Selective catalytic synthesis of fine chemicals: opportunities and trends

Roger A. Sheldon

Laboratory for Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

Abstract

Recent, environmentally-driven trends in the manufacture of fine chemicals are reviewed. Comparison of alternative processes on the basis of their atom utilization and E factor (kg byproducts/kg product) is discussed. The use of chromium-substituted molecular sieves (CrAPO-5 and 11 and Cr silicalite) as recyclable solid catalysts for benzylic and allylic oxidations, the oxidation of secondary alcohols to ketones and the selective decomposition of alkyl hydroperoxides, is described. New developments in the use of zeolite-encapsulated metal complexes as solid catalysts for oxidations and reductions are reviewed. The use of palladium(0) trisulfonated triphenylphosphine complex as a catalyst for carbonylation in water is reported. Finally, the use of supported aqueous phase catalysts in various processes, including enantioselective hydrogenation, is briefly reviewed.

Keywords: Catalytic oxidation; Redox molecular sieves; Ship-in-the-bottle catalysts; Catalytic carbonylation; Organometallic catalysis in water; Supported aqueous phase catalysis; Enantioselective catalysis

1. Introduction

One of the foremost challenges currently facing the Chemical Industry is the need for alternative production technologies that are cleaner, safer and more environmentally friendly. Processes should be efficient in both energy and raw materials consumption and produce minimal waste. As we have noted elsewhere [1–3] the amount of byproducts produced, largely in the form of inorganic salts, per kilogram of product generally increases substantially on going downstream from bulk to fine chemicals and specialties (Table 1). This is partly due to the fact that the production of fine chemicals and specialties generally involves multi-step syntheses and partly to the widespread use of stoichiometric reagents rather than catalytic methods.

Table 1
The E factor

Industry segment	Product tonnage	kg byproduct/kg product
Bulk chemicals	10^4–10^6	$< 1 \to 5$
Fine chemicals	10^2–10^4	$5 \to > 50$
Pharmaceuticals	10–10^3	$25 \to > 100$

Fine chemicals manufacture, which is primarily the domain of synthetic organic chemists, is rampant with classical 'stoichiometric' technologies that generate large quantities of inorganic waste. Examples which readily come to mind are stoichiometric reductions with dissolving metals and metal hydrides, stoichiometric oxidations with permanganate and hexavalent chromium compounds, halogenations, sulfonations, diazotizations, nitrations and Friedel–Crafts acylations, to name but a few.

2. Atom selectivity

Obviously the key to waste minimization is selectivity in organic synthesis. In addition to the standard definition of selectivity-yield divided by conversion-organic chemists also distinguish between different types of selectivity in complex organic molecules: chemoselectivity (competing reactions at different functional groups), regioselectivity (e.g. ortho vs. para substitution in aromatics) and stereoselectivity (enantio- or diastereoselectivity). However, one category of selectivity is, generally speaking, completely disregarded by organic chemists: what we shall call the atom selectivity or atom utilization.

The atom utilization concept is a useful tool for quickly evaluating the (theoretical) amount of waste, defined as everything but the desired product, that is produced by alternative processes to a particular molecule. It is obtained by dividing the molecular weight of the desired product by the sum total of the molecular weights of all products formed in the stoichiometric equation. Some examples for typical synthetic transformations — reduction of a ketone to an alcohol, oxidation of a secondary alcohol to a ketone and C–C bond formation via conversion of an OH to a CO_2H group — are illustrated in Fig. 1. Theoretical E factors (kg waste per kg product) are readily derived from the atom utilization. In practice the E factor is substantially higher, partly due to a chemical yield of less than 100% and, more importantly, to the use of excess reagent and/or neutralization steps involved in product isolation. Moreover, the E factor also includes solvent losses.

Fig. 2 depicts catalytic alternatives for the same transformations, i.e. catalytic hydrogenation, oxidation and carbonylation. In this context it is worth noting that catalytic hydrogenation has long been an integral part of the organic chemist's arsenal of reduction techniques. This is not the case, however, with catalytic oxidation and cabonylation.
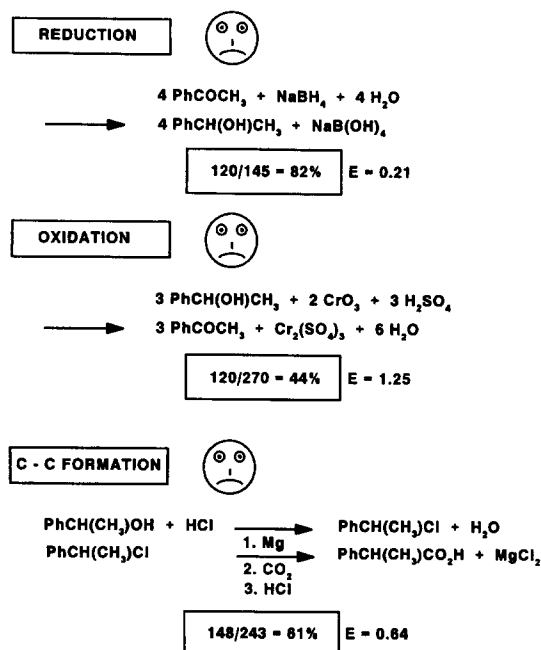
For example, stoichiometric oxidations with

Fig. 1. Atom utilization of stoichiometric reagents.

chromium(VI) reagents, such as Jones' reagent (CrO_3 in aqueous sulfuric acid/acetone), Collins' reagent (pyridine/CrO_3 in CH_2Cl_2) and Corey's reagent (pyridinium chlorochromate in CH_2Cl_2) are widely used in organic
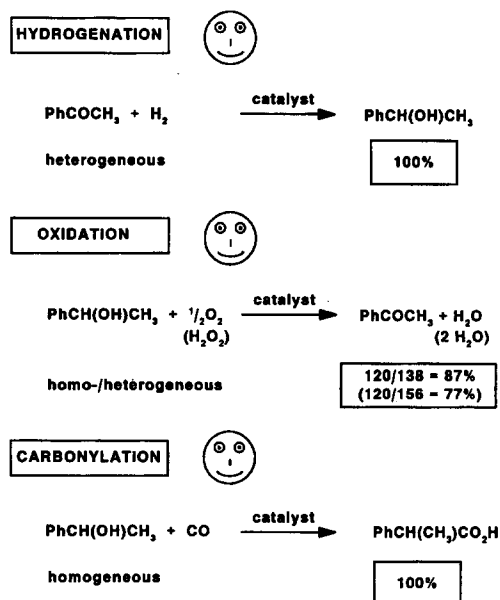

Fig. 2. Atom utilization of catalytic processes.

synthesis. Indeed, the authors of a monograph on the subject published in 1984 noted that "Chromium oxidation is a simple process which can be easily performed in the laboratory and scaled up in industry as well ... Chromic acid is the most popular reagent of this type used in organic chemistry for well over a century" [4].

3. Catalysis in organic synthesis

In bulk chemicals manufacture, traditional environmentally unacceptable processes have largely been replaced by cleaner, catalytic alternatives. For example, more than 50% of the five million tons of acetic acid produced annually on a worldwide basis is generated via the rhodium-catalyzed carbonylation of methanol (Reaction 1). The process involves one step from inexpensive basic chemicals and has an atom utilization of 100% [5].

$$CH_3OH + CO \xrightarrow{[Rh^I / CH_3I]} CH_3CO_2H$$

$$(1)$$
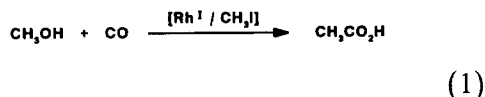
An elegant example of a high atom utilization process for the manufacture of a pharmaceutical is provided by ibuprofen, an over-the-counter analgesic with an annual volume of about 8000 tons. In the Hoechst–Celanese process (Fig. 3) ibuprofen is produced in two catalytic steps, hydrogenation and carbonylation, with 100% atom utilization from p-isobuty-
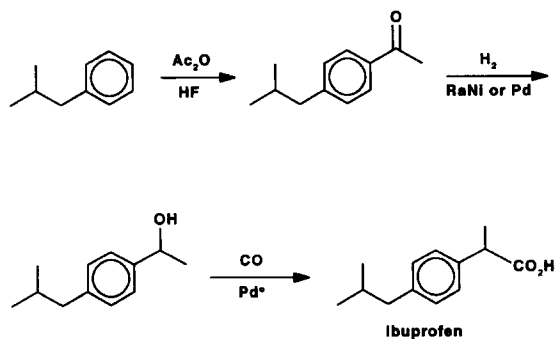
lacetophenone [6]. The latter is produced by Friedel–Crafts acylation of isobutylbenzene in liquid hydrogen fluoride. In this step the hydrogen fluoride, which acts as both a reagent and a solvent, is completely recycled, thus circumventing the generation of large amounts of inorganic waste characteristic of traditional aluminium chloride-mediated aromatic acylations.

Comparing alternative processes solely on the basis of the *amount* of waste generated is obviously a gross oversimplification. A more sophisticated assessment should take both the amount and the *nature* of the waste into account. To this end we proposed [1–3] the 'environmental quotient' (EQ), which is obtained by multiplying the E factor by an arbitrarily assigned unfriendliness quotient, Q. For example, if innocuous salts such as NaCl are assigned a Q value of 1, then heavy metal salts, e.g. chromium, could be given a value of, say 100 or 1000, depending on toxicity. Such figures are obviously debatable and will vary from one company, or even one production site, to another. Nevertheless, alternative processes can be quantitatively assessed on this basis. A further refinement of this approach leads to the concept of environmental profile analysis, in which processes are assessed on the basis of three cost factors: raw materials and energy consumption, and waste generation.

4. Toxic reagents and solvents: trends and opportunities

In addition to the increasingly stringent environmental regulations regarding the disposal of aqueous effluent and solid waste, ever tightening safety regulations are making the transport, storage and use of many hazardous and/or toxic chemicals prohibitive. The ever increasing list includes, for example, phosgene, dimethyl sulfate, formaldehyde/hydrogen chloride, sodium azide, hydrogen fluoride, peracetic acid, and even chlorine and bromine. In the future their industrial use is likely to be confined to a

Fig. 3. Hoechst–Celanese ibuprofen process.

small group of experts who are properly
equipped to handle and contain these materials.
In some cases, catalytic alternatives may pro-
vide an answer, e.g. catalytic carbonylation in-
stead of phosgene and solid acids as substitutes
for hydrogen fluoride.

Similarly, many toxic and/or hazardous or-
ganic solvents, such as diethyl ether, benzene
and chlorinated hydrocarbons, are under consid-
erable pressure to be replaced. The best solvent
is no solvent and if a solvent (diluent) is needed
it should preferably be water. The development
of efficient catalysts for reactions in two-phase
aqueous/organic systems could be the answer
in some cases (see later). This trend obviously
creates opportunities for the replacement of tra-
ditional chemical processes by biocatalytic al-
ternatives in aqueous media.

Another important trend is towards the devel-
opment of better separation techniques. Even in
catalytic processes efficient recovery and recy-
cling of the catalyst is an essential prerequisite
for economic and environmental viability. In
this context we should bear in mind that fine
chemicals are often complex, multifunctional
molecules with limited volatility and thermal
stability, thus necessitating processing in the
liquid phase. The use of heterogeneous catalysts
in liquid phase processes allows for catalyst
recovery by simple filtration. Alternatively, the
use of water soluble catalysts in two-phase sys-
tems allows for facile catalyst recovery and
recycling by simple phase separation. In this
context there is also a marked trend towards the
combination of reaction and separation steps,
e.g. by employing (catalytic) membranes.

5. Redox molecular sieves: recyclable solid catalysts for liquid phase oxidations

Most catalytic oxidations in the liquid phase
involve the use of homogeneous catalysts, usu-
ally in the form of soluble metal salts [7]. In
some cases, e.g. in terephthalic acid production
by catalytic oxidation of p-xylene in acetic

acid, this is not a problem as the product crys-
tallizes out and the catalyst-containing mother
liquors are recycled. In many cases, however, it
would be advantageous to use a heterogeneous
catalyst. Moreover, a major problem associated
with soluble oxometal (M=O) catalysts is their
propensity towards deactivation via oligomer-
ization to inactive μ-oxo complexes. This can
be circumvented by site isolation of discrete
oxometal species in an inorganic matrix, e.g. in
the framework of a zeolite or related molecular
sieve. We coined the generic name redox
molecular sieve [8–10] to describe such materi-
als. Redox molecular sieves have several advan-
tages compared to conventional supported oxi-
dation catalysts. Unlike amorphous materials,
molecular sieves possess a uniform microenvi-
ronment consisting of well-defined channels and
cavities. Metal-substituted molecular sieves also
appear to be more stable towards leaching of the
metal compared to conventional supported cata-
lysts, which is probably due to the more diffi-
cult accessibility of the M–O bonds which at-
tach the metal to the surface. Situating the
catalytic site on the internal surface of a molec-
ular sieve also provides the possibility for shape
selective catalysis. Furthermore, the size and
hydrophobic/hyrophilic character of the redox
cavity can be 'fine tuned' to give 'tailor made'
oxidation catalysts. Hence, such materials can
be regarded as 'mineral enzymes'.

The first example of a redox molecular sieve
was the titanium(IV) silicalite (TS-1) catalyst,
developed by Enichem workers [11]. TS-1 cat-
alyzes a variety of synthetically useful oxida-
tions with 30% aqueous hydrogen peroxide un-
der mild conditions. Examples include olefin
epoxidation, alcohol oxidation, ketone ammoxi-
mation and phenol hydroxylation (Fig. 4). Based
on the remarkable results obtained with TS-1
we envisaged [10] a whole family of redox
molecular sieves, with tunable activities and
selectivities, based on the substitution of redox
metals in molecular sieves of varying pore di-
ameter and hydrophobicity. Indeed, the scope
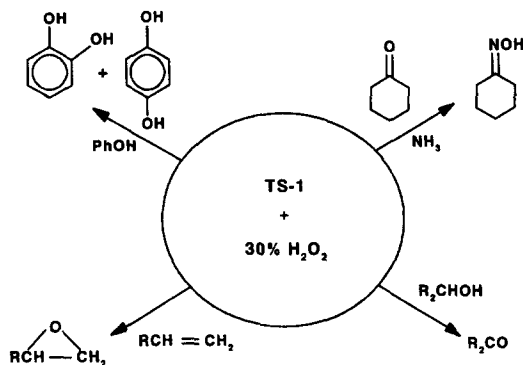for developing unique oxidation catalysts based
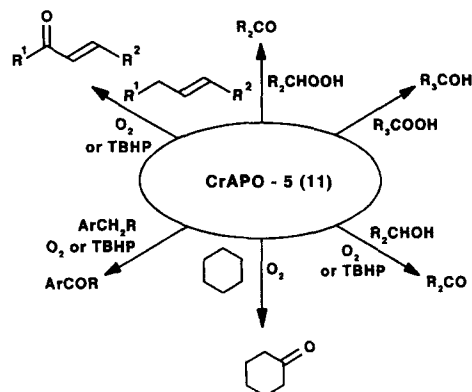
Fig. 4. Oxidations catalyzed by TS-1.

Fig. 5. Selective oxidations catalyzed by CrAPO-5 [11].

on the concept of site isolation of redox metals in silicalites, zeolites, aluminophosphates (AL-POs) and silicoaluminophosphates (SAPOs) is enormous.

6. Chromium-substituted molecular sieves

The oxidations catalyzed by TS-1, e.g. epoxidation and ketone ammoximation, are typical for catalytic oxygen transfer processes involving a peroxometal species (ROOM) as the active oxidant [8]. This category of reagent is, generally speaking, not effective for certain oxidative transformations, e.g. benzylic and allylic oxidations. The latter are typical catalytic oxygen transfer processes involving an oxometal species (M=O) as the active oxidant [8]. Alcohol oxidations, in contrast, can involve either pathway [8]. Chromium is an example of a redox metal that typically involves an oxometal species as the putative intermediate. Moreover, as noted above stoichiometric hexavalent chromium oxidants are widely used in organic synthesis. Because of the serious environmental problems associated with chromium-containing waste much effort has been focused on the use of catalytic amounts of chromium in conjunction with oxygen donors such as tert-butyl hydroperoxide (TBHP). These have generally involved the use of soluble chromium catalysts [12]. Since even catalytic amounts of chromium could present serious environmental problems we have

investigated the use of chromium-substituted molecular sieves as recyclable solid catalysts for selective oxidations.

We found that CrAPO-5 or CrAPO-11 are effective catalysts for a variety of synthetically useful oxidations using TBHP or O_2 as the stoichiometric oxidants (Fig. 5). Examples include benzylic [13–16] and allylic [17] oxidations, oxidation of secondary alcohols to the corresponding ketones [14–16,18] and the selective decomposition of secondary alkyl hydroperoxides [19,20] to the corresponding ketones.

For example, a series of alkylaromatics afforded the corresponding aralkyl ketones with TBHP in the presence of CrAPO-5 (3 m%) at 80°C (Table 2). Chlorobenzene was used as the solvent in order to simplify the analyses but we note that in practice an excess of the alkylaromatic substrate would probably be used as the

Table 2
CrAPO-5-catalyzed oxidations of alkylaromatics with TBHP [14]

$$ArCH_2R \xrightarrow[PhCl/80°C/16h]{TBHP/CrAPO-5} ArCOR$$

$ArCH_2R$	Conv. (%) [a]	Sel. (%) [a]
Ethylbenzene	70	90
p-Ethyltoluene	68	97
n-Propylbenzene	59	93
n-Butylbenzene	59	92
Diphenylmethane	50	94
p-Ethylanisole	13	41
3-Ethylpyridine	43	80

[a] Based on substrate.

solvent. Oxidation of 3-ethylpyridine under the same conditions afforded 3-acetylpyridine [21]. Subsequently, we found that chromium silicalite also catalyzes selective benzylic oxidations with TBHP [22].

The TBHP could be replaced by O_2 in these oxidations although we found that in the latter case it was better to add a small amount of (10 m%) of TBHP to initiate the reaction. In the oxidation of both secondary alcohols and alkylaromatics the CrAPO-5 catalyst could be recovered and recycled several times without loss of activity or selectivity, although recalcination was sometimes necessary to maintain activity at the same level. Elemental analysis of the mother liquors confirmed that no chromium had been leached from the catalyst. That the chromium is situated on the internal surface was confirmed in experiments with triphenylmethyl hydroperoxide. As expected no reaction was observed [19] with this hydroperoxide which is too bulky to enter the micropores of the catalyst.

We assume that the oxidations of hydrocarbons and alcohols with TBHP involve oxidation of the substrate by $Cr(VI)=O$ followed by reoxidation of $Cr(IV)$ with TBHP, i.e. an oxometal mechanism. When O_2 is the oxidant we assume that the substrate undergoes initial CrAPO-catalyzed autoxidation to the corresponding hydroperoxide. The latter then undergoes catalytic decomposition and/or functions as the oxidant. In short, chromium-substituted molecular sieves appear to have considerable scope for application in the catalytic synthesis of fine chemicals.

7. Ship-in-the-bottle catalysts

A special example of the immobilization of metal catalysts in intrazeolite space comprises the so-called ship-in-the-bottle catalysts. In this approach a transition metal complex is immobilized by encapsulation in the cavities of a zeolite or a related molecular sieve. This can be achieved by assembling the complex by intrazeolite synthesis from ligand components that have

access to the micropores or by zeolite synthesis around a preformed complex [23]. Ship-in-the-bottle catalysts combine the advantages of homogeneous and heterogeneous catalysts and, at the same time, provide an environment conducive to shape selectivity.

Initial studies were focused on iron phthalocyanine (FePc) encapsulated in faujasites (X and Y) [23,24]. More recently this was extended to the use of the 18-membered ring aluminophosphate VPI-5 [25,26] and EMT [27], the hexagonal polymorph of faujasite, as the zeolite host. The encapsulated metal complexes can be used as heterogeneous catalysts for selective hydrogenation [28,29] or oxidation [25–27].

For example, FePc-Y catalyzed the oxidation of cyclohexane, to a mixture of cyclohexanol and cyclohexanone, with TBHP as the oxidant [25]. Turnover numbers of 6000 were observed, compared to 25 with homogeneous FePc, indicating that encapsulation stabilizes the phthalocyanine ligand towards oxidative degradation. A further increase in catalyst activity was obtained by substitution of the phthalocyanine periphery with electron-withdrawing nitro groups [30]. More recently, ruthenium perfluorophthalocyanine complexes encapsulated in zeolite NaX ($Ru-F_{16}Pc-X$) were shown to be active (turnover frequency ca. 125 h^{-1}) catalysts for the room temperature oxidation of cyclohexane with TBHP (Table 3) [31]. The ship-in-the-bottle $RuF_{16}Pc$ complex showed no sign of deactivation, in contrast to the iron analogue.

Another recent development is the use of faujasite-encapsulated manganese(II) bipyridyl complexes as catalysts for the oxidation of cy-

Table 3
Comparison of ruthenium phthalocyanine catalysts in cyclohexane oxidation with TBHP [31]

Catalyst	Time (h)	Conv. (%)	Selectivity (%)		TBHP efficiency (%)	TOF (h^{-1})
			ketone	alcohol		
RuPc	5	47	72	27	30	7.5
$RuF_{16}Pc$	24	83	78	22	48	15
$RuF_{16}Pc-X$	192	86	98	1	97	125

clohexene [32,33] to adipic acid using 30% aqueous hydrogen peroxide as the oxidant at room temperature. The reaction proceeds via initial epoxidation followed by ring opening to the 1,2-diol and subsequent oxidative cleavage. The turnover frequency was 15 h^{-1} and H$_2$O$_2$ efficiency 47–62% at cyclohexene conversions of 9–17%.

Although the oxidations studied so far have been limited to simple substrates, such as cyclohexane and cyclohexene, these ship-in-the-bottle catalysts have obvious potential for broad application in the synthesis of fine chemicals. Moreover, it is but a small step to the design of chiral ship-in-the-bottle complexes for both enantioselective oxidation and reduction. Indeed, the recently reported [34] synthesis of zeolite encapsulated metal–Schiff's base complexes, analogous to the manganese (salen) complexes used for homogeneous catalytic asymmetric epoxidation [35], would appear to offer considerable promise in this direction.

8. Catalytic conversions in liquid–liquid biphasic systems

Another approach to facilitating the recovery and recycling of soluble transition metal complex catalysts is to conduct the reaction in a biphasic, liquid–liquid system, whereby the catalyst is dissolved in one phase and the substrate and product in the other phase. Recovery and recycling of the catalyst can then be accomplished by simple phase separation. This approach meshes with another important trend (see earlier), i.e. the use of water as a reaction medium in general and for organometallic catalysis in particular [36,37]. Transition metal complexes can be easily rendered water soluble by, for example, incorporating polar substituents (–CO$_2$Na, –SO$_3$Na and R$_3$N$^+$–) into phosphine ligands.

A benchmark in the development of organometallic catalysis in biphasic aqueous media is the Ruhrchemie/Rhône-Poulenc pro-

cess for the hydroformylation of propene (Reaction 2). The water soluble catalyst is a rhodium complex of the sodium salt of trisulfonated triphenylphoshine. About 300,000 tons of n-butyraldehyde are produced annually using this process.
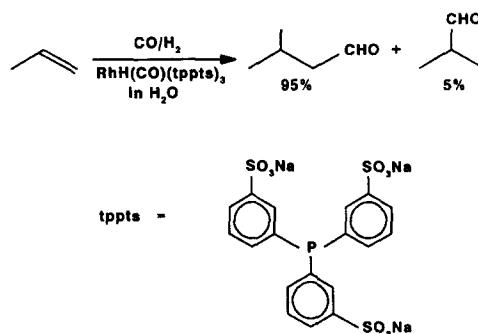
$$(2)$$

The commercial success of this process has led to a flourish of activity in the area of organometallic catalysis in water and the technique has been successfully applied to, inter alia, catalytic hydrogenation and alkylation of 1,3-dienes with C–H acids [36,37]. Recently we showed [38,39] that an in situ generated (tppts)$_3$Pd^0 complex is an effective catalyst for the carbonylation of benzylic-type alcohols in aqueous media. For example, the water-soluble substrate, 5-hydroxymethylfurfural (HMF) was converted to the new compound, 5-formylfuran-2-acetic acid (Reaction 3). The mild conditions contrast with the forcing conditions (110–150°C and 50–150 bar) that are required for analogous carbonylations in organic media. HMF is of potential interest as a renewable basic chemical derived from carbohydrate feedstocks.
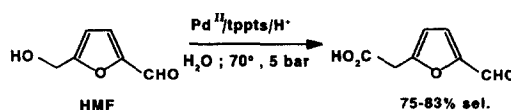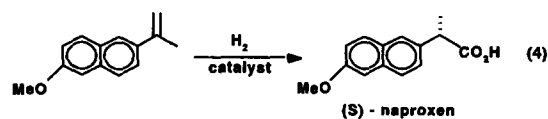

$$(3)$$

9. Supported aqueous phase (SAP) catalysis

An attractive method to heterogenize homogeneous catalysts, which is an extension of the organometallic catalysis in aqueous media mentioned above, is via immobilization of water soluble organometallic complexes in a thin aqueous film on a high-surface area hydrophilic support such as silica or controlled-pore glasses [40]. The resulting catalyst is placed in contact with a water-immiscible liquid phase containing reactant molecules and reaction then takes place at the water–organic interface. The catalyst can be recovered by simple filtration. This technique has been applied to olefin hydroformylation using RhH(CO)(tppts)$_3$ as the catalyst [41].

Just as with the liquid biphasic systems mentioned above, SAPs readily lend themselves to enantioselective catalysis by employing water soluble ligands. For example SAP–Ru–BINAP(SO$_3$Na)$_4$ catalyzed the enantioselective (70% ee) hydrogenation of an (S)-naproxen precursor (Reaction 4) [42]. Interestingly, the enantioselectivity improved to 96% ee when the catalyst was contained in a thin film of ethylene glycol, with chloroform/cyclohexane as the immiscible organic phase [43] (Scheme 1).

Based on these exciting results we conclude that supported aqueous (liquid) phase catalysts have considerable potential for the (enantio)selective synthesis of fine chemicals. In this context it is also worth mentioning the recently described [44] fluorous biphasic system in which a fluorocarbon is used as a second phase to contain the catalyst. This novel concept, although employed so far only in liquid–liquid systems, should also be adaptable to supported liquid phase catalysis.

10. Concluding remarks

Hopefully this review has shown that there are many exciting developments in the application of environmentally benign catalytic processes to fine chemicals synthesis. Moreover, many of these exciting developments are taking place at the interface between homogeneous and heterogeneous catalysis.

Scheme 1.

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