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An Expedient Synthesis of Perfluorinated Tetraazamacrocycles: New Ligands for Copper-Catalyzed Oxidation under Fluorous Biphasic Conditions

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Conjugate additions of cyclam to perfluorohexyl vinyl sulfone and sulfoxide, which act as efficient fluorous Michael acceptors, readily give access to new fluoro-ponytail tetraazamacrocycles in good yields. The solubility of the *N*-tetrasubstituted macrocycles depends dramatically on the nature of the polar function (SO or SO_2): the sulfoxide cyclam derivative is soluble in perfluorodecaline (pfd) and perfluoromethylcyclohexane (pfmc) while the sulfonyl derivative is almost insoluble in organic or fluorous solvents. In agreement with the well known affinity of cyclam for copper(II) ions, stable copper complexes of the fluorous macrocyclic ligands have been isolated and characterized. In chloroform/methanol, complexes with four perfluorinated tails have been obtained from reaction of the tetra-*N*-perfluorohexylsulfinyl-substituted macrocycle with copper nitrate and copper perfluorocarboxylate. In trifluoroethanol, a selective retro-Michael reaction has been observed and the same reaction specifically gives copper complexes of the tri-*N*-substituted macrocycle. Complexes with three and four fluorous tails associated with perfluorocarboxylate counteranions are soluble in fluorous solvents (pfd and pfmc). These copper complexes were tested as catalysts for the oxidation of cyclohexene by molecular oxygen in the presence of *tert*-butyl hydroperoxide (tbhp). The oxidation reactions proceed under fluorous biphasic conditions and the catalyst can be recovered and reused. Quenching experiments indicate that cyclohexenyl hydroperoxide is the main oxidation product of the reaction performed with or without tbhp. Interestingly, these perfluorinated copper complexes are good, recyclable catalysts for the oxidation of cyclohexene by molecular oxygen without tbhp at room temperature and 65 °C.

Introduction

During the last decade fluorous biphasic chemistry has evolved into a rich and fruitful research area due to its potential as a new paradigm for green chemical processes.[1,2] In the fluorous biphasic system approach, the low miscibilities of fluorocarbons with most organic solvents allow the separation of catalysts or reagents modified with perfluorinated tags in the fluorocarbon phase from substrates or products dissolved in the organic phase. The development of various fluorous reagents and catalysts has enabled fluorous technology to be increasingly applied to the isolation of reaction products and the recovery of recyclable catalysts or reagents.[1,2] Since its introduction by Horváth et al.,[3] fluorous biphasic catalysis (FBC) has been applied to a variety of catalytic reactions.[1,2,4–7] More recently, the thermomorphic properties of light fluorous compounds have been used to develop separation processes without using fluorous solvents.[8]

Although numerous fluoro-ponytail phosphane and amine ligands have been prepared,[1–8] their syntheses remain an important challenge and there is still a great demand for new fluorous ligands and fully characterized robust transition metal complexes. In this context, additional methodologies are required to introduce perfluorinated tags onto various backbones. We anticipated that conjugate addition of amines to perfluorinated Michael acceptors would be a straightforward, general, and versatile approach for the synthesis of fluorous ligands. This reaction introduces methylene spacers between the heteroatom of the ligand and the fluorous tail, which should mitigate the strong electron-withdrawing effect of the perfluoroalkyl group and preserve the metal-binding properties of the heteroatom. Moreover, this method allows the introduction of the fluorous tags in the final step of the synthetic route and hence avoids cumbersome purification steps. Hetero-Michael additions have proven to be useful synthetic tools for the functionalization of various amines and phosphanes.[9–14] Although some conjugate additions to fluorinated acceptors have been reported,[15] hetero-Michael additions have seldom been used to introduce perfluorinated chains.[16]

We recently disclosed a multi-gram scale preparation of vinyl tridecafluorohexyl sulfoxide (**1**) and vinyl tridecafluorohexyl sulfone (**2**) in four steps starting from commercially available mercaptoethanol.[17] Our synthetic plan avoids the

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use of toxic reagents and could be extended to various perfluorinated chain lengths (Figure 1). Compounds **1** and **2** have proven to be good dienophiles in Diels–Alder cycloadditions, with an enhanced reactivity compared to non-fluorous analogs such as phenyl vinyl sulfoxide.[18]

1 **2**

Figure 1. Vinyl tridecafluorohexyl sulfoxide (**1**) and vinyl tridecafluorohexyl sulfone (**2**).

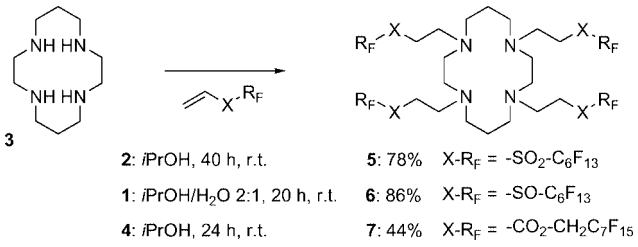
Since non-fluorous α,β-unsaturated sulfones and sulfoxides are excellent Michael acceptors and react with a number of carbon and heteroatom nucleophiles,[9,10,12–14] we anticipated that **1** and **2** would be valuable fluorous reagents for the preparation of fluoro-ponytail amine ligands. We first focused on a well known and widely studied macrocyclic ligand, namely 1,4,8,11-tetraazacyclotetradecane (cyclam, **3**). Cyclam and its *N*-substituted derivatives have high affinities for transition metal cations, with a marked selectivity for copper(II) ions, and give very stable copper complexes [the stability constants ($\log K$) are 27.2 and 18.3, respectively, for cyclam and tetramethylcyclam].[19] This suggests that fluoro-ponytail macrocycles resulting from the conjugate addition of cyclam to **1** and **2** will provide robust catalysts for fluorous biphasic catalysis. Only a few examples of fluorocarbon-soluble macrocycles have been reported so far. They include a perfluoro(oxy)alkenic cyclam derivative obtained by *N*-alkylation with the corresponding tosylate[6] and a fluoro-ponytail derivative of 1,4,7-triazacyclononane prepared by *N*-alkylation with C_8F_{17}-$(CH_2)_3I$.[7] These macrocycles have been found to be effective ligands in metal-catalyzed oxidations of hydrocarbons and alcohols.

We describe here the straightforward syntheses of new perfluorinated macrocycles by hetero-Michael addition of cyclam, as well as preliminary studies of the catalytic activity of their copper complexes for the oxidation of cyclohexene under FBC conditions.

Results and Discussion

Synthesis of Perfluorinated Tetraazamacrocycles

As depicted in Scheme 1, the perfluorinated vinyl sulfone and sulfoxide **1** and **2** proved to be excellent Michael acceptors and afforded fluoro-ponytail macrocycles **5** and **6**, respectively. The tetra-*N*-substituted perfluorinated cyclam derivative **5** is readily obtained by treating cyclam **3** with vinyl sulfone **1** in 2-propanol at room temperature. Compound **5** precipitates out of the reaction mixture and is conveniently isolated by filtration in 78% yield; the excess of fluorous Michael acceptor can be recovered. Under the same experimental conditions (*i*PrOH, room temp., 36 h), the reaction of cyclam with vinyl sulfoxide **2** affords the fluoro-ponytail macrocycle **6** in a slightly lower yield (66%), in agreement with the lower reactivity of the double bond compared to that of vinyl sulfone **1**.[9,10] The addition of water as a co-solvent favors the Michael addition[12,20] and allows the isolation of cyclam derivative **6** by filtration in good yield (86%; Scheme 1). In order to compare the reactivity of our fluorous vinyl sulfone and sulfoxide with classical Michael acceptors, as well as the stability and the properties of the corresponding fluorous macrocycles, the macrocycle **7** was prepared from the commercially available perfluorinated acrylate **4**. Under similar experimental conditions, the tetra-*N*-substituted macrocycle was obtained in lower yield. The lower reactivity of acceptor **4**[14] as well as the partial solubility of **7** in the reaction medium, which renders its isolation more tedious, both account for the poor isolated yield.



Scheme 1. Synthesis of fluoro-ponytail tetraazatetracyclotetradecanes.

All the macrocycles were fully characterized. In each case, elemental analyses and mass spectra confirmed the grafting of four fluorous tails onto the cyclam skeleton. The observed numbers of NMR signals are in agreement with the symmetry of the macrocycles.

Although their fluorine contents are quite similar, the solubility and stability of macrocycles **5**–**7** in organic and fluorous solvents depend dramatically on the polar function (X) of the Michael acceptor. The main solubilities of fluorinated azamacrocycles **5**–**7** are summarized in Table 1. The tetra-perfluorinated ester derivative **7** is soluble in most organic solvents as well as in perfluoromethylcyclohexane (pfmc). Nevertheless, the presence of a perfluorocarbon chain close to the ester function makes it sensitive to transesterification and hydrolysis, and we observed that fast transesterification occurs in methanol or trifluoroethanol (tfe) and that partial hydrolysis readily takes place in the presence of water.

The tetrasulfone **5** is not soluble, even at high temperatures, in most organic and perfluorinated solvents, except benzotrifluoride (btf). On the other hand, sulfoxide **6** exhibits enhanced solubilities with a thermomorphic behavior, as expected from its fluorine content (about 55%). Macrocycle **6** can be dissolved in hot chloroform or hot thf, and is rather soluble in polar fluorous solvents such as perfluoromethylcyclohexane (room temp.) and perfluorodecaline (pfd; 80 °C) but poorly soluble in nonpolar fluorinated solvents like Fluorinert® and perfluorohexane.[1h]

Macrocycle **6** is stable in either cold or warm solutions of organic and fluorous solvents. Nevertheless, it is worth noting that in trifluoroethanol, both sulfone **5** and sulfoxide

Table 1. Solubilities of perfluorinated macrocycles **5**–**7** and copper complexes **9** and **10** in different solvents.[a]

	wt.-% F	Fluorinert®	pfd[b]	pfmc[c]	btf[d]	$CHCl_3$ toluene	Acetone EtOAc	thf	CH_3CN dmf	MeOH	tfe[e]
5[f]	53.6	N	N	N	S	N	N	N	N	N	S
5[g]		N	nd	nd	S	P[h]	N	N	N	N	S
6[f]	55.6	N	N	S	P	N	N	N	N	N	S
6[g]		N	S	S	S	P	N	S	N	N	S
7[f]	56.5	N	N	S	N	S	S	S	N	N	S
7[g]		N	N	S	N	S	S	S	S	S	S
9a[f]	50.3	N	N	N	P	nd	nd	nd	nd	nd	P
10a[f]	47.2	N	N	N	N	nd	nd	nd	nd	nd	P
9b[f]	57.9	N	S	S	N	N	N	N	N	N	S
9b[g]		N	S	S	S	N	N	P	N	N	S
10b[f]	57.1	N	S	N	N	N	N	N	N	S	S
10b[g]		N	S	S	S	P[i]	N	N	N	S	S

[a] 8×10^{-3} M; S = soluble, P = partly soluble, N = not soluble, nd = not determined. [b] Perfluorodecaline. [c] Perfluoromethylcyclohexane. [d] Benzotrifluoride. [e] Trifluoroethanol. [f] At room temperature. [g] At 80 °C. [h] Partly soluble in hot toluene, not soluble in hot $CHCl_3$. [i] Partly soluble in hot $CHCl_3$, not soluble in hot toluene.

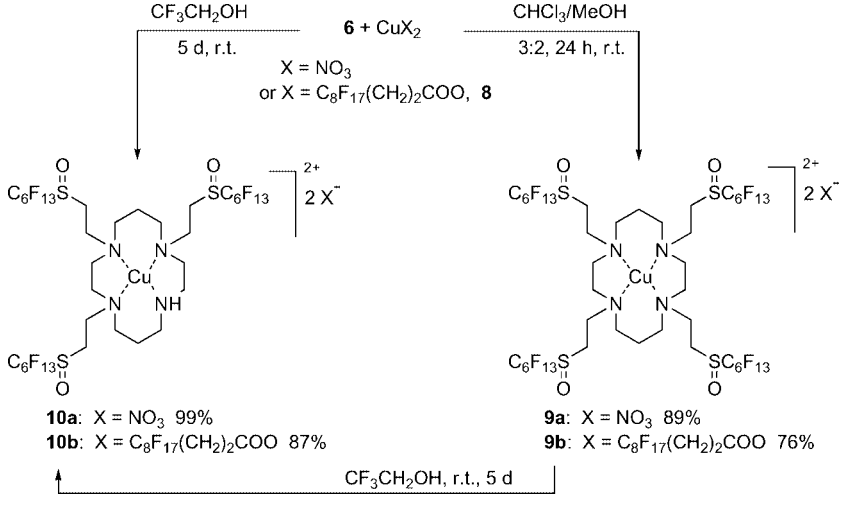
6 are soluble, but after a short period of time (1 h), retro-Michael reactions occur that generate a complex mixture of mono-, di-, and trifunctionalized cyclams.

Of the three new perfluorinated macrocycles **5**–**7**, the sulfoxide derivative **6** appears to be the most suitable ligand for use in catalytic processes owing to its stability and solubility.

Synthesis of Perfluorinated Copper Complexes

Copper complexes **9a** and **9b**, with nitrate or perfluorocarboxylate counteranions, respectively, were readily obtained by treating the fluorous macrocycle **6** with copper nitrate or copper perfluorocarboxylate (**8**)[7a] in chloroform/methanol (Scheme 2): the complexes precipitate out of the reaction medium and are readily isolated as pure compounds (blue powders) in fairly good yields. Elemental analysis confirmed the stoichiometry and the purity of complexes **9a** and **9b**. Their ESI mass spectra display a signal at *m*/*z* 920–921, which is assigned to the $[\mathbf{6} + Cu]^{2+}$ ion, i.e. to the 1:1 complex, without counteranion. The visible spectra of complexes **9a** and **9b** show broad adsorption bands at 624 and 674 nm, respectively, consistent with a copper(II)–N4 square-planar complex.[21] The absorption wavelength and the extinction coefficient for complex **9a** are close to those of other copper(II) complexes of tetra-*N*-substituted cyclams associated with nitrate or triflate counteranions.[21] The red shift of the absorption band observed for complex **9b** may result from coordination of the perfluorocarboxylate anion (in one or both of the axial positions).

Surprisingly, when the fluorous macrocycle **6** was treated with copper nitrate or copper perfluorocarboxylate in tfe or in a tfe/methanol mixture, the tri-*N*-substituted complexes **10a** or **10b** were selectively isolated in good yields (Scheme 2). This result is important considering the difficulties encountered in building trifunctionalized cyclam skeletons in short reaction sequences. A close examination of the reaction in tfe revealed that the tetrasubstituted complex **9b** is first formed and then slowly decomposes into **10b**. An acid-catalyzed retro-Michael process may account for the formation of complex **10b**. Nevertheless, we have not observed this specific retro-Michael process in other solvents, even in the more acidic hexafluoroisopropanol.[22]



Scheme 2. Preparation of perfluorinated copper(II) complexes **9a**,**b** and **10a**,**b**.

The fluorine and copper contents of **10a** and **10b** confirm the presence of three fluorous tails as well as the 1:1 stoichiometry of the copper complex. The ESI mass spectra of **10a** and **10b** display a signal at *m*/*z* 723–724, which is assigned to the 1:1 doubly charged copper complex without counteranion. The visible spectra of *N*-trisubstituted complexes **10a** and **10b** show adsorption bands at 583 and 635 nm, respectively. Their absorption wavelengths are lower than those of the tetra-*N*-substituted complexes **9a** and **9b** (vide supra). This is in good agreement with previously reported characteristics of non-fluorous cyclam complexes, whereby the introduction of *N*-substituents tends to produce a change in the ligand field properties and a shift to higher wavelengths is observed as the number of *N*-substituents is increased.[21a]

As can be seen in Table 1, fluoro-ponytail copper complexes **9** and **10** are almost insoluble in organic solvents. Their solubility in fluorous solvents mainly depends on the nature of the counteranion and is not significantly affected by the number of fluorous tails. As expected, perfluorocarboxylate complexes **9b** and **10b** exhibit the highest affinities for fluorous phases and are soluble in pfmc and pfd. Nitrate complexes **9a** and **10a** are not soluble in perfluorinated solvents.

The experimental conditions developed for the synthesis of complexes from **6** could not be applied to the synthesis of complexes derived from ligand **5** due to the poor solubility of this macrocycle. Thus, treatment of **5** with the copper(II) perfluorocarboxylate **8** in btf gave an insoluble purple powder. Nevertheless, a careful analysis of this powder revealed the presence of a complex mixture of the expected copper complex accompanied by vinyl sulfone **2** and other retro-Michael products. Attempts to synthesize copper complexes from the macrocycle **7** bearing perfluorinated ester tails also failed and led to complex mixtures of partially hydrolyzed and transesterified azamacrocycles derivatives, whatever the experimental conditions tested.

Oxidation of Cyclohexene (11) Catalyzed by Copper Complexes 9b and 10b under Fluorous Biphasic Conditions

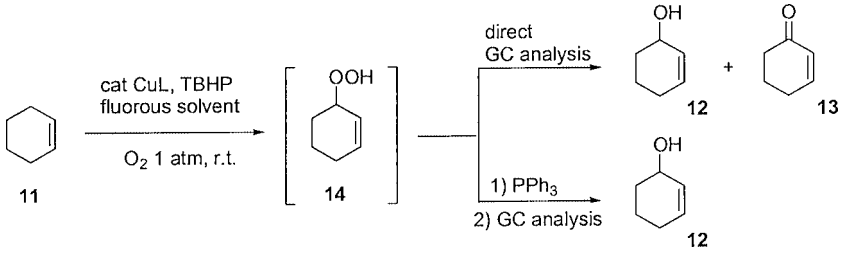
Macrocycle **6** gives access to stable copper complexes **9** and **10** bearing four or three perfluorinated chains, respectively, which are soluble in fluorous solvents as perfluorocarboxylate derivatives **9b** and **10b**. In order to test the potential of the fluoro-ponytail azamacrocycle **6** and to compare its performance with previously reported fluorous amine ligands,[6,7] we investigated the oxidation of cyclohexene **11** by molecular oxygen in the presence of *tert*-butyl hydroperoxide (tbhp) catalyzed by complexes **9b** and **10b** under biphasic fluorous conditions (Scheme 3).

The oxidation results are presented in Table 2. All the experiments were carried out at room temperature under biphasic conditions and O_2 atmospheric pressure: the catalyst was solubilized in pfd (or pfmc) and the organic phase was the substrate itself; no additional solvent was used. In typical experiments (Table 2), the molar ratios between the substrate (cyclohexene **11**), tbhp, and the catalyst were 40:0.5:0.008 (i.e. 0.02 mol-% catalyst and 1.25 mol-% tbhp). GC analysis of the organic phase showed that the oxidation of cyclohexene gave a mixture of cyclohexenol (**12**) and cyclohexenone (**13**; Table 2). In some cases, traces of cyclohexene oxide were also detected.

In the presence of copper perfluorocarboxylate (**8**), mild oxidation of cyclohexene is observed but the conversion decreases dramatically when the fluorous phase is recycled (entries 2 and 3). This can be rationalized by the poor stability of complex **8** and demonstrates that stable complexes are required.

The stable copper complexes **9b** and **10b** show catalytic activity with oxidation yields and turnover numbers (TON) similar to those previously reported for other fluoro-ponytail ligands derived from cyclam, tacn, or bipyridine.[6,7] Complex **9b** gave oxidation yields of 320–550% (with respect to tbhp) and TONs of 200–350. More importantly, the fluorous phase can be recovered and recycled, with good preservation of the catalytic activity, for up to five runs (entries 4–8, 9, and 10). The catalytic activity decreases slightly to around 80–85% in the second run and then remains constant in further experiments, thus indicating a remarkable stability of the macrocyclic copper complex. The decrease of activity for the second run can be easily explained by some leaching of complex **9b** into the organic phase during the first experiment. As complex **9b** is not soluble in cyclohexene, this phenomenon stopped after the second run. Complex **10b**, which bears three perfluorinated tails, shows a slightly lower activity than **9b**, with oxidation yields of about 200% and a TON of 100 (entries 15–17). Its catalytic activity decreased significantly during recycling (60% and 50% of its initial value for the second and third runs, respectively).

The catalytic oxidation of cyclohexene was further investigated in the presence of the most efficient catalyst (**9b**) in order to improve the oxidation yields and to get further



Scheme 3. Catalytic oxidation of cyclohexene.

Table 2. Catalytic activity of copper complexes **9b** and **10b** for the FBC oxidation of cyclohexene.[a]

Entry	Catalyst	Run	Solvent	Vol. [mL]	Cat[b] [mol-%]	Product mmol	Selectivity [%][c] **12**	**13**	Conversion[d]	TON[e]
1	–	–	pfd[f]	4	–	0.4	56	27	73	–
2	**8**	1	pfd	4	0.02	0.7	40	54	136	85
3		2				0.3	42	47	53	33
4	**9b**	1	pfd	4	0.02	2.8	37	58	556	347
5		2				1.7	35	58	336	210
6		3				1.6	29	57	312	195
7		4				1.7	30	56	345	216
8		5				1.6	31	56	319	199
9	**9b**	1	pfd	2	0.02	2.0	23	71	394	246
10		2				1.6	37	60	329	206
11	**9b**	1	pfd	4	0.08	2.7	44	51	548	86
12		2				0.5	38	55	108	17
13	**9b**	1	pfmc[g]	4	0.02	1.2	39	57	240	150
14		2				0.9	45	51	181	113
15	**10b**	1	pfd	4	0.02	0.9	42	53	177	110
16		2				0.5	37	57	107	67
17		3				0.4	38	55	88	55
18	**10b**	1	pfmc	4	0.08	1.7	36	59	340	53

[a] Unless otherwise mentioned: cyclohexene (40 mmol, 4 mL), tbhp (500 μmol, 55 μL), catalyst (8 μmol), molar ratios 5000:62.5:1, 48 h, room temperature. [b] With respect to cyclohexene. [c] Traces of cyclohexene oxide are present. [d] Conversion (%) calculated relative to tbhp. [e] Turnover Number: mol of substrate oxidized/mol of catalyst. [f] Perfluorodecaline. [g] Perfluoromethylcyclohexane.

mechanistic insights. Oxidation yields and TON for the first and second runs were quite similar when the experiments were carried out in pfd or pfmc (entries 4–6, 13–14), which are both good solvents for **9b**. Since the solubility of molecular oxygen is higher in the latter,[23] these results seem to indicate that the concentration of molecular oxygen in the fluorous phase is not a limiting parameter, as previously reported.[24] On the other hand, for a given amount of catalyst, reducing the volume of the fluorous phase by a factor of two results in a marked improvement in the oxidation yield, up by about 400%, and of the TON, up by about 250 (entries 9 and 10) with 80% of activity remaining in the second run. An increased interfacial area under these conditions, which could favor contact between the substrate and the catalyst, may account for these results. Experiments performed in the presence of 0.08 mol-% of complex **9b** give higher conversions but low TONs, with a marked fall in activity for the second run (entries 11 and 12). A large leakage of the catalyst to the organic phase could be the origin of this observation.

It is known that the tbhp/O_2 oxidation process is an autoxidation process involving cyclohexene hydroperoxide (**14**): tbhp acts as an initiator to generate alkoxy or peralkoxy radicals, which react with cyclohexene to produce a cyclohexenyl radical that is trapped by O_2 and induces propagation of the radical reaction.[6,7,25] In agreement with this proposed mechanism, the amount of tbhp can be significantly reduced: experiments performed at low tbhp/cyclohexene molar ratios (0.25 and 0.05 mol-%) gave very high oxidation yields (2050 and 6400%) and TONs of 240 and 330 (Table 3). The formation of **14** as the major oxidation product in the catalytic oxidation is clearly evidenced by quenching the reaction mixture with PPh_3 (Table 3).[25] As recently emphasized by Shul'pin et al.,[25] when a hydroperoxide is the main oxidation product it is completely or partly decomposed in the GC to produce a mixture of alcohol and ketone. On the other hand, the addition of PPh_3 before GC analysis reduces the hydroperoxide into the corresponding alcohol, which can be properly quantified. The results of GC analyses after quenching with PPh_3 clearly demonstrate that **14** is the main oxidation product (Table 3). Moreover, the quantification of **12** allows a precise quantification of the real oxidation yield: with 1.25 mol-% of tbhp (standard procedure) the oxidation yields reach 1044, 558, and 540%, with TONs of 652, 348, and 329, respectively, for the first, second and third runs (Table 3, entry 1). In the presence of smaller amounts of tbhp (0.05 mol-%) oxidation yields of more than 22000% with a TON of 515 were achieved. The catalytic activity decreases to around 50–55% in the second run and then remains constant in further experiments (Table 3, entry 2). More unexpectedly, we found that the FBC oxidation of cyclohexene catalyzed by complex **9b** can be performed without tbhp with a TON of about 460 and with 50–55% of remaining catalytic activity for the second and third runs (Table 3, entry 3). Quenching experiments show that **14** is also the main oxidation product in the absence of tbhp at room temperature.

High oxidation yields are obtained when the catalytic reactions are performed at 65 °C without tbhp − TONs higher than 1300 are achieved and the catalytic activity remains constant for the second and third runs (Table 3, entry 4). At 65 °C cyclohexenone and cyclohexenol, which result from the decomposition of cyclohexene hydroperoxide, are the main oxidation products. Further studies are currently under way to investigate the possible mechanism of this direct oxidation and to determine the role of the perfluorinated medium, which has recently been proved to boost autoxidation processes.[26]

Table 3. FBC oxidation of cyclohexene: influence of the quantity of tbhp and comparison of the results before and after quenching of the reaction by addition of PPh_3.[a]

Entry	tbhp[b] [mol-%]	Conversion[c]	No PPh_3 Run 1	Run 2	Run 3	With PPh_3 Run 1	Run 2	Run 3
1	1.25 (55 μL)	*n*	2.8	1.7	1.6	5.2	2.8	2.7
		12	37	35	29	91	96	95
		13	58	58	57	7	0	0
		TON	347	210	195	652	348	329
2	0.045 (2 μL)	*n*	2.6	1.4	1.5	4.1	2.2	2.3
		12	39	40	36	93	96	96
		13	55	54	56	4	0	0
		TON	330	175	185	516	273	285
3	0	*n*	3.8	1.0	1.2	3.7	1.8	1.9
		12	34	38	38	93	95	97
		13	61	53	54	4	0	1
		TON	472	125	149	457	222	244
4	0[e]	*n*[d]	5.0	5.7	5.4	5.4	5.3	5.4
		12[d]	30	41	41	30	44	42
		13[d]	70	58	59	70	54	58
		TON[d]	1262	1434	1356	1344	1316	1350

[a] Reaction conditions: perfluorodecaline: 4 mL; cyclohexene: 40 mmol; catalyst **9b**: 8 μmol; variable amounts of tbhp; 48 h; room temperature. [b] With respect to cyclohexene; volume in brackets. [c] *n*: Amount of oxidation products (mmol); relative molar ratios (%) of cyclohexenol (**12**) and cyclohexenone (**13**). [d] After 24 h. [e] At 65 °C.

Conclusions

A convenient and ready access to fluoro-ponytail tetraazamacrocycles through a conjugate addition of cyclam to perfluorohexyl vinyl sulfone (**2**) and sulfoxide (**1**) has been described. Perfluorohexyl vinyl sulfone and sulfoxide have been revealed to be excellent Michael acceptors and the application of this methodology for the preparation of other fluorous ligands is currently in progress in our laboratory. The solubility of the tetra-*N*-substituted fluorous macrocycles depends dramatically on the nature of the polar groups in the fluorous tails. The macrocycle bearing perfluorinated sulfinyl arms (**6**) is soluble in fluorous solvents like pfd and pfmc, while the tetrakis(perfluorohexylsulfonyl)cyclam derivative **5** is almost insoluble in organic or fluorous solvents. The linkage of fluorous tails via an ethylsulfinyl spacer does not affect the metal-binding ability of the macrocycle: stable copper complexes with three and four perfluorinated tails have been isolated from macrocycle **6**, depending on the solvent used for the preparation. Copper complexes associated to perfluorocarboxylate counteranions are soluble in fluorinated solvents like pfd or pfmc and have been successfully used in fluorous biphasic catalysis. Fluorous copper complex **9b** catalyzes the oxidation of cyclohexene by molecular oxygen. This catalyst is robust and can be recovered and reused with acceptable conservation of the catalytic activity. Further application of these fluorous complexes to other transformations is now in progress.

Experimental Section

All chemicals were purchased from Sigma, Aldrich, or Fluka and were used without further purification. Organic solvents were purchased from SDS and perfluorinated solvents from Apollo (including trifluoroethanol). ^{1}H NMR spectra were recorded with a Bruker AC300 (300 MHz) or AC200 (200 MHz) spectrometer using the residual peak of $CHCl_3$ (δ = 7.27 ppm) as an internal standard. ^{19}F NMR spectra were recorded with a Bruker AC300 (282 MHz) or AC200 (188 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR were recorded with a Bruker AC300 (75 MHz) or AC200 (50 MHz) spectrometer with the central peak of $CDCl_3$ (δ = 77 ppm) as an internal reference. Mass spectra were obtained with a HP MS 5989B spectrometer. IR spectra were recorded for samples in KBr on an Impact 400D Nicolet spectrophotometer. The elementary analyses were performed at the Laboratoire Central d'Analyses, (Vernaison, France). Melting points were determined on a Mettler FP61 melting point apparatus. UV/Vis measurements were performed at 25 °C using a Perkin–Elmer Lambda 19 spectrophotometer. GC analyses were performed with a Shimadzu GC-14A equipped with a column Chrompack CP Sil 19 CB (30 m × 0.25 mm; film thickness: 0.25 μm). Chromatograms were recorded and integrated with a Shimadzu C-R5A Chromatopac. The temperature of the oven was programmed as follows: 50 °C (for 2 min) then raised from 50 °C to 250 °C (rate: 10 °C min^{-1}), and finally 250 °C for 10 min. The injector and detector temperatures were set to 270 °C. Hydrogen, air, and helium pressures were 0.5, 0.5, and 1 kg cm^{-2}, respectively.

Perfluorooctylethylcopper(II) dicarboxylate (**8**) was prepared according to the procedure described by Fish.[7a] Perfluorohexyl vinyl sulfone and sulfoxide were synthesized as described previously.[17]

1,4,8,11-Tetrakis(2-perfluorohexylsulfonylethyl)-1,4,8,11-tetraazacyclotetradecane (5): A solution of 2-(perfluorohexylsulfonyl)ethene (**2**; 3.18 mmol, 1.30 g) and cyclam (0.5 mmol, 0.1 g) in 2-propanol (20 mL) was stirred at room temperature for 40 h. The precipitate was filtered and washed with dichloromethane (50 mL) to give a white powder (0.39 mmol, 0.72 g) in 78% yield; R_f = 0.5 (CH_2Cl_2/MeOH, 95:5); m.p. decomposes at 158 °C. ^{1}H NMR (200 MHz, $PhCF_3$, $CDCl_3$): δ = 3.48 (t, $^3J_{H,H}$ = 6.0 Hz, 8 H), 3.20 (t, $^3J_{H,H}$ = 6.0 Hz, 8 H), 1.78 (m, 4 H), 1.71 ppm (m, 16 H). IR (KBr): $\tilde{\nu}$ = 2928, 2800, 1357, 1235, 1209, 1145 cm^{-1}. $C_{42}H_{36}F_{52}N_4O_8S_4$ (1840.1): calcd. C 27.40, H 1.97, N 3.04, S 6.97; found C 27.45, H 1.92, N 3.07, S 7.44.

1,4,8,11-Tetrakis(2-perfluorohexylsulfinylethyl)-1,4,8,11-tetraazacyclotetradecane (6): A solution of 2-(perfluorohexylsulfinyl)ethene (**1**; 9.62 mmol, 3.79 g) and cyclam (1.65 mmol, 0.33 g) in a mixture

of 2-propanol (14 mL) and water (7 mL) was stirred at room temperature for 20 h. The precipitate was filtered and washed with dichloromethane (50 mL) to give a white powder (1.38 mmol, 2.45 g) in 86% yield; R_f = 0.5 (CH_2Cl_2/MeOH, 95:5); m.p. decomposes at 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.18–2.47 (m, 32 H), 1.78 ppm (m, 4 H). ^{19}F NMR (188 MHz, $CDCl_3$): δ = –80.89 (m, 3 F), –115.4 (m, 1 F), –119.5 (m, 3 F), –122.0 (m, 2 F), –122.9 (m, 2 F), –126.2 ppm (m, 2 F). IR (KBr): $\tilde{\nu}$ = 2960, 2809, 1362, 1235, 1199, 1147, 692 cm^{-1}. MS (ESI+): *m/z* (%) 889 [M + 2H$^+$], 729 (100) [M – C_6F_{13}]$^{2+}$, 705 (25) [M – SOC_6F_{13}]$^{2+}$. $C_{42}H_{36}F_{52}N_4O_4S_4$ (1776.1): calcd. C 28.39, H 2.04, F 55.60, N 3.15, S 7.22; found C 28.53, H 1.99, F 55.57, N 3.08, S 7.83.

1,4,8,11-Tetrakis[2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctylpropionyloxy)ethyl]-1,4,8,11-tetraazacyclotetradecane (7): The acrylate **4** (1.36 g, 3.0 mmol) was added to a solution of cyclam (0.1 g, 0.5 mmol) in 2-propanol (20 mL). This solution was stirred for 1 d and then left to stand for another day at room temperature. The precipitate was then filtered and the insoluble material washed with methanol (10 mL) to give a white powder (0.44 g, 0.22 mmol) in 44% yield; R_f = 0.5 (CH_2Cl_2/MeOH, 90:10); m.p. decomposes at 117 °C. ^{1}H NMR (200 MHz, [D$_6$]acetone): δ = 4.86 (t, $^3J_{H,F}$ = 13.8 Hz, 8 H), 2.77 (t, $^3J_{H,H}$ = 6.0 Hz, 8 H), 2.52 (t, $^3J_{H,H}$ = 6.0 Hz, 24 H), 1.58 ppm (m, 4 H). ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 171.7, 59.7 (t, $^2J_{C,F}$ = 26 Hz), 52.3, 52.1, 50.1, 32.8, 25.1 ppm. ^{19}F NMR (188 MHz, [D$_6$]acetone): δ = –77.0 (m, 3 F), –115.2 (m, 2 F), –117.9 (m, 4 F), –118.7 (m, 2 F), –119.1 (m, 2 F), –122.2 ppm (m, 2 F). IR (KBr): $\tilde{\nu}$ = 2965, 2934, 2806, 1752 cm^{-1}. MS (ESI+): *m/z* (%) 1009 (100) [M + 2H$^+$]. $C_{54}H_{44}F_{60}N_4O_8$ (2016.2): calcd. C. 32.16, H 2.20, N. 2.78; found C 32.08, H 2.24, N 2.82.

[1,4,8,11-Tetrakis(2-perfluorohexylsulfinylethyl)-1,4,8,11-tetraazacyclotetradecane]copper(II) Dinitrate (9a): A solution of copper nitrate trihydrate (5.63×10^{-2} mmol, 13.6 mg) and **6** (5.63×10^{-2} mmol, 100 mg) in a mixture of chloroform (3.2 mL) and methanol (2.1 mL) was stirred for 24 h. The precipitate was filtered then washed with methanol (10 mL) to give a blue powder (5.0×10^{-2} mmol, 98 mg) in 89% yield; m.p. decomposes at 179 °C. IR (KBr): $\tilde{\nu}$ = 2975, 2929, 1362, 1235, 1203, 1143, 666 cm^{-1}. UV/Vis (trifluoroethanol): λ_{max} (ε) = 624 nm (199 M^{-1}cm^{-1}), 308 (5495). MS (ESI+): *m/z* (%) 920–921 (100) [M^{2+}]. $C_{42}H_{36}CuF_{52}N_6O_{10}S_4$ (1964.5): calcd. C 25.68, H 1.85, F 50.29, N 4.28; found C 25.95, H 1.89, F 50.1, N 4.51.

[1,4,8,11-Tetrakis(2-perfluorohexylsulfinylethyl)-1,4,8,11-tetraazacyclotetradecane]copper(II) Bis[3-(Perfluorooctyl)propionate] (9b): A solution of **8** (5.63×10^{-2} mmol, 58.8 mg) and **6** (5.63×10^{-2} mmol, 100 mg) in a mixture of chloroform (0.67 mL) and methanol (0.45 mL) was stirred for 24 h. The precipitate was filtered then washed with chloroform (40 mL) to give a blue powder (4.3×10^{-2} mmol, 120.8 mg) in 76% yield; m.p. decomposes at 176 °C. IR (KBr): $\tilde{\nu}$ = 2812, 1363, 1294, 1204, 1137 cm^{-1}. UV/Vis (trifluoroethanol): λ_{max} (ε) = 674 nm (646 M^{-1}cm^{-1}), 328 (3800) ppm. MS (ESI+): *m/z* (%) 920–921 (27) [M^{2+}]. $C_{64}H_{44}CuF_{86}N_4O_8S_4$ (2821.0): calcd. C 27.23, H 1.57, Cu 2.25, N 1.98; found C 26.74, H 1.55, Cu 2.80, N 2.11.

[1,4,8-Tris(2-perfluorohexylsulfinylethyl)-1,4,8,11-tetraazacyclotetradecane]copper(II) Dinitrate (10a): A solution of copper nitrate trihydrate (2.81×10^{-2} mmol, 6.8 mg) and **6** (2.81×10^{-2} mmol, 50 mg) in trifluoroethanol (2.0 mL) and methanol (0.5 mL) was stirred for 5 d then concentrated in vacuo to give a blue powder. This powder was triturated in chloroform (15 mL), and the insoluble powder was then washed with water (30 mL) and dried in vacuo to give a blue powder (2.80×10^{-2} mmol, 44 mg) in 99% yield; m.p. decomposes at 154 °C. IR (KBr): $\tilde{\nu}$ = 3457, 2940, 1383, 1235, 1199, 1147 cm^{-1}. UV/Vis (trifluoroethanol): λ_{max} (ε) = 583 nm, 345. MS (ESI+): *m/z* (100) 723–724 [M^{2+}]. $C_{34}H_{33}CuF_{39}N_6O_9S_3$ (1569.0): calcd. C 26.00, H 2.12, Cu 4.05, F 47.18, N 5.35; found C 26.47, H 2.24, Cu 3.77, F 47.46, N 4.83.

[1,4,8-Tris(2-perfluorohexylsulfinylethyl)-1,4,8,11tetraazacyclotetradecane]copper(II) Bis[3-(perfluorooctyl)propionate] (10b): A solution of **8** (5.63×10^{-2} mmol, 58.8 mg) and **6** (5.63×10^{-2} mmol, 100 mg) in trifluoroethanol (4 mL) was stirred for 5 d. After filtration, the filtrate was concentrated in vacuo, stirred in chloroform (20 mL) for 1 h and filtered to give a blue powder (4.90×10^{-2} mmol, 95 mg) in a yield of 87%; m.p. decomposes at 135 °C. IR (KBr): $\tilde{\nu}$ = 3428, 1598, 1363, 1245, 1199, 1147, 661 cm^{-1}. UV/Vis (trifluoroethanol): λ_{max} (ε) = 635 nm (263 M^{-1}cm^{-1}), 302 (6309). MS (ESI+): *m/z* 723–724 (100) [M^{2+}]. $C_{56}H_{41}CuF_{73}N_4O_7S_3$ (2427.0): calcd. C 27.70, H 1.70, Cu 2.62, N 2.31, S 3.96; found C 27.23, H 1.71, Cu 2.80, N 2.31, S 3.89.

Reaction Between 8 and 5: A solution of **8** (5.44×10^{-2} mmol, 56.8 mg) and **5** (5.44×10^{-2} mmol, 100 mg) in (trifluoromethyl)benzene (10 mL) was stirred for 48 h at room temperature. Concentration in vacuo gave a violet powder (5.44×10^{-2} mmol, 156.9 mg); m.p. decomposes at 104 °C. The TLC analysis revealed the presence of vinyl sulfone **1**. IR (KBr): $\tilde{\nu}$ = 2781, 1352, 1230, 1194 cm^{-1}. UV/Vis (trifluoroethanol): λ_{max} (ε) = 320 nm (272 M^{-1}cm^{-1}), 298 (1706). MS (ESI+): *m/z* 1574 ($C_{26}H_{30}F_{26}N_4O_4S_2$[Cu($O_2CCH_2CH_2$-$C_8F_{17}$])$^+$. $C_{64}H_{44}CuF_{86}N_4O_{12}S_4$ (2885.): calcd. C 26.63, H 1.54, Cu 2.20, N 1.94, S 4.44; found C 27.28, H 1.78, Cu 2.25, N 2.05, S 4.30.

General Procedure for Fluorous Biphasic Catalysis: Catalyst **9b** (22.6 mg, 8 μmol) and perfluorodecaline (4 mL) were added to a Schlenk tube followed by cyclohexene (4.0 mL, 40 mmol), 1,2-dichlorobenzene (0.25 mL, 2 mmol, internal standard), and *tert*-butyl hydroperoxide (55 μL, 0.5 mmol). These were then placed under an oxygen atmosphere. The reaction mixture was then stirred (1250 min^{-1}) for 48 h at room temperature. The reaction was monitored by GC. After 48 h a 50-μL sample was taken from the organic phase, diluted with diethyl ether (25 μL) and 0.1 μL of this solution was injected into the GC.

For experiments with reduction of the intermediate cyclohexenyl hydroperoxide an excess of solid PPh_3 (PPh_3 was slowly added until the end of exothermic phenomena) was added to the sample 10 min before injection into the GC. The amounts of oxidation products were determined using 1,2-dichlorobenzene as the internal standard.

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