New and improved catalysts for transition metal catalysed radical reactions

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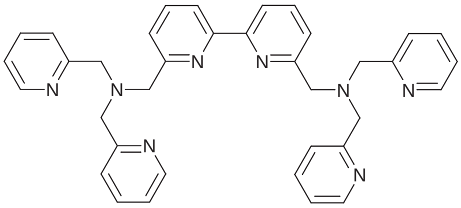
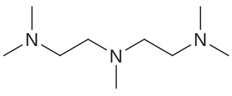
New Cu^{I} and Fe^{II} complexes displayed considerable improvements in atom transfer radical addition reactions.

Inter- and intra-molecular radical addition reactions are powerful tools for synthetic organic chemistry. In particular, those reactions initiated by reductive methods such as organotin hydride reduction of ω-haloolefins are well-known processes for the promotion of carbon–carbon bond formation for intramolecular addition and ring construction.[1,2] In contrast, atom transfer radical addition (ATRA) reactions make use of the redox properties of transition metal complexes in order to initiate the reaction by homolytic cleavage of a carbon–halogen bond. As a result, and in contrast to the Kharash addition, the termination step introduces a versatile halogen atom into the product which is then useful for further functionalisation. Thus, a new class of catalysts, most commonly transition metal complexes such as $RuCl_2(PPh_3)_2$,[3] $FeCl_2(P(OEt)_3)_3$,[4] Co(Di-Meglyoxime)$_2$,[5] CuCl(bpy)[3] or a mixture of iron metal and copper bromide,[6] can be used in ATRA reactions. However, only limited success has been reported and only a few examples have appeared which describe cyclisations of allylic trichloroacetates[7] or trichloroacetamides[8] to produce γ-lactones and lactams, respectively, or additions of trihalo compounds such as CCl_4,[9] trichloroacetic acid or esters[10] to olefins. Competing telomerisation is often considered to be a drawback.

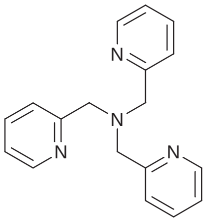
Here we report that the use of new copper and iron complexes, for such reactions as the addition of CCl_4 to oct-1-ene and the cyclization of unsaturated trichloroacetates, which lead to a considerable improvement in terms of catalytic activity.



L1

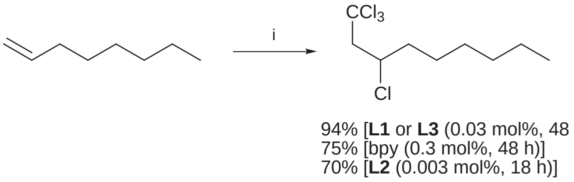


L2



L3

Ligands **L1**, **L2** and **L3** were synthesised according to literature procedures.[11] The catalyst was prepared *in situ* by reacting copper(I) or iron(II) chloride with 1 equiv. of ligand. Whatever the ligand used, the addition of CCl_4 to oct-1-ene proceeds smoothly and affords the corresponding 1:1 adduct. In a typical procedure, oct-1-ene (0.2 M in 1,2-dichloroethane) and CCl_4 (1.1 equiv.) were allowed to react under argon with various amounts of complex (from 30 to 3%) at 80 °C for 18–48 h. Flash chromatography through a short silica gel column and distillation under reduce pressure afforded 1,1,1,3-tetrachlorononane in almost quantitative yield (Scheme 1).



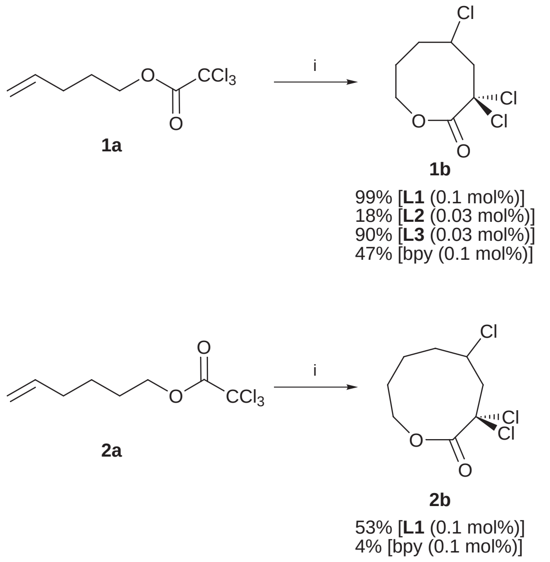
Scheme 1 *Reagents and conditions*: i, CuCl–ligand, CCl_4

The remarkable solubility of the catalysts, even in concentrated mixtures, and the low quantity of catalyst required in order to complete the reaction represent the major improvement. Thus, even with only 0.003 equiv. of an equimolar mixture of CuCl and ligand **L2**, the tetrachloro adduct is formed in 70% yield, making these systems truly catalytic.

The most significant result was the possibility of using a simple tridentate polyamine (**L2**). This ligand is obtained in a one step procedure from a very cheap starting material. These new complexes induce a faster addition reaction than the widely used Cu(I)Cl/bpy complex. In order to find a catalyst which is less oxygen and water sensitive, we have also investigated the activity of the corresponding iron(II) complexes. Although the iron(II)(bpy) complex was almost inactive, those obtained with **L1** and **L2** exhibit good catalytic activity.‡

Emboldened by these results, we then studied the ability of these catalysts to induce the cyclisation of unsaturated trichloroacetates and particularly pent-4-enyl trichloroacetate **1a** and hex-5-enyl trichloroacetate **2a**. We report herein the synthesis of the eight- and higher-membered lactones by a cyclisation process *via* an *endo* mechanism (Scheme 2). The trichloroacetates were treated at 80 °C (0.1 M in 1,2-dichloroethane) with various amounts of catalyst under argon.

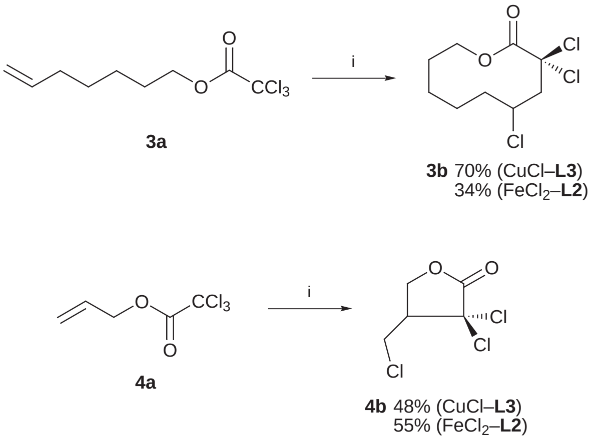
The complexes reported herein are far better catalysts than the previously described CuCl–bpy system.[3] For instance, ligand **L1** in the presence of copper(I) (0.1 mol%) converted quantitatively pent-4-enyl trichloroacetate **1a** into lactone **1b**. Using the same conditions the yield reached only 47% with CuCl–bpy. The CuCl–**L2** system proved to be not as effective in the catalysis of intramolecular reactions, but when $FeCl_2$ was used instead of CuCl, it was possible to obtain a good yield of cyclisation product.§ In all of the experiments described, no significant amount of telomers could be detected. It has been previously reported that with a high stoichiometric ratio of Cu^{I}Cl–bpy (30%), significant telomer formation occurs. The lactone formation yield remains average (60%), but all the ester is consumed. The same phenomena could be observed when more that 10% catalyst was used, whatever the final concentration. These results indicate that the concentration of radicals (free or metal-bonded) remains high during the reaction and that the kinetic constant of cyclisation might be smaller than the telomerisation constant.



Scheme 2 *Reagents and conditions*: i, CuCl–ligand, 1,2-dichloroethane, 80 °C

The cyclisation of hex-5-enyl trichloroacetate **2a** gave only a low yield of lactone **2b** in the presence of CuCl–bpy (0.1 mol%), but this yield is subsequently improved by the use of either the CuCl–L1 or the $FeCl_2$–L2 systems.[¶] In the cyclisation experiments with **2a**, a substantial difference between the yield of cyclisation products and the total conversion, based on the disappearance of **2a**, was noted. The difference in mass balance is probably due to the tendency for **2a** to give oligomers and particularly dimers, which have been characterised by mass spectrometry, because of the increase in ring size.

We have also observed reactions which were impossible to perform with CuCl–bpy;[7] for instance the cyclisation of hept-6-enyl trichloroacetate **3a** afforded the cyclic *endo* lactone **3b** in 70% yield in the presence of CuCl–**L3** (Scheme 3). It was also possible to catalyse the *exo* cyclisation of prop-2-enyl trichloroacetate **4a** with 48% yield in the presence of the same catalyst. In the latter case the $FeCl_2$–**L2** system also proved to be effective.



Scheme 3 *Reagents and conditions*: 1,2-dichloroethane, 80 °C, CuCl–**L3** or $FeCl_2$–**L2** catalysts (0.1 mol%)

As previously observed,[3,12] the cyclisation of esters with long unsaturated chains (**1a**, **2a**, **3a**) proceeds *via* an *endo* pathway. This is due to the fact that the most stable conformation for the ester function (s-*trans*) does not impede the cyclisation process if the carbon chain is long enough. With the unsaturated ester **4a**, only the less favourable conformation (s-*cis*) can give rise to the cyclisation product. In this case the formation of a five-membered ring *via* an *exo* pathway is preferred. The but-3-enyl trichloroacetate lies in an intermediate position. It was impossible for us to obtain cyclisation products, we could only detect cyclic dimers and telomers by mass spectrometry. The formation of a six-membered ring lactone *via* the s-*cis* conformation is not favourable and the butenyl chain is not long enough to allow a cyclisation process *via* the s-*trans* conformation. These results are consistent with those reported by O-Yang in the case of α-iodo esters.[12]

As a conclusion, the use of new ligands represents a significant improvement for the catalytic activity of copper(I) and iron(II) complexes in ATRA reactions by reducing the required amount of complex by a factor of 10 to 100. Moreover, they are soluble in the reaction mixture and catalyse reactions which are impossible to perform with the $Cu^{I}Cl$–bpy complex. The metal could also act as a template and allow the notoriously difficult cyclisation of eight- and nine-membered ring lactone precursors as suggested previously.[7] We are currently trying to relate the redox potentials of these complexes to their catalytic activity.

We are indebted to Dr B. Maillard for fruitful discussion and to the Région Aquitaine for financial support.

Notes and References

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[‡] In the presence of an 1:1 mixture of $FeCl_2$–ligand (0.03 mol%), the yields were respectively: **L1**, 65% (48 h); **L2**, 75% (18 h); bpy, 4% (18 h).

[§] Replacement of CuCl–**L2** by $FeCl_2$–**L2** allowed us to obtain **1b** in 62% yield.

[¶] A 50% yield of **2b** was obtained by using the $FeCl_2$–**L2** mixture (0.03 mol%)

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Received in Cambridge, UK, 14th April 1998; revised manuscript received, 29th June 1998; 8/04915G