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Synthesis of Perfluoroalkylated Bipyridines - New Ligands for Oxidation Reactions under Fluorous Triphasic Conditions

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Abstract:

Fluorous soluble bipyridines bearing two perfluoroalkylated side chains in the 6,6'- or 4,4'-positions have been prepared in good yields *via* etherification of 6,6'-bis(chloromethyl)-2,2'-bipyridine or *C*-alkylation of 6,6'-dimethyl-2,2'-bipyridine. The new ligands L exhibit amphiphilic behaviour with respect to certain fluorous-organic biphasic systems. Nevertheless, their ruthenium complexes $(RuL_n)X$ generated *in situ* are efficient catalysts for the epoxidation of *trans*-stilbene in a fluorous triphasic system $CH_2Cl_2/H_2O/C_8F_{18}$ in the presence of $NaIO_4$. The fluorous phase, where $(RuL_n)X$ is trapped, can be used up to four times without major loss of catalytic activity.

Key words: Catalysis; Nitrogen heterocycles, Perfluoroalkyl compounds; Ruthenium and compounds

Fluorous Biphasic chemistry offers many conceivable advantages over classical homogeneous chemistry, including the easy and effective separation and recycling of metal complexes in catalytic reactions [1] [2]. Fluorous Biphasic variants of catalytic oxidation of hydrocarbons have been reported by us and several other groups [3-5]. Indeed, perfluorocarbons dissolve large amounts of molecular oxygen and they are very stable under oxidizing conditions. We were particularly involved in the Fluorous Biphasic modification of biomimetic oxidation reactions catalyzed by metal complexes of perfluoroalkylated ligands such as porphyrins, tetraazamacrocycles and N,N'-bis(salicylidene)ethylenediamines. The synthesis of these tetradentate ligands have been optimized and the factors affecting their solubility in perfluorocarbons have been identified [3].

In pursuit of new biomimetic Fluorous Biphasic oxidation systems, we became interested in simpler bidentate ligands already used in non-haem monooxygenase enzyme modelling [6]. Bipyridines have a particularly rich coordination chemistry and they were successfully used for generating *in situ* transition metal complexes that are able to catalyze the oxidative functionalization of hydrocarbons [7]. Moreover, simple modifications of such nitrogen ligands may be envisaged in order to achieve selective solubility in fluorinated solvents. In fact, the synthesis of 2,2'-bipyridines bearing perfluoroalkylated tails in the 4,4'-positions was reported [8]. The fluorine load of these amphiphilic molecules (typically about 48%) was lower than that required for the solubilization of tetradentate ligands in perfluorocarbons (60%), but it was high enough for increasing the hydrophobic and fluorophilic character of the ligands, thus allowing their incorporation into liposomes. Unfortunately, the reported synthetic approach entails the presence of functional groups, for instance carbon-carbon double bonds, that are incompatible with oxidizing conditions.

Here we describe the simple and convenient preparation of three new perfluoroalkylated bipyridines having a considerable fluorine load, with a structure fully adequate for use as ligands in catalytic oxidations (Scheme 1 and 2). This was proved in the epoxidation of *trans*-stilbene both in an aqueous/organic two-phase system (Table 2) and in an unusual aqueous/organic/fluorous three-phase system (Table 3).

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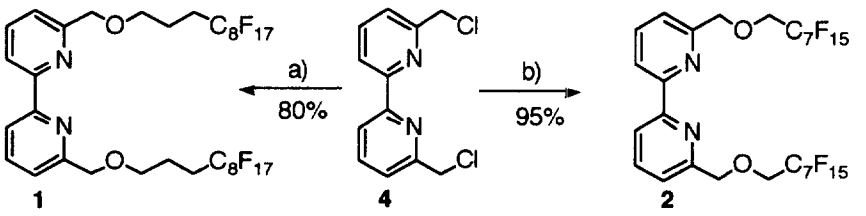
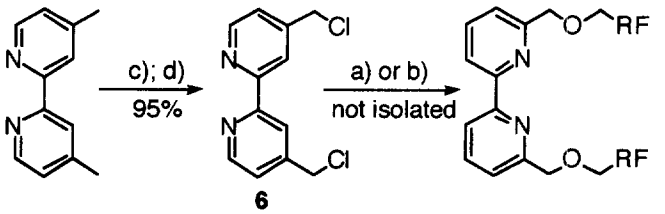


a) $C_8F_{17}(CH_2)_3OH$ (1.5 eq); NaH (3 eq); THF, reflux 16h

b) $C_7F_{15}CH_2OH$ (1.5 eq); NaH (3 eq); THF, reflux 16h

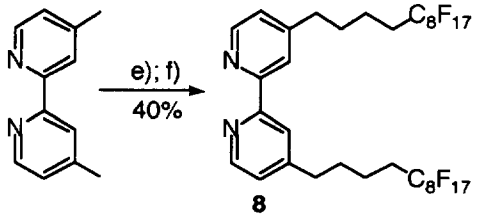


c) LDA; TMSCl; THF, -78 °C

d) $CFCl_2CCl_2F$; CsF, Cs_2CO_3; DMF, 25 °C

Scheme 1

Ethers are among the few organic compunds which show a residual solubility in perfluorocarbons [9]. Moreover, the ether bond is stable toward hydrolysis and oxidizing conditions. Bipyridines **1** and **2** featuring two perfluoroalkyl chains (R_F) linked in the 6,6' positions were thus synthesised *via* etherification of 6,6'-bis(chloromethyl)-2,2'-bipyridine **4** with $C_8F_{17}(CH_2)_3OH$ **5** and $C_7F_{15}CH_2OH$ respectively. Bipyridine **4** and alcohol **5** were prepared according to literature procedures [10, 5b], whereas $C_7F_{15}CH_2OH$ is commercially available. The use of a strong base such as NaH gave better results in the functionalization of **4**: under milder reaction conditons (*e.g.* KOH or K_2CO_3 in the presence of a phase transfer catalyst) relevant amounts of monoalkyl derivatives were detected by ^{1}H-NMR in the reaction mixture, and isolation of the desired compounds was difficult. Attempts to synthesize 2,2'-bipyridines with R_F in the 4,4' positions following the same route were less fruitful. 4,4'-Bis(chloromethyl)-2,2'-bipyridine **6** was conveniently prepared from 4,4'-dimethyl-2,2'-bipyridine by slightly modifying the procedure reported by Fraser and coworkers [11]. However, both perfluoroalkylated alcohols reacted with **6** leading to a complex mixture from which the expected bis(*O*-alkylated) compounds could not be isolated.



e) LDA; THF, -78 °C → 0 °C

f) $C_8F_{17}(CH_2)_3I$; THF, -78 °C → RT

Scheme 2

R_F substituents were conveniently introduced in the 4,4' positions through a simple coupling reaction previously described for the *C*-alkylation of 4,7-dimethyl-1,10-phenantroline (Scheme 2) [12]. The dianion obtained from 4,4'-dimethyl-2,2'-bipyridine and LDA was treated *in situ* with $C_8F_{17}(CH_2)_3I$ **7** [5b] at low temperature affording bipyridine **8** in 40 % yield.

Although the fluorine content of **1**, **2** and **8** approaches 60%, these new bidentate nitrogen ligands exhibit an amphiphilic behaviour with respect to organic solvents and perfluorocarbons. They are readily soluble in Et_2O, THF and CH_2Cl_2 but also in perfluoromethylcyclohexane and *n*-C_8F_{18}. The partition coefficient (w/w) of the new ligands in 50/50 vol% *n*-C_8F_{18}/CH_2Cl_2 is reported in Table 1. The preference for the organic solvent is striking in the case of ligand **1** and only ligand **2** shows a slightly higher affinity for the fluorous phase than for CH_2Cl_2.

Table 1. Partition Coefficient (w/w) of Perfluoroalkylated Bipyridines in 50/50 vol% *n*-C_8F_{18}/CH_2Cl_2.[a]

Ligand	MW	% of F	Partition Coefficient
1	1136	56.9	0.25
2	980	58.2	1.08
8	1105	58.5	0.67

[a] To a solution of 100 mg of ligand in the minimal volume of *n*-C_8F_{18} an identical volume of CH_2Cl_2 was added. The mixture was stirred at 20 °C for 2 h, then the two phases were separated and the solvents evaporated under reduced pressure. The ligand content of each phase was determined by weighing the residue.

The perfluoroalkylated bipyridines were tested in the ruthenium-catalyzed epoxidation of *trans*-stilbene under aqueous-organic conditions, according to the procedure devised by Balavoine and coworkers (Table 2) [13]. Reactions carried out in the presence of perfluoroalkylated bipyridines afforded *trans*-stilbene epoxide in good yields, with complete conversion of the substrate. Comparison with the results obtained with the hydrophilic ligand 2,2'-bipyridine, shows that the lipophilic nature of the new ligands does not lower the catalytic activity of the system. On the contrary, selectivity for the epoxide remains high even at 25 °C. At that temperature the oxidative cleavage of the C-C double bond becomes an important side-reaction when 2,2'-bipyridine is used as the ligand [13].

Table 2. Ruthenium Catalyzed Epoxidation of *trans*-Stilbene with $NaIO_4$ in H_2O/CH_2Cl_2 [13].[a]

Entry	Ligand	T (°C)	t (min)	Yield [b]
1	2,2'-Bipyridine	25	90	45
2	**1**	25	90	77
3	**2**	25	90	70
4	**8**	25	90	87
5	2,2'-Bipyridine	0	15	83
6	**1**	0	15	79
7	**2**	0	15	84
8	**8**	0	15	92

[a] Molar ratio $NaIO_4$ /*trans*-Stilbene/Ligand/$RuCl_3$ = 100/40/6/1; [b] *trans*-Stilbene epoxide. Determined by GC in the presence of hexadecane as internal standard.

There is now some evidence that the fluorous partition coefficient of Fluorous Biphasic catalysts depends also on the overall number of R_F tails in its structure [3] [14]. Although the true nature of the catalyst generated *in situ* from $RuCl_3$/Bipyridine/$NaIO_4$ is still unknown, ruthenium(II) bipyridyl complexes such as $[RuX(Bipy)_2]^{2+}$ (X = H_2O) seem to be the most plausible candidates [15]. Then the fluorous affinities of the ruthenium catalysts generated from **1**, **2** and **8** might be higher than that of the starting ligands. This hypothesis was tested by running the epoxidation of *trans*-stilbene in an aqueous/organic/fluorous three-phase system at 0 °C (Table 3) [16]. The reaction was complete after 15 min with all three new ligands. The fluorous phase

recovered by simple decantation was used for four further runs without addition of $RuCl_3$. In the case of ligands **1** and **8** a decrease in the epoxide yield was observed after three runs, the decrease being slower in the presence of ligand **8**. With ligand **2** the epoxide yield declined significantly only in the fifth run. If the partition coefficients of the ruthenium complexes had matched those of the corresponding ligand a much quicker loss of catalytic activity would have been observed. Indeed, the residual content of the most fluorophilic complex in the fluorous phase would have halved at each cycle.

Table 3. Ruthenium Catalyzed Epoxidation of *trans*-Stilbene with $NaIO_4$ in $H_2O/CH_2Cl_2/n$-C_8F_{18} (0.75/1/1/ v/v/v) [16].[a]

Ligand	Yield [b] (1st Run)	Yield (2nd Run)	Yield (3rd Run)	Yield (4th Run)	Yield (5th Run)
1	96	95	95	68	44
2	92	88	85	83	50
8	95	97	94	78	71

[a] Molar ratio $NaIO_4$ /*trans*-Stilbene/Ligand/$RuCl_3$ = 100/40/6/1; [b] *trans*-Stilbene epoxide. Determined by GC in the presence of hexadecane as internal standard.

The present results show that easily available ligands such as bipyridines can be conveniently used in Fluorous Chemistry and prove that Fluorous Triphasic Systems, previously described for the purification of fluorous reagents [17], can also be applied to catalytic reactions.

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References and Notes

1. Horváth, I. T.; Rábai J. *Science* **1994**, *266*, 72-75.
2. a) Curran, D. P. *Chemtracts. Org. Chem.* **1996**, *9*, 75-87; b) Montanari, F.; Pozzi, G.; Quici, S. *Chim. Ind. (Milan)* **1998**, *80*, 469-475; c) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641-650.
3. a) Pozzi, G.; Montanari, F.; Quici, S. *Chem. Commun.* **1997**, 69-70; b) Pozzi, G.; Cavazzini, M.; Quici, S.; Fontana, S. *Tetrahedron Lett.* **1997**, *38*, 7605-7608; c) Pozzi, G.; Cinato, F.; Montanari, F.; Quici, S. *Chem. Commun.* **1998**, 877-878.
4. a) Klement, I.; Lütjens, H.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1454-1456; b) Lhermitte, F.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6667-6670.
5. a) Juliette, J. J. J.; Horváth, I. T.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1610-1612; b) Vincent, J. M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2346-2349; c) Ravikumar, K. S.; Barbier, F.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1998**, *54*, 7457-7464.
6. Funabiki T (Ed.) *Oxygenases and Model Systems*; Kluwer Academic Press: Dordrecht, 1997.
7. Ménage, S.; Collomb-Dunand-Sauthier, M.-N.; Lambeaux, C.; Fontecave, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1885-1886 and references therein reported.
8. Garelli, N.; Vierling, P. *J. Org. Chem.* **1992**, *57*, 3046-3051.
9. Hildebrand, J. H.; Fisher, B. B.; Benesi, H. A *J. Am. Chem. Soc.* **1950**, *72*, 4348-4351.
10. Newcome, G.R.; Kiefer, G. E.; Kohli, D. K; Xia, Y.-J.; Fronczek, F. R.; Baker, G. R. *J. Org. Chem.* **1989**, *54*, 5105-5110.
11. Fraser, C. L.; Anastasi, N. R.; Lamba, J. J. S. *J. Org. Chem.* **1997**, *62*, 9314-9317.
12. Menger, F. M.; Lee, J.-J. *J. Org. Chem.* **1993**, *58*, 1909-1916.
13. Balavoine, G.; Eskenazi, C.; Meunier, F.; Rivière, H. *Tetrahedron Lett.* **1984**, *25*, 3187-3190.
14. Herrera, V.; Derege, P. J. F.; Horváth, I. T.; Lehusebo, T.; Hughes, R. P. *Inorg. Chem. Comm.* **1998**, *1*, 197-199.
15. Bailey, A. J.; Griffith, W. P.; Savage, P. D. *J. Chem. Soc., Dalton Trans.*, **1995**, 3537-3542.
16. **Fluorous Triphasic epoxidation of *trans*-stilbene:** A solution of ligand in n-C_8F_{18} (1 ml, 0.027M) and an aqueous solution of $RuCl_3 \cdot 6H_2O$ (0.75 ml, 0.0037 M) were stirred for 15 hours at RT in a Schlenk tube under N_2. To the two-phase mixture a solution of *trans*-stilbene in CH_2Cl_2 (1 ml, 0.2 M) was added and the three-phase mixture was cooled to 0 °C. $NaIO_4$ (100 mg, 0.47 mmol) was added and after 15 min the stirring was stopped. The epoxide content of the organic phase was determined by GC. The fluorous phase was transferred into a second Schlenk tube containing a fresh solution of substrate plus aqueous $NaIO_4$ and used as such for a new run.
17. Curran, D. P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1175-1196 and references therein reported.