Kinetic Studies of Olefin Epoxidation with Hydrogen Peroxide in 1,1,1,3,3,3-Hexafluoro-2-propanol Reveal a Crucial Catalytic Role for Solvent Clusters

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Abstract: The epoxidation of cyclooctene and 1-octene with hydrogen peroxide was studied kinetically in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol)/1,4-dioxane mixtures. In the case of cyclooctene, no additional catalyst was applied, whereas the epoxidation of 1-octene was run in the presence of phenylarsonic acid as catalyst. For both reaction types, two kinetic regimes can be distinguished: at low HFIP concentration ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \leqslant 0.15$), both the catalyzed and the uncatalyzed reaction show first order dependence on the HFIP concentration. This result is interpreted by the HFIP "charge template" for the uncatalyzed epoxidation (as postulated by Shaik and Neumann) and by the formation of an arsonic acid mono-HFIP ester for the catalyzed reaction. At high HFIP concentration ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \geqslant 0.5$), both reaction types are up to *ca.* 5 orders of magnitude faster and show *ca.* 12th order dependence on the HFIP concentration. We propose that the dramatic accelerations observed at high HFIP concentrations are brought about by HFIP clusters. Based on literature data (Fioroni, Roccatano, Hong, Suhm), it is concluded that the epoxidation reactions studied here take place in a HFIP coordination sphere comprising *ca.* 12 HFIP molecules, and that this coordination sphere effects the enormous increases in epoxidation rates. This mechanistic model bears resemblance to enzymatic reactions taking place in and being catalyzed by a protein matrix.

Keywords: arsonic acids; epoxidation; fluorinated alcohols; hydrogen peroxide; kinetics; solvent clusters

Introduction

The catalytic oxidation of olefins to epoxides is an extremely important transformation, both from academic and industrial points of view. Much effort in this field has been devoted to the efficient use of hydrogen peroxide as the terminal oxidant: H_2O_2 is a mild and cheap reagent, with water as the only side-product.[1] Recently, fluorinated alcohols such as 2,2,2-trifluoroethanol (TFE) and in particular 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) have attracted considerable attention as solvents for epoxidations with hydrogen peroxide: In these solvents, electron-rich olefins such as cyclooctene (**1**) can be epoxidized even *without* additional catalysts [Scheme 1, Equation (1)].[2–4] Under these conditions, even "difficult" olefins, such as terminal ones, react with H_2O_2, albeit at relatively low rates/yields [Scheme 1, Equation (2)]. Furthermore, the catalytic power of known epoxidation catalysts such as methyltrioxorhenium (MTO), organoseleninic acids or arsane oxides is potentiated in TFE or HFIP.[5–7] We have recently reported that arsonic acids in HFIP represent even more efficient catalyst systems for the epoxidation of such "difficult" terminal olefins, e.g., 1-octene (**3**). In the presence of 1 mol % of phenylarsonic acid (**5**), quantitative conversion to the epoxide **4** is achieved within *ca.* 4 h, whereas <10% conversion occurs in the absence of the arsonic acid catalyst [Scheme 1, Equations (2) and (3)].[8] In solvents such as 1,4-dioxane, no significant conversion of the olefin takes place even in the presence of the arsonic acid catalyst.[8]

In view of the remarkably beneficial effect on H_2O_2 epoxidations, the question arises as to what the mechanistic role of the fluorinated alcohols actually is. Based on theoretical studies, Neumann, Shaik et al. concluded that the fluoro alcohol provides a charge template, complementary to the H_2O_2-alkene moiety, and thereby brings about a specific stabilization of the transition state of olefin epoxidation.[9,10] The structure of the transition state aggregate proposed by Neumann and Shaik, consisting of olefin (ethylene), H_2O_2 and HFIP, is shown in Figure 1. This model considers only the effects of the fluoro alcohol solvent and does not take into account the role of an arsonic acid catalyst. To shed further light on the function of both the fluoro alcohol solvent and the arsenic acid catalyst, we undertook a thorough kinetic investigation of the influence of the solvent composition on the rate of epoxidation, both in

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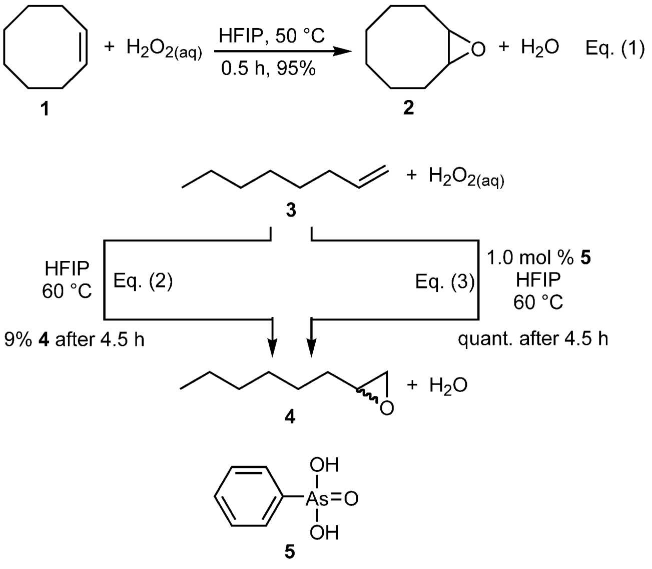


Scheme 1. Epoxidation of cyclooctene (**1**) and 1-octene (**3**).

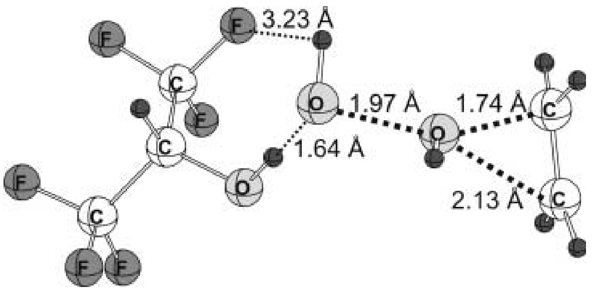


Figure 1. Transition state of the H_2O_2 epoxidation of ethylene; charge template by HFIP, as proposed by Neumann and Shaik.[9]

the presence and in the absence of an arsonic acid catalyst. As it turned out, dramatic accelerations were observed in both cases *only* at *high* HFIP concentrations, indicative of *solvent clusters* playing an important role as catalytically competent entities under “high HFIP conditions”.

Results and Discussion

A total of 41 epoxidation reactions were run, using both the rather unreactive 1-octene (**3**) and the highly reactive internal olefin cyclooctene (**1**) as substrates. Aqueous hydrogen peroxide served as the oxidant, either in the presence or in the absence of phenylarsonic acid (**5**) as catalyst. The initial concentration of substrate, the catalyst loading and the temperature (50 °C) were kept constant for all reactions. Mixtures of HFIP and 1,4-dioxane were employed as solvents. Dioxane was chosen as the co-solvent since it is miscible with all other components, and especially HFIP, in all ratios. This procedure enabled us to examine the two types of reactions [1-octene (**3**)/phenylarsonic acid (**5**); cyclooctene (**1**)/no arsonic acid catalyst] over the entire concentration range from 0% HFIP up to 100% HFIP as solvent. All reactions were carried out with a large excess of hydrogen peroxide, rendering all epoxidations pseudo-zero order in oxidizing agent. The reactions were monitored by GC, as shown in Figures 2c and 3c for four arbitrarily chosen HFIP concentrations. First, the epoxidation of the two olefins **1** (with no additional catalyst) and **3** [in the presence of phenylarsonic acid (**5**)] had been determined to be first order in substrate and oxidant (and arsonic acid catalyst for olefin **3**). Consequently, the individual rate constants were extracted from the slope of the resulting straight line in a logarithmic plot of the substrate concentration *vs.* time (Figures 2b and 3b).

Indeed, the rates of olefin conversion varied tremendously. Yields of epoxide **2** from 0.27% after 54 h up to 95% after 30 min [for the reaction of cyclooctene (**1**), in the absence of arsonic acid], and of epoxide **4** from 1.5% after 39 h up to 80% after 5 min [for the epoxidation of 1-octene (**3**) in the presence of 1 mol % of phenylarsonic acid (**5**)] were observed. These numbers already demonstrate the extraordinary accelerating effect of HFIP on both types of reactions. Even more interestingly, the influence of HFIP is not “linear” over the entire concentration range: For both reaction types, we observed two kinetic regimes, i.e., fairly slow rate increases for the epoxidations in the region of low HFIP concentration (up to $n_{\mathrm{HFIP}}/n_{\mathrm{total}} \leqslant 0.15$) and a progressive, non-linear acceleration for high HFIP concentrations ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \geqslant 0.5$).

All measured rate constants k were scaled by the rate constants k_0 of the two background reactions involving no HFIP, affording the relative rate constants k_{rel}. The increase in rate ($k_{\mathrm{rel}} - k_0$) for the two types of reactions is depicted in a double logarithmic plot $\log_{10}(k_{\mathrm{rel}} - k_0)$ over the HFIP concentration $\log_{10}$ ([HFIP]) (Figures 2a and 3a). Please note that the range of reactivities (rate constants) extends over *ca.* 5 orders of magnitude for both reactions!

The slope of the double logarithmic plot $\log_{10}(k_{\mathrm{rel}} - k_0) = \mathit{const.} + a \cdot \log_{10}[\mathrm{HFIP}]$ (Figures 2a and 3a) yields the kinetic order a of HFIP for both reaction types.[12] Our analysis revealed two distinct kinetic regimes for each reaction. In both cases, we found the reactions to be clearly first order ($a_{\mathrm{I}} = 0.92 \pm 0.26$ and 0.95 ± 0.10) in HFIP at low HFIP concentrations ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \leqslant 0.15$). This suggests that only *one* HFIP molecule is involved in the rate-determining step (or a preceding equilibrium). In the case of the arsonic acid-free epoxidation of cyclooctene [**1**, Scheme 1, Eq. (1)], this result is in accordance with the postulated charge template of HFIP, complementary to the H_2O_2-alkene moiety, which involves *one* HFIP molecule and leads to a substantial stabilization of the epoxidation transition state (Figure 1).[9] However,

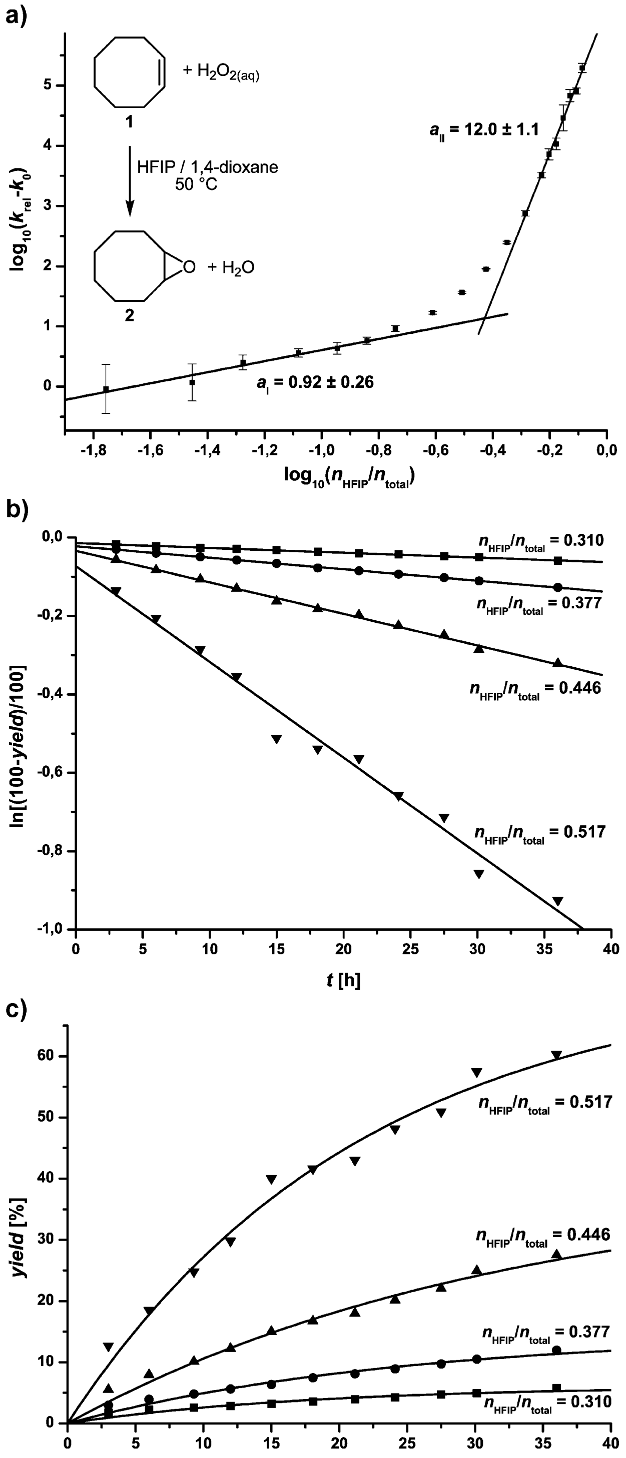


Figure 2. Epoxidation of cyclooctene (**1**) in HFIP/dioxane mixtures, no arsonic acid catalyst. **a)** Double logarithmic plot of the increase of rate constants of cyclooctene (**1**) epoxidation as a function of HFIP concentration; **b)** first-order analysis of cyclooctene (**1**) conversion as a function of time; **c)** formation of cyclooctene epoxide (**2**) as a function of time for four arbitrarily chosen HFIP concentrations.

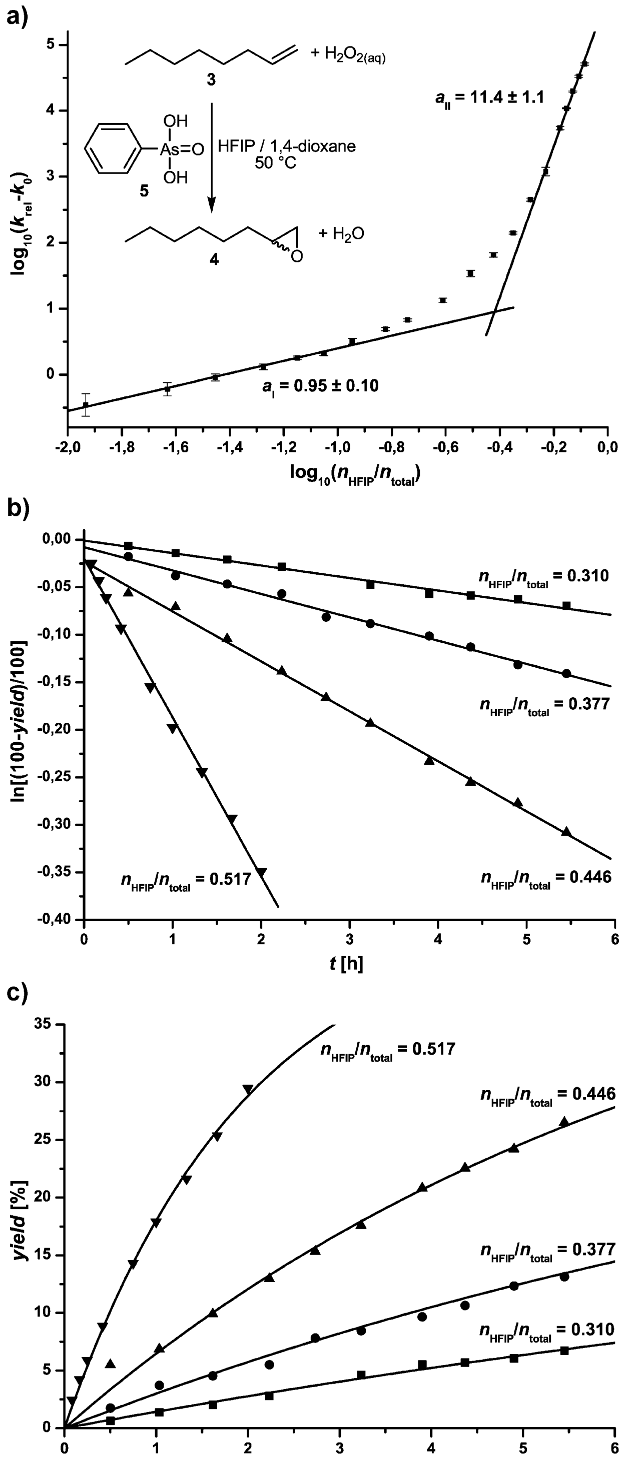
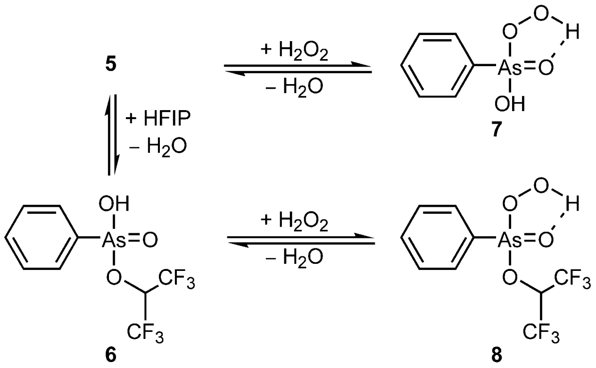


Figure 3. Epoxidation of 1-octene (**3**) in HFIP/dioxane mixtures, phenylarsonic acid (**5**) as catalyst. **a)** Double logarithmic plot of the increase of rate constants of 1-octene (**3**) epoxidation as a function of HFIP concentration; **b)** first-order analysis of 1-octene (**3**) conversion as a function of time; **c)** formation of 1-octene epoxide (**4**) as a function of time for four arbitrarily chosen HFIP concentrations.



Scheme 2. Intermediates postulated in the arsonic acid-catalyzed epoxidation of olefins with H_2O_2 in HFIP.

in the "high-HFIP" range of the cyclooctene (**1**) epoxidation ($n_{HFIP}/n_{total} \geqslant 0.5$, Figure 2a), the kinetic order a_{II} in HFIP was found to be $a_{II} = 12.0 \pm 1.1$! Consequently, in this regime, the influence of HFIP on the rate-determining step is of higher complexity, and definitely requires a number of HFIP molecules larger than one.

In the case of the arsonic acid-catalyzed epoxidation of the electron-poor terminal olefin 1-octene (**3**), we interpret the first-order dependence on HFIP in the "low HFIP" range ($n_{HFIP}/n_{total} \leqslant 0.15$) by the reversible formation of the mono-HFIP ester **6** of phenylarsonic acid (**5**, Scheme 2). Spontaneous ester formation is well documented for arsonic acids[13], and we were able to detect the mono-HFIP ester **6** under the reaction conditions by ESI-mass spectrometry.[14] The perarsonic acids **7** and **8** shown in Scheme 2 have not been isolated yet. However, quantum mechanical studies of ours revealed that they are likely intermediates in the arsonic acid-catalyzed epoxidation of olefins with hydrogen peroxide.[16] It appears reasonable to assume that the formation of the ester **6** raises the Lewis acidity of the arsenic centre of the catalyst and thereby activates it towards the nucleophilic attack by H_2O_2. By the same token, the reactivity of a perarsonic acid HFIP ester (such as **8**, Scheme 2) towards oxygen transfer to an olefin should be increased compared to the parent perarsonic acid **7** (Scheme 2). The exact nature of the HFIP ester activation is currently being investigated by means of computational chemistry.

In the region of high HFIP concentration ($n_{HFIP}/n_{total} \geqslant 0.5$) and in the presence of phenylarsonic acid (**5**), we observed the rate of the epoxidation of 1-octene (**3**) to be non-linearly dependent on the HFIP concentration. Under these conditions, the kinetic order of HFIP was determined to be $a_{II} = 11.4 \pm 1.1$ (Figure 3a). In other words, in the region of high HFIP concentration ($n_{HFIP}/n_{total} \geqslant 0.5$), we find the rates of both the epoxidation of cyclooctene (**1**; no arsonic acid catalyst) and of 1-octene [**3**; in the presence of phenylarsonic acid (**5**)] to rise with about the *twelfth* power of the HFIP concentration ($a_{II} = 12.0 \pm 1.1$ and 11.4 ± 1.1; Figures 2a and 3a). This enormous rate acceleration is not understandable by the previously mentioned one-to-one interactions of HFIP with the oxidant (hydrogen peroxide) or the catalyst (arsonic acid). "Simple" bulk properties of HFIP such as the dielectric constant can be excluded as well. Upon addition of 2-propanol to HFIP, the ε of the mixture first rises from 18 (pure HFIP) to *ca.* 23 at *ca.* 35 vol % 2-propanol, and then decreases to $\varepsilon = 20$ for pure 2-propanol.[15] With dioxane as the co-solvent, a steady decrease from $\varepsilon = 18$ to $\varepsilon = 2$ is observed.[15] Nevertheless, the effects of these two co-solvents on the reaction rates are very similar.[15] The sum of the data indicate that an entirely new species is formed at high HFIP concentration that is responsible for the remarkable catalytic effect. It has previously been reported that fluorinated alcohols, such as HFIP, have an inherent tendency to form clusters due to their strong hydrogen bonding abilities.[17,18] Fioroni, Roccatano et al. studied the aggregation behaviour of HFIP by molecular dynamics simulations.[17] Besides an expected[19] tendency of the HFIP molecule to form stable dimers, they observed a distinct second coordination sphere *comprising approximately 13 HFIP molecules.* This result is quite remarkably coherent with the kinetic order found by us for the "high HFIP" kinetic regimes (11.4 ± 1.1; 12.0 ± 1.1). We therefore conclude that the epoxidation reactions studied here take place in such a type of HFIP coordination sphere, and that this coordination sphere brings about the dramatic rate acceleration observed under "high HFIP conditions". This situation resembles the rate acceleration effected by the protein matrix in enzymatic catalysis: In many instances, co-factors are catalytically active themselves, but it is the "embedding" into the apo enzyme that brings about the tremendous turnover rates typical for enzymes. Further work in this laboratory aims at the elucidation of the structure and dynamics of the "HFIP matrix".

Conclusion

The epoxidation of cyclooctene (**1**) and 1-octene (**3**) with hydrogen peroxide was studied kinetically in HFIP/dioxane mixtures, both in the presence and in the absence of an arsonic acid catalyst. For both reactions, two kinetic regimes can clearly be distinguished: At low HFIP concentration ($n_{HFIP}/n_{total} \leqslant 0.15$), both the catalyzed and the uncatalyzed reaction show first order dependence on the HFIP concentration. This result is interpreted by the HFIP "charge template" for the uncatalyzed epoxidation (Shaik, Neumann, ref.[9]) and by the formation of a catalytically competent arsonic acid mono-HFIP ester for the catalyzed reaction. At high HFIP concentration ($n_{HFIP}/n_{total} \geqslant 0.5$), both reaction types are accelerated dramatically (by *ca.* 5 orders of magnitude) and show *ca.* 12th order dependence on

HFIP concentration. Therefore, we propose that the dramatic accelerations observed at high HFIP concentrations are brought about by HFIP clusters. Based on literature data concerning the aggregation behaviour of HFIP (Fioroni, Roccatano, Goto, Suhm et al., refs.[17–19]), it is concluded that the epoxidation reactions studied here take place in an HFIP coordination sphere comprising *ca.* 12 HFIP molecules, and that this coordination sphere effects the enormous increases in epoxidation rates. This mechanistic model bears resemblance to enzymatic reactions taking place in and being catalyzed by the protein matrix.

Experimental Section

General Procedure for the Kinetic Analysis of the Epoxidation of Cyclooctene (1) in HFIP/Dioxane Mixtures

In a GC-vial, 7.5 µL of an equimolar mixture of cyclooctene (**1**, 3.4 mg, 31 µmol) and bromobenzene (4.9 mg, 31 µmol; internal standard) were dissolved in mixtures of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 1,4-dioxane with a total volume of 1.20 mL. The solution was stirred magnetically at 50 °C. The reaction was started by the injection of 50 µL of aqueous H_2O_2 (42% w/w, 0.71 mmol).

General Procedure for the Kinetic Analysis of the Phenylarsonic acid (5)-Catalyzed Epoxidation of 1-Octene (3) at Low HFIP Concentrations

First, a stock solution of phenylarsonic acid (**5**, 201 mg, 0.993 mmol) in 1,4-dioxane (25.0 mL) and an equimolar mixture of 1-octene and bromobenzene were prepared. In a GC-vial, 8.6 µL of the mixture of 1-octene (**3**, 3.5 mg, 31 µmol) and bromobenzene (4.9 mg, 31 µmol) were dissolved in 800 µL of the stock solution of phenylarsonic acid (**5**, 6.43 mg, 31.8 µmol). Furthermore, mixtures of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 1,4-dioxane with a combined volume of 400 µL were added. The mixture was stirred magnetically at 50 °C. The reaction was started by injecting 50 µL of aqueous H_2O_2 (42% w/w, 0.71 mmol).

General Procedure for the Kinetic Analysis of the Phenylarsonic acid (5)-Catalyzed Epoxidation of 1-Octene (3) at High HFIP Concentrations

A stock solution of phenylarsonic acid (**5**, 128 mg, 0.636 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 10.0 mL) was prepared. In a GC-vial, 8.6 µL of an equimolar mixture of 1-octene (**3**, 3.5 mg, 31 µmol) and bromobenzene (4.9 mg, 31 µmol) were dissolved in 500 µL of the stock solution of phenylarsonic acid (**5**, 6.43 mg, 31.8 µmol). Furthermore, mixtures of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 1,4-dioxane with a combined volume of 700 µL were added. The mixture was stirred magnetically at 50 °C. The reaction was started by injecting 50 µL of aqueous H_2O_2 (42% w/w, 0.71 mmol).

Reaction Monitoring

Samples (50 µL) were taken periodically, diluted with dichloromethane (200 µL), quenched over MnO_2 and analyzed by GC (HP-5MS, 30 m). The response factors of the epoxides compared to the internal standard (bromobenzene) were determined (by calibration) to be 1.330 for cyclooctene oxide (**2**), and 1.255 for 1-octene oxide (**4**).

Calculation of Rate Constants

All reactions were run in triplicate and analyzed as first-order kinetics in substrate by plotting $\ln[(100 - yield(\text{epoxide}))/100]$ *vs.* time t as shown in Figures 2b and 3b. Rate constants k_{rel} were determined as the relative slopes of the resulting linear fits. The rate constants for the background reactions k_0 originated from the corresponding plots of the HFIP-free reactions. All error bars shown resulted from the standard error of the slope fitting parameter for a 95% confidence interval.

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References and Notes

[1] R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977–1986.

[2] K. Neimann, R. Neumann, *Org. Lett.* **2000**, *2*, 2861–2863.

[3] M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *Synlett* **2001**, 248–250.

[4] K. S. Ravikumar, J.-P. Bégué, D. Bonnet-Delpon, *Tetrahedron Lett.* **1998**, *39*, 3141–3144.

[5] G.-J. ten Brink, B. C. M. Fernandes, M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *J. Chem. Soc. Perkin Trans. 1* **2001**, 224–228.

[6] M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *J. Chem. Soc. Perkin Trans. 1* **2000**, 377–380.

[7] M. C. A. van Vliet, I. W. C. E. Arends, R. A. Sheldon, *Tetrahedron Lett.* **1999**, *40*, 5239–5242.

[8] A. Berkessel, M. R. M. Andreae, *Tetrahedron Lett.* **2001**, *42*, 2293–2295.

[9] S. P. de Visser, J. Kaneti, R. Neumann, S. Shaik, *J. Org. Chem.* **2003**, *68*, 2903–2912.

[10] An analogous complementary charge template to the transition state was recently suggested as the mechanistic basis for electrophilic aromatic chlorinations and the haloperoxidation of chloride by H_2O_2 which takes place effectively in fluorinated alcohols: ref.[11]

[11] R. Ben-Daniel, S. P. de Visser, S. Shaik, R. Neumann, *J. Am. Chem. Soc.* **2003**, *125*, 12116–12117.

[12] The exact expression of the rate constants k_{rel} as a function of the HFIP concentration [HFIP] is

$$k_{\mathrm{rel}} = k_0 + \sum_i k_i \cdot [\mathrm{HFIP}]^{a_i} \text{ (exp. 1)}$$

with the individual contributions from different kinetic regimes *i*. Therefore, the more precise graphical analysis of higher order contributions would require a preceding subtraction of the lower order contributions, e.g., plotting of $\log_{10}(k_{\mathrm{rel}} - k_0 - k_{\mathrm{I}}[\mathrm{HFIP}])$ *vs.* $\log_{10}([\mathrm{HFIP}])$ for $a_i > 1$. This was done as well for both types of reactions but yielded the exactly the same results. Therefore, the corresponding expression 1 for both cases is clearly dominated by the first-order terms ($a_{\mathrm{I}} = 0.92 \pm 0.26$ and 0.95 ± 0.10) in the region of low HFIP concentration ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \leqslant 0.15$), and by the twelfth order terms ($a_{\mathrm{II}} = 12.0 \pm 1.1$ and 11.4 ± 1.1) at higher HFIP concentration ($n_{\mathrm{HFIP}}/n_{\mathrm{total}} \geqslant 0.5$). No additional distinct kinetic regimes could be detected.

[13] S. E. Jacobson, F. Mares, P. M. Zambri, *J. Am. Chem. Soc.* **1979**, *101*, 6946–6950.

[14] *m/z* $\mathrm{PhAsO_3H^-}$ (**5**) = 201; *m/z* $\mathrm{PhAsO_2\text{-}O\text{-}CH(CF_3)_2^-}$ (**6**) = 351; see ref.[15]

[15] B. Megido-Almaraz; dissertation, University of Cologne, **2003**.

[16] A. Berkessel, J. A. Adrio, to be published elsewhere.

[17] M. Fioroni, K. Burger, A. E. Mark, D. Roccatano, *J. Phys. Chem. B* **2001**, *105*, 10967–10975.

[18] D.-P. Hong, M. Hoshino, R. Kuboi, Y. Goto, *J. Am. Chem. Soc.* **1999**, *121*, 8427–8433.

[19] H. Schaal, T. Häber, M. A. Suhm, *J. Phys. Chem. A* **2000**, *104*, 265–274.