Fluorous Biphasic Catalysis: Synthesis and Characterization of Copper(I) and Copper(II) Fluoroponytailed 1,4,7-Rf-TACN and 2,2'-Rf-Bipyridine Complexes—Their Catalytic Activity in the Oxidation of Hydrocarbons, Olefins, and Alcohols, Including Mechanistic Implications


Abstract: In this contribution on fluorous biphasic catalysis (FBC), we present the synthesis and characterization of new copper complexes, and define their role, as precatalysts, in the FBC oxidation of hydrocarbons, olefins, and alcohols. Thus the previously reported, but poorly characterized, fluoroponytailed ligand, 2,2'-Rf-Bipyridine (Rf = -(CH2)3C8F17) 2, as well as the new CuII fluoroponytailed carboxylate synthon complex [Cu(C8F17(CH2)2CO2)2(Rf-tacn)] 3, will be addressed. Moreover, the reaction of previously described ligands, 1,4,7-Rf-TACN 1, or 2,2'-Rf-bipyridine 2 with 3 afforded new perfluoroheptane-soluble CuII complexes, [Cu(C8F17(CH2)2CO2)(Rf-tacn)] 4 and [Cu(C8F17(CH2)2CO2)(Rf-bipy)] 5, respectively. The reaction of 1 with [Cu(CH3CN)4]PF6 or [CuCl] provided new CuI complexes, which could be isolated and fully characterized as [Cu(Rf-taen)]X, in which X = PF6 (6) or X = Cl (7) (soluble in perfluorohexane). The CuII and CuI complexes, 4–7, were characterized by elemental analysis, mass spectrometry, and IR, diffuse reflectance UV/Vis, and EPR spectroscopies; complex 7 was also characterized by 1H and 19F{1H} NMR spectroscopy. Complexes 4 and 5, as well as 6 and 7 generated in situ, were evaluated as precatalysts for hydrocarbon and olefin functionalization. The oxidation reactions of these substrates in the presence of the necessary oxidants, tert-butyl hydroperoxide (TBHP) and oxygen gas, proceeded under FBC conditions for 5, 7, and CuI salts with 2. However, the complexes with ligand 2 could not be recycled, owing to significant ligand dissociation. The CuII complex 4, with the ligand 1, provide the oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde under single-phase FBC conditions at 90 °C with TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) and O2; the precipitate 4, can be utilized for an additional four catalytic cycles without loss of activity. Plausible mechanisms concerning these FBC oxidation reactions will be discussed.

Keywords: biphasic catalysis · copper · mechanisms · N ligands · oxidation

Introduction

The efficient, catalytic synthesis of alcohols, aldehydes, ketones, and epoxides from alkanes and alkenes is a cornerstone of global industrial research for the preparation of a variety of products for world-wide consumption.[1] Homogeneous catalytic oxidation is more selective toward the above-mentioned products and, in addition, the reactions are carried out at lower temperatures than those used in heterogeneous catalytic oxidation. Thus, the development of a homogeneous oxidation process for alkane and alkene functionalization has been an important goal in numerous industrial and academic laboratories.[1] In order for this process to be industrially practicable in view of economical and environmental concerns, new and innovative approaches for the separation of the homogeneous catalyst from the oxidation products are still needed. In recent years, Horváth and Rábai introduced the concept of fluorous biphasic catalysis (FBC),[2] and demonstrated that by using fluorocarbon solvents and modifying the homogeneous catalyst’s ligand structure with long-chain perfluoroalkane derivatives (fluoroponytails) to make the precatalyst soluble in the fluorocarbon phase, the products of the catalytic reaction would be soluble in a separate solvent.
phase that is immiscible in the fluorocarbon phase; by removing this second phase, the products are easily separated from the precatalyst. It should also be noted that the miscibility of perfluoroalkanes and perfluoroethers with the products of alkane and alkene oxidation, such as alcohols, aldehydes, ketones, and epoxides, is extremely low or nonexistent.[9] This latter critical characteristic, and the fact that perfluoroalkanes and perfluoroethers are very interesting for their nonpolarity and extremely low intermolecular forces, makes them ideal solvents for homogeneous biphasic catalytic processes. The FBC concept has now been amply demonstrated with the conversion of many examples of classic organic catalytic reactions to the FBC paradigm,[4] amongst them oxidation reactions.[8] However, there is still an urgent need to synthesize and fully characterize new fluoroponytailed ligands and their metal complexes for unequivocal structural identification, and in order to understand the mechanisms of the oxidation chemistry under FBC reaction conditions.[20]

In this paper, we report on the synthesis and characterization of new CuI and CuII complexes with the previously described fluorocarbon-soluble 1,4,7-triazacyclononane (Rf-TACN)[7a] and bipyridine (Rf-bpy).[10d] 2 ligands that contain the fluoroponytail, C8F17-(CH2)3-. We demonstrate their catalytic activity with hydrocarbons and olefins under FBC oxidation conditions, with tert-butyl hydroperoxide (TBHP) and the necessary oxygen gas, at room temperature. Furthermore, the oxidation of alcohols to aldehydes, under FBC conditions, has also been performed with TEMPO (2,2,6,6-tetramethylpiperidinol-1-oxo) and oxygen gas at 90°C, involving one phase during the reaction and two phases on cooling to room temperature. We also provide EPR results to ascertain the fate of the precatalyst, while presenting plausible mechanisms for all of these transformations under FBC conditions.

Results and Discussion

Synthesis and characterization of Rf-CuI and Rf-CuII complexes: In the field of FBC, several CuI derivatives with fluoroponytailed amine ligands have been previously synthesized. These complexes were prepared in situ from either CuCl or CuBr·SMes2 and the corresponding ligands, Rf-macrocycles[7b] or Rf-bipyridine,[10d] and were evaluated in the oxidation of alkanes and alkenes[8] or the oxidation of alcohols,[9] respectively. Several other Cu complexes containing tri- or tetradentate amine ligands have been prepared in situ in a similar manner, and have been used as precatalysts for the cyclization of unsaturated esters[12] or living radical polymerizations[13] under FBC conditions. However, these complexes, usually generated in situ, were not isolated or characterized properly. The synthesis consisted of the addition of an excess of the CuI salt to a perfluorocarbon solution of the fluoroponytailed amine ligand, and the new fluorocarbon-soluble compound was characterized in some cases[8] by the UV/Vis spectrum of the resulting green solution. We believe that not only the green color of the perfluorocarbon solutions, but also the UV/Vis data, tentatively demonstrated that the oxidation of the fluoroponytailed CuI complexes to CuII derivatives was occurring. Thus, we wanted to synthesize and isolate not only the CuI, but also CuII fluoroponytailed complexes, as both CuI and CuII salts and complexes have previously displayed catalytic activity in the homogeneous oxidation of hydrocarbons, olefins, and alcohols.[14]

The fluoroponytailed ligands employed in this study were the previously described fluorocarbon soluble 1,4,7-triazacyclononane (Rf-TACN),[7a] 1 and bipyridine (Rf-bpy).[10d] 2 ligands (Figure 1) that contained the C8F17-(CH2)3- group. The convenient three carbon spacer in the fluoroponytail was necessary, not only to insulate the amine from the powerful electron-withdrawing effect of the perfluoroalkyl group, but also to avoid a facile elimination reaction of HI when synthesizing fluoroponytailed amine ligands by alkylation reactions with CF3(CH2)3I. The latter compound, along with ligand 1, have been previously reported by Fish et al.[7a] Although ligand 2 has been prepared before, its synthesis was not completely described, and its characterization was not

Abstract in Spanish: En esta contribución en catalisís bifásica fluorada (FBC) presentamos la síntesis y caracterización de nuevos complejos de cobre y definimos su papel, como precatalizadores, en la oxidación FBC de hidrocarburos, olefinas y alcoholos. Así, se describe la preparación y caracterización del ligando fluorado (Rf-tacn)[7a] que había sido publicado anteriormente pero sin datos experimentales sobre síntesis o caracterización, y la preparación del compuesto sintón carboxilato [Cu(C8F17(CH2)2CO2)]2, 3. La reacción de los ligandos previamente descritos 1,4,7-Rf-TACN, 1, o 2,2-Rf-bipiridina, 2 con 3 permiten la formación de compuestos de CuI solubles en perfluoroheptano como [Cu(C8F17(CH2)2CO2)2(Rf-TACN)], 4, y [Cu(C8F17(CH2)2CO2)2(Rf-bpy)], 5, respectivamente. La reacción de 1,4,7-Rf-TACN, 1, con [Cu(CH3CN)4]PF6 o [CuCl] genera nuevos compuestos de CuI que pueden ser aislados y caracterizados completamente como [Cu(Rf-TACN)X]X, con X = PF6, 6, o X = Cl, 7 (soluble en perfluoroheptano). Los compuestos de CuI y CuII, 4–7, se han caracterizado por análisis elemental, espectrometría de masas, IR, UV/Vis (reflectancia difusa) y espectroscopía de EPR. El derivado 7 ha sido caracterizado también por espectroscopía de RMN de 1H y 19F(H). Los compuestos 4 y 5, así como los derivados 6 y 7, generados in situ, se evaluaron como precatalizadores en la funcionalización de hidrocarburos y olefinas. Las reacciones de oxidación de estos sustratos, en presencia de los oxidantes necesarios, hidroperóxido de tert-butilo (TBHP) y oxígeno gas, se consiguieron en condiciones FBC para 5, 6 y sales de CuI con el ligando 2. No obstante, los compuestos con 2 no pudieron reciclar debido a una gran disociación del ligando. El compuesto de CuI, 4, con el ligando Rf-TACN, 1, permite la oxidación de alcoholos 4-nitro-bencílico a 4-nitro-benzaldeído en condiciones FBC, monofase a 90°C, con TEMPO (2,2,6,6-tetrametilpiperidina-N-oxilo) y O2: el precatalizador, 4, puede ser utilizado durante cuatro ciclos catalíticos adicionales, sin pérdida de actividad. Se discutirán mecanismos posibles para estas reacciones de oxidación en condiciones FBC.
Figure 1. Perfluoroponytailed amine ligands 1 and 2.

Figure 2. Tentative structure of compound 3.

Figure 3. Tentative structure of compound 4.

Figure 4. Tentative structure of compound 5.

The addition of ligands 1 or 2 to perfluoroheptane suspensions of 3 allowed the total (for 1) or partial (for 2) solubilization of the CuII complex at room temperature, giving deep green solutions. In order to isolate these compounds, we added ligands 1 and 2 to blue solutions of 3 in CH3Cl2, which almost immediately produced green solids that could be isolated and characterized as [Cu(CF3(CF2)CO2)(CH3)2] (3) and [Cu(CF3(CF2)CO2)2(RBF-tacn)] (4) and [Cu(CF3(CF2)CO2)2(RBF-bpy)] (5). Unfortunately, none of the Cu complexes reported gave single crystals suitable for X-ray analysis.

Complex 4 was found to be totally soluble in perfluoroheptane, while its UV/Vis spectrum in this solvent had only one absorption band at 272 nm, which could be assigned to the fluorour ligand. However, its diffuse reflectance spectrum (solid state) showed two bands at 1013 and 700 nm that could be directly attributed to a CuII complex. The stoichiometry of 4 was confirmed by elemental analysis and its LSIS-MS spectrum displayed a signal at m/z 2063 (75%), which could be assigned to the [M – [CuF3(CH2)2CO2]]+ ion. The IR spectrum had bands corresponding to the carboxylate group, in addition to those that can be assigned to the RBF-TACN ligand. It appears that the carboxylate group in 4 (tentative structure in which RBF = (CH2)2-) in Figure 3) was in a monodentate rather than a chelating or bridging coordination mode, resulting in the bigger difference (ν = 229 cm⁻¹) observed between the asymmetric and symmetric C–O stretches (ν = 1632 and 1403 cm⁻¹, respectively) in its IR spectrum.

Compound 5 was not soluble in cold perfluoroheptane, but it could be solubilized in hot perfluoroheptane (above 40°C). Again, elemental analysis and LSIS-MS confirmed the composition of the compound. The UV/Vis spectrum, recorded in perfluoroheptane, showed one absorption band at λ = 246 nm, which can be assigned to the fluorour ligand, but its diffuse reflectance spectrum (solid state) showed one intense absorption band at 680 nm in accordance with values found for other CuII complexes.

In order to ensure the fluorocarbon solubility of the CuII complexes of ligands 1 and 2, we appended fluorous ponytailed groups to the metal complex we were going to utilize as a synthet, as previously discovered by Fish et al., since metal complexes with multiple charges and counter anions, such as ClO4⁻, PF6⁻, or even Cl⁻ would be very difficult to solubilize in perfluorocarbons. Thus, the new CuII complex [Cu(CF3(CH2)2CO2)] (3), was synthesized by reaction of CuSO4·5H2O in acetone with two equivalents of the triethylammonium salt of the 3-RF-alkylpropionic acid C8F17(CH2)2CO2H; elemental analysis of 3 revealed a metal/carboxylate coordination to the CuII to a monodentate mode. The stoichiometry of 3 in accordance with the bidentate coordination mode of the Rf-TACN ligand, and [Cu(CF3(CH2)2CO2)2(Rf-tacn)] (4) in Figure 4) was in accordance with values found for other CuII complexes.

The intense absorption band displayed by Vis spectrum in the solid state by using diffuse reflectance measurements of the Cu complexes reported gave single crystals suitable for X-ray analysis.
been previously shown that the in situ synthesis of CuI-fluorous amine derivatives could be achieved by using the CuI salt and the corresponding fluoro-pontailed ligands. The addition of 1 to [Cu(CH3CN)4]PF6 or CuCl afforded an off-white ([Cu(Rf-tacn)]PF6 6) and a white ([Cu(Rf-tacn)Cl] 7) solid in moderate (36%) and high (78%) yields, respectively (Figure 5). Satisfactory elemental analyses were obtained for both compounds, and their LSIMS-MS spectra had signals that corresponded to the monocationic complexes, [Cu(Rf-tacn)]+, at m/z 1573 for 6 (60%) and 7 (88%). Complex 6 was only soluble in trifluorotoluene; however, compound 7 was totally soluble in cold perfluoroheptane and partly soluble in CHCl3, allowing for its characterization by 1H and 19F{1H} NMR spectroscopy in CDCl3. UV/Vis data for 6 were also obtained in perfluoroheptane, revealing two absorption bands at 212 and 260 nm. However, its solubility in CH3Cl2, or even in CHCl3, was not enough to perform a cyclic voltammetric study. In addition, the EPR spectra of 6 and 7 were silent, as expected for CuI diamagnetic complexes. We also found that 6 and 7 were light sensitive, and that they could be easily oxidized to CuII species (especially 6) after several hours at room temperature. However, they could also be kept for longer periods of time at –20°C under argon, while being protected from direct light exposure.

We mentioned in the introduction that the combination of CuBr·SM2 and 2 had produced a deep green solution in perfluoroheptane,[8] but the characterization of this putative CuI complex had not been reported thus far. When we attempted the reaction between CuCl and 2 in trifluorotoluene in order to synthesize the compound analogous to 7, we immediately obtained a deep green solution, from which a deep green solid was isolated. Although its LSIMS-MS spectrum displayed a prominent signal at m/z 1167 (100%), which can be assigned to the species [M – Cl]+, its elemental analysis did not fit with a stoichiometry of a complex like [Cu(Rf-bpy)Cl]. This complex was partly soluble in trifluorotoluene and in cold perfluoroheptane (it was soluble in hot perfluoroheptane) and thus we were not able to obtain its NMR or UV/Vis spectra in perfluoroheptane solution. However, its green color, as well as its EPR spectrum, indicated that a partial oxidation to a CuII complex had occurred.

The EPR spectra of solid, powdered samples of compounds 3, 4, 5, and 7, as well as the solid from the reaction of CuCl and 2, were measured at room temperature. Figure 6 shows the EPR spectra of all the samples studied (spectra a–e). In all cases except for the CuI compound 7 (spectrum d), the EPR spectra had signals from several CuII complexes. In the cases of the CuII complexes, 3 (spectrum a), 4 (spectrum b), and 5 (spectrum c), as well as the putative CuI complex from CuCl and 2 (spectrum e), there were strong indications of intermolecular exchange reactions.[17] This was particularly evident in the EPR spectrum of compound 3 (spectrum a), and the spectrum recorded with the solid from the reaction of CuCl and 2 (spectrum e). In these EPR spectra, similar features appeared at g1 = 2, g2 = 2.06 (spectrum a), and g1 = 2.15, g2 = 2.06 (spectrum e), suggesting a mixture of CuII complexes. In accordance with the nature of 7, a CuI complex, no indication of a CuII complex was detected in its silent EPR spectrum (spectrum d).

Functionalization of alkenes, alkanes, and alcohols using copper(I) complexes and in-situ-generated [Cu(Rf-ligand)]+ derivatives as precatalysts

Oxidation of alkenes and alkanes: The FBC oxidation results for substrates cyclohexene, cyclohexane, and toluene in the presence of fluoro-pontailed copper complexes are presented in Table 1. All of the experiments were carried out under biphasic conditions in perfluoroheptane; the upper phase was the substrate itself (Scheme 1). CuII complexes 4 and 5 were dissolved in perfluoroheptane; however, we found it more...
The oxidation of alkenes and alkanes always provided a mixture of alcohols and ketones. As previously described,[7a,b,d] Table 1 demonstrates that the olefin with allylic hydrogens, cyclohexene, provides the highest yield of oxidation products with TBHP/O2. In the absence of O2 or TBHP, only negligible amounts of cyclohexenol and cyclohexene were detected, which is fully indicative of an autoxidation reaction, that is, both were necessary for oxidation to proceed (Table 1, entries 4 and 5).[7b]

All of the complexes derived from the ligand 1 showed catalytic activity (Table 1, entries 1–3, 7–9), but only 7 (prepared in situ from CuCl and Rf-TACN) afforded yields or TON that could be compared with those previously reported for CuCl and the fluoropolytaurmacyclic ligands derived from tetraazaclotetradecane (Rf-CYCLAM)[7b] or [M(C13F7(CH2)2CO2)2(Rf-tacn)] (M = Mn, Co).[7a,d] The first system afforded yields of 514% and TON of 320 for the oxidation of cyclohexene to cyclohexenol and cyclohexene oxide after eight hours.[7b] The latter complexes gave yields of 650% and TON of 131 (M = Mn) after three hours or 750%, TON = 156 (M = Co) after 20 hours.[7a,d] We found that for the same substrate, yields of 136% (with a TON of 85) were obtained after eight hours (entry 3) for 7, while after 24 hours (same conditions, entry 7) the yields and TON were increased to 425% and 276, respectively. More importantly, we were able to recover the fluorous phase and recycle it for a second (entry 8) or a third (entry 9) catalytic reaction. The overall yield was then 938% and the TON = 609, with the catalytic activity decreasing to around 75% in the second run and to half of the initial value in the third experiment. With the Cu/Rf-CYCLAM system, the catalytic activity in a second run decreased to half of its initial value (yield 248%, TON 155), and the authors mentioned that the hydrocarbon layer turned increasingly blue.[7b] Moreover, in a second run [Mn(C13F7(CH2)2CO2)2(Rf-tacn)] afforded a yield of 400% (vs 650% in the first run).[7a,d]

We believed that 6 (formed in situ from [Cu(CH3CN)4]PF6 and 1) was not an efficient catalyst (entry 2) under FBC conditions, owing to its lack of solubility in perfluorohexane, as shown with the isolated compound. The reaction of cyclohexene with 7 (formed in situ) in the presence of oxidants (H2O2/O2) was also studied (entry 6) but no oxidation products were formed. Although complexes of CuII and CuI with the Rf-bpy ligand 2 (entries 7–11) did catalyze the oxidation of cyclohexene (TBHP/O2), they could not be recycled (see complex 5, entries 10 and 11; CuCl and ligand 2 (entries 13 and 14). We found that after the reaction had taken place, the fluorous phase turned colorless, while the organic layer became blue, indicating that CuII ions were present in this upper layer. We believe that the different behavior between the compounds with Rf-TACN and Rf-bpy ligands might be due to the different coordination modes of these ligands to the CuII and CuI centers, which may be related to the steric and electronic properties of the catalytic active sites, as well as their stability constants. In all oxidation experiments, it was observed that the TBHP employed as a free radical initiator was converted to tert-butyl alcohol and acetone, indicative of tert-butoxy radical formation.[7a,d] We also attempted the oxidation of cyclohexene and toluene with the best catalytic system, 7, generated in situ, and, as described for the [M(C13F7(CH2)2CO2)2(Rf-tacn)] (M = MnII, CoII) systems,[7a,d] the yields of oxidation products were much lower than for cyclohexene (entries 15 and 16, Table 1).

Table 1. Alkene and alkane functionalization with fluorous CuII and CuI complexes under FBC conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Oxidant</th>
<th>Precatalyst</th>
<th>t [h]</th>
<th>Substrate converted[b] [μmol]</th>
<th>Selectivity alcohol [%][c]</th>
<th>Ketone/d</th>
<th>Total yield [%][d]</th>
<th>TON[e]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohexene</td>
<td>TBHP/O2</td>
<td>4</td>
<td>8</td>
<td>175</td>
<td>3.2</td>
<td>96.8</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexene</td>
<td>TBHP/O2</td>
<td>[Cu(CH3CN)4]PF6 + Rf-TACN (6)</td>
<td>8</td>
<td>86</td>
<td>1.3</td>
<td>98.7</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexene</td>
<td>TBHP/O2</td>
<td>CuCl + Rf-TACN (7)</td>
<td>8</td>
<td>678</td>
<td>27</td>
<td>73</td>
<td>136</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>cyclohexene</td>
<td>O2</td>
<td>7</td>
<td>8</td>
<td>12</td>
<td>–</td>
<td>100</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>cyclohexene</td>
<td>TBHP</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>–</td>
<td>100</td>
<td>3</td>
<td>1.6</td>
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<tr>
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<td>H2O2</td>
<td>7</td>
<td>8</td>
<td>8</td>
<td>–</td>
<td>100</td>
<td>1.5</td>
<td>0.9</td>
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<tr>
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<td>cyclohexene</td>
<td>TBHP/O2</td>
<td>7</td>
<td>24</td>
<td>2210</td>
<td>21.8</td>
<td>78.2</td>
<td>425</td>
<td>276</td>
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<tr>
<td>8</td>
<td>cyclohexene</td>
<td>TBHP/O2</td>
<td>fluorous recovered phase from entry 7</td>
<td>24</td>
<td>1601</td>
<td>29.3</td>
<td>70.7</td>
<td>308</td>
<td>200</td>
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<tr>
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<td>TBHP/O2</td>
<td>fluorous recovered phase from entry 8</td>
<td>24</td>
<td>1068</td>
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<td>84.4</td>
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<td>fluorous recovered phase from entry 10</td>
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<td>13</td>
<td>–</td>
<td>100</td>
<td>12</td>
<td>8</td>
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<tr>
<td>12</td>
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<td>TBHP/O2</td>
<td>[Cu(CH3CN)4]PF6 + Rf-bpy</td>
<td>8</td>
<td>681</td>
<td>12.1</td>
<td>87.9</td>
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<tr>
<td>13</td>
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<td>CuCl + Rf-bpy</td>
<td>8</td>
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<td>86.2</td>
<td>113</td>
<td>74</td>
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<tr>
<td>14</td>
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<td>TBHP/O2</td>
<td>fluorous recovered phase from entry 13</td>
<td>8</td>
<td>62</td>
<td>–</td>
<td>100</td>
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<td>8</td>
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<tr>
<td>15</td>
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<td>TBHP/O2</td>
<td>7</td>
<td>24</td>
<td>39</td>
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<td>5</td>
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<tr>
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<td>TBHP/O2</td>
<td>7</td>
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<td>87</td>
<td>48.4</td>
<td>51.6</td>
<td>17</td>
<td>13</td>
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</table>

[a] Conditions: Hydrocarbon phase: Substrate (S) = 40 mmol; o-dichlorobenzene (internal standard) = 2 mmol; 70% TBuOOH (O) = 500 μmol. Fluorocarbon phase: precatalyst (8 μmol, see experimental section) in perfluoroheptane (2 mL). Molar ratio S/O/C = 62.5:1. T = 298 K. Reactions were carried out in the dark in the presence of molecular oxygen. Products were identified by comparison with authentic samples by GC. [b] Determined by GC using the internal standard method. [c] μmol product/μmol converted substrate. [d] Based on the added TBuOOH. [e] μmol converted substrate/μmol precatalyst.

**Oxidation of alcohols**: The oxidation of alcohols to aldehydes or ketones under FBC conditions has been performed under an oxygen atmosphere both by Knochel et al. with a catalytic system consisting of CuBr−SMe₂ and 2, prepared in situ, at 90 °C and by Uemura et al. with Pd(OAc)₂ and fluoroponytailed pyridines prepared in situ at 80 °C. In the first example, the initiator was TEMPO and in the second case, they used 3 Å molecular sieves. However, while the Cu system used a small amount of fluorous ligand (2 mol%), the Pd system needed a much larger amount of fluorous ligand (20 mol%). Benzyl and allylic alcohols reacted faster than aliphatic alcohols for both systems and, in general, high yields were obtained.

The recyclability of the Cu system was demonstrated for the oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde. The reaction was performed eight times without a major loss of catalytic activity. In the Pd system, the recyclability of the precatalyst was demonstrated for six runs. It should also be noted that no mechanistic information was available for this transformation nor for the role of TEMPO in this FBC oxidation reaction. More importantly, we believed that the reaction between Cu salts and 2 also gave Cu complexes during the reaction, while the oxidation of alcohols with TEMPO/O₂ with CuⅡ salts in a homogeneous system also suggested that CuⅡ ions were responsible for initiating the oxidation.[19] We then decided to study the CuⅡ complex 4 under single-phase FBC reaction conditions[4f] at 90 °C with 4-nitrobenzyl alcohol in the FBC oxidation to 4-nitrobenzaldehyde (Scheme 2).

The initial FBC mode at room temperature (Scheme 2) includes 4 in the lower perfluoroheptane layer, while the substrate alcohol, chlorobenzene, and TEMPO were in the upper organic layer (Table 2). At 90 °C, in a now single homogeneous phase, under an oxygen atmosphere for four hours, conversion to the aldehyde was at 63% (entry 1) and 61% (entry 2) in the first and second runs, respectively, showing that catalytic activity did not change during the second run. This preliminary experiment helped to optimize the FBC reaction conditions (entries 3–5). We found it was necessary to increase the amount of catalyst to 3.5 mol% and the reaction time from 4 to 8 hours to obtain a 96% conversion to the benzaldehyde product.

### Table 2. Oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde under FBC conditions using 4 as precatalyst.[b]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>% mol catalyst</th>
<th>% mol TEMPO</th>
<th>t [h]</th>
<th>Conversion [%][h]</th>
<th>TON[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3.4</td>
<td>4</td>
<td>63</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>RFP[4] from entry 1</td>
<td>–</td>
<td>3.4</td>
<td>4</td>
<td>61</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>3.5</td>
<td>6</td>
<td>4</td>
<td>65</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3.5</td>
<td>6</td>
<td>8</td>
<td>96</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>RFP from entry 4</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>94</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>RFP from entry 5</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>92</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>RFP from entry 6</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>90</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>RFP from entry 7</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>92</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>RFP from entry 8</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>91</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>RFP from entry 9</td>
<td>–</td>
<td>6</td>
<td>8</td>
<td>83</td>
<td>24</td>
</tr>
</tbody>
</table>

[a] Conditions: hydrocarbon phase: 4-nitrobenzyl alcohol, TEMPO; fluororous phase: 4 in perfluoroheptane (2 mL). Reactions were carried out at 90 °C in the presence of molecular oxygen. [b] Measured by 1H NMR. [c] μmol converted substrate/μmol catalyst. [d] Recovered fluorour phase.

### Autoxidation mechanism and the fate of the [Cu(R₉-tacn)]⁺ precatalyst in the oxidation of alkenes and alkanes

The TBHP/O₂ initiated oxidation reactions presented here are in agreement with an autoxidation mechanism involving alkoxy (RO') or alkoxyperoxy (ROO⁺) radicals, in which the reaction is initiated by tBuO' or tBuO₂⁺ radicals produced from redox reactions (Haber–Weiss process with Cu(I/Cu(II)). This mechanism is similar to that proposed by Fish et al. with the [Mn(C₈F₁₇(CH₂)₂CO₂)(R₉-tacn)] catalytic system.[7a,d] It has been previously reported that in the case of the substrate cyclohexene, the allylic radical that forms is then trapped by O₂ (k > 1 × 10⁹ M⁻¹ s⁻¹) to provide cyclohexenylperoxy radicals, which are able (ROO−H = 90 kcal mol⁻¹) to homolytically remove a hydrogen from benzylic or allylic C−H bonds (85 kcal mol⁻¹), and hence propagate the radical reactions.[19, 20] The secondary cyclohexenyl hydroperoxide that is formed then decomposes catalytically in the presence of the [Cu(R₉-tacn)Cl] precatalyst to give the alcohol and the ketone products. Scheme 3 defines the initiation, propagation, termination, and product-forming steps for the sequence of reactions [Eqs. (1)−(8)].[7a,d] Moreover, the lower yields observed in the case of cyclohexene are consistent with the stronger C−H bond (95 kcal mol⁻¹),[10] which implicates the cyclohexenylperoxy radical and thus causes a lowering of the rate of the propagation step. The chain termination step presumably comes mainly from the coupling of two cyclohexenylperoxy radicals to give alcohol, ketone, and O₂ [Russell-type mechanism, Scheme 3, Eq. (7)].[7a,d]
In order to determine the redox chemistry occurring with the starting complex, [Cu(Rf-tacn)Cl] 7, the best catalytic system we found for the oxidation of cyclohexene under FBC conditions, we carried out the following EPR experiments (Figure 7, spectra a–c). Compound 7 was dissolved in perfluoroheptane and then cyclohexene, o-dichlorobenzene (as internal standard), and TBHP were added. The reaction started in the presence of O₂ and an aliquot from the perfluoroheptane phase was removed and immediately frozen at liquid nitrogen temperature (LNT) in an EPR tube, after two hours of reaction. The EPR spectrum (measured at 77 K) is shown in Figure 7 (spectrum a). There was no indication of a CuII signal in this initial spectrum. This was in accordance with the oxidation state of the precatalyst 7, whose CuI center had also been previously confirmed by an EPR spectrum of a solid sample (Figure 6, spectrum d).

The catalytic results (Table 1, entry 1) have shown that the CuII complex with the Rf-TACN ligand, 4, catalyzes the oxidation of cyclohexene, but to a smaller extent than 7, or the CuII complex 5. The reason for which 7 was a recoverable catalyst, while its catalytic activity in the second and third run decreases to 75 and 50%, respectively, could possibly be the formation of a CuII complex that could be easily reduced to a CuI complex, as designated by the Haber–Weiss process. In contrast, the low catalytic activity of the CuII catalytic system with 4 might be a consequence of not being able to efficiently generate the CuI complex [Scheme 3, Eq. (2)], because of a presumed kinetic effect [Scheme 3, Eq. (2)].[7a,d] The fact that Equation (1) (Scheme 3) involves the generation of the tert-butoxy radical implicates the CuI/CuII redox couple.

More importantly, the behavior of the CuII complex 5, with ligand 2, was quite different (Table 1, entries 10 and 11). In this example, the reduction to the CuI complex appears to be more facile, possibly because of the different electronic properties of the fluoropontailed ligand 2. Unfortunately, we were not able to isolate the corresponding CuI compound analogous to 7. We also determined that 5 was not recoverable under FBC conditions and that after the reaction had taken place, the free ligand 2, as well as CuII ions, could be observed in the organic phase, as analyzed by mass spectrometry.

Mechanism and fate of the [Cu(C₁₈F₃₇(CH₂)₂CO₂)(Rf-tacn)](4) precatalyst in the oxidation of 4-nitrobenzyl alcohol

We have shown that an isolated Rf-CuII complex 4 can be a recyclable and efficient precatalyst for the oxidation of
alcohols under FBC conditions at 90°C with TEMPO/O₂. The mechanism of this reaction was thus of interest. Moreover, several years ago Semmelhack et al. [17] reported on the oxidation of alcohols to aldehydes with oxygen and Cu⁰ ions, mediated by a nitrosonium ion that was generated from the TEMPO radical. The catalytic cycle proposed by these authors is shown in Scheme 4. The Cu⁰ ions are reduced to Cu²⁺ in a one-electron oxidation of TEMPO 8 to the nitrosonium ion 9 [Scheme 4, Eq. (9)]. The alcohol is then oxidized by 9 [Eq. (10)], generating the aldehyde and hydroxylamine 10; rapid syn-propportionation of 10 with 9 regenerates 8 [Eq. (11)]. Finally, Cu²⁺ is regenerated by oxygen gas, in a process that consumes protons and provides Cu⁰ and water [Eq. (12)].

This catalytic cycle was based on the reactions and electrochemical studies that indicated that Cu⁰ could indeed oxidize 8 to 9.

In order to verify the Semmelhack mechanism,[17] we used EPR spectroscopy to follow the redox chemistry of the starting fluoruous catalyst 4 during the oxidation of 4-nitrobenzyl alcohol with TEMPO/O₂ at 90°C under FBC conditions. To reiterate, precatalyst 4 was recoverable and recyclable, while its catalytic activity did not decrease over the course of five runs. We carried out an EPR catalytic experiment (Figure 3, spectra a–d) as was described above for the oxidation of cyclohexene. Precatalyst 4 was dissolved in perfluoroheptane, and then chlorobenzene, TEMPO, and 4-nitrobenzyl alcohol were added to the reaction mixture. The reaction started at 90°C in the presence of O₂, and after 30 min, followed by cooling to room temperature, an aliquot was removed from the perfluoroheptane phase and immediately frozen at 77 K in an EPR tube. The EPR spectrum is shown in Figure 8 (spectrum a, at LNT). The spectrum shows a narrow central signal at about g = 2.006, which can be associated with the TEMPO radical. This was further confirmed by measuring this radical in perfluoroheptane at 77 K. The spectrum of the reaction mixture also has a Cu⁰ signal, with g₁ = 2.26(1) and g₂ = 2.06(1). A₁ = 520(5) MHz and A₂ < 50 MHz.[18] After 3.5 h, both signals decrease (spectrum b), and after 6 h the signals have decreased further (spectrum c). After 8 h, we observed a recovery of the signal corresponding to the Cu²⁺ species (spectrum d). An EPR spectrum of the upper phase (chlorobenzene layer), after the reaction had taken place, showed an EPR signal that can be assigned to the TEMPO radical. Thus, TEMPO appears to be regenerated as was proposed in Scheme 4. It is clear from the silent EPR spectrum after 3.5 h (Figure 8, spectrum c) that the initial Cu⁰ complex 4 is reduced to the Cu¹ complex and is then regenerated to a Cu²⁺ complex (spectrum d). This is in accordance with the mechanism proposed by Semmelhack et al.[17] (Scheme 4) and with the catalytic results reported in this paper (Table 2). After 4 h, a 65% yield of aldehyde was obtained; however, by leaving the reaction for longer periods of time, a nearly 100% yield of aldehyde (Table 2) was formed, concomitant with a full recovery of 4. We believe that the TEMPO was also regenerated, but probably ended up in the organic phase where it was destroyed during the work-up procedure; TEMPO was then replenished during the next catalytic run.

We also wish to propose an alternative mechanism to Semmelhack’s, described above for the oxidation of alcohols to aldehydes, that can reasonably fit the experimental data presented, and is favored by Sheldon et al.[19] This is shown in Scheme 5. It entails the coordination of the alcohol to the Cu¹ center, followed by a β-hydrogen elimination, which forms the Cu¹ hydride, the aldehyde, and a proton.[19] The regeneration of the Cu¹ center is now the role of the TEMPO radical, which abstracts hydrogen from Cu¹H to give TEMPOH, while the TEMPO radical can be regenerated by O₂. Both mechanistic Schemes 4 and 5 indicate that the presence of Cu⁰ is critical for the oxidation of the alcohol to the aldehyde. The mechanistic differences are in the role of the TEMPO radical, and we are in the process of attempting to differentiate between the two pathways.
Conclusions

In summary, we have prepared and fully characterized by several standard spectroscopic techniques new CuI and CuII complexes with fluoroponytailed amine ligands. To the best of our knowledge, the reported CuI and CuII fluoroponytailed derivatives were previously unknown, as the previously reported fluoroponytailed CuI complexes had been prepared in situ and their characterization was incomplete or nonexistent. More importantly, in many previously reported Cu complexes that were studied, in their synthesis or catalytic reactivity, there was no information concerning the oxidation state of the resulting Cu complexes. We have now rectified this situation by isolating and fully characterizing all of the CuI and CuII compounds reported in either synthesis or under catalytic reactivity, in this FBC contribution.

All of the reported novel CuI and CuII complexes were evaluated in the FBC oxidations of hydrocarbons and olefins with TBHP/O₂. The most promising catalytic systems were the [Cu(R₇-tacn)Cl]₂, as well as the CuII and CuI complexes with the R₇-bpy ligand. However, only 7 could be totally separated from the organic phase by a simple decantation process and thus recycled for three runs. EPR experiments showed that the oxidation process occurs by an autoxidation mechanism, with formation of alkenes or alkyl hydroperoxides as the key intermediates, which are then catalytically decomposed by the [Cu(R₇-tacn)]²⁺ catalyst, probably at the solvent interface, to provide the alcohol and ketone products.[7a-d] However, this precatalyst was found to be less efficient after the third run, possibly because of the concentration of the CuI complex that could not be readily reduced to the initial CuII complex under the normal Haber–Weiss reaction conditions.

Furthermore, the CuII complex [Cu(C₂F₇(C₄H₉)CO₂)₂(R₇-tacn)] was an efficient and recoverable precatalyst for the oxidation of 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde with TEMPO/O₂, under single phase FBC conditions at 90 °C, with catalytic activity being maintained even after five runs. The EPR experiments can be interpreted in two ways. In one mechanism, this CuII complex was reduced to CuI by the TEMPO radical and then oxidized again to the initial CuII complex by O₂, while also regenerating TEMPO, and producing the aldehyde. The other mechanism involves the CuII mediated β-hydrogen elimination providing a CuI, which reacts with TEMPO to recycle CuII and TEMPO-H, while regenerating TEMPO with O₂. Future FBC studies will focus on gas to liquid technology, as well as further studies on FBC oxidation mechanisms.

Experimental Section

All manipulations involving organolithium reagents and hygroscopic TACN were performed under an inert atmosphere of dry argon, using Schlenk techniques, and all solvents were dried and degassed before use. R₇-TACN I was prepared as described previously from a nitrogen atom alkyl reaction between commercial TACN and C₈F₁₇(CH₂)₃I. LNT temperature; 0.4 mT modulation amplitude, 100 KHz modulation scan range, 2 mW microwave power, 9.51 GHz microwave frequency, RT or LNT using an immersion quartz Dewar. These frozen solutions were measured at LNT using an immersion quartz Dewar. The microwave frequency was determined with a Hewlett Packard HP5350B frequency counter. For detecting CuI complexes, the conditions were as follows: 3200 ± 125 MHz scan range, 2 mW microwave power, 9.51 GHz microwave frequency, RT or LNT temperature, 0.4 mT modulation amplitude, 100 KHz modulation frequency, conversion time, 163.84 ms (see below).

Preparation of fluoroponytailed ligands and their copper complexes

4,4'-Diheptadecafluoroundecyl-2,2'-bipyridine (R₁-bpy, 2): LDA, prepared in situ from bisopropylamine (2.37 mmol, 0.33 mL) and nBuLi (2.42 mmol, 2.12 mL) in dry THF (60 mL) at −78 °C, was treated with 4,4'-dimethyl-2,2'-bipyridine (0.95 mmol, 0.17 g). The temperature was allowed to rise from −78 to 0 °C over 1 h. After cooling down again to −78 °C, C₈F₁₇(CH₂)₉I (2.08 mmol, 1.21 mL) in dry THF (5 mL) was added. The reaction mixture was stirred at this temperature for 5 h and then warmed up to room temperature overnight. After total removal of the THF, the residue was extracted with CH₂Cl₂/THF (50 mL, 1:1) and washed with H₂O (3 × 15 mL). The organic layer was dried over Na₂SO₄, and all solvents were concentrated to ≈1 mL. Subsequent addition of cold n-pentane (6 mL) afforded pure 2 as a beige powder (0.361 g, 35%).

1H NMR (CDCl₃, 25 °C): δ = 8.57 (d, 2H; J(1H,1H) = 5.1 Hz, 2H; J₁, J₂), 7.84 (s, 1H; H₁), 7.13 (d, 3J(HH) = 5.1 Hz, 2H; H₂), 2.74 (t, 3J(HH) = 7.5 Hz, 4H; -CH₂(CH₂)₃), 2.08 (m, 8H; CH₂(CH₂)₃CH₂-C₂F₅), 1.40 (s, 4H; -CH₂(CH₂)₃CH₂-C₂F₅). 19F{1H} NMR (CDCl₃, 25 °C): δ = −16.2, 155.6, 149.15, 123.88, 121.12 (d), 120–120 (4m, vbr), 34.8, 30.4 (t), 29.6, 19.7, 0.7 (t); 13C{1H} NMR (CDCl₃, 25 °C): δ = −81.7 (3F; CF₂), −115.4 (2F; CF₂), −123.0 (6F; CF₂), −124.8 (2F; CF₂), −127.3 (2F; CF₂); LSIMS-MS: m/z (%): 1105 (5) [M]+, 645 (100) [M − [(CH₃)₂C₂F₅]+];
elemental analysis calecd (%) for C13H26F5O7N2: C 36.64, H 1.95, N 2.69.

[Cu(CF3(CH2)3C8F17)2]PF6 (3): Triethylamine (0.39 mL, 2.80 mmol) was added to a solution of CF3(CH2)3C8F17OH (1.35 g, 2.80 mmol) in acetone (15 mL). This solution was added to a suspension of CuSO4·5H2O (0.34 g, 1.37 mmol) in acetone (30 mL). After 24 h stirring at room temperature, complex 3 precipitated as a blue powder, which was collected by filtration and washed with Et2O to give the title compound (0.098 g, 69%). Complex 3 was totally soluble in trifluorotoluene, partly soluble in dichloromethane, and insoluble in acetic acid, Et2O, n-hexane, MeOH, H2O, and perfluoroheptane. IR: v = 1573, 1420 cm⁻¹ (C=O); UV/Vis (diffuse reflectance): λ = 266 nm (28%); elemental analysis calecd (%) for C13H26F5O7N2Cu: C 27.66, H 1.82, N 2.09.

[Cu(CF3(CH2)3C8F17)2]Cl (4): CuCl was added to a suspension of Rf-TACN (0.151 g, 0.1 mmol) was added to a Schlenk tube (previously purged with Ar) was charged with a perfluoroheptane solution (2 mL) of the precatalyst (8 mol%, 0.027 mmol, 0.070 g). The hydrocarbon phase (upper layer of the biphasic system) consists of 40 mol% of substrate (cyclohexene 4.05 mL, cyclohexane 1 mL) and 60 mol% CuCl2PF6 (3 mol%, 69.2 mg). Added reaction mixture (protected from light exposure) was stirred under an O2 atmosphere at ambient temperature (for 8 or 24 h, see Table 1). After the reaction had taken place, the two phases were separated by decantation and analyzed by GC. In some cases, the fluorous phase could be reused for further runs (see Table 1), in which case perfluoroheptane (0.5 mL) and a new load of substrate/oxidant/internal standard were added, and the reaction mixture proceeded under the conditions described above.

Standard catalytic oxidation of alcohols under FBC conditions: For the preparation of 4-nitrobenzaldehyde, a 25 mL Schlenk tube (previously purged with Ar) was charged with a perfluoroheptane solution (2 mL) of 3.5 mol% of (4 0.027 mmol, 0.070 g). The hydrocarbon phase (upper layer of the biphasic system) consists of 40 mol% of substrate (4.05 mL, cyclohexane 1 mL) and 60 mol% CuCl2PF6 (3 mol%, 69.2 mg) in chlorobenzene (2 mL). TEMPO (6 mol%, 0.04 mmol, 0.009 g) was then added, and the biphasic reaction mixture was stirred under an O2 atmosphere at 90°C (for 4 or 8 h, see Table 2). After the reaction, the Schlenk tube was cooled to room temperature and the two phases were separated by decantation. The fluorous phase was washed with chlorobenzene (3 × 2 mL), and the combined organic layers were diluted with EtOAc (30 mL) and washed successively with 10% (by weight) sodium bicarbonate and water (40 mL). After drying (MgSO4), filtration, and complete evaporation of the solvent under reduced pressure, the crude product was weighed and analysed by 1H NMR. The fluorous phase was separated and used directly (after adding 0.5 mL of perfluoroheptane) for further reaction runs.

EPR-FBC experiment A: Using standard oxidation conditions for cyclohexene, as outlined in Table 1, with precatalyst 7 generated in situ, alcohols of the perfluoroheptane layer were removed and immediately frozen at LNT in an EPR tube (Figure 7, EPR spectra a–c).

EPR-FBC experiment B: Using standard oxidation conditions for 4-nitrobenzyl alcohol, as outlined in the experimental section using 4 as the precatalyst, aliquots of the perfluoroheptane layer were removed (after cooling down the reaction mixture at RT) and immediately frozen at LNT in an EPR tube (Figure 8, EPR spectra a–d).

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