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Glycerol-based solvents as green reaction media in epoxidations with hydrogen peroxide catalysed by bis[3,5-bis(trifluoromethyl)-diphenyl] diselenide†

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A family of glycerol-based solvents, consisting of eighteen 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes, both symmetrically and unsymmetrically substituted at terminal positions, has been tested as new solvents in cyclooctene epoxidation with hydrogen peroxide, using a diselenide catalyst, but also without a catalyst. A quantitative relationship between the reactivity and solvent polarity properties has been developed through statistical linear regression analyses, and the predictive ability of the resulting equation has been demonstrated.

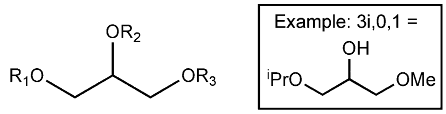
Introduction

One of the 12 principles of green chemistry is to circumvent the use of toxic solvents. Solvents are responsible for a large part of the waste generated by chemical processes. In many cases, organic solvents cannot simply be left out or replaced by water, for instance when solid substances are involved. There is, therefore, a definite need to develop sustainable and non-toxic organic solvents,[1] which have solvating properties comparable to *e.g.* dichloromethane, namely polar and non-coordinating.

In general, organic solvents are chemical substances derived from petrol. Five of the ten air contaminants most abundant in the atmosphere are organic solvents, and most solvents have been labelled as toxic or hazardous substances by the European program REACH (*Registration, Evaluation, Authorisation, and Restrictions of Chemicals*).[2] Both environmental restrictions in chemical compounds and the need for sustainable resources have propelled chemistry to discover and develop renewable materials. Current research has been going on in trying to find new renewable solvents. One possible approach is to start from vegetable oils. A new solvent will have to meet the demands for sustainability, in terms of renewability, non toxicity, and non volatility, and should exhibit a small environmental impact.[3] Glycerol-based solvents are highly promising in this respect.

Glycerol is currently produced as a concomitant product in biodiesel preparation. This increase in availability of low-price glycerol has initiated new research and industrial processes for making chemicals from glycerol.[4] A wide family of glycerol derivatives, consisting of 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes, both symmetrically and unsymmetrically substituted at terminal positions, has recently been synthesized, and the possible role of these glycerol based solvents as solvents has been evaluated through physico-chemical measurements.[5]

In this work a selected group of this family of glycerol derivatives, consisting of eighteen 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes (Scheme 1) was tested for their potential to act as the solvent in catalyzed epoxidation reactions, using aqueous hydrogen peroxide as oxidant and electrophilic chemo- or metal compounds as catalysts.[6] Classically, this area is dominated by dichloromethane and 2,2,2-trifluoroethanol (TFE) as solvents.



R = H (0); Me (1) ; Et (2); iPr (3i); Bu (4); tBu (4t); iBu (4i);
CF_3CH_2 (3F); $CF_3CF_2CH_2$ (5F); $CF_3CF_2CF_2CH_2$ (7F);

Scheme 1 Structures and simplified nomenclature for glycerol based solvents.

Olefin epoxidation is a key transformation in organic synthesis both on a laboratory and an industrial scale.[7] The use of hydrogen peroxide for selective epoxidations is highly desirable because it is readily available, the active oxygen content is high, and it is clean, since the only by-product formed is water.

Our focus was on the use of an arylseleninic acid as a catalyst in epoxidation of olefins.[8] At present, this is one of the most active catalysts reported for epoxidation with hydrogen peroxide.[9] The success of this catalyst is largely due to the beneficial influence of trifluoroethanol on hydrogen peroxide. Physico-chemical and theoretical studies have indicated that fluorinated alcohols act as a template, activating oxygen transfer through

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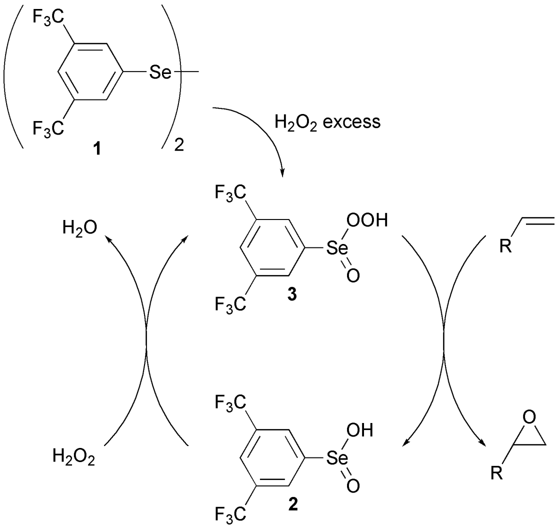
multiple hydrogen bonding.[10] It thus makes HOOH a more active oxidant, that can even oxidize olefins in the absence of catalysts. Trifluoroethanol is, however, highly volatile, toxic and expensive, and a sustainable alternative for this solvent would therefore be highly desirable. In our chosen catalytic reaction system, the diselenide catalyst is oxidized by hydrogen peroxide to give the corresponding arylseleninic acid which is the actual catalytic species for epoxidation (Scheme 2).[11]



Scheme 2 Catalytic epoxidation with arylseleninic acid-hydrogen peroxide system.

It has been repeatedly proven that solvents have critical and dominating effects on reaction systems. Many studies have been published concerning solvent effects, characterization of solvent properties and definition of solvent polarity parameters.[12]

Quantitatively defining the nature of a solvent may be difficult because a single numeric parameter, representing either a macroscopic or microscopic property, cannot properly represent all aspects of solvation. Solvent properties can be described in many ways, mainly based on chemical (reaction kinetics and equilibria) and spectroscopical measurements, which have led to a high number of solvent polarity scales.[12] One of the most successful is undoubtedly E_T^N,[12b] based on the solvatochromism of the Dimroth and Reichardt betain, and that has been determined for hundreds of solvents and solvent mixtures. The combination of several solvent polarity scales in multiparametric models has also been applied to many chemical problems. In particular, the Kamlet–Abboud–Abraham–Taft equation,[13] based on the π^*,[14] α and β polarity scales,[15] is one of the most widely used.

In this work, we have used some of these approaches in connection with multivariant regression analyses to study the relationships between solvent properties and the rate of the epoxidation reaction.

Results and discussion

We started by studying the epoxidation of cyclooctene using diselenide **1** as precatalyst and H_2O_2 as oxidant in different solvents. Cyclooctene was chosen as the substrate as good conversions to the epoxide were obtained in relative short amounts of time, making analyses more straightforward. A variety of solvents was selected to get a heterogeneous and representative group. Therefore, 13 common solvents and 18 glycerol derivatives were tested: 2,2,2-trifluoroethanol (TFE), dichloromethane (DCM), *n*-butanol (*n*-BuOH), *n*-hexanol (*n*-HxOH), ethanol (EtOH), 2-propanol (2-PrOH), *i*-propyl ether (*i*-Pr_2O), diethylene glycol dibutyl ether (DEGDBE), etyleneglycol dimethyl ether (EGDME), 1,4-dioxane (Diox), and glycerol derivatives: 1,3-dimethoxy-2-propanol (101), 1-methoxy-3-*tert*-butoxy-2-propanol (104t), 1-*n*-butoxy-3-*tert*-butoxy-2-propanol (404t), 1,3-di-*n*-butoxy-2-propanol (404), 1,3-bis(2,2,2-trifluoroethoxy)-2-propanol (3F03F), 1,3-bis(2,2,3,3,3-pentafluoropropoxy)-2-propanol (5F05F), 1,3-bis(2,2,3,3,4,4,4-heptafluorobutoxy)-2-propanol (7F07F), 1,2,3-trimethoxypropane (111), 1,2-dimethoxy-3-isopropoxypropane (113i), 1,2-dimethoxy-3-isobutoxypropane (114i), 1-butoxy-2-methoxy-3-isopropoxypropane (3i14), 1,2-dimethoxy-3-*tert*-butoxypropane (114t), 1,3-di-*n*-butoxy-2-methoxypropane (414), 1,2,3-tri-*n*-butoxypropane (444), 1-isopropoxy-2-methoxy-3-(2,2,2-trifluoroethoxy)propane (3i13F), 1-*tert*-butoxy-2-methoxy-3-(2,2,2-trifluoroethoxy)-propane (4t13F), 1-*n*-butoxy-2-methoxy-3-(2,2,2-trifluoro-ethoxy)propane (413F), and 2-methoxy-1,3-bis(2,2,2-trifluoroethoxy)-propane (3F13F).

The highest turnover frequency (TOF_0) and the fastest total conversion in the reaction was achieved using trifluoroethanol as solvent, but some glycerol-based solvents, mostly bearing fluorinated alkyl chains (3F03F, 5F05F, 7F07F and 3F13F) also showed fast conversions and high turnover frequencies (Fig. 1).† Some of these solvents performed better than dichloromethane, which was considered the second best solvent for this system.

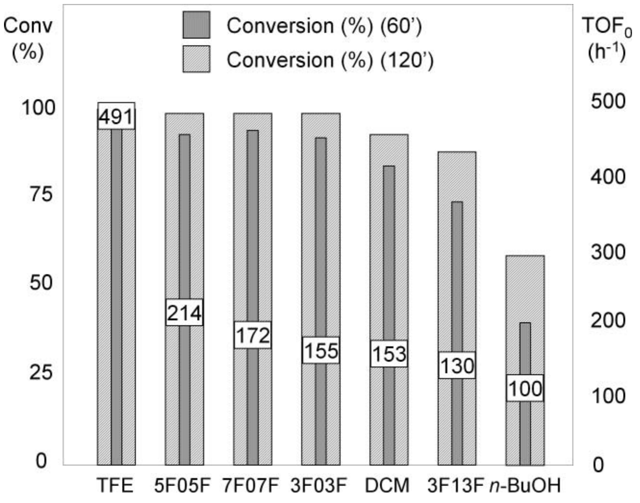


Fig. 1 Rate of cyclooctene epoxidation in different solvents.

For a better understanding of the properties of the solvents influencing the activity of the epoxidation rate, all data was subjected to a principal component analysis (PCA),[16] including the initial TOF and the conversions at set times. The PCA transforms variables x_n, of the primary matrix of data (X), into new variables y_n. These new variables of matrix Y are orthogonal and normalized. By transforming X into Y, it is possible to reduce the amount of data without losing information. In our case, a single y_1 variable already contained 93% of the overall

Table 1 Variable y_1 for solvents leading to the best results in cyclooctene epoxidation. Higher values indicate higher reactivity

Solvent	y_1
TFE	3.38
5F05F	1.59
3F03F	1.46
7F07F	1.42
DCM	1.29
3F13F	0.90
n-BuOH	–0.07

variance (indicating the high correlation between the TOF_0 and the conversions at different reaction times), so this transformed variable was subsequently used as a reactivity index for statistical analyses of solvent effects. Table 1 gathers the y_1 values obtained for the best solvents.

After preliminary analyses using different combinations of solvent polarity parameters, the following parameter set was chosen for the regression studies: E_T^N, π^*, α, β and Log*P*.[17] These parameters represent to a different extent dipolarity, hydrophobicity and the hydrogen bond ability of solvent. A complete list of the parameter values of all solvents tested can be found in the ESI.†

Using the above-mentioned solvent parameters, a fairly good linear relationship between solvent properties and reactivity in the epoxidation of cyclooctene was found, as summarized in eqn (1):

$$y_1 = 0.26\mathrm{Log}P + 2.33E_T^N + 0.31\pi^* - 2.30\beta + 1.15\alpha - 0.67$$
$$N = 28;\ R^2 = 0.907;\ s = 0.37 \quad (1)$$

By examining the coefficients of this equation, it can be established that a high reactivity is associated with solvents with high hydrogen-bond donor (HBD) ability, but low hydrogen-bond acceptor (HBA) ability (*i.e.* with a low Lewis basicity), as indicated by the magnitude and sign of the E_T^N, α, and β coefficients, respectively. Dipolarity and hydrophobicity seem to have a secondary role in this system, as illustrated by the small coefficients of the π^* and log*P* parameters.

To asseverate the predictive ability of the regression model, it is important to check the robustness of eqn (1) towards the solvent set used to derive it. If the linear regression model is robust enough it will be able to reliably predict the reactivity results on other glycerol-based solvents. To accomplish this, the initial group of solvents was divided in two subgroups: subgroup A, consisting of ten common organic solvents and six glycerol-based solvents, and subgroup B, compiled of the remaining glycerol-based solvents (Table 2).

Using subgroup A, a new linear regression equation was derived (eqn (2)). It is important to note that the qualitative conclusions reached with eqn (1) are also maintained with eqn (2), as illustrated by the relative weight of regression coefficients.

$$y_1 = 0.21\mathrm{Log}P + 1.31E_T^N + 0.93\pi^* - 2.11\beta + 1.51\alpha - 0.80$$
$$N = 16;\ R^2 = 0.916;\ s = 0.41 \quad (2)$$

Eqn (2) was used to predict the epoxidation results with the solvents in subgroup B, which constitutes an authentic predictive test. Fig. 2 displays the predicted values for subgroups A and B showing eqn (2) in comparison to the experimentally determined line. The predicted values show a similar quality in both cases, indicating that the model developed is robust and is not strongly affected by the initial selection of solvents.

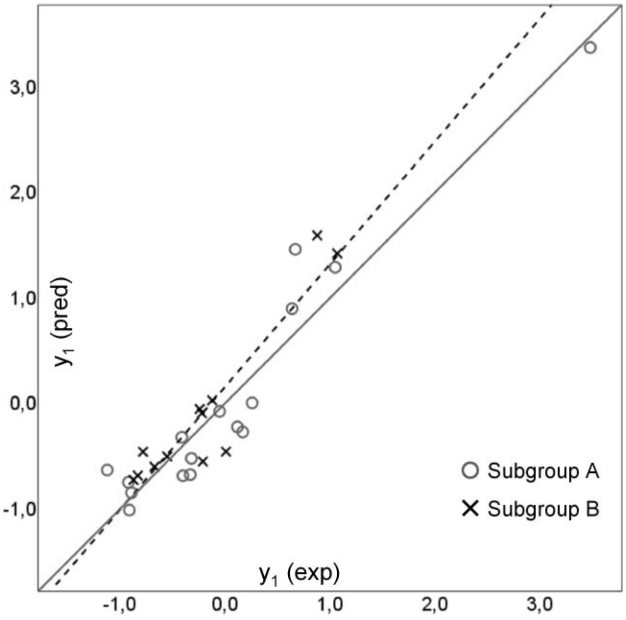


Fig. 2 Experimental *versus* predicted reactivity values using eqn (2). The dashed line corresponds to the regression line, whereas the continuous line would correspond to a perfect fit.

However, one point needs further clarification. The epoxidation of cyclooctene when TFE is used as a solvent could be considered, from a strict statistical viewpoint, as an outlier. It can be shown that by removing it from the regression analysis, neither the relative importance of parameters in the resulting equation (eqn (3)) nor the *R* regression coefficient changed significantly.

$$y_1 = 0.21\mathrm{Log}P + 1.22E_T^N + 0.77\pi^* - 2.54\beta + 1.89\alpha - 0.56$$
$$N = 15;\ R^2 = 0.808;\ s = 0.42 \quad (3)$$

We can therefore conclude that the linear regression models developed for this system are strong enough to allow reliable predictions of the behaviour of new glycerol-based solvents.

As already mentioned (*vide supra*) epoxidation of alkenes with hydrogen peroxide can be carried out in phenol[18] or in fluorinated alcohols, such as TFE and HFIP, without any catalyst, achieving medium to high conversions.[19] Furthermore,

Table 2 Calibration and prediction subgroups of solvents used for testing the model robustness

Subgroup	Solvents
A	TFE > 3F03F > DCM > 3F13F > *n*-HxOH > *n*-BuOH > EtOH > 404 > 2-PrOH > 444 > *i*-Pr_2O > 101 >DEGDBE > 111 > EGDME > Diox
B	5F05F > 7F07F > 413F > 3i13F > 4t13F > 404t > 114i > 414 > 104t > 3i14 > 114t > 113i

it has been recently demonstrated through a series of elegant experimental and theoretical works,[10] that the origin of this behaviour lies in the enhanced electrophilicity of the hydrogen peroxide oxygen atoms through hydrogen bonding with strong HBD solvents. In our case, the fluorinated glycerol-derived solvents have a HBD ability that is intermediate between those of common alcohols and fluorinated alcohols.

However, our glycerol-derived solvents present the advantage that they can be used at higher temperatures compared to TFE, due to their high boiling point, giving room for improvement in the solvent-catalyzed reactions. Furthermore, due to their much lower vapour pressure, they are, in principle, less harmful and more easily recoverable than TFE, increasing the sustainability of the process.

We therefore conducted the epoxidation of cyclooctene at different temperatures, using two of our fluorinated glycerol-derived solvents (Fig. 3).

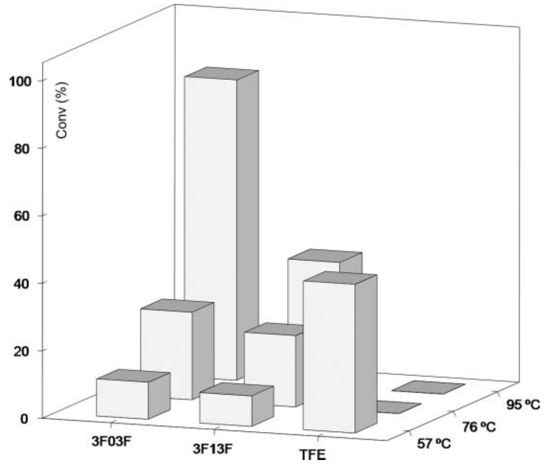


Fig. 3 Epoxidation of cyclooctene with H_2O_2 at elevated temperatures in the absence of selenium derivatives.

An increase in the reaction temperature resulted in a parallel increase of the cyclooctene conversion, although the yield of the epoxide product was a little bit lower due to the faster hydrolysis at higher temperature. It is worth noting that at 95 °C the cyclooctene conversion in 3F03F reached 90% (60% epoxide yield), largely outperforming TFE, and opening the door to new, greener applications of these solvents in the solvent-catalyzed epoxidation reactions with hydrogen peroxide.

Experimental

The epoxidation of alkenes was carried out at 25 °C, using the following conditions: 1 mol% of selenide compound **1**, bis[3,5-bis(trifluoro-methyl)diphenyl] diselenide,[20] was dissolved in 2 mL of solvent. Next, 4 mmol of hydrogen peroxide (50%) was added. After the solution became colourless, 0.4 mmol of veratrole was added (internal standard) followed by 2 mmol of cyclooctene. Reactions were followed by taking samples at regular times. Those samples were dissolved in ethyl acetate, and some manganese dioxide was added to quench the excess of hydrogen peroxide in the sample. Samples were dried over sodium sulfate and analyzed by GC.

Glycerol derivatives were synthesized by using alcohols to open the epoxide ring of commercially available glycidyl ethers, which can be obtained from glycerol.[21] These reactions were performed using benign procedures.[5]

Stability of solvents

In no case were by-products coming from solvent oxidation in the reaction conditions found. Furthermore, neither peroxide compounds nor by-products from decomposition were observed when solvents were put under 50 bar O_2 (8%) at 100 °C for 4 hours. These results indicate the remarkable stability of the solvents employed under oxidation conditions, even in the case of secondary alcohols.

Assessment of toxicity of used compounds

The toxicities of certain glycerol based solvents like 101, 202 or 404 are very low ($LD_{50} > 3000$ mg kg^{-1}, oral in mice),[22] compared to, for instance, butanol ($LD_{50} = 2680$ mg kg^{-1}). Unfortunately, these data are not available for all of the described solvents. For our glycerol based fluorinated solvents it is reasonable to look at the toxicity values of structurally related compounds. Trifluoroethanol has an $LD_{50} = 366$ mg kg^{-1}, oral in mice,[23] and for 2,2,2-trifluoroethyl ethyl ether this value is even higher ($LD_{50} = 5100$ mg kg^{-1}, intraperitoneal in rats).[24] Moreover all compounds have a low volatility, compared to conventional solvents, which makes them safer for operation.

The toxicity of the selenium catalyst is not known, but a previous report has shown that substituted aromatic diselenides—the catalyst precursor—have values for $LD_{50} \approx 500$ mg kg^{-1} (intraperitoneal in mice).[25] This is already much lower compared to the inorganic form of Se, namely SeO_2 which has a LD_{50} of 3.6 mg kg^{-1} (intraperitoneal in rats). This, combined with the fact that the selenium catalyst can easily be separated from the products *via e.g.* column chromatography or distillation, makes this a safe catalyst for operation.

Conclusions

A new group of renewable solvents has been successfully tested in the selenium-catalyzed epoxidation of cyclooctene with hydrogen peroxide as oxidant. Results were in some cases comparable to using standard organic solvents and even better in other cases. Moreover, a quantitative relationship between solvent polarity properties and the rate of epoxidation has been established, leading to the conclusion that the best solvents for this transformation should have high hydrogen bond donor ability, but a low hydrogen bond acceptor (Lewis basicity) ability. The robustness of this regression model has been tested and it can be successfully used to predict the behaviour of new glycerol-derived solvents in this epoxidation reaction on the basis of their physical properties.

The use of these solvents in uncatalyzed epoxidation reactions has also been tested. Their relatively high boiling points allow reaching almost complete cyclooctene conversions at moderate reaction temperatures, opening the door to new, greener applications of these solvents.

New experimental studies are currently underway to extend the applicability of these catalytic systems to other substrates and oxidation reactions, as well as to test the possibility of catalyst recovery and the corresponding results will be reported in due course.

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