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N-containing Fluorous Ligands for Aerobic Oxidations in Fluorous Biphasic Systems

Gianna Ragagnin

aus

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Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Professor Dr. Paul Knochel betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

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Gianna Ragagnin

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1. Gutachter: Prof. Dr. Paul Knochel
2. Gutachter: Prof. Dr. Heinz Langhals

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Papers related to this thesis work:

- Contribution to *e*-eros (Electronic Encyclopedia of Reagents for Organic Synthesis [Potassium tris(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17,-triacontafluoro-(8,10-heptadecanedionato) rhutenate], **2001**.

- G. Ragagnin, B.Betzemeier, S.Quici, P.Knochel "Copper catalyzed aerobic oxidation of alcohols using fluorous biphasic catalysis" *Tetrahedron* **2002,** *58*, 3985-3991.

- Ragagnin Gianna and Paul Knochel "New Fluorous benzimidazolic Ligands for aerobic Ru-Catalyzed Epoxidations in Fluorous Biphase System", *manuscript in preparation*.

"The difference between a drunk and an alcoholic
is that a drunk doesn't have to attend all those meetings."

Arthur Lewis

Therefore:

working with alcohols results in strange side-effects.

Alle mie nonne.

Table of Contents

Experimental section

Introduction

1 Overview

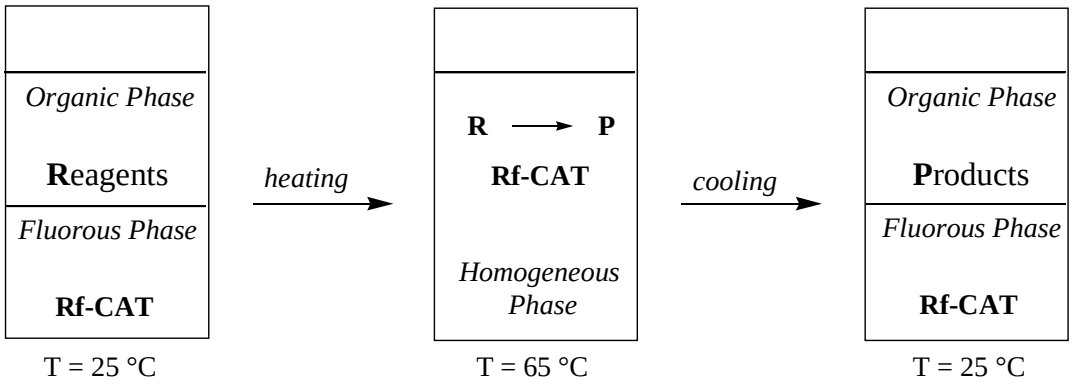
The development of environmentally friendly technologies is nowadays a critical point for the chemical industry. Some of the aspects related to this problem are concerning the use of non-toxic, safe solvents and reagents as well as the possibility of catalyst recycling. In this respect, there is an increasing demand for new methods which can meet these needs. While the use of solid supports with liquid and/or gaseous reactants, as applied in heterogeneous catalysis, allows a facile separation of reactants from the catalyst, the poor miscibility of the phases often results in lower yields or longer reaction rates. On the other hand, homogeneous catalysis is characterized by higher catalyst performances, but separation of the product may be costly and tedious, especially if an expensive catalyst has to be separated and recovered.
In this respect, the use of liquid-liquid biphase processes[1], where the first phase dissolves selectively the catalytically active species, and the second one contains educts and products, could be a convenient solution for the commercial application of many useful chemical reactions. Many catalysts can be made selectively soluble in one of the two phases simply by attaching an appropriate tag to the ligand molecule.
An example is represented by the use of aqueous/organic biphasic systems, which have found several interesting applications[2]. The aqueous phase allows the dissolution of many inorganic metal salts in a cheap and environmentally safe solvent, while the organic solvent leads to the efficient separation of the products. The main limitations are concerning reactions which must be carried out with exclusion of moisture, or where water-sensitive compounds must be employed.

The *F*luorous *B*iphase *S*ystem (shortly: FBS) technique, which has been introduced by *Vogt* and *Kaim*[3], and brought to the scientific community by the seminal work of *Horváth* and *Rábai*[4], represents an important solution to these problems. In this system, one of the two phases consists in a *fluorous* medium, where the term "fluorous" indicates a compound which contains a highly fluorinated organic ponytail of at least six carbons length, based upon sp^3-hybridized carbon[5].

[1] B. Cornils, *Angew. Chem* **1995**, *107*, 1709.
[2] I.E. Markó, P.R. Giles, M. Tsukazaki, S.M. Brown, C.J. Urch *Science* **1996**, *274*, 2044.
[3] M. Vogt, PhD Thesis, Rheinisch-Westfälische Technische Hochschule Aachen, **1991.**
[4] I.T. Horváth, J. Rábai *Science* **1994**, *266*, 72.
[5] J.A. Gladysz, D.P. Curran *Tetrahedron* **2002**, *58*, 3823.

Due to the strenght of the C-F bond (116 kcal/mol for CH_3-F, compared to other Me-X bonds: CH_3-H = 99 kcal/mol, CH_3-O = 86 kcal/mol)[6], perfluorocarbons display very low chemical reactivity, low polarity, low toxicity and, therefore, low flammability, which allow them to be considered suitable candidates for being safe and environmentally friendly solvents.
In addition, they undergo very weak intramolecular Van der Waals interactions, due to the low polarizability of the electrons of the C-F bond and low availability of the lone-pair of the fluorine atom[7]. This implies that their miscibility with the most common organic solvents is very little, and, in contrast, an exceptional solubility of small molecules like gases is expected. In fact, molecular oxygen displays much higher solubility in perfluorocarbons in comparison to other organic solvents. For example, the solubility of O_2 expressed in molar fraction is $4.56 \cdot 10^{-3}$ in perfluoromethylcyclohexane, while is only $8.16 \cdot 10^{-5}$ in the case of THF[8].

A further property of strategic importance in catalysis concerns the relationship between temperature and the miscibility of perfluorocarbons with non-fluorous organic solvents. A fluorous solvent like perfluorooctane or perfluorooctyl bromide becomes completely miscible with toluene at ca. 60-70 °C, leading to a homogeneous phase which completely separates when cooled back to room temperature (Scheme 1).



Rf-CAT : Fluorous catalyst

Scheme 1. *Fluorous Biphase System (FBS)*

[6] T. Hiyama *Organofluorine Compounds: chemistry and applications*, Springer-Verlag Berlin Heidelberg, **2000.**
[7] (a) J.G. Riess *New J. Chem.* **1995** *19*, 893; (b) V.W. Sadtler, M.P Krafft, J.G.Riess *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1976.
[8] (a)E.P. Wesseler, R. Iltis, L.C. Clarc *J. Fluorine Chem.* **1977**, *9*, 137; (b) C.M. Sharts, H.R. Reese *J. Fluorine Chem.* **1978**, *11*, 637; (c) L.P. Barthel-Rosa, J.A. Gladysz *Coord. Chem. Rev.* **1999**, *190-192*, 587.

Thus, a fluorous biphase system can combine the advantages of homogeneous catalysis with biphase product separation by running the reaction at higher temperatures and separating the products at lower temperatures. The fluorous phase can then be separated and recycled for one or more reaction runs.
The availability of fluorous solvents within a wide range of boiling points, ranging from 56 °C for perfluorohexane to 220 °C for perfluorotripentylamine, makes possible the performing of reactions under various conditions.

1.1 The Fluorous Catalyst

A suitable catalyst for reactions in FBS must be selectively soluble in fluorous solvents. This is achieved by attaching fluorous ponytails to the active site of the catalyst in appropriate number and size. The term "appropriate" is quantitatively described by the concept of *specific fluorophilicity*, which has been introduced da *Rábai* and coworkers[9] and by the Hildebrand parameters of the fluorous solute and the two solvents. This last value can be obtained through theoretical calculations and predicts the partition of a fluorous molecule in fluorous biphase system.

Roughly, the solubility behaviour depends on the following parameters:

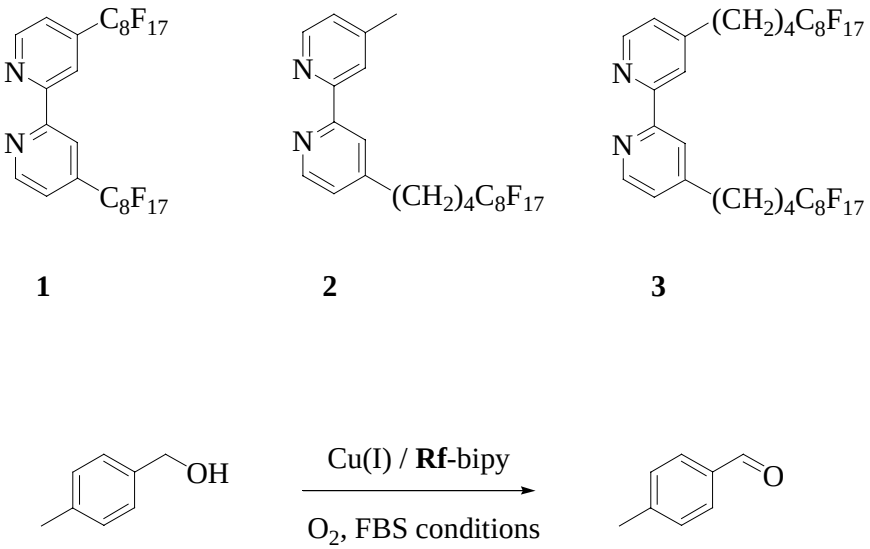
- *fluorine content*: at least 60 wt.% of F is required, but a too high F-content increases the synthetic costs. In addition, the increase of molecular weight diminishes the overall solubility;
- *length of the fluorous ponytails*: longer chains increase fluorophilicity but decrease absolute solubility;
- *number of fluorous ponytails*: a higher ponytail number results in better partition coefficients than the lengthening of a single one;
- *structure and distribution of the ponytails*: influence the direction of the intermolecular attractive interactions.

The design of a fluorous catalyst must also take in account the strong electron-withdrawing properties of the fluorine atom. This is particulary important because the presence of one or

[9] L.E. Kiss, I. Kövesdi, J. Rábai *J. Fluorine Chem.* **2001**, *108*, 95.

more fluorous chains can dramatically change the electronic properties and consequently the reactivity of fluorous reagents and catalysts. Therefore, the insertion of insulating methylene groups of appropriate length is often required. It has been demonstrated[10] that three methylene units are usually sufficient for electronic insulation of the active site.

An example of these effects is given by the comparison of the reactivities of the following fluorous bipyridines Cu(I) complexes, in the aerobic FBS *Markó* oxidation[11] of 4-methyl-benzylalcohol[12] (Scheme 2):



1 **2** **3**

Scheme 2. *Oxidation of 4-methyl-benzylalcohol with fluorous bipyridine catalysts*

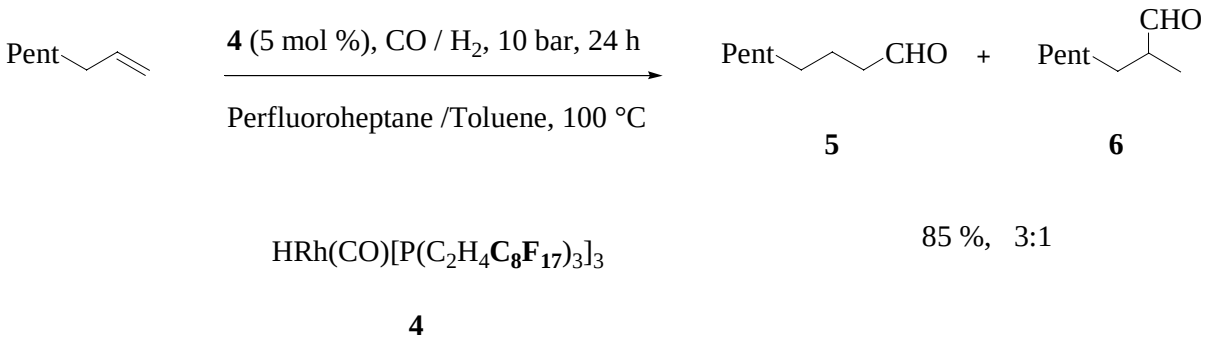
While the bipyridine 1 without spacer led to a yield of aldehyde of only 41 % in the first run, complete conversion and recovered yields of 91-93 % were observed with the ligands 2 and 3. Due to the higher fluorophilicity, catalyst recyclability up to 5 runs was possible in the case of ligand **3**, while the bipyridine **2** dropped its activity significantly already at the third cycle.

[10] I.T. Horváth, G. Kiss, P.A. Stevens, J.E. Bond, R.A. Cook, E.J. Mozelesky, J. Rábai *J. Am. Chem. Soc.* **1998**, *120*, 3133.

[11] (a) I.E. Markó, P.R. Giles, M. Tsukazaki, I. Chellé-Regnaut, A. Gautier, S.M. Brown, C.J. Urch *J.Org.Chem* **1999**, *64*, 2433; (b) I.E. Markó, P.R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C.J. Urch, S.M. Brown *J.Am..Chem Soc.* **1997**, *119*, 12661; (c) I.E. Markó, M. Tsukazaki, P.R. Giles, S.M. Brown, C.J. Urch *Angew. Chem* **1997**, *109*, 2208.

[12] (a) B. Betzemeier, , PhD Thesis, LMU Universität München, **2001**; (b) S. Quici, M. Cavazzini, S. Ceragioli, F. Montanari, G. Pozzi, *Tetrahedron Lett.* **1999**, *40*, 3647.

A broad variety of fluorous catalysts for reactions in FBS has been developed. The first work of Horváth and Rábai[4] concerned the hydroformylation of olefines by using a rhodium complex with a fluorous phosphine (Scheme 3):

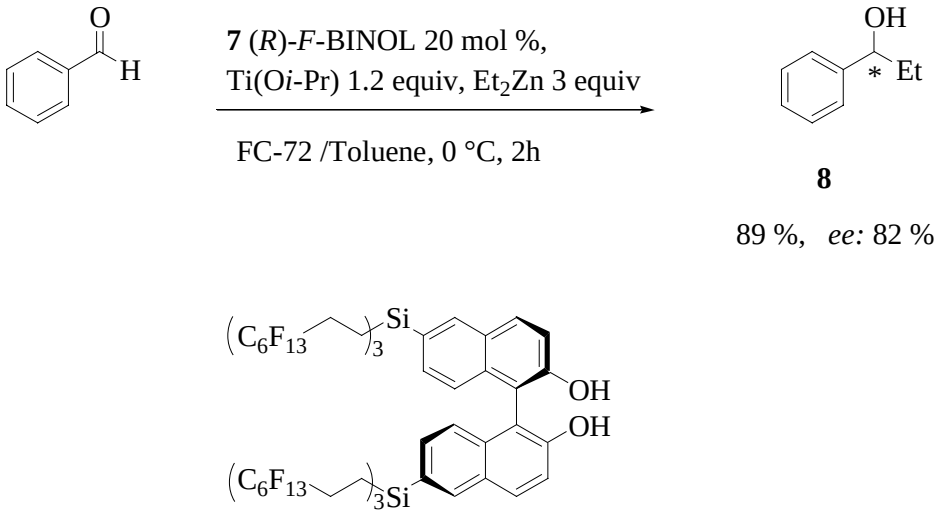


Scheme 3. *Hydroformylation in FBS*

Next to the fluorous version of classical transition metal complexes, like the Wilkinson catalyst[13] or the Vaska complex[14], a number of fluorous porphyrins[15], *salen*-complexes[16], phosphites[17], diketonates[3,18], cyclopentadienes[19], 1,4,7-triazacyclononanes[20] and many other[21] have been prepared over the last decade for cross-coupling reactions, alkylations, hydrogenations and a variety of other catalyzed reactions.

The FBS catalysis has also been used in asymmetric reactions[22]. For example, *Curran* and coworkers[23] developed a fluorous chiral Ti-BINOL derivative for the catalytical alkylation of aromatic aldehydes with diethylzinc. The catalyst can be recycled up to 5 runs without loss of activity and enantioselectivity (Scheme 4):

[13] J.J.J. Juliette, I.T. Horváth, J.A. Gladysz *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1610.
[14] M.A. Guillevic, A. Arif, I.T. Horváth, J.A. Gladysz *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1612.
[15](a)G. Pozzi, S. Banfi, A. Manfredi, F. Montanari, S. Quici *Tetrahedron* **1996**, *52*, 11879; (b) G. Pozzi, F. Montanari, S. Quici *J. Chem. Soc. Chem. Comm.* **1998**, 877.
[16](a) M. Cavazzini, S. Quici, G. Pozzi *Tetrahedron* **2002**, *58*, 3943; (b) M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi *Eur. J. Org. Chem.* **2001**, *24*, 4639.
[17] T. Mathivet, E. Monflier, Y. Castanet, A. Mortreux, J-L. Couturier *Tetrahedron* **2002**, *58*, 3877
[18](a)I. Klement, H. Lütjens, P. Knochel *Angew. Chem.* **1997**, *109*, 1605; (b) B. Betzemeier, F. Lhermitte, P. Knochel *Tetrahedron Lett.* **1998**, *39*, 6667.
[19](a) J. Kvicala, T. Briza, O. Paleta, K. Auerová, J. Cermák *Tetrahedron* **2002**, *58*, 3847; (b) R.P. Hughes, H.A. Trujillo *Organometallics* **1996**, *15*, 286.
[20] J-M. Vincent, A. Rabion, V.K. Yachandra, R.H. Fish *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2346
[21]For some reviews on fluorous catalysis: (a) B. Cornils *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2057; I.T. Horváth *Acc. Chem. Res.* **1998**, *31*, 641; (c) E. de Wolf, G. van Koten, B-J. Deelman *Chem. Soc. Rev.* **1999**, *28*, 37; B. Betzemeier, P. Knochel *Top. Curr. Chem*. **1999**, *206*, 61; (e) R.H. Fish *Chem. Eur. J*. **1999**, *5*, 1677; (f) E.G. Hope, A.M. Stuart *J. Fluorine Chem.* **1999**, *100*, 75; (g) C. Rocaboy, J.A. Gladysz *Actualite Chimique* **2000**, *9*, 47.
[22] For a review: Q-H. Fan, Y-M. Li, A.S.C. Chan *Chem. Rev*. **2002**, *102*, 3385.
[23] Y. Nakamura, S. Takeuchi, Y. Ogho, D.P. Curran *Tetrahedron* **2000**, *41*, 57.



Scheme 4. *Asymmetric alkylation of aromatic aldehydes with a chiral fluorous BINOL complex in FBS*

1.2 Special fluorous techniques

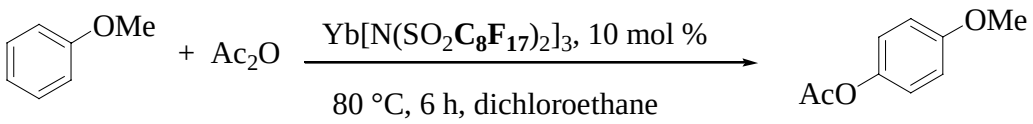
Recently, several modifications of the classical FBS protocol were provided.

The first interesting approach is the FBS catalysis without fluorous medium[24]. A fluorous catalyst, which at room temperature is insoluble in the organic phase containing the starting material, forms a homogeneous phase when the system is heated over the melting point temperature, allowing a homogeneous catalysis. At the end of the reaction, the mixture is cooled and the catalysts separates again from the product solution, ready to be recycled without further purification. *Mikami* and coworkers[25] applied the method to aromatic acylation by using a fluorous lanthanide complex as Lewis acid (Scheme 5).

In this case the absence of spacer at the fluorous ponytails plays a key role for the enhancement of the Lewis acidity, demonstrating how the tuning of the electron-withdrawing effect of the fluorous tag can be a powerful tool for increasing the activity of a fluorous catalyst.

[24] M. Wende, R. Meier, J.A. Gladysz *J. Am. Chem. Soc.* **2001**, *123*, 11490

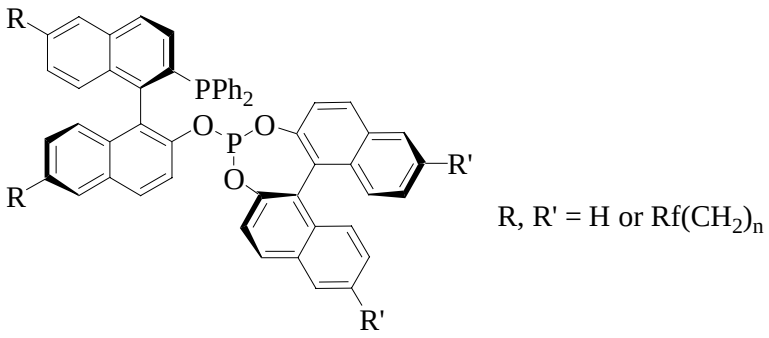
[25] K. Mikami, Y. Mikami, H. Matsuzawa, Y. Matsumoto, J. Nishikido, F. Yamamoto, H. Nakajima *Tetrahedron* **2002**, *58*, 4015



9 78 %

Scheme 5. *Fluorous catalysis without fluorous solvent*

The high affinity of fluorocarbons for gases led to the possibility of replacing quite expensive fluorous solvents with supercritical carbon dioxide (*sc*CO_2), where fluorous ligands can dissolve very well. As an example, *Ojima* and coworkers[26] have synthesized a fluorous BINAPHOS ligand for the rhodium-catalyzed asymmetric hydroformylation of alkenes (Scheme 6).



10

Scheme 6. *Fluorous BINAPHOS*

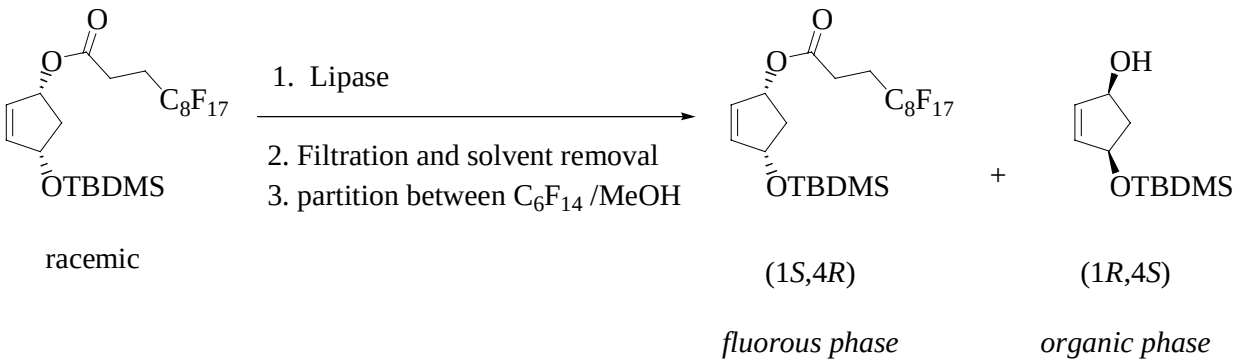
A last example of the several possibilities offered by the fluorous technologies is given by the labeling of organic molecules with fluorous tags. This method has been widely used by *Curran* as well as other groups[27] in the synthesis of natural products and complex molecules. If the products of a reaction are labeled with a suitable fluorous ponytail, the further delabeling in selective conditions led to a mixture of fluorous and non-fluorous compounds, which can be separated by simple extraction with fluorocarbons.

Theil[27c] and *O'Hagan*[27d] have applied this method for the enzyme-catalyzed separation of enantiomers, by esterification of a racemic carboxylic acid or alcohol with a perfluorinated

[26] D. Bonafoux, Z. Hua, B. Wang, I. Ojima *J. Fluorine Chem* **2001**, *112*, 101.

[27] (a) D.P. Curran *Green Chem*. **2001**, G3 –G7; (b) D.P. Curran *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 1174; (c) B. Hungerhoff, H. Sonnenschein, F. Theil *J. Org. Chem*. **2002**, *67*, 1781; (d) P. Beier, D. O'Hagan *Chem. Comm.* **2002**, *16*, 1680

alcohol or acid, respectively. Incubation with a commercially available lipase in appropriate conditions led to selective detagging of only one of the two enantiomers. Extraction with a fluorous/organic biphase system allows to recover the unreacted enantiomer in the perfluorocarbon phase in good yield, while the untagged derivate can still be found in the organic layer (Scheme 7).



Scheme 7. *Lipase-catalyzed enantiomer-selective detagging*

1.3 Oxidations in FBS

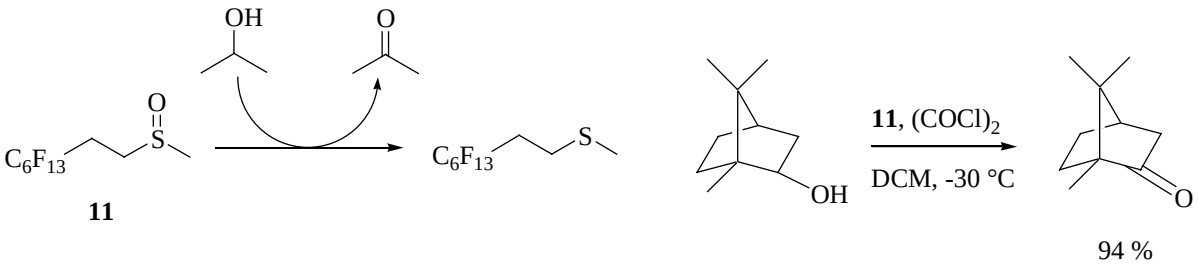
Oxidation reactions are of substantial interest for industrial and synthetic applications. Therefore, there is a constant search for methods which allow high yields and selectivities, satisfactory reaction rates and low costs. The use of cheap and environmentally benign oxidants like hydrogen peroxide and molecular oxygen is also an important priority. In this case, water, the main byproduct, is easily and safely removed.

The fluorous medium is especially suitable for oxidation reactions as the solubility of dioxygen is very high in fluorous solvent[28] and perfluoroalkanes are extremely resistant to oxidation. In addition, most oxidations lead to highly polar products, resulting in a easier separation. Consequently, a wide range of oxidation procedures has been adapted to the FBS synthesis, including oxidations of alcohols[29], aldehydes[30] and sulfides[18a], alkene epoxidations[16, 31], Swern[32] and Baeyer-Villiger oxidations[12a,33].

[28] Perfluoroalkanes have also been used as blood substitutes: (a) E.P. Wesseler, R. Iltis, L.C. Clark *J. Fluorine Chem.* **1977**, *9*, 137; J.G. Riess, M. Le Blanc *Pure Appl. Chem*. **1982**, *54*, 2383; (c) K. Yamanouchi, C. Heldebrant *Chemtech* **1992**, 354.

[29] (a) G. Ragagnin, B. Betzemeier, S. Quici, P. Knochel *Tetrahedron* **2002**, *58*, 3985; (b) B. Betzemeier, M.Cavazzini, S. Quici, P. Knochel *Tetrahedron Lett.* **2000**, *41*, 4343.

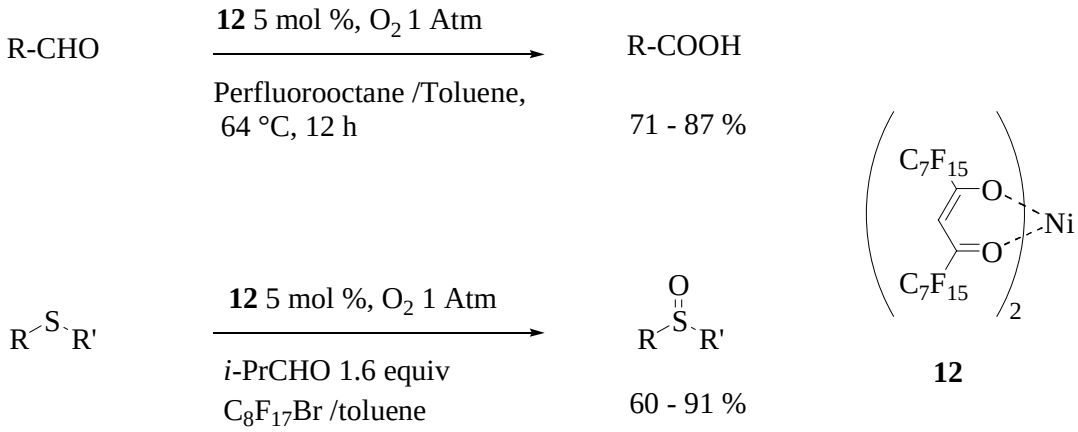
Toxic or stench reactants like selenides[28,34] or the byproduct of the Swern reaction dimethyl sulfide have been tagged with fluorous ponytails, leading to harmless but still effective oxidants (Scheme 8):



Scheme 8. *Fluorous Swern reaction*[32]

The fluorous reagent can be recovered for reuse through a simple continuous fluorous extraction and reoxidation with hydrogen peroxide.

In our group, aerobic catalyzed[18a,b] and non-catalyzed[35] protocols in fluorous media have been performed with good results (Scheme 9 and 10). In the case of the ligand **12**, recycling of the fluorous catalyst was possible up to 12 runs without any loss of activity.



Scheme 9. *Ni-catalyzed aerobic oxidation of aldehydes and sulfides in FBS*

[30] G-J ten Brink, J.M. Vis, I.W.C.E. Arends, R.A. Sheldon *Tetrahedron* **2002**, *58*, 3977

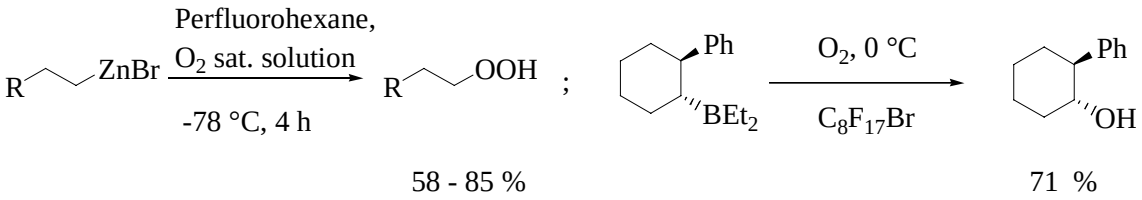
[31] J. Legros, B. Crousse, D. Bonnet-Delpon, J-P. Bégué *Tetrahedron* **2002**, *58*, 3993.

[32] D. Crich, S. Neelamkavil *J. Am. Chem. Soc.* **2001**, *123*, 7449.

[33] X. Hao, O. Yamazaki, A. Yoshida, J. Nishikido *Tetrahedron Lett.* **2003**, *44*, 4977.

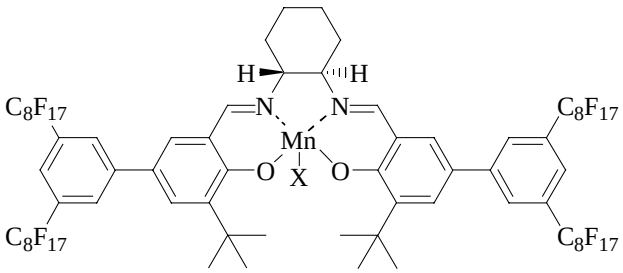
[34] B. Betzemeier, F. Lhermitte, P. Knochel *Synlett* **1999**, 489

[35] (a)I. Klement, P. Knochel *Synlett* **1995**, 1113; (b) I. Klement, P. Knochel *Synlett* **1996**, 1004.



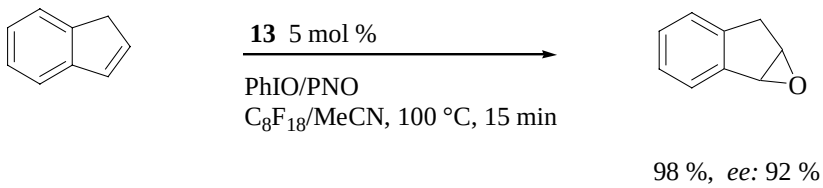
Scheme 10. *Non-catalyzed aerobic oxidations of organozinc bromides to hydroperoxides and of organoboranes to alcohols in fluorous media*

Enantioselective oxidation reactions can be performed successfully with FBS catalysis as well. This is of special importance in the synthesis of chiral compounds, eg. natural products. The group of *Pozzi* has first synthesized and extensively studied a large variety of fluorous chiral salen Co- and Mn- complexes[16], which allow the preparation of chiral epoxides from the corresponding olefines (Scheme 11). It has been shown that results in fluorous phase are better than those obtained with other immobilized chiral catalytic systems and recycling of the fluorous catalyst was possible up to four runs.



X = $C_7F_{15}COO^-$

13



98 %, *ee:* 92 %

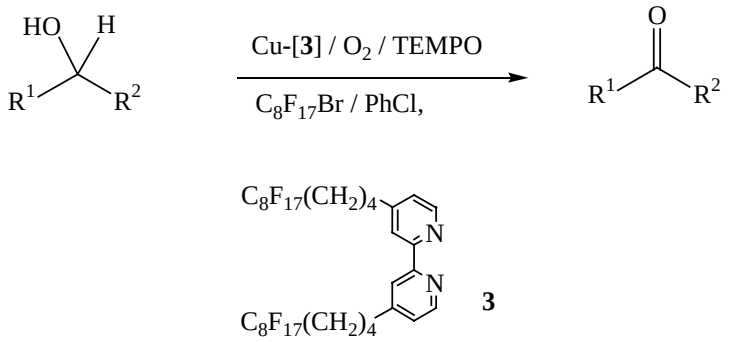
Scheme 11. *An example of a "second generation" of fluorous chiral (salen)Mn(III) complex and application to olefine epoxidation*

The search for new protocols in the field of oxidation is still in progress, especially regarding stereo- and enantioselective reactions. Since few very effective and selective catalytic methods are known, as well as the exact mechanisms involved in such reactions, further studies in this direction are continuously increasing. Therefore, the synthesis of new and more efficient fluorous oxidation catalysts is still an open challenge.

2 Objectives

After the development of the successful fluorous bipyridine **3** for the aerobic oxidation of alcohols, the further step was the improvement of the reaction conditions, in order to achieve better yields and reaction rates for the oxidation of secondary aliphatic alcohols.
The following approaches were investigated:

- influence of Cu salts, acidic conditions and products
- influence of TEMPO and *F*-TEMPO
- stereoselectivity of the catalyzed reaction



Scheme 12. *Aerobic oxidation of alcohols in FBS using F-bipyridine as ligand*

The constant need for oxidations employing environmentally-friendly oxidants as molecular oxygen, as well as the possibility of catalyst recycling, led in the second part of this work to the search for suitable ligands for the oxidation reactions in FBS:

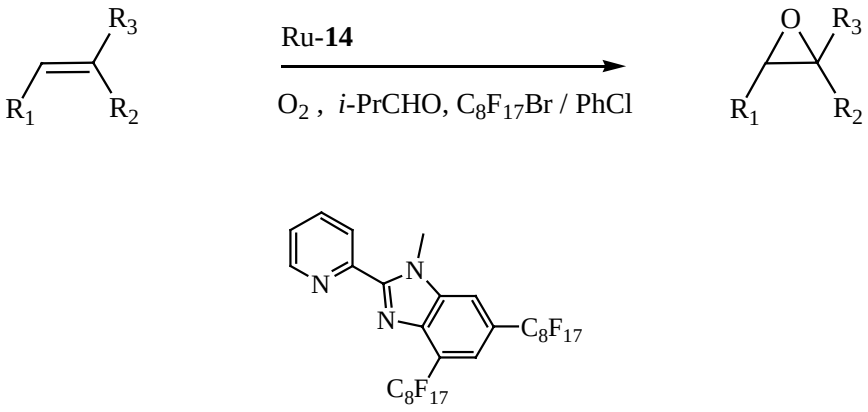
- aerobic C-C and C-N oxidative coupling
- aerobic epoxidation of alkenes

In order to reach these objectives, the steps to follow were:

- design and synthesis of novel fluorous ligands,
- achievement of selective solubility of them and their metal complexes in fluorous solvents vs. organic solvents,
- use of these complexes in FBS catalysis.

The work was mainly focused on the preparation of fluorous *N*-containing ligands, with particular attention to pyridyl- and imidazolyl derivatives.

The novel ligand pyridine-benzoimidazole (Rf_2Bimpy) **14** has been successfully employed in the Ru-catalyzed aerobic epoxidation of alkenes. Conditions and range of applicability have been investigated as well.



14

Scheme 13. *Ru-catalyzed epoxidation in FBS*

Results and Discussion

1 Cu-Catalyzed Alcohol Oxidation

The oxidation of alcohols to aldehydes and ketones represents one of the most important transformations in organic chemistry, both at a laboratory and industrial scale[36]. Therefore, there is a constant need for methods which are, at the same time, effective and employing safe and cheap oxidants. Most of the classical protocols involve the use of toxic chemicals, like several chromium(VI) salts or hypochlorites and other halogenated agents, which must be often used in stoichiometric ratio and generate large amounts of pollutants (e.g. chromium waste) as byproducts[36]. In addition, the effective removal of such reagents from the products is often costly and difficult. Another point concerns the selectivity of the oxidation reaction in the case of primary alcohols. In some cases, undesired byproducts like carboxylic acids can be obtained.

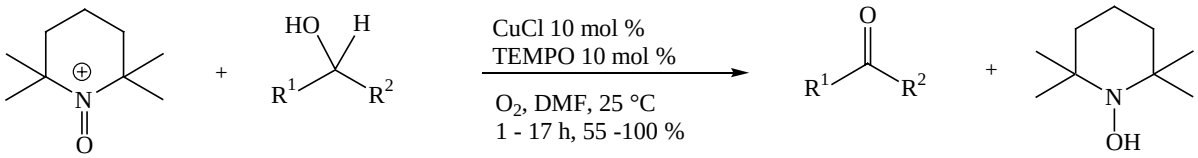
In this respect, the use of catalytic protocols with cheap, environmentally friendly oxidants like oxygen, air or hydrogen peroxide represents a highly valuable field of investigation. Molecular oxygen is particulary interesting for its availability and the absolute safety of its byproduct water, but is rather inert in the absence of an opportune radical initiator. Free radicals and transition metals should be good candidates for dioxygen activation, due to their ability of single-electron exchange. Several metals, like palladium, iron, ruthenium or cobalt, have been employed in oxidation catalysis, as salts or complexes. Among them, copper is one of the cheapest and most effective for alcohol oxidation.

A very attractive protocol for the selective conversion of primary and secondary alcohols to aldehydes and ketones has been introduced by *Semmelhack*[37] and coworkers. It involves 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) and CuCl as catalysts for dioxygen activation (Scheme 14):

[36] (a) R.A. Sheldon, J.K. Kochi, in: *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press: New York, **1981**; (b) S.V. Ley, J. Norman, W.P. Griffith, P. Marsden *Synthesis* **1994**, 639; (c) G. Procter, in: *Comprehensive Organic Synthesis*, S.V. Ley, Ed. Pergamon: Oxford **1991**, Vol. 7, p. 305.

[36] For an exaustive review: M. Hudlický, *Oxidations in Organic Chemistry* ACS Monograph 186, **1990**.

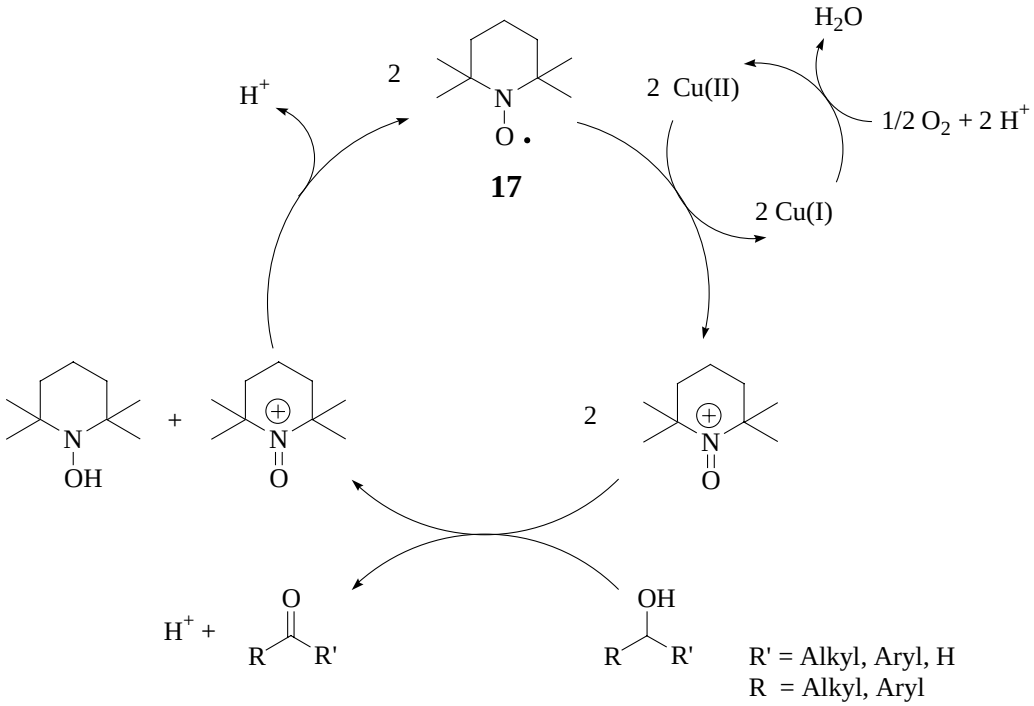
[37] (a) M.F. Semmelhack, C.S. Chou, D.A. Cortes *J. Am. Chem. Soc.* **1983**, *105*, 4492; (b) M.F. Semmelhack, C.R. Schmid, D.A. Cortes, C.S. Chou *J. Am. Chem. Soc.* **1984**, *106*, 3374; (c) M.F. Semmelhack, C.R. Schmid, D.A. Cortes *Tetrahedron Lett.* **1986**, *27*, 1119.



15 **16**

Scheme 14. *Semmelhack aerobic alcohol oxidation*

The oxoammonium salt **15** plays a key rule to avoid overoxidation of primary alcohols to carboxylic acids. A general postulated mechanism is the following (Scheme 15):



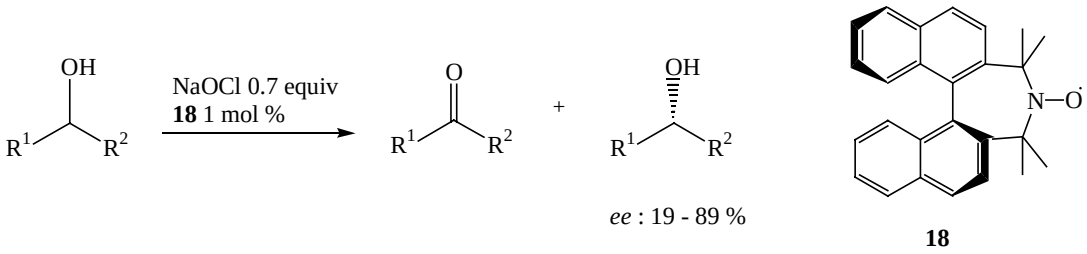
Scheme 15. *Postulated mechanism for the TEMPO mediated Cu-catalyzed alcohol oxidation*

The nitroxyl radical **17** is the intermediate in the catalytic cycle and the absence of α-hydrogens is fundamental for its stability[38]. Rigorous anhydrous conditions are not necessary. In Semmelhack's experiment, it was found that also the counterion at the Cu(I) salt seems to influence the conversion rate. Primary, allylic and benzylic alcohols react faster than

[38] (a) E.G Rozantsev, V.D. Sholle *Synthesis* **1971**, 190; (b) E.G Rozantsev, V.D. Sholle *Synthesis* **1971**, 401.

secondary ones; several studies suggested the influence of both electronic and steric factors, depending on the reaction conditions[39].

Despite the large amount of studies on the TEMPO-mediated oxidation of alcohols, many mechanistic aspects are still not clear. However, the direct interaction of the oxoammonium salt with the alcohol molecule has been proved in several works[40,40]. An interesting application employs a chiral nitroxyl radical which led to the enantioselective oxidation of racemic alcohol mixtures with discrete *ee* of the recovered enantiomer[41] (Scheme 16):



Scheme 16. *Enantioselective alcohol oxidation with chiral nitroxyl radical*

1.1 Alcohol Oxidation in FBS

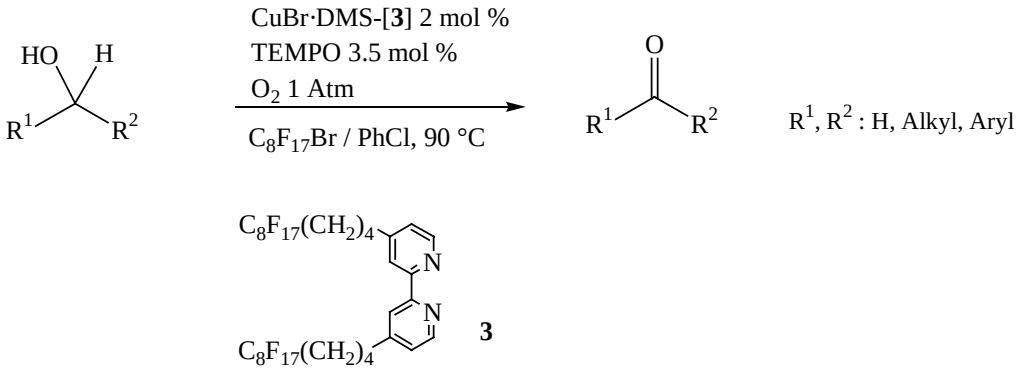
The Semmelhack and Markó protocols for alcohol oxidation have found a suitable application in FBS catalysis[12,29(b)]. The reaction in fluorous medium presents both the advantages of catalyst recycling and improved solubility of oxygen, leading to a higher reactivity. *Knochel et al*[42] developed a successful FBS procedure where the Cu(I) salt has been immobilized in the fluorous phase by complexation with the fluorous bipyridine **3**, while TEMPO and alcohol were dissolve in the organic phase. In comparison to the Semmelhack protocol, the amount of catalyst and TEMPO could be reduced to 2.0 and 3.5 mol %, respectively (Scheme 17).

[39] For an excellent review: A.E.J. de Nooy, A.C. Besemer, H. van Bekkum *Synthesis* **1996**, 1153.

[40] (a) A.E.J. de Nooy, A.C. Besemer, H. van Bekkum *Tetrahedron* **1995**, *51*, 8023; (b) S. Kishioka, T. Ohsaka, T. Tokuda *Chem. Lett.* **1998**, 343

[41] S.D. Rychnovsky, T.L. McLernon, H. Rajapaske *J. Org. Chem.* **1996**, *61*, 1194

[42] ref. 29(b)

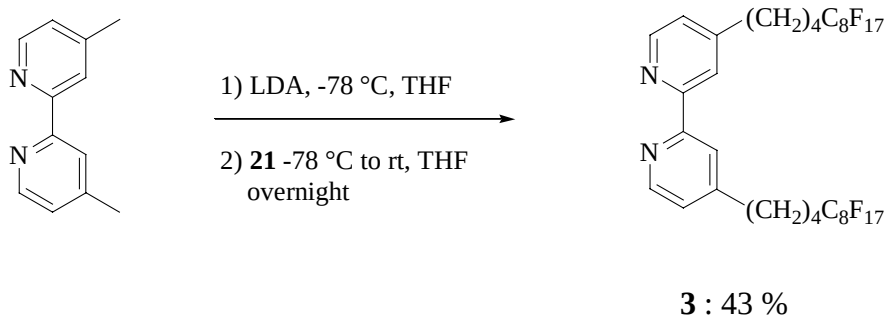


Scheme 17. *Aerobic oxidation of alcohols in FBS*

The complex is formed *in situ* by 1:1 reaction of the fluorous ligand with $CuBr{\cdot}Me_2S$ in perfluorooctyl bromide, leading to a homogeneous brown solution which is readily oxidized by air to form a soluble green complex, due to the formation of Cu(II) species. By using the freshly prepared brown catalyst or the already oxidized green one, no difference in reactivity was observed in the case of 4-nitro-benzylalcohol oxidation. This is in agreement with the proposed mechanism, which involves the simultaneous presence of Cu(I) and Cu(II) in the reaction mixture. Attemps to characterize the exact geometry and composition of the complex by X-ray analysis failed, because of the difficulty to obtain suitable single crystals out of the fluorous phase.

1.1.1. Ligand synthesis

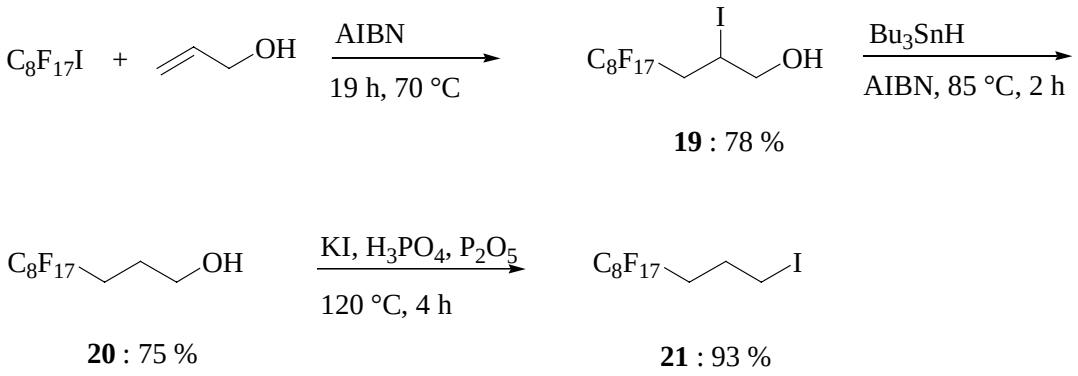
The fluorous bipyridine has been first synthesized in the *Pozzi* group[12(b)] (Scheme 18) by deprotonation of 4,4'-dimethylpyridine with LDA, followed by alkylation with $C_8F_{17}(CH_2)_3I$ (**21**):



3 : 43 %

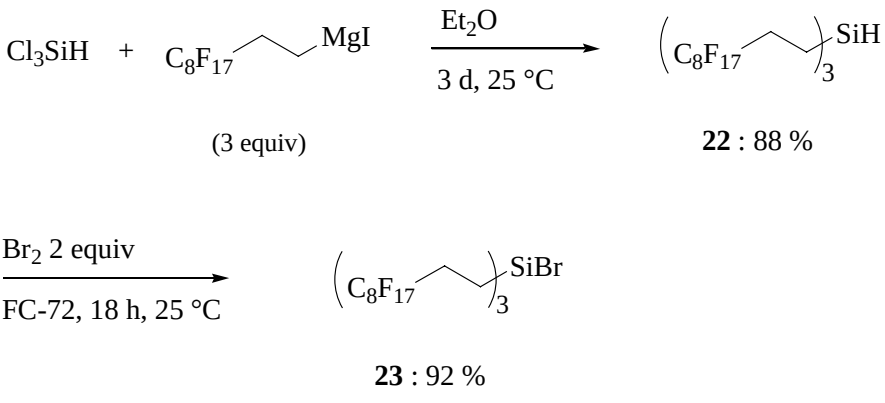
Scheme 18. *Synthesis of the bipyridile catalyst*

The synthesis of the ligand involves the preparation of the versatile fluorous ponytail **21** in three steps. The convenient four carbon spacer in the fluorous tag is necessary not only for an effective insulation of the catalytic center from the electron-withdrawing effect of the perfluorinated chain, but also to avoid the easy elimination of HI when synthesizing fluorous molecules by alkylation with $C_8F_{17}(CH_2)_2I$. A first version of the synthesis has been reported by *Fish et al*[43], which has been further modified by *Pozzi* and our group[44] (Scheme 19):



Scheme 19. *Synthesis of the C_3 ponytail building block*

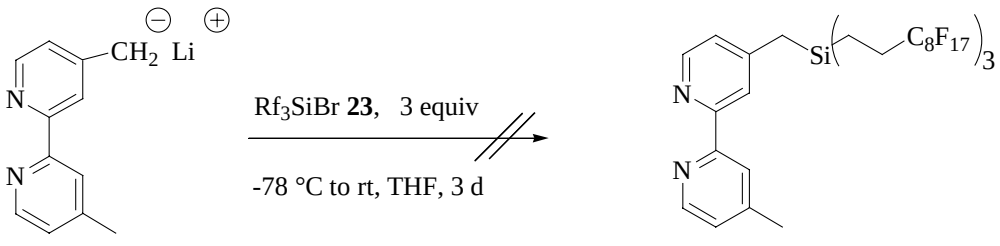
In order to increase the ligand fluorophilicity, the introduction of three fluorous ponytails has been considered. Following the synthetic strategy of *Takeuchi* and *Curran*[45], a convenient method could be the use of the fluorous silyl building block, which can be further used in alkylation reactions (Scheme 20):



Scheme 20. *Synthesis of the fluorous silyl building block*

[43] J-M. Vincent, A. Rabion, V.K. Yachandra, R.H. Fish *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2346.
[44] G. Pozzi, G. Ragagnin, *unpublished results.*
[45] ref. 23

Formation of the monolithium salts of 4,4'-dimethylpyridine with LDA, followed by quenching with **23** did not lead to the desired product **25**, even in presence of a large excess of reagent. This is probably due to the moderate reactivity of the anion **24**, combined with the high steric hindrance of the bromide **23** (Scheme 21).



24 **25**

Scheme 21. *Attempted synthesis of perfluoro-silyl tagged bipyridine*

1.2 Reactivity improvement for aliphatic secondary alcohols

In the previous work[29b] from our group it has been shown that the FBS system TEMPO/Cu efficiently catalyses the oxidation of benzylic, allylic and primary aliphatic alcohols to the corresponding ketones and aldehydes. Furthermore, in the oxidation of 4-nitro-benzylalcohol the catalyst has been recycled up to 8 times without significant loss of activity, with reaction rates of 1 – 1.5 h and almost quantitative yields for each run. As expected, in the case of secondary aliphatic alcohols yields and reaction rates decrease dramatically by enhanced steric hindrance at the hydroxyl moiety. For example, while 2-decanol was completely oxidized within 8 h in the above reported conditions, 4-tridecanol showed a GC conversion of only 31 % after 17 h. In addition, a worse recyclability (only up to 3 - 4 runs for 2-decanol, of the fluorous phase has been observed when a secondary aliphatic alcohol is oxidized, suggesting that substrate or product can inhibit the catalytic activity.

Thus, the main target of further investigations was the search of optimized reaction conditions in order to achieve satisfactory yields and reaction rates for secondary aliphatic alcohols as well. Two alcohols have been chosen as model compounds for this purpouse:

- *4-Nitro-benzylalcohol* as readily oxidizable alcohol. Typical reaction conditions: 1 h reaction time, 98 % recovered yield with 2 mol % catalyst and 3.5 mol % TEMPO.

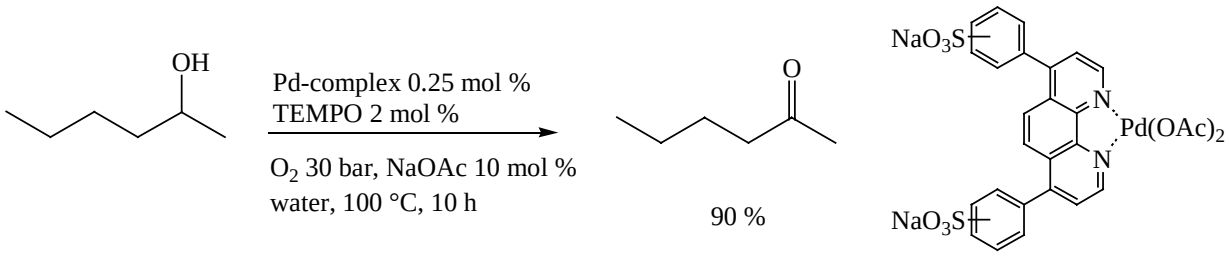
- *2-Decanol* as a secondary aliphatic alcohol with moderate reactivity. Typical reaction conditions: 8 h reaction time, 88 % recovered yield with 2 mol % catalyst and 3.5 mol % TEMPO.

1.2.1 Solvents and temperature

For this reaction, the influence of the solvent couple plays a negligible role on reactivity. However, perfluorooctyl bromide (*PFOB*) is preferred for the better solubilization of the complex in comparison to other fluorous solvents, due to its polarity. Chlorobenzene has already been proved to be the best choice in these reaction conditions, due to the moderate volatility at 90 °C. This temperature represents also the best compromise between reactivity and volatility of reagents and products.

1.2.2 Metal and counterions

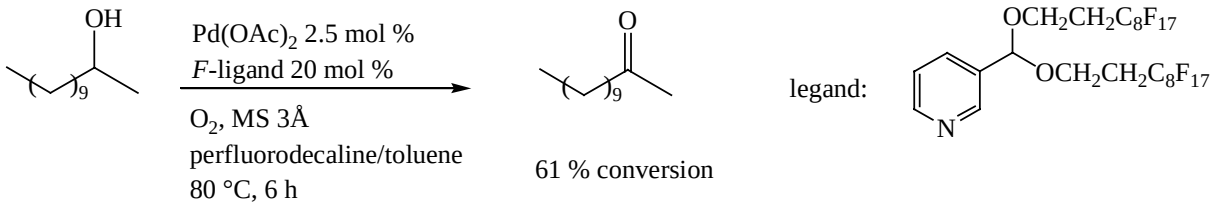
The use of other metals coordinated to the bipyridine 3 has been considered for FBS aerobic alcohol oxidation. Among them, Pd(II) and Co(II) have been chosen for their already proved effectiveness in such a transformation. A modified protocol for the aerobic TEMPO-mediated alcohol oxidation was developed by *Sheldon* and coworkers[46], who performed a Pd(II)-catalyzed reaction in water, using bathophenantroline disulphonate as a ligand (Scheme 22):



Scheme 22. *Pd(II) catalyzed alcohol oxidation in water*

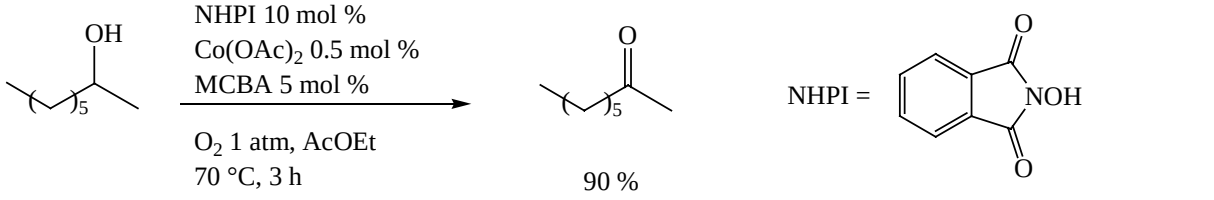
[46] G-J. ten Brink, I.W.C.E. Arends, R.A. Sheldon *Science* **2000**, *287*, 1636

Uemura and coworkers[47] reported the synthesis of several fluorous pyridines for Pd(II)-catalyzed alcohol oxidation in FBS with moderate alcohol conversions observed (Scheme 23):



Scheme 23. *Pd(II) catalyzed alcohol oxidation in FBS*

An effective Co(II)-catalyzed oxidation of aliphatic substrates in presence of *N*-hydroxyphthalimide (NHPI) has been performed in the *Ishii* group[48] (Scheme 24):



Scheme 24. *Co(II) catalyzed alcohol oxidation*

In order to test the catalytic activity of these metals in comparison with the previous *F*-Cu-catalyst, the 1:1 complexes of **3** with $Co(OAc)_2$ and $Pd(OAc)_2$ have been prepared and used in the oxidation of 4-nitro-benzylalcohol. Both complexes have been prepared *in situ* in the same way used for the preparation of the Cu-complex, leading to homogeneous fluorous phases in PFOB. A 2 mol % catalyst was employed to have an easy comparison with the Cu-catalyzed oxidation, while the other conditions are adapted from the literature protocols. No conversion of substrate was observed under the following reaction conditions:

- **Pd(II)**: *2 mol % F-catalyst; 3.5 mol% TEMPO, 2 mmol educt, T = 90 °C; PFOB/PhCl* Formation of Pd-black observed in organic phase after 20 min heating, even in presence of 10 mol % $AcOEt_4N$ as a base. Only traces (5 % conversion) of aldehyde were detected after 1 h reaction time.

[47] T. Nishimura, Y. Maeda, N. Kakiuchi, S. Uemura *J. Chem. Soc. Perkin Trans. 1* **2000**, *24*, 4301

[48] T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi, Y. Ishii *J. Org. Chem.* **2000**, *65*, 6502

- **Co(II)**: *0.2 – 2 mol % F-catalyst; NHPI 10 mol %, MCBA 5 mol %, 2 mmol alcohol, T = 90 °C, PFOB/PhCl or AcOMe.* The cobalt complex was retained in the fluorous phase (UV-vis. analysis), but no catalytic effect was detected. Furthermore, the formation of a homogeneous phase at 90 °C was inhibited by the poor solubility of NHPI in the reaction mixture.

These results clearly show that copper is the metal of choice for the TEMPO-mediated alcohol oxidation.

Semmelhack reported that several cupric salts with noncoordinating counterions were effective catalysts, with the best results given by CuCl, suggesting that the anion could influence the reactivity. We studied the formation of a soluble complex in PFOB of a variety of Cu(I) and Cu(II) salts, and their performances in the oxidation of 4-nitro-benzylalcohol under standard conditions (Table 1).

Table 1. *Influence of counterions on reactivity*

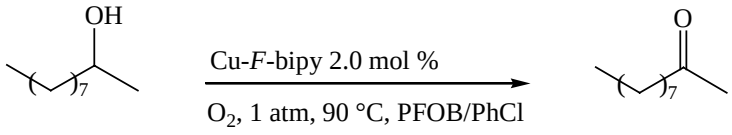
Cu salt	Formation of a soluble complex	Alcohol conversion (%, 1 h)
CuCl	---	---
$CuBr_2$	yes	80
CuI	yes	64
CuCN	---	---
$Cu(OTf)_2$	---	---
$Cu(OPiv)_2$	yes	63

CuCl and CuCN failed in giving soluble complexes with the bipyridine **3** in fluorous phase, while $Cu(OTf)_2$ provided an amorphous gummi precipitate which was not soluble in fluorous solvents. Among the salts forming soluble fluorous complexes, better results were provided by $CuBr_2$, which are comparable with those obtained using CuBr·DMS. Slighty lower reactivity was observed for CuI and $Cu(OPiv)_2$.

1.2.3 The co-catalyst TEMPO

Several pathways for the TEMPO-mediated alcohol oxidation have been proposed, but a detailed explanation is still missing. The determining step should be the formation of an adduct between the oxoammonium salt (Scheme 15) and the alcohol molecule, with abstraction of the α-proton to form the carbonyl product. It has been found by *van Bekkum et al*,[49] that acid or basic conditions can strongly influence the contribution of steric effects, but their results are related to a system TEMPO/hypochlorite/bromide. They showed that in an alkaline environment steric effects become more important, while acidic conditions lead to similar reaction rates for primary and secondary alcohols.
In our system, we found that the addition of one equivalent of a strong acid, like perfluoroheptanoic acid, did not change neither the oxidation rates for both 1-decanol and 2-decanol, nor the difference of reactivity between the two alcohols. Instead, the addition of one equivalent of a noncoordinating base which acts as a proton scavenger, like 2,6-di-*t*-butyl-pyridine or *N*,*N*,*N'*,*N'*-tetramethyl-naphthalene-1,8-diamine, reduces the reaction rates by a factor of 0.5, probably because protons are required in the catalytic cycle for the conversion of oxygen to water.

Effects of the TEMPO amount on oxidation rates have been evaluated. By using 3.5 mol % of co-catalyst, satisfactory results were obtained mainly for benzylic, allylic and primary aliphatic substrates, but the need to improve reaction rates and recyclability of the fluorous phase for aliphatic secondary alcohols led us to study the effect of larger amount of TEMPO for these substrates. For the oxidation of 2-decanol to 2-decanone the following GC conversions and the catalyst recyclability with different amounts of TEMPO (10, 20, 30 and 50 %) have been observed (Table 2):



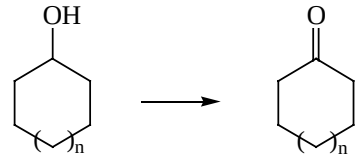
[49] see ref. 40 and references therein.

Table 2. *Relationship between the TEMPO amount, conversion of 2-decanol and catalyst recyclability.*

% mol TEMPO	*Run*	*GC conversion / %*	*time / h*
10	1	100	2
	2	48	2
	3	27	2
20	1	100	2
30	1	100	2
50	1	100	2
	2	100	2
	3	75	2
	4	37	2

Table 2 shows that a 10 mol % of the nitroxyl radical is sufficient to obtain satisfatictory reaction rates in the case of 2-decanol, but effective catalytic activity decreases already from the second run. No improvement of reaction rates was observed when the percentage is increased to 20, 30 or 50 mol %. Only a modest enhancement of effective catalyst recyclability of two runs has been observed with a 50 mol % of TEMPO. It could be due to the higher concentration of available oxidant, in this case almost stoichiometric rather than catalytic. Therefore, recyclability seems not to be strictly dependent on the co-catalyst amount.

By using 10 mol % of cocatalyst in the oxidations of cyclohexanol, cycloheptanol and cyclooctanol, the influence of the steric hindrance of the aliphatic part seems to play a role not only on reactivity but also on catalyst recyclability (Table 3):



n = 1, 2, 3

Conditions: Cu-*F*-bipy 2.0 mol %, TEMPO 10 mol %, O_2 1 atm, 90 °C, PFOB/PhCl

Table 3. *Dependence of conversion and catalyst recyclability on the ring size of cycloalkanoles.*

Alcohol	*Run*	*GC conversion / %*	*time[a] / min*
Cyclohexanol	1	100	30 (30)
	2	96	30 (40)
	3	56	30 (60)
	4	71	60 (2 h)
Cycloheptanol	1	100	30 (30)
	2	82	30 (60)
	3	40	60 (3 h)
Cyclooctanol	1	90	60 (90)
	2	31	60 (4 h)

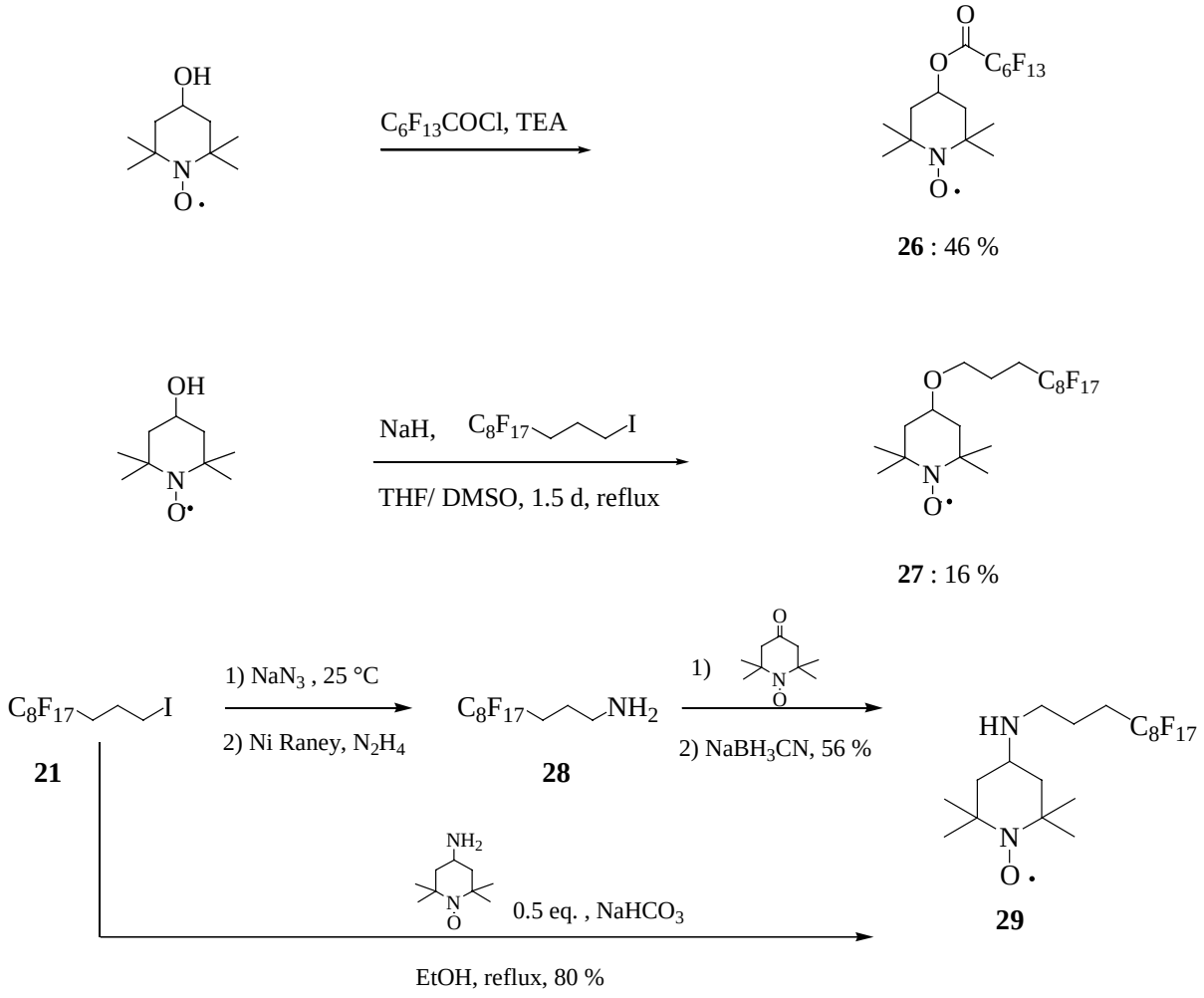
[a]: in brackets time for complete conversion

In all cases reaction times diminished after the first run, but this effect is more remarkable by increasing the ring size, as clearly showed in the oxidation of cyclohexanol versus cyclooctanol. For the less sterical hindered alcohol, complete conversion in the second run was achieved with reaction rates comparable to the first cycle, while the fluorous phase employed in the cyclooctanol oxidation dropped dramatically its activity already at the second run. As expected, cycloheptanol showed a intermediate behaviour.

These effects of the ring size suggest that the alcohol or its oxidation product could be involved in a slow poisoning effect of the Cu catalyst. In three parallel experiments, 0.04 mmol of the fluorous Cu-catalyst in 2 mL PFOB was formed with the usual procedure. To the first two solutions were added, respectively, one mmol of 2-decanone and one mmol of 2-decanol, leaving the third solution as a blank. The solutions were stirred at 90 °C for 1 h, then cooled to rt and extracted with chlorobenzene. To each of these pre-treated fluorous solution was added a chlorobenzene phase containing 2 mmol of 2-decanol and 10 mol % of TEMPO, and the oxidations carried out under the usual conditions. Comparison of GC conversions after 2 h showed that the catalyst pre-treated with the ketone lost significantly its activity, resulting in a 37 % conversion versus a 100 % of the blank solution. The pre-treatment with 2-decanol showed the same reactivity of a freshly prepared solution. The experiment was repeated three times with the same protocol, giving comparable results. This evidence suggests that ketones can significantly influence the catalyst reactivity, probably by

coordination to the metal centre with an unknown mechanism. It is reasonable to assume that after some catalytic cycles this slow poisoning effect leads to deactivation of the fluorous phase in the case of aliphatic alcohols, even if no loss of copper in the organic phase is observed.

The main disadvantages of using the TEMPO radical in oxidation processes are related to the relatively high cost of this compound and often difficult chromatographic separation from the ketone or the aldehyde after workup of the reaction mixture. A convenient solution of this problem could be the synthesis of perfluorotagged TEMPO derivatives, which should be recycled in the fluorous phase. A series of fluorous TEMPO have been prepared, following standard synthetic protocols[50] (Scheme 25).



Scheme 25. *Synthesis of fluorous TEMPO derivatives*

[50] (a) M. Kupfer, R. Stoesser, S. Schramm, D. Pretscher, W. Damerau *Zeitschr. für Chemie* **1989**, *29*, 175; (b) J.P. Conroy, K.K. Fox *Chem. Phys. Lipids* **1995**, *78*, 129; (c) G. Sosnovsky, N.U.M. Rao, J. Lukszo, R.C. Brasch *Zeitschr. Naturforsch. Teil B* **1986**, *41B*, 1293; (d) H. Trabelsi, F. Szönyi, N. Michelangeli, A. Cambon *J. Fluorine Chem.* **1994**, *69*, 115.

All these fluorous TEMPO derivatives showed poor selectivity for the solubility in the biphasic system perfluorooctyl bromide/chlorobenzene, with partition coefficients close to 1 as determined by GC measurements. In the case of the compound **29**, a higher solubility in the organic phase has been observed, due to the presence of the very polar secondary amine group. Functionalization of the molecule with two fluorous ponytails was not achieved, even by using harsher reaction conditions and a large excess of the fluorous iodide **21** in the second synthetic pathway. However, proofs on catalytic activity have been performed with a 3.5 mol % of **26** and **27** under the standard FBS oxidation protocol for 4-nitro-benzylalcohol (Table 4).

Table 4. *Oxidation of 4-nitrobenzylalcohol with fluorous TEMPO*

TEMPO derivative	*run*	*GC conversion / %*	*time / h*
Perfluoroester **26**	1	100	3.0
Perfluoroether **27**	1	100	1.5

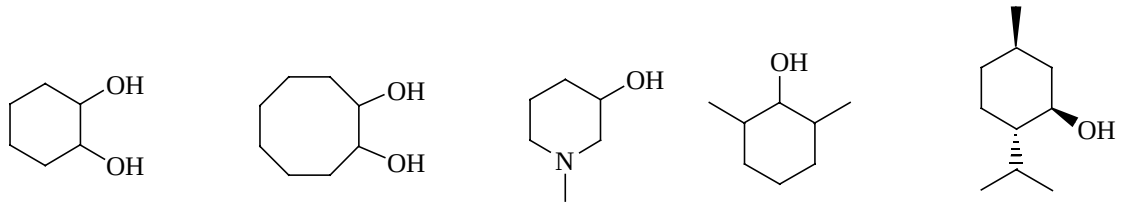
There is a difference in reactivity between the two TEMPO derivatives, which cannot be explained by simple sterical hindrance, being it comparable in both cases. The perfluoroester **26** showed a remarkably lower reactivity in comparison to the fluorous ether **27** and the standard TEMPO oxidation. Reaction rate for **27** is anyway worse than for simple TEMPO. No degradation of the title compounds has been observed.

1.3 Compatibility with functional groups

To test the applicability of the method, the oxidation of a variety of alcohols has been carried out, using the optimized amount of 10 mol % of the co-catalyst TEMPO (Table 5). In the preliminary work[29b] of our group was already demonstrated the compatibility with aromatic and aliphatic bromides, in 2-bromo-benzylalcohol or 11-bromo-undecan-1-ol oxidation. Substrates containing double bond functionalities, like cinnamyl alcohol, myrtenol, and citronellol (entry **36**) are stable under our reaction conditions and no isomerisations or other side reactions at the olefine were observed. Nitro groups (entry **35**), esters (entry **37**) and nitriles are well tolerated. In this last case (entry **38**), a slight degradation of the TEMPO during the reaction was observed, but oxidation to the corresponding ketone proceeded

smoothly to full conversion, with satisfactory reaction rate. An isopropyl substituent (entry **39**) at the aromatic ring, which is potentially oxidizable to hydroperoxide in presence of oxygen at temperatures around 100 °C, was stable under the reported reaction conditions.

A number of alcohols that are unreactive toward this system remains (Scheme 26):



30 **31** **32** **33** **34**

Scheme 26. ***Unreactive alcohols (entries* 30 *and* 33*: mixtures of isomers)***

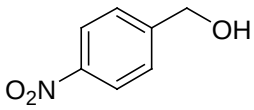
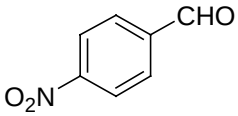
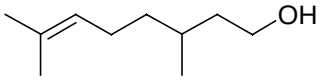
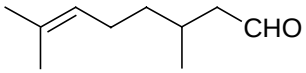
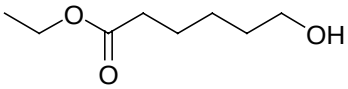
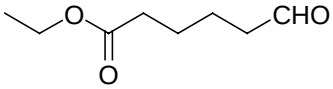
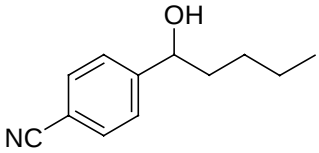
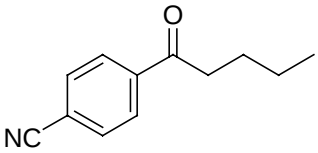
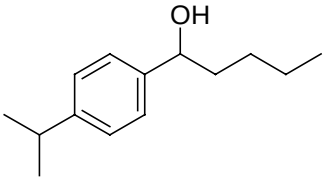
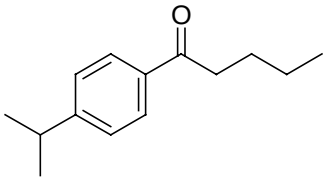
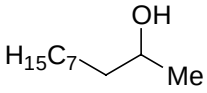
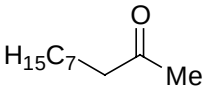
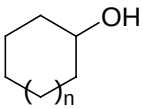
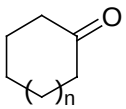
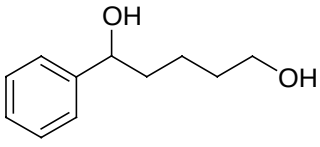
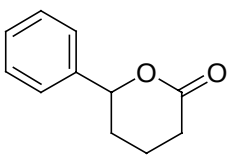
In the case of diols **30** and **31** this lack in reactivity is probably due to inhibitive coordination at the Cu centre, while for 2,6-dimethyl-cyclohexanol and menthol (entries **33** and **34**) the steric hindrance should play a determining role. In the case of the aminoalcohol **32** cleavage of Cu from the fluorous phase was observed. Similar effects have been reported by *Sheldon et al*[51] in the TEMPO-mediated Ru-catalyzed aerobic oxidation of alcohols. They observed no reactivity with substrates containing heteroatoms (N, O, S) close to the hydroxyl moiety.

As showed in Table 5, reaction times for complete conversions in the first run are between 0.5 and 2.0 hours for aromatic substrates, as well as for not too sterically hindered secondary aliphatic alcohols. These results clearly show the better performance of the Cu-TEMPO-catalyzed oxidation in FBS, when compared to other biphasic systems. For example, *Ansari* and *Gree*[52] reported reaction times of 60 h for the complete conversion of cyclohexanol to cyclohexanone, by using 5 mol % of CuCl and TEMPO at 65 °C in the ionic liquid [bmim][PF_6]. Under our conditions the same result was achieved in 0.5 h (entry **41**).

[51] A. Dijksman, A. Marino-González, A. Mairata i Payeras, I.W.C.E. Arends, R.A. Sheldon *J. Am. Chem. Soc.* **2001**, *123*, 6826.

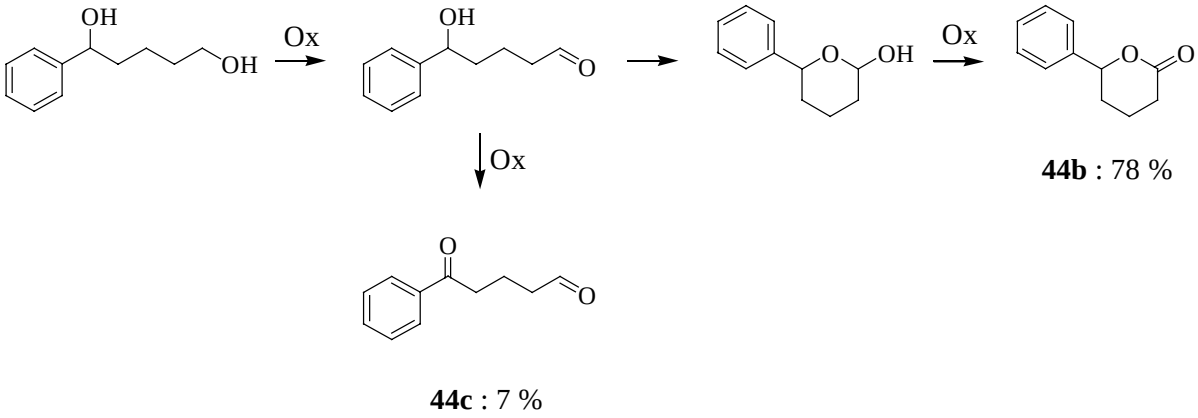
[52] I.A. Ansari, R. Gree *Org. Lett.* **2002**, 4, 1507.

Table 5. *Aldehydes and ketones obtained by the oxidation of alcohols under fluorous biphasic conditions.*

Entry	Alcohol	Product	Yield[a] / %	Reaction time[b] / h
1	 **35a**	 **35b**	98	1.0[c]
2	 **36a**	 **36b**	92	1.0
3	 **37a**	 **37b**	89	1.5
4	 **38a**	 **38b**	97	1.5
5	 **39a**	 **39b**	95	2.0
6	 **40a**	 **40b**	88	2.0
				
7	n = 1 **41a**	cyclohexanone **41b**	74	0.5
8	n = 2 **42a**	cycloheptanone **42b**	82	0.5
9	n = 3 **43a**	cyclooctanone **43b**	85	1.5
10	 **44a**	 **44b**	78	2.0

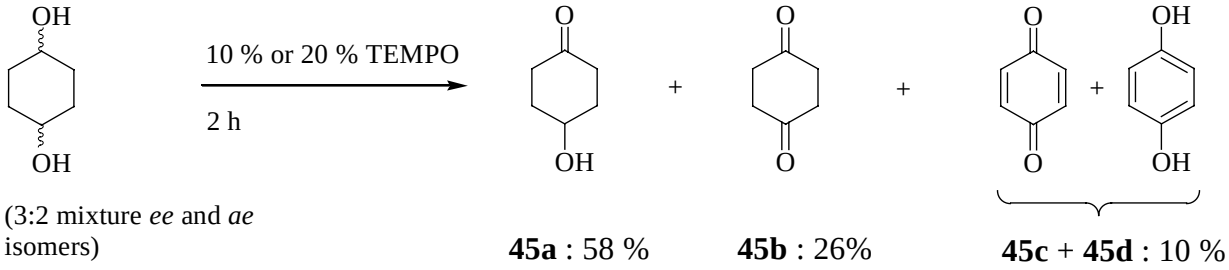
[a] Isolated yield of analytically pure product; [b] Reaction time for the first run; [c] 3.5% TEMPO.

As previously highlighted, there is a clear selectivity for primary alcohols versus secondary hydroxyl groups. This difference in reactivity is observed even when the latter is in a reactive benzylic position, as shown with the diol **44a**. In this case, the primary hydroxyl is first converted to aldehyde, which forms a lactol intermediate that is further oxidized to lactone (Scheme 27). Since hemiacetals are usually formed in the presence of an acid catalyst, this could suggest a slighty acidic environment rather than basic under these reaction conditions, according to the proposed mechanism (see Scheme 15) which involves formation of protons in the catalytic cycle. Only a small amount of the dicarbonylic byproduct **44c** was formed.



Scheme 27. *Intramolecular competition between primary and secondary benzylic hydroxyl groups*

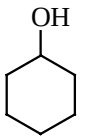
In the oxidation of 1,4-cyclohexanediol not only the hydroxyl functions are oxidized, but also abstraction of β-protons is observed, with formation of a 10 % of the semiquinone complex. This behaviour is observed only with this substrate and no similar examples were found in the literature. Larger amounts of TEMPO or longer reaction times do not led to further oxidation of the hydroxyketone **45a** (Scheme 28), for which a 3:1 ratio between equatorial and axial conformation of the unreacted hydroxyl group was found.



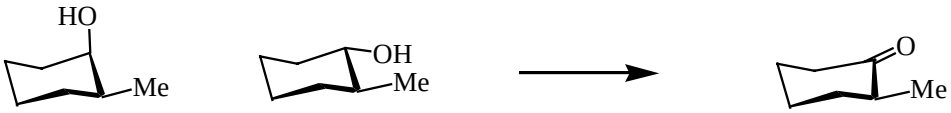
Scheme 28. *Oxidation of 1,4-cyclohexandiol*

1.4 Selectivities in cyclohexanols oxidation

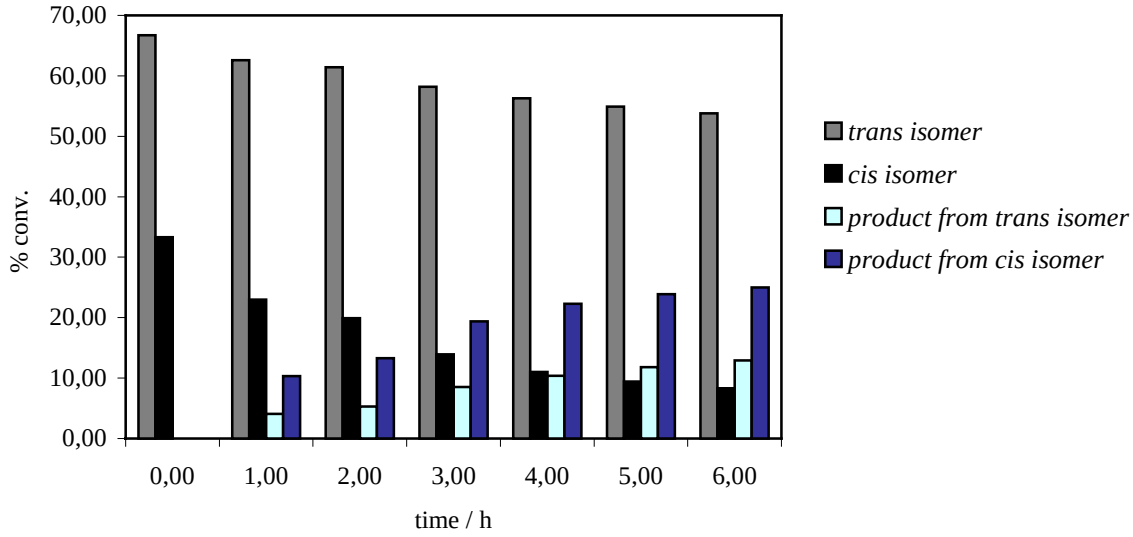
In our experiments, an unexpected difference in reactivity under the standard conditions was observed between the oxidations of cyclohexanol and *trans* 4-*t*-butyl-1-cyclohexanol, which seems not merely justified by direct steric hindrance, being the *t*-butyl group in a far position. While cyclohexanol is readly completely oxidized to cyclohexanone after 30 min, a GC conversion of only 28 % was measured after 3 h for the substituted alcohol. Furthermore, in the oxidation of a 33:67 *cis*- *trans*- mixture of 2-methyl-1-cyclohexanol, a higher reactivity of the *cis*- isomer is found (Scheme 29):



conversion, 30 min: 100 % conversion, 3 h: 28 %



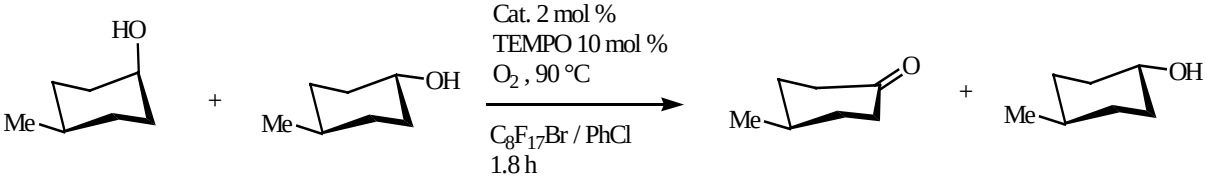
47a *cis : trans* 33 : 67 **47b**



Scheme 29. *Oxidation of* cis- *and* trans- *2-methyl-1-cyclohexanol (absolute conversions are shown)*

This allowed us to investigate the behaviour of several *cis*- *trans*- mixtures of substituted cyclohexanols. In all cases, a remarkable selectivity was found for the oxidation of the isomer bearing the hydroxyl group in *axial* position, regardless of the substituent position in the ring, as seen, for instance, for entry **48**. As an example, an almost equimolar 47:33 *cis*- *trans*-mixture of 4-methyl-cyclohexanols (entry **46**) leads to the selective oxidation of the *cis*-isomer in 1.8 h, whereas the *trans*-alcohol remains almost unreacted, allowing to isolate the latter in 49 % yield after chromatographic purification (Scheme 30). Reaction times are comparable for all the cyclic alcohols, except for 2-methyl-cyclohexanol **47a** where the sterical hindrance of the methyl group plays a direct role (Table 6).

These results could be of remarkable interest especially in the synthesis of bioactive molecules like fragrances or steroids[53].



46a *cis* : *trans* 47 : 53 **46b** : 49 % 45 %

Scheme 30 *Stereoselectivity in the oxidation of 4-methyl-cyclohexanol*

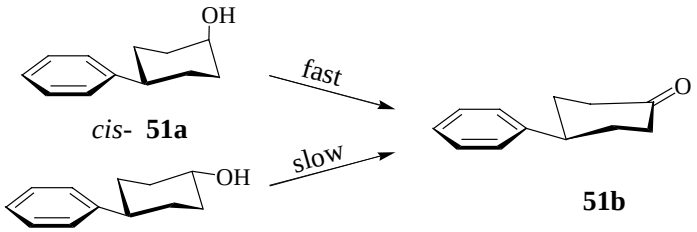
Table 6. *Stereoselectivity in substituted cyclohexanol oxidation*

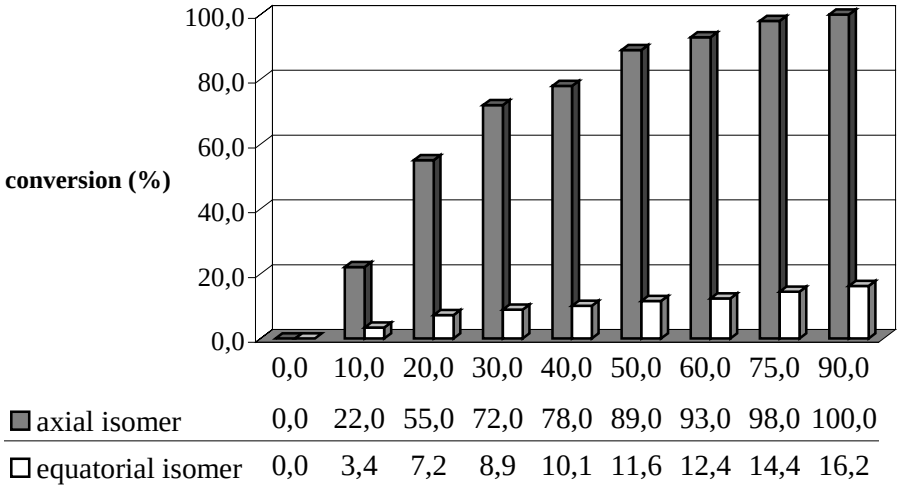
Cyclohexanol derivative		Ratio *cis:trans*[a]	Reaction time[b] / h	Stereochemistry of unreacted alcohol[a]	Yield of unreacted alcohol[c] / %	Yield of ketone[c] / %
4-methyl-cyclohexanol	**46a**	47 : 53	1.8	*trans*	49	**46b** : 45
2-methyl-cyclohexanol	**47a**	33 : 67	9.5	*trans*	50	**47b** : 38
3-methyl-cyclohexanol	**48a**	34 : 66	1.2	*cis*	29	**48b** : 62
4-*i*-Pr-cyclohexanol	**49a**	32 : 68	1.5	*trans*	65	**49b** : 28
4-*t*-Bu-cyclohexanol	**50a**	25 : 75	1.7	*trans*	70	**50b** : 20
4-phenyl-cyclohexanol	**51a**	50 : 50	1.5	*trans*	46	**51b** : 49

[a] Determined by ^{1}H NMR analysis at the C*H*OH proton
[b] Time for complete conversion of the most reactive isomer, chiral GC analysis determination.
[c] Isolated yield of analytically pure product, calculated on the basis of the initial reaction mixture.

[53] (a) L.F. Fieser, S. Rajagopalan *J. Am. Chem. Soc.* **1950**, *72*, 3935; (b) J. Schreiber, A. Eschenmoser *Helv. Chim. Acta* **1955**, *38*, 1529.

This behaviour has been also verified in absence of mutual competition, through separate oxidations of two isomers in the case of 4-phenyl-cyclohexanol **51a**. It was clearly shown that the reaction rate of the axial alcohol is 6.5 to 8 times faster than that of the equatorial one (Scheme 31).





Scheme 31. *Conversion vs. time(min) in separate oxidations of 4-phenyl-cyclohexanol*

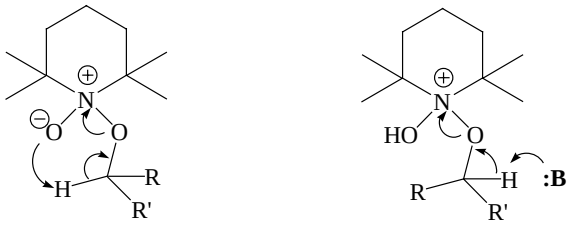
A satisfactory mechanistic explanation has not been provided yet. The selectivity between the axial and the equatorial isomers in favour of the axials have already been found by using other oxidative systems, like chromic acid[54] or zeolites[55], but no examples for the case of TEMPO-mediated aerobic oxidation are known so far. In the case of chromic acid oxidation the difference in reactivity was explained by assuming differences in the relative energy content of the two isomers, due to conformational ground-state compression.

Chung and *Kim*[56] found complementar selectivities by using as oxidants *N*-bromosuccinimide, which allows higher rates for axial isomers, or sodium hypochlorite,

[54] E.L. Eliel, S.H. Schroeter, T.J. Brett, F.J. Biros, J-C. Richer *J. Am. Chem. Soc.* **1966**, *88*, 3327.
[55] E.J. Creyghton, S.D. Ganeshie, R.S. Downing, H. van Bekkum *J. Mol. Cat. A: Chemical* **1997**, *115*, 457.
[56] K. Chung, S.J. Kim *Bull. Korean. Chem. Soc.* **1986**, *7*, 111.

which allows higher rates for equatorial isomers. They found also a dependence on basic or acidic conditions.

In the TEMPO-mediated alcohol oxidation, *van Bekkum et al.*[40] postulated the formation of the adducts **52** or **53**, depending on the medium conditions. In the presence of an acidic environment they hypotized that a third species **B** could be involved in the hydride abstraction formation. (Scheme 32)

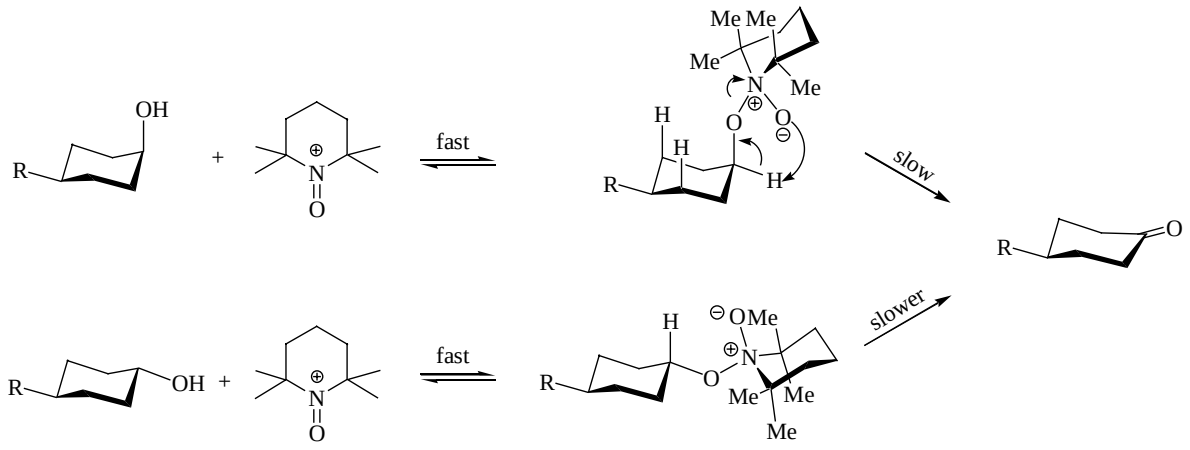


52 **53**

basic medium acidic medium

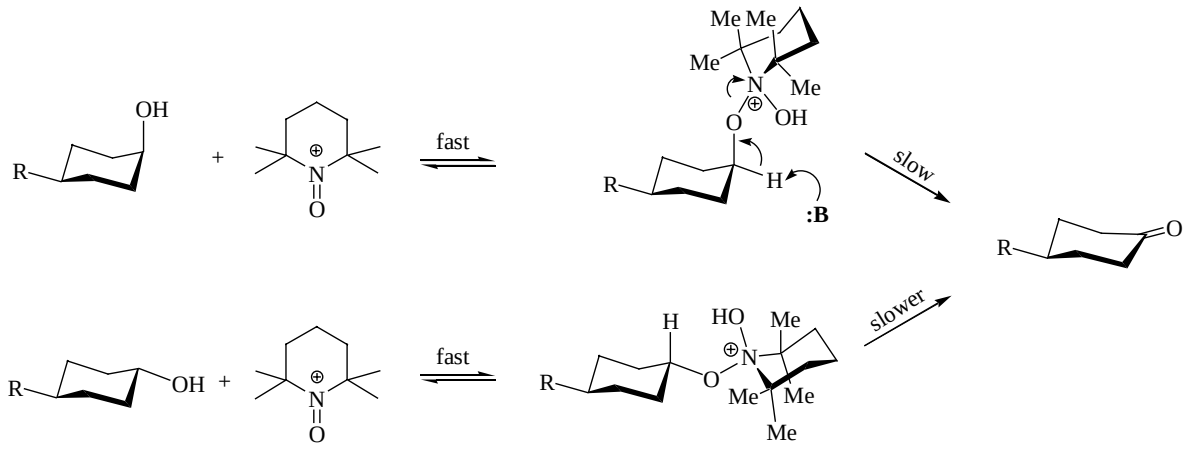
Scheme 32. *Postulated intermediates according to* van Bekkum *et al.*

Mechanistics explanations based on these intermediates could be also taken into account for the observed chemoselectivities in cyclohexanol series, as well as stereoelectronic effects. If intermediate **52** is formed, the same explanation for the above reported chromic acid oxidation can be assumed, wherein steric effects control the reaction rates (Scheme 33):



Scheme 33. *Possible pathway involving an intermediate of type* **52**

By assuming the formation of intermediate **53**, α-proton abstraction by **B** could be also favoured in the axial alcohol, because of lower sterical hindrance compared to the equatorial isomer; in this case the available "free" angles for **B** attack are of ca. 270° for the axial isomer vs. ca. 180° for the equatorial one (Scheme 34).



Scheme 34. *Possible pathway involving an intermediate of type **53.***

Direct hydride abstraction by a Cu(II) species, with formation of Cu(I)H, has also been postulated by *Fish et al.*[57] in a recent detailed study on Cu-catalyzed alcohol oxidation in FBS. Nevertheless, effects on oxidation of cyclic alcohols have not been investigated yet.

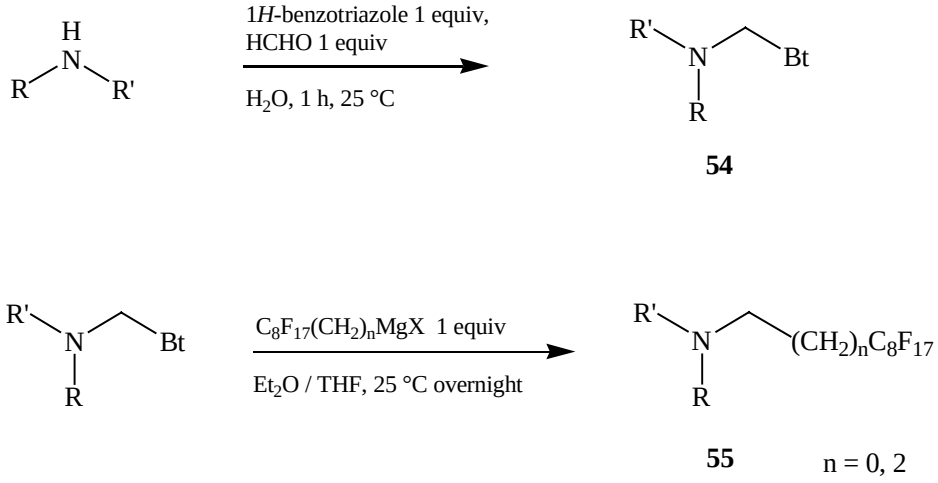
1.5 Fluorous tertiary amines and their use as ligands

Fluorous tertiary amines have already been used in FBS oxidation of alkanes and alkenes[58]. Several Cu(I) complexes were prepared in a similar way and have been utilized as precatalysts for the cyclisation of unsaturated esters or living radical polymerisation under FBS conditions[59]. A particularly convenient synthetic protocol has been developed by *Katritzky*[60] and coworkers, and applied to the synthesis of fluorous amines. Using this method, we synthesized a series of fluorous amines, whose use in Cu-catalyzed alcohol oxidation has been briefly investigated.

[57] M. Contel, C. Izuel, M. Laguna, P.R. Villuendas, P.J. Alonso, R.H. Fish *Abstracts of Papers, 226th ACS National Meeting*, New York, US, September 7-11 2003.
[58] See ref. 44.
[59] (a) F. De Campo, D. Lastécouères, J-M. Vincent, J-B. Verlhac *J. Org. Chem.* **1999**, *64*, 4969; (b) D.M. Haddleton, S.G. Jackson, S.A.F. Bon *J. Am. Chem. Soc.* **2000**, *122*, 1542
[60] (a) A.R. Katritzky, Z. Zhang, M. Qi *Tetrahedron Lett.* **1997**, *38*, 7015; (b) A.R. Katritzky, B. Pilarsky, L. Urogdi *J. Chem. Soc. Perkin Trans. 1* **1990**, 541.

The synthesis of fluorous amines from direct alkylation can often be challenging, due to the lower reactivity of fluorous iodides and to the steric hindrance at the nitrogen atom, as already seen, for example, in the synthesis of the fluorous TEMPO derivative **29**. Several methods have been developed in the fluorous literature to solve this problem. The *Katritzky* synthetic approach is particularly attractive because of the limited number of steps and yields from moderate to quantitative, which easily lead to multigram-scaled syntheses. In addition, the method allows to introduce directly a spacer of various length between the nitrogen atom and the fluorous tag.

In the first step, a C-1 spacer bonded to the leaving group benzotriazole is directly attached through amination of formaldehyde in mild conditions and almost quantitative yields, starting from a secondary amine. The aminal **54** is then treated with an appropriate Grignard reagent to obtain the tertiary amine **55** (Scheme 35).



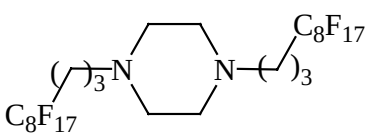
Scheme 35. *Synthetic protocol for fluorous tertiary amines*

The fluorous Grignard reagents have been prepared starting from commercially available perfluorooctyl iodide or $C_8F_{17}(CH_2)_2I$, by exchange with phenylmagnesium bromide[61] or by direct Mg insertion[62], respectively.

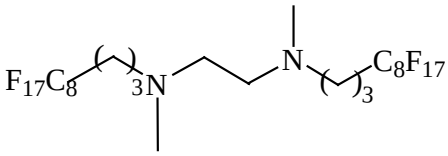
In this way, a number of fluorous tertiary diamines containing two fluorous ponytails have been prepared in moderate to good yields (35 – 80 %, Scheme 36).

[61] (a) R.D. Chambers, W.K.R. Musgrave, J. Savory *J. Chem. Soc. Abstracts* **1962**, 1993; (b) E.T. McBee, C.W. Roberts, A.F. Meiners *J. Am. Chem. Soc.* **1957**, *79*, 335.

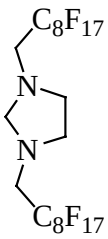
[62] P. Wipf, J.T. Reeves *Tetrahedron Lett.* **1999**, *40*, 5139



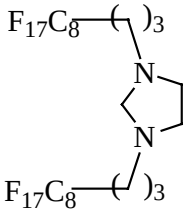
56 : 80 %



57 : 67 %



58 : 42 %



59 : 35 %

Scheme 36. *Fluorous amines synthesized with the* Katritzky *method*

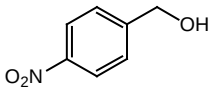
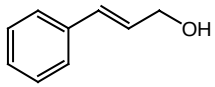
All the compounds showed a highly selective solubility in perfluorooctyl bromide versus a dichloromethane or chlorobenzene phase. 1:1 Complexes between the diamines in Scheme 36 and CuBr·DMS have been prepared in PFOB by a procedure similar to the one employed for the fluorous bipyridine **3**. Only the fluorous imidazolidine **58** failed in the complex formation, due to the insufficient insulating properties of the C-1 spacer at the nitrogen atoms. The brown Cu(I) complexes are slowly oxidized to green Cu(II) complexes when exposed to air and are selectively soluble in PFOB vs. chlorobenzene.

Among these compounds, the diamine **57** can be considered the fluorous analogous (*Rf_2DMEDA*) of TMEDA, which has already been used as catalyst when complexed with copper or other metals in a variety of transformations[63]. Since it is a liquid at rt, its solubilization in fluorous solvents is easier in comparison to other fluorous amines. Therefore, it has been tested as a ligand for Cu(I) in the Semmelhack aerobic alcohol oxidation, as a possible alternative to the bipyridine ligand, whose synthesis is more tedious.

[63] for some recent examples of Cu complexes of TMEDA as catalysts see: (a) P. Schulte, G. Groger, U. Behrens *Zeitschr. Anorg. Allgem. Chem.* **1999**, *625*, 1447; (b) G. Heuger, S. Kalsow, R. Gottlich *Eur. J. Org. Chem.* **2002**, *7*, 1687; E. Balogh-Hergovich, Z. Greczi, J. Kaizer, G. Speier, M. Reglier, M. Giorgi, L. Parkányi *Eur. J. Org. Chem.* **2002**, *11*, 1848.

Oxidations of two reactive alcohols, and two aliphatic secondary substrates have been performed with 2 mol % of catalyst and 10 mol % of TEMPO at 90 °C, under standard conditions. Results of a first oxidation run are summarized in Table 7:

Table 7. *Comparison between the ligands fluorous bipyridile and the fluorous diamine **57** in alcohol oxidation.*

	Rf_2Bipy		***Rf_2DMEDA***	
Alcohol	*GC conv.[a] %*	*time / h*	*GC conv.[a] %*	*time / h*
	100 (93)	1.0	100 (98)	1.5
	100 (79)	1.0	100 (89)	1.0
2-Decanol	100 (88)	2.0	51 (nd)	3.0
Cyclooctanol	100 (85)	1.5	48 (nd)	3.0

[a] : in brackets are the yields of analytically pure product

The readily oxidizable substrates 4-nitro-benzylalcohol and cinnamyl alcohol showing reaction times of 1.5 and 1.0 h respectively, which are comparable to those obtained by using the fluorous bipyridine ligand. Performances of the Cu-Rf_2DMEDA catalyst drop dramatically in the case of secondary aliphatic alcohols, with partial conversions of only 51 and 48 % after 3 h reaction in the first run, and degradation of TEMPO in the case of 2-decanol.

1.6 Summary

In summary, the reaction parameters for the fluorous version of Semmelhack aerobic oxidation of alcohols have been investigated in order to improve reaction rates for aliphatic secondary alcohols.

- Copper (I or II) is the most suitable metal catalyst to carry out this oxidation reaction using TEMPO as co-catalyst. Influence of counterion and acidic or basic environment was studied.

- Effects of TEMPO amounts on reaction rates and catalyst recyclability have been investigated. The aliphatic residue of secondary alcohols influences the recyclability of fluorous phase and a poisoning effect of the product on catalytic activity has been found. Synthesis and application of fluorous TEMPO derivatives have been studied as well.

- The system tolerates a variety of functional groups, making it suitable for oxidation of several types of substrates.

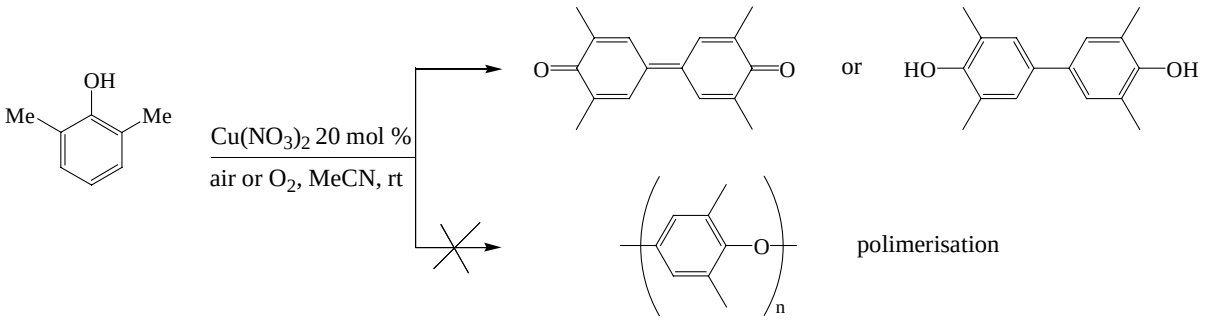
- A useful chemoselectivity between axial and equatorial hydroxyl groups in cyclohexanols has been found and possible explanations were discussed.

- A variety of fluorous amines has been synthesized and their complexes with copper were prepared. Rf_2DMEDA was tested as a ligand in the Cu-catalyzed alcohol oxidation.

2 Oxidative Coupling in FBS

Transformations with molecular oxygen have found useful applications not only in the preparation of "oxigenated" compounds like epoxides, carboxylic acids or ketones, but also in cross-coupling reactions for the formation of carbon-carbon (C-C), carbon-nitrogen (C-N) and carbon-oxygen (C-O) bonds. Several methods employ catalytic amounts of various metals, as salts or in combination with appropriate ligands, which often are pyridines.

Aerobic phenol homocoupling has always attracted much attention[64] as a useful tool for the synthesis of natural products like alkaloids[65] or lignans[66]. In this transformation, a C-C bond between positions in *para*- or *ortho*- to a phenol group are formed when the compound is treated with oxygen and a metal catalyst, usually copper. By changing reaction conditions and substituents at the phenol ring, various products or polymers can be obtained[67] (Scheme 37).



Scheme 37. *Aerobic phenol oxidative coupling*

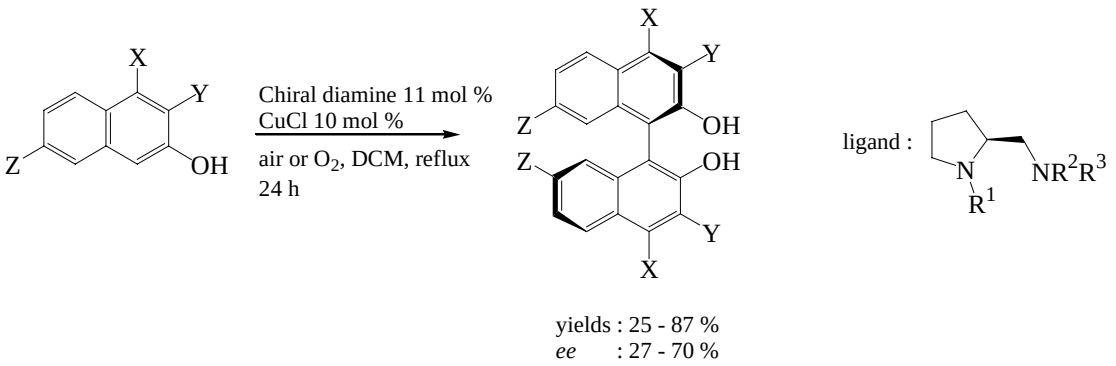
[64] For some recent patents and papers, see: (a) K. Ishii, M. Hiramatsu, M. Miyamoto *Jpn. Kokai Tokkyo Koho* **2003** JP 2003128610; (b) G. Kaplan, *U.S. Pat. Appl. Publ.* **2003** US 2003050515; (c) D-R. Hwang, C-P. Chen, B-J. Uang *Chem. Comm.* **1999**, *13*, 1207.

[65] W.I Taylor, A.R. Battersby *Oxidative Coupling of Phenols* Dekker, New York **1967**, and ref. citated therein.

[66] (a) R.S. Ward, D.D. Hughes *Tetrahedron* **2001**, *57*, 5633; (b) P. Cotelle, H. Vezin *Tetrahedron Lett.* **2003**, *44*, 3289.

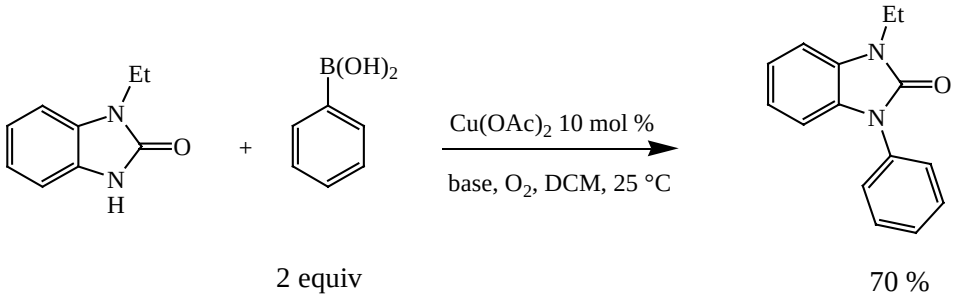
[67] S. Tsuruya, Y. Kishikawa, R. Tanaka, T. Kuse *J. Catal.* **1977**, *49*, 254.

Recent interesting applications have been developed in the *Nakajima*[68] group by performing asymmetric syntheses of BINOL derivatives using chiral diamine-copper complexes (Scheme 38):



Scheme 38. *Synthesis of chiral BINOL derivatives by aerobic oxidative coupling*

C-N and C-O heterocoupling between amines or phenols and arylboronic acids has been recently performed[69] by using copper as a primary oxidant in mild conditions. The method is of particular interest for the synthesis of pharmaceuticals, crop-protection chemicals and new materials. When the reaction is carried out in presence of oxygen or air, only catalytic amounts of the metal salt have to be used. The method leads to the synthesis of various functionalized arylamines in good yields (Scheme 39).



Scheme 39. *Aerobic Cu-catalyzed C-N coupling with arylboronic acids*

[68] (a) M. Nakajima, K. Kanayama, I. Miyoshi, S. Hashimoto *Tetrahedron Lett.* **1995**, *36*, 9519; (b) M. Nakajima, I. Miyoshi, K. Kanayama, S. Hashimoto, M. Noji, K. Koga *J. Org. Chem.* **1999**, *64*, 2264.

[69] (a) D.M.T. Chan, K.L. Monaco, R-P. Wang, M.P. Winters *Tetrahedron Lett.* **1998**, *39*, 2933; (b) A.P. Combs, S. Saubern, M. Rafalski, P.Y.S. Lam *Tetrahedron Lett.* **1999**, *40*, 1623; (c) P.Y.S. Lam, G. Vincent, C.G. Clark, S. Deudon, P.K. Jadhav *Tetrahedron Lett.* **2001**, *42*, 3415; (d) J.C. Antilla, S.L. Buchwald *Org. Lett.* **2001**, *3*, 2077.

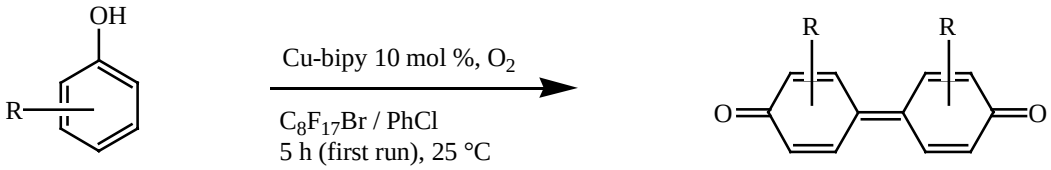
Due to the wide synthetic applications of the aerobic Cu-catalyzed aryl coupling, it was of interest trying to adapt these methods to the synthesis in FBS. The system Cu-*F*-bipyridine already used in FBS alcohol oxidation was employed, in analogy to literature protocols where Cu(II) salts have been complexed with pyridine or amines.

The advantages of the biphase catalysis should be:

- immobilization and recovery of the catalyst in fluorous phase;
- better performances of the catalytic system due to the excellent solubilization of dioxygen in fluorous medium.

2.1 Aerobic phenol homocoupling in FBS

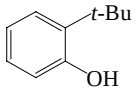
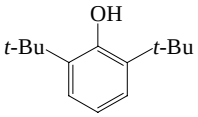
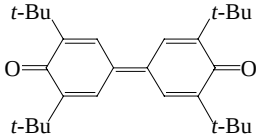
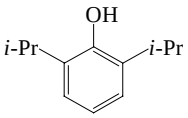
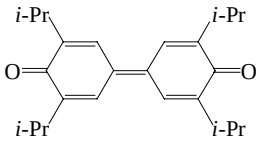
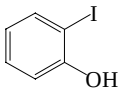
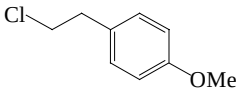
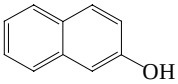
The aerobic phenol homocoupling has been performed in a biphasic system PFOB/ chlorobenzene, by using a 10 mol % of CuBr·DMS in a 1:1 complex with the fluorous bipyridine **3** at room temperature, under O_2 bubbling. This ratio metal : ligand should allow the formation of a dinuclear Cu complex, which has been postulated to be the active catalyst for this reaction[70].
The reactivity of different phenols has been investigated by changing number and nature of ring substituents, as shown in Table 8.



Scheme 40. *Oxidative coupling in FBS*

[70](a) P.J. Baesjou, W.L. Driessen, G. Challa, J. Reedijk *J. Am. Chem. Soc.* **1997**, *119*, 12590; (b) N. Kitajima, T. Koda, Y. Iwata, Y. Moro-oka *J. Am. Chem. Soc.* **1990**, *112*, 8833.

Table 8. *Oxidative coupling of phenols in FBS*

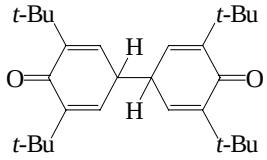
Entry	Phenol	Product	yield[a]	reaction time
1	 **60**	mixture of products	(100 % conversion)	2 h
2	 **61a**	 **61b**	98	2 h
3	 **62a**	 **62b**	99	5 h (2^{nd} run : 7 h)
4	 **63**	no reaction	nd	3 h
5	 **64**	no reaction	nd	3 h
6	 **65**	no reaction	---	3 h

[a] Isolated yield of analytically pure product

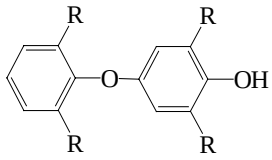
In agreement with literature data[71], the observed reactivities are higher for substrates bearing electron-donating groups. This is shown in the entries 2 and 3, where reaction times are remarkably shorter when increasing the electron-donating properties of the substituent (*tert*-butyl versus isopropyl). In presence of an electron-withdrawing group as an iodine (entry 4) no reaction was observed. From analytical data, 100 % selectivity for the 4,4' diquinone was observed in entries 2 and 3, with no diphenols, polymers or ethers of type **67** detected in the final product. In the oxidation of substrate **61a**, an intermediate of M/Z = 410, which could be assigned to a partially oxidized species **66**, was detected during the reaction course from fragmentation pattern in GC/MS measurements. The signal disappeared completely when full conversion of the starting material was achieved, in favour of a product of M/Z = 408, which has been identified as the diquinone **61b**.

The methoxy phenol **64** showed no reactivity in these conditions, probably due to its inabilty to form a final diquinone.

[71] S.R. Waldvogel *Synlett* **2002**, 533.



66



67

Only in the case of the monosubstituted phenol **60** a complex mixture of products, mainly of high molecular weight, was detected. Since in this compound both positions 2 and 4 can undergo coupling with other phenol molecules, a possible explanation is the assumption of a poor selectivity for this type of substrate. Finally, in the case of naphthol **65** no traces of product were detected, even if a change of colour in both fluorous and organic phases was observed.

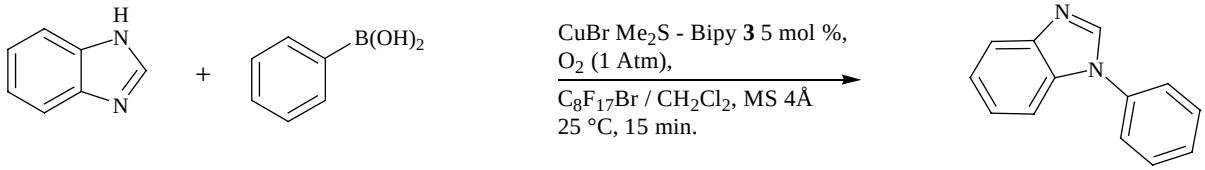
An attempt of catalyst recycling was carried out for entry 2. The fluorous phase could be reused for a second run, but a longer reaction time was necessary to achieve full conversion.

2.2 Aerobic C-N coupling with arylboronic acids in FBS

The aerobic oxidative coupling between arylboronic acids and arylamines has been performed on the basis of the *Lam*[72] paper, where a 10 mol % of $Cu(OAc)_2$ was employed and the reaction carried out at room temperature or 50 °C in the presence of oxygen or air atmosphere. The synthetic protocol depends on the substrate; in most cases, one equivalent of co-oxidant like TEMPO or pyridine N-oxide, and/or two equivalents of base like pyridine or TEA must be added. A 90 % conversion after 15 min was reported.

The reaction in FBS was performed by using a 5 mol % of the *in situ* formed complex between CuBr·DMS and the bipyridine **3**, in a biphasic system PFOB/DCM at room temperature and under oxygen atmosphere. Dry solvents and MS 4Å were employed to avoid homocoupling of phenylboronic acid. Benzimidazole was chosen as substrate, since it does not require neither co-oxidants nor bases under the Lam conditions (Scheme 41).

[72] Ref. 70(c)

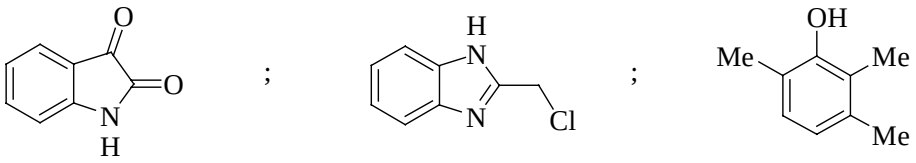


2 equiv **68**

Scheme 41. *C-N oxidative coupling in FBS*

Full conversion to the arylated benzimidazole **68** was provided after 15 min reaction. However, complete leaching of Cu from the fluorous phase was observed, with formation of an homogeneous green organic solution, which indicates a probable competitive complexation of the metal by non-fluorous species. After decantation overnight, a greenish Cu precipitate was formed at the interface of the two layers. The product was recovered in 88 % yield from the dichloromethane phase and the fluorous-solid phases recycled for a further run, providing the desired product in 79 % yield after 30 min. Irreversible cleavage of Cu from the fluorous phase was again observed. Small amounts of biphenyl and phenol were detected as byproducts.

Under the same reaction conditions no conversion was observed for the following substrates:



69 **70** **71**

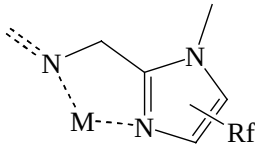
In the case of 2,3,6-trimethylphenol **71** no homocoupling byproduct was detected.

The addition of one equivalent of the fluorous diamines **56** or **57** was tested in the reaction between benzimidazole and phenylboronic acid in order to avoid cleavage of Cu from the fluorous phase by competitive complexation. Both amines failed in keeping the catalyst in the fluorous layer. Furthermore, no results were obtained when one equivalent of these amines was added in further attempts of oxidative coupling with the substrates **69** and **70**.

2.3 Synthesis of fluorous imidazoles as ligands for C-N oxidative coupling

Chelate ligands containing benzimidazole and imidazole rings are able to coordinate a number of metals, and it was found that some of these complexes are catalytically active[73]. In addition, imidazole plays an important role in cytochrome *c* oxidase in the coordination of the metal centers and stabilization of dioxygen complexes[74].

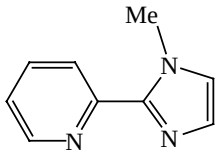
Therefore, the synthesis of fluorous ligands containing imidazole rings, as an alternative to the use of fluorous bipyridines or tertiary amines in aerobic FBS catalysis, could be of interest. A possible backbone should have the following structure, with M indicating the metal ion and Rf a number of fluorous tags:



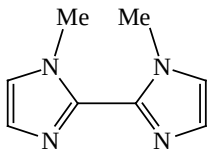
Design of fluorous imidazole ligands must take in account:

- presence of at least two fluorous ponytails, in order to achieve an adequate fluorophilicity
- presence of two nitrogen-containing rings as donors for metal coordination
- protection at the 1-*N* position, in order to avoid reaction with arylboronic acids when the ligand is used in C-N oxidative coupling experiments

Suitable ligand cores which respond to these requirements are provided by *N*-methylated 2,2'-biimidazole and 2-(2'-pyridinyl)-imidazole (scheme 42).



2-(2'-pyridinyl)-imidazole



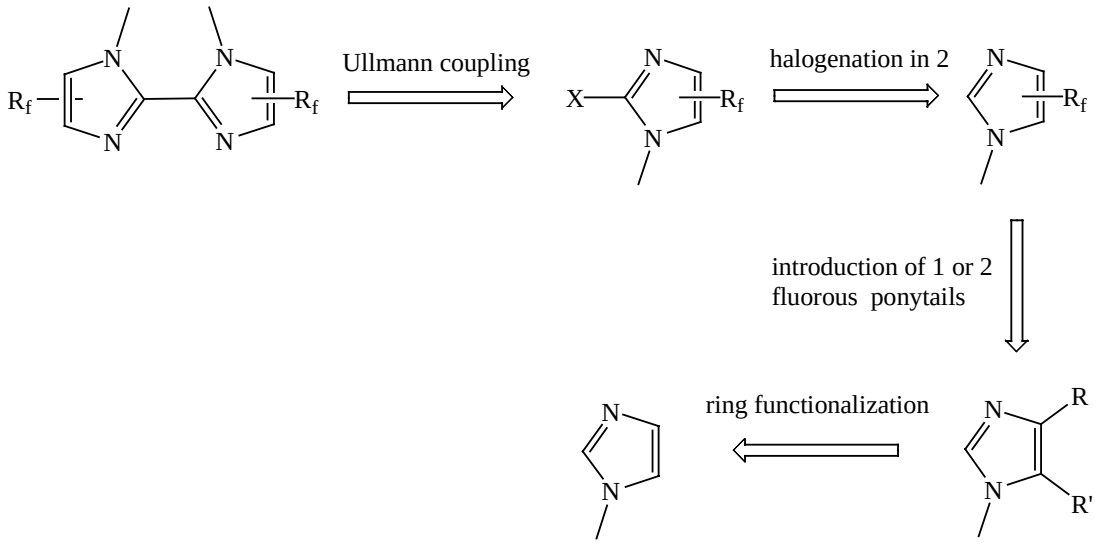
2,2'-biimidazole

Scheme 42. *Backbones for the synthesis of fluorous imidazole ligands*

[73] (a) S. Elgafi, L.D. Field, B.A. Messerle, T.W. Hambley, P. Turner *J. Chem. Soc., Dalton Trans.* **1997**, 2341; (b) S. Burling, L.D. Field, B.A. Messerle *Organometallics* **2000**, *19*, 87; (c) P.K. Byers, A.J. Canty, R.T. Honeyman *J. Organomet. Chem.* **1990**, *385*, 417; (d) M.C. Done, T. Rüther, K.J. Cavell, M. Kilmer, E.J. Peacock, N. Brassaud, B.W. Skelton, A.H. White, *J. Organomet. Chem.* **2000**, *607*, 78.

[74] (a) S. Ferguson-Miller, G.T. Babcock *Chem. Rev.* **1996**, *96*, 2889; (b) B.A. Averill *Chem. Rev.* **1996**, *96*, 2951

On the basis of literature procedures[75] for the synthesis of biimidazoles, a convenient retrosynthetic approach for the fluorous derivatives involves the functionalisation of a 1-*N*-protected imidazole in position 4 or 5, followed by halogenation in position 2 and further *Ullmann* coupling (Scheme 43).



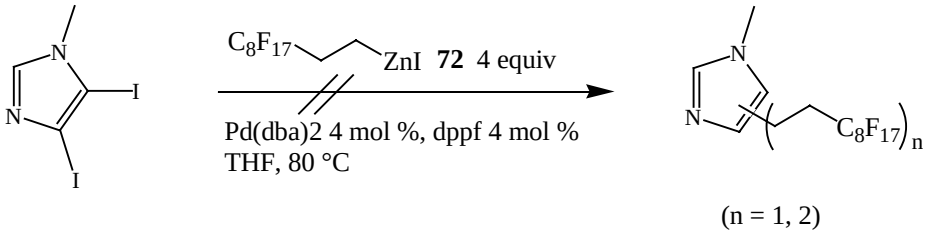
Scheme 43. *Retrosynthetic approach for fluorous 2,2'-biimidazoles*

Two approaches to the introduction of fluorous ponytails in the ring have been carried out:

1) from halogenated imidazoles, in order to insert the fluorous ponytail by halogen-metal exchange and further cross-coupling reactions with fluorous organometallics.
2) from 4,5-dicyano-1*N*-methylimidazole. The cyano group should act as a versatile functionality in the reaction with fluorous Grignard reagents.

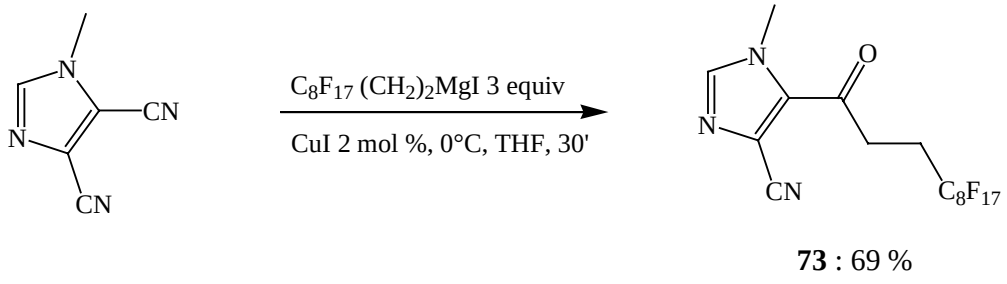
[75] P.G. Apen, P.G. Rasmussen *J. Am. Chem. Soc.* **1991**, *113*, 6178.

Several attempts to introduce a fluorous tag starting from halogenated imidazoles failed, as, for example, in the case of *Negishi* coupling between 4,5-diiodo-1*N*-methylimidazole and the fluorous zinc reagent 1,1,2,2-tetrahydroperfluorodecylzinc iodide **72** (Scheme 44):



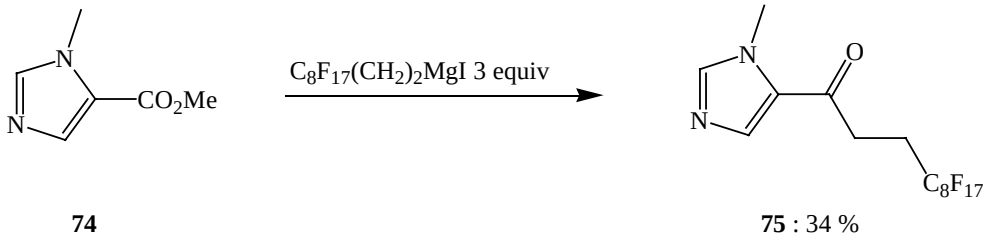
Scheme 44. *Attempt of imidazole functionalization by* Negishi *cross-coupling*

Reaction of 4,5-dicyano-1*N*-methylimidazole with the fluorous Grignard reagent 1,1,2,2-tetrahydroperfluorodecylmagnesium iodide lead to the formation of the fluorous cyanoimidazole ketone **73** in good yield, with selectivity for the alkylation in position 5 (Scheme 45). By addition of a large excess of the Grignard reagent in presence of a 2 mol % of CuI as a catalyst, no further alkylations have been observed neither at the second nitrile functionality nor at the carbonylic center. By raising the reaction temperature to 50 °C and with longer reaction times, only degradation of **73** was observed, without detectable formation of stable dialkylated products.



Scheme 45. *Reaction between 4,5-dicyano-1N-methylimidazole and fluorous Grignard*

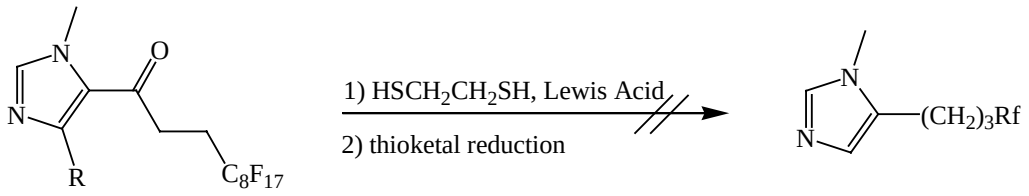
A similar behaviour has been found in the reaction of the ester 1-methyl-5-imidazole-methylcarboxylate **74** with the same fluorous Grignard, leading to the ketone **75** as the only product (Scheme 46).



74 **75** : 34 %

Scheme 46. *Reaction between 1-methyl-5-imidazole-methylcarboxylate and fluorous Grignard*

The exceptional stability of these fluorous ketones does not let to a further reduction of the carbonyl moiety by several reagents. This step is required in the ligand synthesis to improve the ligand fluorophilicity by reducing the already high polarity of the imidazole core.
For example, attempts to form thioketals out of the ketons **73** and **75** for a futher reduction with Ni to saturated alkyl species failed even by employing strong Lewis acids and harsher reaction conditions (Scheme 47). Reduction under the extreme Wolff-Kishner conditions did not lead to the desired products as well.

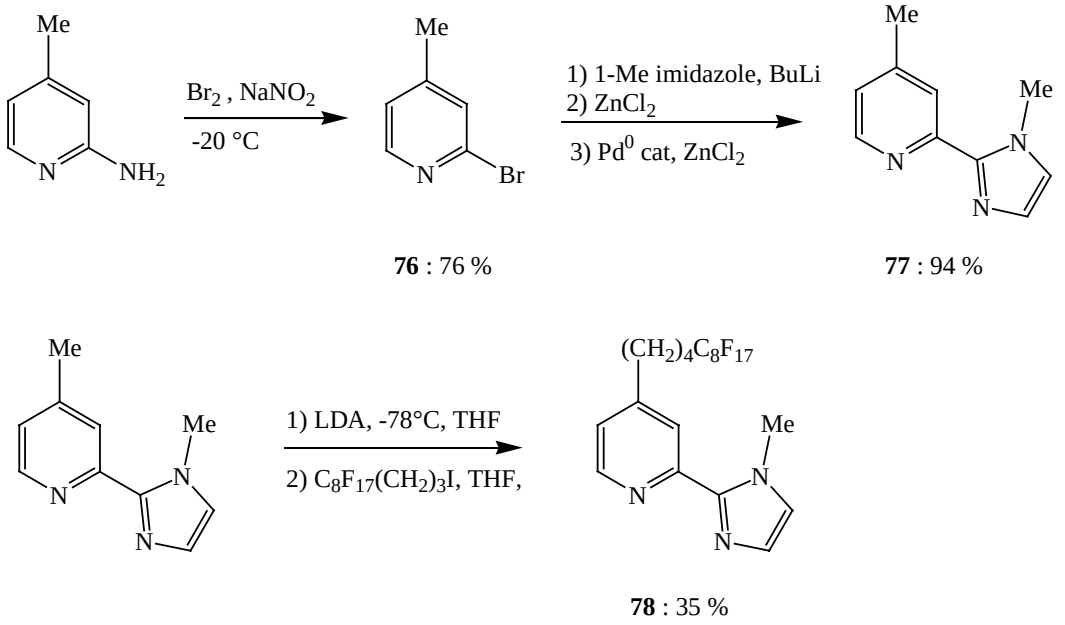


73 : R = CN
75 : R = H

Scheme 47. *Attempted synthesis of thioketal derivatives from ketones **73** and **75**.*

Due to these synthetic problems, the direct functionalization of imidazoles with fluorous ponytails and, consequently, the synthesis of fluorous biimidazole, was abandoned.

The synthesis of fluorous mixed pyridine-imidazole derivatives must therefore involve the attachment of fluorous tags at the pyridine instead at the imidazole ring. This was achieved in the synthesis of the fluorous 2-(2'-pyridinyl)-imidazole ligand **78** (Scheme 48).



Scheme 48. *Synthesis of the fluorous 2-(2'-pyridinyl)-imidazole **78.***

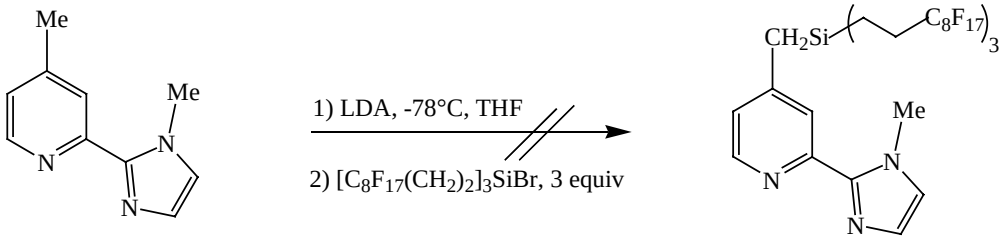
The ligand is prepared in three steps from the cheap starting material 2-amino-4-methyl-pyridine, which is converted in good yield to the corresponding 2-bromopyridine **76**[76]. The synthesis of the 2-(2'-pyridinyl)-imidazole **77** is achieved in one-pot reaction and excellent yield by selective lithiation at the 2 position of 1-methylimidazole, followed by a modified *Negishi* coupling with **76** in the presence of an excess of $ZnCl_2$ and 0.5 mol % of $Pd(PPh_3)_4$[77]. Deprotonation with LDA at the pyridine methyl group of **78**, and further quenching with the fluorous iodide **21** lead to the expected ligand.

Compound **78** shows a selective solubility in perfluorooctyl bromide in a biphasic system PFOB/chlorobenzene, while by changing the organic solvent to dichloromethane, partial leaching of the title compound in the organic layer was detected by gaschromatographic measurements. The 1:1 *in situ* complexation with CuBr·DMS provided a brown homogeneous fluorous solution, which is oxidized after few seconds to a blue-green Cu(II) complex in the presence of air. The complex was tested in the C-N oxidative coupling between benzoimidazole and phenylboronic acid, under the same conditions of the coupling reaction described in Scheme 41. Full conversion to the arylated benzimidazole **68** was achieved in 15 min, but complete cleavage of the copper complex from the fluorous phase was observed. Complete leaching of **78** from the perfluorinated layer at the end of the reaction was also

[76] U.S. Schubert, C. Eschbaumer, M. Heller *Org. Lett.* **2000**, *2*, 3373
[77] A.S. Bell, D.A. Roberts, K.S. Ruddock *Tetrahedron Lett.* **1988**, *39*, 5013

observed. This suggest that the fluorous ligand could be involved in the formation of more complex, "organophilic" structures of unknown composition, where it is coordinated to copper together with the benzoimidazole species.

In this respect, attempts to increase the ligand fluorophilicity by introduction of a higher number of fluorous tags have been carried out by using the silyl fluorous building block **23**. As in the case of the attempted synthesis of bipyridine **25**, no conversion to the fluorous silylated desired product **79** was detected (Scheme 49).



79

Scheme 49. *Attempted synthesis of a fluorous silylated 2-(2'-pyridinyl)-imidazole derivative*

2.4 Summary

Applications of catalysis in FBS for aerobic oxidative, Cu-catalyzed, C-C and C-N coupling have been investigated.

- aerobic oxidative homocoupling of phenols in FBS leads to selective formation of diquinones in very good yields in the case of electron-rich substrates.

- C-N coupling between arylboronic acids and arylamines showed strong limitations due to the recyclability of the copper catalyst, which is completely removed from the fluorous medium during the reaction. The addition of stoichiometric amounts of fluorous tertiary amines does not improve the results.

- The attempted synthesis of suitable fluorous imidazole-containing ligands lead to the discovery of unusual (un)reactivities of fluorous ketone derivatives. A particularly high fluorophilicity is required in order to keep the ligands in the fluorous phase when experiments on C-N oxidative coupling are performed.

3 Ruthenium catalyzed aerobic epoxidation in FBS

The epoxidation of olefins is a reaction of primary importance in organic chemistry because epoxides are key building blocks for the preparation of complex organic molecules and resins. Common laboratory-scale methods usually use stoichiometric amounts of reactive oxidants like peracids,[78] which pose safety hazards in large-scale industrial reactions. Development of environmental-friendly procedures, which employ molecular oxygen, aqueous hydrogen peroxide or *tert*-butyl hydroperoxide, is highly desirable. Advances have been made by using these oxidants in the presence of catalytic amounts of transition metal as Ru, Mn[79] or Ni[80].
Ruthenium complexes are versatile catalysts for a number of organic oxidations and reductions, and a large variety of ligands has been prepared and tested[81], including porphyrines, macrocyclic tertiary amines or Schiff bases. In many cases, high yields and turnovers have been attained, but major drawbacks are still related to leaching/deactivation, leading to gradual decline in activity of the catalyst, of which the synthesis can often be tedious as in the case of porphyrine derivatives.

Therefore, development of efficient protocols which allow reuse of ruthenium would be of interest for a number of reactions. In this respect, the use of FBS catalysis with fluorous complexes of this metal is particularly attractive. In our group, FBS epoxidation of olefines was performed in good yields and recyclability up to 12 runs, by using the aerobic *Mukaiyama*[82] protocol in the presence of a ruthenium complex with the fluorous diketonate[83] **12** and two equivalents of 2-methyl-propionaldehyde as co-oxidant (Scheme 50).

[78] W. Gerhartz, Y.S. Yamamoto, L. Kandy, J.F. Rounsaville, G. Schulz, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Eds. Verlag Chemie, Weinheim, **1987**, Vol. A9, p.531.

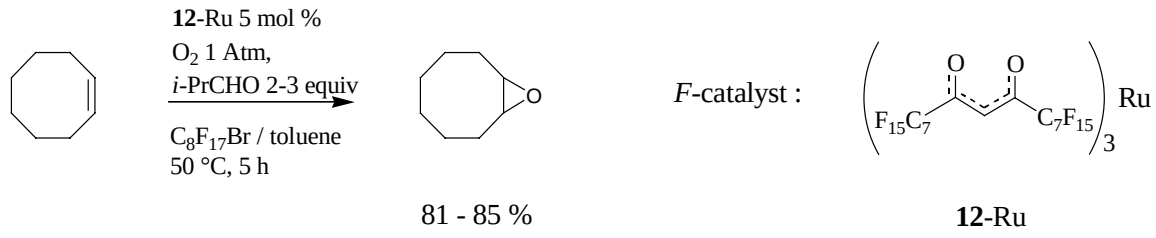
[79] (a) D. De Vos, T. Bein *Chem. Comm.* **1996**, 917; (b) D.E. De Vos, B. F. Sels, M. Reynaers, Y.V. Subba Rao, P.A. Jacobs *Tetrahedron Lett.* **1998**, *39*, 3221.

[80] B.B. Wentzel, P.A. Gosling, M.C. Feiters, R.J.M. Nolte *J. Chem. Soc., Dalton Trans.* **1998**, 2241 and references citated therein.

[81] (a) J.T. Groves, R. Quinn, *J. Am. Chem. Soc.* **1985**, *107*, 5790; (b) W-H. Cheung, W-Y. Yu, W-P. Yip, N-Y. Zhu, C-M. Che *J. Org. Chem.* **2002**, *67*, 7716, and references citated therein.

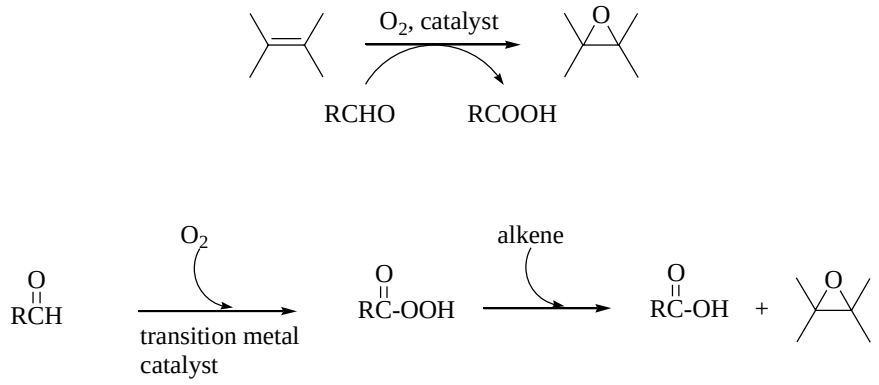
[82] (a) T. Yamada, T. Takai, O. Rholde, T. Mukaiyama *Chem. Lett.* **1991**, 1; (b) T. Yamada, T. Takai, O. Rholde, T. Mukaiyama *Chem. Lett.* **1991**, 5.

[83] see ref. 18(a).

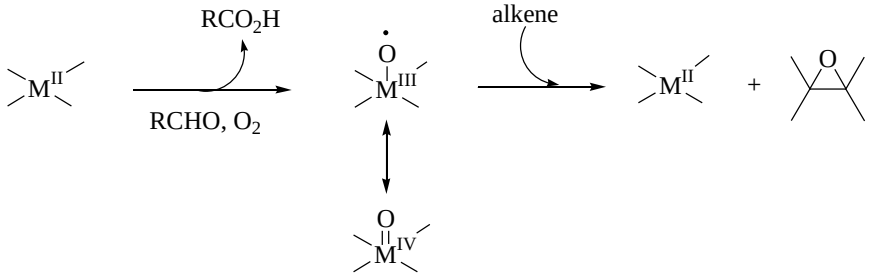


Scheme 50. *FBS Ru-catalyzed epoxidation by using* Mukaiyama *conditions.*

The *Mukaiyama* epoxidation requires molecular oxygen as terminal oxidant, in the presence of a metal catalyst, like Ru or Ni, and an aldehyde, which is converted to the corresponding carboxylic acid. Several studies have been carried out on this reaction, but the mechanism is still unclear. Two different pathways have been proposed[84], which involve a peracid or oxo-metal species as intermediates (Scheme 51):



Peracid epoxidation mechanism



Oxo-metal epoxidation mechanism

Scheme 51. *Proposed pathways for the* Mukaiyama *epoxidation*

[84] (a) K. Yanai, R. Irie, Y. Ito, T. Katsuki *Mem. Fac. Sci., Kyushu Univ., Ser. C* **1992**, *18*, 213; (b) W. Nam, H.J. Kim, S.H. Kim, R.Y.N. Ho, J.S. Valentine *Inorg. Chem.* **1996**, *35*, 6632; (c) K. Kaneda, S. Haruna, T. Imanaka, M. Hamamoto *Tetrahedron Lett.* **1992**, *45*, 213.

In the peracid pathway, it is supposed that the role of the metal catalyst is limited only to the generation of a peracid, which should be the real epoxidizing agent. In the oxo-metal pathway, the transfer of an oxygen atom from dioxygen to the alkene is mediated by a radical oxo-metal species formed in the complex active site. The last mechanism seems to be more probable, since formation of radical species at the metal center was observed by EPR measurements. Still no satisfying explanation is given for the need of two equivalents of aldehyde in the epoxidation reaction.

3.1 Synthesis of the catalyst

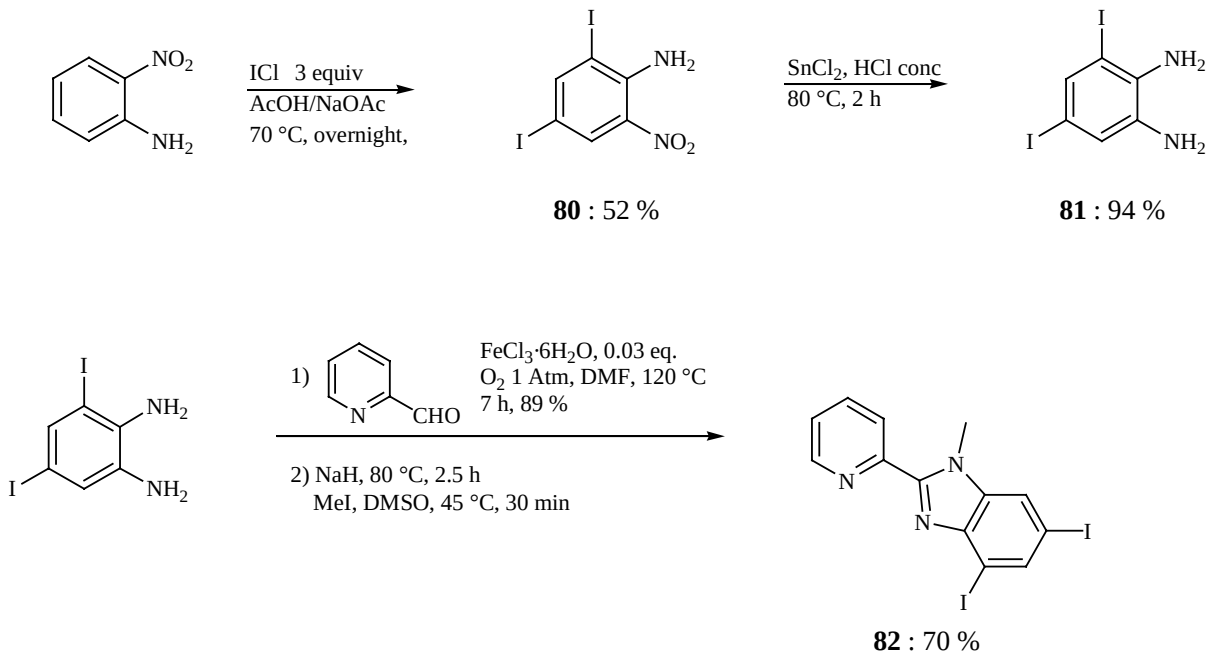
From previous attempts to prepare a suitable mixed ligand pyridine-imidazole for C-N oxidative coupling in FBS, the synthesis of two novel fluorous pyridine-benzimidazole ligands (*RfBimpy*) was developed. The first stage involves the preparation of the diiodo *N*-methylated pyridinyl-benzimidazole **82** building block (*I_2Bimpy*) in four steps, starting from cheap, commercially available 2-nitroaniline. Selective diiodination with ICl[85] in position 3 and 5, followed by reduction of the nitro group by $SnCl_2$/HCl[86], lead to the phenylendiamine **81**, which condenses with an equivalent of pyridine-2-carboxyaldehyde, in the presence of oxygen and a catalytic amount of $FeCl_3$[87], to provide 4,6-diiodo-2-pyridin-2-yl-1-*H*-benzoimidazole. The latter is readily methylated with methyl iodide, selectively providing **82** as a main isomer[88], which is easily obtained pure by simple recrystallisation from dichloromethane. (Scheme 52)

[85] S. Höger, K. Bonrad, A. Mourrau, U. Beginn, M. Möller *J. Am. Chem. Soc.* **2001**, *123*, 5651.

[86] Y. Tsubata, T. Suzuki, T. Miyashi, Y. Yamashita *J. Org. Chem.* **1992**, *57*, 6749.

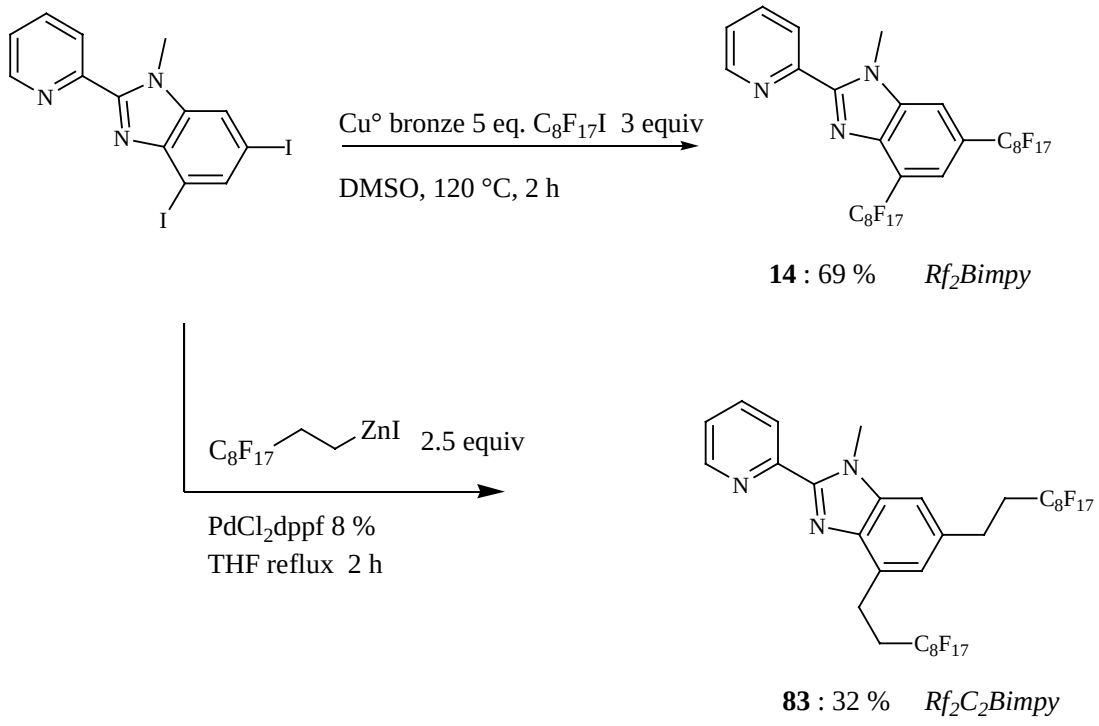
[87] M.P. Singh, S. Sasmal, W. Lu, M.N. Chatterjee *Synthesis* **2000**, 1380

[88] a 1- 5 % of the 5,7-diiodo isomer was detected.



Scheme 52. *Synthesis of the building block I_2Bimpy*

Starting from *I_2Bimpy* **82,** two different fluorous versions, with or without spacer, could be prepared (Scheme 53):



Scheme 53. *Synthesis of fluorous* Bimpy *ligands*

Rf_2Bimpy **14** is obtained in good yield by classical *Ullman* coupling with perfluorooctyl iodide in the presence of a large excess of Cu bronze. To achieve complete disubstitution on the benzimidazole ring, an excess of the fluorous iodide must also be employed.
Difunctionalization with a C-2 spacer fluorous ponytail occurs in moderate yield in the case of *Rf_2C_2Bimpy* **83**, by *Negishi* cross-coupling between **82** and the fluorous zinc reagent 1,1,2,2-tetrahydroperfluorodecylzinc iodide, in the presence of $PdCl_2$dppf as a catalyst. During the reaction course, complete disappearing of the starting material **82** was detected, but product degradation has been observed in the presence of silyl impurities contained in the zinc reagent. This could probably be assumed as a reason for the low recovered yield, since **83** is stable in its pure form.

Both compounds are selectively soluble in PFOB versus chlorobenzene and dichloromethane. The presence of the title compounds in solution can be quickly and easily verified both by quantitative GC analysis and qualitative UV-vis measurements, since they exhibit a characteristic blue fluorescence when exposed to UV light (295 nm).
The formation of complexes *in situ* with a number of transition metal salts in PFOB has been investigated in order to attain suitable catalysts for FBS oxidations (Table 9). The salts were dissolved in the minimum amount of a polar organic solvent (acetone, MeCN or dimethylsulfide in the case of CuBr·DMS), which did not affect the complex formation.

Table 9. ***Formation of complexes between Rf_2Bimpy, Rf_2C_2Bimpy and various metal salts.***

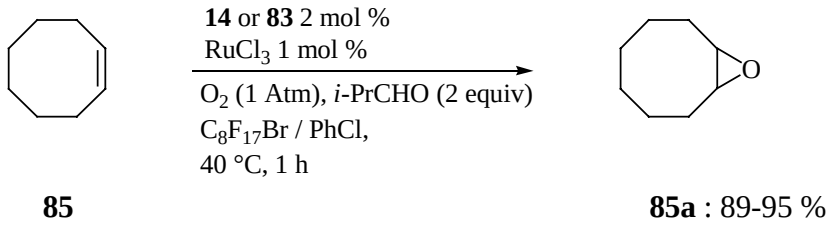
Metal salt	*Ratio metal : ligand*	*Rf_2Bimpy*	*Rf_2C_2Bimpy*
$CoCl_3$	1 : 1	---	---
CuBr·DMS	1 : 1	---	---
$CuCl_2$	1 : 1	green insoluble precipitate	---
$CuBr_2$	1 : 1	red insoluble precipitate	red insoluble precipitate
$Cu(NO_3)_2$	1 : 1	blue insoluble precipitate	---
$Ru(acac)_3$	1 : 1	---	---
$RuCl_3 \cdot xH_2O$	1 : 1, 1 : 2	red homogeneous solution	red homogeneous solution

Both compounds failed in providing 1:1 complexes with Co(III) and Cu(I) as in the case of CuBr·DMS. Coordination with Cu(II) salts lead to the formation of precipitates in the case of *Rf_2Bimpy*, which were not soluble neither in fluorous, nor in organic solvents. In this case, *Rf_2Bimpy* shows a better coordination ability in comparison with the analogous *Rf_2C_2Bimpy*, for which the formation of a Cu(II) complex was detected only with the bromide salt. The remarkable relationship between colour of the complexes and counterion at the copper suggests that the anion should also be involved in the coordination sphere of the fluorous complex. In the case of Ru(III), successful coordination was obtained with $RuCl_3$ for both ligands, leading to red complexes which are selectively soluble in PFOB versus chlorobenzene.

3.2 FBS epoxidations with Ru(III)-*Rf_2Bimpy*

The Ru(III) complexes with *Rf_2Bimpy* and *Rf_2C_2Bimpy* were tested in the epoxidation of olefines in a biphasic system PFOB/chlorobenzene. The use of dichloromethane as organic phase results in partial leaching of the complex in the organic layer. A metal/ligand ratio of 1:2 was used, in analogy to the structure of Ru-porphyrines which have already been used in Ru-catalyzed epoxidations. After formation of the complex, no free ligand was detected in both organic and fluorous phases.

For this epoxidation, the classical *Mukaiyama* protocol, which involves oxidation with molecular oxygen in the presence of two equivalents of isobutyraldehyde, was used. Optimized conditions for the epoxidation of *cis*-cyclooctene involve the use of a 1 mol % of ruthenium salt at 40 °C (Scheme 54). Complete conversion is achieved after only 1 h reaction time.



85 **85a** : 89-95 %

Scheme 54. *Epoxidation of* cis-*cyclooctene with Ru(III) complexes of Rf_2Bimpy and Rf_2C_2Bimpy in FBS*

Little or no conversion was detected in the absence of catalyst or aldehyde. Both complexes showed the same catalytic activity in the epoxidation of cyclooctene. Interestingly, a change of colour from red to dark blue was observed during the first 15 min of the reaction, indicating a possible different coordination, or variation of oxidation number of the Ru species. The colour of the complex remains red in the absence of the aldehyde, even under continuous oxygen flow.

Full conversion of isobutyraldehyde to the corresponding carboxylic acid was also detected from GC monitoring during all these reactions; no competitive complexation with the Ru species by this acid was observed in organic phase.

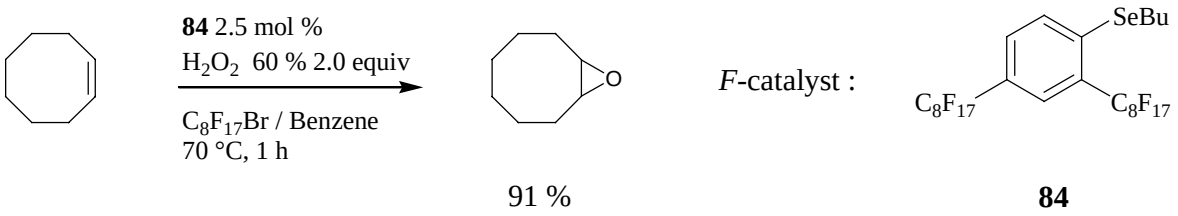
For epoxidation experiments, the ligand **14** *Rf_2Bimpy* was chosen, due to the higher fluorous content (62 %) in comparison with *Rf_2C_2Bimpy* (58 %). Experiments of catalyst recyclability in the epoxidation of cyclooctene were carried out by using the complex Ru(*Rf_2Bimpy*)$_2$. The blue fluorous phase was reused up to 10 times without apparent loss of activity, resulting in full conversion of the substrate (Table 10).

Table 10. *Epoxidation of cyclooctene by recycling the Ru complex of ligand **14***

Run	Yield[a] (%)	t (h)	Run	Yield[a] (%)	t (h)
1	89	1 h 15 min	6	91	1
2	91	1	7	90	1
3	93	1	8	90	1
4	90	1	9	93	1
5	95	1	10	92	1

[a]: recovered yields

These results show superior performances of the Ru(Rf_2Bimpy)$_2$ catalyst in comparison with the previously developed fluorous Ru-diketonate Ru-**12** (see Scheme 50). Only 1 mol % of catalyst is needed, in comparison with 5 mol % of Ru-**12**, and full conversion of cyclooctene is achieved in only 1 h reaction time, versus 5 h required in the case of Ru-**12** for the epoxidation of the same compound. In addition, the novel Ru(Rf_2Bimpy)$_2$ catalyst displays similar results for the selenium-catalyzed epoxidation in FBS, which has been recently performed in our group by using the fluorous selenide **84** (Scheme 55). Also in this case, a smaller amount of Ru(Rf_2Bimpy)$_2$ has to be employed, as well as a lower reaction temperature (40 °C versus 70 °C) for the above reported transformation.

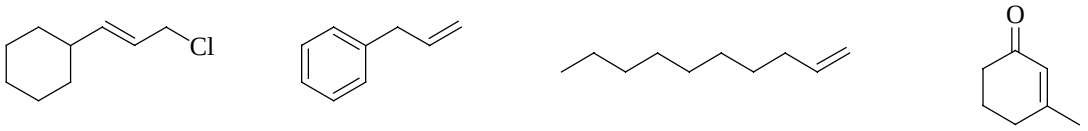


91 %

84

Scheme 55. *Se-catalyzed epoxidation in FBS*

A number of alkenes have been tested in the Ru-catalyzed epoxidation with $Ru(Rf_2Bimpy)_2$ in order to evaluate compatibility with functional groups and reactivity at the double bond (Table 11). As expected, alkenes bearing terminal double bonds or electron-withdrawing substituents showed a lower reactivity, as in the case of 1-chloro-3-cyclohexyl-2-propene **95**, allylbenzene **96**, 1-decene **97** and 3-methyl-cyclohex-2-enone **98**.

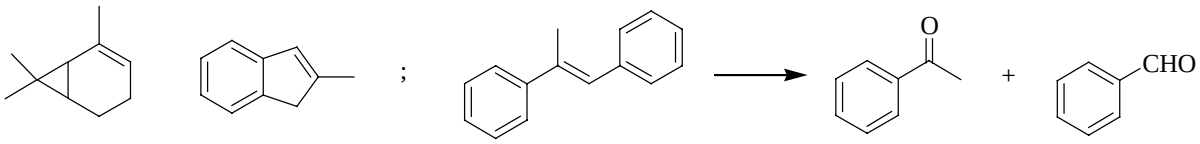


95 **96** **97** **98**

The first two compounds were converted to the corresponding epoxides at very low rates (10 - 18 % conversion) in the first 30 min, but further oxidation did not occur when leaving the reaction mixture for longer times or by addition of another equivalent of isobutyraldehyde. Partial degradation of the starting material was observed for 1-decene. Finally, no traces of oxidated products were detected with the unsaturated ketone **98**.

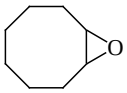
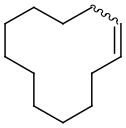
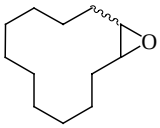
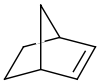
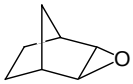
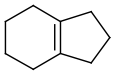
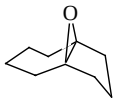
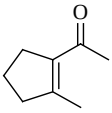
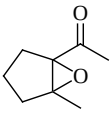
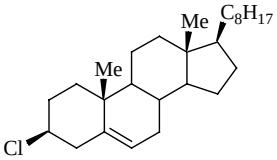
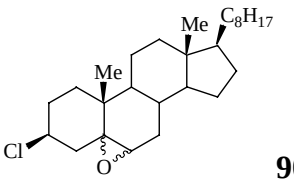
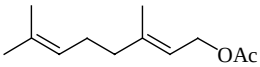
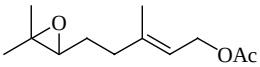
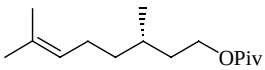
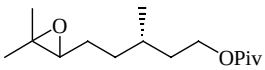
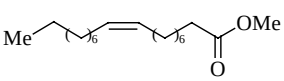
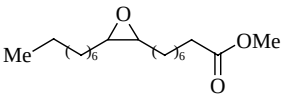
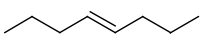
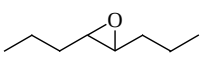
Decomposition with formation of complex reaction mixtures was observed with substrates which can potentially undergo rearrangements, as the carene **99** and 2-methyl-indene **100**.

For methylstilbene **101** mainly formation of the fragmentation products benzaldehyde and acetophenone in equimolar ratio was observed. The epoxide was detected by GC/MS analysis as unstable intermediate during the reaction course.



99 **100** **101**

Table 11. *Epoxides obtained by the aerobic oxidation of the alkenes **85-94** by using $Ru(Rf_2Bimpy)_2$ and isobutyraldehyde.*

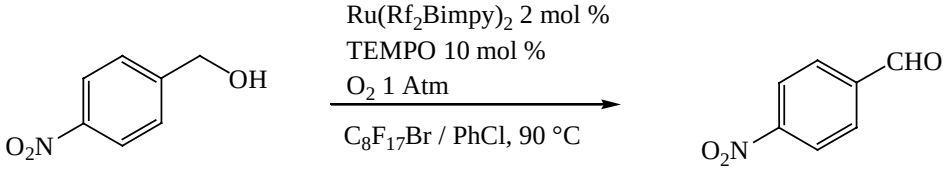
Entry	Alkene		Product		Reaction time	Yield (%)[a]
1		**85**		**85a**	1 h	89-95
2		**86**[b]		**86a**	50 min	92[c]
3		**87**		**87a**	1 h 15 ‘	83
4		**88**		**88a**	30 min	74
5		**89**		**89a**	1 h	73
6		**90**		**90a**	2.5 h	94[d]
7		**91**		**91a**	1 h	81
8		**92**		**92a**	40 min	92
9		**93**		**93a**	1 h	95
10		**94**		**94a**	1.5 h	78

[a] Yield of analytically pure product
[b] mixture of E/Z isomers
[c] mixture of *syn*- and *anti*- stereoisomers
[d] mixture of α and β stereoisomers (2 : 3)

In Table 11 are reported the results of the epoxidation for a variety of alkenes. In general, satisfactory yields and reaction rates were obtained. In the epoxidation of cyclic olefines, the ring size does not affect the reactivity, as shown for cyclooctene **85** and cyclododecene **86**. For norbornene **87**, epoxidation occurs until 88 % conversion, but longer reaction times always lead to the formation of mixtures, suggesting that non-selective rearrangements could take place. Addition of one equivalent of proton scavenger resulted in a complete inhibition of reactivity. Halogens (entry 6) and ester functionalities (entries 7, 8, 9) are well tolerated, and no degradation was observed. Protection of hydroxyl groups is required, as for citronellol pivalate **92**. Attempts of epoxidation of the unprotected citronellol lead to partial leaching of ruthenium in fluorous phase. Polysubstituted olefines react well, as shown for the hexahydroindene **88,** for which complete conversion was achieved in only 30 min, and geranyl acetate **91**, for which 100 % selectivity for the double bond in 6- position was obtained. An excellent reactivity was showed by the ketone **89**, which is particularly surprising when compared with the completely unreactive 2-methyl-cyclohexenone **98**. A difference in reactivity was also observed between *Z*- and *E*-4-octene. While the latter (entry 10) is completely converted to the desired epoxide, the *cis*- isomer undergo decomposition in the same reaction conditions.

3.3 FBS alcohol oxidation with Ru(III)-*Rf_2Bimpy*

On the basis of the work of *Sheldon*[52] on the TEMPO-mediated aerobic alcohol oxidation catalyzed by $RuCl_2(PPh_3)_3$, investigations on the ability of Ru(III)-*Rf_2Bimpy* to catalyze the same reaction were done. On this purpose, oxidation of 4-nitro-benzylalcohol was carried out in the same conditions as seen for the TEMPO/Cu-*F*-bipyridine system, by using 2 mol % of the Ru catalyst and 10 % TEMPO in a PFOB/chlorobenzene biphasic system, under O_2 atmosphere at 90 °C (Scheme 56).



Scheme 56. *FBS alcohol oxidation with Ru(III)-Rf_2Bimpy*

Partial conversion to 4-nitro-benzaldehyde of only 27 % after 1.5 h was observed, with cleavage of Ru from the fluorous phase and degradation of the co-catalyst TEMPO. Performing the reaction at lower temperature did not avoid the Ru leaching and the TEMPO degradation. A possible explanation could be a competitive complexation of the metal by species derivated from the TEMPO catalyst.

These results confirm the superiority of the fluorous Cu-bipyridine complex for the alcohol oxidation in FBS. However, further investigations on the Ru(III)-*Rf_2Bimpy* catalytic activity in FBS deserve to be carried out as, for example, in Ru-catalyzed FBS reductions with molecular hydrogen or oxidation of other substrates.

3.4 Summary

Two novel fluorous pyridine-benzimidazole ligands *Rf_2C_2Bimpy* and *Rf_2Bimpy* have been synthesized and complexes with several copper and ruthenium salts have been prepared. The 1:2 complexes between $RuCl_3$ and these ligands are stable and selectively soluble in perfluorooctyl bromide.

Ru(*Rf_2Bimpy*)$_2$ has been employed in the aerobic Ru-catalyzed Mukaiyama epoxidation. Good results have been achieved for the epoxidation of several substrates. Relationships between alkene structure, functional group tolerance and reactivity have been investigated.

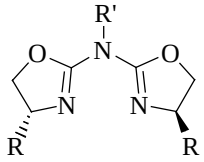
The use of the title complex for the TEMPO-mediated, Ru-catalyzed aerobic oxidation of alcohols to aldehydes did not lead to satisfactory results.

Further investigations on applicability of this catalyst for other Ru-catalyzed reactions in FBS should be developed.

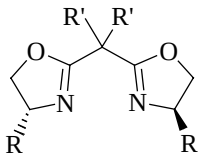
4 Fluorous oxazolines

Asymmetric catalysis in fluorous chemistry is a field of growing interest, and most recent applications include kinetic resolution of terminal epoxides[89], Ru-catalyzed hydrogenations[90] or Pd-catalyzed alkylation of prochiral allylic acetates[91].

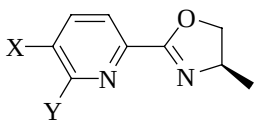
In the area of organic asymmetric catalysis, oxazoline derivatives have been introduced as versatile ligands for a variety of transformations[92], including copper-catalyzed cyclopropanation[93], ruthenium-catalyzed oxidations[94] or palladium-catalyzed allylic alkylation[95], as a C_2-symmetrical center or mixed ligand (Scheme 57).



102



103

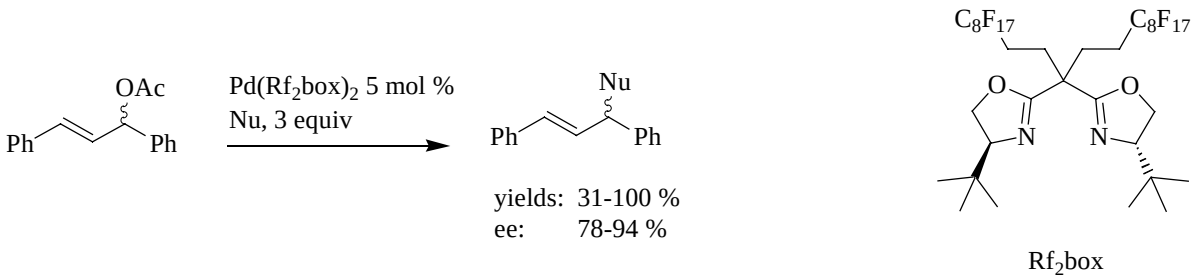


104

Scheme 57. *Examples of oxazoline ligands*

Immobilized versions of oxazoline ligands have been developed[96] and applied in copper-catalyzed cyclopropanation and palladium-catalyzed allylic alkylation, with good results. Therefore, it is of interest to prepare fluorous oxazolines for FBS asymmetric catalysis. Recently, the groups of *Pozzi*[97] and *Sinou*[98] prepared fluorous bisoxazolines (*Rf*-box) of type **103** for Cu-catalyzed styrene cyclopropanation and Pd-catalyzed allylic alkylation, respectively (Scheme 58).

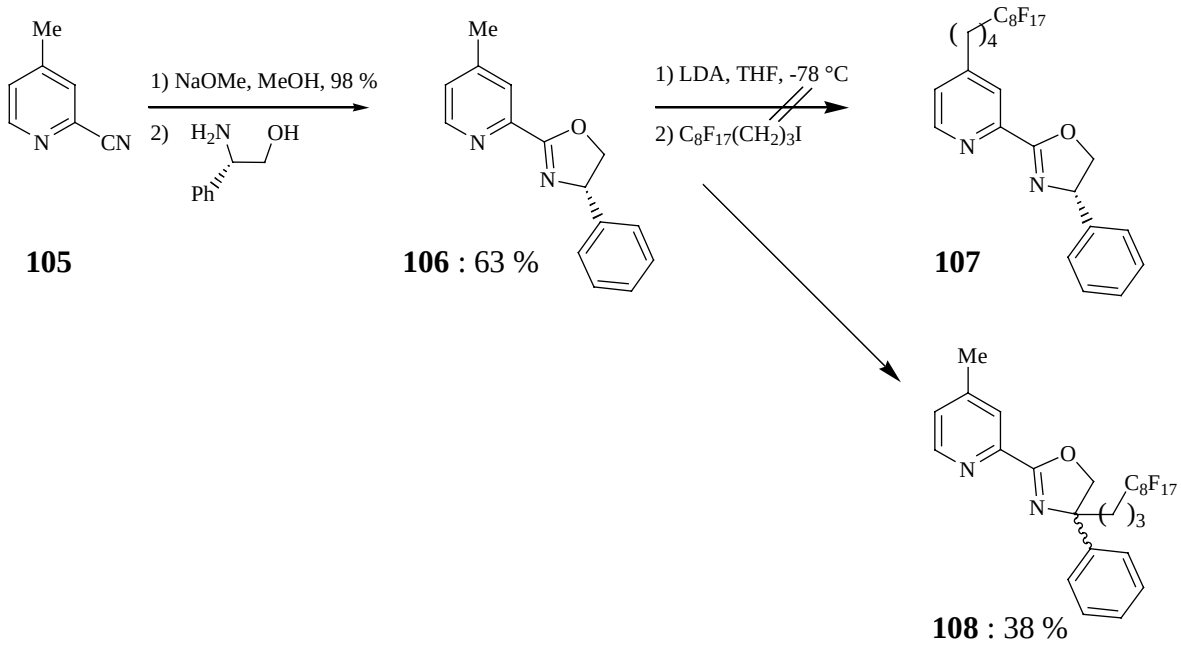
[89] M. Cavazzini, S. Quici, G. Pozzi, *Tetrahedron* **2002**, *58*, 3943
[90] D.J. Birdsall, E.G. Hope, A.M. Stuart, W. Chen, Y. Hu, J. Xiao *Tetrahedron Lett.* **2001**, *42*, 3053
[91] D. Maillard, J. Bayardon, J.D. Kurichiparambil, C. Nguefack-Fournier, D. Sinou *Tetrahedron: Asymmetry* **2002**, *13*, 1449.
[92] For a review: A.K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1.
[93] M. Glos, O. Reiser *Org. Lett.* **2000**, *2*, 2045.
[94] N. End, A. Pfaltz *Chem. Comm.* **1998**, 589.
[95] G. Chelucci, S. Deriu, G.A. Pinna, A. Saba, R. Valenti *Tetrahedron: Asymmetry* **1999**, *10*, 3803.
[96] (a) A. Cornejo, J.M. Fraile, J.I. Garcia, E. Garcia-Verdugo, M.J. Gil, G. Legarreta, S.V. Luis, V. Martinez-Merino, J.A. Mayoral *Org. Lett.* **2002**, *4*, 3927; (b) K. Hallmann, E. Macedo, K. Nordström, C. Moberg *Tetrahedron: Asymmetry* **1999**, *10*, 4037
[97] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Pozzi, *Eur. J. Org. Chem.* **2003**, 1191.
[98] J. Bayardon, D. Sinou *Tetrahedron Lett.* **2003**, *44*, 1449



Scheme 58. Sinou *fluorous asymmetric allylic alkylation*

We briefly investigated the possibility to prepare fluorous oxazolinylpyridines of type **104** for application in asymmetric Pd-catalyzed allylic alkylations or Cu-catalyzed allylic oxidation of cyclohexene. The most convenient synthetic pattern involves the functionalization of the pyridine ring, but an opportune spacer has to be introduced, since electron-withdrawing substituents limit the catalytic activity[97]. The oxazoline ring could be easily built starting from the 2-cyano-picoline **105**, which was quantitatively converted to the corresponding imidate with methanol and furthermore coupled with the aminoalcohol (*S*)-(+)-2-amino-2-phenyl-ethanol, providing the oxazolinylpyridine **106** in a 63 % yield.

Further deprotonation with LDA, followed by quenching with the fluorous iodide **21** did not lead to the desired product **107**. Instead, only alkylation at the oxazoline ring was found, providing the racemic fluorous oxazolinylpyridine **108** in moderate yield (Scheme 59).



105

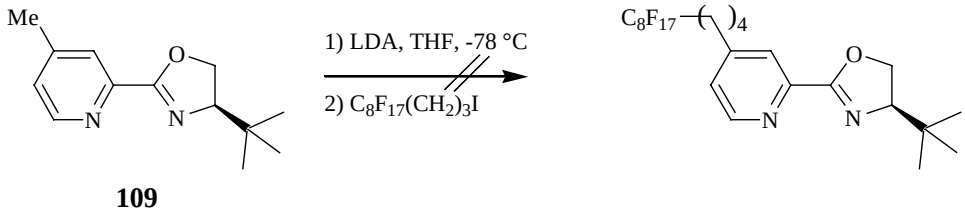
106 : 63 %

107

108 : 38 %

Scheme 59. *Attempted synthesis of a fluorous oxazolinylpyridine*

Alternatively, a more sterically hindered oxazolinylpyridine, like the *t*-butyl derivative **109**, was tested. Again, no alkylation was observed for this compound (Scheme 60).



109

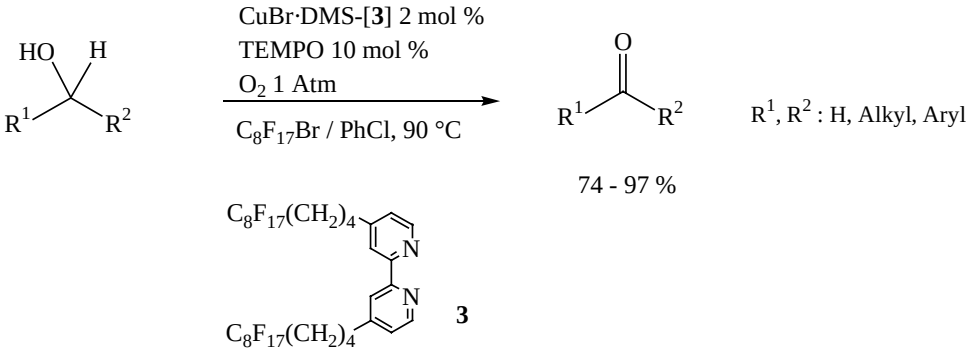
Scheme 60. *Attempted synthesis of a fluorous oxazolinylpyridine*

Therefore, an alternative strategy for the synthesis of fluorous oxazolinylpyridines must be developed, starting, for instance, from opportune polyhalogenated pyridines. The presence of at least two fluorous ponytails should be also taken in account, in order to achieve a satisfactory fluorophilicity.

5 Summary and Overlook

This work has been focused on the development of new fluorous ligands and methods for the oxidation of organic substrates by using the Fluorous Biphase System (FBS) protocol.

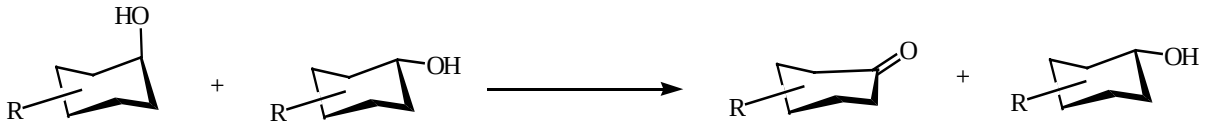
In the first part, the FBS version of *Semmelhack* aerobic oxidation of alcohols, catalyzed by the radical TEMPO and a fluorous complex between CuBr and the perfluorinated bipyridine **3**, was subject of a detailed study in order to elucidate the chemical behaviour of the less reactive secondary aliphatic alcohols.



Scheme 61. *Cu-catalyzed alcohol oxidation in FBS*

It was found that an optimal amount of 10 mol % TEMPO can help to increase yields and reaction times in the first catalytic cycle. However, the presence of an aliphatic residue inhibits an efficient reuse of the fluorous phase, and a poisoning effect attributable to the product ketone was observed. Therefore, the problem of reactivity of secondary aliphatic substrates cannot be trivially solved.

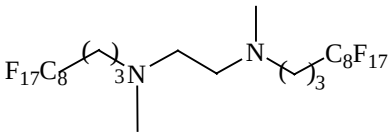
An interesting chemoselectivity was observed for the first time in the oxidation of substituted cyclohexanols by using this protocol. An axial hydroxyl group is oxidized faster that a corresponding equatorial one. Similar selectivities can be achieved by using other oxidative systems, but in our case a clear advantage is related to the environmental-friendly aspects of this FBS protocol. This selectivity can find a possible convenient application in oxidations of bioactive substrates.



cis- trans- mixture

Scheme 62. *Chemoselectivity in cyclohexanols oxidation*

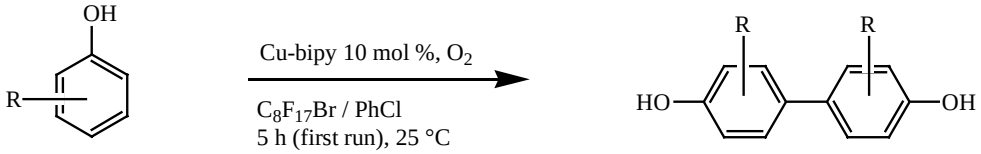
A variety of fluorous tertiary amines has been synthesized by using the simple end efficient *Katritzky* protocol, among them the fluorous version **57** of the versatile TMEDA. These amines readly provide complexes with Cu(I).



57

Rf_2DMEDA was tested as a ligand in the Cu-catalyzed alcohol oxidation, where the superiority of the bypiridine catalyst was demonstrated. However, due to the wide field of application for TMEDA, its fluorous version could find several further uses in organic synthesis.

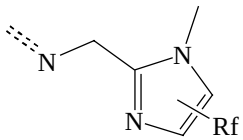
The second part of this work was focused on the applicability of copper-catalized aerobic C-C and C-N oxidative coupling to the FBS synthesis. Satisfactory results were obtained for the aerobic phenol homocoupling in the case of electron-rich substrates.



Scheme 63. *Phenol oxidative homocoupling in FBS*

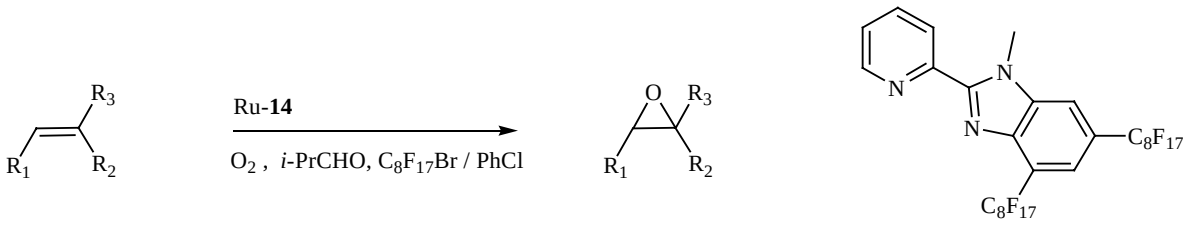
C-N coupling between arylboronic acids and arylamines showed strong limitations due to the leaching of copper from the fluorous medium during the reaction.

In the next part, the synthesis of novel perfluorotagged imidazole ligands of general structure **110** was investigated. Direct functionalization of the imidazole ring was found to be difficult, due to the peculiar electronic properties of both fluorous ponytail and heterocycle.



110

Two novel fluorous pyridine-benzimidazole ligands *Rf_2C_2Bimpy* and *Rf_2Bimpy* have been synthesized. The 1:2 complex between $RuCl_3$ and *Rf_2Bimpy* has been successfully tested in the *Mukaiyama* epoxidation protocol, leading to satisfactory results for a variety of substrates.

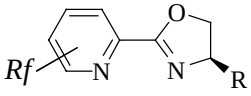


Rf_2Bimpy **14**

Scheme 64. *Ru-catalyzed epoxidation in FBS with Rf_2Bimpy as ligand.*

The use of the title complex for the TEMPO-mediated, Ru-catalyzed aerobic oxidation of alcohols to aldehydes did not let to satisfactory results. However, further investigations on applicability of this catalyst for other Ru-catalyzed reactions in FBS should be developed.

Finally, a short glance was taken at the possibility to prepare fluorous oxazolinyl pyridines of type **111**:



111

The main problem was related to an effective functionalization of the pyridine ring with fluorous ponytails, which is not easily achieved by standard protocols. Therefore, alternative synthetic strategies should be developed.

Experimental Section

1. General Conditions

All reactions were carried out with magnetic stirring and, if air or moisture sensitive, under Argon in flame-dried glassware. Syringes and cannules used for transferring of reagents and solvents were purged with argon prior to use.

Reagents and Solvents

When needed, dry solvents stored under argon were used. The solvents were distilled over drying agents as stated below:

- CH_2Cl_2, DMF, Pentane: CaH_2
- Diethyl ether, Hexane, THF: Na/benzophenone
- Toluene: Na
- Pyridine, Triethylamine: KOH
- Perfluorinated solvents, Chlorobenzene: MS 4Å

Reagents of > 98 % purity were used as obtained, as well as perfluorooctyl bromide.
Perfluorooctyl iodide was distilled under high vacuum.
n-Butyllitium was used as 1.5 M solution in hexane.

Titration of organometallic reagents

Organomagnesium and organolitium solutions were titrated using the Paquette's method[99].
The concentrations of organozinc solutions were determined by back titration of iodine with aqueous $Na_2S_2O_3$.

[99] H-S. Lin, L. A. Paquette *Synth. Commun.* **1994**, *24*, 2503.

Chromatography

Thin layer chromatography (TLC) was carried out by using aluminium plates covered with SiO_2 (Merck 60, F-254). Detection was performed under UV-light and/or by treatment with one of the following solutions :
$KMnO_4$ (0.3 g), K_2CO_3 (20 g), KOH (0.3 g) in water (300 mL)
Phosphormolybdic acid (5 g), $Ce(SO_4)_2$ (2.0 g), H_2SO_4 (12 mL) in water (230 mL).

Flash column chromatography was performed with flash silica gel 60 (0.040 - 0.063 mm) from Merck

Gas Chromatography (GC): Hewlett Packard 6890 equipped with flame ionisation detector. In gaschromatographic determinations, decane or tetradecane were added as internal standard.

Column A: 5 % Phenylmethylpolysiloxane (HP Ultra 2) 12 m x 0.2 mm
Column B: 5 % Phenylmethylpolysiloxane (HP %) 5 m x 0.25 mm

Analytical data

- *Melting points*: were determined on a Buchi B-540 apparatus and are uncorrected

- *NMR spectra*: were measured on Brucker ARX 200, AC 300 or WH 400 instruments. Chemical shifts are reported as d-values in ppm related to the deuterated solvent peak: $CDCl_3$ (δ_H: 7.27, δ_C. 77.0). The following abbreviations were applied to indicate signal multiplicities: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), as well as br (broad).

- *Infrared (IR) spectra*: were recorded from 4000-400 cm^{-1} on a Nicolet 510 Ft-IR or a Perkin-Elmer 281 IR spectrometer. Samples were measured either as a film between NaCl plates or (for solids) as KBr tablets. The absorption bands are reported in wave numbers (cm^{-1}) and the following abbreviations are applied: br (broad), s (strong), m (medium), w (weak).

- *Electron Impact Mass (EI, 70 eV) spectra*: were recorded on a Varian MAT CH 7A instrument. High resolution mass spectra (HRMS) were recorded on a Varian Mat 711 instrument. A GC/MS from Hewlett-Packard HP 6890/MSD 5973 was used for the combination of gas chromatography with mass spectroscopic detection.
  Column C: 5 % Phenylmethylpolysiloxane (HP 5) 30 m x 250 µm x 0.25 mm

- *Elemental analysis*: was carried out on a Heraeus CHN-Rapid-Elementanalyzer in the microanalytical laboratories of the Department Chemie und Pharmazie, LMU Munich.

2 Typical Procedures (TP)

2.1 Typical procedures for oxidations in Fluorous Biphase System

TP 1: Typical procedure of alcohol oxidation in FBS (method A)

A 25 mL-Schlenk-flask, equipped with a stirrer and a O_2-inlet, was charged with the bipyridine **3** (44.0 mg, 40 μmol, 2 mol %) dissolved in perfluorooctyl bromide (2 mL) and $CuBr{\cdot}Me_2S$ (9.2 mg, 40 μmol, 2 mol %) dissolved in a small amount of dimethyl sulfide, leading to a green-brown solution. After stirring for 0.5 h a solution of the alcohol (2 mmol) and TEMPO (32.0 mg, 200 μmol, 10 mol %) in chlorobenzene (2 mL) was added. The biphasic reaction mixture was stirred at 90 °C while a gentle stream of oxygen was passing. At the end of the reaction, the mixture was cooled to 0 °C, the organic layer was decanted and the fluorous phase was washed with chlorobenzene (3 x 2 mL). The combined organic phases were diluted with ether (30 mL) and washed with brine. After drying ($MgSO_4$), filtration, evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography (eluent: diethyl ether-pentane, ratio depending on the ketone). The fluorous phase was used directly for further reaction runs.

Modified workup procedure (method B)

This procedure is suitable when chromatographic separation between product and TEMPO is difficult (e.g. 2-decanol, cycloheptanone and other aliphatic alcohols).
The reaction mixture is treated with a concentrated aqueous solution of $NaHSO_3$ and 10 mL MeOH. A white, copious precipitate of the bisulphite adduct is obtained, which is filtered, washed with ether and added to a 10 % solution of Na_2CO_3 in water, then stirred to a complete dissolution. The product is recovered by extraction from the aqueous phase with ether (3 x 20 mL). The organic solution is dried ($MgSO_4$), filtered and the solvent evaporated under vacuum, yielding analytically pure product.

TP 2: Typical procedure of alkene epoxidation in FBS

A 25 mL-Schlenk-tube, equipped with a stirrer and a O_2-inlet was charged with the fluorous benzimidazole **14** (52.0 mg, 50 μmol, 2 mol %) dissolved in perfluorooctyl bromide (2.5 mL), and $RuCl_3 \cdot xH_2O$ (36 % Ru, 7 mg, 25 μmol, 1 mol %) dissolved in a small amount of acetone, leading to a red solution. After stirring for 0.5 h a solution of the alkene (2 mmol) and *i*-PrCHO (288.0 mg, 4 mmol, 2 eq.) in chlorobenzene (2 mL) was added. The biphasic reaction mixture was stirred at 40 °C while a gentle stream of oxygen from a balloon was passing. The colour of the reaction mixture changes from red to deep blue. At the end of the reaction, the mixture was cooled to 10 °C, the organic layer was decanted and the fluorous phase was washed with chlorobenzene (3 x 2 mL). The chlorobenzene is removed in vacuo and the residue diluted with dichloromethane (30 mL). The organic phase is treated with cold NaOH (0.1 M, 20 mL) and washed with brine. After drying over $MgSO_4$, filtration and evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography (eluent: diethyl ether-pentane, ratio depending on the epoxide). The blue fluorous phase was used directly for further reaction runs.

2.2 Typical procedures for preparation of starting materials

TP 3: Synthesis of benzotriazole diamine derivatives[100]

A 250 mL round-bottomed flask is charged with benzotriazole (60 mmol) and water (100 mL), obtaining a white suspension. The diamine (30 mmol) is added to the mixture, resulting in a clear solution which is stirred 15 min at rt. A solution of formaldehyde in water (37%, 4.90 mL, 60 mmol) is then added dropwise under energic stirring. A white powder separates immediately, with exotermic reaction (to avoid formation of a massive precipitate, additional water and/or MeOH can be added). The resulting suspension is stirred for an additional 30 min, then filtered and the excess of water removed *in vacuo* by azeotropic distillation with toluene. The white precipitate is dried overnight under high vacuum, yielding 73 – 93 % of analytically pure product.

TP 4: Synthesis of fluorous tertiary amines

The fluorous Grignard (22 mmol) in Et_2O is charged to a 250 mL dry Schlenk flask under Ar atmosphere at rt. A solution of the benzotriazole amine derivative (10 mmol in 100 mL dry THF) was then added dropwise at rt (reaction slighty exotermic). A white turbidity is formed and the mixture is let stirring overnight at rt. The brown suspension is quenched with a saturated NH_4Cl aqueous solution, then washed with 50 mL of an aqueous NaOH solution 10 % m/v. The aqueous phase is extracted with diethyl ether (3 x 20 mL) and the collected organic phases are evaporated *in vacuo*, then diluted with diethyl ether and dried over $MgSO_4$. The ether is removed, yielding a crude solid which can be purified by recrystallisation in an opportune solvent to remove the fluorous impurities (mainly homocoupling from Grignard solution).

[100] A.R.Katritzky, B.Pilarski, L.Urogdi *J. Chem.Soc. Perkin Trans.* **1990,** 541.

TP 5: Reduction of ketones to cis/trans cyclohexanols[101]

A dry 25 mL Schlenk flask, equipped with magnetic stirrer, was charged under Ar atmosphere at rt with the catalyst $RhCl(PPh_3)_3$ (40 mg, 0.04 mmol), giving a homogeneous red solution. A solution of the ketone (4.30 mmol) and diphenylsilane (0.946 mg, 5.13 mmol, 1.2 equiv) in 4 mL dry benzene was added to the catalyst. The yellow mixture was then diluted with an additional 3 mL of dry benzene and stirred under Ar at rt until complete conversion. The benzene was removed *in vacuo* and the residue boiled at T = 100 °C for 30 min in 20 ml of a solvent mixture of H_2O/MeOH 1:1 containing a large excess (3 equiv) of TsOH. After cooling, the solvents were removed in vacuo and 30 mL of diethyl ether were added. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent removed, yielding a crude which was purified by flash chromatography on silica gel.

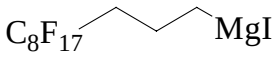
[101] K.Felföldi, I.Kapocsi, M.Bartók *J. Organometallic Chem.* **1989,** *362*, 411

3 Synthesis of fluorous Organometallic Reagents

Synthesis of perfluorooctylmagnesium bromide[62]

A dry 250 mL Schlenk flask with Ar inlet and magnetic stirring is charged with 10 mmol of perfluorooctyl iodide and 10 mL dry diethyl ether at –78 °C. A solution of PhMgBr (10 mmol) in dietyl ether is added dropwise at –78 °C and stirred 10 min. The complete exchange is checked by GC/MS analysis. The Grignard is stable only at –78 °C and must be used immediately.

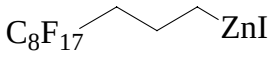
Synthesis of 1,1,2,2,3,3-hexahydro-perfluoroundecan-1-magnesium iodide



A 250 mL three-necked dry Schlenk flask, equipped with a reflux condenser, Ar-inlet and a 50 mL dropping funnel is charged with 100 mL dry diethyl ether and Mg powder (4.37 g, 180 mmol, 3 eq.) under Ar atmosphere at RT. 5 mL of a solution of 1,1,2,2-tetrahydro-1-iodoperfluorodecane (34. g, 60 mmol) in 40 mL dry diethyl ether are added to the Mg suspension and stirred while careful heating with the heat gun for few seconds. The operation is repeated several times till activation of Mg. The remaining solution of the fluorous iodide is added dropwise at RT within 1 h. The reaction must be spontaneously exotermic (35–40 °C). Typical yields are around 75 % (checked by iodolysis and hydrolysis of a sample, and titration), Wurtz homocoupling being the most byproduct.

The solution can be stored at 0 °C and is stable within several months.

Synthesis of 1,1,2,2,3,3-hexahydro-perfluoroundecan-1-zinc iodide[102]



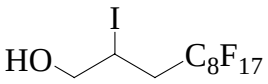
A dry 100 mL Schlenk flask equipped with Ar inlet and magnetic stirrer is charged with Zn powder (9.82 g, mmol) in 5 mL dry THF and dibromoethane (10 mg/mmol Zn). Heat gently with heat gun until development of a continuous flow of bubbles (Zn activation). After cooling at rt, TMSCl (0.75 mL) is added dropwise (rather exotermic reaction), followed by slow addition of a solution of the fluorous iodide (50 mmol in 30 mL dry THF). The reaction is exothermic and the temperature should be kept around 35 – 40 °C. Stirr an additional hour, then cannulate the solution and centrifuge it at 2000 rpm for 1 h. Concentration is checked by iodolysis, idrolysis and titration.
The solution can be stored at 0 °C and is stable within several months.

[102] S.C. Berk, M.C.P. Yeh, N. Jeong, P. Knochel *Organometallics* **1990**, *9*, 3035

4 Cu(II)-catalyzed Aerobic Oxidation of Alcohols in FBS

4.1 Synthesis of Fluorous Ponytails

Synthesis of 1,1,2,3,3-pentahydro-2-iodo-perfluoroundecan-1-ol (19)



A dry, argon flushed 50 mL Schlenk tube was charged with fresh distilled allyl alcohol (2.20 g, 38 mmol) and perfluorooctyl iodide (18.1 g, 33 mmol). The mixture was melted at 70 °C under argon and AIBN (200 mg, 1.2 mmol) was added under vigorous stirring. After 2 h the mixture was cooled to rt and an additional portion of AIBN (200 mg) was added, then the temperature was raised to 70 °C. The procedure was repeated identically other 2 times. After the 4th addition of AIBN the mixture was let stirr overnight at 70 °C, with formation of a yellowish paste, which was recrystallised from hot pentane. The pure product is purified by flash chromatography (pentane/diethyl ether 1:2), yielding **19** as white solid (15.57 g, 78 %).

Mp: 95-96 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 1334 (w), 1205 (s), 1148 (s), 1044 (w), 661 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 4.44 (m, 1H), 3.82 (m, 2H), 3.20-2.60 (m, 2H), 2.03 (bs, 1H).

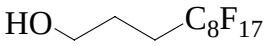
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 122-108 (bm), 67.9, 37.6 (t), 21.7.

^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -79.8 (3F), -111.1 ÷ -113.5 (m, syst. AB, 2F), -120.5 (s, 2F), -120.8 (bs, 4F), -121.7 (s, 2F), -122.4 (s, 2F), -125.1 (s, 2F).

MS (EI, 70 eV m/e (rel. int.)): 603 (4), 477 (100), 457 (35), 389 (9), 339 (6), 169 (6), 131 (6), 119 (8), 69 (16), 57 (16).

$C_{11}H_6F_{17}IO$	Calcd.	C, 21.87	H, 1.00
	Found	C, 21.89	H, 1.11

Synthesis of 1,1,2,2,3,3-hexahydro-perfluoroundecan-1-ol (20)



A dry, argon flushed 100 mL Schlenk tube was charged with the perfluoroiodoalcohol **19** (7.60 g, 13 mmol) of in 40 mL degassed dry toluene and the resulting suspension was heated to 60 °C under argon till dissolution. The mixture was cooled to 40 °C, then 50 mg of AIBN and fresh distilled Bu_3SnH (4 mL, 15 mmol) were added. The solution was heated to 85 °C under stirring until all the iodoalcohol disappeared (30 min - 2 h). An additional portion of stannane must be added if the conversion is not complete. After partial removing of the toluene in vacuo and cooling, the product separates from the solution as white needles, which were dissolved in diethyl ether and treated with a saturated aqueous solution of KF until no more white solid is formed. The organic phase is recovered, washed with brine and dried over $MgSO_4$, the solvent removed in vacuo, yielding **20** as a white solid (4.66 g, 75 %).

Mp: 43-45 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3393 (m), 2957 (w), 1635 (w), 1333 (m), 1204 (s), 1149 (s), 1021 (m), 658 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 3.66 (t, *J* = 5.8 Hz, 2H), 2.28-2.01 (m, 2H), 1.78 (m, 2H), 1.57 (s, 1H).

^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 120-100 (bm), 63.0, 28.4, 23.5.

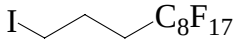
^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -80.3 (s, 3F), -112.6 (s, 2F), -122.1 (s, 2F), -122.5 (s, 4F), -123.1 (s, 2F), -124.1 (s, 2F), -126.0 (s, 2F).

MS (EI, 70 eV m/e (rel. int.)): 477 ([M^+ - 1], 9), 441 (20), 394 (71), 345 (13), 281 (6), 181 (15), 169 (27), 145 (10), 139 (10), 131 (71), 119 (49), 109 (49), 100 (28), 91 (64), 77 (46), 69 (100), 59 (29).

$C_{11}H_7F_{17}O$ Calcd. 478.0226

Found 477.0109 [M^+ - 1]

Synthesis of 1,1,2,2,3,3-hexahydro-1-iodo-perfluoroundecane (21)



A 250 mL round bottomed flask, equipped with a reflux condenser and a magnetic stirrer, was cooled to 0 °C and carefully charged with 24 mL of H_3PO_4 85 % and 11.7 g of P_2O_5 while stirring. KI (7.00 g, 42 mmol) and the perfluoroalcohol **20** (4.76 g, 10 mmol) where added to the mixture at the same temperature and the resulting suspension was heated to 120 °C. The brown-black mixture was stirred for 4 h, then cooled to 0 °C in ice bath. 20 mL of water were carefully added (very exothermic reaction!), followed by 100 mL of diethyl ether. The phases were separated and the aqueous one was washed three times with diethyl ether (30 mL). The ether phases are collected and washed with 2 % aqueous $Na_2S_2O_3$ until iodine disappeared. Washing with brine, drying over $MgSO_4$, and further removal of the solvent in vacuo, yielded analytically pure **21** as white solid (5.470 g, 93%).

Mp:

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 2962 (w), 1334 (m), 1246 (s), 1203 (s), 1149 (s), 805 (m), 659 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 3.17 (t, *J* = 6.2 Hz, 2H), 2.28-2.01 (m, 4H).

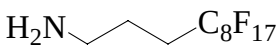
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz):121-106 (m), 31.0 (t), 23.4, 2.7.

^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -79.9 (s, 3F), -112.8 (m, 2F9, -120.7 (s, 2F), -121.0 (s, 4F), -122.5 (s, 2F), -125.2 (s, 2F), -125.2 (s, 2F).

MS (EI, 70 eV m/e (rel. int.)): 588 (2), 461 (100), 395 (47), 377 (6), 169 (10), 154 (35), 131 (26), 126 (18), 119 (19), 91 (26), 77 (13), 69 (38).

$C_{11}H_6F_{17}I$ HRMS Calcd. 587.9243
Found 587.9248

Synthesis of 1,1,2,2,3,3-hexahydro-1-amino-perfluoroundecane (28)



To a round-bottomed 50 mL flask equipped with magnetic stirrer and reflux condenser were added the fluorous iodide **21** (4.983 g, 8.0 mmol), NaN_3 (1.041 g, 16 mmol) and trioctymethylammonium chloride (188 mg) in 5 mL H_2O. The suspension was refluxed under vigorous stirring at 100 °C for

7 h. After cooling to rt, the mixture was decanted, and the upper aqueous phase separated. The white organic phase was kept in the same flask, where Ni-Raney (50 mg) and a solution of hydrazine monohydrate (0.306 g, 6.1 mmol) in 5 mL H_2O were added at rt. The emulsion was vigorously stirred and heated to 60 °C for 16 h. After cooling, the mixture was extracted with 30 mL diethyl ether and the organic phase was washed with water (3 x 20 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue distilled under high vacuum, yielding pure **28** as a waxy solid (2.40 g, 56 %).

IR (KBr, cm^{-1}) $\tilde{\nu}$ 3380 (b), 3296 (w), 2952 (w), 2952 (w), 2876 (w), 1242 (s), 1204 (s).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 2.79 (t, *J* = 7 Hz, 2H), 2.27-2.01 (m, 2H), 1.80-1.66 (m, 2H), 1.24 (bs, 2H).

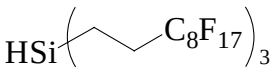
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 110-120 (m), 41.3, 28.6, 24.1.

^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -81.3 (s, 3F), -114.6 (s, 2F), -122.1 (s, 2F), -122.4 (s, 4F), -123.2 (s, 2F), -123.9 (s, 2F), -126.5 (s, 2F).

MS (EI, 70 eV m/e (rel. int.)): 446 (M^+-1, 0.5), 458 (7), 69 (20), 30 (100).

$C_{11}H_8F_{17}N$ HRMS Calcd. 476.0307
Found 476.0318

Synthesis of tri(1,1,2,2-tetrahydroperfluorodecyl)-silane (22)



To a 100 mL Schlenk flask with Ar inlet was added a solution of the fluorous Grignard reagent 1,1,2,2-tetrahydroperfluorodecylmagnesium iodide (19 mmol) in diethyl ether, followed by $HSiCl_3$ (0.6 mL, 6.0 mmol), dropwise at rt under Ar atmosphere. The solution was vigorously stirred at rt for 3 days, while a slight exotermic reaction with turbidity formation took place. The mixture was then quenched dropwise with 20 mL water , the ether phase separated and the solvent removed *in vacuo*. The pure product was obtained by Kugelrohr distillation, yielding a white waxy solid (7.35 g, 88%), which is stable within several months when stored at 4 °C.

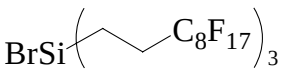
IR (Film, cm^{-1}) $\tilde{\nu}$: 2949 (w), 2140 (w), 1239 (s), 1206 (s), 1150 (s), 919 (w), 705 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 1.22 (m, 6H), 2.34 (m, 6H).

^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -81.6 (9F), -114.2 (6F), -122.3 (12F), -123.1 (6F), -123.8 (6F), -126.9 (6F).

Data are in agreement with the literature[103]

Synthesis of bromo-tri(1,1,2,2-tetrahydroperfluorodecyl)-silane (23)



To a 100 mL Schlenk flask with Ar inlet was added a solution of the fluorous silane **22** (8.220 g, 6.0 mmol) in 10 mL perfluorohexane (FC-72), followed by the dropwise addition of Br_2 (2.14 g, 13.2 mmol) at 0 °C under Ar atmosphere, leading to an orange solution. The mixture was then stirred 18 h at rt under continuous Ar flow to remove HBr. The excess of bromine was removed by washing the fluorous phase with dry DCM (7 x 10 mL) under Ar. The fluorous solvent was removed under high vacuum, yielding a white solid (8.0 g, 92 %), which was used directly for the next steps without further purification. The compound is moisture-sensitive and must be stored rigorously under Ar at low temperature.

IR (KBr, cm^{-1}) $\tilde{\nu}$: 2950 (w), 1240 (s), 1209 (s), 1148 (s), 912 (w), 706 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 200 MHz): 2.21 (m, 6H), 1.13 (m, 6H).

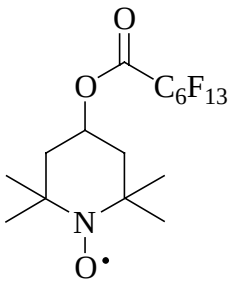
^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -81.6 (9F), -116.0 (6F), -122.0 (12F), -122.8 (6F), -123.4 (6F), -126.4 (6F).

Data are in agreement with the literature[105]

[103] D. Schwinn, W.Bannwarth *Helv. Chim. Acta* **2002**, *85*, 255

4.2 Synthesis of Fluorous TEMPO and Pyridines

Synthesis of perfluoroheptanoic acid 2,2,6,6-tetramethyl-piperidin-4-oxyl ester (26)



To a two-necked 100 mL Schlenk flask with Ar inlet were added 4-hydroxy-2,2,6,6-tetramethyl-piperidin-1-oxyl (0.733 g, 4.3 mmol) and dry TEA (0.513 g, 5.1 mmol) in 20 mL dry diethyl ether. To this solution was added dropwise at 0 °C a solution of perfluoroheptane acid chloride in 10 mL dry diethyl ether. The mixture was stirred at the same temperature for 2 h, with formation of a precipitate, which was filtered off. The orange solution was washed with water (3 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*, giving a residue which was purified by flash chromatography (eluent DCM) on silica gel. The product was obtained as a crystalline orange solid (1.01 g, 46 %).

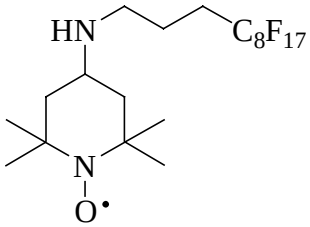
Mp : 64 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3293 (w), 2980 (w), 2830 (w), 1204 (s), 1150 (s), 655 (m).

MS (EI, 70 eV m/e (rel. int.)): 518 (M^+, 56), 504 (5), 431 (12), 377 (8), 154 (37), 139 (35), 124 (100), 109 (77), 81 (15), 69 (18), 41 (20).

$C_{16}H_{17}NO_3F_{13}$	HRMS	Calcd.	518.0969
		Found	518.0972

Synthesis of (1,1,2,2,3,3-hexahydroperfluoroundecyl)-(2,2,6,6-tetramethyl-piperidin-4-oxyl)-amine (29)



To a 50 mL round-bottomed flask were added 4-oxo-2,2,6,6-tetramethyl-piperidin-1-oxyl (285 mg, 1.67 mmol) and the fluorous amine **28** (1.01 g, 2.12 mmol) in 5 mL dry ethanol. The solution was stirred for 3 days at rt until complete conversion was observed. $NaBH_3CN$ (155 mg, 2.46 mmol) was then added and the mixture stirred for an additional 3 days at rt. The solution was extracted with diethyl ether/water (10 + 10 mL), the organic phase washed with water, dried over $MgSO_4$ and the solvent removed *in vacuo* giving an orange residue which was purified by flash chromatography (diethyl ether/DCM 1 : 4 + 1 % TEA). The product was obtained as an orange solid (590 mg, 56 %).

Alternatively, it can be prepared from 4-amino-2,2,6,6-tetramethyl-piperidin-1-oxyl (341 mg, 2.0 mmol) and the fluorous iodide **21** (2.640 g, 2.2 mmol) in 10 mL ethanol, in presence of $NaHCO_3$ (2.00 g, 24 mmol). After refluxing for 24 h at 100 °C, evaporation of the solvent and purification by flash chromatography (DCM/diethyl ether 4:1 + 1 % TEA) on silica gel, **29** was obtained as only product (1.00 g, 80 %).

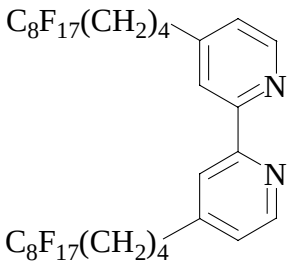
Mp : 88-90 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3435 (b), 3293 (w), 2978 (w), 2936 (w), 2870 (w), 1364 (w), 1245 (s), 1203 (s), 1150 (s), 657 (m).

MS (EI, 70 eV m/e (rel. int.)): 631 (3), 558 (13), 544 (27), 530 (100), 502 (7), 169 (4), 82 (5), 69 (3), 56 (6).

$C_{20}H_{24}N_2OF_{17}$ HRMS Calcd. 631.1618
Found 631.1600

Synthesis of 4,4'-bis(1,1,2,2,3,3,4,4-octahydroperfluorododecyl)-2,2'bipyridine (3)



A dry, Ar flushed 100 mL Schlenk flask was charged with 1.0 mL (7.5 mmol) of dry diisopropylamine in 20 mL dry THF and cooled to –78 °C. A solution of *n*-BuLi in hexane (6.2 mmol) was then added and the mixture was stirred 30 min at –78 °C. A solution of 4,4'-dimethylpyridine (500 mg, 2.7 mmol) in 50 mL dry THF was then cannulated to the LDA solution. The resulting deep-brown mixture was stirred 30 min at –78 °C, then warmed up to –4°C, stirred for an additional 30 min and cooled again to –78 °C. The fluorous iodide **21** (3.65 g, 6.2 mmol) was added and stirred for 20 min at –78 °C, then warmed up to 25 °C and stirred overnight. The colour changes from deep brown to blue, green and then yellow. THF is then carefully removed *in vacuo* and the crude dissolved in 150 mL Et_2O. The suspension was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the yellow residue recrystallised from 20 mL methanol, yielding **3** as a pale yellow solid (700 mg, 43 %).

Mp : 121 – 122 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 2942 (w), 1597 (w), 1205 (s), 1149 (s), 657 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.505 (d, *J* = 4.8 Hz, 2H), 8.18 (s, 2H), 7.06 (dd, *J* = 4.8 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 4H), 2.12-1.94 (m, 4H), 1.79-1.18 (m, 8H).

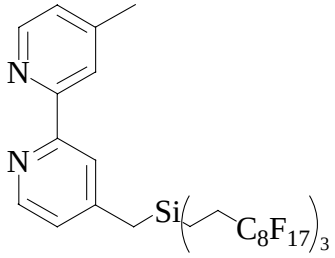
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 156.6, 152.0, 149.6, 140-110 (bm), 35.5, 31.4 (t), 30.2, 20.3.

^{19}F NMR ($CDCl_3$, 400 MHz): -79.9 (6F), -113.0 (m, 4F), -120.8 (s, 4F), -121.0 (s, 8F), -121.6 (s, 4F), -122.0 (s, 4F), -125.2 (m, 4F).

MS (EI, 70 eV m/e (rel. int.)): 1104 (2), 1084 (7), 735 (1), 671 (5), 657 (5), 644 (100), 198 (1), 104 (1).

$C_{34}H_{22}N_2F_{34}$	HRMS	Calcd. 1104.1241
		Found 1104.1200

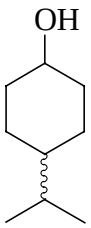
Attempted synthesis of 4'-methyl-4-[tri(1,1,2,2,3,3-esahydroperfluoroundecyl)]silanylmethyl-2,2'-bipyridine (25)



A dry, Ar flushed 250 mL Schlenk flask was charged with dry diisopropylamine (283 mg, 2.8 mmol) in 10 mL dry THF and cooled to –78 °C. A solution of *n*-BuLi in hexane (2.3 mmol) was then added and the mixture was stirred 30 min at –78 °C. A solution of 4,4'-dimethylpyridine (368 mg, 2.0 mmol) in 30 mL dry THF was then cannulated to the LDA solution. The resulting deep-brown mixture was stirred 30 min at –78 °C, then warmed up to –4°C, stirred for an additional 30 min and cooled again to –78 °C. The fluorous bromosilane **23** (3.48 g, 2.4 mmol) was added to the bipyridine solution and stirred for 20 min at –78 °C, then warmed up to rt and stirred overnight. The colour changes from deep brown to blue, green and then yellow. THF is then carefully removed *in vacuo* and the crude dissolved in 150 mL Et_2O. The suspension was washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. After further purification procedures only the starting material 4,4'-dimethylpyridine and various perfluorinated byproducts were isolated. NMR analysis of the fractions did not show the desired product.

4.3 Alcohol Oxidations

Synthesis of *cis-/trans*-4-isopropyl-cyclohexanol (49a)



Prepared according to TP 5 from 4-isopropyl-cyclohexanone (600 mg, 4.3 mmol), Wilkinson catalyst $(PPh_3)_3RhCl$ (40 mg, 1 mol %) and diphenylsilane (0.946 g, 5.1 mmol) in 8 mL benzene.

Reaction time: 45 min at rt. Purification by flash chromatography (eluent pentane/diethyl ether 1:1) on silica gel yielded the two separate isomers as colourless liquids (overall yield: 373 mg, 61 %, *cis: trans* 32 : 68).

trans- isomer:

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 3.516 (m, 1H), 2.08-1.94 (m, 2H), 1.75-1.70 (m, 2H), 1.55-1.38 (m, 2H), 1.30-0.90 (m, 5H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 71.7, 43.5, 36.2, 32.8, 28.3, 20.3.

MS (EI, 70 eV, m/e (rel. int.)): 141 ([M^+ - H], 0.1), 124 (23), 109 (24), 95 (7), 81 (100), 67 (16), 55 (26).

cis- isomer:

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 3.98 (s, 1H), 1.80-1.70 (m, 2H), 1.60-1.25 (m, 9H), 1.13-0.95 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 6H).

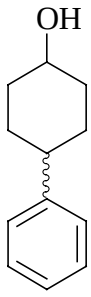
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 67.2, 43.7, 33.1, 32.5, 24.0, 20.3.

MS (EI, 70 eV, m/e (rel. int.)): 142 (0.1), 124 (26), 109 (16), 95 (5), 81 (100), 67 (15), 55 (25).

$C_9H_{18}O$ (M = 142.24 g mol^{-1}) Elemental analysis (*trans*) Calcd. C : 76.00 H : 12.76
Found C : 75.95 H : 12.80

Data are in agreement with literature values[104].

Synthesis of *cis-/trans*-4-phenyl-cyclohexanol (51a)



Prepared according to TP 5 from 4-phenyl-cyclohexanone (1.742 g, 10.0 mmol), Wilkinson catalyst (93 mg, 1 mol %) and diphenylsilane (2.208 g, 12.0 mmol) in 20 mL benzene. Reaction time: 45 min at rt. Purification by flash chromatography (eluent pentane/diethyl ether 1:1) on silica gel

[104] A.H. Lewin, S. Winstein *J. Am. Chem. Soc.* **1962**, *84*, 2464.

yielded the two separate isomers as white solids (637 mg *cis*- isomer, 718 mg *trans*- isomer, overall yield 77 %, ratio *cis: trans* 47 : 53).

trans- isomer:

Mp: 120 °C

IR (KBr, pellet, cm^{-1}) $\tilde{\nu}$: 3433 (s), 3028 (w), 2924 (s9, 2854 (m), 1425 (m), 1062 (s), 758 (m), 699 (s).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 7.24-7.09 (m, 5H), 3.60 (m, 1H), 2.41 (m, 1H), 2.02 (m, 2H), 1.86 (m, 2H), 1.54-1.33 (m, 5H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 146.9, 128.8, 127.2, 126.5, 71.0, 43.8, 36.3, 32.8.

MS (EI, 70 eV, m/e (rel. int.)): 176 (8), 158 (100), 143 (88), 130 (57), 117 (38), 104 (52), 91 (44), 78 (17), 65 (5).

cis- isomer:

Mp: 72 °C

IR (KBr, pellet, cm^{-1}) $\tilde{\nu}$: 3362 (bs), 3027 (w), 2935 (s), 2858 (m), 1493 (m), 1444 (m), 957 (s), 758 (m), 702 (s).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 7.35-7.20 (m, 5H), 4.14 (bs, 1H), 2.56 (m, 1H), 2.08-1.80 (m, 4H), 1.80-1.65 (m, 5H).

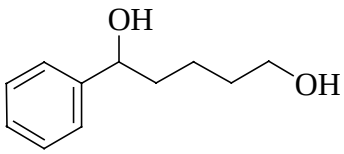
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 146.8, 128.5, 127.1, 126.5, 67.8, 43.5, 36.2, 32.8.

MS (EI, 70 eV, m/e (rel. int.)): 176 (87), 158 (22), 143 (41), 130 (33), 117 (65), 104 (100), 91 (60), 78 (17), 59 (9).

$C_{12}H_{16}O$ (M = 176.25 g mol^{-1}) Elemental analysis (*cis*) Calcd. C : 81.77 H : 9.15

Found C : 81.69 H : 9.22

Synthesis of 1-phenyl-pentane-1,5-diol (44a)



To a dry, two necked 100 mL Schlenk flask, equipped with magnetic stirrer and reflux condenser was added $LiAlH_4$ powder (1.90 g, 50 mmol) and covered with 30 mL dry diethyl ether. 5-oxo-5-phenyl-pentanoic acid (1.92 g, 10 mmol) was then added at 0 °C in small portions and the resulting suspension refluxed at 40 °C for 3 h. After cooling at 0 °C, the mixture was carefully quenched with EtOAc and then neutralized to pH = 5 with aqueous H_2SO_4 2.5 %. The solid was filtered off and the resulting two phases separated. The organic one was concentrated in vacuo and residual water distilled off by azeotropic distillation with toluene. The residue was extracted with ethanol/acetone 1:1, the eventual solid filtered off and the filtrate concentrated under high vacuum, giving a pale yellow solid (1.795 g, 99 %).

Mp: 47 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3315 (bs), 3062 (m), 2943 (s), 2857 (m), 1473 (m), 1454 (m), 1316 (m), 1088 (s), 1049 (s), 761 (s), 706 (s).

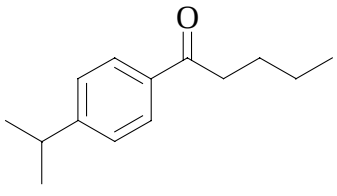
^{1}H NMR (δ/ppm, d_6-DMSO, 300 MHz): 7.27 (m, 5H), 5.07 (d, *J* = 4.4 Hz, 1H), 4.45 (m, 1H), 4.30 (m, 1H), 3.40 (bs, 2H), 1.62-1.42 (m, 2H), 1.38 (m, 4H).

^{13}C NMR (δ/ppm, d_6-DMSO, 75 MHz): 147.1, 128.6, 127.2, 126.5, 126.4, 73.0, 61.4, 33.2, 22.6.

MS (EI, 70 eV, m/e (rel. int.)): 180 (10), 162 (2), 133 (4), 120 (3), 107 (100), 79 (46).

$C_{11}H_{16}O_2$ (M = 180.24 g mol^{-1}) Elemental analysis Calcd. C : 73.30 H : 8.95
Found C : 73.38 H : 9.01

Synthesis of 1-(4-isopropylphenyl)-1-pentanone (39b)



Prepared according to TP 1 from the corresponding alcohol (426 mg, 2.1 mmol) and TEMPO (32 mg, 0.2 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **39b** as a colourless liquid (405 mg, 95 %, method A).

IR (Film, cm^{-1}) $\tilde{\nu}$: 3031 (w), 2961 (s), 2932 (m), 1683 (s), 1607 (s), 1413 (m), 1184 (m), 111 (m), 844 (w)

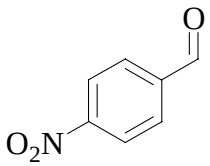
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.86 (t, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7 Hz, 2H), 1.33 (m, 2H), 1.63 (m, 2H), 2.85 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 14.3, 22.9, 24.1, 27.0, 34.6, 38.6, 127.0, 128.7, 135.4, 154.7, 200.6

MS (EI, 70 eV, m/e (rel. int.)): 203 (M^+ - 1), 189 (1), 162 (65), 161 (37), 148 (22), 147 (100), 91 (21)

$C_{14}H_{20}O$ (M = 204.21 g mol^{-1}) Elemental analysis Calcd. C: 82.3, H: 9.87
Found C: 82.0, H: 9.54.

Synthesis of 4-nitrobenzaldehyde (35b)



Prepared according to TP 1 from the corresponding alcohol (306 mg, 2.0 mmol) and TEMPO (11 mg, 0.07 mmol). Reaction time: 1 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **35b** as a yellow solid (294 mg, 98 %, method A).

Mp: 105 °C

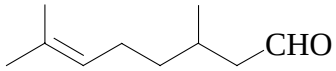
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 10.15 (s, 1H), 8.36 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 189.8, 150.4, 139.4, 129.9, 123.6

MS (EI, 70 eV, m/e (rel. int.)): 151 (100), 150 (96), 120 (8), 105 (17), 77 (44), 74 (11), 65 (7), 51 (29).

Data are in agreement with those of an authentic sample (Acros).

Synthesis of 3,7-dimethyl-oct-6-enal (Citronellal) (36b)



Prepared according to TP 1 from the corresponding alcohol (312 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **36b** as a colourless oil with citronella scent (283 mg, 92 %, method A).

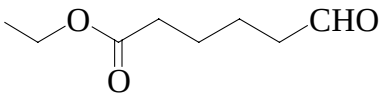
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 9.68 (t, *J* = 2.4 Hz, 1H), 5.013 (m, 1H), 2.304 (m, 1H), 2.173 (m, 1H), 1.939 (m, 3H), 1.612 (s, 3H), 1.531 (s, 3H), 1.360-1.118 (m, 2H), 0.902 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 202.0, 130.7, 123.0, 50.0, 35.9, 26.8, 24.7, 24.4, 18.9, 16.6.

MS (EI, 70 eV, m/e (rel. int.)): 154 (12), 139 (14), 136 (11), 121 (39), 111 (29), 95 (72), 84 (21), 69 (100), 55 (43).

Data are in agreement with those of an authentic sample (Aldrich).

Synthesis of 6-oxohexanoic acid ethyl ester (37b)



Prepared according to TP 1 from the corresponding alcohol (320 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.5 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **37b** as a colourless oil (281 mg, 89 %, method A).

IR (Film, cm^{-1}) $\tilde{\nu}$: 2718 (m), 1742 (s), 1485 (m), 1380 (m), 1310 (m).

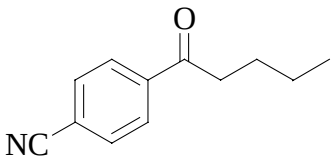
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 9.77 (t, *J* = 2.3 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.33 (m, 2H), 2.24 (m, 2H), 1.60 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 202.6, 173.9, 60.7, 44.2, 33.4, 23.8, 22.7, 14.3.

Data are in agreement with literature values[105].

[105] B.M. Trost, T.R. Verhoeven *J. Am. Chem. Soc.* **1980**, *102*, 4743.

Synthesis of 1-(4-cyanophenyl)-1-pentanone (38b)



Prepared according to TP 1 from the corresponding alcohol (378 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.5 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **38b** as a white solid (362 mg, 97 %, method A).

Mp: 38 °C

IR (KBr, cm^{-1}) $\tilde{\nu}$ 3049 (w), 2956 (m), 2233 (m), 1686 (s), 1406 (m), 1206 (m), 854 (m), 574 (w).

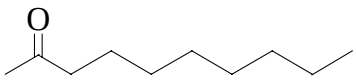
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.88 (t, *J* = 7.2 Hz, 3 H), 1.33 (m, 2 H), 1.66 (m, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 7.69 (d, *J* = 11.6 Hz, 2H), 7.97 (d, *J* = 11.6 Hz, 2H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 14.3, 22.7, 26.5, 39.0, 116.6, 118.4, 128.8, 132.9, 140.4, 199.4;

MS (EI, 70 eV, m/e (rel. int.)): 187 (6), 158 (7), 145 (79), 130 (100), 102 (41), 90 (1), 76 (5), 51 (3).

$C_{12}H_{13}NO$ (M = 187.24 g mol^{-1}) Elemental analysis Calcd. C : 76.98, H : 7.00, N: 7.48
Found C : 77.09, H : 7.10. N: 7.36

Synthesis of 2-decanone (40b)



Prepared according to TP 1 from the corresponding alcohol (340 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1 - 3 h. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **40b** as a colourless oil (279 mg, 88 %, method A).

IR (film, cm^{-1}) $\tilde{\nu}$ 3419 (b), 2956 (s), 2856 (s), 1719 (s), 1466 (m), 1359 (m), 1163 (m) 720 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.808 (t, *J* = 6.4 Hz**,** 3H), 1.20 (m, 10H), 1,48 (m, 2H), 2.06 (s, 3H), 2.34 (t, *J* = 7.2 Hz**,** 2H)

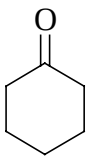
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 209.8, 44.2, 32.2, 30.2, 29.7, 29.6, 29.5, 24.3, 23.0, 14.5

MS (EI, 70 eV, m/e (rel. int.)): 156 (4), 98 (4), 85 (4), 71 (26), 58 (100).

$C_{10}H_{20}O$ (M = 156.27 g mol^{-1}) Elemental analysis Calcd. C : 76.86 H : 12.90

Found C : 76.90 H : 12.92

Synthesis of cyclohexanone (41b)



Prepared according to TP 1 from the corresponding alcohol (200 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **41b** as a colourless oil (145 mg, 74 %, 1st run, method A).

IR (film, cm^{-1}) $\tilde{\nu}$ 3407 (b), 2938 (m), 2863 (m), 1713 (s), 1449 (w), 1222 (w), 1118 (s), 617 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 1.670-1.729) (m, 2 H), 1.795-1.877 (m, 4 H), 2.306 (m, 4 H).

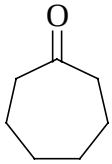
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 212.4, 42.3, 27.4, 25.3

MS (EI, 70 eV, m/e (rel. int.)): 98 (65), 83 (14), 69 (37), 55 (100).

$C_6H_{10}O$ (M = 98.14 g mol^{-1}) Elemental analysis Calcd. C : 73.43 H : 10.27

Found C : 73.39 H : 10.31

Synthesis of cycloheptanone (42b)



Prepared according to TP 1 from the corresponding alcohol (232 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1 h. Purification by formation of the bisulfite adduct yielded **42b** as a colourless oil with menthol scent (184 mg, 82 %, method B).

IR (film, cm^{-1}) $\tilde{\nu}$: 2928 (s), 2858 (s), 1702 (s), 1466 (m), 987 (m), 941 (m).

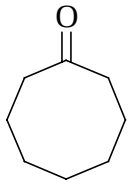
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.462-2.219 (m, 4H), 1.565-1.148 (m, 8H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 214.5, 43.8, 30.5, 24.2.

MS (EI, 70 eV, m/e (rel. int.)): 112 (42), 84 (32), 68 (100), 55 (95).

$C_7H_{12}O$ (M = 112.17 g mol^{-1}) Elemental analysis Calcd. C : 74.95 H : 10.78
Found C : 74.99 H : 10.74

Synthesis of cyclooctanone (43b)



Prepared according to TP 1 from the corresponding alcohol (258 mg, 2.0 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.5 h. Purification by formation of the bisulfite adduct yielded **43b** as a colourless solid (215 mg, 85 %, method B).

Mp: 38 °C

IR (KBr, cm^{-1}) $\tilde{\nu}$: 3382 (b), 2930 (s), 1699 (s), 1467 (m), 1446 (m), 1333(m), 1205 (m), 1098 (w), 845 (m), 521 (w)

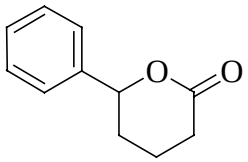
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.371-2.413 (m, 4 H), 1.819-1,901 (m, 4 H), 1.492-1.571 (m, 4H), 1.321-1.369 (m, 2H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 218.6, 42.3, 27.5, 26.0, 25.1

MS (EI, 70 eV, m/e (rel. int.)): 126 (18), 98 (100), 84 (49), 69 (27), 55 (81).

$C_8H_{14}O$ (M = 126.20 g mol^{-1}) Elemental analysis Calcd. C : 76.14 H : 11.18
Found C : 76.19 H : 11.14

Synthesis of 5-phenyl, 5-hydroxypentanoic acid lactone (44b)



Prepared according to TP 1 from the diol 44a (376 mg, 2.1 mmol), TEMPO (32 mg, 0.2 mmol). Reaction time: 2 h. Purification by flash chromatography (pentane/diethyl ether 2:1) on silica gel yielded **44b** as a white solid (289 mg, 78 %, method A).

Mp: 69 °C

IR (KBr, pellet, cm^{-1}) $\tilde{\nu}$: 3034 (w), 2965 (m), 2906 (w), 1719 (s), 1455 (m), 1247 (s), 1049 (s), 937 (m), 759 (m), 704 (m).

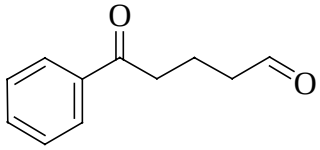
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 1.73-1.85 (m, 1 H), 1.90 (m, 2 H), 2.09 (m, 1 H), 2.45-2.67 (m, 2 H), 5.27 (dd, 1 H), 7.27 (m, 5 H)

^{13}C-NMR (δ/ppm, $CDCl_3$, 75 MHz): 18.8, 29.7, 30.7, 81.9, 125.9, 128.5, 128.8, 140.0, 171.6.

MS (EI, 70 eV, m/e (rel. int.)): 176 (36), 132 (8), 120 (9), 104 (100), 91 (9), 77 (25), 51 (10).

$C_{11}H_{12}O_2$ (M = 176.21 g mol^{-1}) Elemental analysis Calcd. C : 74.98 H : 6.86
Found C : 74.82 H : 6.78

5-oxo-5-phenyl-pentanal (44c) was obtained as a byproduct (colourless liquid, 30 mg, 7 %)



IR (film, cm^{-1}) $\tilde{\nu}$: 3062 (w), 2940 (m), 2827 (m), 1724 (s), 1685 (s), 1597 (m), 1450 (m).

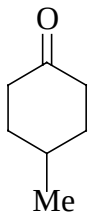
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 9.73 (s), 7.86 (d, *J* = 8.4 Hz, 2H), 7.51-7.36 (m, 3H), 2.97 (t, *J*= 7 Hz, 2H), 2.51 (t, *J* = 7 Hz, 2H), 2.00 (m, 2H).

^{13}C-NMR (δ/ppm, $CDCl_3$, 75 MHz): 202.3, 199.7, 137.1, 133.5, 129.0, 128.4, 43.5, 37.7, 16.9.

MS (EI, 70 eV, m/e (rel. int.)): 176 (0.1), 158 (8), 148 (18), 120 (22), 105 (100), 77 (39), 51 (9).

$C_{11}H_{12}O_2$ (M = 176.21 g mol^{-1}) Elemental analysis Calcd. C : 74.98 H : 6.86
Found C : 74.75 H : 6.98

Synthesis of 4-methylcyclohexanone (46b)



Prepared according to TP 1 from the corresponding alcohol (230 mg, 2.0 mmol, 47:53 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.8 h (*cis* isomer). Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **46b** as a colourless oil (101 mg, 45 %, method A).

IR (film, cm^{-1}) $\tilde{\nu}$ 3413 (b), 2955 (m), 2929(m), 2871 (m), 1716 (s), 1460 (w), 1121 (s) 616 (m).

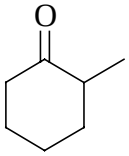
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.77 (d, *J* = 6.3 Hz, 3H), 1.17 (m, 2 H), 1.57-1.71 (m, 1 H), 1.71-1.80 (m, 2H), 2.08-2.12 (m, 4 H);

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 212.6, 41.2, 35.1, 31.5, 21.3;

MS (EI, 70 eV, m/e (rel. int.)): 112 (41), 94 (8), 83 (25), 70 (20), 55 (100).

$C_7H_{12}O$ (M = 112.17 g mol^{-1}) Elemental analysis Calcd. C : 74.95 H : 10.78
Found C : 74.89 H : 10.83

Synthesis of 2-methylcyclohexanone (47b)



Prepared according to TP 1 from the corresponding alcohol (231 mg, 2.0 mmol, 33:67 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol). Reaction time: 9.5 h (*cis* isomer). Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **47b** as a colourless oil (86 mg, 38 %, method A).

IR (film, cm^{-1}) $\tilde{\nu}$ 3402 (b), 2932 (s), 2861 (m), 1712 (s), 1449 (m), 1123 (s), 616 (w).

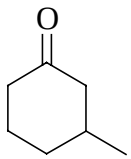
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.43-2.21 (m, 3 H), 1.99-2.11 (m, 2 H), 1.88-1.76 (m, 1 H), 1.73-1.72 (m, 2 H), 1.43-1.28 (m, 1 H), 0.997 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 213.9, 45.7, 42.2, 36.5, 28.3, 25.5, 15.1.

MS (EI, 70 eV, m/e (rel. int.)): 112 (52), 84 (24), 68 (100), 56 (58).

$C_7H_{12}O$ (M = 112.17 g mol^{-1}) Elemental analysis Calcd. C : 74.95 H : 10.78
Found C : 75.01 H : 10.70

Synthesis of 3-methylcyclohexanone (48b)



Prepared according to TP 1 from the corresponding alcohol (228 mg, 2.0 mmol, 34:66 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.2 h (*trans* isomer). Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **48b** as a colourless oil (139 mg, 62 %, method A).

IR (film, cm^{-1}) $\tilde{\nu}$ 3407 (b), 2955 (s), 2871 (m), 1715 (s), 1456 (m), 1225 (m), 1114 (m), 514 (w).

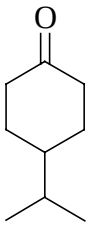
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.321-2.087 (m, 3H), 2.000-1.723 (m, 4H), 1.646-1.496 (m, 1H), 1.310-1.182 (m, 1H), 0.928 (m, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 212.2, 50.3, 41.5, 34.5, 33.6, 25.6, 22.4.

MS (EI, 70 eV, m/e (rel. int.)): 112 (29), 79 (5), 69 (100), 56 (44).

$C_7H_{12}O$ (M = 112.17 g mol^{-1}) Elemental analysis Calcd. C : 74.95 H : 10.78
Found C : 74.88 H : 10.82

Synthesis of 4-isopropyl-cyclohexanone (49b)



Prepared according to TP 1 from the corresponding alcohol (286 mg, 2.0 mmol, 32:68 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol) Reaction time: 1.5 h (*cis* isomer). Purification by flash chromatography (pentane/diethyl ether) on silica gel yielded **49b** as a colourless liquid (79 mg, 28 %, method A).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.85 (d, *J* = 6.4 Hz, 6 H), 1.32-1.58 (m, 4 H), 1.88-1.99 (m, 2 H), 2.17-2.37 (m, 4 H)

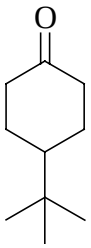
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 19.0, 28.6, 30.7, 40.1, 41.5, 211.5.

MS (EI, 70 eV, m/e (rel. int.)): 140 (90), 122 (18), 107 (34), 93 (23), 83 (25), 69 (100), 54 (12).

$C_9H_{16}O$ (M = 140.22 g mol^{-1}) Elemental analysis Calcd. C : 77.09 H : 11.50
Found C : 76.98 H : 11.59

Data are in agreement with an authentic sample (Lancaster).

Synthesis of 4-*t*-butyl-cyclohexanone (50b)



Prepared according to TP 1 from the corresponding alcohol (320 mg, 2.0 mmol, 25:75 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol) Reaction time: 1.7 h (*cis* isomer). Purification by flash chromatography (pentane/diethylether 1:1) on silica gel yielded **50b** as a white solid (63 mg, 20 %, method A).

Mp: 48 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3412 (w), 2967 (s), 1728 (s), 1333 (m), 1162 (m), 943 (w).

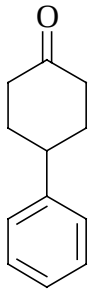
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 0.922 (s, 9 H), 1.375-1.549 (m, 3 H), 2.006-2.147 (m, 2 H), 2.256-2.438 (m, 4 H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 28.0, 32.8, 41.7, 47.1, 212.9.

MS (EI, 70 eV, m/e (rel. int.)): 154 (38), 98 (97), 83 (33), 69 (16), 57 (100).

$C_{10}H_{18}O$ (M = 154.25 g mol^{-1}) Elemental analysis Calcd. C : 77.87 H : 11.76
Found C : 77.89 H : 11.73

Synthesis of 4-phenyl-cyclohexanone (51b)



Prepared according to TP 1 from the corresponding alcohol (350 mg, 2.0 mmol, 50:50 *cis*:*trans* mixture), TEMPO (32 mg, 0.2 mmol). Reaction time: 1.5 h (*cis* isomer). Purification by flash chromatography (pentane/diethyl ether 1:1) on silica gel yielded **51b** as a white solid (169 mg, 49 %, method A).

Mp: 79 °C

IR (KBr, cm^{-1}) $\tilde{\nu}$ 3434 (b), 3027 (w), 2929 (m), 2867 (m), 1711 (s), 1496 (m), 1167 (m), 760 (s), 703 (s), 439 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 1.98 (m, 2 H), 2.20-2.31 (m, 2 H), 2.53 (m, 4 H), 3.05 (tt, *J* = 12 and 3.3 Hz, 1 H), 7.28 (m, 5 H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 34.4, 41.8, 43.2, 127.0, 127.1, 129.0, 145.2, 211.5.

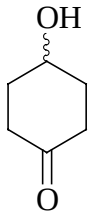
MS (EI, 70 eV, m/e (rel. int.)): 174 (92), 145 (16), 130 (14), 115 (21), 104 (100), 91 (77), 78 (12), 57 (20).

$C_{12}H_{14}O$ (M = 174.24 g mol^{-1}) Elemental analysis Calcd. C : 82.72 H : 8.10
Found C : 82.69 H : 8.12

Oxidation of 1,4-cyclohexanediol

According to TP 1, 1,4-cyclohexanediol (233 mg, 2.0 mmol) was oxidized in presence of TEMPO (32 mg, 0.2 mmol). Reaction time: 2.5 h. Purification by flash chromatography (gradient of eluition from pentane/diethyl ether 2:3 to pure diethyl ether) on silica gel yielded the following products:

4-Hydroxy-cyclohexanone (45a)



White solid (132 mg, 58 %).

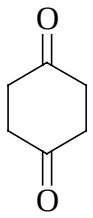
^{1}H NMR (δ/ppm, CD_3OD, 300 MHz): 4.86 (s, 1H), 3.69 (m, C*H*OH *axial*), 3.53 (m, C*H*OH *equatorial*), 2.60-2.22 (m, 2H), 2.21-1.15 (m, 6H).
Ratio –*OH* equatorial / axial : 3 : 1.

^{13}C NMR (δ/ppm, CD_3OD, 75 MHz): 210.2, 67.3, 37.7, 34.6.

MS (EI, 70 eV, m/e (rel. int.)): 114 (90), 98 (45), 83 (18), 73 (33), 68 (43), 59 (92), 55 (100).

$C_6H_{10}O_2$ (M = 114.14 g mol^{-1}) Elemental analysis Calcd. C : 63.14 H : 8.83
Found C : 63.11 H : 8.89

Cyclohexane-1,4-dione (45b)



White solid (58 mg, 26 %).

Mp: 78 °C

IR (KBr, cm^{-1}) $\tilde{\nu}$: 2860 (w), 1920 (w), 1699 (s), 1579 (s), 1209 (m), 1094 (m), 794 (m).

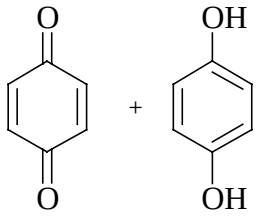
^{1}H NMR (δ/ppm, CD_3OD, 300 MHz): 2.65 (s, 4H)

^{13}C NMR (δ/ppm, CD_3OD, 75 MHz): 208.4, 36.7.

MS (EI, 70 eV, m/e (rel. int.)): 112 (100), 83 (9), 56 (60).

$C_6H_8O_2$ (M = 112.13 g mol^{-1})	Elemental analysis	Calcd.	C : 64.27	H : 7.19
		Found	C : 64.23	H : 7.22

1,4-Benzoquinone (45c), 1,4-hydroquinone (45d) (semiquinone)



yellowish solid (22 mg, 10 %)

^{1}H NMR (δ/ppm, CD_3OD, 300 MHz): 6.53 (s).

^{13}C NMR (δ/ppm, CD_3OD, 75 MHz): 187.2 (*q*), 149.4 (*hq*), 136.6 (*q*), 115.7 (*hq*).

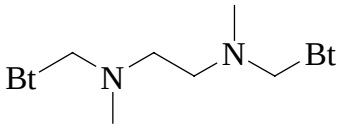
hydroquinone: **MS** (EI, 70 eV, m/e (rel. int.)): 110 (100), 81 (31), 56 (18).

quinone: **MS** (EI, 70 eV, m/e (rel. int.)): 108 (100), 82 (42), 80 (34), 54 (73).

Data are identical to those of authentic samples (*hydroquinone*: Riedel de Haen; *quinone*: Acros).

4.4 Synthesis of fluorous tertiary amines

Synthesis of *N*,*N*'-bis-benzotriazol-1-ylmethyl-*N*,*N*'-dimethyl-ethane-1,2-diamine (55a)



Prepared according to TP 3 from *N*,*N*'dimethyl-ethane-1,2-diamine (2.64 g, 30 mmol), aqueous formaldehyde (4.90 mL of a 37 % solution, 60 mmol), and 1*H*-benzotriazole (7.19 g, 60 mmol) in 100 mL water. Reaction time: 30 min at rt. The precipitate is filtered as described and dried to yield pure product as a white powder (10.30 g, 98 %).

Mp: 161-164 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3073 (w), 2954 (w), 2829 (m), 1450 (m), 1214 (s), 1050 (s), 976 (m), 766 (s), 750 (s).

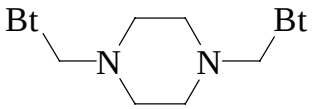
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.05 (d, *J* = 8.4 Hz, 2H), 7.65-7.30 (m, 6H), 5.51 (s, 4H), 2.84 (s, 1,2' isomer), 2.80 (s, 1,1' isomer), 2.43 (s, 8H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 40.8, 52.1, 69.3, 110.2, 120.3, 124.3, 127.9, 134.3, 146.1.

MS (EI, 70 eV m/e (rel. int.)): 350 (2), 232 (9), 188 (14), 132 (100), 119 (17), 104 (23), 91 (13), 77 (35), 57 (15).

$C_{18}H_{22}N_8$ HRMS Calcd. 350.1967
Found 350.1983

Synthesis of *N,N'*-bis-benzotriazol-1-ylmethyl-piperazine (55b)



Prepared according to TP 3 from piperidine (2.586 g, 30 mmol), aqueous formaldehyde (4.90 mL of a 37 % solution, 60 mmol), and 1*H*-benzotriazole (7.190 g, 60 mmol) in 150 mL water. Reaction time: 30 min at rt. The precipitate is filtered as described and dried to yield pure product as a white powder (9.72 g, 93 %).

Mp: 227 °C (dec.)

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3072 (w), 2948 (w), 2826 (m), 1616 (m), 1453 (m), 1232 (m), 1157 (s), 1003 (m), 738 (s).

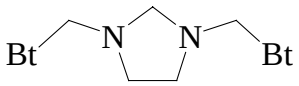
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.05 (d, *J* = 8.4 Hz, 2H), 7.55-7.30 (m, 6H), 5.40 (s, 4H), 2.68 (s, 8H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 50.4, 69.4, 110.2, 120.3, 124.3, 128.0, 134.0, 146.2.

MS (EI, 70 eV m/e (rel. int.)): 230 (100), 132 (68), 110 (35), 104 (21), 91 (12), 77 (25).

$C_{18}H_{20}N_8$ HRMS Calcd. 348.1811
Found 346.1681 [M^+- 2H]

Synthesis of *N,N'*-bis-benzotriazol-1-ylmethyl-imidazolidine (55c)



Prepared according to TP 3 from 1,2-ethylenediamine (1.830 g, 30 mmol), aqueous formaldehyde (7.30 mL of a 37 % solution, 90 mmol), and 1*H*-benzotriazole (7.190 g, 60 mmol) in 250 mL water. Reaction time: 30 min at rt. The precipitate is filtered as described and dried to yield pure product as a white powder (7.310 g, 73 %).

Mp: 121 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3057 (w), 2940 (w), 2840 (m), 1453 (m), 1196 (m), 1112 (m), 1061 (m), 1017 (m), 742 (s),

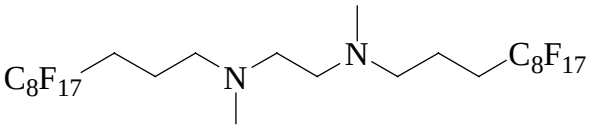
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.00 (d, *J* = 8.4 Hz, 2H), 7.50-7.22 (m, 6H), 5.44 (s, 4H), 3.98 (s, 1,2' isomer), 3.85 (s, 1,1' isomer), 2.98 (m, 4H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 49.4, 65.4, 70.5, 110.1, 120.3, 124.4, 128.1, 133.8, 146.3.

MS (EI, 70 eV m/e (rel. int.)): 333 (0.3), 215 (100), 132 (83), 119 (14), 104 (18), 83 (15), 77 (34), 64 (9).

$C_{17}H_{18}N_8$ HRMS Calcd. 334.1654
Found 333.1597 [M^+- H]

Synthesis of *N,N'*-dimethyl-*N,N'*-di(1,1,2,2,3,3-esahydro)perfluoroundecyl-ethane-1,2-diamine (57)



Prepared according to TP 4 from the fluorous Grignard reagent 1,1,2,2,tetrahydroperfluorodecylmagnesium iodide (12.6 mmol) and the aminal **55a** (2.180 g, 6 mmol) in 50 mL dry THF, at rt under Ar atmosphere. Reaction time: 15 h. After washing with aqueous NaOH and extraction with diethyl ether the collected organic phases were evaporated in vacuo, giving a white solide and a brown liquid phase containing the pure product, which was separated. (4.052 g, 67 %)

IR (Film, ZnS, cm^{-1}) $\tilde{\nu}$: 2957 (w), 2802 (w), 1464 (w), 1242 (s), 1204 (s), 970 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.45 (s, 4H), 2.42 (t, *J* = 6.4 Hz, 4H), 2.22 (s, 6H), 2.21–1.96 (m, 4H), 1.84-1.66 (m, 4H).

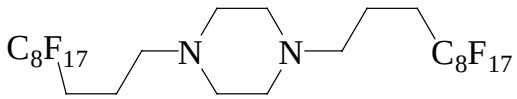
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 123-104 (m), 55.8, 54.4, 41.3, 27.7, 17.1

^{19}F NMR ($CDCl_3$, 400 MHz): -80.1 (t, 6F), -113.4 (m, 4F), -120.9 (s, 4F), -121.1 (s, 8F), -121.9 (s, 4F), -122.6 (s, 4F), -125.3 (m, 4F).

MS (EI, 70 eV m/e (rel. int.)): 1008 (0.1), 1005 (0.2), 518 (4), 504 (100), 485 (1), 466 (1), 57 (1).

$C_{26}H_{22}N_2F_{34}$ HRMS Calcd. 1008.1241
Found 1008.1250

Synthesis of 1,4-di(1,1,2,2,3,3-esahydro)perfluoroundecyl-piperazine (56)



Prepared according to TP 4 from the aminal **55b** (3.480 g, 10 mmol) and the fluorous Grignard reagent 1,1,2,2,tetrahydroperfluorodecylmagnesium iodide (22 mmol) in 100 mL dry THF at rt under Ar atmosphere. Reaction time: 15 h. After washing with aqueous NaOH and extraction with diethyl ether the purification of the residue was done by recrystallisation from pentane, yielding **56** as a pale brown solid. (8.049 g, 80 %).

Mp: 86-88 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 2957 (w), 2817 (w), 1221 (s), 1149 (s), 657 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 2.46 (s, 8H), 2.40 (t, *J* = 7.2 Hz, 4H), 2.26-1.97 (m, 4H), 1.85-1.70 (m, 4H).

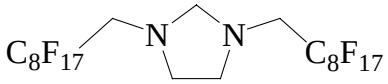
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 128-106 (m), 57.1, 53.0, 28.8 (t), 17.7

^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -81.2 (t, 6F), -114.6 (m, 4F), -122.2 (s, 4F), -122.4 (s, 8F), -123.2 (s, 4F), -123.8 (s, 4F), -126.6 (s, 4F)

MS (EI, 70 eV m/e (rel. int.)): 1006 (5), 987 (7), 559 (100), 516 (20), 490 (16), 119 (4), 98 (9), 70 (48), 56 (49), 42 (55).

$C_{26}H_{22}N_2F_{34}$ HRMS Calcd. 1006.1084
Found 1006.1090

Synthesis of 1,3-di(1,1-dihydro)perfluorononyl-imidazolidine (58)



Prepared according to TP 4 from the aminal **55c** (1.672 g, 5 mmol), the fluorous Grignard reagent perfluorooctylmagnesium iodide (12 mmol) and BF_3·Et2O (48 % solution, 5 mmol) in a solvent mixture 5:2 dry diethyl ether/dry THF at –78 °C under Ar atmosphere. Reaction time: 13 h, the mixture has let warm up overnight from –78 °C to rt. Purification by slowly addition of 30 mL a saturated aqueous $NaHCO_3$ solution, with formation of two phases. The aqueous one was washed with diethyl ether (3 x 15 mL), then the collected organic phases were dried over $MgSO_4$ and the solvent removed in vacuo, with formation of a biphasic system. The fluorous lower phase is separated and the crude recrystallised from pentane, yielding **58** as a pale yellow solid (1.966 g, 42 %).

Mp: 126 °C

IR (KBr, pellet, cm^{-1}) $\tilde{\nu}$: 3429 (w), 1675 (w), 1245 (s), 1148 (s), 661 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 3.58 (s, 2H), 3.16 (t, *J* = 16.8 and 1.4 Hz, 4H), 2.38 (s, 4H)

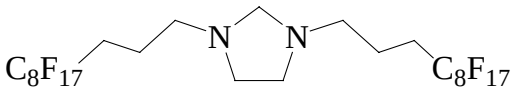
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 124-108 (bm), 78.2, 54.6 (t), 53.7.

^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -79.8 (s, 6F), -115.4 (s, 4F), -120.9 (s, 12F), -121.7 (s, 4F), -122.2 (s, 4F), -125.1 (s, 4F).

MS (EI, 70 eV m/e (rel. int.)): 936 (22), 935 (100), 915 (12), 665 (4), 565 (12), 487 (18), 462 (26), 181 (14), 169 (16), 131 (80), 101 (14), 69 (71), 51 (49).

$C_{21}H_{10}N_2F_{34}$ HRMS Calcd. 936.0302
Found 936.0313

Synthesis of 1,3-di(1,1,2,2,3,3-esahydro)perfluoroundecyl-imidazolidine (59)



Prepared according to TP 4 from the aminal **55c** (1.672 g, 5 mmol) and the fluorous Grignard reagent 1,1,2,2,tetrahydroperfluorodecylmagnesium iodide (12 mmol) in a solvent mixture 3:1 dry diethyl ether/dry THF at rt under Ar atmosphere. Reaction time: 13 h. After washing with aqueous NaOH and extraction with diethyl ether the purification of the residue was done by recrystallisation from PhCl, obtaining a yellow solid (1.736 g, 35 %).

Mp: 110 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3436 (w), 2958 (w), 1624 (w), 1207 (s), 1149 (s), 657 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 3.30 (s, 2H), 2.73 (s, 4H), 2.52 (t, *J* = 7 Hz, 4H), 2.25-1.95 (m, 4H), 1.80-1.60 (m, 4H)

^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 128-108 (bm), 76.3, 53.9, 51.9, 28.7 (t), 19.7.

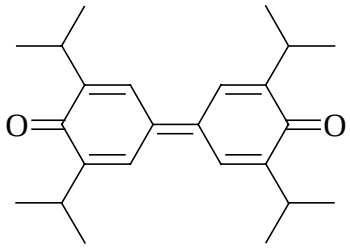
^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -79.8 (s, 6F) –113.1 (s, 4F), -120.7 (s, 4F), -120.9 (s, 8F), -121.7 (s, 4F), -122.4 (s, 4F), -125.1 (s, 4F).

MS (EI, 70 eV m/e (rel. int.)): 992 (100), 973 (11), 571 (9), 545 (18), 504 (45), 490 (31), 132 (17), 119 (12), 91 (13), 69 (7), 57 (15), 42 (11).

$C_{25}H_{18}N_2F_{34}$ HRMS Calcd. 992.0928
Found. 992.0935

5 Cu(II)-catalyzed Oxidative Coupling in FBS

Synthesis of 3,5,3’,5’-tetraisopropyl-bicyclohexylidene-2,5,2',5'-tetraene-4,4’-dione (61b)



To the fluorous phase prepared according to TP 1 and containing the Cu(II)-*F*-bipyridyl was added a solution of 2,5-diisopropylphenol (108 mg, 0.6 mmol) in 3 mL PhCl. A gentle stream of molecular oxygen was passing during 5 h at 25 °C under vigorous stirring. The solution turned from yellow to dark red. At the end of the reaction the chlorobenzene phase was separated and the fluorous phase washed with PhCl (3 x 3 mL). The collected organic phases were evaporated *in vacuo*, yielding **61b** as a red powder (105 mg, 99 %).

Mp: 178 °C

IR (KBr, pellet, cm^{-1}) $\tilde{\nu}$: 2963 (s), 2871 (w), 1717 (m), 1592 (m), 1463 (m), 1181 (m). 817 (w).

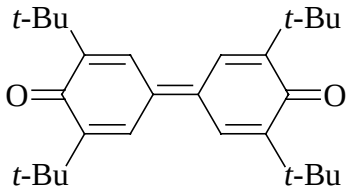
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 1.21 (d, *J* = 6.8 Hz, 24H), 3.23 (m, 4H), 7.64 (s, 4H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 21.0, 26.7, 124.6, 135.4, 147.5, 186.6.

MS (EI, 70 eV, m/e (rel. int.)): 352 (100), 349 (46), 337 (93), 309 (53), 296 (10), 281 (13), 267 (12), 253 (10), 221 (8), 191 (119, 178 (11), 147 (9), 97 (8).

$C_{24}H_{32}O_2$ (M = 352.51 g mol^{-1}) Elemental analysis Calcd. C : 81.77 H : 9.15
Found C : 81.69 H : 9.23

Synthesis of 3,5,3',5'-tetra *t*-butyl-bicyclohexylidene-2,5,2',5'-tetraene-4,4'-dione (62b)



To the fluorous phase prepared according to TP 1 and containing the Cu(II)-*F*-bipyridyl was added a solution of 2,5-di-*t*-butylphenol (206 mg, 1.0 mmol) in 3 mL PhCl. A gentle stream of molecular oxygen was passing during 2 h at 25 °C under vigorous stirring. The solution turned from yellow to deep brown. At the end of the reaction the chlorobenzene phase was separated and the fluorous phase washed with PhCl (3 x 2 mL). The collected organic phases were evaporated *in vacuo*, yielding pure **62b** as deep red crystals (201 mg, 98 %).

Mp: 245 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 2959 (m), 2866 (m), 1606 (s), 1459 (m), 1363 (s), 1262 (m), 1091 (s), 899 (m), 515 (w).

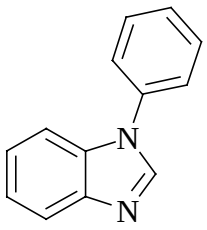
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz):1.36 (s, 36 H), 7.70 (s, 4H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 185.5, 149.5, 135.1, 125.0, 35.0, 28.6.

MS (EI, 70 eV, m/e (rel. int.)): 408 (100), 393 (32), 336 (26), 351 (53), 309 (32), 295 (21), 281 (11), 267 (8), 253 (9), 239 (8), 165 (6), 57 (50).

$C_{28}H_{40}O_2$ HRMS Calcd. 408.3028
Found. 408.3057

Synthesis of 1-phenyl-1-*H*-benzoimidazole (68)



To the fluorous phase prepared in dry PFOB according to TP 1, and containing the Cu(II)-*F*-bipyridyl, was added a solution of phenylboronic acid (54 mg, 0.39 mmol) in 3 mL dry DCM containing 100 mg of MS 4 Å. 1-*H*-benzoimidazole (29 mg, 0.24 mmol) was further added to the biphasic system. A gentle stream of molecular oxygen was passing during 15 h at 25 °C under vigorous stirring. Formation of a greenish emulsion in the DCM phase was observed. The two phases were decanted overnight and the organic one was separated, the solvent evaporated and the crude purified by flash cromatography (eluent EtOAc) on silica gel, yielding **68** as a white solid (41 mg, 88 %).

Mp: 94 °C

IR (KBr pellets, cm^{-1}): 3071 (m), 1558 (m), 1500 (m), 1453 (m), 1292 (w), 1230 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.12 (s, 1H), 7.89 (m, 1H), 7.62-7.40 (m, 6H), 7.40-7.23 (m, 2H)

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 143.5, 139.9, 139.8, 139,7, 128.2, 126.6, 125.3, 123.5, 123.4, 120.2, 109.5.

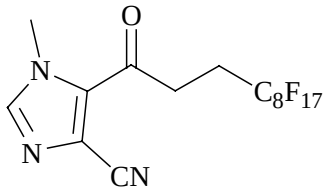
MS (EI, 70 eV, m/e (rel. int.)): 194 (100), 166 (4), 140 (3), 77 (3), 66 (2), 51(2).

$C_{13}H_{10}N_2$ (M = 194.23 g mol^{-1}) Elemental analysis Calcd. C: 80.39 H: 5.19 N: 14.42

Found C: 80.33 H: 5.18 N: 14.49

6. Synthesis of fluorous imidazoles

Synthesis of 1-methyl-5-(2,2,3,3,tetrahydroperfluoroundecanoyl)-1*H*-imidazole-4-carbonitrile (73)



To a dry, two-necked Schlenk flask equipped with reflux condenser and Ar inlet was added a solution of the fluorous Grignard reagent 1,1,2,2,tetrahydroperfluorodecylmagnesium iodide (11.0 mmol) in diethyl ether. A solution of 1-methyl-4,5-dicyano-imidazole (660 mg, 5.0 mmol) and CuBr (29 mg, 0.2 mmol) in 10 mL dry THF was then added dropwise at rt under Ar atmosphere, while a slighty exotermic reaction occurred with formation of a white precipitate. The mixture was stirred 2 h at rt, then refluxed for an additional 30 min. The dark mixture was treated with 20 mL of aqueous H_2SO_4 15 % and refluxed at 100 °C for 30 min. After quenching with 10 mL of saturated, aqueous NH_4Cl, the ether phase was recovered, the aqueous layer washed with THF (3 x 20 mL) and the collected organic phases concentrated in vacuo. The crude was recrystallised from diethyl ether, yielding **73** as a yellow powder (2.0 g, 69 %). No addition of the Grignard reagent to the second cyano group has been detected.

Mp: 152 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3121 (w), 2231 (w), 1683 (m), 1204 (s), 1153 (s), 656 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 7.57 (s, 1H), 3.82 (s, 3H), 3.27 (t, *J* = 7.4 Hz, 2H), 2.58-2.44 (m, 2H).

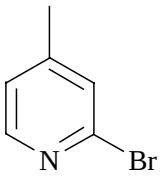
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 191.1, 147.2, 140.3, 109.7, 107.7, 120-105 (m), 33.3, 30.0, 24.9 (t).

^{19}F NMR ($CDCl_3$, 400 MHz): -81.2 (t, 3F), -114.6 (m, 2F), -122.1 (s, 2F), -122.3 (m, 4F), -123.1(s, 2F), -123.8 (s, 2F), -126.5 (m, 2F).

MS (EI, 70 eV m/e (rel. int.)): 581 (8), 562 (10), 162 (5), 134 (100), 106 (2).

$C_{16}H_8N_3F_{17}$ HRMS Calcd. 581.0396
Found 581.0501

Synthesis of 2-bromo-4-methyl pyridine (76)



To a 250 mL round-bottomed flask, containing 54 mL of an aqueous solution of HBr 48 %, was added at rt 2-amino-4-methyl pyridine (10.8 g, 0.100 mol) in small portions. After dissolution, the mixture was cooled to –20 °C. To the suspension was added Br_2 (15 mL, 0.292 mol) dropwise over 30 min, keeping the temperature at –20 °C. The resulting paste was vigorously stirred 1.5 h at the same temperature, then $NaNO_2$ (18.5 g, 0.268 mol) in 25 mL water was added and the mixture warmed to 15 °C over 1 h and stirred for an additional hour. The mixture was cooled again to –20 °C and treated with a cold solution of NaOH (80.0 g, 2.0 mol) in 100 mL water, then let to warm up to rt and stirred for 1 h. Extraction of the organic compounds with EtOAc, followed by drying over $MgSO_4$ and concentration in vacuo, gave a crude which was purified by flash cromatography (eluent pentane/diethyl ether 3:2) on silica gel. Analytically pure **76** was obtained as orange oil. (13.07 g, 76 %).

IR (Film, cm^{-1}) $\tilde{\nu}$: 3053 (w), 2920 (w), 1591 (s), 1464 (s), 1374 (s), 1221 (m), 1079 (s), 849 (s).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.12 (d, *J* = 5.1 Hz, 1H), 7.23 (s 1H), 6.98 (d *J* = 5.1 Hz 1H), 2.25 (s, 3H)

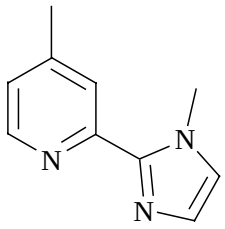
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 149.2, 148.7, 141.3, 127.7, 122.8, 19.7

MS (EI, 70 eV m/e (rel. int.)): 173 (48), 171 (60), 92 (100), 91 (13), 65 (55), 57 (26).

C_6H_6NBr (M = 172.02 g mol^{-1}) Elemental analysis Calcd. C : 41.89 H : 3.52 N : 8.14

Found C : 41.81 H : 3.48 N : 8.20

Synthesis of 4-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-pyridine (77)



A dry, Ar flushed three-necked 100 mL Schlenk flask was charged with 820 mg (10 mmol) of 1-methylimidazole and 10 mL dry THF, then cooled at –78°C. *n*-BuLi in hexane (10.2 mmol) was added dropwise and stirred for an additional 30 min. A solution of anhydrous $ZnCl_2$ (10 mmol) in 10 mL dry THF was added, leading to the formation of a white precipitate. The mixture was allowed to warm up to rt over 30 min and then treated with $Pd(PPh_3)_4$ (60 mg, 0.052 mmol), followed a solution of the pyridine **76** (g, 6.5 mmol) in 5 mL dry THF. The mixture was refluxed for 1.5 h, then cooled slighty. Anhydrous $ZnCl_2$ (2.60 g, 19 mmol) was added and reflux continued for an additional 4 h (GC/MS shown complete conversion). The solution was cooled, poured into 200 mL of a solution of EDTA N, the pH adjusted to 8 with aqueous sodium carbonate, then extracted with 3 x 100 mL DCM. The combined organic phases were dried over $MgSO_4$, filtered and the crude purified by chromatography on silica gel (AcOEt, 1% TEA), yielding 663 mg (3.8 mmol , 60 %) of a yellow oil.

IR (Film, cm^{-1}) $\tilde{\nu}$: 3394 (m), 3108 (w), 2956 (w), 2925 (w), 1604 (s), 1497 (m), 1464 (m), 1280 (m), 860 (m), 751 (m).

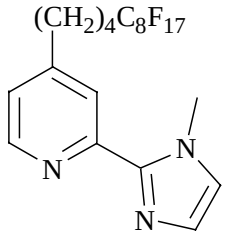
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.42 (d, *J* = 5 Hz, 1H), 8.01 (s, 1H), 7.10 (d, *J* = 1.2 Hz, 1H), 7.03 (m, 1H), 6.95 (d, *J* = 1.2 Hz, 1H), 4.11 (s, 1H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 150.6, 148.5, 148.2, 145.4, 128.1, 124.6, 124.0, 123.9, 36.6, 21.4.

MS (EI, 70 eV m/e (rel. int.)): 173 (44), 172 (100), 145 (6), 119 (14), 92 (5), 65 (4).

$C_{10}H_{11}N_3$ (M = 173.21 g mol^{-1}) Elemental analysis Calcd. C : 69.34 H : 6.40 N : 24.26
Found C : 69.35 H : 6.38 N : 24.28

Synthesis of 4-[(1,1,2,2,3,3,4,4-octahydro)-perfluorododecyl]-2-(1-methyl-1*H*-imidazol-2-yl)-pyridine (78)



A dry, argon flushed 100 mL flask was charged with 196 mg (1.9 mmol) of dry diisopropylamine in 10 mL dry THF and cooled to –78 °C. A solution of *n*-BuLi in hexane (1.6 mmol) was then added and the mixture was stirred 30 min at –78 °C. A solution of the pyridine **77** (260 mg, 1.5 mmol) in 10 mL dry THF was then added dropwise to the LDA solution. The resulting red-orange solution was stirred 30 min at –78 °C, then warmed up to –4°C, stirred for an additional 30 min and cooled again to –78 °C. The fluorous iodide Y (1.178 g, 2.0 mmol) was added and stirred for 20 min at –78 °C, then warmed up to rt and stirred overnight. The colour changed from red to green and then yellow within 30 min. THF is then carefully removed *in vacuo* and the crude dissolved in 50 mL Et_2O. The ocra solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash cromatography on silica gel (eluent EtOAc), yielding a white crystalline solid (300 mg 32 %).

Mp: 87 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3437 (w), 3143 (w), 2956 (w), 1064 (m), 1245 (s), 1212 (s), 1153 (s), 1031 (w), 657 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.47 (d, *J* = 5.2 Hz, 1H), 8.03 (s, 1H), 7.11 (s, 1H), 7.03 (m, 1H), 6.96 (s, 1H), 4.13 (s, 3H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.15-2.02 (m, 2H), 1.82-1.74 (m, 2H), 1.70-1.62 (m, 2H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 151.1, 150.9, 148.3, 145.0, 128.1, 124.3, 122.6, 122.5, 120–100 (m), 36.2, 34.9, 30.7 (t), 29.7, 19.9.

^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -79.7 (t, 3F), -113.2 (m, 2F), -120.6 (s, 2F), -120.8 (s, 4F), -121.6 (s, 2F), -122.4 (s, 2F), -125.0 (m, 2F).

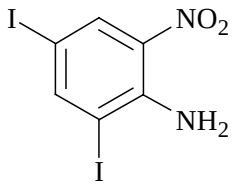
MS (EI, 70 eV m/e (rel. int.)): 633 (16), 614 (8), 264 (3), 200 (12), 186 (9), 173 (100), 118 (2), 93 (2), 69 (2).

$C_{21}F_{17}H_{16}N_3$	HRMS	Calcd.	633.1073
		Found	633.1055

7 Ru(III)-catalyzed Epoxidations in FBS

7.1 Catalyst synthesis

Synthesis of 2,4 diiodo-6-nitro-phenylamine (80)



To a 100 mL round-bottomed flask were added 2-nitroaniline (0.690 g, 5 mmol), NaOAc (0.92 g, 11.2 mmol) and 5 mL glacial AcOH. A solution of ICl (1.82 g, 11.2 mmol) in 3 mL glacial AcOH was added dropwise during 30 min at rt. The stirring was continued for 30 min while a white precipitate separates from the solution, then the mixture was heated at 80 °C for an additional 7 h. The mixture was extracted with warm DCM (7 x 10 mL), the solvent removed in vacuo and the residue recrystallised from diethyl ether, yielding analytically pure **80** as a yellow solid (0.900 g, 46 % yield).

Mp: 150 °C (dec.)

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3452 (m), 3343 (m), 3081 (w), 1605 (m), 1491 (s), 1344 (m), 1258 (m), 1087 (w), 877 (w), 761 (w), 661 (w), 539 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.37 (s, 1 H), 8.06 (s, 1 H), 6.61 (bs, 2 H)

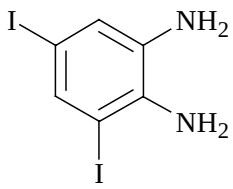
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 152.7, 143.9, 135.5, 88.8, 76.2

MS (EI, 70 eV m/e (rel. int.)): 390 (100), 343 (24), 216 (23), 189 (3), 127 (3) 90 (19), 63 (10).

$C_6H_4N_2O_2I_2$ (M = 389.92 g mol^{-1}) Elemental analysis Calcd. C : 18.48 H : 1.03 N : 7.18

Found C : 18.38 H : 1.11 N : 7.12

Synthesis of 3,5-diiodo-benzene-1,2-diamine (81)



A 100 mL round-bottomed flask was charged with **80** (8.142 g, 20.8 mmol), 35 mL HCl 37 % and $SnCl_2$ (14.82 g, 78 mmol). The mixture was stirred for 2 h at 70 °C, then let to cool at rt and stirr overnight. The brown suspension was treated with NaOH 20 % to pH 12, then extracted with DCM (8 x 50 mL). The collected organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated, yielding **81** as a yellowish solid (6.80 g , 94 %).

Mp: 106 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3384 (m), 3281 (m), 1611 (m), 1562 (m), 1468 (s), 1403 (m), 1281 (m), 843 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 7.39 (s, 1 H), 6.88 (s, 1 H), 3.67 (bs, 4 H)

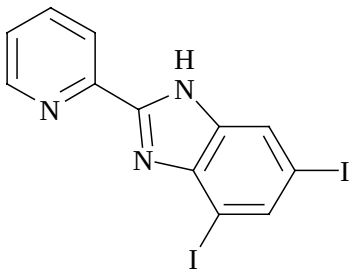
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 135.8, 134.9, 134.5, 123.8, 85.7, 80.2

MS (EI, 70 eV m/e (rel. int.)): 360 (100), 233 (21), 180 (3), 127 (3), 106 (8), 78 (4), 52 (4).

$C_6H_6N_2I_2$ (M = 359.93 g mol^{-1}) Elemental analysis Calcd. C : 20.02 H : 1.68 N : 7.78

Found C : 19.90 H : 1.71 N : 7.82

Synthesis of 4,6-diiodo-2-pyridin-2-yl-1-*H*-benzoimidazole



To a 50 mL two-necked flask, equipped with reflux condenser and magnetic stirrer, were added the diamine **81** (1.152 g, 3.2 mmol) in 15 mL DMF and, dropwise, a solution of 2-carboxypyridinaldehyde (0.321 g, 3.0 mmol) in 15 mL DMF. The resulting homogeneous brown

solution was let stirr at 80 °C for 1 h. Disappearing of the diamine was monitored by GC/MS. $FeCl_3 \cdot 6H_2O$ (40 mg, 0.15 mmol) was added to the solution, which was then stirred at 120 °C for 7 h with O_2 bubbling through. The solvent was removed in vacuo and the black residue purified by flash cromatography, yielding the product as a pale orange solid (1.186 g, 89 %).

Mp: 190-193 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3420 (s), 3055 (w), 1594 (w), 1443 (m), 1284 (m), 927 (w), 729 (w), 581, (w), 540 (w).

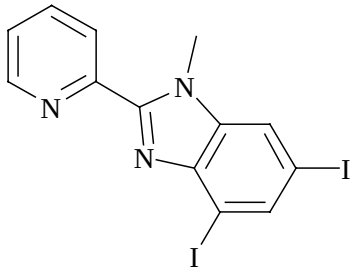
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.61 (d, *J* = 4.6 Hz, 1H), 8.42 (bs, 1H), 7.92 (bs, 2H), 7.87 (td, *J* = 7.8 and 1.8 Hz, 1H), 7.39 (m, 1H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 151.4, 149.6, 147.6, 140.1, 139.9, 137.8, 125.8, 125.6, 122.6.

MS (EI, 70 eV m/e (rel. int.)): 447 (100), 223 (5), 193 (41), 105 (4), 88 (6), 78 (9).

$C_{12}H_7I_2N_3$ HRMS Calcd. 446.8729
Found 446.8757

Synthesis of 4,6-diiodo-1-methyl-2-pyridin-2-yl-1-*H*-benzoimidazole (82)



To a dry 100 mL Schlenk flask was added under Ar atmosphere the benzoimidazole synthesized in the previous step (2.682 g, 6 mmol) in 30 mL dry DMSO, followed by the addition of NaH (suspension in mineral oil, 60%, 0.264 g, 6.6 mmol) in small portions. The mixture was heated at 60 °C for 2.5 h, with gas formation and colour changing from yellow to deep red. The solution was cooled to rt and MeI (1.029 g, 7.2 mmol) was added dropwise, then the mixture was let stirr 2 h at 45 °C and overnight at rt. A yellow precipitate was formed, which was filtered, and recrystallised from 10 mL warm DCM. The brown DMSO solution was extracted with H_2O/DCM , the organic phases collected, the solvent removed in vacuo and the residue recristallised 3 times from warm DCM. The collected solids yielded **82** as yellow needles (1.907 g, 70 %).

Mp: 199-201 °C

IR (KBr pellets, cm^{-1}) $\tilde{\nu}$: 3437 (m, b), 3048 (w), 2952 (w), 1580 (m), 1464 (s), 1435 (s), 1318 (m), 914 (m), 833 (m), 794 (m), 612 (m).

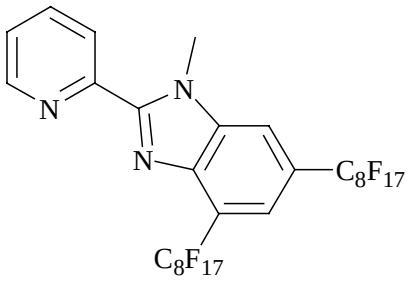
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.60 (m, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 7.92 (s, 1H), 7.77 (dt, *J* = 7.8 and 1.8 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 4.13 (s, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 151.1, 150.1, 149.0, 144.5, 139.6, 137.7, 137.3, 125.9, 124.6, 119.6, 89.2, 88.8, 87.1, 41.4, 33.8, 30.1

MS (EI, 70 eV m/e (rel. int.)): 461 (100), 383 (13), 333 (8), 230 (3), 103 (7), 88 (7), 78 (7).

$C_{13}H_9I_2N_3$ HRMS Calcd. 460.8886
Found 460.8860

Synthesis of 4,6-diperfluorooctyl-1-methyl-2-pyridin-2-yl-1-*H*-benzoimidazole (14) (*Rf_2Bimpy*)



To a dry two-necked 100 mL Schlenk flask equipped with reflux condenser and Ar-inlet was added Cu° bronze (1.59 g, 25 mmol), which was activated by flame heating under high vacuum. After cooling at rt, $C_8F_{17}I$ (5.46 g, 10 mmol) in 6 mL dry DMSO was added under Ar flow and the mixture stirred at 120 °C for 1 h. The benzimidazole **82** (0.992 mg, 2.0 mmol) was then added at rt and the resulting dark mixture stirred at 120 °C for 3 h. After cooling at rt the reaction was quenched dropwise with 30 mL of an aqueous concentrated ammonia solution, which was extracted with diethyl ether (5 x 40 mL), washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo and further recrystallisation from a cold solution pentane/diethyl ether 1:2 gave **14** as a white solid (1.442 g, 69 %).

Mp: 134 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3440 (m), 2922 (w), 2856 (w), 1635 (w), 1208 8s), 1150 (s), 666 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 8.73 (d, *J* = 4 Hz, 1H), 8.51 (d, *J* = 7.8 Hz, 1H), 7.89 (td, *J* = 7.8 and 1.6 Hz, 1H), 7.87 (s, 1H), 7.73 (s, 1H), 7.42 (m, 1H), 4.40 (s, 3H)

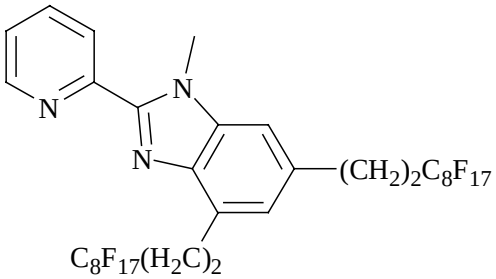
^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 148.6, 147.7, 137.2, 136.1, 136.0, 122-113 (bm), 32.3, 28.7.

^{19}F NMR ($CDCl_3$, 400 MHz): -79.7 (t, 6F), -107.4 (m, 4F), -120.1 (s, 8F), -120.7 (s, 8F), -121.6 (s, 4F), -125.0 (s, 4F);

MS (EI, 70 eV m/e (rel. int.)): 1045 (100), 1025 (19), 967 (1), 706 (6), 676 (23), 626 (6), 338 (2), 307 (3), 258 (7), 168 (1).

$C_{29}H_9F_{34}N_3$ HRMS Calcd. 1045.0254
Found 1045.0230

Synthesis of 4,6-(1,1,2,2-tetrahydroperfluorodecyl)-1-methyl-2-pyridin-2-yl-1-*H*-benzoimidazole (83) (*Rf_2C_2Bimpy*)



A dry, Ar flushed three-necked 100 mL Schlenk flask equipped with magnetic stirrer and reflux condenser was charged with 10 mL dry THF and $PdCl_2$dppf (120 mg, mmol), then stirred for 15 min at rt. A solution of the diiodobenzimidazole **82** (0.992 g, 2.0 mmol) in 25 mL dry THF was added to the orange suspension and stirred for an additional hour at rt. A solution of 1,1,2,2,3,3-esahydro-perfluoroundecylzinc iodide (4.5 mL of 0.967 M solution, 4.36 mmol) was added dropwise, leading to a brown suspension, which became yellow after reflux. Reflux was continued for an additional 2 h until GC/MS shown disappearing of the starting material. The solution was cooled, the solvent removed in *vacuo* and the residue extracted with 100 ml diethyl ether, then washed with brine and dried over $MgSO_4$. The crude was purified by flash chromatography (eluent pentane/EtOAc 1:2 + 1 % TEA) on silica gel, yielding **83** as a white solid (705 mg, 32%).

Mp: 104 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 2961 (w), 1591 (w), 1470 (w), 1204 (s), 1150 (s), 724 (w), 659 (w).

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 8.68 (d, *J* = 3.6 Hz, 1H), 8.37 (d, *J* = 6 Hz, 1H), 7.84 (td, *J* = 5.4 and 0.9 Hz, 1H), 7.34 (m, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 4.25 (s, 3H), 3.37 (m, 2H), 3.06 (m, 2H), 2.73 (m, 2H), 2.45 (m, 2H).

^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 149.7, 149.6, 147.5, 139.5, 136.7, 135.8, 133.7, 130.4, 123.9, 123.8, 122.6, 121.6, 122-108 (m), 107.0, 32.7 (t), 31.8, 30.5 (t), 28.7.

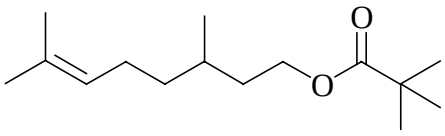
^{19}F NMR (δ/ppm, $CDCl_3$, 400 MHz): -79.7 (t, 6F), -113.4 (s, 4F), -120.5 (s, 4F), -120.6 (s, 8F), -120.8 (s, 4F), -121.6 (s, 4F), -122.3 (s, 4F), -125.0 (s, 4F).

MS (EI, 70 eV m/e (rel. int.)): 1101 (100), 1082 (24), 732 (55), 682 (23), 668 (25), 355 (2), 334 (3), 281 (4), 207 (3).

$C_{33}F_{34}H_{17}N_3$ HRMS Calcd. 1101.088
Found 1101.044

7.2 Epoxidations

Synthesis of 3,7-dimethyl-oct-6-enyl pivalate (92)



A dry 50 mL Schlenk flask was charged with a solution of citronellol (1.560 g, 10.0 mmol) and TEA (2.02 g, 20.0 mmol) in 20 mL dry DCM. The solution was cooled to 0 °C and pivaloyl chloride (2.019 g, 15.0 mmol) was added dropwise under stirring. A precipitate separates and the suspension was vigorously stirred 36 h at rt, then treated with 15 mL of an aqueous solution HCl 1M. The organic layer was separated and washed with 15 mL of a cold aqueous solution Na_2CO_3 1M, then washed with water and dryed over $MgSO_4$. Removal of the solvent *in vacuo* gave pure **92** as a pale yellow oil (2.332 g, 97 %).

IR (Film, cm^{-1}) $\tilde{\nu}$: 2960 (s), 2930 (s), 1816 (w), 1743 (s), 1229 (m), 1130 (m), 1052 (w).

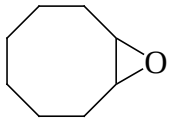
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 5.08 (m, 1H), 4.08 (m, 2H) 2.05-1.90 (bm, 2H), 1.67 (s, 3H), 1.56 (s, 3H), 1.65-1.05 (m, 7H), 1.01 (s, 9H), 0.90 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 172.9, 131.7, 125.0, 62.9, 48.5, 37.3, 36.0, 31.1, 30.0, 26.1, 25.8, 19.7, 18.0.

MS (EI, 70 eV m/e (rel. int.)): 239 (0.1), 138 (60), 123 (100), 109 (38), 99 (35), 95 (98), 81 (100), 69 (86), 57 (70).

$C_{15}H_{28}O_2$ (M = 240.38 g mol^{-1}) Elemental analysis Calcd. C : 74.95 H : 11.74
Found C : 74.89 H : 11.75

Synthesis of 1,2-cyclooctene oxide (85a)



Prepared according to TP 4 from *cis*-cyclooctene (220 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 60 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **85a** as a white solid (225 mg, 89 %).

Mp: 53 °C

IR (Film, cm^{-1}) $\tilde{\nu}$: 2928 (s), 2855 (s), 1464 (m), 1069 (m), 923 (m), 861 (m), 787 (m).

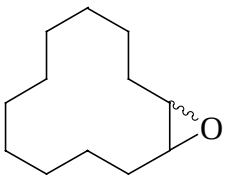
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.96-2.80 (m, 2H), 2.20-2.09 (m, 2H), 1.65-1.20 (m, 10H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 65.4, 27.0, 26.7, 26.1.

MS (EI, 70 eV m/e (rel. int.)): 126 (2), 111 (15), 97 (33), 93 (12), 83 (41), 67 (66), 57 (41), 55 (100).

$C_8H_{14}O$ (M = 126.20 g mol^{-1}) Elemental analysis Calcd. C : 76.14 H : 11.18
Found C : 76.18 H : 11.15

Synthesis of 1,2-cyclododecene oxide (86a)



Prepared according to TP 4 from cyclododecene (333 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 50 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **86a** as a colourless viscous oil (335 mg, 92 %). 6:1 mixture of two isomers (*syn* and *anti*).

IR (film, cm^{-1}) $\tilde{\nu}$: 2930 (s), 2860 (s), 1468 (s), 1385 (m), 986 (m), 913 (m), 805 (m).

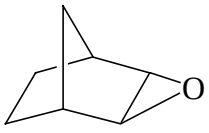
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.67-2.63 (m, 2H), 2.15-2.07 (m, 2H), 1.56-1.11 (m, 16 H), 1.03-0.88 (m, 2H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 60.4, 31.8, 27.1, 25.9, 25.4, 24.4, 24.3.

MS (EI, 70 eV m/e (rel. int.)): 182 (2), 164 (3), 149 (5), 135 (26), 121 (49), 111 (66), 109 (26), 97 (68), 81 (91), 67 (89), 55 (100).

$C_{12}H_{22}O$ ($M = 182.3$ g mol^{-1}) Elemental analysis Calcd. C: 79.06 H:12.16
Found C: 78.92 H:12.29

Synthesis of 3-oxa-triciclo[3.2.1.0.^{2,4}]octane (87a) (Norbornene oxide)



Prepared according to TP 4 from norbornene (188 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 75 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **87a** as a colourless oil (183 mg, 83 %)

IR (film, cm^{-1}) $\tilde{\nu}$: 2964 (s), 2874 (s), 1450 (w), 1387 (m), 1315 (m), 977 (m), 850 (s).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.99 (s, 2H), 2.37 (s, 2H), 1.42-1.11 (m, 5H), 0.64-0.59 (m, 1H)

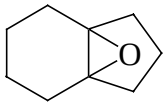
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 51.4, 36.7, 26.8, 25.1

MS (EI, 70 eV m/e (rel. int.)): 110 (6), 95 (23), 91 (20), 81 (100), 79 (73), 67 (29), 54 (26).

$C_7H_{10}O$ (M = 110.15 g mol^{-1}) Elemental analysis Calcd. C : 76.33 H : 9.18

Found C : 76.28 H : 9.25

Synthesis of 10-oxa-tricyclo[4.3.1.0.^{1,6}]decane (88a)



Prepared according to TP 4 from 2,3,4,5,6,7-hexahydro-1*H*-indene (188 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 30 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **88a** as a colourless oil (204 mg, 74 %).

IR (Film, cm^{-1}) $\tilde{\nu}$: 2938 (s), 2862 (s), 1703 (m), 1445 (m), 1241 (s), 1213 (s), 1153 (m), 744 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.30-1.60 (m, 6H), 1.60-0.90 (m, 8H).

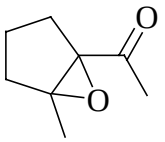
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 64.0, 35.1, 30.1, 20.7, 18.8.

MS (EI, 70 eV m/e (rel. int.)): 138 (20), 120 (21), 110 (20), 97 (100), 95 (22), 91 (13), 82 (25), 79 (28), 67 (89), 54 (15).

$C_9H_{14}O$ (M = 138.21 g mol^{-1}) Elemental analysis Calcd. C : 78.21 H : 10.21

Found C : 78.18 H : 10.25

Synthesis of 1-(5-methyl-6-oxa-bicyclo[3.1.0]hex-1-yl)-ethanone (89a)



Prepared according to TP 4 from 1-(2-methyl-cyclopent-1-enyl)-ethanone (248 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 60 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **89a** as a colourless oil (205 mg, 73 %)

IR (Film, cm^{-1}) $\tilde{\nu}$: 2962 (m), 2934 (m), 1704 (s), 1358 (m), 1099 (w), 745 (m).

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.27-1.10 (bm, 6H), 1.38 (s, 3H).

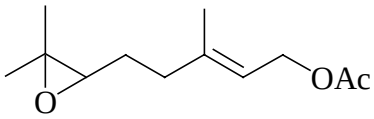
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 207.0, 74.5, 71.7, 33.7, 28.9, 28.2, 19.2, 16.2.

MS (EI, 70 eV m/e (rel. int.)): 140 (48), 125 (28), 97 (100), 83 (45), 79 (12), 69 (33), 55 (35).

$C_8H_{12}O_2$ (M = 140.18 g mol^{-1}) Elemental analysis Calcd. C : 68.54 H : 8.63

Found C : 68.48 H : 8.89

Synthesis of 6,7-epoxynerylacetate (91a)



Prepared according to TP 4 from geranyl acetate (393 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 60 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **91a** as a colourless oil (344 mg, 81 %). Only epoxidation at the 6-position was detected (NMR analysis).

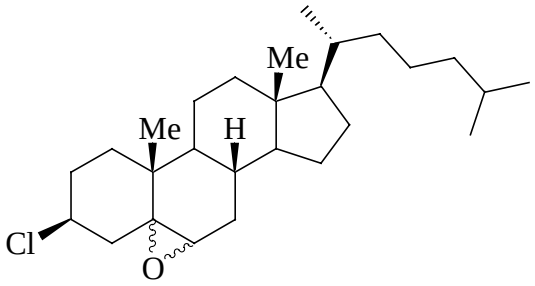
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 5.38 (m, *J* = 7.1 Hz, 1H), 4.58 (d, *J* = 7.3 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.17 (m, 2H), 2.05 (s, 3H), 1.72 (s, 3H), 1.25-1.05 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 170.7, 141.6, 120.0, 63.6, 60.9, 58.4, 28.7, 27.6, 24.9, 23.3, 20.9, 18.7.

MS (EI, 70 eV m/e (rel. int.)): 212 (0.1), 152 (10), 126 (16), 109 (39), 94 (25), 85 (100), 81 (95), 71 (79), 67 (36), 59 (56).

$C_{12}H_{20}O_3$ (M = 212.29 g mol^{-1}) Elemental analysis Calcd. C : 67.89 H : 9.50
Found C : 67.96 H : 9.44

Synthesis of 3β-chloro-5,6-epoxycholestan (90a)



Prepared according to TP 4 from 3β-Chlorocholest-5-ene (810 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 2.5 h. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **90a** as a white solide (791 mg, 94 %). A 2:3 mixture of α- and β- epoxide was obtained (NMR analysis).

IR (Film, cm^{-1}) $\tilde{\nu}$: 2950 (s), 2868 (s), 1715 (w), 1467 (m), 1240 (m), 1022 (w), 741 (w).

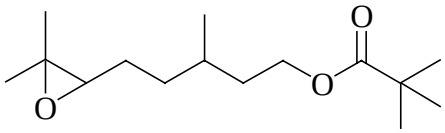
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 4.20-4.01 (m, 1H, *anti*), 3.86-3.78 (m, 1H *syn*), 3.08 (d, *J* = 2.2 Hz, 1H *syn*), 2.92 (d, J = 4.4 Hz, 1H *anti*), 2.39 (t, J = 12.4 Hz, 1H *anti*), 2.35 (t, 13.1 Hz, *syn*), 2.20-0.80 (m, 42 H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 65.9, 63.6, 63.1, 59.6, 56.9, 56.7, 56.3, 56.2, 56.0, 51.4, 43.2, 42.7, 42.4, 42.3, 41.5, 39.8, 39.6, 39.4, 38.9, 36.3, 35.7, 34.8, 34.3, 32.9, 32.8, 32.7, 29.8, 28.8.

MS (EI, 70 eV m/e (rel. int.)): 420 (17), 402 (18), 384 (28), 366 (20), 289 (27), 265 (34), 261 (66), 247 (29), 211 (26), 193 (28), 158 (29), 149 (100), 135 (45), 120 (44), 107 (55), 93 (61), 67 (34), 55 (51).

$C_{27}H_{45}ClO$ HRMS Calcd. 420.3159
Found 420.3168

Synthesis of 5-(3,3-dimethyl-oxiranyl)-3-methyl-pentan-1-yl pivalate (92a)



Prepared according to TP 4 from (mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 40 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **92a** as a colouless oil (470 mg, 92 %)

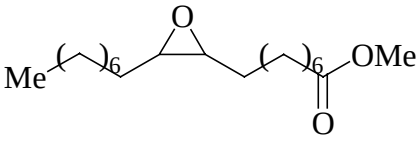
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 4.10 (m, 2H), 2.74-2.52 (m, 1H), 1.75-1.25 (bm, 7H), 1.30 (s, 3H), 1.26 (s, 3H), 1.06 (s, 9H), 0.92 (d, *J* = 6.4 Hz, 3H),

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 172.9, 62.9, 58.2, 37.3, 35.5, 33.6, 29.8, 26.4, 24.9, 21.1, 19.4, 19.3, 18.8.

MS (EI, 70 eV m/e (rel. int.)): 255 (0.1), 199 (2), 155 (26), 137 (12), 129 (16), 117 (41), 111 (27), 99 (100), 96 (31), 83 (61), 69 (65), 57 (88).

$C_{15}H_{28}O_3$ (M = 256.38 g mol^{-1}) Elemental analysis Calcd. C : 70.27 H : 11.01
Found C : 70.34 H : 10.96

Synthesis of methyl epoxyoleate (93a)



Prepared according to TP 4 from methyl oleate (593 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 60 min. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **93a** as a colourless oil (594 mg, 95 %)

IR (Film, cm^{-1}) $\tilde{\nu}$: 2929 (s), 2856 (s), 1740 (s), 1465 (m), 1170 (s), 725 (w).

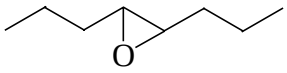
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 3.53 (s, 3H), 2.76-7.73 (m, 2H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.52-1.03 (m, 26H), 0.75 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 174.5, 57.6, 57.5, 51.8, 34.3, 32.3, 30.0, 29.7, 29.6, 29.5, 29.4, 28.1, 28.0, 27.0, 26.9, 25.3, 23.0, 14.4.

MS (EI, 70 eV m/e (rel. int.)): 312 (1), 227 (11), 199 (30), 183 (17), 171 (23), 167 (13), 155 (100), 153 (22), 139 (24), 127 (39), 125 (18), 109 (34), 97 (56), 87 (70), 74 (92), 55 (100).

$C_{19}H_{36}O_3$ (M = 312.49 g mol^{-1}) Elemental analysis Calcd. C : 73.03 H : 11.61
Found C : 73.07 H : 11.55

Synthesis of 4-octene oxide (94a)



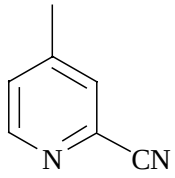
Prepared according to TP 4 from *trans*-4-octene (224 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol). Reaction time: 1.5 h. Purification by flash chromatography (pentane/diethyl ether 9:1) on silica gel yielded the epoxide **94a** as a colourless oil (200 mg, 78 %)

^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 2.75-2.60 (m, 2H), 1.60-1.45 (m, 8H), 0.94 (t, J = 7Hz, 6H)
^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 58.8, 34.2, 19.1, 14.0.
MS (EI, 70 eV m/e (rel. int.)): 128 (1), 99 (27), 85 (10), 81 (12), 72 (79), 57 (100), 55 (65).
The data are in agreement with literature values[106].

[106] J.L. Courtneidge, M.Bush *J. Organomet. Chem* **1992**, *437*, 57.

8. Synthesis of Oxazolines

Synthesis of 2-cyano-4-methyl pyridine (105)



To a dry 100 mL round-bottomed flask equipped with reflux condenser and Ar inlet were added the bromopicoline **76** (4.30 g, 25 mmol) and anhydrous CuCN (3.358 g, 37.5 mmol) in 35 mL dry DMSO at rt under Ar. The solution was heated to 180 °C and stirred at this temperature for 10 min. The dark solution was treated with 100 mL H_2O/EtOAc 1:1 and the aqueous layer extracted with EtOAc (4 x 20 mL). The collected organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give pure **105** (1.652 g, 56 %) as a white solid.

Mp: 86 °C

IR (KBr, pellets, cm^{-1}) $\tilde{\nu}$: 3436 (m), 3050 (m), 2984 (w), 2926 (w), 2235 (m), 1600 (s), 1471 (m), 1297 (m), 1027 (m), 992 (s), 841 (s), 462 (s).

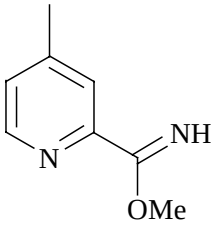
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.49 (d, *J* = 5 Hz, 1H), 7.46 (s, 1H), 7.27 (d, *J* = 5 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 151.2, 149.1, 134.3, 129.8, 128.2, 117.7, 21.3.

MS (EI, 70 eV m/e (rel. int.)): 118 (100), 91 (33), 64 (11), 63 (8), 51 (5).

$C_7H_6N_2$ (M = 118.14 g mol^{-1}) Elemental analysis Calcd. C : 71.17 H : 5.12 N: 23.71
Found C : 71.07 H : 5.15 N: 23.78

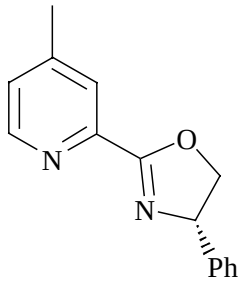
Synthesis of 4-methyl-pyridine-2-carboximidic acid methyl ester



To a 100 mL round-bottomed flask was charged with the cyano-pyridine **105** (1.18 g, 10 mmol) and NaOMe (54 mg, 1.0 mmol) in 30 mL methanol at rt. The solution was stirred 3 days at rt and the formation of the imidate monitored by GC/MS. After addition of two drops of AcOH, evaporation of the methanol *in vacuo* gave a yellowish oil (1.470 g, 98 %) which was used directly for the next step without further purification.

MS (EI, 70 eV m/e (rel. int.)):150 (10), 119 (84), 107 (27), 93 (100), 65 (21).

Synthesis of 4-methyl-2-[(*S*)-4-phenyl-4,5-dihydro-oxazolidin-2-yl]-pyridine (106)



To a 100 mL round-bottomed flask equipped with reflux condenser was added the above imidate (1.350 g, 9.0 mmol), and (*S*)-(+)-2-amino-2-phenyl-ethanol (1.37 g, 10 mmol) in 35 mL DCM. The mixture was stirred at 40 °C for two days. After removal of the solvent in vacuo, the residue was recrystallised from MeOH, giving pure **106** as a yellowish viscous liquid. (1.351 g, 63 %).

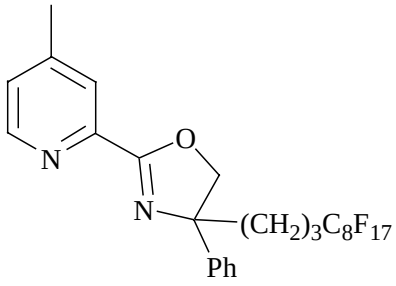
^{1}H NMR (δ/ppm, $CDCl_3$, 300 MHz): 8.51 (d, *J* = 5.1 Hz, 1H), 7.96 (s, 1H), 7.26-7.16 (m, 6H), 5.38 (m, 1H), 4.82 (m, 1H), 4.32 (t, *J* = 8.6 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (δ/ppm, $CDCl_3$, 75 MHz): 164.5, 149.9, 148.4, 146.9, 142.2, 129.2, 128.1, 127.2, 127.1, 125.5, 75.7, 70.7, 21.3.

MS (EI, 70 eV m/e (rel. int.)): 238 (53), 208 (100), 180 (13), 132 (2), 118 (24), 107 (12), 89 (23), 65 (11).

$C_{15}H_{14}N_2O_3$ (M = 238.28 g mol^{-1}) Elemental analysis Calcd. C : 75.61 H : 5.92 N : 11.76
Found C : 75.64 H : 5.95 N : 11.70

Synthesis of 4-methyl-2-[4-(1,1,2,2,3,3-esahydroperfluoroundecyl)-4-phenyl-4,5-dihydro-oxazolidin-2-yl]-pyridine (108)



A dry, argon flushed 100 mL flask was charged with dry diisopropylamine (98 mg, 1.9 mmol) in 5 mL dry THF and cooled to –78 °C. A solution of *n*-BuLi in hexane (0.85 mmol) was then added and the mixture was stirred 30 min at –78 °C. A solution of the pyridinyloxazoline **106** (176 mg, 0.74 mmol) in 5 mL dry THF was then added dropwise to the LDA solution. The resulting blue solution was stirred 30 min at –78 °C. The fluorous iodide Y (588 mg, 1.0 mmol) was added and stirred for 20 min at –78 °C, then warmed up to rt and stirred overnight. The colour turned to orange within 30 min. THF is then carefully removed *in vacuo* and the crude dissolved in 50 mL Et_2O. The ocra solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography on silica gel (eluent EtOAc), yielding **108** as a white crystalline solid (197 mg, 38 %).

Mp: 88 °C

^{1}H NMR (δ/ppm, $CDCl_3$, 400 MHz): 8.58 (d, *J* = 4.8 Hz, 1H), 8.02 (s, 1H), 7.44-7.22 (m, 6H), 4.65-4.49 (m, 2H), 2.43 (m, 3H), 2.30-1.65 (m, 6H).

^{13}C NMR (δ/ppm, $CDCl_3$, 100 MHz): 161.3, 148.6, 147.0, 145.5, 144.5, 127.6, 126.1, 125.6, 124.7, 124.5, 77.9, 41.3, 29.9 (t), 29.7, 28.7, 20.0, 14.3.

^{19}F NMR (δ/ppm $CDCl_3$, 400 MHz): -79.7 (s, 3F), -113.2 (m, 2F), -120.6 (s, 2F), -120.8 (bs, 4F), -121.6 (s, 2F), -122.6 (s, 2F), -125.1 (s, 2F).

MS (EI, 70 eV m/e (rel. int.)): 698 (1), 685 (1), 679 (2), 578 (2), 251 (5), 237 (100), 221 (16), 209 (5), 119 (44), 91 (39), 77 (8), 69 (4), 65 (10), 53 (6).

$C_{26}H_{19}N_2OF_{17}$ HRMS Calcd. 698.1226
Found. 698.1220

Abbreviations

Ac	acetyl
AIBN	Azoisobutyronitrile
approx.	approximately
Bz	benzotriazole
Bp	boiling point
b	broad
Bu	butyl
c	concentration
Calcd.	calculated
cat.	catalytic
conc.	concentrated
d	doublet
dr	diastereomeric ratio
DBE	dibromoethane
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulphoxide
equiv	equivalent
EI	electron ionisation
Et	ethyl
EtOAc	ethyl acetate
F-	fluorous
FBS	Fluorous Biphase System
FC-72	perfluorohexane
FG	functional group
GC	gas chromatography
h	hour
HRMS	high resolution mass spectroscopy
i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant

LDA	lithiumdiisopropylamine
M	molar
Me	methyl
min	minute
Mp	melting point
MS	mass spectroscopy
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
Ph	phenyl
PFOB	Perfluorooctyl bromide
q	quartet
quant.	quantitative
R_f	fluorous ponytail
RT	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
TEA	triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidin-*N*-oxyl radical
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TP	typical procedure
UV	ultra-violet

CURRICULUM VITAE

Name : Gianna Ragagnin
Birth date: 02/10/1973
Birth place: Conegliano, Italy
Nationality: Italian.

Education

2000-2003: PhD in Organic Chemistry at LMU University, München, Germany. Supervisor: Prof. Dr. P. Knochel;
Thesis subject: 'N-containing Fluorous Ligands for Aerobic Oxidations in Fluorous Biphase System".

1992-1998: M. Sci. in Organic-biological Chemistry, University of Padova (Italy) Supervisor: Prof. M. Vidali.
Thesis subject: "Receptor-ligand binding: development of a computer program and application to ellipticine-DNA system".

July 1992: Certificate from State Industrial Technical Secondary School "J.F. Kennedy", Pordenone (Italy). Specialization: Industrial Chemistry.
Short dissertation about: "Qualitative and quantitative determination of synthetic dyes in soft drinks".

Work experiences

2001-2003: Assistant in the Organic Chemistry laboratory (Praktikum I and II) for Chemistry undergraduate students at the LMU University München.

20/7/99-23/12/99: Responsible of Chemical Laboratory in the company: Plastic Omnium Lander S.p.A. - Vigonza, Italy.

17/6/1999-2/7/1999: lab. technician in the firm: Dolisos s.r.l., in Padova, Italy .

1/8/1992-30/9/1992: Practica in a Public Health Laboratory ("Presidio Multizonale di Prevenzione") in Pordenone, Italy, dept. Food Analysis.
Subject: "Performing of a semiquantitative analytical method for determination of added gluten in wheat flour".

Languages Italian (native speaker);
English (written, spoken; level: fluent);
German (written, spoken; level: good);
Swedish (written, spoken; basic level).

Conferences, posters and publications

16th International Symposium of Fluorine Chemistry, Duhram (UK), 16-21 July 2000.

Poster presented at the 16th International Symposium of Fluorine Chemistry, Duhram (UK), 16-21 July 2000: B. Betzemeier, M. Cavazzini, J. Siriex, G. Ragagnin, S. Quici, P. Knochel : Copper catalyzed aerobic oxidation of alcohols in fluorous biphasic conditions.

Poster presented at the COST-RTN Meeting, Padova (Italy) 15-17 February 2002: G. Ragagnin, P.Knochel: Chemoselective aerobic oxidation of cyclic alcohols using fluorous biphasic catalysis.

Talks and results presentation at the periodic COST-RTN Meetings:

München	(March 2001)
Padova	(February 2002)
S. Andrews	(October 2002)
Budapest	(June 2003)

Contribution to *e*-eros (Electronic Encyclopedia of Reagents for Organic Synthesis [Potassium tris(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17,-triacontafluoro-(8,10-heptadecanedionato) rhutenate], **2001**.

G. Ragagnin, B.Betzemeier, S.Quici, P.Knochel "Copper catalyzed aerobic oxidation of alcohols using fluorous biphasic catalysis" *Tetrahedron*, **2002** *58*, 3985-3991.

Ragagnin Gianna and Paul Knochel "New Fluorous benzimidazolic Ligands for aerobic Ru-Catalyzed Epoxidations in Fluorous Biphase System", *manuscript in preparation*.