New copper(I) and iron(II) complexes for atom transfer radical macrocyclisation reactions

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New Cu(I) and Fe(II) complexes have been synthesized and proved to be efficient catalysts for atom transfer radical addition (ATRA) reactions. The catalytic activity was found to be greater than existing atom transfer systems based upon CuCl(bipyridine) or $RuCl_2(PPh_3)_3$, for example. The addition of a reducing agent considerably improved the efficiency of the usual procedures.

Introduction

The synthesis of macrolactones has received considerable attention during the past ten years due to their presence in natural substances[1] and to their biological activity against tumorous disease[2] for example.

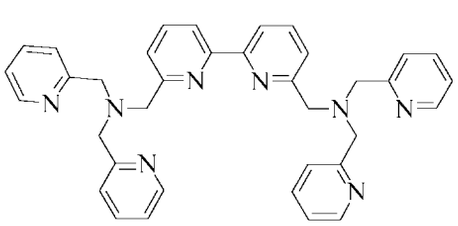
Synthetic methods allowing the preparation of 8- to 10-membered or higher lactones are scarce and generally involve high dilution techniques or the aid of a template structure. With the exception of esterification reactions, few methods have been reported for the synthesis of lactones from an acyclic precursor. Radical methods are powerful tools for carbon–carbon bond formation by intramolecular addition of a carbon radical to an unsaturated system; organotin hydride mediated cyclisation of ω-iodoalkyl unsaturated esters has been successfully reported by Porter *et al.*[3] Radical methods have also been used for the preparation of macrocyclic ethers using syringe-pump techniques in order to avoid oligomerisation or direct reduction of the substrate.[4] Atom transfer radical addition (ATRA) reactions, which make use of the redox properties of transition metal complexes in order to initiate the reaction by homolytic cleavage of a carbon–halogen bond, could be used as an alternative to organotin hydride for the generation of a carbon centered radical. Moreover, the termination step introduces a versatile halogen atom into the product which is then useful for further functionalisation. It can also be expected that the metal could play a crucial role in the control of the cyclisation process as the radical is generated in the vicinity of the metal complex. Thus, a new class of catalysts, which are most often transition metal complexes such as $RuCl_2(PPh_3)_3$,[5] $FeCl_2(P(OEt)_3)_3$,[6] Co(dimethylglyoxime)$_2$,[7] CuCl(bpy)[5] (bpy = 2,2′-bipyridine) or a mixture of iron metal and copper bromide,[8] has been described in ATRA reactions. Speckamp *et al.* have reported the synthesis of 5- to 8-membered lactones by cyclisation of unsaturated trichloroacetates using Cu(I)Cl(bpy) as a catalyst.[9] The major problems associated with the use of this catalyst are its low solubility in the reaction solvent and the poor conversion in the attempts to prepare higher lactones; in the latter case, oligomerisation of the starting material is generally observed. Recently, more active copper catalysts have been described for the preparation of cyclic lactams and their application in atom transfer polymerisation has been reported.[10]

Results and discussion

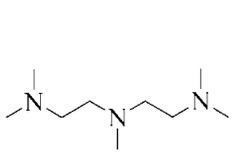
We recently reported the preparation of copper(I) or iron(II) complexes that could circumvent the problems associated with poor solubility and conversion.[11] Due to their better solubility and higher catalytic activity, only small amounts of the complex (3 to 10 mol%) are required for completion of the reaction. We describe herein the results obtained in the cyclisation of unsaturated trichloroacetates bearing carbon chains of up to seven carbon atoms. Introduction of a poly(ethyleneglycol) chain into the unsaturated moiety of these esters allowed us to obtain 9- to 18-membered macrocyclic lactones.

Ligands **L1**, **L2** and **L3** were synthesised according to literature procedures.[12] The catalyst is prepared *in situ* by reacting copper(I) or iron(II) chloride with one equivalent of the ligand. Suitable radical precursors **2a**–**i** were readily prepared from the appropriate alkenyl alcohol or ethylene glycol precursors. In a typical procedure, treatment of allyl alcohol **1a** with trichloroacetyl chloride in dichloromethane at 0 °C in the presence of triethylamine furnished the trichloroester **2a** in 65% yield (Scheme 1).

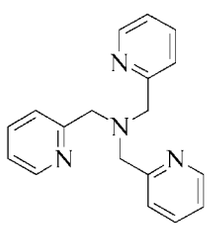
The cyclisation reactions were performed in 1,2-dichloroethane at 80 °C for 12–48 h under an argon atmosphere. Work up was performed by chromatography of the reaction mixture on silica using petroleum ether–ethyl acetate as eluent. The nature and the amount of the catalyst, as well as the reaction yields, are indicated in Table 1. The yields of cyclisation of both pent-4-enyl trichloroacetate **2c** and hex-5-enyl trichloroacetate **2d** were subsequently improved by the use of these new catalyst



L1



L2



L3

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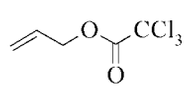
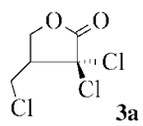
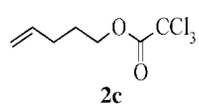
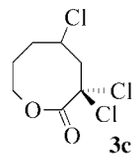
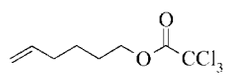
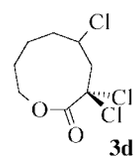
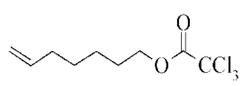
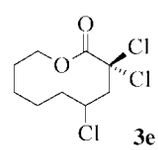
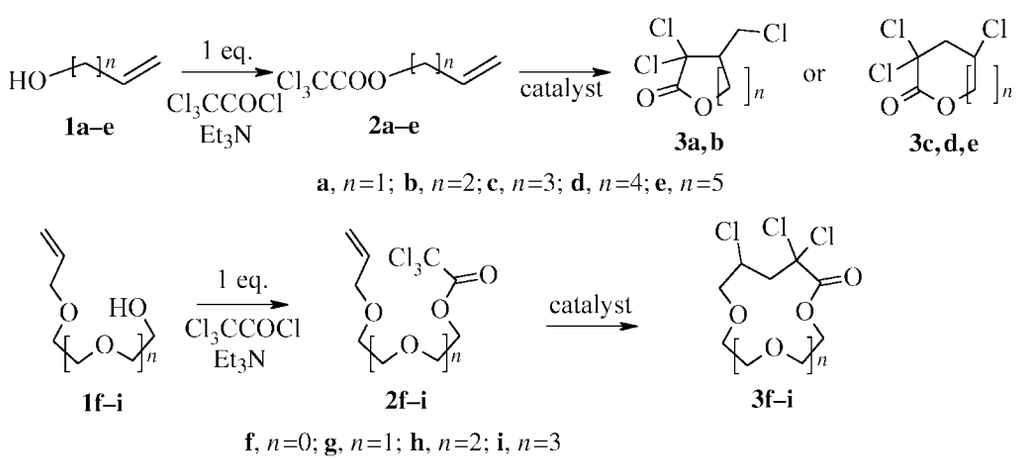
Table 1 Cyclisations of unsaturated trichloroesters in 1,2-dichloroethane at 80 °C (one equivalent of ligand with respect to the metal)

Precursor	Product	Catalyst (ratio)	Yield (%)
 **2a**	 **3a**	CuCl·**L3** (10 mol%) $FeCl_2$·**L2** (10 mol%)	48 55
 **2c**	 **3c**	CuCl·**L1** (10 mol%) $FeCl_2$·**L2** (0.3 mol%) CuCl·**L3** (3 mol%) CuCl·bpy (10 mol%)	99 46 90 47
 **2d**	 **3d**	CuCl·**L1** (10 mol%) $FeCl_2$·**L2** (3 mol%) CuCl·**L3** (10 mol%) CuCl·bpy (10 mol%)	53 50 53 4
 **2e**	 **3e**	CuCl·**L1** (10 mol%) CuCl·**L3** (10 mol%) $FeCl_2$·**L2** (10 mol%) CuCl·bpy (30 mol%)	51 70 34 5

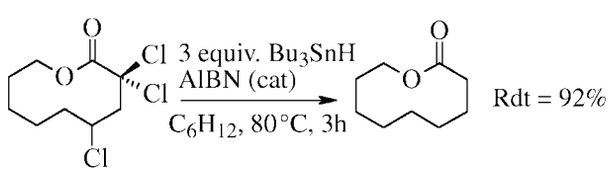


Scheme 1 Synthetic scheme for the preparation of unsaturated trichloroesters.

systems. The best result was obtained with ligand **L1** which allowed quantitative conversion in the case of **2c**. The use of complexes $FeCl_2$·**L2** or CuCl·**L3**, depending on the substrate, allowed us to decrease considerably the complex–substrate ratio without significant alteration of the yield. Ligand **L2** associated with copper(I) gave very poor results, but surprisingly when used with iron(II) chloride a very efficient catalyst was obtained and trichloroester **2c** was converted to lactone **3c** in 46% yield even in the presence of 0.3 mol% of catalyst. Moderate yields of large ring lactones were obtained in the presence of these new catalysts even though it was nearly impossible to obtain cyclised products **3d** or **3e** with the copper(I)–bipyridine complex.

The structure of compound **3e** was proven by complete reduction of the racemic mixture to the unsubstituted derivative **4**[13] with Bu_3SnH–AIBN (Scheme 2). When the unsaturated side chain possesses more than three carbon atoms the cyclisation process proceeds in an *endo* manner (Scheme 3). Indeed, the most stable conformation for the ester function (s-*trans*) does not impede the cyclisation step if the carbon chain is long enough (compounds **2c**–**i**).

With an unsaturated shorter chain (*e.g.* compound **2a**) only the less favourable conformation (s-*cis*) can give rise to the



Scheme 2 Reduction of trichlorolactone **3e** by 3 equivalents of Bu_3SnH.

cyclisation product and an *exo* pathway is observed, as previously reported by Barth and Yang (Scheme 3).[14] However, whatever the catalyst, while conversions are very high, isolated yields remain modest due to partial oligomerisation of the substrates. With the but-3-enyl precursor **2b** no cyclisation products were observed. In this case, only the s-*cis* conformation could lead to the cyclised products as the chain is not long enough to allow any significant overlap of the radical and alkene orbitals in the s-*trans* conformation and the *endo* or *exo* cyclisation rate constants are probably lower than those for intermolecular addition, thus only oligomerisation could be observed.

In order to lower the catalyst *versus* substrate ratio, a

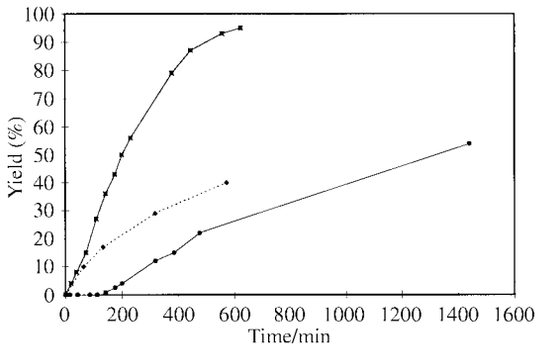
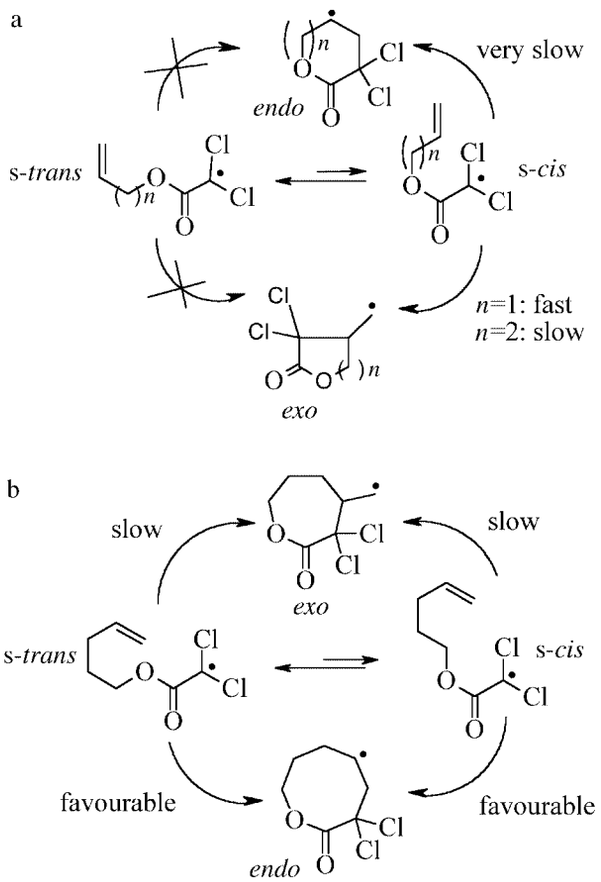


Fig. 1 Cyclisation reaction of substrate **2c** in the presence[a] of: (◆) CuCl·**L2** ratio 1:1; (■) CuCl·**L2**·Fe(0) ratio 1:1:10; (●) Fe(0)·**L2**. ([a] The ratios are given in mol% relative to the substrate.)



Scheme 3 Interpretation of radical cyclisation step a) for short chain (n = 1 or 2) b) for long chain (n = 3, 4 or 5).

reducing agent iron(0) was added to the reaction mixture. The best results were obtained with a 1:10 ratio of CuCl:Fe(0) (in mol%) giving a twofold increase in yield within the same reaction time. Surprisingly, we observed a perfect correlation between the conversion (95%) and the yield (95%) due to minor oligomerisation processes and an enhancement of the catalytic activity (Fig. 1).

If CuCl is omitted from the reaction vessel the cyclisation still proceeds in the presence of a mixture of only the ligand and iron powder. However, a latency phase could be observed before the beginning of the conversion and the reaction rate is lowered. This latency phase could be due to the slow dissolution of traces of iron oxides and hydroxides in the presence of the ligand as iron powder alone failed to mediate the cyclisation of trichloroesters. The incapacity of iron metal for such catalysis has been previously observed in apolar solvents.[15] As displayed in Fig. 1, an additional effect is observed when iron powder is added to a copper complex. We suggest that the use of iron(0) either accelerates the halogen transfer from copper(II) to the cyclic radical or allows the reduction of the copper(II), formed by the dimerisation reaction, back to the active catalyst.

For substrate **2d**, the introduction of the reducing agent did not exert any significant effect as the yield and the conversion were not modified to a large extent. When we applied this methodology to substrate **2e** the ratio of catalyst could be decreased twofold without any modification of the yield and conversion.

In all the experiments described, no significant amounts of telomers were detected as observed with the CuCl·bpy complex. Due to the better solubility and higher activity of our new complexes, we were able to perform the cyclisation reaction with less than 10 mol% of catalyst.

We also tested the ability of these complexes to catalyse the cyclisation of larger unsaturated trichloroesters bearing polyether chains. The metal is expected to act as a template and thus enhance the cyclisation process. We report here that 9- to 18-membered polyether rings are readily accessible from ω-polyoxyalkenols using copper(I) or iron(II) complexes. As far as we know, the use of these types of catalysts for macrocyclisation reactions and especially for polyether synthesis has been neglected. Pirrung *et al.* previously described the synthesis of 9- and 10-membered lactones [in the presence of CuCl·bpy (30 mol%)] using a rigid backbone in the alkenyl chain and reported that this catalyst failed to mediate cyclisation of higher lactones.[5]

In the presence of the CuCl·**L3** complex, the cyclisation of the trichloroacetates **2f** and **2g** proceeds smoothly with poor yields. Using the $FeCl_2$·**L2** complex, the conversion reached 95% and the yield was notably improved, probably due to the higher solubility of the resulting complex and a possible template effect due to the higher acidity of iron(II) (Table 2). In these examples competing telomerisation also occurred, principally with shorter chains, the cyclisation and telomerisation rate constants being similar. Comparatively, when the chain is long enough, as in the case of **2h** and **2i**, the cyclisation process is more favourable and yields of lactone are reasonable even with the CuCl·**L3** complex. The selectivity of the cyclisation is noteworthy as the reaction proceeded cleanly and no side-products were detected. As previously described for the trichloroacetates **2a**–**e**, the introduction of iron(0) (10 mol%) notably improved the kinetics of the reactions but had no effect on the yield, however decomposition of the cyclized product occurred during the reaction and disappearance of the lactone could be monitored by GC analysis. These side-reactions also occurred in the absence of the reducing agent and explain the low yields obtained with the former substrates.

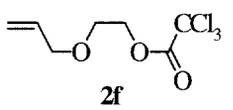
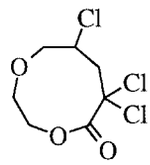
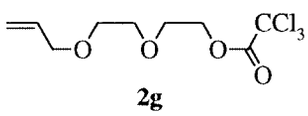
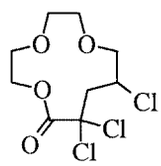
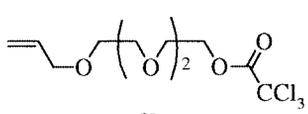
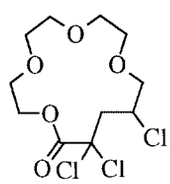
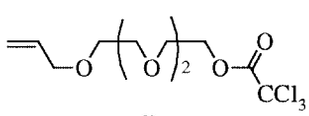
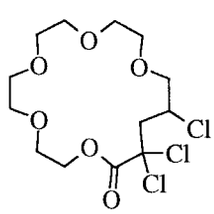
In conclusion, we have reported that the use of new complexes of iron(II) or copper(I) successfully mediated atom transfer radical cyclisation reactions of various trichloroacetates in the presence of very low quantities of catalyst. While previous systems did not allow the synthesis of large rings, the CuCl·TPA(**L3**) complex [TPA = tris(pyridin-2-ylmethyl)amine] displayed a very high catalytic activity and excellent selectivity. Cyclisation of medium rings is also possible and in the case of eight- and nine-membered lactones, the use of the CuCl·**L2** complex associated with iron(0) proved to be a significant improvement. The synthesis of five-membered rings was also described and the selectivity of this process was found to be greater than that reported with CuCl·bpy.

Experimental

General requirements

All reactions were carried out under an inert atmosphere of dry nitrogen and argon for intramolecular cyclisation. Proton and carbon nuclear resonance (^{1}H and ^{13}C NMR) spectra were recorded in $CDCl_3$, unless indicated otherwise, using either a

Table 2 Cyclisations of polyoxaalkenyl trichloroesters in 1,2-dichloroethane at 80 °C (one equivalent of ligand with respect to the metal)

Precursor	Product	Catalyst[a]	Yield (%)
 **2f**	 **3f**	$FeCl_2$·**L2** CuCl·**L3** CuCl·bpy	56 29 11
 **2g**	 **3g**	$FeCl_2$·**L2** CuCl·**L3** CuCl·bpy	60 29 10
 **2h**	 **3h**	$FeCl_2$·**L2** CuCl·**L3** CuCl·bpy	60 70 10
 **2h**	 **3i**	$FeCl_2$·**L2** CuCl·**L3** CuCl·bpy	60 70 10

[a] Catalyst to substrate ratio was 10 mol% in all the experiments.

Bruker AC200 (200 MHz, 50 MHz) or an AC250 (250 MHz, 63 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. CH_2Cl_2 and $(CH_2Cl)_2$ were distilled from $CaCl_2$ powder and stored under an atmosphere of dry nitrogen. Dry THF and Et_2O were distilled from sodium benzophenone prior to use. Petroleum ether and ethyl acetate were also distilled for chromatographic purposes. Other commercially available starting materials were used without further purification. Elemental analysis were performed by the Service Central d'Analyse (CNRS-Vernaison).

Typical procedure for trichloroacetylation of alkenols

Trichloroacetyl chloride (0.165 mol) was dissolved in dichloromethane (450 ml) and cooled down to 0 °C. Alkenol (0.15 mol) was slowly added, then triethylamine (0.3 mol) in dichloromethane solution (100 ml) was added dropwise to the reaction mixture. After 2 hours at 0 °C, a 2 M solution of hydrochloric acid (120 ml) was poured into the reaction flask. The organic phase was washed with a saturated solution of sodium hydrogen carbonate and water until the pH reached 7. After drying over magnesium sulfate, the solvent was removed under vacuum. The resulting crude product was purified on a silica gel column (eluent: petroleum ether–ethyl acetate, 90 : 10 for compounds **2a**–**e** and 50 : 50 for compounds **2f**–**i**). Compounds **2c** and **2d** were synthesized according to literature procedures.[5]

Trichloroacetic acid prop-2-enyl ester 2a. Yield (65%). IR ν_{max}(film)/cm^{-1} 3070, 2940, 1760 (Found: C, 29.21; H, 2.53; O, 16.04; Cl, 51.51. $C_5H_5Cl_3O_2$ requires C, 29.52; H, 2.48; O, 15.73; Cl, 52.28%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 4.8 (m, 2H, CH_2O), 5.3–5.5 (m, 2H, CH_2=), 5.8–6.05 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 69.5 (CH_2O), 100.0 (CCl_3), 120.4 (CH_2=), 129.9 (CH=), 163.0 (C=O); *m*/*z* (CI): 202 (1%, M), 167 (1, M − Cl), 132 (7, M − 2Cl), 97 (100, M − 3Cl), 57 (87, M − $COCCl_3$).

Trichloroacetic acid but-3-enyl ester 2b. Yield (55%). IR ν_{max}(film)/cm^{-1} 3080, 2960, 1760 (Found: C, 32.05; H, 3.22; O, 15.07; Cl, 48.64. $C_6H_7Cl_3O_2$ requires C, 33.14; H, 3.24; O, 14.71; Cl, 48.91%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 2.5 (m, 2H, CH_2-CH=), 4.4 (m, 2H, CH_2O), 5.1–5.3 (m, 2H, CH_2=C), 5.7–5.9 (m, 1H, CH_2=CH); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 32.1 (CH_2), 67.7 (CH_2O), 90.0 (CCl_3), 117.9 (CH_2=), 132.1 (CH=), 161.5 (C=O).

Trichloroacetic acid hept-6-enyl ester 2e. Yield (82%). IR ν_{max}(film)/cm^{-1} 3010, 2970, 1760 (Found: C, 40.89; H, 4.38. $C_9H_{13}Cl_3O_2$ requires C, 41.62; H, 4.51%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 1.35–1.5 (m, 4H, CH_2CH_2), 1.8 (m, 2H, CH_2CH=), 2.1 (m, 2H, CH_2CH_2O), 4.36 (m, 2H, CH_2O), 4.95 (m, 2H, CH_2=), 5.79 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 24.8 (CH_2CH_2CH=), 27.8 (CH_2CH_2O), 28.0 (CH_2), 33.2 (CH_2CH=), 69.2 (CH_2O), 89.9 (CCl_3), 114.5 (CH_2=), 138.2 (CH=), 161.8 (C=O).

Trichloroacetic acid 3-oxahex-5-enyl ester 2f. Yield (82%) (Found: C, 34.45; H, 3.56. $C_7H_9Cl_3O_3$ requires C, 33.94; H, 3.64%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.3 (m, 2H, CH_2-$OCOCCl_3$), 3.55 (m, 2H, $CH_2CH_2OCOCCl_3$), 4.0 (m, 2H, =$CHCH_2O$), 4.7 (m, 2H, CH_2=), 5.35 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 65.4 ($CH_2OCOCCl_3$), 66.8 (CH_2CH_2-

$OCOCCl_3$), 71.86 (=$CHCH_2O$), 89.53 (CCl_3), 117.11 (CH_2=), 134.00 (CH=), 161.69 (C=O).

Trichloroacetic acid 3,6-dioxanon-8-enyl ester 2g. Yield (99%) (Found: C, 37.78; H, 4.36. $C_9H_{13}Cl_3O_4$ requires C, 37.05; H, 4.46%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.52 (m, 2H, CH_2O), 3.61 (m, 2H, CH_2O), 3.7 (m, 2H, CH_2O), 3.97 (m, 2H, CH_2CH=), 4.2 (m, 2H, CH_2O), 5.15 (m, 2H, CH_2=), 5.8 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 68.06 ($CH_2OCOCCl_3$), 68.09, 69.17, 70.61, 71.95 (other CH_2), 89 (CCl_3), 116.83 (CH_2=), 134.36 (CH=), 161.67 (C=O).

Trichloroacetic acid 3,6,9-trioxadodec-11-enyl ester 2h. Yield (69%) (Found: C, 38.92; H, 4.89. $C_{11}H_{17}Cl_3O_5$ requires C, 39.34; H, 5.07%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.41 (m, 8H, CH_2O), 3.55 (m, 2H, CH_2), 3.81 (m, 2H, CH_2CH=), 4.25 (m, 2H, CH_2OCO), 5.05 (m, 2H, CH_2=), 5.82 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$; Me_4Si) 70.35, 70.26, 70.15, 70.07, 68.81 (other CH_2), 67.75 ($CH_2OCOCCl_3$), 71.56 (=$CHCH_2O$), 89.4 (CCl_3), 116.39 (CH_2=), 134.16 (CH=), 161.29 (C=O).

Trichloroacetic acid 3,6,9,12-tetraoxapentadec-14-enyl ester 2i. Yield (79%) (Found: C, 40.89; H, 5.36. $C_{13}H_{21}Cl_3O_6$ requires C, 41.11; H, 5.53%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.37 (m, 12H, CH_2O), 3.54 (m, 2H, *CH*$_2$$CH_2OCO$), 3.78 (2H, m, CH_2CH=) 4.26 (m, 2H, CH_2OCO), 5.35 (m, 1H, CH=); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 67.88 ($CH_2OCOCCl_3$), 67.95, 69.00, 70.19, 70.21, 70.25, 70.39, 70.42, 71.7 (other CH_2), 89.35 (CCl_3), 116.44 (CH_2=), 134.41 (CH=), 161.39 (C=O); *m*/*z* (FAB, 70 eV): 379 (M + 1), 235 (M − $COCCl_3$).

Typical procedure for cyclisation of alkenyl trichloroacetates

All the reactions were carried out under an argon atmosphere in 1,2-dichloroethane (0.2 M). The ligand (10 to 100 μmol), the reaction mixture containing the substrate (1 mmol) and the metal salt (10 to 100 μmol) were degassed separately using the freeze–pump–thaw procedure (three cycles). The ligand was then added in order to generate the active catalyst.

3,3-Dichloro-4-chloromethyltetrahydrofuran-2-one 3a. IR ν_{max}(film)/cm^{-1} 2960, 1760; δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.3–3.4 (m, 1H, CHCl), 3.8 (dd, *J* 9.5, 11.5 Hz, 1H) and 4.0 (dd, *J* 4.6, 11.5 Hz, 1H) (CH_2Cl), 4.2 (dd, *J* 8.8, 9.3 Hz, 1H) and 4.7 (dd, *J* 7.1, 9.3 Hz, 1H) (CH_2O); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 39.2 (CH_2Cl), 52.9 (CHCl), 68.2 (CH_2O), 78.2 (CCl_2), 166.7 (C=O); *m*/*z* (CI, NH_4^+): 167 (1, M − Cl), 132 (32, M − 2Cl), 97 (100, M − 3Cl).

Compounds 3c, 3d: See reference 5. 3,3,5-Trichlorooxecan-2-one **3e**. IR ν_{max}(film)/cm^{-1} 2970, 1770; δ_H(250 MHz; $CDCl_3$, Me_4Si) 1.5–2.2 (m, 8H), 2.9 (dd, *J* 3.7, 15.4 Hz, 1H) and 3.2 (dd, *J* 8.4, 15.4 Hz, 1H) (CH_2CCl_2), 3.83 (m, 2H, CH_2O), 4.22–4.30 (m, 1H, CHCl); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 20.3, 23.5, 24.7, 29.2 (CH_2), 49.3 (CH_2CCl_2), 56.4 (CHCl), 69.6 (CH_2O), 82.4 (CCl_2), 164.1 (C=O).

6,6,8-Trichloro-1,4-dioxacyclononan-5-one 3f. (Found: C, 35.09; H, 3.6; O, 19.29; Cl, 41.33. $C_7H_9Cl_3O_3$ requires C, 33.96; H, 3.60; O, 19.39; Cl, 42.97%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 3.05–3.16 (m, 2H, CH_2CCl_2), 3.56–3.86 (m, 2H, CH_2O), 4.36 (m, 1H, CHCl), 4.44 (m, 2H, CH_2OCO); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 50.5 (CH_2CCl_2), 55.7 (CHCl), 65.9 (CO_2CH_2), 70.6 ($CO_2CH_2CH_2$), 77.9 (CH_2O), 82.1 (CCl_2), 165 (C=O).

9,9,11-Trichloro-1,4,7-trioxacyclododecan-8-one 3g. (Found: C, 37.26; H, 4.61; O, 21.95; Cl, 36.43. $C_9H_{13}Cl_3O_4$ requires C, 37.08; H, 4.49; O, 21.95; Cl, 36.48%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 2.90–3.15 (m, 2H, CH_2CCl_2), 3.41–3.67 (m, 6H, other CH_2O), 3.7 (m, 2H, $CO_2CH_2CH_2$), 4.05 (m, 1H, CHCl), 4.42 (m, 2H, CO_2CH_2); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 51.3 (CH_2CCl_2), 53.4 (CHCl), 66.5 (CO_2CH_2), 68.5 ($CO_2CH_2CH_2$), 70.7 (CH_2O), 70.8, 74.1, 82.5 (CCl_2), 165.3 (C=O).

12,12,14-Trichloro-1,4,7,10-tetraoxacyclopentadecan-11-one 3h. (Found: C, 39.75; H, 4.62; O, 23.93; Cl, 31.98. $C_{11}H_{17}Cl_3O_5$ requires C, 39.60; H, 4.53; O, 23.98; Cl, 31.88%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 2.84–3.11 (m, 2H, CH_2CCl_2), 3.33–3.81 (m, 12H, CH_2O), 4.01 (m, 1H, CHCl), 4.38 (m, 2H, CO_2CH_2); δ_C(62.9 MHz; $CDCl_3$, Me_4Si), 48.9 (CH_2CCl_2), 55.1 (CHCl), 66.3 (CO_2CH_2), 67.7 ($CO_2CH_2CH_2$), 69.6 (CH_2O), 69.9, 70.2, 70.5, 74.1, 82.2 (CCl_2), 164.9 (C=O).

15,15,17-Trichloro-1,4,7,10,13-pentaoxacyclooctadecan-14-one 3i. (Found: C, 41.14; H, 5.61; O, 24.32; Cl, 29.58. $C_{13}H_{21}Cl_3O_6$ requires C, 41.13; H, 5.58; O, 25.28; Cl, 28.01%); δ_H(250 MHz; $CDCl_3$, Me_4Si) 2.76–3.08 (m, 2H, CH_2CCl_2), 3.49–3.65 (m, 14H, other CH_2O), 3.78 (m, 2H, $CO_2CH_2CH_2$), 4.11 (m, 1H, CHCl), 4.40 (m, 2H, CO_2CH_2); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 48.81 (CH_2CCl_2), 55.1 (CHCl), 66.6 (CO_2CH_2), 68.1 ($CO_2CH_2CH_2$), 69.2 (CH_2O), 70.4, 70.5, 70.7, 70.8, 72.0, 74.4, 83.1 (CCl_2), 165.1 (C=O).

Procedure for the reduction of compound 3e to 1-oxacyclodecan-2-one 4

To a solution of tributyltin hydride (403 mg, 1.39 mmol) in cyclohexane (2.2 ml) was slowly added a cyclohexane (5 ml) solution of **3e** (110 mg, 0.42 mmol) and AIBN (1.38 mg, 0.008 mmol). After 3 hours at 80 °C, the reaction mixture was diluted with cyclohexane (30 ml) and a saturated solution of potassium chloride (15 ml) was added. The aqueous layer was extracted three times with 10 ml of cyclohexane. The organic phases were evaporated to dryness and the resulting brown oil dissolved in acetonitrile. The resulting solution was washed three times with petroleum ether and evaporation provided 60 mg (yield, 92%) of a yellowish oil. δ_H(250 MHz; $CDCl_3$, Me_4Si) 0.9–1.4 (m, 12H, CH_2 cyclic), 1.8–2.1 (m, 2H, CH_2C=O), 3.6–3.8 (m, 2H, CH_2O); δ_C(62.9 MHz; $CDCl_3$, Me_4Si) 24.7 (CH_2CH_2C=O), 25.4 ($CH_2CH_2CH_2O$), 25.5 ($CH_2CH_2CH_2C$=O), 28.2 (CH_2CH_2O), 28.5 ($CH_2CH_2CH_2CH_2O$), 28.7 ($CH_2CH_2CH_2CH_2C$=O), 33.9 (CH_2C=O), 63.6 (CH_2O), 164.2 (C=O).

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