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# Copper(I) Complexes Mediated Cyclization Reaction of Unsaturated Ester under Fluoro Biphasic Procedure

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The concept of a “fluoro biphasic system” (FBS) has been introduced recently by Horváth and Rabái.[1] In this approach, the catalyst is confined to the fluorocarbon phase whereas the substrate and the reaction products are dissolved in an organic solvent. The system is biphasic at low temperature and becomes homogeneous at a higher temperature. The major advantages of the FBS is the very simple workup since the reaction products remain in the organic phase, allowing easy recovery of the catalyst for another reaction sequence. Moreover, due to their chemical inertness, perfluorinated compounds are environmentally friendly. This approach has been applied for many organic reactions such as organotin hydride reduction,[2] Stille coupling reaction,[3] or addition of allyl tin derivatives onto aldehydes.[4] Oxidation reaction catalysts such as ruthenium or nickel complexes,[5] manganese,[6] and cobalt or copper complexes[7] as well as a hydroformylation catalyst[8] or the fluorinated analogue of Vaska’s complex[9] have been prepared with ligands bearing perfluoroalkyl side chains.

In this paper, we report an efficient FBS-based catalysis for atom transfer radical additions (ATRA). This technique uses a low valent metal to induce the radical cleavage of a carbon−halogen bond. The metal-bonded radical can react in a radical-like process. As the transition metal mediated cleavage of the carbon−halogen bond is reversible, the reacted radical gives a new halogenated product by reductive elimination and allows the recovery of the catalyst at the end of the reaction.[10] This concept has been developed extensively by Speckamp and coworkers to perform copper(I)-catalyzed radical cyclization of unsaturated trichloro ester.[11] The major drawback of these reactions is the large amount of metal complex (ca. 30 mol %) required in order to complete the reaction. We recently reported the preparation of copper(I) and iron(II) complexes that allow high reaction turnovers even with a very low catalyst/substrate ratio (3 mol %).[12]

In this note, we describe the synthesis of two perfluoroalkylated polyamines as potential ligands for copper or other transition metals. The copper complexes associated with a reducing agent (iron powder) allow the radical cyclization of an unsaturated trichloro ester in high yield using the FBS procedure with an efficient recovery of the catalyst.

The required perfluorinated ligands, the tri and tetradentate ligands **4** and **5** are prepared by standard techniques for introduction of perfluoroalkyl chains.[6,13] A three methylene carbon spacer is also introduced in order to insulate the amine from the strong electron-withdrawing effect of the perfluoroalkyl group. This procedure has been already described and involves the radical addition of perfluorooctyl iodide to allyl alcohol to provide the iodo alcohol **1** (Scheme 1). Reduction of compound **1** by tributyltin hydride afforded **2** in 88% yield. Subsequent tosylation of compound **2** provided the key material **3** for the peralkylation reaction of diethylenetetramine and tris(aminoethyl)amine. The perfluorinated ligands **4** and **5** were obtained respectively in 65% and 54% yields. These ligands are totally soluble in perfluorohexane and could be purified by successive washings with $CH_2Cl_2$.

We also used the permethylated ligand **6** as a reference for reactions performed in nonperfluorinated medium. The cyclization of pent-4-enyl trichloroacetate **7** was realized in the presence of a 1:1 mixture of ligand and copper(I) chloride. Under such catalysis, this substrate has been reported to provide the endo lactone **8**.[11,12] We reported that the use of ligand **6** (1 mol %) associated with Cu(I)Cl resulted in a significantly enhanced yield compared to CuCl/bipyridine (Scheme 2).[12]

Experiments with ligands **4** and **5** in the presence of Cu(I)Cl were achieved in a fluorous biphasic procedure. The use of a cosolvent (trifluorotoluene) allowed the homogenization of the two phases at 80 °C although the system remained biphasic at room temperature. The results are collected in Table 1. Careful deoxygenation of the reaction mixture was necessary as low traces of dioxygen (even in the presence of a reducing agent) considerably decrease the reaction yield, leading to irreproducible results. When deoxygenation was performed by the “freeze−pump−thaw” method (three cycles), reproducible yields were obtained.

Using the FBS procedure (entries 1 and 2 compared to entry 3), the reaction proceeds slowly compared to the

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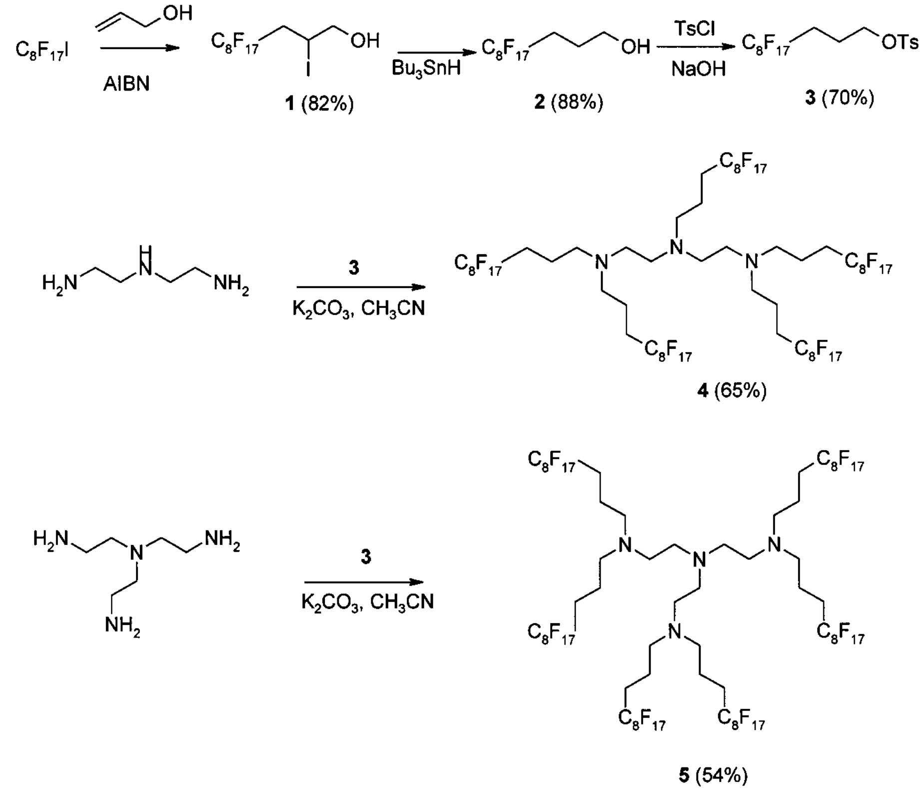
**Scheme 1. Synthetic Pathway for the Preparation of Perfluorinated Ligands 4 and 5**



**Scheme 2. Intramolecular Cyclization of Trichloro Ester 7**

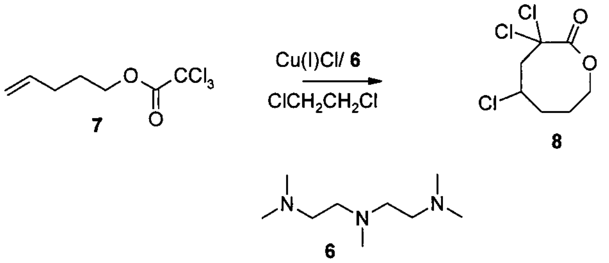


**Table 1. Conversion of Trichloro Ester 8 under Homogeneous and FBS Catalysis**

| entry | catalyst[a] | catalyst ratio, mol % | lactone **8**, % yield | reaction time, h |
|---|---|---|---|---|
| 1 | CuCl/**4** | 1 | 34 | 20 |
| 2 | CuCl/**5** | 1 | 48 | 20 |
| 3 | CuCl/**6** | 1 | 50 | 10 |
| 4 | CuCl/**4** | 5 | 88 | 20 |
| 5 | CuCl/**5** | 5 | 97 | 10 |
| 6 | CuCl/**4**/Fe | 1 | 91 | 20 |
| 7 | CuCl/**4**/Fe | 5 | 99 | 10 |
| 8 | CuCl/**5**/Fe | 1 | 98 | 20 |
| 9 | CuCl/**5**/Fe | 5 | 99 | 10 |
| 10 | CuCl/**6**/Fe | 1 | 99 | 10 |

[a] Metal to ligand stoichiometry is 1:1. When added, iron powder is in a 10:1 ratio vs copper catalyst.

experiment done in non-perfluorinated solution. The yield and the reaction kinetic could be improved by raising the catalyst/substrate ratio to 5% (entries 4 and 5). Iron powder was then added to the reaction mixture in the FBS catalysis. This resulted in a considerable enhancement of the yield that became almost quantitative even in the presence of 1% of the catalyst (entries 6 and 8). A control experiment was performed with ligand **6** in non-perfluorinated medium giving the same enhancement of the reaction yield (entry 10). Turnovers of about 100 were obtained when the reducing agent (iron powder) was associated with the copper catalyst. Iron powder could be substituted by copper dust without modification of the reaction rate. A fluoro biphasic experiment (iron powder added) was also performed without addition of the cosolvent (trifluorotoluene). The reaction mixture remains partially biphasic at the reaction temperature (80 °C). Low miscibility of the fluorous and the organic phase lowered the reaction rate, but conversion of trichloro ester **7** was observed. In this experiment the yield of lactone **8** reached 60% after 10 h (with 5 mol % Cu(I)Cl:**5** catalyst).

The use of iron powder, alone or associated with Cu(I)Br, has been previously reported to catalyze radical additions of halogen derivatives on olefins in dipolar solvents.[14] To evaluate the role of iron powder, the course of the reaction, performed in non-perfluorinated homogeneous phase, was monitored by gas chromatography. The results are displayed in Figure 1. When iron powder is mixed with ligand **6** even in the absence of copper chloride, slow conversion of the substrate occurred, associated with a latency phase that is probably due to dissolution of traces of iron oxides or hydroxides into the reaction mixture. We tested that iron powder alone did not catalyze the conversion of trichloro ester **7**, as previously observed in nonpolar solvents such as 1,2-dichloroethane. The association of a copper complex and iron had a significant effect on the kinetics of the ATRA reaction and nearly quantitative conversion was observed within 10 h.

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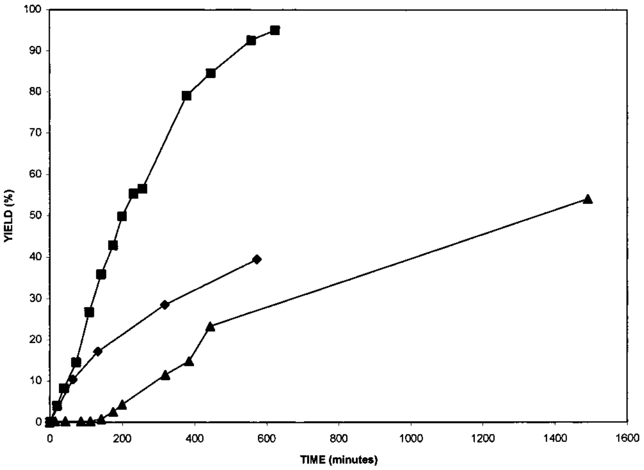

**Figure 1.** Course of the conversion of **7** in the presence of iron powder and ligand **6** (▲), Cu(I)Cl and ligand **6** (♦), Cu(I)-Cl and ligand **6** in the presence of iron powder (■).

**Table 2. Recycling of the Catalyst (CuCl:4 or 5:Fe; 1:1:10; 5% molar in copper)**

| run | % yield (ligand **5**) | % yield (ligand **4**) |
|---|---|---|
| 1 | 96 | 92 |
| 2 | 95 | 89 |
| 3 | 93 | – |
| 4 | 91 | – |

We also tested the efficiency of a fluorous biphasic procedure in the recycling of the catalyst. After each run, the organic phase is removed by decantation under argon, and the reaction medium is refilled with a new aliquot of substrate and trifluorotoluene. When a second run is performed, the yield of lactone **8** is not affected (Table 2). After the fourth run, the conversion of trichloro ester **7** was not modified although the reaction kinetics was slightly lowered. The amount of metal salts that remains in the organic phase was measured by atomic absorption spectroscopy. Only 1–2% of the copper was leached in the organic phase after each run. When iron powder was added, traces of iron salts (<0.15% of the total iron) were detected in the organic phase. The limitation in the recycling processes of the catalyst was the tedious separation of the perfluorinated and organic phases in an oxygen-free environment.

ATRA reactions are known to proceed via a reversible electron-transfer reaction from the metal complex to the halogen derivative leading to a proposed metal bonded radical. This radical can further rearrange to produce a new cyclized radical in the case of unsaturated derivatives such as compound **7**. Then, the cyclization product is formed in the termination step which is reverse of the initiation one. Other reaction pathways for the metal-bonded radicals are duplication processes for instance. This leads to catalyst consumption as the metal center remains in its oxidized state. The synergic action of iron powder and a copper(I) catalyst whatever the reaction conditions (homogeneous in a fluoro biphasic system) could be due to the constant recycling of the active catalyst by the coreducing agent, allowing the reaction to proceed to completion.

The procedure developed herein is truly catalytic and allows a high conversion of the substrate as well as nearly quantitative recycling of the catalyst. This procedure could also be used in metal center controlled living radical polymerization. We are currently trying to prepare catalysts that could avoid the tedious degassing processes of the reaction medium.

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## Experimental Section

**General.** DMF, $CH_2Cl_2$ and $CH_3CN$ were dried over $CaH_2$ and distilled prior to use. 1,2-Dichloroethane was used as received. Other commercially available starting materials were used without purification. Elemental analyses were performed by the Service Central d'Analyse de Vernaison (CNRS). Melting points are uncorrected.

**Starting Materials.** Perfluoro compounds **1** and **2** were synthesized according to the method described by Fish et al.[6] The ligand **6** was prepared by permethylation of the corresponding polyamine with a formic acid–formaldehyde mixture. Pent-4-enyl trichloroacetate (**7**) was synthesized from pent-4-en-1-ol and trichloracetyl chloride in the presence of $Et_3N$.[10]

**Typical Procedure for ATRA Reactions.** All the reactions were carried out under inert atmosphere (argon). The ligand (10 to 50 $\mu$mol) and the reaction mixture containing the substrate (1 mmol), the metal salt (10 to 50 $\mu$mol), and iron powder (100 to 500 $\mu$mol) when specified were degassed separately using the "freeze–pump–thaw" procedure (three cycles). The ligand was then added in order to generate the active catalyst. For monophasic reactions the solvent was 1,2-dichloroethane (8 mL). Fluorous biphasic reactions were performed in a mixture of perfluoroheptane (2 mL), trifluorotoluene (4 mL), and 1,2-dichloroethane (2 mL). The reaction mixture was treated by flash chromatography through a short silica gel column affording the lactone **8**. This compound was identical to the lactone synthesized by Pirrung et al.[10]

**Toluene-4-sulfonic Acid 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,-11-Heptadecafluoroundecyl Ester (3).** Alcohol **2** (9.56 g, 20 mmol) and toluene-4-sulfonyl chloride were dissolved in $CH_2Cl_2$ (100 mL). A 50% w/w aqueous sodium hydroxide solution (50 mL) was then added, and the reaction mixture was heated at 50 °C for 24 h. The suspension was cooled and decanted. The organic phase was washed three times with water (30 mL). After drying ($MgSO_4$) and filtration, the solvent was evaporated and compound **3** was obtained as a solid in 70% yield. The product could be recrystallized from hexane (mp 60 °C). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 1.9 (m, 2H), 2.2(m, 2H), 2.4 (s, 3H), 4.1 (t, 6.9 Hz, 2H), 7.3 (d, 8.1 Hz, 2H), 7.7 (d, 8.1 Hz, 2H).

**Pentakis-*N*-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)-1,4,7-triazaheptane (4).** A suspension of toluene-4-sulfonate **3** (6.95 g, 11 mmol), 1,4,7-triazaheptane (206 mg, 2 mmol), and potassium carbonate (2.07 g, 15 mmol) in $CH_3CN$ was heated to reflux for 48 h under $N_2$. The reaction mixture was filtered, and the solid was washed with trifluoro toluene. The combined filtrates were evaporated, and the residue was dissolved in perfluorohexane (50 mL). The solution was washed three times with $CH_2Cl_2$ (30 mL), and the solvent was evaporated leaving a pale yellow oil (3.1 g, 65%). $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 1.75 (m, 12H), 2.12 (m, 12H), 2.50 (m, 18H). FAB/MS: [M + 1] 2404. Anal. Calcd for $C_{59}H_{38}F_{85}N_3$: C, 29.48; H, 1.59; N, 1.75. Found: C, 29.37; H, 1.60; N, 1.97.

**Tris-[2-di-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)aminoethyl]amine (5).** This compound was synthesized using the procedure described above, starting from tris(2-aminoethyl)amine. Ligand **5** was obtained in 55% yield. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ 1.72 (m, 12H), 2.11 (m, 12H), 2.50 (m, 12H), 2.69 (m,12H). FAB/MS: [M + 1] 2907. Anal. Calcd for $C_{70}H_{48}F_{102}N_4$: C, 29.75; H, 1.66; N, 1.93. Found: C, 30.40; H, 1.89; N, 2.44.

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