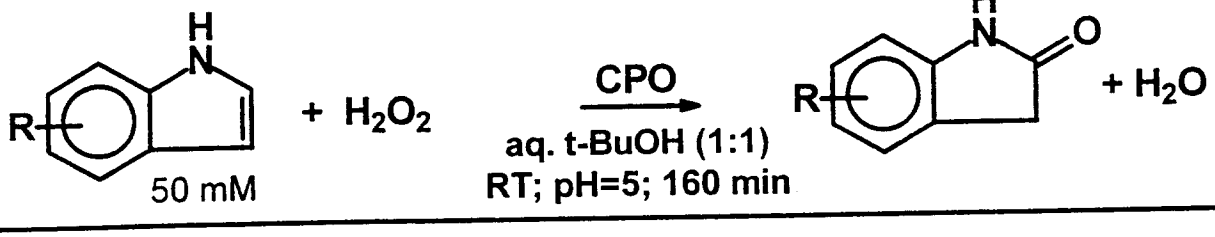
R = H Me
MeO Cl



Examples with >99 % ee and >50 % conversion within 2 h

M.P.J. van Deurzen, I.J. Remkes, F. van Rantwijk and R.A. Sheldon,
J. Mol. Catal. A, 117 (1997) 329

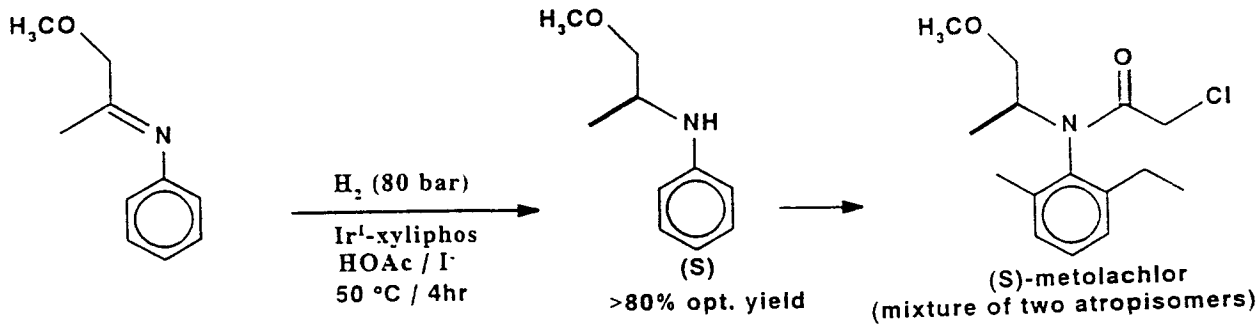
CPO-Catalyzed Regioselective Oxidation of Indoles

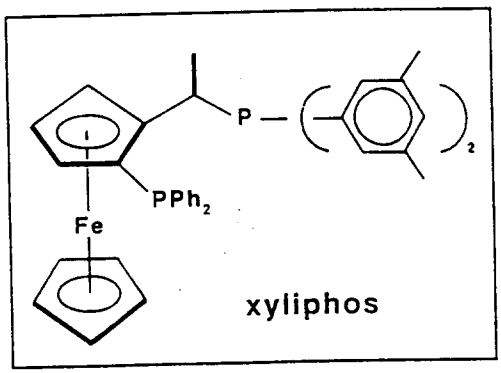


R	CPO (kU)	Yield (%)	Purity (%)
H	1	96	96
4-Cl	6	70	76
5-Cl	2	99	99
5-Br	3	86	95
5-CH_3	6	92	94
5-OCH_3	6	93	95
6-Cl	2	96	99
7-azaindole	2	97	99

M.P.J. van Deurzen, F. van Rantwijk and R.A. Sheldon, J. Mol. Catal. B, 2 (1996) 33

ASYMMETRIC HYDROGENATION OF AN IMINE

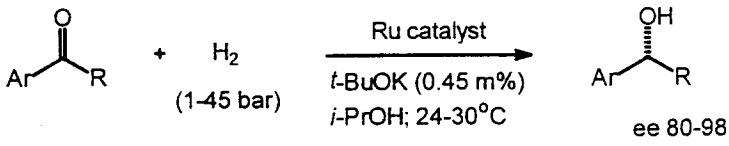


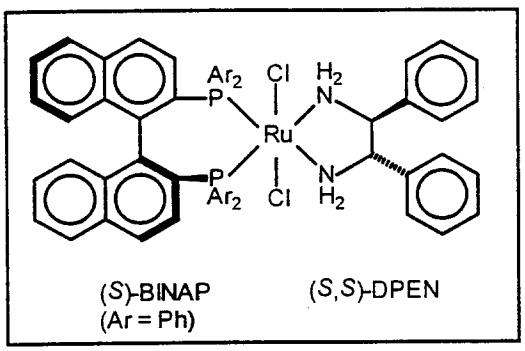


- S/C = 750.000
- TOF (initial) = 1.8 x 10^6 h^{-1} (1mio turnovers in 6 hrs)
- Pilot plant scale

R.R. Bader and H.U. Blaser, 4th Int.Symp.Het.Catalysis & Fine Chemicals, Basel, (1996)

Highly efficient asymmetric hydrogenation of ketones





e.g. Ar = Ph; R = CH_3

S/C = 2,400,000

30°C/45 bar/48 h

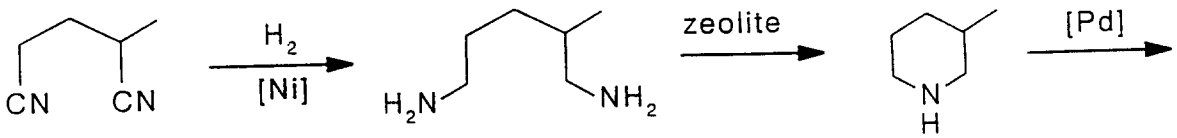
100% yield; 80% ee

TOF = 228000 h^{-1}
at 30% conv.

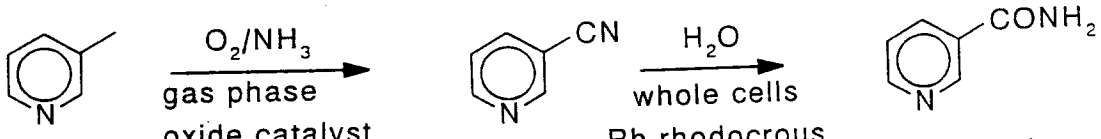
Rate 100x faster with preformed complex

R. Noyori et al., Angew. Chem. Int. Ed. 37 (1998) 1703-1707

PROCESS INTEGRATION : LONZA NICOTINAMIDE PROCESS



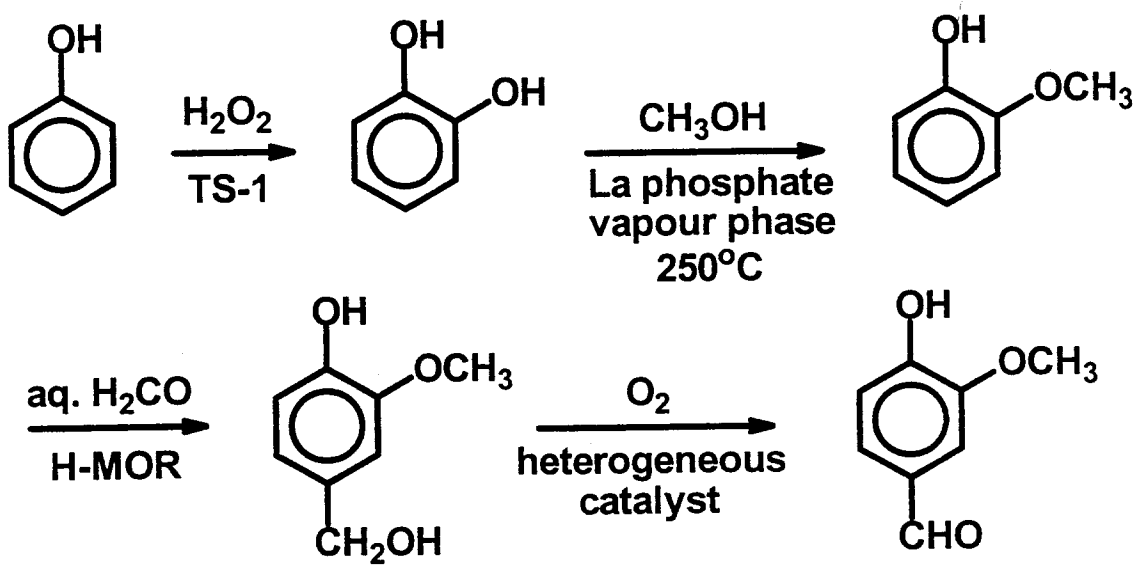
by product of
Nylon 6,6 manuf.



nicotinamide
(vitamin B_3)

J. Heveling, Chimia , 50 , 114 ,(1996)

Catalytic Vanillin Synthesis: Rhone Poulenc



- 4 steps, all employing a heterogeneous catalyst

S. Ratton, Chem. Today, March/April, 1998, 33; C Moreau et al., Catalysis of Organic Reactions, F.E. Herkes, Ed., 1998, p. 51

CONCLUSIONS & PERSPECTIVES

TRENDS IN (FINE) CHEMICALS MANUFACTURE

- **High atom efficiencies / low E factors**
- **Stoichiometric reagents → catalytic processes**
- **Recyclable (solid) acids & bases**
- **Oxidation / reduction / C-C bond forming**
- **Novel reaction media (aqueous or fluorous biphasic, ionic liquids)**
- **Biocatalysis / enantioselective catalysis**
- **Process integration & catalyst recycling**

⇓

CATALYTIC METHODS FOR ECONOMICAL & ENVIRONMENTAL BENIGN ORGANIC SYNTHESIS