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Catalysis for fine chemicals: towards specificity with polyphasic media

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Abstract

Three examples of the work undertaken at the Institut de Recherches sur la Catalyse for the selective preparation of fine chemicals in polyphasic media are presented and discussed:

1. diastereoselective hydrogenation of 1,2-disubstituted arenes to cyclohexyl derivatives,
2. chemoselective oxidation of anilines, and
3. regioselective alkoxycarbonylation of styrene derivatives to 2-arylpropionic esters.

Factors influencing the selectivity of these reactions are discussed in the light of concepts from molecular chemistry.

Keywords: Review; Chemoselectivity; Regioselectivity; Diastereoselectivity; Fine chemicals

1. Introduction

Liquid phase conversion of many functionalised organic molecules (i.e., functional alkenes and arenes, ketones, alcohols, esters, etc.) usually requires soluble salts or complexes of transition metal cations, especially when specific reagents like oxygen donors (hydrogen peroxide and alkyl hydroperoxides), carbon monoxide, etc. are used [1]. Furthermore, homogeneous asymmetric catalysis with chiral ligand-modified transition metal complexes has proved to be an efficient tool for the synthesis of pure enantiomers via hydrogenation, epoxidation, carbonylation, codimerisation, etc. [2]. Despite good activities and very often excellent selectivities, there are several problems encountered with these catalysts, particularly catalyst separation, recovery and recycling after reaction.

The current tendency is to replace them by their immobilised counterparts: for example, the catalysts can be linked to an organic, inorganic or hybrid support [3], dissolved in a solvent immiscible with the reagents [4], entrapped in a matrix like zeolites [5] or associated with dendrimers [6]. The combination of these different approaches are also imaginable, supported aqueous phase catalysis being one of the most recent advances [7]. The development of heterogeneous catalysts based on supported metals modified by chiral inductors has also received increasing attention, mainly for asymmetric hydrogenation [8]. Finally, at the frontier between molecular species and bulk materials, metal colloids and clusters, especially ligand-stabilised ones are going to open new routes for specific applications [9].

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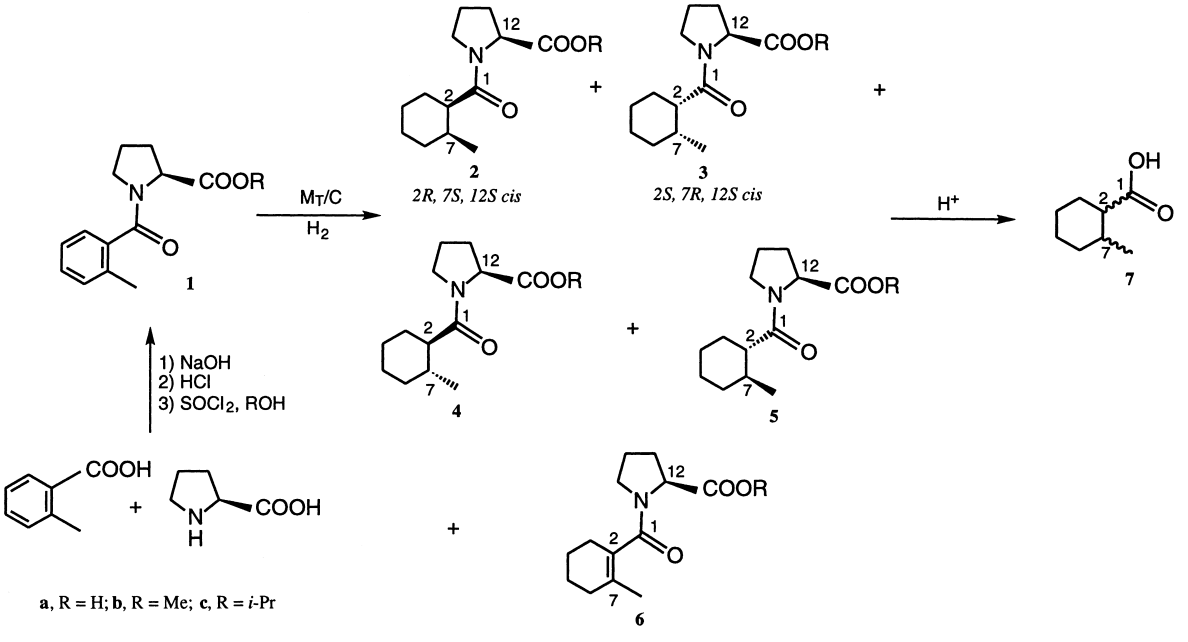
We present them under three aspects of the application of polyphasic media developed at IRC in the fields of hydrogenation, oxidation and carbonylation. The general goals of these studies are:

1. to explore new routes combining concepts of molecular chemistry and constraints of applied catalysis,
2. to design catalytic systems with the aim of achieving specificity, viz. catalytic reactions with neither undesirable isomers nor by-products, and taking into account more and more stringent environmental regulations, and
3. to understand the corresponding underlying phenomena.

2. Diastereoselective hydrogenations

Chiral cyclohexyl compounds are useful optically active synthons ("chirons") or auxiliaries for the synthesis of various biologically active compounds [10]. Classical routes to these intermediates usually involve asymmetric Diels–Alder reactions between 1,3-dienes and homochiral N- or O-propenoyl derivatives. Enzymatic resolution of the hydrogenation product of vanillic acid has also been reported as an alternative route [11]. Asymmetric hydrogenation of disubstituted arenes should provide an elegant access to these intermediates. However, enantioselective reduction of disubstituted arenes has never been achieved with homogeneous or heterogeneous catalysts. In fact, hydrogenation of 2-methylanisole in the presence of colloidal rhodium stabilised by a chiral lipophilic amine ((R)-*N*,*N*-dioctylcyclohexyl-1-ethylamine) provides a very low, but detectable, enantioselectivity (1% by chiral GPC) [8,12]. Although the mechanism of chiral induction is still a matter of controversy, it is generally accepted that the chiral inductor and the substrate should be somehow bonded together. Covalent bonding should provide the strongest interaction. This diastereoselective approach has been successfully used for the hydrogenation of disubstituted arenes into the corresponding cyclohexyl derivatives [13].

Coupling of *o*-toluic acid with (S)-proline followed by esterification of the carboxylic group gives methyl *N*-(2-methylbenzoyl)-(S)-prolinate **1b** whose aromatic ring could be hydrogenated on a carbon-supported transition metal catalyst (Scheme 1). Hydrogenation was performed in alcoholic solvents



Scheme 1.

under 5 MPa hydrogen pressure at room temperature in the presence of different supported ruthenium, rhodium, palladium and platinum. The *cis* diastereomers **2b** and **3b** are the main fully hydrogenated products (>97%) together with variable amounts (<30%) of the cyclohexenic compound **6b**. The corresponding diastereomeric excesses (d.e.) are defined as:

$$\text{d.e.} = 100 \times [\%\mathbf{2} - \%\mathbf{3}]/[\%\mathbf{2} + \%\mathbf{3}]$$

After cleavage of the chiral inductor by protonolysis, the cyclohexyl carboxylic acids **7** are recovered without change of configuration.

Several conformers are expected for **1** owing to possible rotations centred on the amido and carboxylato groups. Molecular mechanics calculations performed with the MAD programme show that four conformers are accessible with energy differences within 3 kJ/mol (Fig. 1). Interconversion of structures A and C, and B and D are not possible because of the high energy barrier of rotation around the C_1–C_2 bond due to severe steric interactions between the methyl substituent on the aromatic ring and the prolinate group. ^{1}H NMR spectroscopy reveals the presence of two doublets of doublets for H-12 (δ 4.2 and 4.6 ppm) in a 20/80 ratio assigned to conformers D and B [14].

Since the aromatic moiety and the chiral auxiliary are associated in a well-defined molecular entity, the effects of reaction parameters on the extent of diastereoselectivity can be studied in a reproducible way. A systematic study of all the factors which may influence the diastereoselectivity of the reaction has been undertaken: reaction conditions, bulkiness and configuration of the chiral auxiliary, catalyst morphology, nature of the metal, effect of additives. All these parameters act on diastereoselectivity to various extents. The crucial role of proline is clearly demonstrated by the reversal of the products configuration when the (R) enantiomer is used instead of the (S) one.

Table 1 sums up some pertinent results [15]. Only the results concerning the use of rhodium and ruthenium catalysts will be summarised here.

2.1. Hydrogenation on rhodium catalysts

Commercial and ion-exchanged rhodium catalysts supported respectively on carbon and charcoal (CECA

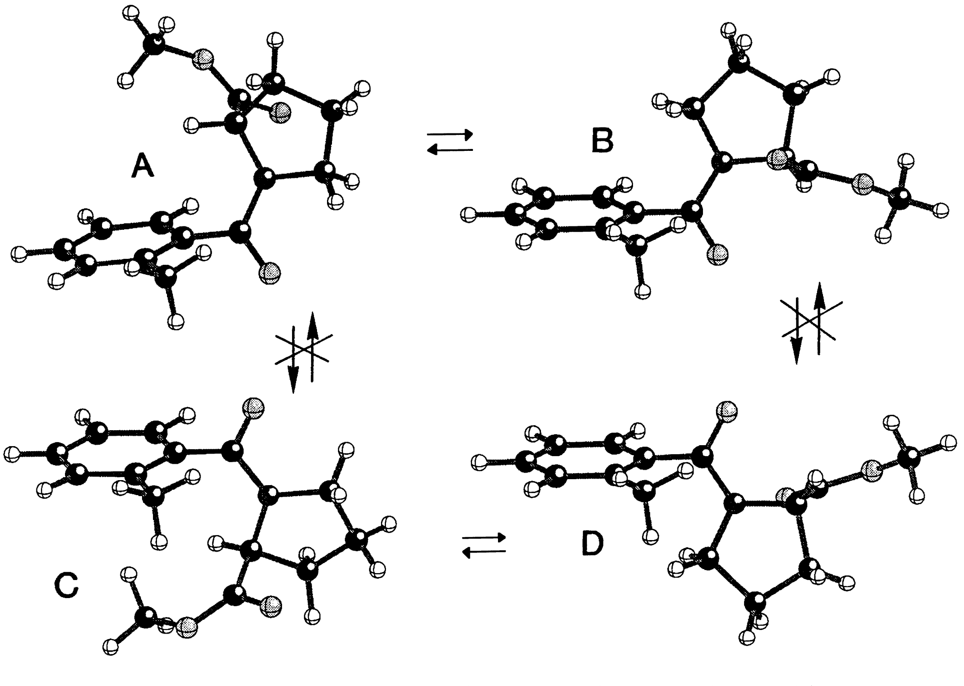


Fig. 1. Ball and stick representation of energetically favoured conformers of **1b**.

Table 1
Diastereoselective conversion of **1b** with different catalysts (reaction conditions: room temperature, pH_2=5 MPa, **1b**=2.5 mmol, catalyst=0.12 mmol metal, solvent=60 ml)

Catalyst	Particle size[a] (nm)	Initial rate (mol h^{-1} mol met^{-1})		Diastereomeric excess (%)[b]		Configuration of major product
		EtOH	*i*-PrOH	EtOH	*i*-PrOH	
5% Rh/C (Aldrich)	1–3	15	15.5	0(17)	0(18)	(2R,7S,12S)
5% Rh/C (Aldrich)[c]	1–3	1.6	8	43(42)	26(15)	(2S,7R,12S)
5.9% Rh/C_C[c]	<2	1.3		42(40)		(2S,7R,12S)
3.9% Rh/C_C[c]	<2	1.2	4.1	48(46)	25(15)	(2S,7R,12S)
3.6% Rh/C_C[c]	3–4	0.3	2	44	28	(2S,7R,12S)
3.1% Rh/C_C[c]	>5	0.05	1	[d]	25	(2S,7R,12S)
4.7% Ru/C_C	<2	0.75		14(21)[e]		(2R,7S,12S)
1.3% Ru/C_N	<1	3.4		19(32)		(2R,7S,12S)
1.3% Ru/C_N[c]	<1	3.4		8(11)[f]		(2R,7S,12S)
4.3% Pt/C[g]	1–2.5	3.5		12		(2S,7R,12S)
3.7% Pd/C[g]	1–2.5	2.3		6		(2S,7R,12S)

[a] Measured by TEM.

[b] Diastereomeric excess at 100% conversion of **1b**. Values in brackets given at 100% conversion of **6**, unless otherwise specified.

[c] Addition of 0.42 mmol EDCA.

[d] Not measurable at 5% conversion of **1b**.

[e] At 38% conversion of **6**.

[f] At 8% conversion of **6**.

[g] Reaction temperature=60°C.

50S) have been used. Pre-treatment of the catalysts under hydrogen flow at different temperatures has an important effect on both activity and diastereoselectivity. In all cases the rate of hydrogenation of **1b** decreases upon saturation of the catalyst with hydrogen. Much more contrasted behaviours are observed for diastereoselective excesses. The improvement in selectivity may be due to particle size, oxidation state and water content, but systematic studies are required in order to clarify the respective role of these factors [15].

Both diastereomers **2b**, **3b** are obtained in nearly the same amounts, therefore leading to a negligible selectivity after complete hydrogenation of the aromatic ring of **1b**. This lack of selectivity is easily understandable if *cis*-addition of hydrogen atoms adsorbed on the metal surface occurs to the less hindered face of the substrate, *viz.* those of conformers B and D. However, a selectivity of 17% for **2b** is observed at the end of the reaction, due to the preferential hydrogenation of **6b** to **2b**. It is believed that **6b** exists as two conformers similar to B and D in the same 80/20 ratio. Faces of B′ and D′ are now affected by the bulkiness of the prolinate moiety: only the face opposite to this group is accessible to hydrogen transfer which is therefore governed by the 80/20 ratio and the amount of **6b** and leads to the observation of 17% d.e.

Addition of amines ([amine]/[Rh]=3.5) significantly reduces the initial reaction rate but gives rise to a dramatic increase of diastereoselectivity, favouring **3b** (Fig. 2) and to a sharp decrease of the formation of intermediate **6b** (<3%) [14]. In the case of *N*-ethyldicyclohexylamine (EDCA), a 48% diastereomeric excess is observed, which slightly varies with the conversion of **1b**. This excess sharply increases with the amine coverage of the rhodium surface up to an amine/rhodium ratio of 3 in the reaction mixture. The nature and structure of the amine have little effect on d.e. Furthermore, the diastereoselectivity does not depends on the particle size (Table 1), therefore suggesting that the substrate is always preferentially adsorbed via the same face. On the other hand, the bulkiness of the ester group and the nature of the solvent have a noticeable effect which is more pronounced for the solvent (i.e., MeOH≈EtOH>*i*-PrOH) than for the alkyl group of the ester (i.e., Me≈*i*-PrOH). Noteworthy, there is practically no solvent effect for the unmodified catalysts [14].

The amine may act in two ways: (i) an interaction between substrate and amine occurring in solution

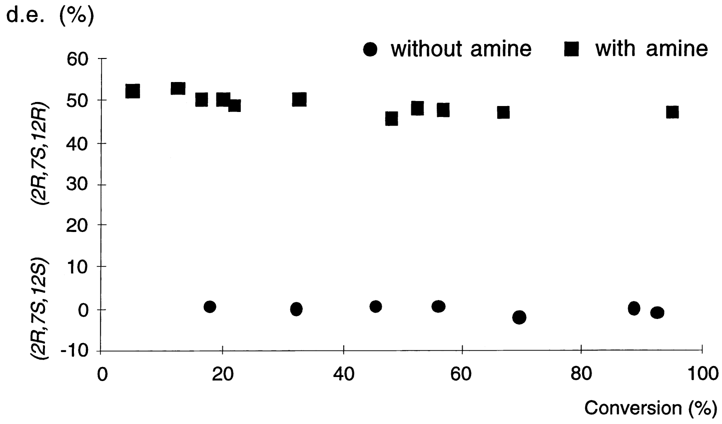


Fig. 2. Diastereomeric excesses for hydrogenation of **1b** in ethanol on 5% Rh/C. Reaction conditions: T=25°C, pH_2=5 MPa, substrate= 2.5 mmol, Rh=0.145 mmol, 60 ml ethanol.

which would modify the geometry of adsorption on the rhodium surface, and (ii) the adsorption of the amine on the rhodium surface which would assign the stereochemistry of adsorption of the substrate.

Although not conclusive against the first hypothesis, ^1H and ^{13}C NMR spectra of methanol solutions of **1b** remain unmodified after increment additions of EDCA. Evidence for the second hypothesis rests on the decrease in catalytic activity [12,14] and on NMR studies carried out at IRC on small colloidal rhodium particles stabilised with amines. Bonding of the amine to the rhodium surface induces steric constraints with govern the approach and adsorption of the reactants. As suggested in Fig. 3(a), the aromatic ring of conformer B or D will adsorb preferentially via the least hindered face, which occupies less space at the surface of the rhodium particle partially covered with EDCA: the generation of **3b** is therefore preferred. Conversely, in the absence of EDCA, these two conformers can be adsorbed on any face of the aromatic ring without significant steric hindrance (Fig. 3(b)).

2.2. Hydrogenation with ruthenium catalysts

Two carbon supported catalysts have been prepared by ion-exchange on CECA 50S (Ru/C_C) and Norit ROX08 (Ru/C_N). The unmodified 1.3% Ru/C_N catalyst lead to a moderate d.e. of 19% in favour of **2b**. This value increases to 32% due to subsequent preferential hydrogenation of **6b**, formed in 29% yield, to **2b** (Table 1). On 4.7% Ru/C_C, the reaction proceeds at a lower rate, giving **2b** with a d.e. of 14% up to complete conversion of **1** [15].

In the presence of EDCA, no inversion of configuration is observed (Fig. 4). Initial reaction rates are similar, showing that the amine coverage of the ruthenium surface is lower than in the case of rhodium, or that the amine is more easily displaced by the incoming substrate. By contrast with the rhodium case, no decrease in the yield of **6b** is observed.

Since ruthenium is a more electropositive metal than rhodium and the particles size is also much smaller (<1 nm vs 1–3 nm), the oxophilicity of ruthenium is much higher than that of rhodium. An interaction may occur between ruthenium surface atoms and the carbonyl and carboxylic groups of **1b**, therefore driving the adsorption of the molecules on the side which holds the oxygen atoms. Conformers B and D provide efficient interactions of the aromatic ring with the ruthenium surface, as sketched in Fig. 5 for conformer B. These conformers which exist in a 80/20 ratio should be hydrogenated into **2b** and **3b**, respectively, hence accounting for the preferred formation of **2b**. This proposal is strengthened by the observation of a larger d.e. for 1.3% Ru/C_N (19%) than for 4.7% Ru/C_C (14%).

3. Selective oxidations with peroxidic compounds

Liquid phase oxidation of organic molecules has been extensively performed with peracids like Caro's

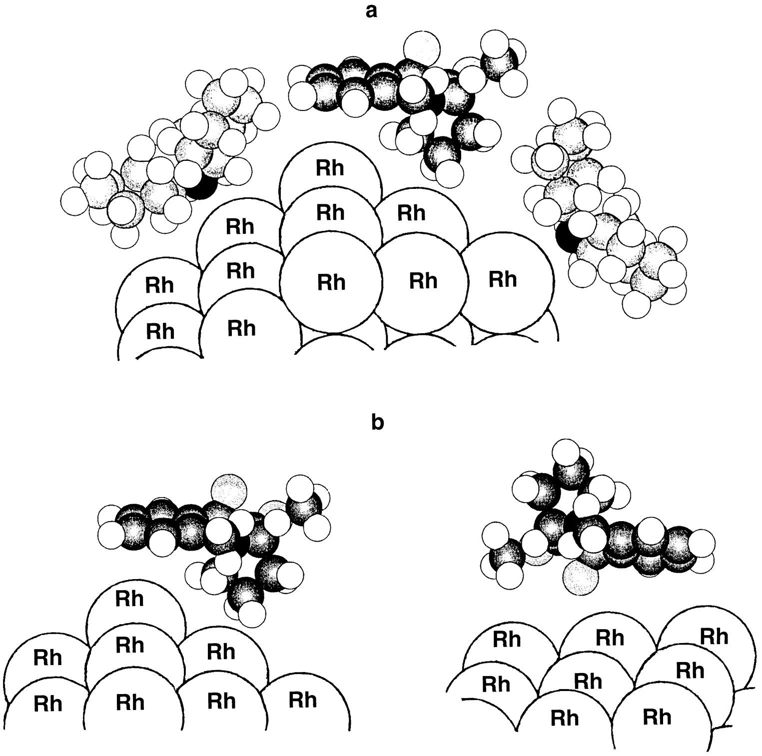


Fig. 3. Scheme of adsorption of **1b** (conformer D) onto (a) a rhodium particle partially covered with EDCA molecules and (b) a rhodium particle in the absence of EDCA.

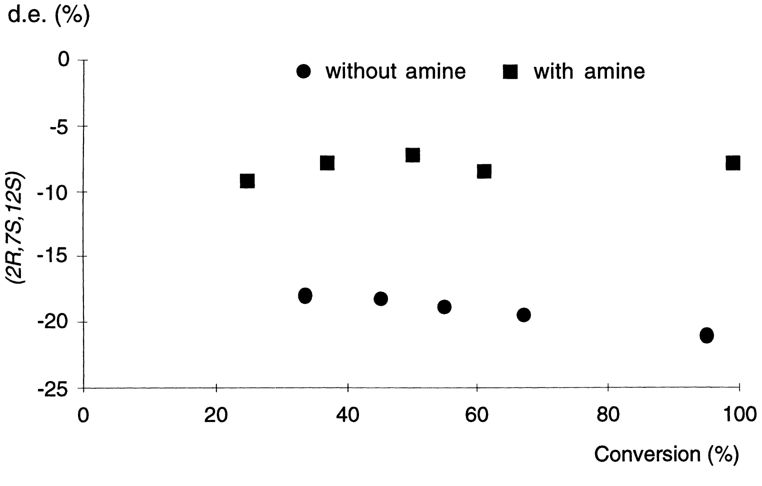


Fig. 4. Diastereomeric excesses for hydrogenation of **1** in ethanol on 1.3% Ru/C_N. Reaction conditions: T=25°C, pH_2=5 MPa, substrate=2.5 mmol, Ru=0.061, 130 ml ethanol.

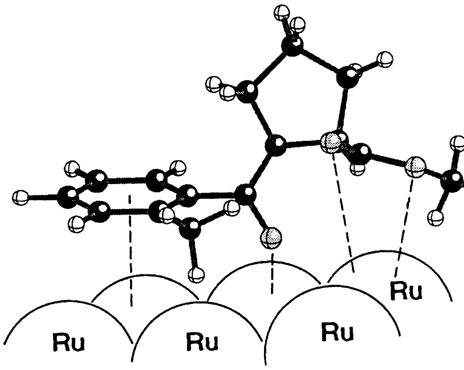


Fig. 5. Scheme of adsorption of **1b** (conformer B) onto a ruthenium surface.

or (perhalo)acetic acid. Such reagents are very corrosive and not acceptable at the industrial scale from environmental considerations. New selective processes have been developed, based on the use of hydrogen peroxide or alkyl hydroperoxides in the presence of catalysts containing early transition metals. As already pointed out, the use of solid catalysts may avoid the difficulties concerning separation, recovery and recycling. Like in solution, the concept of "site isolation" should provide very active catalysts. Early transition metal-substituted molecular sieves are of particular interest: (i) they have very high surface areas and a great accessibility to the active sites, and (ii) the high dispersion of the cations is usually obtained by incorporating low amounts of metal directly in the preparation mixture. There are many examples in the recent literature concerning oxidation reactions over substituted zeolites [16–18]. The recent discovery of mesoporous silicas widens the scope of application in heterogeneously catalysed oxidation reactions [19,20]. We present thereunder a brief account of research performed at IRC on the oxidation of several classes of organic molecules of interest for their applications, mediated by different modified silica-based molecular sieves.

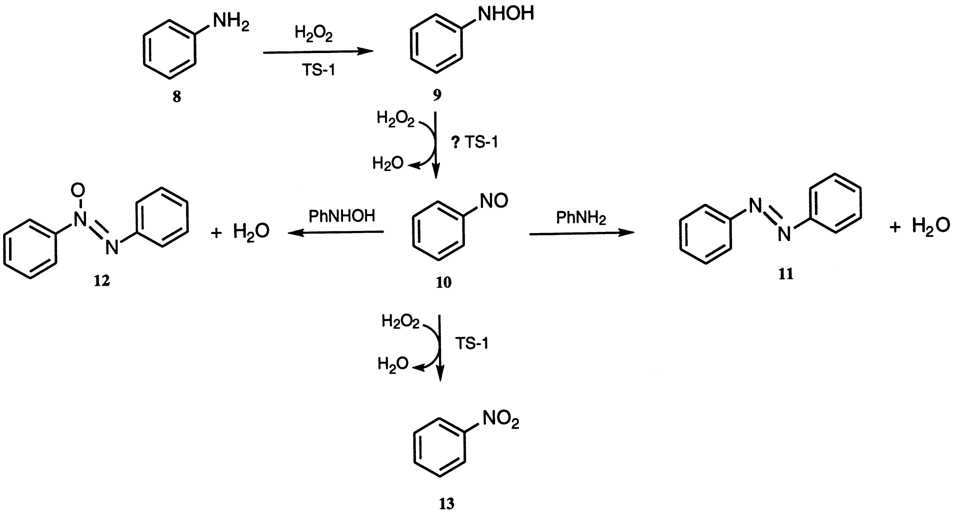
3.1. Oxidation of anilines

Oxidation of aniline **8** with aqueous H_2O_2 (30 wt%) in *t*-butanol is easily performed at 70°C in the presence TS-1 (Si/Ti=85) and Ti-Beta (Si/Ti=112, Si/Al=19) samples [21,22]. For low H_2O_2/substrate ratios, two main products are detected, namely nitrosobenzene **10** and azoxybenzene **12**. Traces of azobenzene **11** are also produced. Phenylhydroxylamine **9** and nitrobenzene **13** which can also be obtained by direct oxidation of aniline, have never been observed under these reaction conditions. As for the hydroxylation of phenol [23], diffusion limitations are observed: for catalyst with crystal sizes <0.6 μm the influence of the size is negligible, but for larger sizes (i.e., 1.3–2.5 μm) the activity strongly decreases [21]. Nitrosobenzene is build at the early stages of the reaction and slowly disappears, while the amount of **12** increases continuously after addition of H_2O_2. In fact, **10** is already formed at 0°C, while significant amounts of **12** are only observed at 40°C [25]. This evolution is consistent with a reaction scheme where consecutive and bimolecular condensation reactions between products and/or unreacted aniline take place (Scheme 2). The oxidation of aniline to **9** is catalysed by the Ti-containing molecular sieve and probably involves the nucleophilic attack of the amine lone pair on the electrophilic oxygen of a Ti-peroxo species arising from the reaction of the catalyst with H_2O_2. It is not clear whether the second step of Scheme 2 necessitates or not the presence of a catalyst.

Studies with other medium-pore zeolites (e.g. TS-48, TAPSO-5) and mesoporous silicas (HMS) have shown that the reaction is limited by the diffusion of reagents and/or products in the channels of the zeolites [22]:

- the formation of **12** occurs at a higher rate with Ti-Beta (pore diameter=0.76 nm) than with TS-1 (diameter=0.63 nm), although both have a three-dimensional channel network,
- for unidimensional channel networks, the rate of formation of **12** increases from TS-48 (pore diameter=0.56 nm) to TAPSO-5 (pore diameter=0.73 nm) and Ti–HMS (pore diameter=2.8 nm).

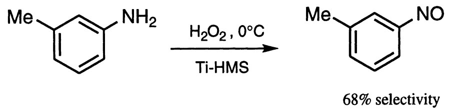
Excellent activities and selectivities are also achieved over Zr–substituted mesoporous silicas (Table 2) [24]. Their behaviour is very similar to that observed over the Ti-containing samples. The initial activity as well as the final selectivity increase with the metal content in the mesoporous silica, indicating that Zr species are involved in catalysis. Noteworthy is the fact that ZrO_2 gives only poor activities, demonstrat-



Scheme 2.

ing the importance of the metal dispersion in the catalyst. No activity is observed with the corresponding V–substituted mesoporous silicas [22].

Substituted anilines can also be selectively converted into their nitroso and azoxy derivatives, depending on the reaction conditions. High conversions are only observed with Ti– or Zr– substituted mesoporous silicas



. They depend on the nature and position of the substituent on the aromatic ring. Electron releasing substituents facilitate the reaction, therefore supporting a nucleophilic attack of the amine on an electrophilic oxygen-donor species. High selectivities in nitroso compounds are obtained when the reaction is run at low temperature [25].

The course of aniline oxidation is completely different when *t*-butylhydroperoxide (TBHP) is used in state of hydrogen peroxide [25]. The reaction does not occur with TS-1, VS-1, TS-48, because the oxidant is too large to enter the channels of the MFI structure. On the other hand, Ti-Beta, Ti–HMS, Zr–HMS and V–HMS are active catalysts for the oxidation of aniline to **11** and **12** at temperatures above 50°C (Table 3). As nitrosobenzene **10** is detected at the early stages of the reaction, TBHP probably reacts according to two mechanisms: oxygen insertion and hydrogen abstraction. Selectivities for **11** and **12** change with the nature of the catalyst. The differences can be explained by the fact that azobenzene **11** can easily penetrate the

Table 2
Oxidation of aniline with hydrogen peroxide over various catalysts

Catalyst	Conversion of $PhNH_2$ (mol%)	Conversion of H_2O_2 (%)	Selectivity of azoxybenzene (%)
TS-1	13	100	95
Ti-Beta	13.7	100	80
Ti–HMS (50)	13.2	100	89
Zr–HMS (100)	11.6	95	95
Zr–HMS (50)	13.7	100	92
Zr–HMS (25)	13.5	100	87

Reaction conditions: 0.5 g catalyst, $H_2O_2/PhNH_2=0.2$, $T=70$°C, solvent=*t*-BuOH. Data are obtained after 4 h reaction. Figures in brackets correspond to the initial silicium to metal ratio.

Table 3
Oxidation of aniline with *t*-butylydroperoxide (TBHP) over various catalysts

Catalyst	Conversion of $PhNH_2$ (mol%)	Conversion of TBHP (%)	Selectivity of azobenzene (%)	Selectivity of azoxybenzene (%)
Ti-Beta	78	95	60	40
Ti–HMS (85)	84	90	8	92
Zr–HMS (50)	86	92	10	90

Reaction conditions: 0.5 g catalyst, $TBHP/PhNH_2=2$, $T=70°C$, solvent=acetonitrile. Data are obtained after 4 h reaction. Figures in brackets correspond to the initial silicium to metal ratio.

mesopores of HMS and be converted into **12**, whereas this cannot be achieved for Ti-Beta whose pore diameter is only 0.76 nm. Very different results are obtained with V–HMS: only nitro derivatives are formed. The lack of azo and azoxy compounds indicates that the reaction proceeds exclusively via electrophilic substitution on the amino group, presumably via a phenylhydroxylamine which arises from the reaction of the corresponding aniline with a very stable vanadium peroxide complex [26].

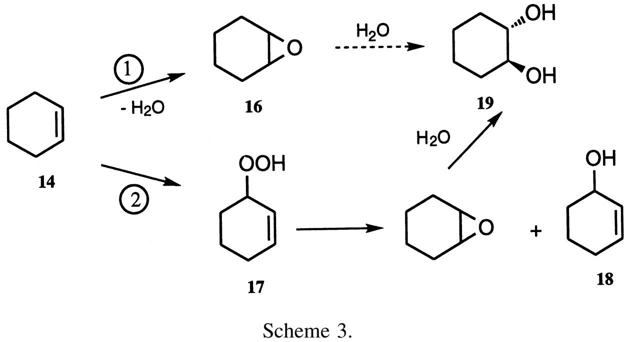
3.2. Epoxidation of cycloolefins

There are very few heterogeneous catalysts providing selective epoxidation of cycloolefins (i.e., cyclohexene **14**, bicyclo[2.2.1]heptene **15**) with hydrogen peroxide. The catalyst should: (i) be hydrophobic, (ii) have accessible active sites, which is not the case for TS-1, and (iii) be neutral in order to avoid the opening of the oxirane ring by water.

Ti– and Zr–HMS catalysts comply to conditions (ii) and (iii), but these materials are rather hydrophilic, therefore leading to products of allylic oxidation. In the case of cyclohexene, both routes have been observed (Scheme 3), route 2 being favoured in the presence of water. This route could be inhibited if the amount of water in the vicinity of the active site is low.

It has been observed that extraction with refluxing ethanol of the amine templates used for the preparation of M–HMS leads to materials with a much higher selectivity for the epoxide than those resulting from calcination (Table 4) [27]. The amount of cyclohexenol **18** also decreases with the amount of the metallic sites. The hydrophobic behaviour of these materials could be explained by the alkylation of the silanols groups with ethanol under the reflux conditions. Moreover, the extent of ring opening of the oxirane is decreasing, owing to a lower acidity of the catalyst. It is noteworthy that 1,2-cyclohexanediol **19** is obtained with a selectivity of about 90% when a Ti-Beta catalyst is used, where aluminium is present in the framework [17]. Even though the strength of the acid sites in Ti– and Zr–HMS is lower to those introduced by aluminium in Ti-Beta, they seem to be strong enough to open the oxirane ring (Table 4) [24].

The epoxidation of bicyclo[2.2.1]heptene **15** has been reported with large pores catalysts like Ti–MCM-41, using TBHP as oxidant [28]. The epoxida-



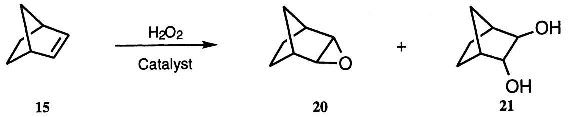
Scheme 3.

Table 4
Epoxidation of cyclohexene with H_2O_2 over various catalysts

Catalyst	Conversion of cyclohexene (%)	Conversion of H_2O_2 (%)	Selectivity of epoxide **16** (%)	Selectivity of cyclohexenol **18** (%)	Selectivity of cyclohexane-diol **19** (%)
Ti–HMS (200/c)[a]	18	95	50	35	15
Ti–HMS (200/alc)[a]	18	98	86	4	10
Ti–HMS (500/alc)[a]	17	94	97	2	1
Zr–HMS (300/c)[a]	15	84	48	31	21
Zr–HMS (300/alc)[a]	16	87	81	9	10
Zr–HMS (1000/alc)[a]	15	79	98	2	0
TS-1[b]	5	7	98		2
Ti-Beta[b]	17	92	4		96
Ti–HMS (50)[b]	18	95	78		22
Zr–HMS (50)[b]	17	97	55		45

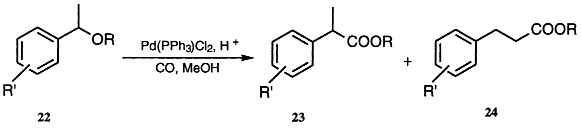
Reaction conditions: 0.5 g catalyst, H_2O_2/cyclohexene=0.2, T=80 (a) or 70°C (b), solvent=diglyme(a) or acetone(b). Data are obtained after 3 h reaction. Figures in brackets correspond to the initial silicium to metal ratio; c means calcined samples and alc, samples treated with refluxing ethanol: see text).

tion also occurs in the presence of hydrogen peroxide [24]. Ti-Beta zeolite shows a quite poor activity in this reaction (Table 5). In contrast, Ti–HMS is relatively active and the epoxide is obtained with a high selectivity. The olefin conversion is rather low due to the relatively low intrinsic activity of Ti species in Ti-containing mesoporous silicas as compared to zeolites [29]. Zr–HMS samples are also active: as for cyclohexene epoxidation, 1,2-diol **21** selectivity increases when comparing with Ti–HMS catalysts.



4. Carbonylation of styrene derivatives

Carbon monoxide is one of the simplest synthons of organic chemistry whose introduction is generally performed via homogeneous catalysis [30]. Carbonylation of 1-substituted-1-aryl ethanes provides an attractive short route to 2-arylpropionic acids which are used as non-steroidal anti-inflammatory drugs [31].



a, R = R' = H; b, R = Me, R' = H; c, R = COEt, R' = H

4.1. General features

We have examined the behaviour of different starting 1-substituted-1-aryl ethanes for this carbonylation reaction and reported large changes in product regioselectivities by variation of the substituents and reaction conditions, and the nature of the catalytic system based on palladium and proton [32,33].

Table 5
Epoxidation of bicyclo[2.2.1]heptene with H_2O_2 over various catalysts

Catalyst	Conversion of bicyclo[2.2.1]heptene (%)	Conversion of H_2O_2 (%)	Selectivity of epoxide **20** (%)	Selectivity of 1,2-diol **21** (%)
Ti-Beta	1.5	78	17	83
Ti–HMS (50)	6.5	82	70	30
Zr–HMS (50)	7.5	74	20	80

Reaction conditions: 0.5 g catalyst, H_2O_2/bicyclo[2.2.1]heptene =0.2, T=70°C, solvent=acetonitrile. Data are obtained after 3 h reaction. Figures in brackets correspond to the initial silicium to metal ratio.

1-Phenylethyl propionate **22c** could be carbonylated (P_{CO}=50 bar) to the corresponding esters **23b**, **24b** in the presence of methanol, $Pd(PPh_3)_2Cl_2$ and $HBF_4 \cdot OEt_2$ as a co-catalyst. This system favours the formation of the linear ester (**23b/23b**+**24b**=0.21). Monitoring of the reaction shows that the carbonylation process proceeds through 1-phenylethanol or the corresponding methyl ether **22b**. This ether is slowly converted under similar conditions to the same products (**23b/23b**+**24b**=0.23). 1-Phenylethanol **22a** is extensively consumed, but again the formation of **22b** is favoured over the production of the expected esters (**23b/23b**+**24b**=0.21). A study of the influence of the phosphine and co-solvent shows practically no influence on the yield of esters and the regioselectivity. The use of other acids provides significant modifications: an increase in the yield of esters is observed with soluble sulphonic acids (**23b/23b**+**24b**=0.22). Addition of LiCl depress the 1-phenylethanol conversion but enhances regioselectivity (**23b/23b**+**24b**=0.50). As expected [31], the use of HCl increases the regioselectivity (**23b/23b**+**24b**=0.73), but at the expense of the yields. The reaction has been extended to other 1-arylethanols with noticeable variations observed on yields and selectivities with the nature of the aryl group.

4.2. *Influence of ion-exchange resins*

The best result has been obtained with the use of Amberlyst 15, a cross-linked sulphonated resin, in methanol (**23b/23b**+**24b**=0.61). Sulphonated resins exhibit a fair acidity (similar to 35% H_2SO_4) but negligible corrosive properties, have an optimal affinity for organic media, are easily prepared and recovered; although they are sensitive to oxidants and have a low thermal stability, these drawbacks are not important in the present case (viz. reducing atmosphere, temperatures below 100°C). It therefore prompts the examination of different grades of these materials [34]. There are two kinds of sulphonated resins whose differences lie in the structure of the polymeric matrix. The first group corresponds to gel-type resins with a continuous tridimensional structure, no specific area and no porosity in the ‘‘dry’’ state. In the presence of a solvent, swelling occurs which induces a temporary porosity. This porosity depends on the extent of reticulation with divinylbenezenes: the greater the reticulation, the smaller the porosity in the swelled state. The second group concerns macroporous or macroreticulated resins which have a sponge-like structure with two distinct phases: surface (external structure) and gel (internal structure). Table 6 sums up some properties of the resins used in this study.

The carbonylation of 1-phenylethanol **22a** has been carried out under standard conditions for comparison of the different resins (Table 7). Some di(1-phenylethyl) ether arising from the dehydration of 1-phenylethanol is detected (<3%). The reaction has also been undertaken in the presence of methyl orthoformate in order to trap the water evolved during the methoxycarbonylation process

$$PhCH(Me)OH + CO + MeOH \longrightarrow PhCH(Me)COOMe + H_2O$$

. Inspection of Table 7 clearly shows that the first reaction to occur is the formation of the ether **22b**, even when the reaction proceeds without methanol, the source of methoxy group being methyl orthoformate. The regioselectivity is now higher than 90%. Carbonylation of **22b** leads to a higher yield which increases with reaction time and acid concentration

Table 6
Representative properties of gel- and macroporous-type sulphonated resins

Name	Acidity (g/mol H^+)	Cross-linking ratio (%)	Porosity (nm), swelled state	Pore diameter (nm)
Dowex 50WX-2-400	206	2	13–20	–
Dowex 50WX-4-400	229	4	–	–
Dowex 50WX-8-400	284	8	12–13	–
Dowex 50WX-12-400	143	12	1-8	–
Dowex 50WX-16-400	256	16	<2	–
Bayer K 2461	236	–	–	40
Bayer K 2661	237	–	–	70
Amberlyst 15	230	–	–	–

Table 7
Carbonylation of 1-phenylethanol (standard conditions: **22a**=50 mmol, resin=amount equivalent to 5 mmol H^+, $Pd(PPh_3)_2Cl_2$=0.5 mmol, CH_2Cl_2=10 ml, P_{CO} =50 bar, T=90°C, reaction time =6 h).

Resin	Conversion(%)	Yield **23b**+**24b** (%)	Yield **22b** (%)	Selectivity **23b** (%)
Dowex 50WX-2-400	97	11	75.5	76
Dowex 50WX-4-400	97	12.5	67	80
Dowex 50WX-8-400	97	12.5	67	83
Dowex 50WX-12-400	97	15	66.5	81
Dowex 50WX-16-400	98	11	77	78
Bayer K 2461	98	15.5	77	62
Bayer K 2661	98	16	60	60
Amberlyst 15	98	13.5	66	62
Dowex 50WX-8-400[a]	98	11	74	83
Dowex 50WX-8-400[b]	99	10	75	90
Dowex 50WX-8-400[c]	99	30	62	91

[a] MeOH=50 mmol, $HC(OMe)_3$=50 mmol, reaction time=20 h.
[b] No MeOH, $HC(OMe)_3$=50 mmol, reaction time=6 h.
[c] No MeOH, $HC(OMe)_3$=50 mmol, reaction time=24 h.

Table 8
Carbonylation of 1-methoxy-1-phenylethane (standard conditions: **22b**=50 mmol, $Pd(PPh_3)_2Cl_2$=0.5 mmol, solvent=10 ml, P_{CO}=50 bar, T=90°C)

Solvent	H^+ (mmol)	Reaction time (h)	Conversion (%)	Yield styrene (%)	Yield **23b** + **24b** (%)	Selectivity **23b** (%)
CH_2Cl_2	10	6	33	3	25	92
CH_2Cl_2	10	12	90	Traces	65	92
CH_2Cl_2	5	6	32	<2	17	92
PhMe	5	6	37	5	20	95
None	10	10	77	Traces	28	92
CH_2Cl_2	10	6	56	2.5	40	93
CH_2Cl_2	5[a]	6	36	2	25	92

[a] $Pd(PPh_3)_2Cl_2$ =1 mmol.

(Table 8). The regioselectivity does not depend on the reaction time. Monitoring the reaction with GC indicates that a rather long induction period (≈3 h) is observed. The reaction can also be performed without solvent. It is noteworthy that the regioselectivity observed for the toluene – Dowex 50WX-8-400 (95%) is completely reversed to that observed for the toluene – $HBF_4{\cdot}OEt_2$ one (10%) [32]. Small amounts of styrene are detected when **22b** is used, especially in presence of solvent (viz. in dichloromethane: 2%, in toluene: 5%). The methoxycarbonylation of styrene leads under the standard reaction conditions a complete conversion with a yield in **23b**+**24b** of 72%, and a regioselectivity of 97%. Further studies are required in order to understand the dramatic effect induced by gel-type resins in the full inversion of regioselectivity.

5. Conclusion

The development of the production of fine chemicals is now facing ecological and economical constraints which are related to the elimination of large amounts of unwanted side-products and waste. In this respect catalysis has an important role to play due to its ability to provide new reaction pathways and to improve selectivity in all its aspects. In this contribution, we have shown three examples taken from the important and fast-growing fields of hydrogenation, oxidation and carbonylation and studied at the Institut de Recherches sur la Catalyse:

- Diastereoselective hydrogenation is an elegant alternative to asymmetric hydrogenation when this one is not operative. This is the case for reduction of 1,2-disubstituted arenes into cyclohexyl derivatives of general interest for pharmaceuticals and agrochemicals. The nature of the metal is a crucial parameter in diastereoselectivity control. It has been shown that the latter can be also controlled by addition of amines. This control arises from metal surface – donor atoms of the substrate or of the additive in a very similar way to ligand modification of the properties of molecular transition metal complexes.
- Chemoselective oxidation of aniline occurs with transition metal-containing molecular sieves in the presence of various oxidising agents. Mesoporous silicas favour the oxidation of the substituted anilines, therefore indicating diffusion control for selectivity. The selectivity is depending on the nature of the oxidising agent and experimental conditions but also of the metal ion present in substitution positions of the silica framework.
- Regioselective alkoxycarbonylation of 1-phenylethanols can be controlled by the nature of the counter ion associated to the protic acid used as co-catalyst to palladium complexes. Sulphonated resins provide the best co-catalysts for the preparation of 2-arylpropionic esters from 1-arylethanols due to a combination of ion-pair effect and other non-bonding interactions which needs further studies to be delineated.

There is no doubt that the examples presented have larger potentialities. We are confident that research undertaken at the interface between molecular and heterogeneous catalyses should provide further catalytic systems for the environmentally friendly preparation of chemicals.

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