# Solvent-Free Organic Syntheses

**Jürgen O. Metzger***

A consequence of the necessity to minimize the amount of toxic waste and by-products from chemical processes is a need for the development of new, more environmentally friendly synthetic methods in which fewer toxic substances are used. Nowadays in the development of new syntheses, ecological points of view must also be taken into consideration and apportioned due importance in the assessment of viability.[1] In this process the solvents are especially important, as they are generally used in large quantities. Many organic solvents are ecologically harmful, and their use should therefore be minimized as far as possible or even avoided altogether. In industry they are of course recycled wherever possible. However, in practice this is only rarely accomplished with complete efficiency, which means that some organic solvent from chemical production will inevitably escape and severely pollute the environment. Alternatives under investigation as solvents for organic reactions are water[2] and supercritical gases, in particular $CO_2$.[3]

The best solvent from an ecological point of view is without a doubt no solvent. There are of course a great many reactions that can already be carried out in the absence of solvent. Examples that spring to mind are the numerous industrially important gas-phase reactions and many polymerizations. Diels–Alder and other pericyclic reactions are also often carried out without solvent. Reports on solvent-free reactions have, however, become increasingly frequent and specialized over the past few years. Areas of growth include reactions between solids,[4] between gases and solids,[5] and on supported inorganic reagents,[6] which in many cases are accelerated or even made possible through microwave irradiation.[7] There are also reactions in which at least one reactant is liquid under the conditions employed, which means that the solvent that would normally be used can simply be left out. This is the subject of this contribution. To begin with, two industrially important examples are discussed, which confirm that a reaction process that is more environmentally friendly can also be economically very acceptable. This is followed by some recent examples—without making any claim to completeness—of solvent-free reactions in which the term "solvent-free" refers solely to the reaction itself. On the other hand, workup processes, except for a few examples, invariably involve the use of solvent. The examples show that these reactions proceed with the same, and in many cases even higher, yield and/or higher selectivity and, because of the higher concentration of the reactants, with greater rapidity.

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*Polypropylene and Polycarbonate*

The method for the manufacture of polypropylene by the Ziegler–Natta process, which has been in widespread use for several decades, involves a polymerization in a relatively volatile solvent, for example a light petroleum fraction. Herein lies the drawback of this process, since in the separation and subsequent drying of the polymer that is formed the solvent cannot be completely recovered. Problems are thus experienced in fulfilling environmental protection requirements. An additional obstacle is the large volume of aqueous waste that is generated during workup of the polymer suspension, which must then be treated. The new polypropylene process from Hoechst[8a] does not require solvent and is carried out at a pressure of 40 bar with a new, highly efficient catalyst.[8b] In this process there are no solvent emissions in the exhaust gases. Small amounts of gaseous hydrocarbons that are formed are incinerated. In the manufacture of the polymer the amount of aqueous waste water accumulated is much smaller, since the amount of catalyst used can be reduced to such low levels that it no longer needs to be washed after the reaction. The raw material input for 1000 kg product was brought down from an original 1185 to approximately 1013 kg by the development of this process. Comparable results have also been achieved in the manufacture of high-density polyethylene.

Polycarbonates are amorphous polymers with excellent handling properties. Their spectrum of applications ranges from baby bottles to compact discs (CDs). Most of the polycarbonate produced is generated by the polycondensation of bisphenol A (Scheme 1) with phosgene in a sodium hydroxide/dichloromethane two-phase system. The solution of the polycarbonate product in dichloromethane is washed with water to remove the by-product NaCl. However, in this washing process some 20 g $L^{-1}$ of the dichloromethane ends up dissolved in the aqueous phase. The dichloromethane must also be removed from the polycarbonate, which is not easy. This means that the polycarbonate will invariably contain some chlorinated impurities, which adversely affects the properties of the polymer.

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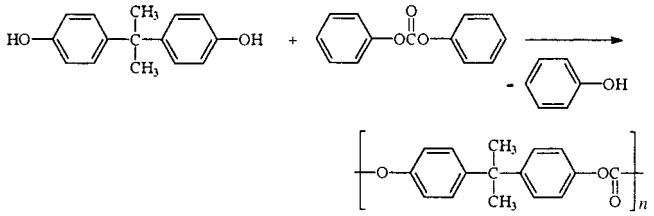
Komiya et al.[9] recently introduced the novel, environmentally friendly process from Asahi Chemical Industry Co. for the production of polycarbonates which requires neither phosgene nor solvent (Scheme 1). In this process bisphenol A undergoes a prepolymerization with diphenyl carbonate in the melt. A simple crystallization of the prepolymer is followed by a solid-state polymerization to a polycarbonate of high molecular weight. Its quality is higher than that of the product of the phosgene process, and the production costs appear to be similar.

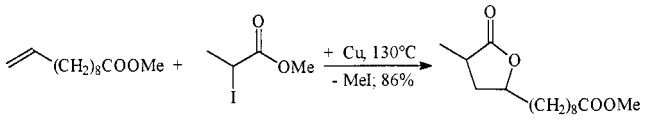


Scheme 1. Solvent-free synthesis of polycarbonate from bisphenol A and diphenyl carbonate.[9]

*Radical Additions*

Intermolecular radical additions have for some time been an integral part of the methodological arsenal of preparative organic chemistry. However, from an ecological point of view the methods that have been used to date suffer from a number of drawbacks that present obstacles to their broad-based industrial application. This applies particularly to the commonly used organotin compounds.

Transition metal complexes and salts which initiate radical reactions through electron transfer processes are a highly promising alternative, all the more so in light of some recent examples which do not require the use of solvents.[10, 11] Thus, $\alpha$-iodo esters undergo addition to alkenes through an electron transfer initiated by metallic copper.[10] The reaction procedure is very simple: The alkene, iodo compound, and commercial copper powder are mixed together without any pretreatment and heated to 130 °C under an inert atmosphere (Scheme 2). After a simple workup the products were

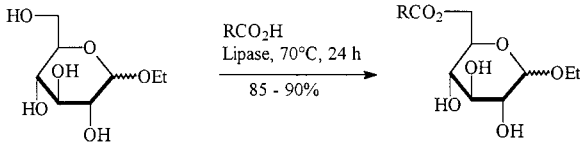


Scheme 2. Copper-initiated radical addition of methyl 2-iodopropionate to methyl 10-undecenoate.[10]

obtained in good yield; the entire reaction was carried out in the complete absence of solvent, as the product was distilled directly from the reaction mixture. The iodo compound could be replaced by the corresponding, more easily accessible bromo compound; in this case an equimolar quantity of sodium iodide is added. The iodo compound is formed initially as an intermediate by a solvent-free Finkelstein reaction. $\alpha$-Iodonitrile[10] and perfluoroalkyl iodides[11] underwent addition to alkenes in a completely analogous solvent-free reaction. Additional points in favor of these solvent-free radical additions are that the yields are generally better than with the conventional methodology and that they also permit additions to 1,2-dialkyl-substituted ethenes.

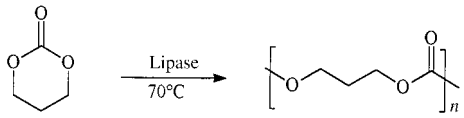
*Enzyme-Catalyzed Reactions*

The selective enzyme-catalyzed acylation of carbohydrates is of great interest, as their fatty acid esters have potentially important applications in detergents, cosmetics, foodstuff, and pharmaceuticals on account of their surface-active properties. Monoacylated sugars have been synthesized by lipase-catalyzed transesterifications of activated esters in pyridine and by protease-catalyzed esterifications in DMF. A most remarkable new development is the use of immobilized lipases for the selective acylation of 1-*O*-ethyl glucopyranoside with free carboxylic acids in the absence of solvent. This afforded 6-*O*-acyl glucopyranosides in 85–90% yield,[12] with small amounts of the 2,6-*O*-diacyl glucopyranosides being formed as by-products. This reaction can also be carried out without problem on a large scale. Thus, 8 kg of glucose was allowed to react with ethanol in the presence of an ion-exchange resin to form 1-*O*-ethyl glucopyranoside. After removal of the ion-exchange resin and the residual ethanol 12.7 kg of coconut oil fatty acids was added to the crude 1-*O*-ethyl glucopyranoside, and the mixture was heated to 70 °C. Then 400 g of immobilized lipase from *Candida antarctica* was added, and the water of reaction that formed was removed under vacuum. After 28 h a conversion of greater than 90% was achieved. After the enzyme was filtered off, a crude product was obtained which contained 70% of the 6-*O*-monoester. After removal of the the excess fatty acid (21%) by distillation, the final product had a 6-*O*-monoester content of greater than 85% (Scheme 3).



Scheme 3. Lipase-catalyzed acylation of 1-*O*-ethyl glucopyranoside with carboxylic acids to 6-*O*-acyl glucopyranosides (R = *n*-$C_7H_{15}$, *n*-$C_9H_{19}$, *n*-$C_{11}H_{23}$, *n*-$C_{13}H_{27}$, *n*-$C_{15}H_{31}$, *n*-$C_{17}H_{35}$).[12]

In another solvent-free process with the same lipase as above, trimethylene carbonate underwent an almost quantitative ring-opening polymerization in 120 h at 70 °C to form poly(trimethylene carbonate).[13] No decarboxylation was detected (Scheme 4). $\omega$-Pentadecalactone was likewise polymerized with lipases in the absence of solvent to form polyesters of high molecular weight.[14]



Scheme 4. Lipase-catalyzed ring-opening polymerization of trimethylene carbonate to linear poly(trimethylene carbonate).[13]

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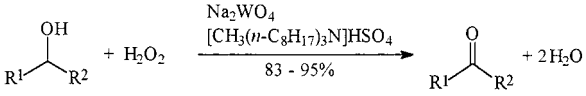
The latter two successful processes were combined in the solvent-free lipase-catalyzed reaction of 1-*O*-ethyl glucoside with trimethylene carbonate or $\varepsilon$-caprolactone to form amphiphilic oligomers and polymers.[15] The products are biodegradable polycarbonates and polyesters that are formed regioselectively by reaction with the terminal OH group of the sugar moiety.

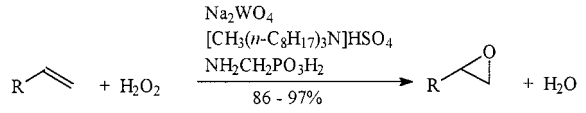
*Catalytic Reactions*

Oxidations are of great importance, and it would be highly desirable to carry them out with environmentally friendly oxidants such as atmospheric oxygen and hydrogen peroxide—30 % $H_2O_2$ if possible. Ideally such reactions should also be carried out without the need for any additional organic solvent. Noyori et al.[16] recently reported an efficient oxidation of secondary alcohols to ketones with sodium tungstate as catalyst and methyltrioctylammonium hydrogen sulfate as phase-transfer catalyst (Scheme 5). The yield in the case of




Scheme 5. Oxidation of secondary alcohols to ketones with 30 % $H_2O_2$.[16]

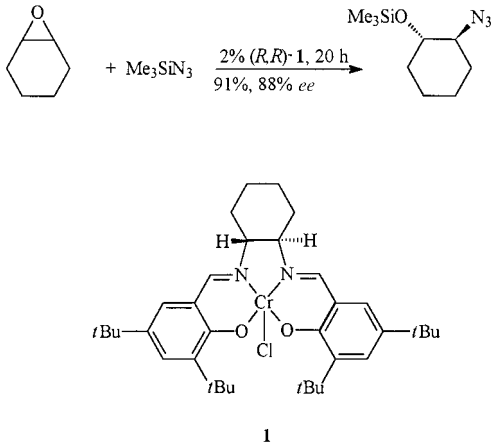
2-octanol was approximately 95 %. Primary alcohols are four to five times less reactive and were generally oxidized to carboxylic acids. More remarkably, unsaturated secondary alcohols, including even allyl alcohols, were oxidized with high selectivity to the ketone. However, if a catalytic quantity of aminomethylphosphonic acid was also added, an efficient epoxidation catalyst was obtained, with which 1-alkenes could be oxidized to the epoxide in greater than 90 % yield using 30 % $H_2O_2$ (Scheme 6).[17]




Scheme 6. Epoxidation of 1-alkenes with 30 % $H_2O_2$ by addition of aminomethylphosphonic acid to the catalytic oxidation system shown in Scheme 5.[17]

The chiral $Cr^{III}$–salen complex **1** is a highly efficient catalyst for the enantioselective ring opening of epoxides with $Me_3SiN_3$.[18] For example, cyclohexene oxide underwent ring opening with 2 % of **1** and $Me_3SiN_3$ in the complete absence of solvent—the product was removed by short-path distillations under reduced pressure from the reaction mixture—in 90 % yield and with 84–88 % *ee* (Scheme 7). The catalyst was easily recovered and could be reused without any loss of activity. The yield and enantioselectivity were similarly high as for the corresponding reaction in diethyl ether.

Several Robinson annellation reactions have been carried out enantioselectively using (*S*)-proline as a chiral catalyst.[19] Remarkably, the enantioselectivity was distinctly higher in the absence of solvent than in DMSO. In contrast, although various enolates have been reported to undergo Michael




Scheme 7. Catalytic enantioselective ring opening of cyclohexene oxide with trimethylsilyl azide using the chiral $Cr^{III}$–salen complex **1**.

additions, for example to methyl vinyl ketone, in good yield in the presence of *N*-benzyl-*N*-methylephedrinium bromide as a chiral phase-transfer catalyst, the reaction is completely unselective. However, if solvent (sodium hydroxide and toluene) was used, the reaction proceeded enantioselectively with *N*-(4-trifluoromethylbenzyl)cinchoninium bromide as catalyst.[20]

*Ionic Reactions*

As has already been pointed out, the Finkelstein reaction can be conducted in situ in the absence of solvent. Alkylations, for example, of purine and pyrimidine bases with alkyl halides and dimethyl sulfate have been carried out by solid/liquid phase-transfer catalysis in the absence of any additional solvent,[21] as have $\beta$-eliminations.[22] Noteworthy is the synthesis of glycosyl isothiocyanates by the reaction of potassium thiocyanate with molten glycosyl bromide at 190 °C.[23]

To summarize, solvent-free reactions are not only of interest from an ecological viewpoint, but in many cases also offer considerable synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure.

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**Keywords:** enzyme catalysis · solvent-free reactions · phase-transfer catalysis · polymerizations · radical reactions

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# Amyloid Aggregates, Presenilins, and Alzheimer's Disease

**Ralf Baumeister* and Stefan Eimer**

Alzheimer's disease is today the most common cause of neurodegenerative death in the western world. The disease is characterized by two fundamental events, the accumulation of insoluble fibrillar aggregates of $\beta$-amyloid peptide (A$\beta$) and the degeneration and death of neurons in the brain regions that are concerned with learning and memory processes. Abnormal protein deposition is also a shared characteristic of other age-related neurodegenerative disesases, such as Parkinson's disease, Huntington's disease, and the Prion diseases. There is increasing evidence that the mechanism of this aggregation may be similar in each of these diseases.[1] Several recent studies have advanced our understanding considerably of the molecular and cellular mechanisms that cause the disease. The purpose of this article is to summarize recent results.

*The Biochemistry of APP Processing and Amyloid Aggregation*

The central role in the pathogenesis of Alzheimer's disease is played by a small, 40 – 42 amino acid long, four kDa peptide called A$\beta$. A$\beta$ is derived from the 695 – 770 amino acid long amyloid precursor protein (APP) by various proteolytic steps that are thought to take place in several intracellular compartments[2] (Figure 1). The detailed mechanism of A$\beta$ production from APP, the exact localization of the three proteases involved, and the functions of A$\beta$ and APP are not yet understood (for review articles see refs. [3, 4]). The 40 amino acid peptide A$\beta$40 is the predominant form that is produced during the metabolism of APP. Under pathological conditions the production of a 42 amino acid variant (A$\beta$42), normally a minor product, is enhanced.

A$\beta$40 is kinetically inert for several days in solution. In the disease state it is converted into a fibrous form, which is relatively resistant to chemical denaturing or proteolytic digestion.[5] This conversion is mediated by a change in the three-dimensional structure of A$\beta$40 and results in an increase in the hydrophobicity of the peptide. The peptide then aggregates and forms an ordered fibrillar morphology. The structural properties of the A$\beta$ aggregates suggest that, in contrast to amorphous precipitates, their formation is seeded and involves polymerization from a nucleus.[1, 6] This process is very slow because of the high entropy of intermolecular interactions.[6] For this reason, the sporadic forms of Alzheimer's disease, which comprise the fast majority of clinical cases, occur late in life (usually between the ages of 75 and 85), although A$\beta$ can be detected much earlier. Another A$\beta$ variant, A$\beta$42, is more hydrophobic and may produce the pathogenic seed in the development of the disease.[6] A$\beta$42 is highly aggregable and is the predominant form of A$\beta$ in senile plaques.[2] Overexpression of APP increases the amount of A$\beta$40 and A$\beta$42 and results in faster aggregation.[7] It is in this context interesting to note that patients with Down's syndrome, who have an additional copy of chromosome 21 on which the APP gene is located, invariantly develop symptoms of Alzheimer's disease and develop them significantly earlier.[3]

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