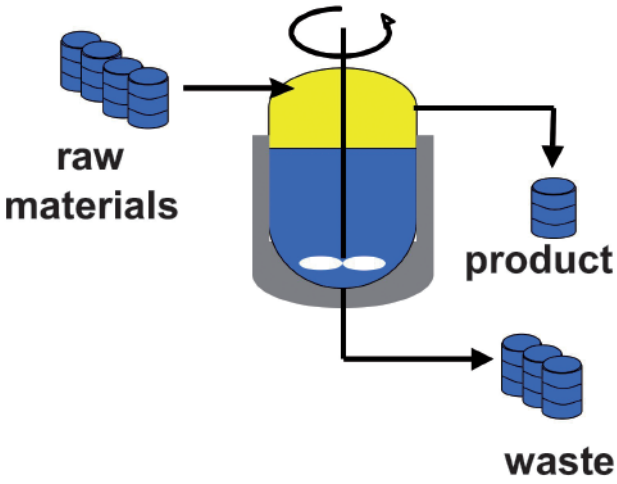
E Factors, Green Chemistry and Catalysis: Records of the Travelling Chemist

Afscheidsrede

Prof. dr. R. A. Sheldon

7 December 2007



E = kg waste / kg product

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Afscheidsrede uitgesproken op vrijdag 7 december 2007 door

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What is now proved true was once only imagined
William Blake

What we need is more imagination, not more knowledge
Albert Einstein

It's better to travel one mile than to read a thousand books
Confucius

E Factors, Green Chemistry and Catalysis:
Records of the Travelling Chemist

Mijnheer de Rector Magnificus,
Leden van het College van Bestuur,
Collegae hoogleraren en andere leden van de universitaire gemeenschap,
Zeer gewaardeerde toehoorders,
Dames en heren.

Hopelijk met uw goedvinden zal ik, vanwege het grote aantal buitenlandse gasten, mijn rede voortzetten in het Engels. Dit past ook bij het nobele streven van de TU naar een zekere internationalisering van het (postgraduate) onderwijs.

1. Introduction to Green Chemistry and Sustainability

Let us begin with some definitions. Our working definition of Green Chemistry can be formulated as follows:

Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

It is important to stress that green chemistry addresses the environmental impact of *both* chemical products and the processes by which they are produced. The guiding principle is the *design* of environmentally benign products and processes (*benign by design*) which is embodied in the 12 Principles of Green Chemistry as formulated by Anastas and coworkers[1,2] at the US Environmental Protection Agency (EPA). The EPA officially adopted the name 'US Green Chemistry Program' in 1993.
According to my definition 'raw materials' includes the source of energy. Green chemistry eliminates waste at source, *i.e.* it is primary pollution prevention rather than waste remediation (end-of-pipe solutions). Prevention is

1. P. T. Anastas and J. C. Warner (Eds.), *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.
2. P. T. Anastas and M. M. Kirchhoff, *Acc. Chem. Res.,* 2002, **35**, 686-693.

better than cure (the first of the twelve principle of green chemistry). In the last fifteen years the concept of green chemistry has become firmly entrenched in both industrial and academic circles and several books have been devoted to the subject[3,4,5,6]. Subsequently, Anastas and Zimmerman[7] proposed the twelve principles of green engineering which embody the same underlying features – conserve energy and resources and avoid waste and hazardous materials – as those of green chemistry, but more from an engineering viewpoint. More recently, a mnemonic, PRODUCTIVELY, has been proposed by Poliakoff *et al.*[8] which captures the spirit of the twelve principles of green chemistry and can be presented as a single slide.
An alternative term, often more favoured by the chemical industry, is sustainable development, a concept which dates back to the late 1980s and can be defined as[9]:

Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.

One could say that sustainability is our ultimate common goal and green chemistry is the means to achieve it.

2. Genesis

In the early 1980's the closure of the phloroglucinol plant at Océ Andeno (later to become part of DSM Fine Chemicals) drew our attention to the problem of waste in the (fine) chemicals industry. The plant was shut down because the high costs of waste disposal precluded economically viable pro-

3. R. A. Sheldon, I. W. C. E. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, 2007.
4. J. H. Clark and D. J. Macquarrie, *Handbook of Green Chemistry and Technology*, Blackwell, Abingdon, 2002.
5. A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001.
6. M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, 2002.
7. P. T. Anastas and J. B. Zimmerman, in *Sustainability Science and Engineering Defining Principles*, Ed. M. A. Abrahams, Elsevier, 2006, pp. 11-32.
8. S. L. Y. Tang, R. L. Smith and M. Poliakoff, *Green Chem*., 2005, **7**, 761.
9. C. G. Brundtland, *Our Common Future*, The World Commission on Environmental Development, Oxford University Press, Oxford, 1987.

duction. The process which we operated in the plant involved vintage 19th century organic chemistry[10]. As shown in Figure 1, it involved the oxidation of 2,4,6-trinitrotoluene (TNT) with potassium dichromate in fuming sulfuric acid (oleum) followed by Béchamp reduction with iron and hydrochloric acid to give, after *in situ* decarboxylation, 1,3,5-triaminobenzene. Subsequent heating of an acidic solution of the latter afforded phloroglucinol in good yield.

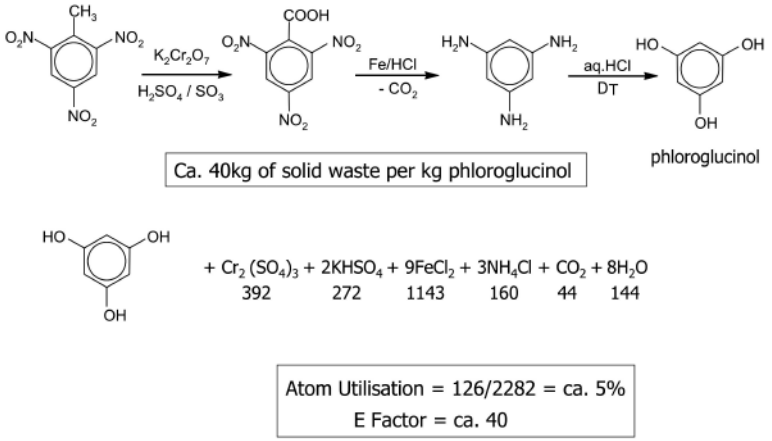


Figure 1. Phloroglucinol manufacture from TNT

This process produced, along with 1 kg of the desired phloroglucinol, ca. 40 kg of solid waste containing $Cr_2(SO_4)_3$, NH_4Cl, $FeCl_2$ and $KHSO_4$. A cursory examination of the stoichiometry of the overall process (see Figure 1) soon reveals the origins of this detritus. Our subsequent analysis of the amount of waste formed in processes for the manufacture of other fine chemicals and pharmaceutical intermediates and some bulk chemicals further revealed that tens of kgs waste per kg product was no exception in the fine chemicals industry.

10. See T. Iwata, H. Miki and Y. Fujita, in *Ullmann's Encyclopedia of Industrial Chemistry*, 1991, vol. A19, p. 347.

This led me to propose the term E(nvironmental) Factor (kgs waste / kg product) as a metric for assessing the environmental acceptability of (potential) manufacturing processes[11,12,13,14,15]. It was elaborated into the now well-known Table of E Factors, to illustrate the problem of waste in different segments of the chemical industry (see later), which I used in an undergraduate course on "Green and Sustainable Chemistry and Technology" here in Delft.

2. Atom utilisation

At about the same time I also began using what I called the *atom utilisation* concept for quickly assessing the environmental acceptability of processes at an early stage, even before any experiments have been performed. This idea arose by analogy with the use of '*syn gas utilisation'*, which I used at Shell in the late 1970's, to roughly assess the commercial viability of various processes for the production of commodity chemicals from syn gas[16], a concept which is currently of significant relevance in the context of commodity chemicals from renewable resources.. The idea was simple; the more atoms of the syn gas that ended up in the product the better. Methanol synthesis, for example, involves 100% syn gas utilisation, while ethylene utilises only 44%(see Figure2).

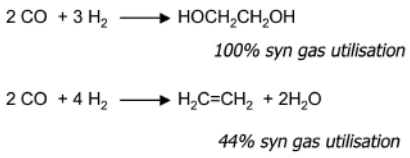


Figure 2. Syn Gas Utilisation

11. R. A. Sheldon, *Chem. Ind. (London)*, 1992, 903-906.
12. R. A. Sheldon, *Chemtech*, March 1994, 38-47.
13. R. A. Sheldon, *Chem. Ind. (London)*, 1997, 12-15.
14. R. A. Sheldon, *J. Chem. Tech. Biotechnol.,* 1997, **68**, 381-388.
15. R. A. Sheldon, *Pure Appl. Chem.,* 2000, **72**, 1233-1246.
16. R. A. Sheldon, *Chemicals from Synthesis Gas*, Reidel, Dordrecht, 1983, p. 15.

I similarly used the concept of oxygen availability to assess the economic and environmental acceptability of different oxygen donors in catalytic oxygen transfer processes (Table 1)[17] The most attractive oxidants are those containing the highest percentage of available oxygen combined with an innocuous coproduct. On this basis hydrogen peroxide earned the accolade "Mr. Clean" [18].

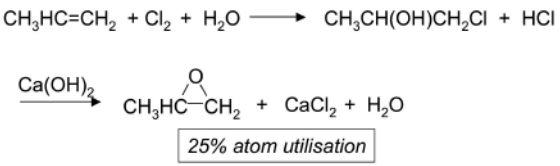
Oxidant	% Active O	Byproduct
H_2O_2	47	H_2O
t-BuOOH	18	t-BuOH
CH_3COOOH	22	CH_3COOH
NaOCl	22	NaCl
KIO_4	8	KIO_3

Table 1. Oxygen availability

Extension of these concepts led to the idea of using *atom utilisation* to assess the (potential) environmental acceptability of processes. An example, which we used to illustrate this concept, was a comparison of the traditional chlorohydrin route to propylene oxide with catalytic oxidation with hydrogen peroxide (see Figure 3). The concept was reported in an interview published in 1991[19]. At about the same time Trost published his elegant paper[20] on the *atom economy* which became the widely accepted terminology, although it is also referred to as *atom efficiency* and the term *atom efficient* is widely favoured. We presented these concepts at the International Symposium on Catalytic Chemistry for Global Environment in Sapporo, Japan in July, 1991 and they were eventually published in 1992[11].

17. R. A. Sheldon, Bull. Soc. Chim. Belg. 1985, 94, 651-670.
18. R. A. Sheldon, *Chemtech,* 1991, 566-579 ; see also R. A. Sheldon, Topics Curr. Chem. 164, 1993, 21-43.
19. *Chem. Eng. Progr*., 1991, **87** (12), 11-13.
20. B. M. Trost, *Science*, 1991, **254**, 1471-1477.

1. PO : Chlorohydrin process



2. PO : Catalytic Oxidation with H_2O_2

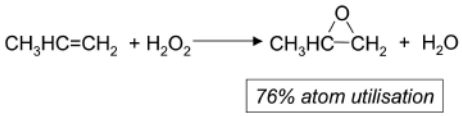


Figure 3. Atom utilisation

3. E Factors and Atom Efficiency as Green Metrics

It is now generally accepted that two useful measures of the (potential) environmental acceptability of chemical processes are the E factor defined as the mass ratio of waste to desired product and the atom efficiency, calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation. The enormity of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry (Table 2).

Industry Segment	Volume (tons/annum)[a]	E Factor (kg waste/kg product)
Bulk Chemicals	10^4-10^6	<1 - 5
Fine chemical Industry	10^2-10^4	5 - >50
Pharmaceutical Industry	10-10^3	25 - >100

[a]. Annual production of the product world-wide or at a single site

Table 2. E factors in the chemical industry

The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids and, in principle, even fuel (although this is often difficult to quantify). There is one exception: we generally excluded water from the calculation of the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted; the water itself is excluded. Inclusion of water used in the process can lead to exceptionally high E factors in many cases and can make meaningful comparisons of processes difficult.

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms of product out. It can be easily calculated from a knowledge of the number of tons of raw materials purchased and the number of tons of product sold, for a particular product or a production site or even a whole company. It is perhaps surprising, therefore, that many companies are not aware of the E factors of their processes. We hasten to point out, however, that this situation is rapidly changing and the E factor is being widely adopted by the fine chemicals, pharmaceutical and even the bulk chemical industry. This was underscored by the following statement in a recent cover article in C&E News[21] : "Another aspect of process development mentioned by all pharmaceutical company process chemists who spoke with C&EN, is the need for determining an E Factor".

As Lord Kelvin said: "To measure is to know" . Fine chemical and pharmaceutical companies always knew that their manufacturing processes were generating substantial quantities of waste but putting a number to it via the conception of the E factor really brought the message home. By publishing the table of E Factors we challenged the fine chemical and pharmaceutical industries to make the paradigm shift from a concept of process efficiency which was exclusively focused on chemical yield to one that is motivated by elimination of waste and maximisation of raw materials utilisation.

21. A. N. Thayer, *C&EN*, August 6, 2007, pp.11-19.

Other metrics have been proposed[22,23] for measuring the environmental acceptability of processes, notably mass intensity proposed by Constable and coworkers of Glaxo Smith Kline and defined as the total mass used in a process divided by the mass of product, *i.e.* MI = E factor + 1. More recently, the Green Chemistry Institute Pharmaceutical Round Table has used the Process Mass Intensity (PMI), which is another name for Mass Intensity, to benchmark the environmental acceptability of processes used by its members (see the Green Chemistry Institute website). The latter include several leading pharmaceutical companies (Eli Lilly, Glaxo Smith Kline, Pfizer, Merck, AstraZeneca, Schering Plough and Johnson & Johnson). The aim was to use this data to drive the greening of the pharmaceutical industry.In our opinion none of these alternative metrics offers any particular advantage over the E factor for giving a mental picture of how wasteful a process is. The ideal (P)MI is 1 whereas the ideal E Factor is 0, which more clearly reflects the ultimate goal of zero waste.

The atom utilisation, atom efficiency or atom economy concept, elegantly promulgated by Trost[24], is an extremely useful tool for rapid evaluation of the amounts of waste that will be generated by alternative processes. In contrast to the E factor, it is a theoretical number, *i.e.* it assumes a chemical yield of 100% and exactly stoichiometric amounts and disregards substances which do not appear in the stoichiometric equation. A theoretical E factor can be derived from the atom efficiency, *e.g.* an atom efficiency of 40% corresponds to an E factor of 1.5 (60/40). In practice, however, the E factor will generally be much higher since the yield is not 100% and an excess of reagent(s) is used and solvent losses and salt generation during work-up have to be taken into account. For example, the phloroglucinol process discussed above has an atom efficiency of ca. 5% which would predict a theoretical E Factor of ca. 20 whereas in practice it is 40.

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22. T. Hudlicky, D. A. Frey, L. Koroniak, C. D.Claeboe and L. E. Brammer, *Green Chem.,* 1999, **1**, 57-59.

23. D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.,* 2002, **4**, 521-527; see also A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.,* 2001, **3**, 1-6; D. J. C. Constable, A. D. Curzons, L. M. Freitas dos Santos, G. R. Green, R. E. Hannah, J. D. Hayler, J. Kitteringham, M. A. McGuire, J. E. Richardson, P. Smith, R. L. Webb and M. Yu, *Green Chem.,* 2001, **3**, 7-9.

24. B. M. Trost, *Angew. Chem. Int. Ed.,* 1995, **34**, 259-281.

All of the metrics discussed above take only the mass of waste generated into account. However, what is important is the environmental impact of this waste, not just its amount, *i.e.* the nature of the waste must be considered. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt. Hence, we introduced the term 'environmental quotient', EQ, obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. For example, one could arbitrarily assign a Q value of 1 to NaCl and, say, 100-1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, etc. The magnitude of Q is obviously debatable and difficult to quantify but, importantly, 'quantitative assessment' of the environmental impact of chemical processes is, in principle, possible. It is also worth noting that Q for a particular substance can be both volume- and location-dependent. For example, the generation of 100-1000 tons per annum of sodium chloride is unlikely to present a waste problem, and could be given a Q of zero. The generation of 10,000 tons per annum, on the other hand, may already present a disposal problem and would warrant assigning a Q value greater than zero. In contrast, when very large quantities of sodium chloride are generated the Q value could decrease again as recycling by electrolysis becomes a viable option, *e.g.* in propylene oxide manufacture *via* the chlorohydrin route. Thus, the Q value of a particular waste will be influenced by its ease of disposal or recycling and in our experience, organic waste is, generally speaking, more easy to dispose of than inorganic waste.

Where do these enormous amounts of waste originate? They comprise primarily inorganic salts, such as sodium chloride, sodium sulfate and ammonium sulfate that are formed in the reaction or in subsequent neutralisation and other work-up steps. One of the reasons that the E factor increases dramatically on going downstream from bulk to fine chemicals and pharmaceuticals is that the latter involve multi-step syntheses. However, the larger E Factors in the fine chemical and pharmaceutical industries are also due to the widespread use of classical stoichiometric reagents rather than catalysts which I shall now discuss .

4. The Role of Catalysis

Examples of the use of stoichiometric inorganic reagents which readily come to mind are reductions with metals (Na, Mg, Zn, Fe) and metal hy-

dride reagents ($LiAlH_4$, $NaBH_4$),and oxidations with permanganate, manganese dioxide and chromium(VI) reagents. A classic example is the phloroglucinol process discussed above, which combines an oxidation with stoichiometric chromium (VI) with a reduction with Fe/HCl. Similarly, a multitude of reactions, *e.g.* sulfonations, nitrations, halogenations, diazotisations and Friedel-Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3) are major sources of waste. The solution is evident: substitution of antiquated stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in chemicals manufacture in general is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2 and NH_3 as the direct source of H, O, C and N. Catalytic hydrogenation, oxidation and carbonylation and hydroformylation are good examples of such highly atom efficient, low-salt processes.

The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral and Lewis acids and stoichiometric bases, such as NaOH, KOH, with recyclable solid acids and bases, preferably in catalytic amounts[25].

The benchmarking exercise of the Pharmaceutical Round Table (see above) clearly identified another major source of waste in the pharmaceutical industry, namely solvent losses which has stimulated the development alternative reaction media (see later).

In the rest of my lecture I shall elaborate on these various aspects of Green Chemistry and Catalysis (see Figure 4) that have formed the basis for the research of the Section of Biocatalysis and Organic Chemistry (BOC) over the last 16 years.

25. R. A. Sheldon and H. van Bekkum (Eds.), *Fine Chemicals Through Heterogeneous Catalysis*, Wiley-VCH, Weinheim, 2001, Chapters 3-7.

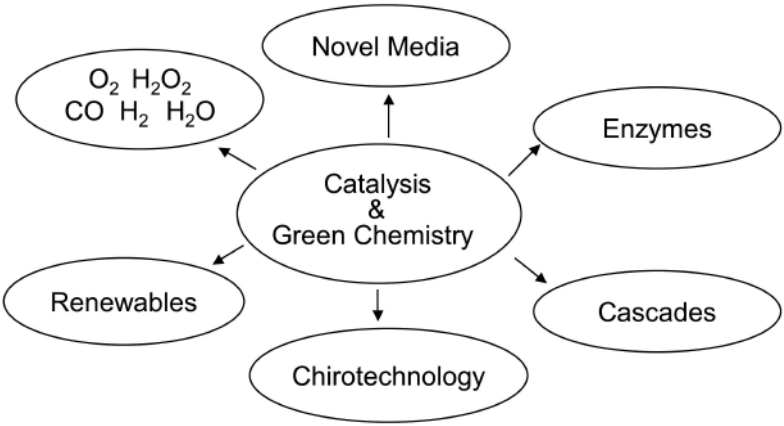


Figure 4. Research Themes of the Section Biocatalysis and Organic Chemistry (BOC).

5. Heterogeneous Catalytic Oxidation

Although catalytic oxidation is widely applied in the bulk chemicals industry[26] there are still a few processes which use stoichiometric inorganic oxidants. A case in point is propylene oxide (PO) manufacture. The chlorohydrin route, which generates ca. 2kgs of $CaCl_2$ for each kg of PO, accounts for more than half of the ca. 4 million tons of propylene oxide produced annually. In the late 1960's the Halcon and ARCO companies developed processes for the epoxidation of propylene with an alkyl hydroperoxide, catalyzed by soluble molybdenum compounds[27]. At Shell Research Laboratories in Amsterdam in the early 1970's I was involved in the development of the Shell SMPO process for the coproduction of styrene monomer and propylene oxide.The key step was the epoxidation of propylene with ethyl benzene hydroperoxide catalyzed by heterogeneous Ti(IV)-

26. R. A. Sheldon and J. K. Kochi, *Metal Catalyzed Oxidations of Organic Compounds*, Academic Press, 1981.
27. R.A Sheldon, Metal-catalyzed Epoxidation of Olefins with Hydroperoxides, in "Aspects of Homogeneous Catalysis", Vol. 4, R. Ugo (Ed.), Reidel, Dordrecht, 1981, pp. 3-70 and references cited therein.

on-silica, the first truly heterogeneous catalyst for this reaction (see Figure 5). In 1973 I proposed that the mechanism of molybdenum catalyzed epoxidations involved oxygen transfer from a metal-alkyl hydroperoxide complex to the olefin via the cyclic transition state (mechanism A in Figure 5)[28]. Sharpless[29] and coworkers subsequently proposed a similar mechanism, which is widely accepted, involving coordination of the oxygen adjacent to the hydrogen in the alkyl hydroperoxide (mechanism B in Figure 5) while Mimoun proposed[30] an alternative mechanism involving an intermediate peroxometal complex (Mechanism C).

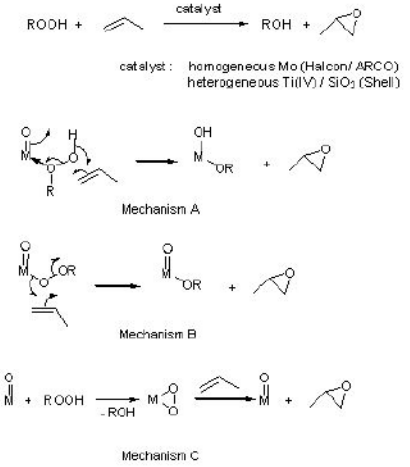


Figure 5. Metal Catalyzed Epoxidation of Propylene with an Alkyl Hydroperoxide

I attributed[31] the high activity of the Ti(IV)-SiO_2 catalyst to the electrophilicity (Lewis acidity) of the Ti(IV) being increased by the silanoxy ligands and to its site isolation in the silica lattice preventing the formation of inactive μ-oxo oligomers.Interestingly, the Shell catalyst was completely inactive when aqueous hydrogen peroxide was used as the oxidant. This could be attributed

28. R.A. Sheldon, Recl. Trav. Chim. Pays-Bas, 1973, **92**, 253.
29. A. O. Chong and K. B. Sharpless, J. Org. Chem., 1977, **42**, 1587.
30. H. Mimoun, I. Seree de Roch and L. Sajus, Tetrahedron, **1970**, 26, 37.
31. R. A. Sheldon, J.Mol. Catal. 1980, **7**, 107.

to the strong inhibitory effect of water and other protic solvents on the Ti(IV)-silica catalyst. Hence, I was quite surprised by the report by Enichem workers[32] in the mid 1980's that the analogous titanium(IV) substituted silicalite-1 (TS-1) was able to catalyse the effective epoxidation of olefins with 30% aqueous hydrogen peroxide in methanol as solvent.The explanation for this different behaviour lies in the hydrophobic nature of the silicalite-1 which enables the selective adsorption of hydrophobic olefins into the pores of this molecular sieve, even in the presence of water or alcohols.
Although the Enichem technology was developed in the mid 1980's its application in PO manufacture was hindered by the relatively high price of hydrogen peroxide. However, Headwaters Technology Innovation (HTI) received a 2007 Presidential Green Chemistry Challenge Award for the development of a palladium-platinum nanocatalyst which enables the direct synthesis of hydrogen peroxide from hydrogen and oxygen in high selectivity below the flammability limit of hydrogen[33]. Combination of this with the Enichem technology enables the direct synthesis of propylene oxide from propylene, hydrogen and oxygen, with water as the sole byproduct (Figure 6). This process is now being commercialised in partnership with Evonik (formerly Degussa).

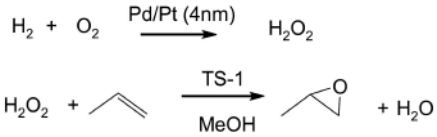


Figure 6. Headwaters-Evonik process to propylene oxide

Similarly, Sumitomo has commercialised a process for caprolactam, the raw material for nylon 6, which involves combining the Enichem technology[34] for ammoximation of cyclohexanone, with NH_3/H_2O_2 over TS-1, with a novel vapour phase Beckmann rearrangement over a high-silica MFI zeolite[35] - affording caprolactam in >98% yield based on cyclohexanone and 93% based on H_2O_2 (Figure 7). The conventional process involves the reac-

32. B. Notari, *Stud. Surf. Sci. Catal.,* 1998, **37**, 413-425.
33. See http://www.epa.gov/greenchemistry/pubs/pgcc/past.html.
34. G. Bellussi and C. Perego, *Cattech,* 2000, **4**, 4- 16.
35. H. Ichihashi and M. Kitamura, *Catal. Today,* 2002, **73**, 23-28; H. Ichihashi and H. Sato, *Appl. Catal. A: General,* 2001, **221**, 359-366.

tion of cyclohexanone with hydroxylamine sulfate (or another salt), producing cyclohexanone oxime which is subjected to the Beckmann rearrangement in the presence of stoichiometric amounts of sulfuric acid or oleum. The overall process generates ca. 4.5kg of ammonium sulfate per kg of caprolactam (Figure 7). In contrast, the Sumitomo process generates two molecules of water as the sole coproduct, *i.e.* it is essentially salt-free. It was gratifying, therefore, that the Sumitomo scientist, Ichihashi, used the E Factor to illustrate the difference between the classical and the new, catalytic process (see Figure 7).

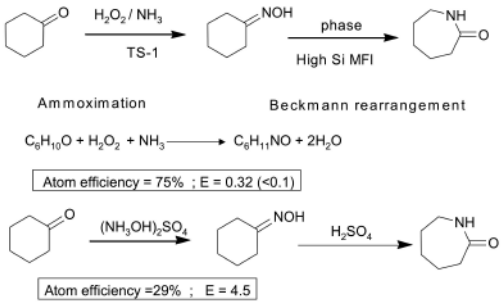
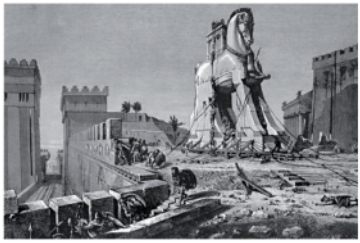


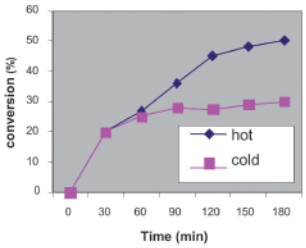
Figure 7. Sumitomo caprolactam process

The remarkable success of TS-1 as a catalyst for a variety of oxidations, including epoxidation, with the green oxidant hydrogen peroxide led to a frenetic activity world-wide on the synthesis of related heterogeneous catalysts for liquid phase oxidations[36]. This was largely based on the expectation that TS-1 formed the tip of an iceberg, that it was the forerunner of whole families of so-called "redox molecular sieves with unique properties. We envisaged that the site-isolation of elements capable of catalysing oxidation processes, in the constrained environment extant in the pores and cavities of molecular sieves, would produce robust, recyclable catalysts with enzyme-like properties, hence the term mineral enzymes or 'zeozymes'.

36. I. W. C. E. Arends, R. A. Sheldon, M. Wallau and U. Schuchardt, *Angew. Chem.Int. Ed*. 1997, **36**, 1144-1163; see also, A. Corma and H. Garcia, Chem. Revs. 2003, **103**, 4307-4365 and 2002, **102**, 3837-389.

To this end we synthesized chromium-substituted molecular sieves, such as chromium aluminophosphate-5 (Cr-AlPO-5), which the graduate student, Jidong Chen, showed to be an active recyclable catalyst for the oxidation of alcohols and alkylaromatic hydrocarbons with alkyl hydroperoxides or molecular oxygen[37]. However, another graduate student, Hans Lempers, subsequently showed[38], by performing a "hot filtration test", that small amounts of chromium were leached into solution, as Cr(VI), by reaction with the alkyl hydroperoxide and that amounts of soluble Cr(VI) as low as 1-2 ppm could account for the observed catalysis (see Figure 8).Such a catalyst can be recycled many times because each time a small amount of the active species is released into the solution like Greek warriors from the Trojan horse[39]. This obviously places severe limtations on the practical utilisation of such catalysts and it is surprising, therefore, that many papers pay scant attention to this aspect. However, since we noted this effect the hot filtration test has been adopted by many workers as a standard protocol for eststablishing true heterogeneity.





Filtration Test for Heterogeneity

A. The metal leaches but is not an active homogeneous catalyst
i.e. catalyst is heterogeneous but not stable.

B. The metal leaches to form an active homogeneous catalyst
i.e. catalysis is homogeneous.

C. The metal does not leach and the observed catalysis is truly heterogeneous

Figure 8. Heterogeneous oxidation catalysts : philosophers' stones or Trojan horses

37. J. D. Chen and R. A. Sheldon, *J. Catal*. 1995, **153**, 1-8.
38. H. E. B. Lempers and R. A. Sheldon, J. Catal. 1998, **175**, 62.
39. R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res*. 1998, **31**, 485-493.

It was subsequently shown by us and others that many, but not all, redox molecular sieves, were not stable catalysts for liquid phase oxidations which induced us to switch our attention from these 'mineral enzymes' to existing protein scaffolds as a basis for developing novel catalysts for oxidations. I shall return to this subject later but first I want to deal with the subject of homogeneous catalysis.

6. Homogeneous Catalysis and Alternative Reaction Media

Homogeneous catalysis is widely used in the chemical industry, for example, in carbonylation, hydroformylation, olefin metathesis and oxidation. Despite the advantages of homogeneous catalysis, such as high activities and selectivities, compared to heterogeneous counterparts, it suffers from the shortcomings of a cumbersome recovery of the catalyst in an active form for recycling and contamination of the product with catalyst residues. An illustrative example is the Boots-Hoechst-Celanese (BCH) process for the manufacture of the analgesic, ibuprofen, with an annual production of several thousands tons. In this process ibuprofen is produced in two catalytic steps (hydrogenation and carbonylation) from *p*-isobutylactophenone (Figure 9) with 100% atom efficiency[40]. This process replaced a more classical route which involved more steps and a much higher E factor. The second step involves a homogeneous palladium catalyst and proceeds with high activity and selectivity. A drawback, however, is the cumbersome separation of the catalyst from the product resulting in contamination of the latter, which is the active pharmaceutical ingredient, with unacceptably high amounts of palladium. This necessitates an expensive purification procedure to afford a product of acceptable purity. This is a problem with homogeneous catalytic processes in general. Attempts to heterogenise homogeneous catalysts by attachment to organic or inorganic supports have, generally speaking, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.

40. V. Elango, M. A. Murhpy, B. L. Smith, K. G. Davenport, G. N. Mott and G. L. Moss, US Pat. 4981995 (1991) to Hoechst-Celanese Corp.

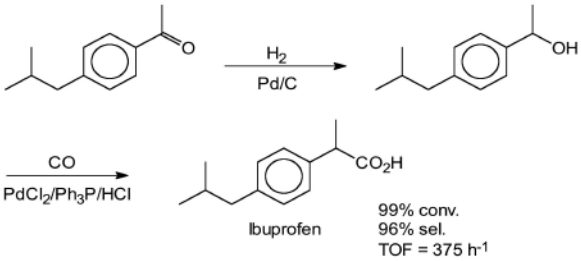


Figure 9. Boots-Hoechst-Celanese process for ibuprofen

There is a definite need, therefore, for systems that have both the advantages of high activity and selectivity of homogeneous catalysts combined with the facile recovery and recycling of their heterogeneous counterparts. This can be achieved by employing a different type of heterogeneous system compared to the traditional solid catalyst with liquid or gaseous reactants, namely liquid-liquid biphasic catalysis, whereby the catalyst is dissolved in one phase and the reactants and product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation.

This meshes with another important issue in green chemistry : the use of organic solvents. So many of the solvents that are favoured by organic chemists, such as chlorinated hydrocarbons, have been blacklisted that the whole question of solvent use requires rethinking and has become a primary focus, especially in the fine chemicals industry[41,42]. In our original studies of E factors of various processes we assumed, if details were not known, that solvents would be recycled by distillation and that this would involve a 10% loss. The benchmarking exercise performed by the GCI Pharmaceutical Round Table (see above) revealed that solvents were a major contributor to the E Factors of pharmaceutical manufacturing processes. Their use results in substantial atmospheric emissions and pollution of ground water.These issues surrounding a wide range of traditional organic solvents have stimu-

41. R.A. Sheldon, *Green Chem.*, 2005, **7**, 267-278.
42. W. Leitner, K. R. Seddon and P. Wasserscheid (Eds.), *Special Issue on Green Solvents for Catalysis*, *Green Chem.*, 2003, **5**, 99-284.

lated the fine chemical and pharmaceutical industries to seek more benign alternatives. The problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and reuse. Alternative solvents should, therefore, provide for their efficient removal from the product and reuse.

Various nonconventional reaction media have been intensely studied in recent years, including *water*[43], *supercritical* CO_2[44], *fluorous biphasic*[45], *and ionic liquids*[46], alone or in liquid-liquid biphasic combinations. We also note that the use of water and supercritical carbon dioxide as reaction media is consistent with the current trend towards the use of renewable, biomass-based raw materials, which are ultimately derived from carbon dioxide and water.

The best solvent is no solvent and if a solvent (diluent) is needed then water has many benefits : it is non-toxic, non-inflammable, abundantly available and inexpensive. Furthermore, performing the reaction in an aqueous biphasic system[47], whereby the catalyst resides in the water phase and the product is dissolved in the organic phase, allows for recovery and recycling of the catalyst by simple phase separation. An example of a large scale application of this concept is the Ruhrchemie/Rhône Poulenc process for the hydroformylation of propylene to *n*-butanal which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst and has an E Factor of 0.1 compared to 0.6-0.9 for conventional monophasic hydroformylation processes[48]

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43. U. M. Lindström, *Organic Reactions in Water*, Blackwell, Oxford, 2007.
44. W. Leitner, *Acc. Chem. Res*., 2002, **35**, 746; P. Licence, J. Ke, M. Sokolova, S. K. Ross and M. Poliakoff, *Green Chem*., 2003, **5**, 99.
45. I. T. Horvath and J. Rabai, *Science*, 1994, **266**, 72; I. T. Horvath, *Acc. Chem. Res.,* 1998, **31**, 641; J. A. Gladysz, D. P. Curran and I. T. Horvath, *Handbook of Fluorous Chemistry*, Wiley, Weinheim, 2004.
46. R. A. Sheldon, *Chem. Commun.,* 2001, 2399; V. I. Parvulescu and C. Hardacre, *Chem. Rev*., 2007, **107**, 2615-2665; R. D. Rogers and K. R. Seddon (Eds.), *Ionic Liquids as Green Solvents; Progress and Prospects*, ACS Symp. Ser. 856, American Chemical Society, Washington DC, 2003.
47. G. Papadogianakis and R. A. Sheldon, in *Catalysis*, Vol. 13, Specialist Periodical Report, Royal Society of Chemistry, Cambridge, 1997, pp. 114-193; G. Verspui, G. Papadogianakis and R.A. Sheldon, *Catal. Today,* 1998, **42**, 449-458.
48. B. Cornils in ref. 43, pp. 366-397.

We developed (in a project with the postdoc, Georgios Papadogianakis and graduate student, Goran Verspui) the use of an analogous palladium(0) complex of the tppts ligand, $Pd(tppts)_3$, for the aqueous biphasic aqueous biphasic carbonylation of alcohols and olefins (Figure 10)[49], e.g. in the above mentioned synthesis of ibuprofen, and showed that product contamination by the catalyst was essentially eliminated. We similarly used, in a project with the graduate student, Gerd-Jan ten Brink, a water soluble palladium complex of a sulfonated phenanthroline ligand for the highly selective aerobic oxidation of primary and secondary alcohols in an aqueous biphasic system, in the absence of any organic solvent (Figure 10)[50]. The liquid product could be recovered by simple phase separation and the aqueous phase, containing the catalyst, used with a fresh batch of alcohol substrate, affording a truly green method for the oxidation of alcohols.

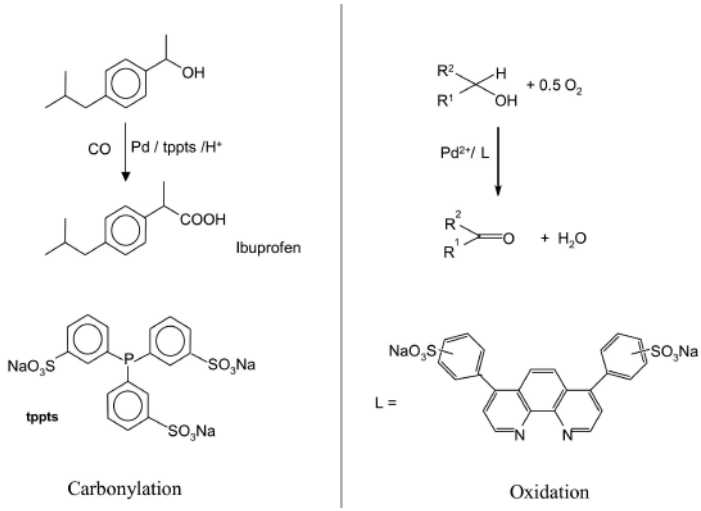

Figure 10.Palladium catalysed aqueous biphasic carbonylation and oxidations

49. G. Papadogianakis, L. Maat and R.A. Sheldon, *J. Chem. Tech. Biotechnol*., 1997, **70**, 83-91.
50. G. J. ten Brink, I. W. C.E. Arends and R. A. Sheldon, *Science,* 2000, **287**, 1636-1639.

An aqueous biphasic system is not the answer in all cases, however. Since the reaction takes place in the aqueous phase the substrate must be at least sparingly soluble in water. Consequently, other alternative reaction media, such as the above mentioned fluorous biphasic systems, supercritical carbon dioxide, and ionic liquids, have also been extensively studied as well as biphasic mixtures of these alternative media. We were the first group, for example, to show that enzymatic processes could be performed in water-free ionic liquids (a project of the graduate student Rute Madeira Lau) (Figure 11)[51,52].

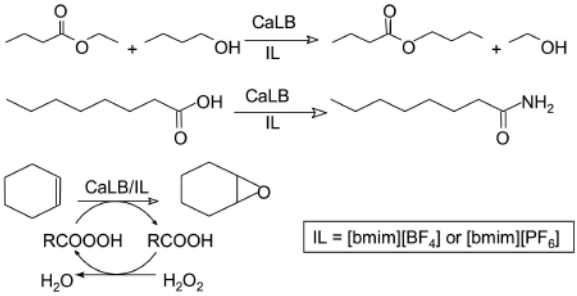

Figure 11. Biocatalysis in anhydrous ionic liquids

However, the problem still remains of how to separate the product from the ionic liquid and recycle the enzyme. This can be achieved by, for example, solvent extraction. This does not necessarily mean that we are back to square one where we have the problems associated with the use of an organic solvent. It is conceivable that an undesirable organic solvent, e.g. a chlorinated hydrocarbon, used in the reaction step could be replaced by a more environmentally organic solvent in the extraction step. Interesting in this context is the use of supercritical carbon dioxide as the mobile phase, to continuously extract the product, while the enzyme remains (as a suspension) in the ionic liquid phase[53]. In a recent variation on this theme[54], the so-called 'miscibility

51. R. Madeira Lau, F. van Rantwijk, K.R. Seddon and R.A. Sheldon, *Org. Lett*. 2000, **2**, 4189-4191.
52. For a recent review of biocatalysis in ionic liquids see: F. van Rantwijk and R. A. Sheldon, *Chem. Rev*., 2007, **107**, 2757-2785.
53. M. T. Reetz, W. Wiesenhoefer, G. Francio, W. Leitner, *Chem. Commun*., 2002, 992-993. P. Lozano, T. de Diego, D.Carrie, M. Vaultier, J. L. Iborra, Chem. Commun., 2002, 692-693.
54. M. C. Kroon, J. van Spronsen, C. J. Peters, R. A. Sheldon and G-J. Witkamp, *Green Chem*., 2006, **8**, 246-249.

switch' was used in a collaboration with the groups of Cor Peters and Geert-Jan Witkamp, to perform a catalytic reaction smoothly in a monophasic ionic liquid/$scCO_2$ mixture followed by lowering of the pressure to afford a biphasic system whereby the catalyst was contained in the ionic liquid phase and the product in the $scCO_2$ phase, enabling their facile separation.

7. Organocatalytic Oxidations with Stable Nitroxyl Radicals.

In recent years we have seen a burgeoning interest in organocatalysis[55], a major advantage of which is the circumvention of many of the problems associated with the use of (homogeneous) metal catalysts as discussed above. In this context I would like to mention the use of stable nitroxyl radicals, such as TEMPO (tetramethylpiperidinyloxyl radical) and its derivatives, as an organocatalyst for the selective oxidation of alcohols[56]. For example, the system comprising catalytic amounts of TEMPO, in conjunction with aqueous sodium hypochlorite (household bleach) is now a widely used method in the fine chemicals industry (Figure 12)[57]. One could, quite rightly, say that

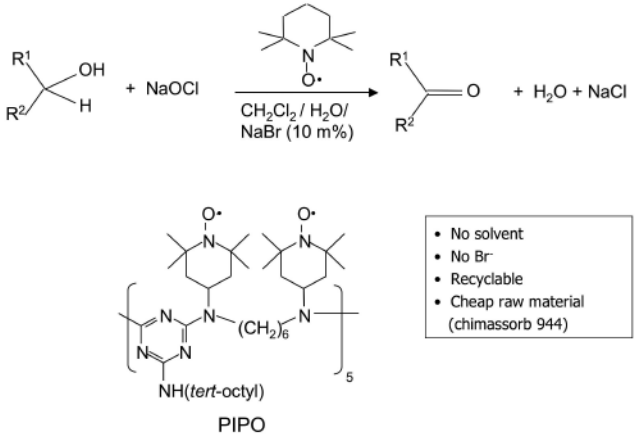

Figure 12. TEMPO and PIPO catalysed oxidations of alcohols with NaOCl.

55. For key references see: A. Berkessel and H. Groerger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005; J. Seayad and B. List, *Org. Biomol. Chem*., 2005, **3**, 719.
56. R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal*. 2004, **346**, 1051-1071.
57. A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1996, 1153.

the use of NaOCl as the stoichiometric oxidant is not particularly green. However, it is worth pointing out, in this context, that 'greenness' is a relative attribute and that NaOCl is certainly greener than many of the traditional stoichiometric reagents used for alcohol oxidation, a pivotal reaction in organic synthesis. These include, for example chromium (VI) (see earlier), permanganate, manganese dioxide, etc.

However, drawbacks of the standard protocol for oxidations with TEMPO/NaOCl are the use of substantial amounts of bromide as a cocatalyst and of dichloromethane as the cosolvent, in addition to the relatively high cost of the soluble TEMPO catalyst, which cannot be readily recycled. Hence, we introduced[58] the use of an oligomeric piperidinyloxyl radical, PIPO, derived from a commercially available and relatively inexpensive polymer additive, chimassorb 944 . This was found (a project with the graduate student, Arne Dijksman) to be more reactive than TEMPO, which enabled the use of more acceptable solvents, such as ethyl acetate or methyl tert-butyl ether, without the need for a bromide cocatalyst (Figure 12).
The use of hypochlorite as the stoichiometric oxidant still remains, in the context of green chemistry and waste minimisation, a shortcoming of these methods. It was originally shown by Semmelhack[59] that TEMPO, in conjunction with copper (I) as a cocatalyst in DMF as solvent, enabled the use of the greener and less expensive molecular oxygen (air) in the oxidation of alcohols. We showed that PIPO could also be successfully used in conjunction with copper(I) under the same conditions. We subsequently showed, in work together with Parick Gamez from the Reedijk group, that a system comprising TEMPO, a bipyridyl complex of copper(II), and a base formed an excellent catalyst for the selective aerobic oxidation of alcohols (Figure13).

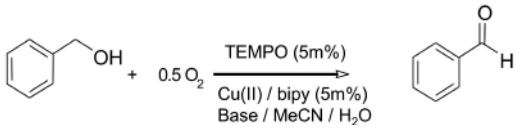

Figure 13. Copper(II)/TEMPO and laccase/TEMPO catalysed aerobic oxidation of alcohols

58. A. Dijksman, I.W.C.E. Arends and R.A. Sheldon, *Chem. Commun*. 2000, 271-272; *Synlett* 2001, **1** 102-104.
59. M. F. Semmelhack, C. R. Schmid, D. A. Cortes and S. Chou, *J. Am. Chem. Soc*., 1984, **106**, 3374.

The almost complete specificity for primary versus secondary alcohol moieties endows this system with enzyme-like qualities. Indeed, copper-dependent oxidases, such as galactose oxidase, catalyse the selective oxidation of primary alcohol moieties *in vivo* and we have shown that the above mentioned Cu(II)/TEMPO systems involve similar copper-centered mechanisms which I do not have time to go into today. We found another copper-dependent oxidase, laccase, to be more interesting in this respect. Laccases occur widely in nature and are involved, for example, in the fungal degradation of lignocellulose in plants. Alcohols do not function as their substrates *in vivo* but in conjunction with TEMPO laccase is able to catalyse the aerobic oxidation of alcohols. The mechanism involves an oxoammonium cation as the active oxidant, analogous to the TEMPO catalysed oxidations with NaOCl described above but different to the other copper/TEMPO systems (work of graduate students, Yuxin Li and, more recently, Inga Matijosyte)[60]. This can be ascribed to the high redox potential of Cu(II) in laccase, an example of the so-called entatic effect whereby the coordination of transition metal ions in proteins in unfavourable geometries can lead to substantial increases in redox potential.This brings me now to the fascinating subject of biocatalysis.

8. Biocatalysis : Inventing New Biotransformations

Biocatalysis has many attractive features in the context of green chemistry: attractive reaction conditions- an aqueous medium at physiological pH and temperature and an environmentally compatible, biodegradable catalyst (an enzyme)- combined with high activities and chemo-, regio- and stereoselectivities in reactions of multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for the functional group activation and protection often required in traditional organic syntheses, affording more environmentally and economically attractive processes with fewer steps and, hence, less waste. Illustrative examples are provided by the substitution of classical chemical processes with enzymatic ones in the synthesis of semisynthetic penicillins and cephalosporins which we have discussed elsewhere[61].

60. I. W. C. E. Arends, Y. X. Li and R. A. Sheldon, *Biocat. Biotrans*. 2006, **24**, 443-448; I. W. C. E. Arends, Y. X. Li, R. Ausan and R. A. Sheldon, *Tetrahedron*, 2006, **62**, 6659-6665.
61. A. Wegman, M. H. A. Janssen, F. van Rantwijk and R. A. Sheldon, *Adv. Synth. Catal.,* 2001, **343**, 559-576.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis. Advances in recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price and the development of *in vitro* evolution has enabled the manipulation of enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, etc.[62]

As Edward De Bono remarked, "If you want to find something new you have to *do* something new" and we have used basically two approaches to finding novel, non-natural biotransformations with practical utility:

1. The mechanism-based organic chemistry strategy .
2. The chemomimetic biocatalysis strategy .

An example of the first strategy is provided by the development of an entirely new enzymatic reaction- lipase catalysed ester ammoniolysis- a project of one of my first graduate students in Delft : Marian de Zoete[63]. The idea was simple : the mechanism of lipase-catalysed hydrolysis of an ester bond (in a triglyceride) involves the formation of a serine hydroxyl group in the active site, affording the so-called acylenzyme intermediate. The latter subsequently reacts with water to afford the observed carboxylic acid product (see Figure 14). A cursory examination of this last step, through the eyes of an organic chemist, easily leads to the notion that other nucleophiles could replace the natural nucleophile, water, to afford a potentially enantioselective route to various carboxylic acid derivatives. In this context our attention was drawn to ammonia as the nucleophile, which could afford a mild method for the (enantioselective) synthesis of amides.The reaction was performed successfully in anhydrous tert-butanol, in order to suppress competing hydrolysis, but it was later shown to be possible starting from the free carboxylic acid[64]. We subsequently demonstrated that the method had broad scope and could be used for the resolution of chiral esters including α- amino acid esters[65]. It is an excel-

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62. K. A. Powell, S. W. Ramer, S. B. del Cardayré, W. P. C. Stemmer, M. B. Tobin, P. F. Longchamp, G. W. Huisman, *Angew. Chem. Int. Ed.,* 2001, **40**, 3948-3959.

63. M. C. de Zoete, A. C. Kock van Dalen, F. van Rantwijk and R. A. Sheldon, *Chem. Commun*. 1993, 1831-1832.

64. M. C. de Zoete, A.C. Kock van Dalen, F. van Rantwijk and R. A. Sheldon, *J. Mol. Catal. B: Enzymatic*, 1996, **2**, 19-25.

65. M. C. de Zoete, A. A. Ouwehand, F. van Rantwijk and R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas*, 1995, **114**, 171-174 ; see also M. A. P. J. Hacking, M. A. Wegman, J. Rops, F. van Rantwijk and R. A. Sheldon, *J. Mol. Catal. B :Enzymatic*, 1998, **5**, 155-157; M. A. Wegman, M. A. P. J. Hacking, J. Rops, P. Pereira, F. van Rantwijk and R. A. Sheldon, *Tetrahedron Asymm*., 1999, **10**, 1739-1750.

lent method for the synthesis of amides under mild conditions and it is surprising, therefore, that industry has not, as far as we know, picked it up as an alternative to chemical amidations which usually require forcing conditions.

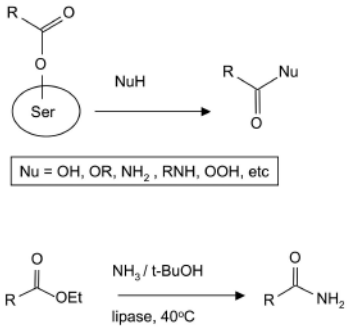


Figure 14. Lipase-catalysed ammoniolysis of esters.

Similarly, lipase catalysed acylation of a primary amine moiety can be used for the resolution of chiral primary amines and BASF successfully developed a process which is operated on a multi-thousand ton scale for the synthesis of a variety of enantiopure amines[66]. Commercially acceptable rates were obtained by using a methoxyacetic acid ester as the acyl donor which can be attributed to hydrogen bonding to the ether oxygen in the active site of the enzyme[67].As shown in Figure 15, the process affords an amide of the reacting enantiomer together with the other enantiomer as the free amine.

In order to recover both amines in optically active form the amide is hydrolysed chemically by reaction with NaOH in aqueous ethylene glycol at 150°C. This "brute force" method would certainly lead to problems with amines containing other functional groups and is in stark contrast with the elegant enzymatic procedure used for the first step.Hence, we reasoned that the use of an enzymatic deacylation would afford an overall green process. An example of what we have called an *easy-on-easy-off* process is shown in Figure 16. In a collaboration with Vytas Svedas of Moscow State University, we used penicillin G amidase from *Alcaligenes faecalis*, which we had been

66. G. Hieber and K. Ditrich, *Chim. Oggi*, 2001, **19(6)**, 16-20.
67. M. Cammenberg, K. Hult and S. Park, *ChemBioChem*., 2006, **7**, 1745-1749.

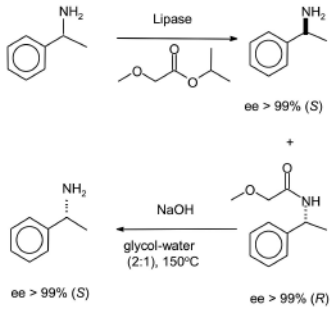


Figure 15. BASF process for enzymatic resolution of amines.

studying in the context of semi-synthetic penicillin and cephalosporin synthesis, as the enzyme for both steps[68]. The acylation was performed in an aqueous medium at pH 10-11 and, after separation of the remaining amine enantiomer, the acylated amine was hydrolysed with the same enzyme by lowering the pH to 7.

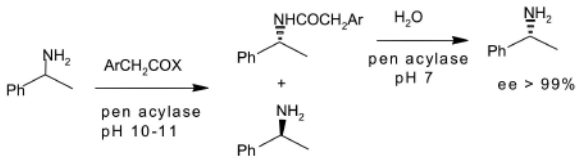


Figure 16. Easy-on- easy-off resolution of amines with penicillin G amidase

However, we are still left with the problem of racemising and recycling the unwanted amine enantiomer. This could be achieved by using a palladium catalysed racemisation in conjunction with the lipase-catalysed resolution. The palladium-on-charcoal catalysed racemisation of amines was first reported by Murahashi and coworkers[69] and was later combined with lipase catalysed acylation to afford a dynamic kinetic resolution (DKR) by Reetz[70]. In recent work of the graduate student, Hilda Ismail, we achieved a DKR of

68. D.T. Guranda, A.I. Khimiuk, L.M. van Langen, F. van Rantwijk, R.A. Sheldon, V.K. Svedas, *Tetrahedron: Asymm*. 2004, **15**, 2901-2906.
69. S.-I. Murahashi, N. Yoshimura, T. Tsumiyama and T. Kojima, *J. Am. Chem. Soc*. 1983, **105**, 5002-5011.
70. M. T. Reetz and K. Schimossek, *Chimia*, 1996, **50**, 668.

α-methyl benzylamine by performing the lipase catalysed acylation in the presence of a palladium nanoparticle catalyst (Figure 17).

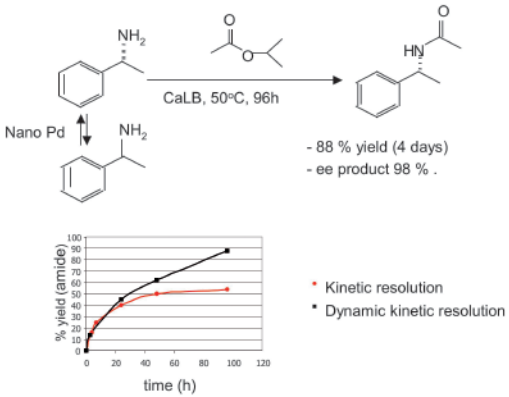


Figure 17. DKR of α-methyl benzylamine

In the past much effort has been devoted to biomimetic catalysis whereby the goal is to construct a simple metal complex capable of emulating the activity of enzymes or even to inventing better, suprabiotic catalysts. Why should Nature have a monopoly on good catalysts? There is still much room for improvement in the catalytic properties of enzymes with non-natural substrates and conditions. However, the biomimetic approach has been largely unsuccessful . The protein structure is the result of millions of years of evolution and it is difficult to emulate.Hence, in the second approach mentioned above we used what I call the chemomimetic biocatalysis strategy. Various transition metals are known to catalyse oxidations and if we place such a metal in the active site of a hydrolytic enzyme then this could perhaps afford a semi-synthetic enzyme capable of mediating (enantioselective) oxidations. For example, the graduate student, Fred van de Velde, developed a semi-synthetic peroxidase using this strategy. Another graduate student, Marion van Deurzen had already shown that the heme-dependent enzyme, chloroperoxidase (CPO), from *Caldariomyces fumago* is able to catalyse a variety of enantio- and regioselective oxidations, such as sulfoxidation (see Figure 18), with the green oxidant hydrogen peroxide[71].

71. M. P. J. van Deurzen, F. van Rantwijk and R. A. Sheldon, *Tetrahedron*, 1997, **53**, 43-46.

However, CPO is rapidly deactivated by hydrogen peroxide via oxidation of its porphyrin prosthetic group which precludes its practical application. On the other hand, vanadium is a well-known catalyst for epoxidations and sulfoxidations with alkyl hydroperoxides (see earlier) and vanadium-dependent peroxidases are also known. They are more stable than the heme peroxidases because they are not encumbered by the sensitive porphyrin ring. It was further known, from the work of Wever[72] in Amsterdam, that the acid phosphatase, phytase, a very inexpensive enzyme that is added to poultry and pig feed, has an active site structure very similar to vanadium peroxidases, but without the vanadium. Hence, we reasoned that the addition of vanadate to phytase should afford a robust and inexpensive peroxidase and this proved to be the case (see Figure 18)[73].

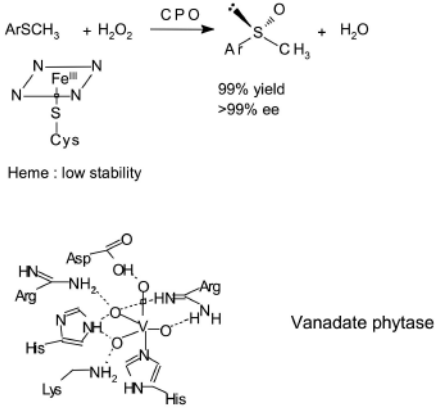


Figure 18. Enantiosulfoxidation with hydrogen peroxide

Gerd-Jan ten Brink, the graduate student that developed the aqueous biphasic catalytic oxidation of alcohols (see earlier), also developed aryl seleninic acids, containing strongly electron withdrawing groups, as effective catalysts for selective epoxidations (Figure 19) with aqueous hydrogen peroxide[74].

72. A. Messerschmidt and R. Wever, *Proc. Nat. Acad. Sci. U. S. A*. 1996, **93**, 392
73. F. van de Velde, L. Konemann, F. van Rantwijk and R. A. Sheldon, *Chem. Commun*., 1998, 1891-1892.
74. G. J. ten Brink, B. C. M. Fernandes, M. C. A. van Vliet, I. W. C. E. Arends and R. A. Sheldon, *J. Chem. Soc. Perkin Trans*. 2001, **11**, 249-253 ; G. J. ten Brink, J. M. Vis, I. W. C. E. Arends and R. A. Sheldon, *J. Org. Chem*., 2001, **66**, 2429-2433.

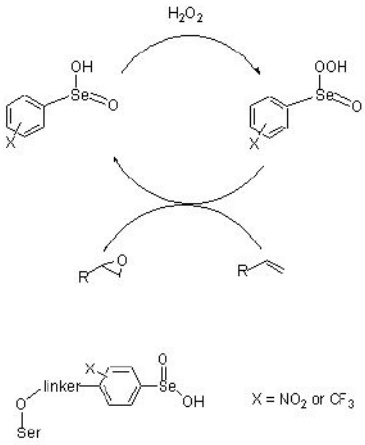


Figure 19. Selenium catalysed epoxidations with hydrogen peroxide

In a project with graduate student John van der Toorn we are attempting to design a chemomimetic biocatalyst by covalent anchoring of an arylseleninic acid moiety in the active site of a serine protease (Figure19).
The enzymes found in Nature are the result of aeons of cumulative natural selection. They were not evolved for biotransformations of non-natural, commercially interesting substrates. In order to make them suited to these tasks they need to be re-evolved but we don't have millions of years to do it. Fortunately, modern advances in biotechnology have made it possible to accomplish this in weeks in the laboratory using *in vitro* techniques such as gene shuffling[75].
An illustrative example is provided by the Codexis process for the production of an intermediate for Pfizer's blockbuster drug Atorvastatin (Lipitor). The two-step process (Figure 20), which received a 2006 Presidential Green Chemistry Challenge Award, involves three enzymes (one for cofactor regeneration).The low activities of the wild-type enzymes formed a serious obstacle to commercialisation but *in vitro* evolution of the individual enzymes, using gene shuffling, afforded economically viable productivities[76].

75. W. P. C. Stemmer, *Nature,*1994, **370**, 389-391.
76. R. J. Fox, C. S. Davis, E. C. Mundorff, L. M. Newman, V. Gavrilovic, S. K. Ma, L. M. Chung, C. Ching, S. Tam, S. Muley, J. Grate, J. Gruber, J. C. Whitman, R. A. Sheldon and G. W. Huisman, *Nature Biotechnology,* 2007, **25**, 338-344.

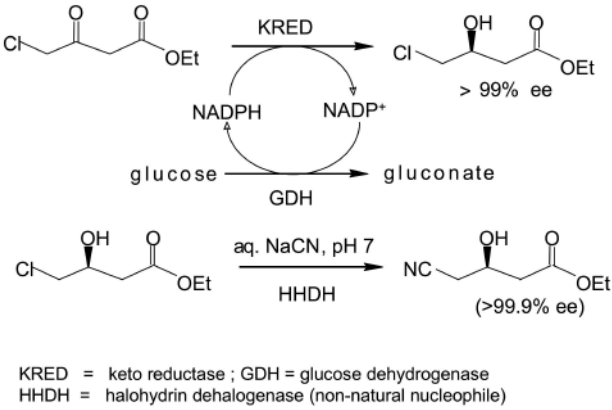


Figure 20. Codexis process for atorvastatin intermediate

9. Enzyme Immobilization ; Cross-Linked enzyme aggregates (CLEAs)

Notwithstanding the many benefits of enzyme catalysis, their commercial application is often impeded by low operational stability and shelf-life in addition to their cumbersome recovery and re-use and the product contamination that is a characteristic feature of most homogeneous catalysts (see earlier). Although these problems can be alleviated by *in vitro* evolution, another approach to rendering enzymes more robust and recyclable is to immobilise them[77]. Among the several methodologies for enzyme immobilisation one that is particularly effective is to immobilise them as cross-linked enzyme aggregates (CLEAs®), an invention of our group (a project of the postdoc Linqiu Cao)[78]. The technique is exquisitely simple, involving standard precipitation of the enzyme from aqueous buffer, e.g with ammonium sulphate, and cross linking of the resulting physical aggregates of enzyme molecules with a bifunctional reagent such as glutaraldehyde (Figure 21). Since selective precipitation is often used to purify enzymes 'cleation' essentially involves combination of purification and immobilisation into a single unit operation and there is no need for the enzyme to be of high purity. Indeed, it could even be possible to isolate an enzyme in immobilised form directly from a fermentation broth.

77. R. A. Sheldon, *Adv. Synth. Catal.*, 2007, **349,** 1289-1307.
78. L. Cao, F. van Rantwijk, R.A. Sheldon, *Org. Lett*. 2000, **2**, 1361-1364.

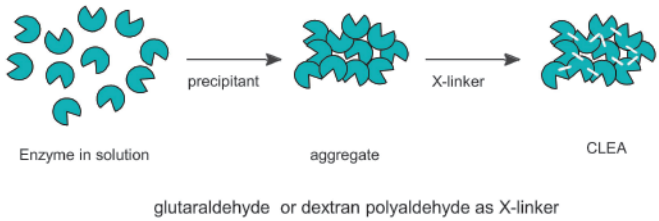


Figure 21. Cross-linked enzyme aggregates (CLEAs).

The method is applicable to a broad range of enzymes, including a variety of hydrolases, lyases and oxidoreductases (see Figure 22). Since they consist almost entirely of protein, CLEAs invariably exhibit high productivities. Furthermore, they often show increased stability towards denaturation by heat, organic solvents or proteolysis, which translates to improved operational stability and shelf-life, and they are readily recovered by filtration or centrifugation and recycled (collaboration with Menno Sorgedrager and Michiel Janssen of CLEA Technologies).

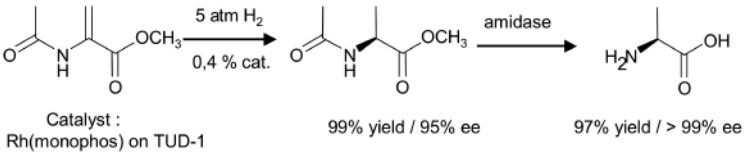
Hydrolases	Oxidoreductases	Lyases
• Pen. acylases (2)	• ADH	•*R*- & *S*- HnLases
• Lipases (7)	• FDH	• PDC
• Esterases (3)	• Glucose oxidase	• DERA
• Proteases (3)	• Galactose oxidase	• Nitrile hydratase
• Nitrilases (2)	• Laccase	
• Aminoacylase	• Catalase	
• Phytase	• Chloroperoxidase	
• Galactosidase		

Figure 22. Examples of successful 'cleation'.

10. Catalytic Cascade Processes

The ultimate in green catalytic processes is to emulate Nature by combining two or more catalysts into (bio)catalytic or chemoenzymatic cascade processes. For example, in our group we have studied the two chemoenzymatic cascade processes shown in Figure 23. In the first example, which was a project of the graduate student, Chretien Simon, the first step involves

a rhodium catalysed asymmetric hydrogenation of a prochiral N-acyl dehydroamino acid ester. The (*S*) product was obtained in 99% yield and 95% ee. An amino acylase was used in the second step to hydrolyse both the amide and ester moieties. This resulted in an upgrading of the enantiopurity, from 95%ee to >99%ee, with little loss in yield, because the acylase was highly *S*-selective. The overall reaction could be performed, without isolation of the intermediate, in water as the only solvent, using an immobilised form of the Rh catalyst in combination with the soluble enzyme or as a CLEA.



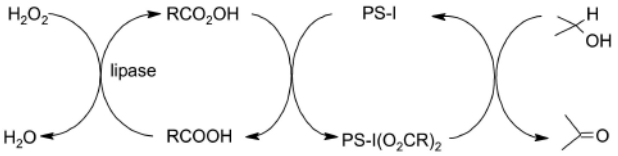


Figure 23. catalytic cascade processes.

In the second example a graduate student, Aleksandra Kotlewska, is trying to develop a chemoenzymatic cascade process for the oxidation of alcohols in which a hypervalent iodine intermediate is the active oxidant (see Figure 23). In a third example (Figure 24) the graduate student Andrzej Chmura has performed a trienzymatic cascade process using a triple–decker combi-CLEA containing an oxynitrilase, a nitrilase and an amidase.

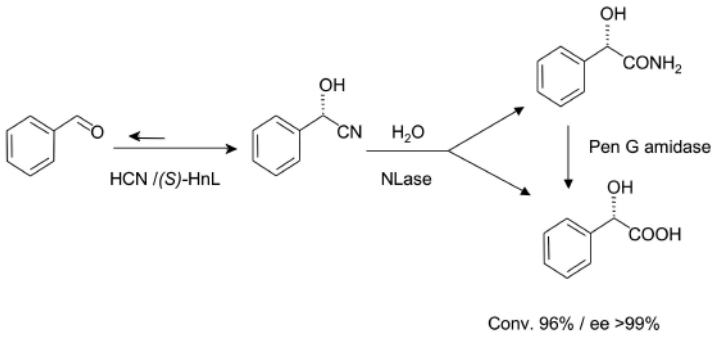


Figure 24. A trienzymatic cascade with a triple-decker combiCLEA

11. Renewable Raw Materials and Green Product Design

Another important goal of green chemistry and sustainablity is the utilisation of renewable raw materials and the *utilisation of biomass rather than crude oil for sustainable fuels and chemicals* has become a top priority item on the political agenda. Here again, the processes used for the conversion of renewable feedstocks – mainly carbohydrates but also triglycerides and terpenes – should produce minimal waste, *i.e.* they should be preferably catalytic in order to be sustainable. We have in the last 16 years been involved in many projects which concerned the catalytic conversion of renewable feedstocks. Indeed, the project of my very first Ph.D. student at the T.U.Eindhoven, Carry Emons, was the synthesis of C3 chiral synthons by catalytic oxidation of carbohydrates[79] and we have subsequently carried out extensive investigations of chemo- and biocatalytic conversions of carbohydrates[80].

The shift from oil to renewable feedstocks will have far-reaching consequences for the commodity chemical industry. The structure of chemical supply chains will be radically altered, creating new opportunities for inno-

79. C.H.H. Emons, B.F.M. Kuster, J.A.J.M. Vekemans and R.A. Sheldon, *Tetrahedron: Asymm*., 1991, **2**, 359-362 and Chimica Oggi, Nov./Dec. 1992, 59-65.
80. See, for example, S.J.H.F. Arts, E.J.M. Mombarg, H. van Bekkum and R.A. Sheldon *Synthesis*, 1997, **6**, 597-613; M. Woudenberg-van Oosterom, H.J.A. van Belle, F. van Rantwijk and R.A. Sheldon, J. *Mol. Catal. A: Chemical*, 1998, **134**, 267-274.

vation in green chemistry and sustainable technologies. It will also be an opportunity to substitute existing products by greener products, e.g. polymers based on renewable feedstocks. For example, an obvious extrapolation is to manufacture polyacrylates from acrylic acid produced from biomass. However, a major application of polyacrylates is as water super absorbents, e.g. in baby diapers, but their poor biodegradability is a serious shortcoming. Hence, an innovation for the longer term could be to produce a polymer, from renewable feedstocks, that is both a super water absorbent and readily biodegradable. Carboxy starch is such a polymer and it can be produced by TEMPO catalysed bleach oxidation of starch. However, as discussed earlier, a greener process would be obtained by substituting the NaOCl with molecular oxygen. This is possible (see earlier) using the copper-dependent enzyme,laccase, as a cocatalyst but the process (Figure 25) is not commercially viable owing to high enzyme costs, a direct result of the low operational stability of laccase. CLEA Technologies has shown, in a collaboration with Hans Boumans of TNO, that the operational stability of a laccaseCLEA is much improved compared to the free enzyme. This paves the way for green and economically viable production of carboxy starch : green chemistry and sustainability *in optima forma,* a green product derived from a sustainable raw material by a green, biocatalytic process.

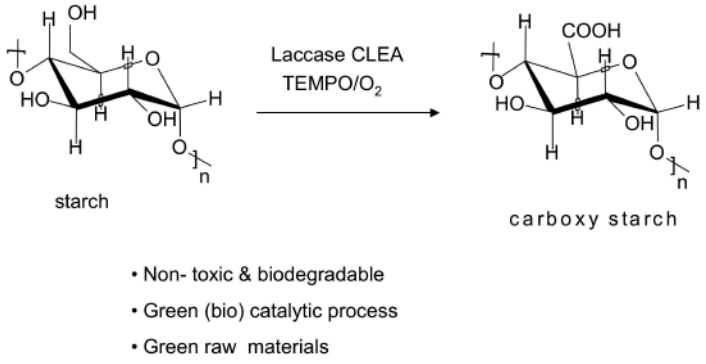


Figure 25. Production of carboxy starch by laccase/TEMPO catalysed oxidation of starch

12. Dankwoord

Dames en heren, het werk in Delft heeft veel voor mij betekend. Hoezo werk? Ik heb het meer ervaren als één lange vakantie. Ik wil graag alle mensen met wie ik de afgelopen 16 jaar heb samengewerkt van harte bedanken voor deze plezierige reis. Dat zijn natuurlijk in de eerste plaats alle naaste medewerkers van de leerstoel Biokatalyse en Organische Chemie met wie ik de directe werkcontacten had. Onderzoek is een team effort en ik wil alle leden van ons team gedurende de afgelopen 16 jaar – alle vaste medewerkers, alle AIO's, post-docs, studenten en stagiaires, externe relaties en sponsoren - van harte bedanken voor hun inzet. Ik voelde mij meer als een dirigent die het beste uit mijn orkest wilde halen.
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Last but not least wil ik afsluiten door mijn oprechte waardering uit te spreken voor de steun van het thuisfront, van onze kinderen Annemarie en Frank, maar in het bijzonder wil ik mijn vrouw, Jetty, bedanken voor de onvoorwaardelijke steun die zij gedurende deze hele reis aan mij gegeven heeft. Niet alleen mijn TU tijdperk maar over de hele bijna veertig jaar durende reis van deze travelling chemist.
Zoals Simon Carmiggelt opmerkte: “Wie samen kan reizen, kan ook samen leven”.
Dames en heren, ik dank u voor uw aanwezigheid en uw aandacht.
Ik heb gezegd!

The significant problems that we face today cannot be solved by the same level of thinking we were at when we created them.
Albert Einstein

The first one now will later be last.
For the times they are a-changin'.
Bob Dylan


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